# Nelson

# Last Minute

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# DEDICATION

To my colleagues in Al-quds University, I introduce my simple collection of pediatrics course; Nelson Last Minute. I hope this work will help saving your time while being crushed with allot of subjects during the whole year. I tried to cover the most important subjects, which every one must pass on.
I depended mainly on Essentials of Pediatrics, Nelson Textbook 18th edition, and our honored teacher's notes and sheets.

I won't to thank all my teachers; specialists and residents in pediatrics ward of Al-Makased hospital for their endless patient while teaching us. **You are our inspiration**. Without your coordinated & well prepared course, this simple comprehensive, gathered and formatted student's collection has no meaning.
Thanks for Dr.Bassam Abu-Libdeh, Dr.Hatem Khamash, Dr.Imad Dweikat, Dr.Samir Khalile, Dr. Abd-Alsalam Abu-Libdeh, Dr.Mutaz Soltan, Dr.Sudkqi Hamadah and all the residents.
Finally, special thanks to my Dad for offering INK and PAPERS :D

NADERA DAMSA

# Collection Contents

# Growth and milestones

# DEVELOPMENT MILLSTONES

| Age | Gross Motor | Visual-Motor/Problem Solving | Language | Social/Adaptive |
|---|---|---|---|---|
| 1 mo | Raises head from prone position | *Birth*: Visually fixes<br>*1 mo*: Has tight grasp, follows to midline | Alerts to sound | Regards face |
| 2 mo | Holds head in midline, lifts chest off table | No longer clenches fists tightly, follows object past midline | Smiles socially (after being stroked or talked to) | Recognizes parent |
| 3 mo | Supports on forearms in prone position, holds head up steadily | Holds hands open at rest, follows in circular fashion, responds to visual threat | **Coos** (produces long vowel sounds in musical fashion) | Reaches for familiar people or objects, anticipates feeding |
| 4 mo | **Rolls over**, supports on wrists, and shifts weight | Reaches with arms in unison, brings hands to midline | **Laughs**, orients to voice | Enjoys looking around |
| 6 mo | Sits unsupported, puts feet in mouth in supine position | Unilateral reach, uses raking grasp, **transfers objects** | Babbles, ah-goo, razz, lateral orientation to bell | Recognizes that someone is a stranger |
| 9 mo | Pivots when sitting, **crawls** well, pulls to stand, cruises | **Uses immature pincer grasp**, probes with forefinger, holds bottle, throws objects | **Says "mama, dada"** indiscriminately, gestures, **waves bye-bye**, understands "no" | Starts exploring environment, plays gesture games (e.g., pat-a-cake) |
| 12 mo | **Walks alone** | **Uses mature pincer grasp**, can make a crayon mark, releases voluntarily | **Uses two words** other than mama/dada or proper nouns, jargoning (runs several unintelligible words together with tone or inflection), one-step command with gesture | Imitates actions, comes when called, cooperates with dressing |
| 15 mo | Creeps up stairs, walks back-wards independently | Scribbles in imitation, builds **tower of two blocks in imitation** | **Uses 4–6 words**, follows one-step command without gesture | *15–18 mo*: **Uses spoon and cup** |
| 18 mo | **Runs**, throws objects from standing without falling, **kicks a ball** | Scribbles spontaneously, builds tower of **3 blocks**, turns 2–3 pages at a time | Mature jargoning (includes intelligible words), **7–10 word vocabulary**, **knows 5 body parts** | Copies parent in tasks (sweeping, dusting), plays in company of other children |
| 24 mo | **Walks up and down steps without help** | Imitates stroke with pencil, builds tower of **7 blocks**, turns pages one at a time, removes shoes, pants, etc. | **Uses pronouns** (I, you, me) inappropriately, follows two-step commands, has a 50–word vocabulary, **uses two-word sentences** | Parallel play |
| 3 yr | Can **alternate feet when going up steps**, pedals tricycle, **broad jump** | **Copies a circle**, undresses completely, dresses partially, dries hands if reminded, unbuttons | Uses minimum of 250 words, 3–word sentences, uses plurals, knows all pronouns, repeats two digits | Group play, shares toys, takes turns, plays well with others, **knows full name, age, gender** |
| 4 yr | **Hops**, skips, alternates feet going down steps | **Copies a square**, buttons clothing, **dresses self completely**, catches ball, **draw 3 parts person** | **Knows colors**, says song or poem from memory, asks questions | Tells "tall tales," plays cooperatively with a group of children |

| Age | Gross Motor | Visual-Motor/Problem Solving | Language | Social/Adaptive |
|---|---|---|---|---|
| 5 yr | Skips alternating feet, jumps over low obstacles, heel-toe walk | **Copies triangle**, ties shoes, spreads with knife | Prints first name, asks what a word means | Plays competitive games, abides by rules, likes to help in household tasks |
| 6yr | Balances on each feet 6 sec | **Draw persone of 6 parts** | Defines word | Understand left & right |

# MILE STONES

## GROSS MOTOR:

- Head control: hold head up momentarily (1month)→ head steady (2months)→pull to sit without head lag(3 months)→ full head control(5 months).
- Back: completely rounded: 1st 4 months → sit with straight back (4 months).
- Prone position: momentarily hold chin (1 month)→ lift chin off couch at angle of 45 (1.5 months)→lift head, upper chest off couch bearing wt on forarms(3 months)→ bear wt on hand with extended arm (6 months)
- Sitting: without support for few minutes (6 months) → with hand support (7 months) → securely for 10 minutes (9months)
- Bear weight on feet on standing ( 6 months)
- Roll prone to supine (6 months)
- Roll supine to prone (7 months)
- Supine: spontaneously lift head off couch (7 months)
- Pull to stand (10 months)
- Crawl (10 months)
- Walk (12 months)
- Run (18 months)
- Kick ball (18 months)
- Jump, stand on one feet momentary catch ball, rid tricycle (3 years)
- Up and down stairs (4 years)
- Skip, hoop, dance (5 years)
- Catch with one hand (10 years)

## FINE MOTOR

- watch mother when she talks to him (1 month)
- smile (1.5 month)
- follow object, turn 90 + follow object across midline (1.5 months)
- follow object, turn 180+ follow object byond midline (3 months)
- hand regard (3 months)
- grasp rattle when placed in his hand (3 months)
- approach objects with his hand (4 months)
- transfer to month (6 months)
- transfer from one hand to ther (7 months)
- if he has on cub in hand, he return it when other one is offered ( 7 months)
- if he has one cub in hand, he return it when other one is offered (7 months)
- bang cub to table (7 months)
- bang tow cups together (8 months)
- **palmar grasp (5 months)**
- **ulnar grasp (6 months)**
- **radial grasp (thumb and index) (8 months)**
- **pincer grasp (1 year)**
- turn 2-3 pages together (18 months)→ turn one page (2years).
- scribble (13 months)
- build tower of 2 cubs (13 months)

- build tower 6 cubs (22 months)
- build tower 9 cubs (3 years)

## LANGUAGE AND SOCIAL

- gargle, coos (3 months)
- turn to sound at ear level (3 months)
- lough loud (4 months)
- bable (Ba,Da,Mam) (6 months)
- like & dislike (6 months)
- fear or stranger (6 months)
- inhibit to No, respond to name (7 moinths)
- chew (7 months)
- uncover toy (8 months)
- double babble (8 months)
- wave bye bye (9 months)
- clapping hand (10 months)
- understand words (10 months)
- peep-bo game (11 months)
- through object to flower (! Year)
- stop putting every thing in his mouth (1 year)
- 1st word (1 year)
- 4-6 words (18 months)
- 2 word sentences (19 months)
- Dress-undress (3 years)
- Dry at night (3 years)

## PRIMITIVE REFLEXES

| Primitive Reflexes | Elicitation | Response | Timing |
|---|---|---|---|
| **Moro reflex** | *Supine*: Sudden neck extension; allow head to fall back about 3 cm | Extension, adduction, and then abduction of UEs, with semiflexion | Present at birth, disappears **by 3–6 mo** |
| **Galant reflex (GR)** | *Prone suspension*: Stroking paravertebral area from thoracic to sacral region | Produces truncal incurvature with concavity toward stimulated side | Present at birth, disappears **by 2–6 mo** |
| **Asymmetric tonic neck reflex (ATNR, "fencer" response)** | *Supine*: Rotate head laterally about 45–90 degrees | Relative extension of limbs on chin side and flexion on occiput side | Present at birth, disappears **by 4–9 mo** |
| **Symmetric tonic neck reflex (STNR, "cat" reflex)** | *Sitting*: Head extension/flexion | Extension of UEs and flexion of LEs/flexion of UEs and LE extension | **Appear at 5 mo**; not present in most normal children; disappears **by 8–9 mo** |
| **Stepping reflex (SR, walking reflex)** | Vertical suspension; hallucal stimulation | Stepping gait | Disappears **by 2–3 mo** |
| **Crossed extension reflex (CER)** | Prone; hallucal stimulation of an LE in full extension | Initial flexion, adduction, then extension of contralateral limb | Present at birth; disappears **by 9 mo** |
| **Plantar grasp** | Stimulation of hallucal areas | Plantar flexion grasp | Present at birth; disappears **by 9 mo** |
| **Palmar grasp** | Stimulation of palm | Palmar grasp | Present at birth; disappears **by 9 mo** |

# GROWTH

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## HEAD CIRCUMFERENCE:

- Average at birth = 35 cm (33-37)
  - If> 37= macrocephaly
  - If<33 = microcephaly
- During whole life increase 22-24 cm → during the first year↑ 12 cm, so it's very imp. Year.
- Rate of growth:
  1. first year ↑ **12cm**: 1st 3 months= 2cm/m (6cm), 2nd 9 months =2/3 cm/m (6cm)
  2. second year only ↑ **2 cm**
  3. 3-18 years ↑ **8 cm** ( 0.5cm/year)
- So:
  - HC at I year old = 35+12=**47cm**
  - HC at 2 years old= 47+ 2 =**51 cm**
  - HC at 18 years old= 51+8=**59 cm**

> **NOTE:**
> **Double** weight at 4-**5** months
> 750*4+450=**3450**
> **Triple** weight at 1 year
> **Quadruple** birth weight at 2 yrs

## WEIGHT

- average at birth = 3250 g (2.5-4 Kg)
  - SGA: small for gestational age = ↓ 2.5 Kg
  - LGA: large for gestational age =↑ 4Kg
- Growth rate:
  1. 1st year ↑ 6kg ( triple weight) : 1st 4 months=750g/m, 2nd 4 months=500g/m, 3ed 4 months=250g/m = 9250g
  2. 2-7 years ↑ 2kg/yr = 20Kg at 7 yrs
  3. 8-13 years = $\frac{\text{age} * 7 - 5}{2}$

## LENGTH

- Average at birth= 50cm (47-55cm)
- Growth rate:
  1. 1st year ↑ 25cm (2cm/m) = **75 cm**
  2. 2nd year ↑ 12cm (1cm/m)= **87cm**
  3. 3ed year ↑ 6cm (0.5cm/m) = **93cm**
  4. 4th year = **1 meter**
  5. 5-18years = 100+(age-4)*5

# Pediatric Nutrition and Nutritional Disorders

# NUTRITIONAL NEEDS

- Infants during the 1st yr of life (a 3-fold increase in weight; a 50% increase in length)
- Continued growth, at lower rates, from 1 yr of age → adolescence.
- Provision of special nutrient needs, during early life, is complicated by:
  1. the young infant's lack of teeth
  2. immature digestive and metabolic processes
  3. Dependence on caregivers.

## DIET OF THE NORMAL INFANT

- The first 6 months, is a period of exceptionally rapid growth and high nutrient requirements relative to body weight.
- There is risk of rapid deterioration in growth and nutritional status, with potential for adverse consequences on neurocognitive development.
- Most infants can start breast-feeding shortly after birth, almost always within 4–6hr.
- The time required for an infant's stomach to empty varies from 1–4hr or more during a single day→ the infant's desire for food will vary at different times of the day
- Infants will have established a suitable & reasonably regular schedule by 1 mo of age.
- By the end of the 1st wk of life, most healthy infants will want 6–9 feedings/24hr.
- Breast-fed infants prefer shorter feeding intervals than formula-fed infants.
- Most infants will be taking 80–90mL per feeding by the end of the 1st wk of life.
- Feeding considered to have progressed satisfactorily if the infant is no longer losing weight by the end of the 1st wk of life & is gaining weight by the end of the 2nd wk.
- most infants will awaken for a middle-of-the-night feeding until 3–6 wk of age, some desire it well beyond 3–6 wk of age.
- Between 4–8 mo of age, many infants will lose interest in the late evening feeding; and by 9–12 mo of age, most will be satisfied with 3 meals/day plus snacks.

## BREASTFEEDING

- Human milk is the ideal and **uniquely superior** food for infants for the first year of life and as the sole source of nutrition for the first 6 months.
- **advantages of breast-feeding :**
  1. advantages to mothers : decreased risk for postpartum hemorrhage, longer period of amenorrhea, reduced risk of ovarian and premenopausal breast cancers, and reduced risk of osteoporosis
  2. Advantages to society : **reduced healthcare costs** owing to lower incidence of illness in breastfed infants and reduced employee absenteeism for infant illness care
- Primary lactation failure is rare; most women can succeed at breastfeeding if given adequate information and support, especially in the early postpartum period.
- Human milk vs. infant formula Characteristics include:
  1. low but highly bioavailable protein content
  2. generous quantity of essential fatty acids
  3. presence of long-chain unsaturated fatty acids (docosa-hexaenoic)
  4. low sodium and solute load
  5. Low but highly bioavailable concentrations of calcium, iron, and zinc, which provide adequate quantities for 6 months.
  6. breast milk does not need to be warmed, does not require a clean water supply, and is generally free of microorganisms.

## BREASTFEEDING INITIATION

- The mother should be comfortable and the infant positioned =mouth-to-breast contact.
- The breast should be supported with the opposite hand, with the thumb and index finger above the nipple to allow the infant easy access it.
- The rooting reflex should be explained to make initiation of breast-feeding easier.
- The entire nipple and most of the areola should be placed in the infant's mouth.
- The infant "latches on" by compressing the lips.
- The mechanics of normal suckling include suction of 4 to 6 cm of the areola,
- compression of the nipple against the palate, stimulation of milk ejection by initial rapid non-nutritive sucking, and extraction of milk from the lactiferous sinuses by a slower suck-swallow rhythm of one per second.

- The infant is removed from the breast by placing a clean finger between the infant's gums and the areola to release suction.
- The mean feeding frequency during the early weeks postpartum is 8 - 12 times per day. decreases throughout the 1st yr of life to only 3-4 at 1 yr of age.

## EXCLUSIVE BREASTFEEDING

- Breastfeeding is the recommended method for feeding during the first 6 months of life.
- **Colostrum**, a high-protein, low-fat fluid, produced in small amounts during the first few postpartum days. Has some nutritional value but primarily has important immunologic and maturational properties.
- Primi. women often experience breast **engorgement** as the milk comes in around the third postpartum day.
  - Breasts hard and painful, nipples nonprotractile, mother's Tm increase slightly.
  - The best management: Enhancement of milk flow.
  - Severe engorgement= areolar rigidity prevent infant from grasping nipple and areola.
- ↑serum bilirubin are present more often in breastfed newborns than formula-fed.
- Feeding frequency in the first 3 days of life of breastfed infants ↓ the level of bilirubin: frequent feedings→ stimulate meconium passage →excretion of bilirubin in the stool.
- **Breastfeeding jaundice**: insufficient milk intake and poor weight gain → exaggerated enteropathic circulation of bilirubin→ increase in unconjugated bilirubin.
- **Breast milk jaundice:** in older breastfed infant, prolonged ↑serum bilirubin , due to presence of an unknown factor in milk that enhances intestinal absorption of bilirubin, diagnosis of exclusion , made only if an infant is thriving, with normal growth and no evidence of hemolysis, infection, or metabolic disease .
- **Exclusively breastfed infants should be supplemented with vitamin D (200 IU/day starting at 2 months of age)**, and possibly fluoride after 6 months.

## ADVANTAGES OF BREAST-FEEDING.

1. Available at the proper temperature and requires no preparation time.
2. Fresh and free of bacteria→ ↓GI disturbances.
3. The protective effects of breast milk against pathogens→ less morbidity.
4. Fewer feeding difficulties incident to allergy and/or intolerance to bovine milk: diarrhea, intestinal bleeding, occult melena, “spitting up,” colic, and atopic eczema.
5. Lower frequency of allergic and chronic diseases in later life than formula-fed infants.
6. Contains bacterial & viral antibodies, high secretory IgA that prevents microorganisms from adhering to the intestinal mucosa.
7. Contains substances that inhibit growth of many common viruses.
8. ↓Incidence or severity of diarrhea, respiratory illnesses, otitis media, bacteremia, bacterial meningitis, NEC.
9. Macrophages in human milk synthesize complement, lysozyme, and lactoferrin: lactoferrin, an iron-binding whey protein that is one-third saturated with iron and has an inhibitory effect on the growth of Escherichia coli in the intestine.
10. The lower pH of the stool of breast-fed favorable intestinal flora (i.e., more bifidobacteria and lactobacilli; fewer E. coli), which helps protect against infections.
11. Contains bile salt–stimulated lipase, kills Giardia lamblia & Entamoeba histolytica.
12. Transfer of tuberculin responsiveness by breast milk =passive transfer of T-cell immunity.
13. Milk supply all the necessary nutrients except,Fluoride & after several months vit D.
14. The psychologic advantages of breast-feeding for both mother and infant .
15. Decrease risk of SIDS, obesity & DM.
16. Better cognitive function.
17. Improve oral motor development and decrease orthodontic problems.

- **Supplements were needed for breastfeed infants:**
  1. 1mg IV of **vitamin K** at birth: as content of human milk is low and contribute to hemorrhagic disease of the newborn
  2. 10µg/d of **vitamin D**: If low maternal vitamin D intake & the infant's exposure to sunlight is limited (e.g., dark-skinned infants).
  3. **iron** -fortified foods or ferrous iron preparation**:** By 4–6 mo of age.
  4. 10µg/d **fluoride** for the first 6 mo of life If the water supply is not adequately fluoridated (=0.3ppm).
- Transmission of HIV by breast-feeding is well documented. Thus, if safe alternatives are available, breast-feeding by HIV-infected mothers is not recommended.

- 2/3 of seronegative breast-fed infants become infected with CMV. Term infants → no symptoms or sequelae/ in preterm the risk of infection is greater→ the use of fresh donor milk for feeding is contraindicated unless the milk is known to be CMV negative.
- hepatitis B virus has been isolated from maternal milk, If a nursing mother acquires hepatitis B, the infant should receive the accelerated protocol of immunization.

## COMMON BREASTFEEDING PROBLEMS

- **Breast tenderness, engorgement, and cracked nipples** are the most common problems encountered by breast-feeding mothers.
  - Engorgement, one of the most common causes of lactation failure, should receive prompt attention because milk supply can decrease quickly if the breasts are not adequately emptied.
  - Applying warm or cold compresses to the breasts before nursing and hand expression or pumping of some milk can provide relief to the mother and make the areola easier to grasp by the nursling.
  - Supportive measures include:
    1. nursing for shorter periods
    2. beginning feedings on the less sore side
    3. air drying the nipples well after nursing
    4. Applying lanolin cream after each nursing session.
  - Severe nipple pain and cracking usually indicate improper latch-on.
  - Temporary pumping, which is well tolerated, may be needed.
- **Mastitis**=lactating woman + fever & chills + malaise
  - Treatment: frequent & complete emptying of the breast + antibiotics.
  - Breastfeeding should not be stopped because the mother's mastitis has no adverse effects on the infant, and abrupt weaning increase the risk of breast abscess.
- **Breast abscess:** if Untreated mastitis. Ttt: incision, regular drainage, antibiotics.
  - Nursing from the contralateral breast can be continued with the healthy infant.
  - If maternal comfort allows, nursing can continue on the affected side.
- mother active tuberculosis, syphilis, or varicella, restarting breastfeeding considered after therapy is initiated.
- Women with genital herpes can breastfeed.

## CONTRAINDICATIONS TO BREAST-FEEDING.

- Provided the mother's milk supply is ample, her diet is adequate, and she is not infected with HIV, there are no disadvantages of breast-feeding for the healthy term infant.
- **maternal contraindications to breast-feeding.**
  1. Mothers with septicemia, active tuberculosis, typhoid fever, breast cancer, or malaria should not breast-feed.
  2. avoid infant nursing & contact on that breast in Herpetic lesions on breast
  3. Maternal HIV infection is a contraindication for breastfeeding in developed countries.
  4. Fresh donor milk for feeding is contraindicated if the milk is known to be CMV positive in preterm.
  5. Substance abuse and severe neuroses or psychoses are contraindications
- **Infantile contraindications**:
  1. Metabolic diseases: galactosemia, maple serup urine disease, organic academia.
  2. Anatomical reasons: cleft lip or cleft palate, extract the breast milk and put it in bottles with special goat nipple.

## ONE OR BOTH BREASTS PER FEEDING

- The infant should empty at least one breast at each feeding; otherwise, it will not be stimulated sufficiently to refill.
- In the early weeks, both breasts should be used at each feeding to encourage maximal milk production.
- After milk supply is established, the breasts may be alternated at successive feedings.
- If milk secretion becomes too great, both breasts may be offered at each feeding but incompletely emptied →decreasing milk production.

## DETERMINING ADEQUACY OF MILK SUPPLY

1. sleeps 2–4hr between feedings
2. gains weight adequately
3. voiding and stooling patterns of the infant.

- Stooling in infants:

- well-hydrated infant voids **6-8 times**/day
- Each voiding should soak not merely moisten a diaper & urine should be colorless.
- By 5 to 7 days, loose yellow stools should be passed at least four times a day.
- Rate of weight gain provides **the most objective indicator of adequate milk intake**.
- Total weight loss after birth should < 7%, and birth weight should be regained by 10d.
- Infant may be hydrated but not achieve adequate energy and nutrient intake.

- The characteristics of the stools of breastfed infants often alarm parents.
  - Stools are unformed, yellow, and seedy in appearance.
  - Parents commonly think their breastfed infant has diarrhea.
  - Stool frequencies vary; during the first 4 to 6 weeks
  - After 6 to 8 weeks, breastfed infants may go several days without passing a stool.
  - **Breastfed infants tend to produce stool more frequently than formula-fed.**
- Infants who are "light sleepers", it should not be assumed automatically that mothers of such infants have a poor milk supply.
- if the infant nurses completely empties both breasts but appears unsatisfied afterward (e.g., does not go to sleep after nursing or sleeps fitfully and awakens after 1–2hr and fails to gain weight satisfactorily→ the milk supply is inadequate.
- Three possibilities should be excluded before assuming that a mother cannot produce sufficient milk:
  1. errors in feeding technique;
  2. remediable maternal factors related to diet, rest, or emotional distress;
  3. physical disturbances of the infant that interfere with nursing or with weight gain.
- Nursing more often than every 2hr, may inhibit prolactin secretion → decrease milk production. This usually is not a problem with feeding at 2hr intervals.
- The desired interval between feedings, ranges from 3–5hr during the 1st yr of life
- Pumping increase milk production & relieve sore nipples → less irritation than suckling.
- Breast milk is safely stored in refrigerator and used for feeding at later time.

## FORMULA FEEDING

### Cow's Milk-Based Formulas


- iron-fortified formula, permits adequate growth of infants and is mimic human milk.
- No vitamin or mineral supplements (other than possibly fluoride after 6 months)
- Cow's milk formulas are composed of :
  1. reconstituted, skimmed cow's milk
  2. skimmed cow's milk & electrolyte-depleted cow's milk whey or casein proteins.
- The fat used in infant formulas is a mixture of vegetable oils, including soy, palm, coconut, corn, oleo, or safflower oils.
- The carbohydrate is lactose, lactose-free cow's milk-based formulas are available.
- The caloric density of formulas is 20 kcal/oz (0.67 kcal/mL) = human milk.
- Formula-fed infants gain weight more rapidly than breastfed infants, especially after the first 3 to 4 months of life.
- Formula-fed infants are at higher risk for obesity later in childhood; this related to differences in feeding practices for formula-fed infants vs. breastfed infants.
- Cow's milk-based infant formulas are used as substitutes for breast milk for infants whose mothers cannot breastfeed or as supplements for breastfeeding.

### Soy Formulas


- Soy formulas provide an alternative to cow's milk-based formula when immune reactions to cow's milk proteins occurs.
- Large number of infants allergic to cow's milk protein also is allergic to soy protein.
- Clinical intolerance to soy protein or cow's milk protein occurs with similar frequency.
- The soy protein is supplemented with **methionine** to improve its nutritional qualities.

- The carbohydrates in soy formulas are glucose, oligomers (smaller molecular weight corn starches) and sucrose.
- The fat mixture is similar to that used in cow's milk formulas.
- Caloric density = cow's milk formulas.
- Soy protein formulas do not prevent the development of allergic disorders in later life,
- Soy protein formulas can be recommended for use:
  1. **vegetarian families** choosing not to serve animal protein formulas
  2. **cows milk protein allergy**
  3. Management of **galactosemia**
  4. **primary and secondary lactose intolerance**.
- **Soy formulas are not recommended for premature infants( birth weights < 1800 g).**

### Therapeutic Formulas

- Designed to treat **digestive and absorptive insufficiency** or **protein hypersensitivity**.
- **Semielemental formulas** include protein hydrolysate formulas.
  1. The major nitrogen source of each of these products is a casein or whey hydrolysate, supplemented with selected amino acids.
  2. Contain an abundance of essential fatty acids from vegetable oil.
  3. Certain brands provide (25% to 50% of total fat) of medium chain TGs, water soluble and more easily absorbed than Long chain FA.
  - galactosemia: hydrolyzed milk formula (**Pregestimil, Nutramigen** = 100% free lactose)
  - useful feature for patients with malabsorption, as:
    1. short gut syndrome
    2. intestinal mucosal atrophy or injury
    3. chronic diarrhea
    4. cholestasis
- **Elemental formulas** that contain
  1. synthetic free amino acids
  2. Varying quantities and types of fat components.
  3. Especially designed for patients with protein allergy or sensitivity.
  4. The carbohydrate content of varies, but all are lactose free; some contain glucose, oligomers and soluble starches.

## Infant Feedings Formulas

| Formula Category | Example Formulas | Features and Typical Uses |
|---|---|---|
| Cow's milk-based (with lactose) | Enfamil Similac Carnation Good Start | Standard substitute for breast milk |
| Cow's milk-based (without lactose) | Lactofree Similac Lactose Free | Useful for transient lactase deficiency or lactose intolerance |
| Premature formula: cow's milk (reduced lactose) | Similac Special Care Enfamil Premature | Indicated for premature and LBW infants. Fat is 50% MCT, higher in many micronutrients |
| Soy protein-based/lactose-free | Prosobee Isomil | Alternative to milk protein-based formulas. Not recommended for premature infants |
| Predigested (Semielemental) | Pregestimil (50% fat MCT)<br>Nutramigen (no MCT)<br>Alimentum (50% fat MCT) | Casein hydrolysate, useful for protein allergies and malabsorptive disorders |
| Elemental | Neocate Elecare | Free amino acids for severe protein allergy or malabsorption |
| **Premature transitional** | Enfacare Neosure | Standard at 22 kcal/oz, intermediate in protein and micronutrients to promote growth post discharge |
| **Fat modified** | Lipisorb Portagen | High MCT, for chylous effusions & some malabsorptive disorders |
| **Prethickened** | Enfamil AR | May be useful for dysphagia, mild GER |
| **Carbohydrate intolerance** | 3232A<br>Ross Carbohydrate Free | All monosaccharides and disaccharides removed; can titrate dextrose or fructose additives to tolerance |

## Composition of Breast Milk and Infant Formulas

| (per dL) | Breast Milk | Standard Formula | Premature Formula | Soy Formula | Nutramigen | Pregestimil |
|---|---|---|---|---|---|---|
| Calories (kcal) | 67 | 67 | 67-81 | 67 | 67 | 67 |
| **Protein** (g) | 1.1 | 1.5 | 2.0-2.4 | 1.7 | 1.9 | 1.9 |
| (% calories) | (6%) | (9%) | (12%) | (10%) | (11%) | (11%) |
| Whey/casein protein ratio | 80/20 | 60/40, 18/82 | 60/40 | Soy protein methionine | Casein hydrolysate + L-cystine, L-tyrosine & L-tryptophan | Casein hydrolysate + L-cystine, L-tyrosine, and L-tryptophan |
| **Fat** (g) | 4.0 | 3.6 | 3.4-4.4 | 3.6 | 3.3 | 3.8 |
| (% calories) | (55%) | (50%) | (45%) | (48%) | (45%) | (48%) |
| MCT (%) | 0 | 0 | 40-50 | 0 | 0 | 55 |
| **Carbohydrate** | 7.2 | 6.9-7.2 | 8.5-8.9 | 6.8 | 7.3 | 6.9 |
| (% calories) | (40%) | (41%) | (42%) | (40%) | (44%) | (41%) |
| Source | Lactose | Lactose | Lactose, corn syrup | Sucrose, Corn syrup | Corn syrup solids, cornstarch | Corn syrup solids, cornstarch, dextrose |
| **Minerals** (/ L) | | | | | | |
| Calcium (mg) | 290 | 420-550 | 1115-1452 | 700 | 635 | 777 |
| Phosph.(mg) | 140 | 280-390 | 561-806 | 500 | 420 | 500 |
| Sodium (mEq) | 8.0 | 6.5-8.3 | 11-15 | 13 | 14 | 14 |
| Vitamin D | Variable | 400 | 1000-1800 | 400 | 400 | 400 |
| Osmolality (mOsm/L) | 253 | 270 | 230-270 | 200-220 | 290 | 290 |
| Renal solute load (mOsm/L) | 75 | 100-126 | 175-213 | 126-150 | 175 | 125 |
| **Comments** | deficient in vitamin K; deficient in $Na^+$, $Ca^{2+}$, protein, vitamin D for VLBW infants | Risk of milk protein intolerance -GI bleeding, anemia, wheezing, eczema | Specifically fortified with additional protein, $Ca^{2+}$, P, $Na^+$, vit. D, & **MCT oil** | for lactose & milk protein intolerance; may lead to soy protein intolerance; rickets in VLBW inf. | Useful for lactose and milk protein intolerance (allergy) | Useful for malabsorption states, lactose and milk protein intolerance (allergy) |

## Notes:

- Rule: breast feeding should be for 1 year, better 2 years.
- Prepare the mother physically and psychologically during pregnancy
- physically: lactol or ointment to moist dry cracked nipple, Manual massage for retracted nipple, electrical bump
- As condition of mother and baby permits let baby to suck as soon as possible.
- Meat could introduce at age >6.5 months
- Eggs must not started before 10 months because the risk of salmonella and allergy.
- Baby must taste egg before 1 year to be sure that he has no allergy to MMR vaccine.
- The baby takes > 90% of his need in the first 5 min.of breast feeding, max. within 10 min.
- Feeding can be Q 3 Hrs or perdemand "crying"→ follow combination of both.
- Adol = Vit D: 2drops/day or expose to sun 1/2 hour if naked 2 hours if partially naked.
- Humanized milk 'improved cow milk': Improved by: fortification with iron, lower Na content, reversal of casein /lactoalbumin ratio= 70/30.
- Human milk 70/30: lactoalbumin(whey) compared to casein is readily digestible, less irritant to GI tract & increase protein synthesis.
- Oz unit → 20 calories
- Total ash content = minerals content.
- Positions for breast feeding: sitting, semi-sitting, lying facing for baby( not on drugs, not deep sleeper, not with huge breast)
- Types of sucking:
  1. nutrient sucking → sucking and swelling.
  2. non- nutrient sucking: using the breast as pacifier , don't let baby to sleep on breast.
- Pacifier can protect against infant sudden death.
- Barbing baby: in aggressive sucking he sucks air with milk so put him in upward position for 2-3 minutes to prevent chocking when milk goes out with air.


Breast-Feeding Positions
Cradle hold
Cross-cradle hold
Lying down
Football hold
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# VITAMIN E DEFICIENCY

- Vitamin E is an antioxidant, but its precise biochemical functions are not known.
- Vitamin E deficiency, **cause hemolysis or neurologic manifestations**
- occurs in:
  1. **premature infant** (if was given: high content of polyunsaturated fatty acids formula)
  2. **malabsorption**
  3. **abetalipoproteinemia**: AR disorder affecting vitamin E transport.

## PATHOGENESIS

- The term *vitamin E* = group of 8 compounds with similar structures & antioxidant activity.
- The best dietary sources of vitamin E are vegetable oils, seeds, nuts, green leafy vegetables, and margarine.
- The majority of vitamin E is located within cell membranes, where it prevents lipid peroxidation and the formation of free radicals.
- Vitamin E deficiency in premature infants causes thrombocytosis, edema, and hemolysis potentially causing anemia.
- vitamin E is plentiful in common foods, primary dietary deficiency is rare except in premature infants and in severe, generalized malnutrition.
- symptomatic disease is most common in children with cholestatic liver disease, cystic fibrosis, celiac disease, short-bowel syndrome, or Crohn disease.
- The autosomal recessive disorder **abetalipoproteinemia** causes fat malabsorption and vitamin E deficiency.
- **ataxia with isolated vitamin E deficiency** (AVED): rare autosomal recessive disorder, patients are unable to incorporate vitamin E into lipoproteins before their release from the liver→ ↓ serum levels of vitamin E.

## CLINICAL MANIFESTATIONS

- severe, progressive **neurologic disorder** in patients with prolonged vitamin E deficiency.
- Clinical manifestations do not appear **until after 1 yr of age**, even in children with cholestasis since birth.
- In premature infants, **hemolysis** due to vitamin E deficiency typically develops during the 2nd month of life. **Edema** may also be present.
- Pts may have **cerebellar disease**, **posterior column dysfunction**, & **retinal disease.**
- **Loss of deep tendon reflexes is usually the initial finding.**
- Some patients have **pigmentary retinopathy**.
- Visual field constriction may progress to **blindness**.
- **Cognition and behavior** may also be affected.
- **Myopathy** and **cardiac arrhythmias** are less common findings.

## DIAGNOSIS

- Serum vitamin E levels increase in the presence of high serum lipid levels, even when vitamin E deficiency is present.
- vitamin E status is best determined by measuring the ratio of vitamin E to serum lipids; a ratio <0.8 mg/g is abnormal.
- Premature infants with hemolysis due to vitamin E deficiency have ↑platelet counts.
- Neurologic involvement may cause abnormal somatosensory evoked potentials and nerve conduction studies.

## TREATMENT

- in neonates, the dose of vitamin E is 25-50 units/day for 1 wk, followed by adequate dietary intake.
- α-Tocopheryl polyethylene glycol succinate (TPGS) is a water-soluble preparation of vitamin E that is absorbed in the absence of bile salts.
  - is effective in children with vitamin E deficiency secondary to severe malabsorption.
  - Typical doses are 20-25 units/kg/day, with adjustment based on the ratio of vitamin E to serum lipids.
  - TPGS enhances absorption of the other fat-soluble vitamins (A, D, and K) and a variety of medications.

# VITAMIN K DEFICIENCY

- Deficiency of vitamin K, which is necessary for the synthesis of clotting factors II, VII, IX, and X, may result in clinically significant bleeding.
- Typically affects infants who experience transient deficiency related to inadequate intake.
- Mild vitamin K deficiency may affect long-term bone and vascular health.

## PATHOGENESIS

- There are 3 forms of **vitamin K-deficiency bleeding (VKDB)** of the newborn
  1. **Early VKDB, *classic hemorrhagic disease of the newborn,***
     - occurs at 1-14 days of age.
     - secondary to :
       A. low stores of vitamin K at birth due to the poor transfer of vit K across placenta
       B. inadequate intake during the 1st few days of life
       C. no intestinal synthesis of vitamin $K_2$ because the newborn gut is sterile.
       D. breast-fed infants due to the low vitamin K content of breast milk
       E. Delayed feeding is an additional risk factor.
  2. **Late VKDB**
     - Most commonly occurs at 2-12 wk of age, can occur up to 6 mo after birth.
     - Almost all are breast-fed infants due to the low vitamin K content of breast milk.
     - Other risk factor is occult malabsorption of vitamin K, such as cystic fibrosis or cholestatic liver disease (e.g., biliary atresia, $\alpha_1$-antitrypsin deficiency).
     - Without vitamin K prophylaxis, the incidence is 4-10/100,000 newborns.
  3. **The 3rd form of VKDB of the newborn**
     - occurs at birth or shortly thereafter.
     - It is secondary to maternal intake of medications (warfarin, phenobarbital, phenytoin) that cross the placenta and interfere with vitamin K function.
- Vitamin K-deficiency bleeding due to fat malabsorption , Potential etiologies include:
  1. cholestatic liver disease
  2. pancreatic disease
  3. intestinal disorders (celiac sprue, IBD, short-bowel syndrome).
  4. Prolonged diarrhea, especially in breast-fed infants
  5. CF: most likely to have vitamin K deficiency( pancreatic + liver disease).
- The combination of poor intake and the use of broad-spectrum antibiotics that eliminate the intestine's vitamin $K_2$-producing bacteria can cause vitamin K deficiency.

## CLINICAL MANIFESTATIONS

- early VKDB, the most common sites of bleeding are:
  1. the gastrointestinal tract
  2. mucosal and cutaneous tissue
  3. the umbilical stump
  4. the post-circumcision site
     - intracranial bleeding is less common.
- **The most frequent site of bleeding in late VKDB is intracranial**
  - cutaneous and gastrointestinal bleeding may be the initial manifestation.
- Intracranial bleeding may cause convulsions, permanent neurologic sequelae, or death.
- Older children with vitamin K deficiency may present with bruising, mucocutaneous bleeding, or more serious bleeding.

## LABORATORY FINDINGS

- the prothrombin time **(PT) is prolonged**.
- When there is mild vitamin K deficiency, the PT is normal
- The partial thromboplastin time **(PTT) is prolonged**, but may be normal in early deficiency because factor VII has the shortest half-life of the coagulation factors (isolated factor VII deficiency does not affect the PTT).
- The platelet count and fibrinogen level are normal.
- Measurement of undercarboxylated factor II (PIVKA-II) : detect mild vitamin K deficiency.
- Determination of blood vitamin K levels is less useful because of significant variation based on recent dietary intake; levels are not always reflective of tissue stores.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

- The diagnosis is established by the presence of a prolonged PT that corrects rapidly after administration of vitamin K. This also stops the active bleeding.
- Other possible causes of bleeding and a prolonged PT include:
  1. **Disseminated intravascular coagulation** (DIC) :most commonly secondary to sepsis, is associated with thrombocytopenia, low fibrinogen, and elevated D-dimers.
  2. Liver failure: decreased production of clotting factors; the PT does not fully correct with administration of vitamin K.
  3. Hereditary deficiencies of clotting factors.
- Bleeding can occur with overdosage of the commonly used anticoagulant warfarin, ingestion of rodent poison & High doses of salicylates.

## TREATMENT

- **Infants** with VKDB should receive 1 mg of IV vitamin K.
- The PT should decrease within 6 hr and normalize within 24 hr.
- For rapid correction in **adolescents**, the IV dose is 2.5-10 mg.
- patient with severe, life-threatening bleeding should receive an infusion of FFP, which corrects the coagulopathy rapidly.
- Children with vitamin K deficiency due to malabsorption require chronic administration of high doses of oral vitamin K (2.5 mg twice/wk-5 mg/day).

## PREVENTION

- Single IM injection of vitamin K (1 mg), is effective, except with severe malabsorption.
- Children at high risk for malabsorption of vitamin K should receive supplemental vitamin K and periodic measurement of the PT.

# VITAMIN A DEFICIENCY

- The most obvious symptoms of vitamin A deficiency are associated with the requirement of this vitamin for the maintenance of epithelial functions.
- The range of normal vitamin A levels is 20-60 µg/dL; a level < 20 µg/dL = deficiency.
- Epithelial changes in the respiratory system→**bronchial obstruction**.
- Characteristic changes due to vitamin A deficiency in the epithelia include a
  1. proliferation of basal cells
  2. hyperkeratosis
  3. formation of stratified, cornified squamous epithelium.
  4. Squamous metaplasia of the renal pelves, ureters, vaginal epithelium, and the pancreatic and salivary ducts → increased infections.
  5. In the urinary bladder, loss of epithelial integrity may result in pyuria and hematuria.
  6. in the skin : dry, scaly, hyperkeratotic patches, commonly on the arms, legs, shoulders, and buttocks.
- The combination of defective epithelial barriers to infection, low immune response, and lowered response to inflammatory stress, all due to insufficient vitamin A, can cause poor growth and serious health problems in children.
- **The most characteristic and specific signs of vitamin A deficiency are eye lesions.** rarely occur before 2 yr of age.
  - An early symptom is delayed adaptation to the dark→ night blindness due to the absence of retinal in the visual pigment,rhodopsin, of the retina.
  - Photophobia is a common symptom
  - **Xerophthalmia is a very characteristic lesion of vitamin A deficiency.** In early vitamin A deficiency, the cornea keratinizes, becomes opaque, is susceptible to infection, and forms dry, scaly layers of cells.
  - In later stages, infection occurs, lymphocytes infiltrate, and the cornea becomes wrinkled; it degenerates irreversibly (keratomalacia), resulting in blindness.
  - The conjunctiva keratinizes and develops plaques (**Bitot spots** )
  - conjunctiva dry **(conjunctival xerosis)**
  - the lacrimal glands keratinize.
  - These eye lesions are primarily diseases of the young and are a major cause of blindness in developing countries.

- Other clinical signs of vitamin A deficiency include:
  1. poor overall growth
  2. diarrhea
  3. susceptibility to infections
  4. anemia
  5. apathy
  6. mental retardation
  7. Increased ICP with wide separation of the cranial bones at the sutures.
  8. Vision problems due to bone overgrowth causing pressure on the optic nerve.

## RICKETS

- **Rickets,** a disease of growing bone, occurs in children only before fusion of the epiphyses, and is due to unmineralized matrix at the growth plates.
- AS growth plate cartilage and osteoid continue to expand, but mineralization is inadequate, the growth plate thickens.
- increase in the circumference of the growth plate and the metaphysis.
- This increases bone width at the location of the growth plates, causing some of the classic clinical manifestations, such as: widening of the wrists and ankles.
- There is a general softening of the bones that causes them to bend easily when subject to forces such as weight bearing or muscle pull. This leads to a variety of bone deformities.
- in developed countries, many cases are secondary to preventable nutritional vitamin D deficiency.

### ETIOLOGY

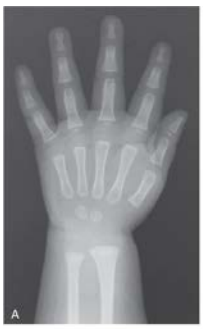
- including:
  1. vitamin D disorders
  2. calcium deficiency
  3. phosphorous deficiency
  4. distal renal tubular acidosis.

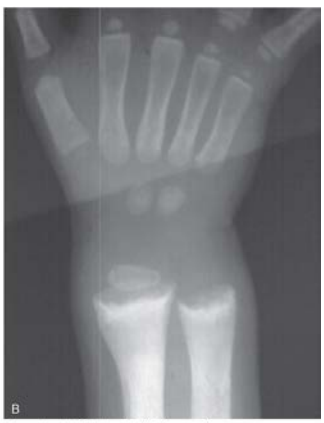
### CLINICAL MANIFESTATIONS

- Most manifestations of rickets are due to skeletal changes.
  1. **Craniotabes,** a softening of the cranial bones
     - detected by applying pressure at the occiput or over the parietal bones.
     - similar to the feel of pressing into a Ping-Pong ball and then releasing.
     - may also be secondary to osteogenesis imperfecta, hydrocephalus, and syphilis
     - normal in newborns, especially near the suture lines, typically disappears within a few months of birth.

  2. **rachitic rosary:** Widening of the costochondral junctions**;** feels like beads of rosary as examiner's fingers move along the costochondral junctions from rib to rib.

  3. **Growth plate widening**→enlargement at the wrists and ankles.
  4. **Harrison groove**: horizontal depression along the lower anterior chest occurs due to pulling of the softened ribs by the diaphragm during inspiration.
     - Softening of the ribs impairs air movement → atelectasis.
     - The risk of pneumonia appears to be elevated in children with rickets.
- Many children present because of skeletal deformities, whereas others:
  1. difficulty walking due to a combination of deformity and weakness
  2. failure to thrive
  3. symptomatic hypocalcemia
- Rachitic changes are most easily visualized on posteroanterior radiographs of the wrist,
  1. Decreased calcification → **thickening of the growth plate**.
  2. **fraying**: The edge of the metaphysis loses its sharp border.
  3. ***cupping***: the edge of the metaphysis changes from a convex or flat surface to a more concave surface. most easily seen at distal ends of the radius, ulna, fibula.
  4. **widening of the distal end of the metaphysis**, corresponding to the clinical observation of thickened wrists and ankles, as well as the rachitic rosary.



5. **Coarse trabeculation of the diaphysis** and **generalized rarefaction**.

- Most cases of rickets are diagnosed based on the classic radiographic abnormalities.

## CLINICAL EVALUATION

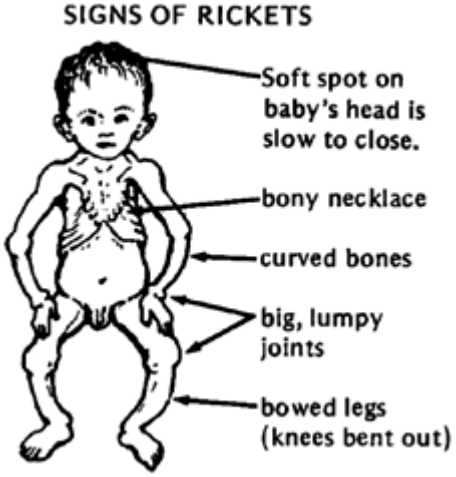
- majority of children with rickets have a nutritional deficiency, initial evaluation →dietary history ( intake of vitamin D and calcium).
- **Cutaneous synthesis** mediated by sunlight exposure is an important source of vitamin D. Children with ↑ skin pigmentation →↓cutaneous synthesis→↑ vitamin D deficiency.
- The presence of **maternal risk** factors for nutritional vitamin D deficiency is an important consideration when a neonate or young infant has rachitic findings.
- The child's **medication** use is relevant because :
  1. anticonvulsants phenobarbital and phenytoin, increase degradation of vitamin D
  2. aluminum-containing antacids interfere with the absorption of phosphate.
- **Malabsorption** of vitamin D : history of liver or intestinal disease. ,rickets may be the presenting complaint.
- **renal disease** (proteinuria, hematuria, urinary tract infections) is an additional significant consideration, given the importance of chronic renal failure as a cause of rickets.
- Children with rickets may have a history of dental caries, poor growth, delayed walking, waddling gait, pneumonia, and hypocalcemic symptoms.
- The family history, large number of **genetic causes** of rickets, most is rare. inquire about leg deformities, difficulties with walking, or unexplained short stature
- A history of a unexplained sibling death during infancy may be present in the child with **cystinosis is the most common cause of Fanconi syndrome in children**.
- The **initial laboratory** tests in a child with rickets should include:
  1. serum calcium
  2. phosphorus
  3. alkaline phosphatase
  4. parathyroid hormone (PTH)
  5. 25-hydroxyvitamin D
  6. 1,25-dihydroxyvitamin $D_3$
  7. creatinine
  8. electrolytes
- glycosuria and aminoaciduria (positive dipstick for protein) : Fanconi syndrome.
- urinary excretion of calcium (24 hr collection for calcium or calcium-creatinine ratio) : hereditary hypophosphatemic rickets with hypercalciuria or Fanconi syndrome.

## CAUSES OF RICKETS

| |
|---|
| **VITAMIN D DISORDERS** |
| Nutritional vitamin D deficiency |
| Congenital vitamin D deficiency |
| Secondary vitamin D deficiency |
| 1. Malabsorption |
| 2. Increased degradation |
| 3. Decreased liver 25-hydroxylase |
| Vitamin D-dependent rickets type 1 |
| Vitamin D-dependent rickets type 2 |
| Chronic renal failure |
| **CALCIUM DEFICIENCY** |
| Low intake |
| Diet |
| Premature infants (rickets of prematurity) |
| Malabsorption |
| Primary disease |
| Dietary inhibitors of calcium absorption |
| **PHOSPHORUS DEFICIENCY** |
| Inadequate intake |
| Premature infants (rickets of prematurity) |
| Aluminum-containing antacids |
| **RENAL LOSSES** |
| X-linked hypophosphatemic rickets* |
| Autosomal dominant hypophosphatemic rickets* |
| Hereditary hypophosphatemic rickets with hypercalciuria |
| Overproduction of phosphatonin |
| Tumor-induced rickets* |
| McCune-Albright syndrome* |
| Epidermal nevus syndrome* |
| Neurofibromatosis* |
| Fanconi syndrome |
| Dent disease |
| **DISTAL RENAL TUBULAR ACIDOSIS** |

## CLINICAL FEATURES OF RICKETS

| |
|---|
| **GENERAL** |
| Failure to thrive |
| Listlessness |
| Protuding abdomen |
| Muscle weakness (proximal) |
| Fractures |
| **HEAD** |
| Craniotabes |
| Frontal bossing |
| Delayed fontanelle closure |
| Delayed dentition; caries |
| Craniosynostosis |
| **CHEST** |
| Rachitic rosary |
| Harrison groove |
| Respiratory infections & atelectasis* |
| **BACK** |
| Scoliosis |
| Kyphosis |
| Lordosis |
| **EXTREMITIES** |
| Enlargement of wrists and ankles |
| Valgus or varus deformities |
| Windswept deformity (combination of valgus deformity of 1 leg with varus deformity of the other leg) |
| Anterior bowing of the tibia and femur |
| Coxa vara: angle between femur shaft and ball is <120. |
| Leg pain |
| **HYPOCALCEMIC SYMPTOMS**[T] |
| Tetany |
| Seizures |
| Stridor due to laryngeal spasm |

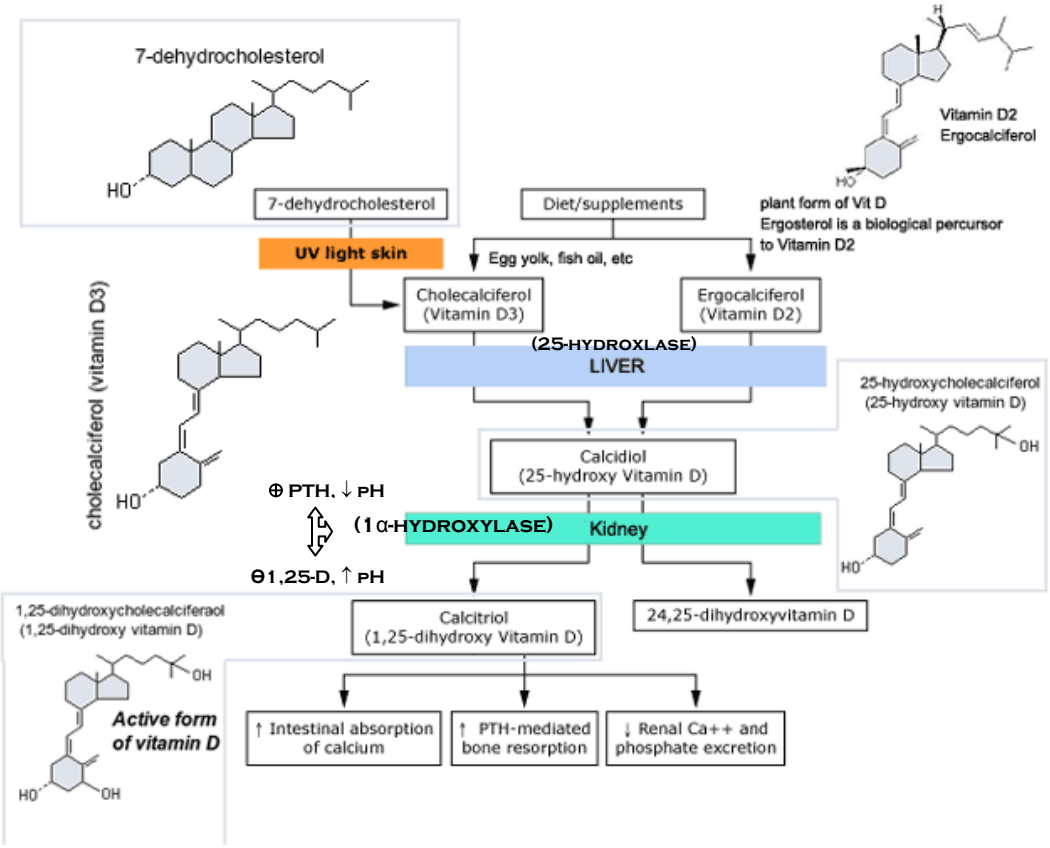


# VITAMIN D DISORDERS

- Vitamin D can be synthesized in skin epithelial cells and therefore technically is not a vitamin.
- Cutaneous synthesis: the most important source of vitamin D

  **7-dehydrochlesterol ⟶ vitamin $D_3$ (3-cholecalciferol)**

  **Ultraviolet B radiation**
- The efficiency of this process is ↓ by melanin→ more sun exposure is necessary for vitamin D synthesis in people with increased skin pigmentation.
- Covering the skin with clothing or applying sunscreen→↓ vitamin D synthesis
- Fish liver oils have a high vitamin D content. Also, fatty fish and egg yolks.
- Breast milk has a low vitamin D content, approximately 12-60 IU/L.
- Supplemental vitamin D may be vitamin $D_2$ (which comes from plants or yeast) or vitamin $D_3$; they are biologically equivalent.
- Vitamin D is transported bound to vitamin D-binding protein to the liver
- 25-hydroxyvitamin D (25-D), the most abundant circulating form of vitamin D.
- measurement of 25-D is the standard method for patient's vitamin D status.
- Most 1,25-D circulates bound to vitamin D-binding protein.




**Fe e D T o y**
- ♣ Calci**F**erol
- ♣ Calci**D**iol
- ♣ Calci**T**riol

- 1,25-D inhibits its own synthesis in the kidney and increases the synthesis of inactive metabolites.
- FUNCTION:
  1. Marked ↑ calcium absorption, which is highly dependent on 1,25-D.
  2. ↑ Phosphorus absorption, less significant because most dietary phosphorus absorption is vitamin D-independent.
  3. 1,25-D also has direct effects on bone, including mediating resorption.
  4. 1,25-D directly suppresses PTH secretion by the parathyroid gland also suppressed by the increase in serum calcium

## NUTRITIONAL VITAMIN D DEFICIENCY

- **Vitamin D deficiency is the most common cause of rickets**
- Vitamin D deficiency most commonly occurs in infancy due to a combination of poor intake and inadequate cutaneous synthesis.
- **Hypocalcemia is a variable** finding due to the actions of the elevated PTH to increase the serum calcium concentration.
- The **hypophosphatemia** is due to PTH-induced renal losses of phosphate, combined with a decrease in intestinal absorption.
- The wide variation in 1,25-D levels (low, normal, or high) is secondary to the upregulation of renal 1α-hydroxylase due to concomitant hypophosphatemia and hyperparathyroidism.
- 1,25-D are normally much lower than the levels of 25-D, even with low levels of 25-D there is still often enough 25-D present to act as a precursor for 1,25-D synthesis
- The level of 1,25-D is only low when there is severe vitamin D deficiency.
- Some patients have a metabolic acidosis secondary to PTH-induced renal bicarbonate-wasting.
- There may also be generalized aminoaciduria.
- A normal PTH level almost never occurs with vitamin D deficiency and suggests a primary phosphate disorder.
- A normal level of 25-D + history of poor calcium intake → isolated calcium deficiency.
- TREATMENT: vitamin D and adequate nutritional intake of calcium and phosphorus.
- There are 2 strategies for administration of vitamin D:
  1. stoss therapy, 300,000-600,000 IU of vitamin D are administered orally or intramuscularly as 2-4 doses over 1 day → daily vitamin D intake of 400 IU/day
  2. daily, high-dose vitamin D, 2,000-5,000 IU/day over 4-6 wk→ daily vitamin D intake of 400 IU/day

## CONGENITAL VITAMIN D DEFICIENCY

- **Congenital rickets,** occurs when there is severe maternal vitamin D deficiency during pregnancy
- These newborns have:
  1. symptomatic hypocalcemia
  2. intrauterine growth retardation
  3. decreased bone ossification
  4. classic rachitic changes.
- Predispose infants to neonatal hypocalcemic tetany.
- Treatment of congenital rickets includes vitamin D supplementation and adequate intake of calcium and phosphorus.

## SECONDARY VITAMIN D DEFICIENCY

- vitamin D deficiency due to:
  1. inadequate absorption : cholestatic liver disease, cystic fibrosis, celiac disease, Crohn disease, intestinal lymphangiectasia and after intestinal resection
  2. decreased hydroxylation in the liver
  3. increased degradation
- Severe liver disease →insufficient enzyme activity → decrease in 25-D formation
- Because of the large reserve of 25-hydroxlase activity in the liver→ requires a loss of >90% of liver function.
- anticonvulsants, such as phenobarbital or phenytoin; the antituberculosis medications isoniazid and rifampin (inducing the P450 system→ ↑ the degradation of vitamin D)
- Treatment of vitamin D deficiency due to malabsorption requires high doses of vitamin D.
- 25-D (25-50 μg/day or 5-7 μg/kg/day) is superior to vitamin $D_3$→ better absorption
- 1,25-D, which is better absorbed in the presence of fat malabsorption
- The dose is adjusted based on monitoring of serum levels of 25-D.

## VITAMIN D-DEPENDENT RICKETS, TYPE 1

- autosomal recessive disorder, have mutations in the gene encoding renal 1α-hydroxylase, preventing conversion of 25-D into 1,25-D.

- present during the 1st 2 yr of life, can have any of the classic features of rickets
- They have normal levels of 25-D, but low levels of 1,25-D
- 1,25-D levels may be at the lower limit of normal: high PTH & low serum phosphorus levels→ ↑ activity of renal 1α-hydroxylase → ↑1,25-D.
- As in nutritional vitamin D deficiency, renal tubular dysfunction may cause a metabolic acidosis and generalized aminoaciduria.
- Long-term treatment with 1,25-D (calcitriol).
- excessive dosing of calcitriol→hypercalciuria and nephrocalcinosis→urinary calcium excretion( target of <4 mg/kg/day)

### VITAMIN D-DEPENDENT RICKETS, TYPE 2

- autosomal recessive disorder of the vitamin D receptor, preventing a normal physiologic response to 1,25-D.
- Levels of 1,25-D are extremely elevated
- Most patients present during infancy, less severely affected patients may not be diagnosed until adulthood.
- 50-70% of children have **alopecia,** which tends to be associated with a more severe form of the disease( alopecia areata to alopecia totalis).
- **Epidermal cysts** are a less common manifestation.
- Treatment: extremely high doses of vitamin $D_2$, 25-D, or 1,25-D.
- Patients who do not respond → long-term intravenous calcium

### CHRONIC RENAL FAILURE

- Decreased activity of 1α-hydroxylase in the kidney→ diminished production of 1,25-D.
- In chronic renal failure, unlike the other causes of vitamin D deficiency, patients have **hyperphosphatemia** as a result of decreased renal excretion
- inadequate calcium absorption and **secondary hyperparathyroidism**
- The rickets may be worsened by the metabolic acidosis of chronic renal failure.
- Failure to thrive and growth retardation may be accentuated because of the direct effect of chronic renal failure on the growth hormone axis.
- Treatment: calcitriol: a form of vitamin D that can act without 1-hydroxylation by the kidney → adequate absorption of calcium and directly suppresses the parathyroid gland.

## CALCIUM DEFICIENCY

- Rickets develops because the diet has low calcium content, typically <200 mg/day.
- Calcium levels may be normal or low
- increased levels of alkaline phosphatase, PTH, and 1,25-D .
- symptomatic hypocalcemia is uncommon.
- There is decreased urinary excretion of calcium
- serum phosphorus levels may be low due to renal wasting of phosphate from secondary hyperparathyroidism.
- dietary supplement (350-1,000 mg/day of elemental calcium) are effective.

## PHOSPHOROUS DEFICIENCY

### INADEQUATE INTAKE:

- exception of starvation or severe anorexia, it is almost impossible to have a diet that is deficient in phosphorus because phosphorus is present in most foods.
- Decreased phosphorus absorption can occur in diseases associated with malabsorption (celiac disease, cystic fibrosis, cholestatic liver disease)

### PHOSPHATONIN

- Phosphatonin is a humoral mediator that decreases renal tubular reabsorption of phosphate → ↓serum phosphorus.
- Phosphatonin decreases the activity of renal 1α-hydroxylase→ decrease in the production of 1,25-D.
- Increased levels of phosphatonin cause many of the phosphate-wasting diseases .

## X-LINKED HYPOPHOSPHATEMIC RICKETS

- X-linked hypophosphatemic rickets (XLH) is the most common genetic disorders causing rickets due to hypophosphatemia.
- **X-linked dominant disorder**.
- In the absence of *the gene,* there is decreased degradation of phosphatonin→ ↑inhibition of phosphate reabsorption in the proximal tubule→ ↑phosphate excretion.
- Phosphatonin inhibits renal 1 α-hydroxylase→ decreased production of 1,25-D.
- Abnormalities of the lower extremities and poor growth are the dominant features.
- Delayed dentition and tooth abscesses are common.
- high renal excretion of phosphate, hypophosphatemia, and increased alkaline phosphatase; PTH and serum calcium levels are normal
- Hypophosphatemia, because it normally upregulates renal 1α-hydroxylase, should lead to an increase in 1,25-D, but these patients have low or inappropriately normal levels.
- Treatment; combination of oral phosphorus and 1,25-D (calcitriol).
- **AD hypophosphatemic rickets** = same gene is affected.

## HEREDITARY HYPOPHOSPHATEMIC RICKETS WITH HYPERCALCIURIA

- HHRH is a rare disorder that is mainly described in the Middle East.
- autosomal recessive Inheritance .
- The primary problem is a renal phosphate leak → hypophosphatemia→ stimulates production of 1,25-D →increases intestinal absorption of calcium→ suppressing PTH.
- Hypercalciuria ensues due to the high absorption of calcium and the low level of PTH, which normally decreases renal excretion of calcium.
- The genetic features of this disorder are unclear.
- The dominant symptoms are:
  1. rachitic leg abnormalities
  2. muscle weakness
  3. bone pain.
- Patients may have short stature, with a disproportionate decrease in the length of the lower extremities.
- some family members have no rickets, but have kidney stones due to hypercalciuria.
- Laboratory findings :
  1. hypophosphatemia
  2. ↑renal phosphate
  3. ↑serum alkaline phosphatase levels
  4. ↑1,25-D levels
  5. ↓ PTH
- Treatment: oral phosphorus replacement

## FANCONI SYNDROME

- Fanconi syndrome is secondary to generalized dysfunction of the renal proximal tubule.
- There are renal losses of phosphate, amino acids, bicarbonate, glucose, urate, and other molecules that are normally reabsorbed in the proximal tubule.
- The most clinically relevant consequences are hypophosphatemia due to phosphate losses and proximal renal tubular acidosis due to bicarbonate losses.
- The findings of aminoaciduria, glucosuria, and a low serum uric acid level are helpful diagnostically.
- Fanconi syndrome in children is often secondary to an underlying genetic disorder. **Cystinosis** is the most common genetic etiology.
- Other causes include **Wilson disease**, **Lowe syndrome**, and **tyrosinemia**.
- Primary familial Fanconi syndrome is extremely rare.
- May secondary to heavy metal exposure or **drug toxicity (valproate, aminoglycosides)**.
- Patients have rickets as a result of hypophosphatemia, with exacerbation from the chronic metabolic acidosis, which causes bone dissolution.
- Failure to thrive is a consequence of both rickets and renal tubular acidosis.
- Patients usually have polyuria and polydipsia.
- Lab findings:

1. hypophosphatemia
2. metabolic acidosis
3. hypokalemia and hyponatremia
4. Most have impaired synthesis of 1,25-D; levels are low
5. few cases, increased levels of 1,25-D→ increases calcium absorption→ hypercalciuria.

| DISORDER | Ca | Pi | PTH | 25-OHD | 1,25-$(OH)_2$D | ALK PHOS | URINE Ca | URINE Pi |
|---|---|---|---|---|---|---|---|---|
| **Vitamin D deficiency** | N, ↓ | ↓ | ↑ | ↓ | ↓, N, ↑ | ↑ | ↓ | ↑ |
| **VDDR, type 1** | N, ↓ | ↓ | ↑ | [Ngr ] | ↓ | ↑ | ↓ | ↑ |
| **VDDR, type 2** | N, ↓ | ↓ | ↑ | [Ngr ] | ↑↑ | ↑ | ↓ | ↑ |
| **Chronic renal failure** | N, ↓ | ↑ | ↑ | [Ngr ] | ↓ | ↑ | N, ↓ | ↓ |
| **Dietary Pi deficiency** | N | ↓ | N, ↓ | [Ngr ] | ↑ | ↑ | ↑ | ↓ |
| **XLH** | N | ↓ | [Ngr ] | [Ngr ] | Relatively Decreased | ↑ | ↓ | ↑ |
| **ADHR** | N | ↓ | [Ngr ] | [Ngr ] | RD | ↑ | ↓ | ↑ |
| **HHRH** | N | ↓ | N, ↓ | [Ngr ] | RD | ↑ | ↑ | ↑ |
| **Tumor-induced rickets** | N | ↓ | [Ngr ] | [Ngr ] | RD | ↑ | ↓ | ↑ |
| **Fanconi syndrome** | N | ↓ | [Ngr ] | [Ngr ] | RD or ↑ | ↑ | ↓ or ↑ | ↑ |
| **Dietary Ca deficiency** | N, ↓ | ↓ | ↑ | [Ngr ] | ↑ | ↑ | ↓ | ↑ |

## HYPERVITAMINOSIS D

- Hypervitaminosis D is secondary to excessive intake of vitamin D.
- The recommended upper limits for long-term vitamin D intake are 1,000 IU for children younger than 1 year old and 2,000 IU for older children and adults.
- Vitamin D intoxication is never secondary to excessive exposure to sunlight, because ultraviolet irradiation can transform vitamin $D_3$ and its precursor into inactive.
- vitamin D increases intestinal absorption of calcium but the dominant mechanism of the hypercalcemia is excessive bone resorption.
- The diagnosis is based on : hypercalcemia + elevated serum 25-D level.
- The signs and symptoms of vitamin D intoxication are secondary to hypercalcemia.
  1. **GI:** nausea, vomiting, poor feeding, constipation, abdominal pain, and pancreatitis.
  2. **cardiac:** hypertension, decreased Q-T interval, and arrhythmias.
  3. **CNS**: lethargy, hypotonia, confusion, disorientation, depression, psychosis, hallucinations, and coma.
  4. **Renal:** DI→ polyuria+dehydration+hypernatremia, ARF, nephrolithiasis, and nephrocalcinosis→CRF
- Deaths are associated with arrhythmias or dehydration.
- The classic findings in vitamin D intoxication are:
  1. hypercalcemia
  2. ↑↑↑25-D (>150 ng/mL)
  3. Hyperphosphatemia
  4. PTH levels decreased due to hypercalcemia.
  5. Hypercalciuria is universally present → nephrocalcinosis
  6. 1,25-D are normal: ↓1α-hydroxylase by low PTH+ hyperphosphatemia+ effect of 1,25-D.
  7. Nephrocalcinosis : ultrasound or CT scan.
  8. Anemia : the mechanism is unknown.

# WATER-SOLUBLE VITAMINS

- Water-soluble vitamins are not "stored" in the body except for vitamin $B_{12}$ → intake alters tissue levels.
- Absorption from the diet is high
- the compounds exchange readily between intracellular and extracellular fluids
- excretion is via the urine.
- Water-soluble vitamins typically function as coenzymes in energy, protein, amino acid, and nucleic acid metabolism; as cosubstrates in enzymatic reactions; and as structural components.

## ASCORBIC ACID

- The principal forms of vitamin C are:
  A. ascorbic acid
  B. Dehydro/ascorbic acid: the oxidized form.
- Ascorbic acid accelerates hydroxylation reactions in many biosynthetic reactions, including hydroxylation of proline in the formation of collagen.
- A deficiency of ascorbic acid results in the clinical manifestations of **scurvy**.
- Infantile scurvy is manifested by:
  3. irritability
  4. bone tenderness with swelling
  5. pseudoparalysis of the legs.
- The disease occur if infants are fed **un-supplemented cow's milk** in the first year of life or if the diet is devoid of fruits and vegetables.
- characterize the progression of the illness:
  1. Subperiosteal hemorrhage
  2. bleeding gums and petechiae
  3. hyperkeratosis of hair follicles
  4. succession of mental changes.
  5. Anemia in chronic scurvy secondary to bleeding, decreased iron absorption, or abnormal folate metabolism.

## B VITAMINS

### Thiamine-B1

- Vitamin $B_1$
- Thiamine is lost during milk pasteurization and sterilization.
- **Infantile beriberi** occurs between 1 and 4 months of age in breastfed infants whose:
  1. mothers have a thiamine deficiency (alcoholism)
  2. infants with protein-calorie malnutrition
  3. infants receiving unsupplemented hyperalimentation fluid
  4. infants receiving boiled milk.
- Thiamine deficiency occurs in alcoholics and has been reported in adolescents who have undergone bariatric surgery for severe obesity.
- Acute **"wet beriberi"** with cardiac symptoms & signs predominates in infantile beriberi.
- Clinical mainfistations:
  1. Anorexia
  2. apathy
  3. vomiting
  4. restlessness
  5. pallor progress to dyspnea
  6. cyanosis
  7. death from congestive heart failure
  8. **characteristic aphonic cry**; they appear to be crying, but no sound is uttered.
  9. peripheral neuropathy
  10. paresthesias.

### Riboflavin- B2

- Vitamin $B_2$
- A deficiency of riboflavin affects glucose, fatty acid, and amino acid metabolism.
- **Ariboflavinosis** is characterized by:
  1. angular stomatitis
  2. glossitis

3. cheilosis
4. seborrheic dermatitis around the nose and mouth
5. eye changes : reduced tearing, photophobia, corneal vascularization, cataracts.

- Subclinical riboflavin deficiencies have been found in:
  1. diabetic subjects
  2. children in families with low socioeconomic status
  3. children with chronic cardiac disease
  4. infants undergoing prolonged phototherapy for hyperbilirubinemia.

**Niacin-B3**

- Niacin is involved in multiple metabolic processes, including fat synthesis, intracellular respiratory metabolism, and glycolysis.
- **Pellagra**, or niacin deficiency disease, is characterized by:
  1. weakness
  2. lassitude
  3. dermatitis
  4. photosensitivity
  5. inflammation of mucous membranes
  6. Diarrhea, vomiting, dysphagia.
  7. dementia (severe cases)

**Vitamin $B_6$** -pyridoxine

- The pyridoxal and pyridoxamine forms of the vitamin are destroyed by heat; heat treatment was responsible for vitamin $B_6$ deficiency and seizures in infants fed improperly processed formulas.
- **Goat's milk is deficient in vitamin $B_6$.**
- Dietary deprivation or malabsorption of vitamin $B_6$ in children results in:
  1. **hypochromic microcytic anemia**
  2. vomiting, diarrhea
  3. **failure to thrive**
  4. listlessness
  5. hyper-irritability
  6. **seizures**
- Children receiving isoniazid or penacillamine may require additional vitamin $B_6$ because the drug binds to the vitamin.
- Vitamin $B_6$ is unusual as a water-soluble vitamin in that **very large doses (≥500 mg/day) have been associated with a sensory neuropathy**.

**Folate**

- Folate functions in transport of single-carbon fragments in synthesis of nucleic acids and for normal metabolism of certain amino acids and in conversion of homocysteine to methionine.
- Folate deficiency characterized by:
  1. **hypersegmented neutrophils**
  2. **macrocytic anemia**
  3. **glossitis**
- Result from a low dietary intake, malabsorption, or vitamin-drug interactions.
- Deficiency can develop within a few weeks of birth because infants require 10 times as much folate as adults relative to body weight but have scant stores of folate in the newborn period.
- Folate is heat labile, and heat-sterilizing home-prepared formula can decrease the folate content by half.
- **Evaporated milk and goat's milk are low in folate**.
- Patients with chronic hemolysis (sickle cell anemia, thalassemia) require extra folate Other conditions with risk of deficiency include pregnancy, alcoholism, and treatment with anticonvulsants (phenytoin) or antimetabolites (methotrexate).
- First occurrence and recurrence of **neural tube defects** are reduced significantly by maternal supplementation during embryogenesis.
- Because closure of the neural tube occurs before usual recognition of pregnancy, all women of reproductive age = folate intake 400 µg/day as prophylaxis.

**Vitamin $B_{12}$**

- The vitamin functions in single-carbon transfers and is intimately related to folate function and interconversions.
- Vitamin $B_{12}$ is essential for normal lipid and carbohydrate metabolism in energy production and in protein biosynthesis and nucleic acid synthesis.
- Dietary sources of the vitamin are animal products only, and **strict vegetarians should take a vitamin $B_{12}$ supplement**.
- Exclusively breastfed infants ingest adequate vitamin $B_{12}$ unless the mother is a strict vegetarian without supplementation.
- Vitamin $B_{12}$ deficiency is rare.
- Early diagnosis and treatment of this disorder in childhood are important because of the danger of irreversible neurologic damage.
- Most cases in childhood result from a specific defect in absorption.Such defects include:
  1. **congenital pernicious anemia** (absent intrinsic factor)
  2. **juvenile pernicious anemia** (autoimmune)
  3. deficiency of transcobalamin II transport.
  4. Gastric or intestinal resection
  5. small bowel bacterial overgrowth
- **CLINICAL MANIFISTATIONS:**
  1. early clinical manifestations of deficiency: the appearance of **hypersegmented neutrophils and macrocytosis** (indistinguishable from folate deficiency)
  2. **neurologic manifestations**, including depression, peripheral neuropathy, posterior spinal column signs, dementia, and coma.
- The neurologic signs do not occur in folate deficiency, but administration of folate may mask the hematologic signs of vitamin $B_{12}$ deficiency, while the neurologic manifestations progress.
- Patients with vitamin $B_{12}$ deficiency also have **increased urine levels of methyl-malonic acid.**
- Most cases of vitamin $B_{12}$ deficiency in infants and children **are not** of dietary origin and require treatment throughout life.
- Maintenance therapy consists of repeated monthly intramuscular injections, although a form of vitamin $B_{12}$ is administered intranasally.

# MINERALS

## ZINC

- Zinc is the second most abundant trace mineral.
- Important in protein metabolism and synthesis, in nucleic acid metabolism, and in stabilization of cell membranes.
- Zinc functions as a cofactor for more than 200 enzymes and is essential to numerous cellular metabolic functions.
- Adequate zinc status is especially crucial during periods of growth and for tissue proliferation (immune system, wound healing, skin and gastrointestinal tract integrity)
- physiologic functions for which zinc is essential include:
  1. **normal growth**
  2. **sexual maturation**
  3. **immune function**.
- Dietary zinc is absorbed (20% to 40%) in the **duodenum and proximal small intestine**
- The best dietary sources of zinc are animal products, including human milk.
- Excretion of zinc occurs from the gastrointestinal tract.
- **Zinc deficiency dwarfism syndrome**:
  1. low levels of zinc in their hair
  2. poor appetite
  3. diminished taste acuity
  4. **hypogonadism**
  5. short stature.
- **Zinc supplementation reduces morbidity and mortality from diarrhea and pneumonia** and enhances growth in developing countries.
- Mild zinc deficiency occurs in:

1. older breastfed infants without adequate zinc intake from complementary foods
2. young children with poor total or bioavailable zinc intake in the general diet.

- Acute acquired severe zinc deficiency occurs:
  1. patients receiving total parenteral nutrition without zinc supplementation
  2. premature infants fed human milk without fortification.
- **Clinical manifestations** of mild zinc deficiency :
  1. **anorexia**
  2. **growth faltering**
  3. **immune impairment**.
- Moderately severe manifestations include:
  1. delayed sexual maturation
  2. rough skin
  3. **hepatosplenomegaly**.
- The signs of severe deficiency include:
  1. acral and periorificial erythematous
  2. scaling dermatitis
  3. growth and immune impairment
  4. diarrhea
  5. mood changes
  6. alopecia
  7. night blindness
  8. photophobia.
- **Diagnosis** of zinc deficiency is challenging.
  - Plasma zinc concentration is most commonly used, but levels are frequently normal in conditions of mild deficiency; levels in moderate to severe deficiency are typically less than 60 µg/dL.
  - Acute infection also can result in depression of circulating zinc levels.
  - The standard for the diagnosis of deficiency is response to a trial of supplementation, with outcomes such as improved linear growth or weight gain, improved appetite, and improved immune function.
  - Because there is no pharmacologic effect of zinc on these functions, a positive response to supplementation is considered evidence of a preexisting deficiency.
  - Clinically an empirical trial of zinc supplementation (1 mg/kg/day) is a safe and reasonable approach in situations in which deficiency is considered possible.
- **Acrodermatitis enteropathica**:
  - autosomal recessive disorder
  - begins within 2 to 4 weeks after infants have been weaned from breast milk.
  - characterized by:
  1. acute perioral and perianal dermatitis
  2. alopecia
  3. failure to thrive.
  - The disease is caused by severe zinc deficiency from a specific defect of intestinal zinc absorption.
  - Plasma zinc levels are markedly reduced, and serum alkaline phosphatase activity is low.
- **Treatment** is with high-dose oral zinc supplements.
- uncommon condition of severe zinc deficiency is due to a defect in the secretion of zinc from the mammary gland→ low milk zinc concentrations.
- Zinc is relatively nontoxic. Excess intake produces nausea, emesis, abdominal pain, headache, vertigo, and seizures.

## FLUORIDE

- Dental enamel is strengthened when fluoride is substituted for hydroxyl ions in the hydroxyapatite crystalline mineral matrix of the enamel →fluoroapatite is more resistant to chemical and physical damage.
- Fluoride is incorporated into the enamel during the mineralization stages of tooth formation and by surface interaction after the tooth has erupted.
- Fluoride is incorporated into bone mineral and protect against osteoporosis later in life.
- The fluoride content of human milk is low and is not influenced by maternal intake.

- If the concentration of fluoride in the drinking water < 0.3 ppm, a supplement of 0.25 mg/day is recommended for infants and children 6 months to 3 years old.
- An infant > 6 months who receives only ready-feed formula or is exclusively breastfed may benefit from supplemental fluoride.
- infants should not receive fluoride supplements before 6 months of age= risk of **fluorosis**.
- Fluorosis commonly stains the teeth.

## CHARACTERISTICS OF MINERAL DEFICIENCIES

| MINERAL | FUNCTION | MANIFESTATIONS OF DEFICIENCY | COMMENTS | SOURCES |
|---|---|---|---|---|
| Iron | Heme-containing macromolecules (e.g., hemoglobin, cytochrome, and myoglobin) | Anemia, spoon nails, reduced muscle and mental performance | History of pica, cow's milk, gastrointestinal bleeding | Meat, eggs, grains |
| Copper | Redox reactions (e.g., cytochrome oxidase) | Hypochromic anemia, neutropenia, osteoporosis, hypotonia, hypoproteinemia | Inborn error, **Menkes kinky hair syndrome** | Liver, oysters, meat, nuts, grains, legumes, chocolate |
| Zinc | Metalloenzymes (e.g., alkaline phosphatase, carbonic anhydrase, DNA polymerase); wound healing | *Acrodermatitis enteropathica:* poor growth, acro-orificial rash, alopecia, delayed sexual development, hypogeusia, infection | Protein-calorie malnutrition; weaning; malabsorption syndromes | Meat, grains, cheese, nuts |
| Selenium | Antioxidant; glutathione peroxidase | Keshan cardiomyopathy in China | Endemic areas; long-term TPN | Meat, vegetables |
| Chromium | Insulin cofactor | Poor weight gain, glucose intolerance, neuropathy | Protein-calorie malnutrition, long-term TPN | Yeast, breads |
| Fluoride | Strengthening of dental enamel | Caries | Supplementation during tooth growth, narrow therapeutic range, fluorosis may cause staining of the teeth | Seafood, water |
| Iodine | Thyroxine, triiodothyronine production | Simple endemic goiter *Myxedematous cretinism:* congenital hypothyroidism *Neurologic cretinism:* mental retardation, deafness, spasticity, normal thyroxine level at birth | Endemic in New Guinea, the Congo; endemic in Great Lakes area before use of iodized salt | Seafood, iodized salt, most food in nonendemic areas |

# Physical Signs of Nutritional Deficiency Disorders

| System | Sign | Deficiency |
|---|---|---|
| General appearance | Reduced weight for height | Calories |
| Skin and hair | Pallor | Anemias (iron, vitamin $B_{12}$, vitamin E, folate, copper) |
| | Edema | Protein, thiamine |
| | Nasolabial seborrhea | Calories, protein, vitamin $B_6$, niacin, riboflavin |
| | Dermatitis | Riboflavin, essential fatty acids, biotin |
| | Photosensitivity dermatitis | Niacin |
| | Acrodermatitis | Zinc |
| | Follicular hyperkeratosis (sandpaper-like) | Vitamin A |
| | Depigmented skin | Calories, protein |
| | Purpura | Vitamins C, K |
| | Scrotal, vulval dermatitis | Riboflavin |
| | Alopecia | Zinc, biotin, protein |
| | Depigmented, dull hair, easily pluckable | Protein, calories, copper |
| Subcutaneous tissue | Decreased | Calories |
| Eye (vision) | Adaptation to dark | Vitamins A, E, zinc |
| | Color discrimination | Vitamin A |
| | Bitot spots, xerophthalmia, keratomalacia | Vitamin A |
| | Conjunctival pallor | Nutritional anemias |
| | Fundal capillary microaneurysms | Vitamin C |
| Face, mouth, and neck | Angular stomatitis | Riboflavin, iron |
| | Cheilosis | Vitamins $B_6$, niacin, riboflavin |
| | Bleeding gums | Vitamins C, K |
| | Atrophic papillae | Riboflavin, iron, niacin, folate, vitamin $B_{12}$ |
| | Smooth tongue | Iron |
| | Red tongue (glossitis) | Vitamins $B_6$, $B_{12}$, niacin, riboflavin, folate |
| | Parotid swelling | Protein |
| | Caries | Fluoride |
| | Anosmia | Vitamins A, $B_{12}$, zinc |
| | Hypogeusia | Vitamin A, zinc |
| | Goiter | Iodine |
| Cardiovascular | Heart failure | Thiamine, selenium, nutritional anemias |
| Genital | Hypogonadism | Zinc |
| Skeletal | Costochondral beading | Vitamins D, C |
| | Subperiosteal hemorrhage | Vitamin C, copper |
| | Cranial bossing | Vitamin D |
| | Wide fontanel | Vitamin D |
| | Epiphyseal enlargement | Vitamin D |
| | Craniotabes | Vitamin D, calcium |
| | Tender bones | Vitamin C |
| | Tender calves | Thiamine, selenium, vitamin C |
| | Spoon-shaped nails (koilonychia) | Iron |
| | Transverse nail line | Protein |
| Neurologic | Sensory, motor neuropathy | Thiamine, vitamins E, $B_6$, $B_{12}$ |
| | Ataxia, areflexia | Vitamin E |
| | Ophthalmoplegia | Vitamin E, thiamine |
| | Tetany | Vitamin D, $Ca^{2+}$, $Mg^{2+}$ |
| | Retardation | Iodine, niacin |
| | Dementia, delirium | Vitamin E, niacin, thiamine |
| | Poor position sense, ataxia | Thiamine, vitamin $B_{12}$ |

# PEDIATRIC UNDERNUTRITION

- Worldwide, protein-energy malnutrition (PEM) is a leading cause of death among children younger than 5 years old.
- COULD BE:
  A. Primary PEM : social or economic factors that result in a lack of food.
  B. Secondary PEM
    1. increased caloric requirements (infection, trauma, cancer)
    2. increased caloric loss (malabsorption)
    3. reduced caloric intake (anorexia, cancer, oral intake restriction, social factors)
- **Classification Guidelines for Pediatric Undernutrition**

| NUTRITION STATUS | WEIGHT/AGE | HEIGHT/AGE | WEIGHT/HEIGHT | % IBW |
|---|---|---|---|---|
| Wasting | Normal or low | Normal | <5th percentile | <85-90% |
| Stunting | <5th percentile | <5th percentile | Normal | Normal |
| Mild malnutrition | Normal or low | Normal | <5th percentile | 81-90% |
| Moderate malnutrition | Normal or low | Normal | <5th percentile | 70-80% |
| Kwashiorkor | Normal or low | Normal or low | Normal (edema) | Normal |
| Marasmus (severe wasting) | Low | Normal or low | <5th percentile | <70% |

## FAILURE TO THRIVE

- One of common diagnosis of pediatric undernutrition.

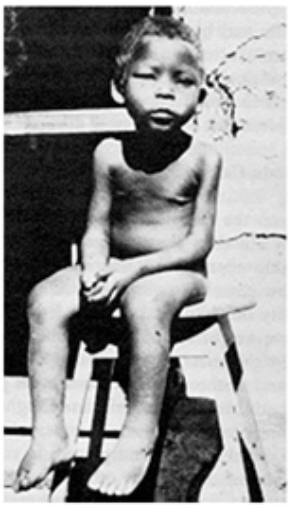
## MARASMUS

- *Marasmus* is the term used for **severe PEM** and is relatively common on a global basis.
- Many secondary forms of marasmic PEM are associated with chronic diseases (cystic fibrosis, tuberculosis, cancer, AIDS, celiac disease).
- The principal **clinical manifestation** in a child with severe malnutrition is **emaciation** with:
  A. body weight < 60% of the median for age or < 70% of the ideal weight for height
  B. Depleted body fat stores.
- Others:
  1. Loss of muscle mass and subcutaneous fat stores is confirmed by inspection or palpation and quantified by anthropometric measurements.
  2. The head appears large, but is proportional to the body length.
  3. Edema is absent.
  4. The skin is dry and thin
  5. The hair is thin, sparse, and easily pulled out.
  6. Apathetic and weak.
  7. Bradycardia and hypothermia signify severe and life-threatening malnutrition.
  8. Atrophy of the filiform papillae of the tongue is common
  9. monilial stomatitis is frequent
- Inappropriate or inadequate weaning practices and chronic diarrhea are common findings in developing countries.

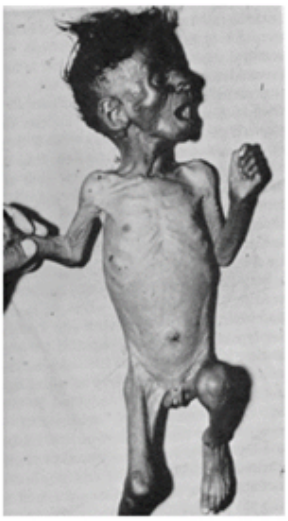
## KWASHIORKOR

- Kwashiorkor is **hypoalbuminemic, edematous malnutrition**
- presents with pitting edema that starts in the lower extremities and ascends with increasing severity→ classically described as being caused by inadequate protein intake in the presence of fair to good caloric intake.
- Other factors, such as acute infection, toxins, and possibly specific micronutrient or amino acid imbalances, are likely to contribute to the etiology.
- The major **clinical manifestation** of kwashiorkor is that the body weight of the child ranges from 60% to 80% of the expected weight for age; weight alone may not accurately reflect the nutritional status because of edema.
- **Physical examination** :
  1. **apathy and disinterest in eating are typical of kwashiorkor (relative)**
  2. maintenance of subcutaneous adipose tissue
  3. marked atrophy of muscle mass

4. Edema varies from a minor pitting of the dorsum of the foot to generalized edema with involvement of the eyelids and scrotum.
5. The hair is sparse, is easily plucked, appears dull brown, red, or yellow-white.
6. Nutritional repletion restores hair color, leaving a band of hair with altered pigmentation followed by a band with normal pigmentation (**flag sign**).
7. Skin changes :
    1. hyperpigmented hyperkeratosis -trunk and extremities
    2. erythematous macular rash (pellagroid) - trunk and extremities.
    3. superficial desquamation over pressure surfaces ("flaky paint" rash). →most severe form of kwashiorkor
8. Angular cheilosis(angular stomatitis)
9. atrophy of the filiform papillae of the tongue
10. monilial stomatitis are common.
11. Enlarged parotid glands and facial edema result in moon faces
12. Enlarged, soft liver with an indefinite edge.
13. The abdomen is distended
14. bowel sounds tend to be hypoactive
15. Lymphatic tissue commonly is atrophic.
16. Chest examination :basilar rales.



kwashiorkor



marasmus

## TREATMENT OF MALNUTRITION

- The basal metabolic rate and immediate nutrient needs decrease in cases of malnutrition.
- When nutrients are provided, the metabolic rate increases, stimulating anabolism and increasing nutrient requirements.
- The body of the malnourished child may have compensated for micronutrient deficiencies with lower metabolic and growth rates; refeeding may unmask these deficiencies.
- The gastrointestinal tract may not tolerate a rapid increase in intake.
- Nutritional rehabilitation should be initiated and advanced slowly to minimize these complications.
- Intravenous fluid should be avoided if possible to avoid excessive fluid and solute load and resultant congestive heart failure or renal failure.
- **Overzealous refeeding has been documented to cause life-threatening abnormalities** of these and other nutrients.
- If edema develops in the child during refeeding, caloric intake should be kept stable until the edema begins to resolve.
- When nutritional rehabilitation is initiated, calories can be safely started at 20% above the child's recent intake.
- If no estimate of the caloric intake is available, 50% to 75% of the normal energy requirement is safe.

- Following these guidelines should help to avoid the **refeeding syndrome**, which is characterized by:
  1. fluid retention
  2. hypophosphatemia
  3. hypomagnesemia
  4. hypokalemia.
- Careful monitoring of laboratory values and clinical status with severe malnutrition is essential.
- caloric intake can be increased 10% to 20% per day, with monitoring for electrolyte imbalances, poor cardiac function, edema, or feeding intolerance.
- Caloric intake is increased until appropriate regrowth or catch-up growth is initiated.
- Catch-up growth refers to gaining weight at greater than 50th percentile for age and may require 150% or more of the recommended calories for an age-matched, well-nourished child.
- A general **"rule of thumb"** for infants and children up to 3 years old is to provide 100 to 120 kcal/kg based on ideal weight for height.
- Protein needs also are increased as anabolism begins and are provided in proportion to the caloric intake.
- Iron supplements are not recommended during the acute rehabilitation phase, especially for children with kwashiorkor, for whom ferritin is often high.
- Additional iron may pose an oxidative stress, and iron supplementation has been associated with higher morbidity and mortality.
- In most cases, cow's milk-based formulas are tolerated and provide an appropriate mix of nutrients.
- If feeding intolerance occurs, consider lactose-free or semielemental formulas.

## COMPLICATIONS OF MALNUTRITION

- Malnourished children are more susceptible to **infection**, especially sepsis, pneumonia, and gastroenteritis.
- **Hypoglycemia** is common after severe fasting, but may be a sign of sepsis.
- **Hypothermia** : signify infection or with bradycardia→decreased metabolic rate Bradycardia and poor cardiac output → **heart failure**, exacerbated by acute fluid or solute loads.
- Vitamin A and zinc deficiencies are common in the developing world and are an important cause of **altered immune response** and increased morbidity and mortality.
- Children may have **permanent growth stunting** (from malnutrition in utero, infancy, or adolescence) and **delayed development** (from malnutrition in infancy or adolescence).

# Obesity

- Many obese children become obese adults.
- The risk of remaining obese increases with age and the degree of obesity also is influenced by family history..
- If one parent is obese, the odds ratio for the child to be obese in adulthood is 3, but this increases to 10 if both parents are obese.
- Obesity runs in families
- The **diagnosis** of obesity depends on the measurement of excess body fat.
- **BMI** is a convenient screening tool that correlates fairly strongly with body fatness in children and adults.
- For children < 2 years old, weight for length greater than 95th percentile may indicate overweight or obesity and warrants further assessment.

## Body Mass Index (BMI) Interpretation

| BMI/Age percentile | Interpretation |
|---|---|
| <5th | Underweight |
| 5-85th | Normal |
| 85-95th | At risk for overweight |
| >95th | Overweight or obese |

## Complications of Obesity

| Complication | Effects |
|---|---|
| Psychosocial | Peer discrimination, teasing, reduced college acceptance, isolation, reduced job promotion* |
| Growth | Advance bone age, increased height, early menarche |
| CNS | Pseudotumor cerebri |
| Respiratory | Sleep apnea, pickwickian syndrome |
| Cardiovascular | Hypertension, cardiac hypertrophy, ischemic heart disease,* sudden death* |
| Orthopedic | Slipped capital femoral epiphysis, Blount disease |
| Metabolic | Insulin resistance, type 2 diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, gout,* hepatic steatosis, polycystic ovary disease, cholelithiasis |

## Diseases Associated with Childhood Obesity

| Syndrome | Manifestations |
|---|---|
| Alström syndrome | Hypogonadism, retinal degeneration, deafness, diabetes mellitus |
| Carpenter syndrome | Polydactyly, syndactyly, cranial synostosis, mental retardation |
| Cushing syndrome | Adrenal hyperplasia or pituitary tumor |
| Fröhlich syndrome | Hypothalamic tumor |
| Hyperinsulinism | Nesidioblastosis, pancreatic adenoma, hypoglycemia, Mauriac syndrome (poor diabetic control) |
| Laurence-Moon-Bardet-Biedl syndrome | Retinal degeneration, syndactyly, hypogonadism, mental retardation; autosomal recessive |
| Muscular dystrophy | Late onset of obesity |
| Myelodysplasia | Spina bifida |
| Prader-Willi syndrome | Neonatal hypotonia, normal growth immediately after birth, small hands and feet, mental retardation, hypogonadism; some have partial deletion of chromosome 15 |
| Pseudohypoparathyroidism | Variable hypocalcemia, cutaneous calcifications |
| Turner syndrome | Ovarian dysgenesis, lymphedema, web neck; XO chromosome |

# Fluid & Electrolytes disturbances

# DISORDERS OF SODIUM

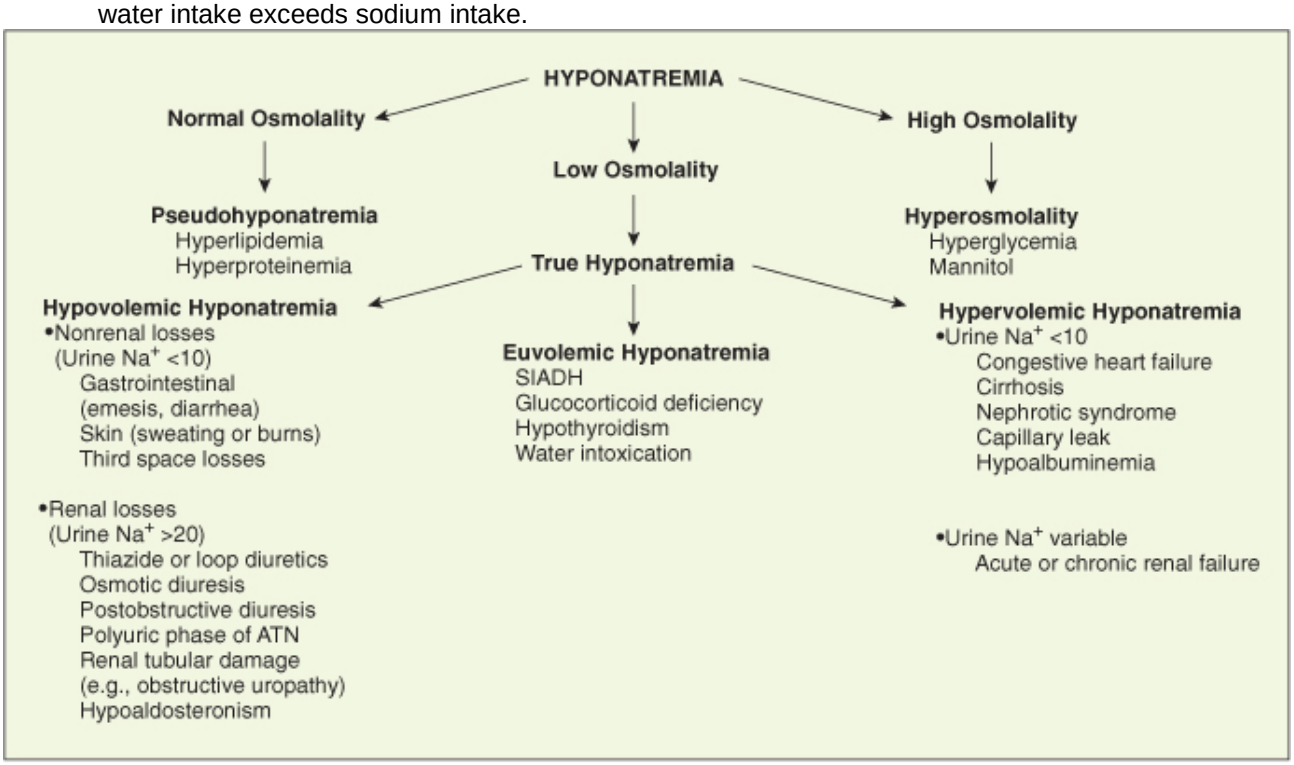
- The kidney regulates sodium balance and is the principal site of sodium excretion.
- Sodium is unique among electrolytes because **water balance**, not sodium balance, usually determines its concentration.
- When the sodium concentration increases→ higher plasma osmolality → increased thirst and increased secretion of ADH → increase the water content of the body→ sodium concentration returns to normal.
- During hyponatremia, the fall in plasma osmolality decreases ADH secretion, and consequent renal water excretion leads to an increase in the sodium concentration.
  - volume depletion stimulates thirst, ADH secretion, and renal conservation of water.
  - Volume depletion takes precedence over osmolality; volume depletion stimulates ADH secretion, even if a patient has hyponatremia.
- The excretion of sodium by the kidney is regulated by patient's effective plasma volume. This volume is mediated by a variety of regulatory systems, including the renin-angiotensin-aldosterone system and intrarenal mechanisms.
- In hyponatremia or hypernatremia, the **underlying pathophysiology** determines the urinary sodium concentration, not the serum sodium concentration.

## HYPONATREMIA

### ETIOLOGY

- **Pseudohyponatremia** is a laboratory artifact that is present when the plasma contains high concentrations of protein or lipid.
  - In true hyponatremia, the *measured* osmolality is low, whereas it is normal in pseudohyponatremia.
- **Hyperosmolality**, from mannitol infusion or hyperglycemia, causes a low serum sodium concentration because water moves down its osmotic gradient from the intracellular space into the extracellular space, diluting the sodium concentration.
  - For every 100 mg/dL ↑ of the serum glucose, the serum sodium ↓by 1.6 mEq/L.
  - Because the manifestations of hyponatremia are due to the low plasma osmolality, patients with hyponatremia owing to hyperosmolality do not have symptoms of hyponatremia.
- In **hypovolemic hyponatremia**, the child has lost sodium from the body.
  - Water balance may be positive or negative, but there has been a higher net sodium loss than water loss; this is due to oral or IV water intake, with water retention by the kidneys, to compensate for the intravascular volume depletion.
  - If the sodium loss due to **nonrenal disease**, the urine sodium is very low, as the kidneys attempt to preserve the intravascular volume by conserving sodium.
  - In **renal salt-wasting diseases**, the urine sodium is inappropriately elevated.
- Patients with hyponatremia and no evidence of volume overload or volume depletion have **euvolemic hyponatremia**.
  - typically have excess of total body water and a slight decrease in total body sodium.
  - they usually appear normal or have subtle signs of fluid overload. Some have an increase in weight
  - In **SIADH**, there is secretion of ADH that is not inhibited by either low serum osmolality or expanded intravascular volume.
  - Retention of water causes hyponatremia, and the expansion of the intravascular volume results in an increase in renal sodium excretion.
  - Hyponatremia in hospitalized patients is due to inappropriately produced ADH secondary to stress in the presence of hypotonic fluids.
  - SIADH is associated with:
    1. pneumonia
    2. mechanical ventilation
    3. meningitis
    4. CNS disorders (trauma)
    5. Ectopic (tumor) production of ADH is rare in children.
  - Infants also can develop euvolemic hyponatremia as a result of consumption of large amounts of water or inappropriately diluted formula in the absence of dehydration.

- In **hypervolemic hyponatremia**, there is an excess of total body water and sodium, although the increase in water is greater than the increase in sodium.
  - **In renal failure**, there is an inability to excrete sodium or water; the urine sodium may be low or high, depending on the cause of the renal insufficiency.
  - Decrease in the effective blood volume, owing to either **third space fluid loss or poor cardiac output** .The regulatory systems attempt to retain water and sodium to correct the problem.The patient's serum sodium concentration decreases because water intake exceeds sodium intake.






## Clinical Manifestations

- Hyponatremia causes a fall in the osmolality of the extracellular space.
- Because the intracellular space then has a higher osmolality, water moves from the extracellular space to the intracellular space to maintain osmotic equilibrium.
- The increase in intracellular water may cause cells to swell.
- **Brain cell swelling** is responsible for most of the symptoms of hyponatremia.
- symptoms of hyponatremia include:
  1. anorexia, malaise & lethargy
  2. nausea, emesis
  3. confusion, agitation
  4. **headache**
  5. **seizures**
  6. coma
  7. decreased reflexes
  8. **hypothermia**
  9. **Cheyne-Stokes respirations.**
  10. **muscle cramps and weakness**
- Symptoms are more severe when hyponatremia develops rapidly; chronic hyponatremia can be asymptomatic owing to a compensatory decrease in brain cell osmolality.

## Treatment

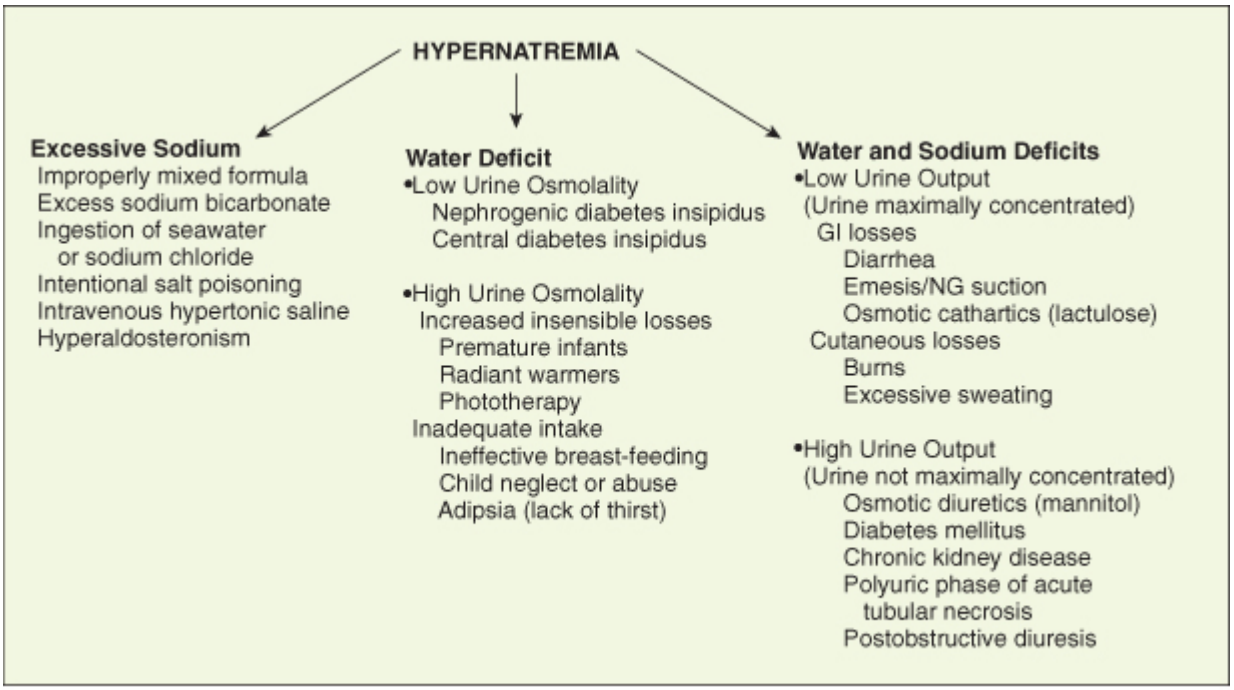
- Rapid correction of hyponatremia can produce **central pontine myelinolysis**.
- Avoiding > 12 mEq/L increase in the serum sodium every 24 hours is prudent, especially if the hyponatremia developed gradually.
- Treatment of **hypovolemic hyponatremia** requires administration of **IV fluids with sodium** to provide maintenance and deficit correction and to replace ongoing losses

- **SIADH**, **water restriction** is the cornerstone of the therapy.
- children with hypothyroidism or cortisol deficiency need specific hormone replacement.
- Acute water intoxication rapidly self-corrects with transient restriction of water intake, which is followed by introduction of a normal diet.
- Treatment of **hypervolemic hyponatremia** centers on **restriction of water and sodium intake**, but disease-specific measures, such as dialysis in renal failure, also may be necessary.

## HYPERNATREMIA

### ETIOLOGY

- **Sodium intoxication** is frequently iatrogenic in a hospital setting resulting from correction of metabolic acidosis with sodium bicarbonate; hypernatremia is accompanied by a metabolic alkalosis.
- In **hyperaldosteronism**, there is renal retention of sodium and resultant hypertension; the hypernatremia is mild.
- Hypernatremia resulting from water losses develops only if the patient does not have access to water or cannot drink adequately because of:
    1. neurologic impairment
    2. emesis
    3. anorexia
    4. Infants with Ineffective breastfeeding- primiparous mother.
- **Hereditary nephrogenic diabetes insipidus** causes massive urinary water losses and dilute urine. it is most commonly an X-linked disorder, it occurs in boys→ severe hypernatremic dehydration and FTT. The defect is in the gene for the ADH receptor.
- **Acquired nephrogenic diabetes insipidus** may be secondary to:
    1. interstitial nephritis
    2. sickle cell disease
    3. hypercalcemia
    4. hypokalemia
    5. medications (lithium or amphotericin)
- High insensible losses of water are common in **premature infants**; the losses increase further as a result of radiant warmers or phototherapy for hyperbilirubinemia.
- Children with extrarenal causes of water loss have high levels of ADH and a very concentrated urine. In contrast, children with DI have dilute urine.
- If the defect is due to **central diabetes insipidus**, the urine output decreases, and the urine osmolality increases in response to administration of an ADH analogue (central causes of ADH deficiency include tumor, infarction, or trauma). There is no response to an ADH analogue in a child with nephrogenic diabetes insipidus.
- When hypernatremia occurs in **conditions with deficits of sodium and water**, the water deficit exceeds the sodium deficit; this occurs only if the patient is unable to ingest adequate water.
    - Most children with **gastroenteritis** do not develop hypernatremia because they drink enough hypotonic fluid to compensate at least partially for stool water losses.
    - Hypernatremia is most likely in a child with diarrhea who has inadequate intake because of emesis, lack of access to water, or anorexia.
    - **Some renal diseases**= **obstructive uropathy, renal dysplasia, and juvenile nephronophthisis**, can cause losses of sodium and water, potentially producing hypernatremia if the patient consumes insufficient water.
    - In situations with combined sodium and water deficits, analysis of the urine differentiates renal and nonrenal etiologies.
        1. extrarenal, the kidney responds to volume depletion with low urine volume, a concentrated urine, and sodium retention (urine sodium <10 mEq/L).
        2. With renal causes, the urine volume is not low, the urine is not maximally concentrated, and the urine sodium may be inappropriately elevated.






## Clinical Manifestations

- Most children with hypernatremia are dehydrated and have the typical signs and symptoms of dehydration.
- Children with hypernatremic dehydration tend to have better preservation of intravascular volume owing to the shift of water from the intracellular space to the extracellular space.
- Blood pressure and urine output are maintained.
- hypernatremic infants are less symptomatic initially and potentially become more dehydrated before seeking medical attention.
- Breastfed infants with hypernatremia often are profoundly dehydrated and underweight from poor nutrition.
- Hypernatremia, even without dehydration, causes CNS symptoms that tend to parallel the degree of sodium elevation and the acuity of the increase:
  1. irritable
  2. restless
  3. weak
  4. lethargic
  5. high-pitched cry
  6. hyperpnea.
  7. Alert patients are very thirsty
  8. nausea may be present
  9. Hypernatremia causes fever
  10. **hyperglycemia** and **mild hypocalcemia**/ unknown.
- **Brain hemorrhage** is the most devastating consequence of hypernatremia.
  - extracellular osmolality increases→ water moves out of brain cells→ decrease in brain volume→ tearing of intracerebral veins and bridging blood vessels as the brain moves away from the skull and the meninges.
  - Patients may have **subarachnoid, subdural, and parenchymal hemorrhage**.
  - **Seizures and coma** are possible sequelae of the hemorrhage, although seizures are more common during treatment.
  - **The cerebrospinal fluid protein is often elevated** in infants with significant hypernatremia, probably owing to leakage from damaged blood vessels.

### Treatment

- As hypernatremia develops, the brain generates idiogenic osmoles to increase the intracellular osmolality and prevent the loss of brain water→most prominent when hypernatremia has developed gradually.
- If the serum sodium concentration is lowered rapidly, there is movement of water from the serum into the brain cells to equalize the osmolality in the two compartments→ brain swelling → seizures or coma.
- Because of the dangers of overly rapid correction, hypernatremia should not be corrected rapidly= <12 mEq/L every 24 hours, a rate of 0.5 mEq/L/hr.
- If a child develops seizures from brain edema → stop hypotonic fluid + infusion of 3% saline, reversing the cerebral edema.
- In a child with hypernatremic dehydration, as in any child with dehydration, the first priority is restoration of intravascular volume with isotonic fluid.
- If the hypernatremia and dehydration are secondary to water loss, as occurs with either form of diabetes insipidus, a more hypotonic IV fluid is appropriate.
- A child with central diabetes insipidus should receive an ADH analogue to prevent further excessive water loss.
- A child with nephrogenic diabetes insipidus requires a urine replacement solution to offset ongoing water losses.
  - Chronically, reduced sodium intake, thiazide diuretics, and nonsteroidal anti-inflammatory drugs can decrease water losses in nephrogenic diabetes insipidus.
- Acute, severe hypernatremia, usually secondary to sodium administration
  - can be corrected more rapidly because idiogenic osmoles have not had time to accumulate.
  - if hypernatremia is severe, it may be impossible to administer enough water to correct without worsening volume overload. Some require loop diuretic or peritoneal dialysis.
- With sodium overload, hypernatremia is corrected with sodium-free IV fluid (D5 in water).

## Disorders of Potassium

- The kidneys are the principal regulator of potassium balance, adjusting excretion based on intake.
- Factors affecting renal potassium excretion include:
  1. aldosterone
  2. acid-base status
  3. serum potassium concentration
  4. renal function.
- The intracellular potassium concentration is 30 times the extracellular.
- A variety of conditions alter the distribution of potassium between the intracellular and extracellular compartments, potentially causing either hypokalemia or hyperkalemia.
- The plasma concentration does not always reflect the total body potassium content.

## HYPOKALEMIA

### Etiology

- Hypokalemia is common in children, with most cases related to **gastroenteritis**.
- **Spurious hypokalemia** in **leukemia and elevated white blood cell** if plasma for analysis is left at room temperature, WBCs take up potassium from the plasma.
- With a **transcellular shift**, there is no change in total body potassium, although there may be concomitant potassium depletion secondary to other factors.
- The transcellular shift of potassium after initiation of **insulin therapy in children with DKA** can be dramatic.
  - These patients have reduced total body potassium owing to urinary losses
  - they often have a normal serum potassium level before insulin therapy from a transcellular shift into the extracellular space secondary to insulin deficiency and metabolic acidosis.
- Children receiving aggressive doses of **β-adrenergic agonists (albuterol)** for asthma can have hypokalemia from the intracellular movement of potassium.

- **Poor intake** is an unusual cause of hypokalemia, unless also associated with significant weight loss (anorexia nervosa)
- **hypokalemia + metabolic acidosis**:
  1. **Diarrhea** has a high concentration of potassium & stool losses of bicarbonate
  2. Proximal or distal renal tubular acidosis [RTA].
  3. DKA
  4. Ureterosigmoidostom
  5. **acetozolamide** (IMP.)
- **the gastric loss of hydrochloride**( emesis or nasogastric suction) → metabolic alkalosis + volume depletion→increase urinary losses of potassium.
- **Loop and thiazide diuretics** lead to hypokalemia and a metabolic alkalosis.
- **Bartter syndrome and Gitelman syndrome** are AR disorders resulting from defects in tubular transporters→ **hypokalemia** and a **metabolic alkalosis**.
  - Bartter syndrome is associated with **hypercalciuria**, often with **nephrocalcinosis**.
  - Gitelman syndrome have low urinary calcium losses, but **hypomagnesemia** secondary to urinary magnesium losses.
- **high aldosterone level**: hypokalemia, metabolic alkalosis, renal retention of sodium, hypertension.
- **Liddle syndrome**, an autosomal dominant disorder caused by constitutively active sodium channels, has the same clinical features as hyperaldosteronism, but the serum aldosterone level is low.

## CLINICAL MANIFESTATIONS

- The heart and skeletal muscle are especially vulnerable to hypokalemia.

1. **ECG CHANGES** :flattened T wave, a depressed ST segment, and the appearance of a **U wave**, which is located between the T wave (if still visible) and P wave.
2. **Ventricular fibrillation and torsades de pointes**
3. Hypokalemia makes the heart especially susceptible to digitalis-induced arrhythmias, such as SVT, ventricular tachycardia, and heart block.
4. **muscle weakness and cramps**.
5. **Paralysis** (generally only at potassium levels <2.5 mEq/L). usually starts with the legs, followed by the arms. Respiratory paralysis→ mechanical ventilation.
6. **rhabdomyolysis**; the risk increases with exercise.
7. slows gastrointestinal motility→ **constipation**, or with levels < 2.5 mEq/L→ **ileus**
8. impairs bladder function→ **urinary retention**.
9. **polyuria** by producing **secondary nephrogenic diabetes insipidus**.
10. Chronic hypokalemia → kidney damage, including **interstitial nephritis** and **renal cysts**.
11. chronic hypokalemia, as in Bartter syndrome, leads to **poor linear growth**.

## DIAGNOSIS

- It is important to review the child's diet and history of gastrointestinal losses or medications.
- The presence of hypertension suggests excess mineralocorticoids.
- Concomitant electrolyte abnormalities are useful clues.
- The combination of hypokalemia and metabolic acidosis is characteristic of diarrhea, distal RTA, and proximal RTA.
- A concurrent metabolic alkalosis is characteristic of emesis or nasogastric losses, aldosterone excess, diuretics, and Bartter syndrome or Gitelman syndrome.
- Alkalosis also causes a transcellular shift of potassium intracellularly and increased urinary losses of potassium.

## TREATMENT

- Factors that influence the therapy of hypokalemia include:
  1. the potassium level
  2. clinical symptoms
  3. renal function
  4. presence of transcellular shifts of potassium
  5. ongoing losses
  6. the patient's ability to tolerate oral potassium.
- Supplementation is more cautious if renal function is decreased because of the kidney's limited ability to excrete excessive potassium.

- The plasma potassium level does not always provide an accurate estimation of the total body potassium deficit because there may be shifts of potassium from the intracellular space to the plasma.
- Because of the risk of hyperkalemia, IV potassium should be used cautiously.
- Oral potassium is safer, albeit not as rapid in urgent situations.
- The dose of **IV potassium is 0.5 to 1 mEq/kg**, given over 1 hour.
- For patients with excessive urinary losses, potassium-sparing diuretics are effective, but they need to be used cautiously in patients with renal insufficiency.
- If hypokalemia, metabolic alkalosis, and volume depletion are present (with gastric losses), restoration of intravascular volume with adequate sodium chloride decreases urinary potassium losses.
- Disease-specific therapy is effective in many of the genetic tubular disorders.

## CAUSES OF HYPOKALEMIA

| |
|---|
| SPURIOUS : High white blood cell count |
| TRANSCELLULAR SHIFTS |
| Alkalemia , Insulin, β-Adrenergic agonists , Hypokalemic periodic paralysis & Drugs/toxins (theophylline, barium, toluene) |
| DECREASED INTAKE |
| EXTRARENAL LOSSES |
| Diarrhea , Laxative abuse, Sweating |
| RENAL LOSSES |
| ***With metabolic acidosis*** : Distal RTA , Proximal RTA, Ureterosigmoidostom, DKA |
| ***Without specific acid-base disturbance:*** |
| Tubular toxins (amphotericin, cisplatin, aminoglycosides) |
| Interstitial nephritis |
| Diuretic phase of acute tubular necrosis |
| Postobstructive diuresis |
| Hypomagnesemia |
| High urine anions (e.g., penicillin or penicillin derivatives) |
| ***With metabolic alkalosis*** |
| *Low urine chloride* Emesis/nasogastric suction, Pyloric stenosis, Chloride-losing diarrhea, Cystic fibrosis, Low-chloride formula, Posthypercapnia, Previous loop or thiazide diuretic use |
| *High urine chloride and normal blood pressure* :Gitelman syndrome, Bartter syndrome, Loop and thiazide diuretics |
| *High urine chloride and high blood pressure* |
| Adrenal adenoma or hyperplasia |
| Glucocorticoid-remediable aldosteronism |
| Renovascular disease |
| Renin-secreting tumor |
| 17α-Hydroxylase deficiency |
| 11β-Hydroxylase deficiency |
| Cushing syndrome |
| 11β-Hydroxysteroid dehydrogenase deficiency |
| Licorice ingestion |
| Liddle syndrome |

# HYPERKALEMIA

## ETIOLOGY

- **Fictitious hyperkalemia** is common in children because of:
  1. hemolysis during phlebotomy or prolonged tourniquet application or fist clinching→ local potassium release from muscle.
  2. when serum levels are measured in patients with markedly elevated white blood cell counts.
- **Frequent or rapid blood transfusions** can increase the potassium level acutely secondary to the high potassium content of blood. Increased intake may precipitate hyperkalemia if there is an underlying defect in potassium excretion.
- The intracellular space has a high potassium concentration, so a **shift of potassium from the intracellular space** to the extracellular space can have a significant impact on the plasma potassium. This occurs with:
  1. acidosis
  2. cell destruction (rhabdomyolysis or tumor lysis syndrome)
  3. insulin deficiency
  4. medications (succinylcholine or β-blockers)
  5. malignant hyperthermia
  6. hyperkalemic periodic paralysis.
- Hyperkalemia secondary to decreased excretion occurs with **renal insufficiency**.
- **Aldosterone deficiency or unresponsiveness to aldosterone** causes hyperkalemia, often with associated metabolic acidosis and hyponatremia.
  - A form of **congenital adrenal hyperplasia**, **21-hydroxylase deficiency**, is the most frequent cause of aldosterone deficiency in children.
  - Male infants typically present with hyperkalemia, metabolic acidosis, hyponatremia, and volume depletion.
  - Female infants with this disorder usually are diagnosed as newborns because of ambiguous genitalia; treatment prevents the development of electrolyte problems.
- **A deficiency in renin**, resulting from kidney damage, can lead to decreased aldosterone production= hyperkalemia + metabolic acidosis **-** hyponatremia.
- **pseudohypoaldosteronism type 1** :
  1. **hyperkalemia**
  2. **metabolic acidosis**
  3. salt wasting leading to **hyponatremia** and **volume depletion**
  4. **aldosterone levels are elevated.**
  - AR variant: defect in the renal sodium channel that is activated by aldosterone.
  - AD form: defect in the aldosterone receptor, milder, remitting in adulthood.
- **Pseudohypoaldosteronism type 2**= **Gordon syndrome**, AD disorder characterized by:
  1. **hypertension** secondary to salt retention
  2. impaired excretion of potassium and acid = **hyperkalemia + metabolic acidosis**.
- The risk of hyperkalemia secondary to medications that decrease renal potassium excretion is greatest in patients with underlying renal insufficiency.

## CLINICAL MANIFESTATIONS

- The most import effects of hyperkalemia are due to the role of potassium in membrane polarization. The cardiac conduction system is usually the dominant concern.
  1. **ECG changes** begin with peaking of the T waves→ increased P-R interval, flattening of the P wave, and widening of the QRS complex occur→ ventricular fibrillation.
  2. Asystole also may occur.
  3. Some patients have paresthesias, weakness, and tingling
- ***cardiac toxicity usually precedes clinical symptoms***

## DIAGNOSIS

- The etiology of hyperkalemia is often readily apparent.
- Spurious hyperkalemia is common in children, so a repeat potassium level is often appropriate.
- The history initially should focus on potassium intake, risk factors for transcellular shifts of potassium, medications that cause hyperkalemia, and the presence of signs of renal insufficiency.

- Initial laboratory evaluation should include creatinine and BUN levels and assessment of acid-base status.
- Many causes of hyperkalemia, such as renal insufficiency and aldosterone insufficiency or resistance, cause a metabolic acidosis that worsens hyperkalemia by the transcellular shift of potassium out of cells.
- Cell destruction, as rhabdomyolysis or tumor lysis syndrome= **hyperphosphatemia**, **hyperuricemia**, and ↑**serum lactate dehydrogenase.**

## Causes of Hyperkalemia

| |
|---|
| **Spurious laboratory value** : Hemolysis, Tissue ischemia during blood drawing, Thrombocytosis, Leukocytosis |
| **Increased intake:** IV or PO**,** Blood transfusions |
| **Transcellular shifts:** Acidemia**,** Rhabdomyolysis, Tumor lysis syndrome, Tissue necrosis**,** Hemolysis/hematomas/gastrointestinal bleeding**,** Succinylcholine, Digitalis intoxication**,** Fluoride intoxication**,** β-Adrenergic blockers**,** Exercise**,** Hyperosmolality, Insulin deficiency**,** Malignant hyperthermia, Hyperkalemic periodic paralysis |
| **Decreased excretion** |
| **Renal failure** |
| **Primary adrenal disease** |
| Acquired Addison disease |
| 21-Hydroxylase deficiency |
| 3β-Hydroxysteroid-dehydrogenase deficiency |
| Lipoid congenital adrenal hyperplasia |
| Adrenal hypoplasia congenita |
| Aldosterone synthase deficiency |
| Adrenoleukodystrophy |
| **Hyporeninemic hypoaldosteronism** |
| Urinary tract obstruction |
| Sickle cell disease |
| Kidney transplant |
| Lupus nephritis |
| **Renal tubular disease** |
| Pseudohypoaldosteronism type 1 |
| Pseudohypoaldosteronism type 2 |
| Urinary tract obstruction |
| Sickle cell disease |
| Kidney transplant |
| **Medications** |
| **ACE inhibitors** |
| Angiotensin II blockers |
| Potassium-sparing diuretics |
| Cyclosporine |
| NSAIDs |
| Trimethoprim |

## Treatment

- A high serum potassium level with ECG changes requires more vigorous treatment.
- An additional source of concern is a patient with increasing plasma potassium despite minimal intake. This situation can occur if there is cellular release of potassium (tumor lysis syndrome), especially in the setting of diminished excretion (renal failure).
- The first action in a child with a concerning elevation of plasma potassium is to stop all sources of additional potassium (oral and IV).
- If the potassium level is > 6 to 6.5 mEq/L, an ECG should be obtained to help assess the urgency of the situation.
- Therapy of the hyperkalemia has two basic goals:
  1. Prevent life-threatening arrhythmias
  2. remove potassium from the body .
- The treatments that acutely prevent arrhythmias all have the advantage of working quickly (within minutes), but do not remove potassium from the body.
- Because none of the measures that remove potassium from the body work quickly, it is important to start them as soon as possible.
- Long-term management of hyperkalemia includes reducing intake via dietary changes and eliminating or reducing medications that cause hyperkalemia.
- Some patients require medications, such as sodium polystyrene sulfonate and loop or thiazide diuretics, to increase potassium losses.
- The disorders that are due to a deficiency in aldosterone respond to replacement therapy with **fludrocortisone**, a mineralocorticoid.

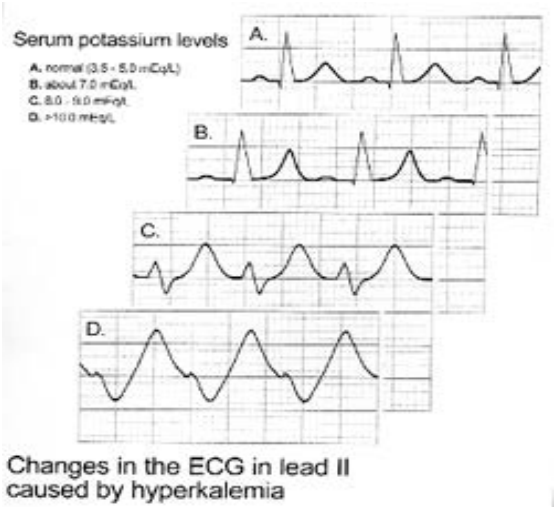
### Treatment of Hyperkalemia

| Rapidly decrease the risk of life-threatening arrhythmias |
|---|
| **Shift potassium intracellularly** |
| Sodium bicarbonate administration (IV) |
| Insulin + glucose (IV) |
| β-Agonist (albuterol via nebulizer) |
| **Cardiac membrane stabilization** |
| IV calcium |
| Remove potassium from the body |
| Loop diuretic (IV or PO) |
| Sodium polystyrene (PO or rectal) |
| Dialysis |

# ECG CHANGES OF POTASIOUM DISORDERS

## HYPERKALEMIA

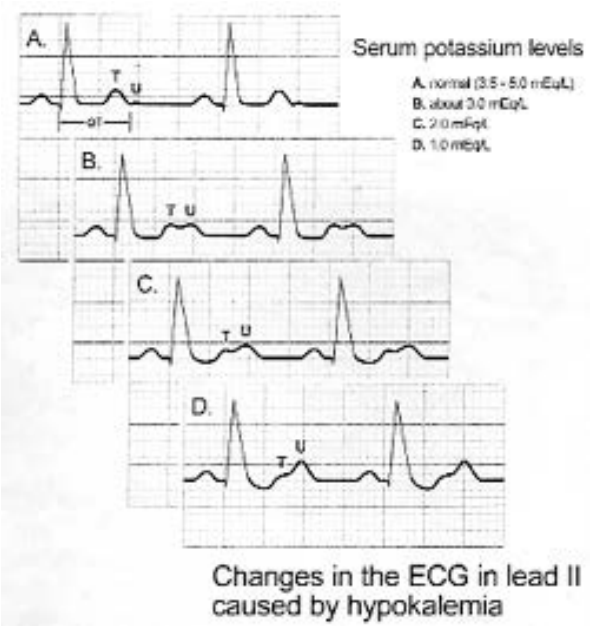
- On the ECG, the **QRS complexes begin to widen** when the serum potassium drops to about 3 mEq/L,
- The **ST segments may become depressed**, and the **T waves may begin to flatten.**
- The **U waves also begin to increase in size**, becoming as tall as the T waves.
- The U waves reach "giant" size and fuse with the T waves when the level drops to 1 mEq/L [2] .



Changes in the ECG in lead II caused by hyperkalemia

## HYPERKALEMIA

- **The QRS complexes may widen** so that they merge with the T waves→"sine wave" appearance.
- **The ST segments disappear** when the serum potassium level reaches 6 mEq/L and the **T waves typically become tall and peaked** at this same range.
- **The P waves begin to flatten and widen** when a patient's serum potassium level reaches 6.5 mEq/L; this effect disappear when levels reach 7-9 mEq/L.
- **Sinus arrest** may occur when the serum potassium level reaches about 7.5 mEq/L
- **cardiac standstill or ventricular fibrillation** may occur when serum levels reach 10 to 12 mEq/L 2 (See fig. 4).



Changes in the ECG in lead II caused by hypokalemia

# Acid-Base Disorders

> **Note:**
> **PH** = 7.4 (7.35-7.45)
> **PCO2**=40 (35-45)
> **HCO2**=24 (20-26)

- PH the negative logarithm of free H concentration
- Acid: proton donor
- Base: proton acceptor
- An **acidosis** is a pathologic process that causes an increase in the hydrogen ion concentration .state of accumulation of acid or loss of base without necessarily alternating PH.
- **alkalosis** is a pathologic process that causes a decrease in the hydrogen ion concentration. state in which there is loss of acid or accumulation of base without necessarily alternating PH
- **Acidemia** is a pH below normal **<7.35**, and **alkalemia** is a pH above normal **>7.45**.
- Academia: acidosis with uttered PH
- Alkalemia : alkalosis with ultered PH
- **appropriate respiratory compensation** for a metabolic process happens quickly and is complete within **12 to 24 hours**.
- In contrast to a rapid respiratory compensation, it takes 3 to 4 days for the kidneys to complete **appropriate metabolic compensation**.
- A **mixed acid-base disorder** is present when there is more than one primary acid-base disturbance.
  - An infant with bronchopulmonary dysplasia = respiratory acidosis from chronic lung disease + metabolic alkalosis from furosemide-induced hypokalemia .

## Appropriate Compensation During Simple Acid-Base Disorders

| Disorder | Expected Compensation |
|---|---|
| Metabolic acidosis | $P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$ |
| Metabolic alkalosis | $P_{CO_2}$ increases by 7 mm Hg for each 10 mEq/L increase in the serum $[HCO_3^-]$ |
| Respiratory acidosis | |
| Acute | $[HCO_3^-]$ increases by 1 for each 10 mm Hg increase in the $P_{CO_2}$ |
| Chronic | $[HCO_3^-]$ increases by 3.5 for each 10 mm Hg increase in the $P_{CO_2}$ |
| Respiratory alkalosis | |
| Acute | $[HCO_3^-]$ falls by 2 for each 10 mm Hg decrease in the $P_{CO_2}$ |
| Chronic | $[HCO_3^-]$ falls by 4 for each 10 mm Hg decrease in the $P_{CO_2}$ |

## METABOLIC ACIDOSIS

- Metabolic acidosis occurs frequently in hospitalized children; **diarrhea is the most common cause.**

### Causes of Metabolic Acidosis

| Normal Anion Gap |
|---|
| Diarrhea |
| **Renal tubular acidosis** (hypokalemic metabolic acidosis) |
| Urinary tract diversions |
| Posthypocapnia |
| Ammonium chloride intake |
| **Acetazolmide (diamox)** (hypokalemic metabolic acidosis) |
| **Increased Anion Gap** |
| Lactic acidosis |
| Ketoacidosis (diabetic, starvation, or alcoholic) |
| Kidney failure |
| Poisoning (e.g., ethylene glycol, methanol, or **salicylates**) |
| Inborn errors of metabolism ex: **Organic acidemia** |

- The plasma anion gap is useful for evaluating patients with a metabolic acidosis.
  $\text{Anion gap} = [Na^+] - [Cl^-] - [HCO_3^-]$
- A normal anion gap is up to 20.
- A decrease in the albumin concentration of 1 g/dL decreases the anion gap by roughly 4 mEq/L.

## METABOLIC ALKALOSIS

### CAUSES OF METABOLIC ALKALOSIS

| **Chloride Responsive (Urinary Chloride <15 mEq/L)** |
|---|
| Gastric losses (emesis or **nasogastric suction**) |
| **Pyloric stenosis** |
| Diuretics (loop or thiazide) |
| Chloride-losing diarrhea |
| Chloride-deficient formula |
| Cystic fibrosis (sweat losses of chloride) |
| Posthypercapnia (chloride loss during metabolic acidosis) |
| **Chloride Resistant (Urinary Chloride >20 mEq/L)** |
| **High blood pressure** |
| Adrenal adenoma or hyperplasia |
| Glucocorticoid-remediable aldosteronism |
| Renovascular disease |
| Renin-secreting tumor |
| 17α-Hydroxylase deficiency |
| 11β-Hydroxylase deficiency |
| Cushing syndrome |
| 11β-Hydroxysteroid dehydrogenase deficiency |
| Licorice ingestion |
| Liddle syndrome |
| **Normal blood pressure** |
| Gitelman syndrome |
| Bartter syndrome (hypokalemic metabolic alkalosis) |
| Base administration(hypokalemic metabolic alkalosis) |

## RESPIRATORY ACID-BASE DISTURBANCES

### CAUSES OF RESPIRATORY ACIDOSIS

| CNS depression (encephalitis or narcotic overdose) |
|---|
| Disorders of the spinal cord, peripheral nerves, or neuromuscular junction (botulism or Guillain-Barré syndrome) |
| Respiratory muscle weakness (muscular dystrophy) |
| Pulmonary disease (pneumonia or asthma, plural effusion, pneumothorax) |
| Upper airway disease (laryngospasm,croup,epiglotitis, forgein body)) |
| **Extreme obesity** (beckwith widman syndrome) |

### CAUSES OF RESPIRATORY ALKALOSIS

| Hypoxemia or tissue hypoxia (carbon monoxide poisoning or cyanotic heart disease) |
|---|
| Lung receptor stimulation (pneumonia or pulmonary embolism, **bronchial asthma**) |
| Central stimulation (anxiety or brain tumor) |
| **Mechanical ventilation** |
| **Early stages of salicylate poisoning** |

# Human Genetics and Dysmorphology

# PATTERN OF INHERITANCE

## TRADITIONAL INHERITANCE:

### chromosomal abnormalities :

- 1/150 newborns
- 60% of spontaneous abortions , 10% of still births
  1. **numerical (aneuploidy-** trisomy or monosomy**, polyploidy-**groups**)**
     - **autosomal :** trisomes :21,18,13
     - **X chromosomes as:** Klinfilter (47,XXY), Turner syndrome (45.X)
  2. **structural abnormalities**(**balanced-** translocation or inversion**, un-balanced**-deletion or duplications)
     - **deletion:** Wolf-Hirshhorn syndrome, Willians syndrome, WAGAR syndrome, Prader Willi syndrome, Alengman syndrome, Miller dieker syndrome, Chromosome 22q11 delection, DiGeorge syndrome, Velocardiofasical syndrome, conotruncal face syndrome
     - **duplication:** Cat eye syndrome, Inverted duplication chromosome 15

### single gene disorders- mendilne disorders

1. autosomal disorders( dominate & recessive)- mutation in one gene of the 22 autosomal chromosomes
   - autosomal dominate : Achondroplasia, NF type1, Tuberous sclerosis, Marfan syndrome, sherocytosis, V Willbran factor deficiency.
   - Recessive: SCD, Tay sacks disease, thalassemia, PKU deficiency and most enzymes deficiencies.
2. X-linked disorders (Dominant & recessive)
   - Recessive: **Duchenne muscular dystrophy, Hemophilia A**
   - Dominant: **Rett syndrome, Inconitinentia pigmenti, Vitamine D resistant Rickets**

> **NOTE:**
> AD disorder that appear as new mutation, recurrence rate= 7%

### multifactorial inheritance

- Polygenic inheritance , not multiple genes but interaction between genetic and environmental factors
- The most common and least understood of genetics disorders
- Common disorders of adult onset: DM,HTN, hyperlipidemia, asthma & atherosclerosis.
- Common birth defects: Spinal bifida, pyloric stenosis, cleft lip & palate, congenital dislocation of hip & hip dysplasia
- Incidence 1/1000, recurrence 3%

## NON-TRADITIONAL INHERITANCE

### mitochondrial inheritance

- Maternal inheritance
- Mitochondrial genes (13) + nuclear genes = control oxidative phosphorylation.
- Number of mitochondria varies in each cell.
- Mutations associated with:
  1. LHON: liver heridetary optic neuropathy
  2. MELAS: myopathy, encephalopathy, lactic acidosis, strokes
  3. MERRF: Myoclonic epilepsy with ragged red fibers

### uniparental disomy

- Inheritance of both members of a chromosome pair from one parent
- By loose of a chromosome (trisomy)- non-disjunctionor duplication of a chromosome ( monosomy)
- This child is homozygous for all genes in the chromosome.
- So child can show an AR disorder even though one of the parents is not a carrier.
- Examples: Cystic fibrosis, Prader willi syndrome, angelman syndrome,
- Male-male transmition of X linked disorders (XY from the father, or XXY with loss of maternal X chromosome)

## Germinal musaicism.

- Mosaicism is the presence of both normal cells and abnormal cells carrying a mutation within a single individual.
- Somatic or germinal
- Germial musaicism:
  - it may passed to offspring
  - not carried by somatic cells
  - detected only if expressed on offspring
  - important because parents may have more than one child with the same mutation.

# MODIFIERS OF INHERITANCE PATTERNS

### Genomic imprinting

- a process of deferential expression of a genetic material depending whether the material has come from male or female parents
- an allele is imprintable when it is capable of being suppressed in its expression by either maternal or parenta; factors , possibly another gen or genes.
- Examples: 15p delection in **Prader willi** and **angelman syndromes**.

### Anticipation

- Progressively manifestations or more severe expression of a disease with succeeding generations.
- Used to be explained as the result of greater awareness of genetic diseases and an increased ability of diagnosis earlier.
- Recently biological basis for the phenomena has been discovered
- In at least 2 disorders ( fragile X syndrome & myotonic dystrophy ) the gene mutation is a repeated trinucleotide sequence that lies in the untranselated portion of the gene.
- The region is transcribed but not translated
- The number of these repeats correlates directly with disease severity and may increase with successive generations.

# INDICATIONS FOR CHROMOSOMAL ANALYSIS:

1. multiple malformations
2. features of Down syndrome
3. mental retardations and several minor malformations
4. ambiguous genetalia
5. recurrent spontaneous abortions or unexplained
6. parents chromosomal analysis in infertility ( causes: 1/3 idiopathic, 1/3 mother, 1/3 father)

# CHROMOSOMAL DISORDERS

- Errors that occur in meiosis, during the production of the gametes, can lead to abnormalities of chromosome structure or number.
- Chromosomal abnormalities cause disorders such as Down syndrome, trisomy 13, trisomy 18, Turner syndrome, and Klinefelter syndrome
- rarer chromosomal duplications, deletions, or inversions.
- Chrom. abnormalities occur in 8% of fertilized ova, but only in 0.6% of live-born infants.
- 50% of spontaneous abortuses have chromosomal abnormalities.
- **The most common aneuploidy chromosomal abnormality found in fetuses is Turner syndrome** (45,X). 99% of 45,X fetuses are spontaneously aborted.
- The fetal loss rate for Down syndrome, the most viable of autosomal aneuploidies=80%.
- Most other chromosomal abnormalities also severely affect fetal viability.
- features suggest the presence of chromosome anomalies, including:
  1. low birth weight (small for gestational age)
  2. failure to thrive
  3. developmental delay
  4. presence ≥3 congenital malformations.

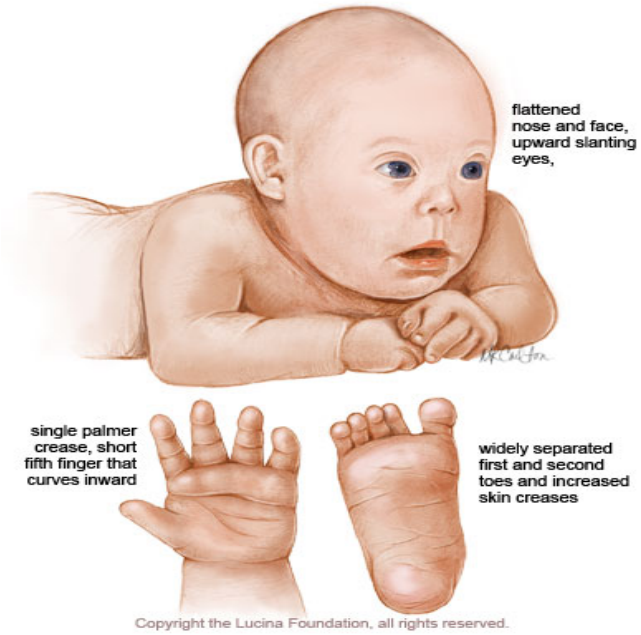
## ABNORMALITIES IN NUMBER (ANEUPLOIDY)

- During meiosis or mitosis, failure of a chromosomal pair to separate properly results in nondisjunction.
- **Aneuploidy** is a change in the number of chromosomes as a result of nondisjunction.
- A cell may have one (**monosomy**) or three (**trisomy**) copies of a particular chromosome.

### TRISOMIES

#### DOWN SYNDROME

- **the most common of all the abnormalities of chromosomal number**.( most common chromosome disorder) Occurring in 1 of every 800 births.
- **the single most common genetic cause of moderate mental retardation**.
- Genatics defect:
  1. **nondisjunction**: most cases (92.5%); in 80%, the nondisjunctional event occurs in maternal meiosis phase I= 47,XX,+21 or 47,XY,+21.
  2. **robertsonian translocation** : In 4.5% of cases, the extra chromosome 21 is part of a robertsonian translocation, which occurs when the long arms (q) of two acrocentric chromosomes (chromosomes 13, 14, 15, 21, or 22) fuse at the centromeres, and the short arms (p), containing copies of ribosomal RNA, are lost. The most common is between 14 and 21= 46,XX,t (14q21q) or 46,XY,t (14q21q).
  3. **mosaicism**: In 3% of cases. There are two populations of cells: one with trisomy 21 and one with a normal complement of chromosomes. nondisjunction event occurs after fertilization and after a few cell divisions or from what is referred to as **trisomic rescue-** The loss of this aneuploidy returns the normal, "rescues" this cell. This is a rescue not of the entire organism, but of some of the cell lines = 47,XX,+21/46XX or 47,XY,+21/46,XY. mildly affected, with wide variations in the clinical findings of these individuals.
- Children with Down syndrome are most likely to be diagnosed in the newborn period.
  1. normal birth weight and length
  2. **hypotonia** : may cause feeding problems and decreased activity
  3. characteristic facial appearance (hypoplastic midface, flattened nasal bridge, upward slanting palpebral fissures, epicanthal folds, and large protruding tongue)
  4. **brachycephaly**, flattened occiput
  5. short broad hands often with a transverse palmar crease
  6. wide gap between the first and second toes.
  7. 40% have **congenital heart disease**. Mostly by endocardial cushion defects, atrioventricular canal, ventriculoseptal or atrioseptal defects, and valvular disease.
  8. 10% of newborns have **gastrointestinal tract anomalies**. The three most common defects are: **duodenal atresia, annular pancreas** & **imperforate anus**.
  9. 1% are found to have **congenital hypothyroidism**. **Acquired hypothyroidism** is a more common problem.




## Clinical Findings That May Be Present with Trisomy 21

- Stature smaller than peer age group
- Developmental delays
- Congenital heart disease (e.g., endocardial cushion defect and ventricular septal defect)
- Structural abnormalities of the bowel (e.g., **tracheoesophageal fistula**, duodenal atresia, annular pancreas, duodenal web, and **Hirschsprung disease**)
- Central hypotonia
- Brachycephaly
- **Delayed closure of fontanels**
- Small midface, hypoplastic frontal sinuses, myopia, and **small (short) ears**
- Lax joints, including laxity of the atlantoaxial articulation (the latter predisposing to **C1-2 dislocation**)
- Short, broad hands, feet, and digits; single palmar crease, **clinodactyly**
- Exaggerated space between first and second toe
- Velvety, loosely adhering mottled skin (cutis marmorata) in infancy; coarse, dry skin in adolescence
- Statistically increased risk for **leukemia <1%**, **Alzheimer disease**, **hypothyroidism**

- **Polycythemia** at birth (hematocrit levels >70%) is common and may require treatment.
- Some show a **leukemoid reaction**, with white blood cell counts of 100,000/mm$^3$. Resembles congenital leukemia, self-limited condition over the first month of life.
- ↑risk for **leukemia** for children with Down syndrome. 10 to 18 times the risk of individuals without Down syndrome.
  - In children < 1 year of age, congenital and infantile leukemia is **acute nonlymphoblastic leukemia.**
  - In > 3 years, the types of leukemia are similar to children without Down syndrome, the predominant type being **acute lymphoblastic leukemia**.
- Down syndrome patients also are more susceptible to infection.
- more likely to develop **cataracts**.
- more prone to **Conductive and/or sensorineural hearing loss**
- more prone to **diabetes mellitus, Obesity, Celiac disease, Epilepsy & ADHD**
- Most males with Down syndrome are sterile; some females have been able to reproduce.
- 10% have **atlantoaxial instability**, an increased distance between the first and second cervical vertebrae, which may predispose to spinal cord injury.
- Most individuals > 35 years of age develop **Alzheimer-like features**.
- 75% are born to women < 35 years old. Because only 5% of all infants are born to women older than 35, but 25% of Down syndrome infants are born to women > 35.
  - The occurrence of trisomy 21 as well as other autosomal trisomies increases with advanced maternal age (≥35 yr).

- Four pregnancy-related markers are studied to develop a risk profile for infant with Down syndrome(second trimester):
  1. maternal serum AFP- ↓
  2. uE3: unconjugated estriol
  3. inhibin A
  4. HCG
  - ♦ This is a screening test; it is able only to identify women who are at increased risk for having an infant with Down syndrome and other trisomies
  - ♦ Amniocentesis should be offered to women who are identified by the screening test to be at increased risk.

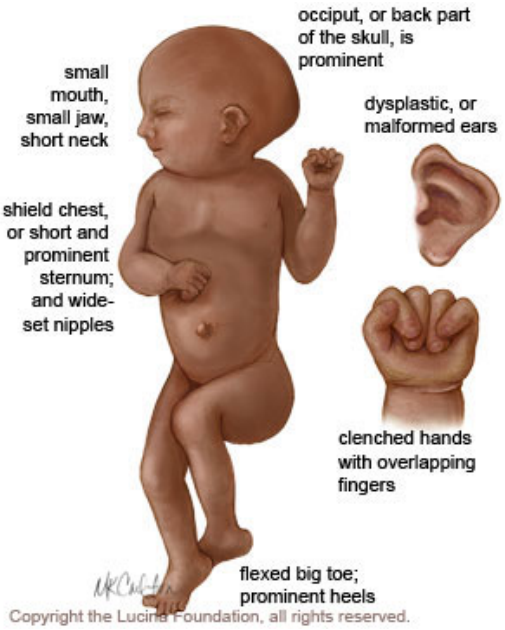
**NOTE:**
↑maternal serum α-fetoprotein (MSAFP):
1. open neural tube defects
2. spinal befida
3. anencephaly
4. Defects of the GI (failure abdominal wall closure) & GU systems.

↓ : Down syndrome & Edward syndrome

- The recurrence risk for parents who have had a child with Down syndrome depends on the child's cytogenetic findings:
  1. If 47,XX,+21 or 47,XY,+21 (i.e., trisomy 21), the recurrence risk = 1% (added to the age-specific risk for women <35 years old; use just the age-specific risk for women >35 years old).
  2. If a translocation, chromosomal analysis of both parents must be performed. In 65% of cases, the translocation is spontaneously, both parents = normal karyotypes, in 35% of cases, one of the parents has a balanced translocation.
     - ♦ if the mother is the carrier, the risk of recurrence is 10%- 15%
     - ♦ if the father is the carrier, risk is 2%- 5%.

## TRISOMY 18

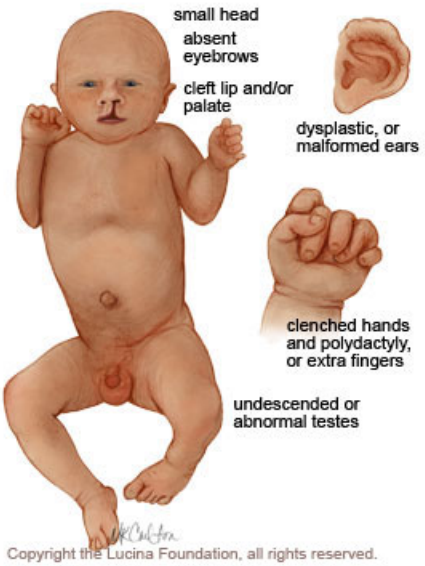
- Trisomy 18 (47,XX,+18 or 47,XY,+18) is the second most common autosomal trisomy.
- occurring in 1 in 7500 live births.
- more common among conceptuses, but > 95% of trisomy 18 conceptuses are spontaneously aborted in the first trimester.
- Trisomy 18 is usually lethal; < 10% of affected infants survive until their first birthday.
- As a result of this poor prognosis, many clinicians favor limited medical intervention for the prolongation of life.
- Clinical features include:
  1. Most are small for gestational age
  2. hypertonia
  3. prominent occiput
  4. receding jaw
  5. low-set and malformed ears
  6. short sternum
  7. rocker-bottom feet
  8. hypoplastic nails
  9. characteristic clenching of fists-the second and fifth digits overlap the third and fourth digits





## TRISOMY 13

- The third of the "common trisomies," trisomy 13 (47,XX,+13 or 47,XY,+13)
- occurring in 1 in 12,000 live births.
- It is usually fatal in the first year of life; only 8.6% of infants survive beyond their first birthday.
- Clinical feature:
  1. small for gestational age
  2. microcephalic
  3. Midline facial defects, such as cyclopia (single orbit), cebocephaly (single nostril), and cleft lip and palate are common
  4. midline CNS anomalies, such as alobar holoprosencephaly.
  5. The forehead is sloping



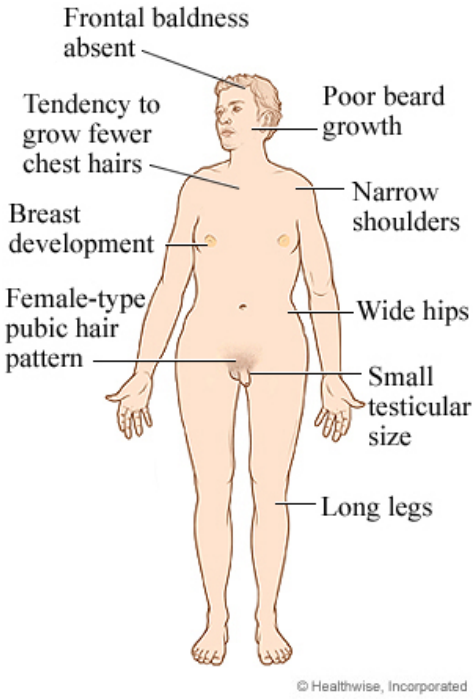
6. ears are often small and malformed
7. microphthalmia or anophthalmia may occur.
8. Postaxial polydactyly of the hands is common
9. clubfeet or rocker-bottom feet
10. Hypospadias and cryptorchidism are common in boys, whereas girls have hypoplasia of the labia minora.
11. Most infants have congenital heart disease
12. punched-out scalp lesion over the left or right occiput called **aplasia cutis congenita**; is pathognomonic for the diagnosis of trisomy 13.

## Findings That May Be Present in Trisomy 13 and Trisomy 18

| | TRISOMY 18 | TRISOMY 13 |
|---|---|---|
| Head and face | Small and premature appearance | **Scalp defects (e.g., cutis aplasia)** |
| | Tight palpebral fissures | Microphthalmia, corneal abnormalities |
| | Narrow nose and hypoplastic nasal alae | **Cleft lip and palate in 60%-80%** of cases |
| | Narrow bifrontal diameter | Microcephaly |
| | Prominent occiput | Microphthalmia |
| | Micrognathia | Sloping forehead |
| | Cleft lip or palate | **Holoprosencephaly (arhinencephaly)** |
| | Microcephaly | **Capillary hemangiomas** |
| | | **Deafness** |
| Chest | Congenital heart disease (e.g., VSD, PDA, and ASD) | **Congenital heart disease** (e.g., VSD, PDA, and ASD) in **80% of cases** |
| | Short sternum, small nipples | **Thin posterior ribs (missing ribs)** |
| Extremities | **Limited hip abduction** | |
| | Clinodactyly and overlapping fingers; index over 3rd, 5th over 4th; closed fist | Overlapping of fingers and toes (clinodactyly)**, Polydactyly** |
| | **Rocker-bottom feet** Hypoplastic nails | Hypoplastic nails, hyperconvex nails |
| General | Severe developmental delays and prenatal and postnatal growth retardation | Severe developmental delays and prenatal and postnatal growth retardation |
| | Premature birth, **polyhydramnios** | ***Renal abnormalities*** |
| | **Inguinal or abdominal hernias** | **Nuclear projections in neutrophils** |
| | Only 5% live longer than 1 year | Only 5% live longer than 6 mo |

## KLINEFELTER SYNDROME

- occurs in 1 in 1000 male births
- **the most common cause of hypogonadism and infertility in males**
- **the most common sex chromosome aneuploidy in humans**
- caused by the presence of an extra X chromosome (47,XXY)=80% .
- The extra X chromosome arises from a nondisjunction in either the sperm or the egg.
- 15% of boys with Klinefelter syndrome are found to be mosaic. 46,XY/47,XXY, but 48,XXYY, 48,XXXY, and 49,XXXXY have been observed.
- The increasing number of X chromosomes is associated with increasing risk of **mental retardation and more dysmorphic features.**
- Prepubertal boys with Klinefelter syndrome appear normal.
- The diagnosis is most often made when the boy is 15 or 16 years old.
  1. progressive development of pubic and axillary hair in the presence of **infantile levels testicular volume** .
  2. Adolescents and young adults tend to be tall, **with long arms and legs**.
  3. During adolescence or adulthood, **gynecomastia** occurs= 50%.
  4. testosterone deficiency and **failure to produce viable sperm & develop later secondary sexual characteristics**, such as development of facial hair, deepening of the voice, and libido.
  5. In adulthood, **osteopenia** and **osteoporosis** develops, so testosterone supplementation is indicated.
- all children born to these men using testicular biopsy, coupled with in vitro fertilization this have had a normal chromosome complement.

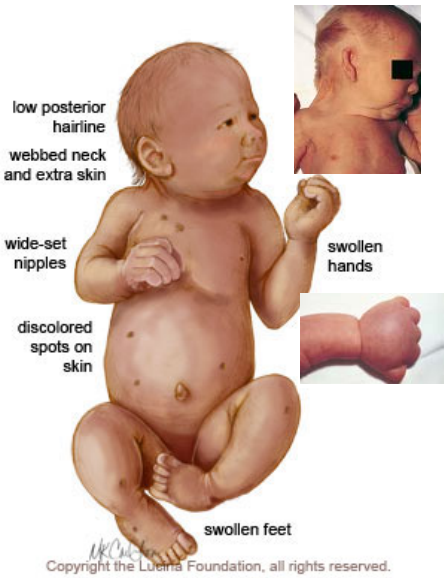




## MONOSOMIES

### TURNER SYNDROME

- Turner syndrome is the only condition in which a monosomic conceptus survives to term
- 99% of embryos with a 45,X karyotype are spontaneously aborted.
- The most common aneuploidy found in studies of conceptuses (accounting for 1.4%, whereas Down syndrome accounts 0.5% of conceptions)
- 45,X fetuses account for 13% of first-trimester pregnancy losses.
- Occurring in 1 in 3200 live female births.
- lack of significant physical or developmental disabilities.
- Women with Turner syndrome have normal intelligence and normal life expectancy.
- Females with Turner syndrome typically have:
  1. **characteristic facial appearance** with low-set, mildly malformed ears triangular-appearing face; flattened nasal bridge; and epicanthal folds.
  2. **webbing of the neck**, with or without **cystic hygroma**
  3. **shieldlike chest with widened internipple distance**
  4. **puffiness of the hands and feet.**
  5. **Congenital heart defect** in 45% (coarctation of the aorta is most common, followed by bicuspid aortic valve; later in life, poststenotic aortic dilation with aneurysm may develop).
  6. **Renal anomalies**, including horseshoe kidney and duplication of the collecting system, >50%.
  7. **Short stature** is a cardinal feature of this condition.
  8. **hypothyroidism** is estimated to occur five times more than in the general population.

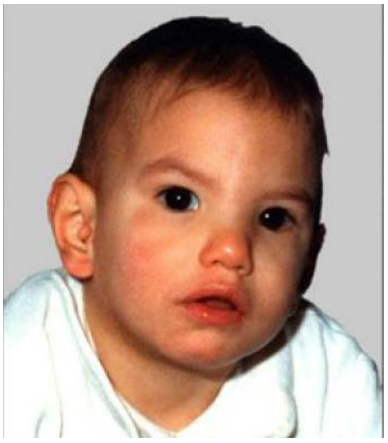


9. **streak gonads (gonadal dysgenesis)** → estrogen deficiency→no secondary sexual characteristics→**amenorrhea**. 10% have normal pubertal development and fertile, in most estrogen replacement require to complete 2nd sexual development.

- The infertility in these women is not corrected by estrogen replacement
- Assisted fertilization technology, using donor ova, has allowed women with Turner syndrome to bear children.
- An adverse effect of pregnancy on the aorta may hasten the development of an aortic aneurysm and the resulting dissection.
- 33% of children with Turner syndrome are diagnosed soon after birth, usually because of congenital heart disease and physical features, such as a webbed neck and puffy hands and feet
- 33% are diagnosed in childhood, often during a workup for short stature
- the final 33% are diagnosed during adolescence, when they fail to develop secondary sexual characteristics.
- The karyotypic spectrum in girls with Turner syndrome is wide.
  - 50% have a 45,X karyotype
  - 15% have an isochromosome Xq, designated 46,X,i(Xq), in which one X chromosome is represented by two copies of the long arm (leading to a trisomy of Xq and a monosomy of Xp)
  - 25% are mosaic, 45,X/46,XX or 45,X/46,XY
  - deletions involving the short (p) arm of the X chromosome (Xp22) can produce the short stature and congenital malformations, and deletions involving Xq often produce only gonadal dysgenesis.
- Turner syndrome is **not associated with advanced maternal or paternal age**. It is a mitotic (rather than meiotic) nondisjunction.

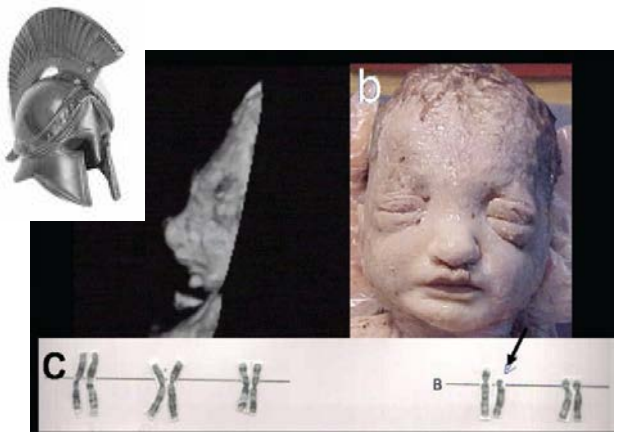
## SYNDROMES INVOLVING CHROMOSOMAL DELETIONS

### CRI DU CHAT SYNDROME



- A deletion of the **short arm of chromosome 5** is responsible for cri du chat syndrome
- clinical features include:
  1. **Characteristic catlike cry** during early infancy, result of tracheal hypoplasia.
  2. low birth weight and postnatal failure to thrive
  3. **hypotonia**
  4. developmental delay
  5. **microcephaly**
  6. craniofacial dysmorphism, including ocular **hypertelorism, epicanthal folds, downward obliquity of the palebral fissures**
  7. low-set malformed ears
  8. **Clefts of the lip and plate**
  9. **congenital heart disease**

### WOLF-HIRSCHHORN SYNDROME




- Partial deletion of **chromosome 4p**.
  1. Marked prenatal and postnatal **growth retardation**
  2. **severe mental retardation**
  3. **abnormal facies** ("Greek helmet"-frontal bossing, high anterior hairline, hypertelorism, ptosis, epicanthal folds)
  4. **microcephaly**
  5. **upward slanted palpebral fissures**
  6. **large, low-set ears** , with preauricular pits or tags
  7. **coloboma** of the iris
  8. **Genital abnormalities,** such as cryptorchidism, scrotal hypoplasia, and hypospadias, are common.

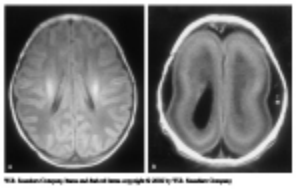
9. **Seizures** are common, occurring in most, if not all. often beginning in the first 2 years of life.

## Williams Syndrome

- Generally easily recognized, is due to a **small deletion of chromosome 7q11**.
- Most children have a de novo deletion, few are from parent in an AD-like pattern.
  1. Congenital heart disease in 80% of affected children, with **supravalvar aortic and pulmonic stenosis and peripheral pulmonic stenosis being the most common**.
  2. normal birth weight, but poor growth, manifesting **short stature**.
  3. **unusual facial appearance**, with median flare of the eyebrows, fullness of the perioral and periorbital region, blue irides with a stellate pattern of pigment, and depressed nasal bridge with anteversion of the nares.
  4. **Moderate mental retardation** (average IQ in the 50 to 60 range) is common
  5. **striking personality**. Loquacious and gregarious, they are frequently described as having a "cocktail party" personality
  6. 10% of children with Williams syndrome have classic features of **autism**.
  7. Patients often have **remarkable musical ability**.

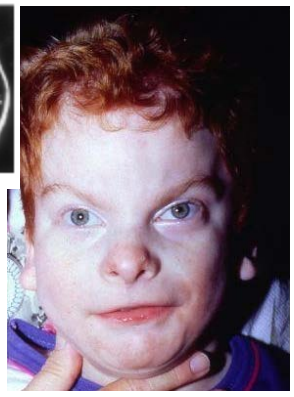
## Aniridia Wilms Tumor Association (WAGR Syndrome)

- WAGR syndrome (**W**ilms tumor, **a**niridia, **g**enitourinary anomalies, and mental **r**etardation) is caused by a de novo **deletion of 11p13**
- Wilms tumor develops in 50% of patients with **aniridia**, genitourinary abnormalities, and **mental retardation**.
  1. Genitourinary abnormalities include **cryptorchidism and hypospadias**.
  2. often have **short stature**.
  3. 50% **microcephaly**.



## Miller-Dieker Syndrome

- Brain abnormalities + dysmorphic facial features.
  1. brain smooth surface and lack of gyri (lissencephaly).
  2. Facial features : bitemporal narrowing, high forehead, occasional vertical ridging of the forehead, small upturned nose, upward slanting palpebral fissures, protuberant upper lip with a thin vermilion border, and low-set and posteriorly rotated ears.
- A deletion of 17p13.3 has been documented in most individuals with Miller-Dieker syndrome.



## Chromosome 22 Deletions

- **Velocardiofacial syndrome**, **conotruncal anomaly face syndrome**, and **DiGeorge syndrome** all are due to deletions of chromosome 22q11.
- There are overlapping clinical findings, and it may be that there is one 22q11.2 syndrome with variant phenotypes rather than three relatively distinct syndromes.

### Velocardiofacial Syndrome

- An AD disorder
- common clinical features include:
  1. **clefting of the palate with velopharyngeal insufficiency**
  2. **conotruncal cardiac defects**
  3. **characteristic facial appearance**: large prominent nose and a broad nasal root.
  4. Speech and language difficulties are common
  5. **mild intellectual impairment**.
  6. 70% have **immunodeficiencies**, largely related to T cell dysfunction.
  7. A wide spectrum of **psychiatric disturbances**, including schizophrenia and bipolar disorder, has been seen in > 33% of affected adults.
- most cases are sporadic, resulting from a de novo deletion, AD inheritance is seen sometimes.

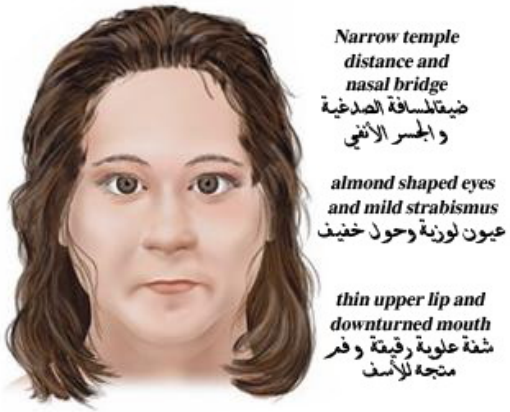
**DiGeorge Syndrome**

- DiGeorge syndrome describes neonatal onset of symptoms with:
  1. **conotruncal cardiac abnormalities**
  2. **hypocalcemia**
  3. **hypoplasia of thymus & parathyroid glands→ immunodeficiency** and in hypocalcemia.
  4. **Dysmorphic features** : micrognathia, cleft palate, velopalatal insufficiency, low-set ears, and hypertelorism.
  5. **mild to moderate mental retardation**.
- There are reports of a similar clinical picture with exposure to alcohol or isotretinoin .

## PRADER-WILLI SYNDROME

- disorder caused by a deletion or disruption of genes in the proximal arm of chrom.15
  1. **Neonatal hypotonia** is one of the hallmark features of this disorder
  2. **poor suck** (with requirement of gavage feedings)
  3. Children aged 1-6 years present with symptoms of **hyperphagia with progressive development of obesity**
  4. **Characteristic facial features** such as narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, and down-turned mouth
  5. **Mild mental retardation is common/ late acquisition of major motor milestones**
  6. **hypogonadism**
  7. **weak cry**
  8. **genital hypoplasia** (eg, cryptorchidism, scrotal hypoplasia, clitoral hypoplasia).
  9. **Sleep disturbances**, ranging from central or obstructive sleep apnea to narcolepsy
  10. **growth hormone deficiency**
  11. Obesity complications (eg, sleep apnea, cor pulmonale, DM, atherosclerosis)
  12. **Small hands and feet**
  13. **Thick viscous saliva**
  14. **Skin picking** (Some patients with PWS have become anemic from chronic rectal bleeding secondary to skin picking.)
  15. **Hypopigmentation**

**NOTE:**
From 1-6 its considered major criteria for PWS diagnosis.



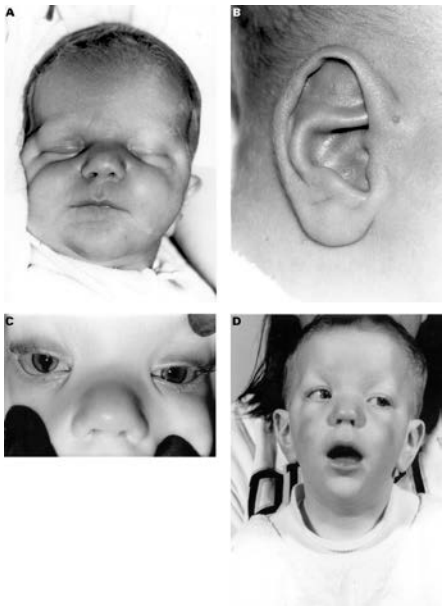

## ANGELMAN SYNDROME

## SYNDROMES INVOLVING CHROMOSOME DUPLICATION

### INVERTED DUPLICATION CHROMOSOME 15

### CAT EYE SYNDROME

- Cat eye syndrome is due to duplication of 22q11.
  1. **iris coloboma** that gives patients' eyes a catlike appearance.< 50% of patients
  2. mild mental retardation or normal intelligence with emotional retardation
  3. **mild hypertelorism**
  4. **downward slanting palpebral fissures**
  5. **micrognathia**
  6. **auricular pits or tags or both & renal agenesis**.
  7. **anal atresia with rectovestibular fistula**



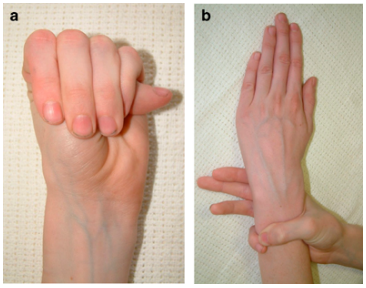
# OTHERS:

## ACHONDROPLASIA

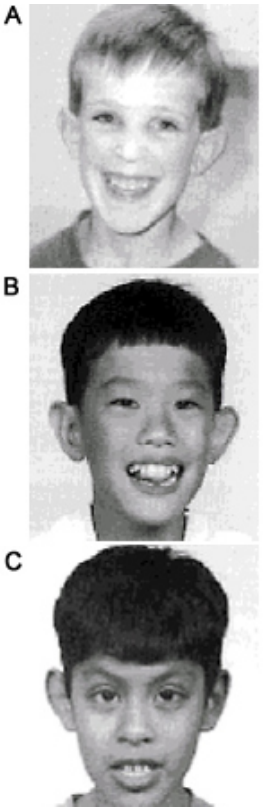
- AD
- Most common skeletal dysplasia
  1. short stature
  2. macrocephaly
  3. flat mid-face with prominent forehead
  4. hearining loss: cause frequent episodes of otitis media.
  5. teeth malocclusion
  6. The limb shortening is greatest in the proximal segments
  7. chest is small compared with the abdomen.
  8. normal life span and intelligence
  9. hyperextensible joints, but extension is restricted at the elbow.

## MARFAN SYNDROME

- autosomal dominantly inherited disorder
- The diagnosis of Marfan syndrome is based on the overall pattern of malformation (typically skeletal, cardiovascular, ocular)
- **Neonatal (infantile, congenital) Marfan syndrome** is more severe than cases observed in older children presenting with:
  1. **hypotonia**
  2. **arachnodactyly**
  3. **joint laxity** and dislocations**,** flexion contractures.
  4. **The face is long**
  5. the **skin is lax** with diminished recoil.
  6. The ears may appear large and pliant.
  7. **Ocular**: disclose megalocornea, iridodonesis, or frank lens dislocation.
  8. **Cardiac** : murmurs of either mitral valve prolapse (MVP) with regurgitation or aortic insufficiency, and aortic root dilatation - echocardiographically.
- Older individuals display :
  1. **tall stature**
  2. **long, thin face** with narrowness of the maxilla and **dental crowding**.
  3. **Ocular abnormalities** : blue sclerae, myopia in 60% of affected individuals, and suspensory ligament laxity with iridodonesis.
  4. **musculoskeletal system** :discloses dolichostenomelia (long, thin limbs), and the arm span exceeds the height (>1.05 times height). The lower segment (distance from pubis to heel) is increased in comparison to the upper segment → diminished upper segment: lower segment ratio ($U_s/L_s$).
  5. **Hand findings** : nonspecific and include long, thin fingers (arachnodactyly) that are hyperextensible.
  6. The thumb may be adducted across the narrow palm (**Steinberg sign**) -A
  7. appreciably overlap the 5th finger when encircling the wrist (**wrist sign**) -B
  8. Long gracile ribs may contribute to various sternal anomalies including **pectus excavatum** ("funnel chest") or **pectus carinatum** ("pigeon breast").
  9. The risk of **scoliosis** among adolescents is increased.
  10. The connective tissue defect →↑ distensibility of lung parenchyma and dura and increases the risks of **spontaneous pneumothorax and dural ectasia**.



## FRAGILE X SYNDROME




- the most common cause of inherited mental retardation and is the second most common cause of genetically associated mental deficiencies after trisomy 21.
- The pattern of inheritance most closely resembles X-linked dominance with variable penetrance.
  1. 20% of male and 5% of female → **seizure disorder**, 50% having persistent seizures that require anticonvulsant therapy. The onset of seizures is 6-24 months.
  2. **Macroorchidism** is universal in adult males
  3. **mild-to-severe mental retardation**
  4. **mitral valve prolapse** is often auscultated
  5. **Autisticlike behavior** in 16-30% of patients
  6. long, thin face with prominent ears, facial asymmetry and a prominent forehead and jaw.
  7. hyperextensible finger joints, hand calluses, double-jointed thumbs, a single palmar crease, and pes planus.
  8. dental overcrowding and a high-arched palate
  9. head circumference > 50th percentile
  10. developmental milestones are achieved as expected or are slightly delayed

# THE APPROACH TO THE DYSMORPHIC CHILD

- **Dysmorphology** is the recognition of the pattern of congenital malformations and dysmorphic features that characterize a particular syndrome.
- **Syndromes** are collections of abnormalities, including **malformations**, **deformations** dysmorphic features, and abnormal behaviors that have a unifying, identifiable etiol

## DEFINITIONS

- **Congenital malformations** are defined as clinically significant abnormalities in eith form or function.
  1. **localized intrinsic** defects in morphogenesis as a result of an event that occurr embryonic or early fetal life. it is often due to mutations in developmental genes
  2. **Extrinsic** factors may cause **disruptions** of the development of apparently norı tissues. include amniotic bands, interruption or disruption of blood supply to developing tissues, or exposure to teratogens.
- **Malformation sequence** is the end result of a malformation that has secondary effects on later developmental events.
  - An example is the **Pierre Robin sequence**. The primary malformation, the failure of the growth of the mandible during the first weeks of gestation→ micrognathia.
    - Micrognathia forces the tongue( normal in size) into an unusual position.
    - tongue blocks the fusion of the palatal shelves = U-shaped cleft palate .
    - After delivery, the normal-sized tongue in the smaller than normal oral cavity leads to **airway obstruction and obstructive apnea**.
- **Deformations** arise as a result of environmental forces acting on normal structures. They occur later in pregnancy or after delivery.
  - Oligohydramnios inhibit lung growth and cause compression of fetal structures, producing clubfoot, dislocated hips, and flattened facies
- **Minor malformations** are variants of normal that occur in < 3% of the population and include findings such as transverse palmar creases, low-set ears, or hypertelorism; when isolated they have no clinical significance.
- A **multiple malformation syndrome** is the recognizable pattern of anomalies that results from a single identifiable underlying cause. It may involve a series of malformations, malformation sequences, and deformations.
- **Dysmorphology** is the art of recognizing the pattern of multiple congenital anomalies that occurs with various malformation syndromes

## Glossary of Selected Terms Used in Dysmorphology

| **Terms Pertaining to the Face and Head** |
|---|
| *Brachycephaly:* Condition in which head shape is shortened from front to back along the sagittal plane; the skull is rounder than normal |
| *Canthus:* The lateral or medial angle of the eye formed by the junction of the upper and lower lids |
| *Columella:* The fleshy tissue of the nose that separates the nostrils |
| *Glabella:* Bony midline prominence of the brows |
| *Nasal alae:* The lateral flaring of the nostrils |
| *Nasolabial fold:* Groove that extends from the margin of the nasal alae to the lateral aspects of the lips |
| *Ocular hypertelorism:* Increased distance between the pupils of the two eyes |
| *Palpebral fissure:* The shape of the eyes based on the outline of the eyelids |
| *Philtrum:* The vertical groove in the midline of the face between the nose and the upper lip |
| *Plagiocephaly:* Condition in which head shape is asymmetric in the sagittal or coronal planes; can result from asymmetry in suture closure or from asymmetry of brain growth |
| *Scaphocephaly:* Condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic |
| *Synophrys:* Eyebrows that meet in the midline |
| *Telecanthus:* A wide space between the medial canthi |
| **Terms Pertaining to the Extremities** |
| *Brachydactyly:* Condition of having short digits |
| *Camptodactyly:* Condition in which a digit is bent or fixed in the direction of flexion (a "trigger finger"-type appearance) |
| *Clinodactyly:* Condition in which a digit is crooked and curves toward or away from adjacent digits |
| *Hypoplastic nail:* An unusually small nail on a digit |
| *Melia:* Suffix meaning "limb" (e.g., amelia-missing limb; brachymelia-short limb) |
| *Polydactyly:* The condition of having six or more digits on an extremity |
| *Syndactyly:* The condition of having two or more digits at least partially fused (can involve any degree of fusion, from webbing of skin to full bony fusion of adjacent digits) |

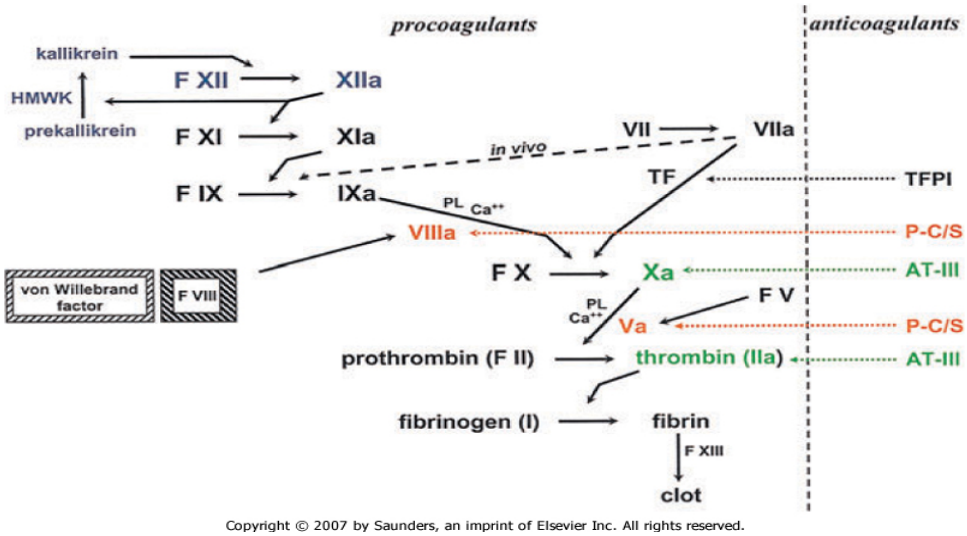
# Diseases of the Blood

## Haemostatic disorders and Anemia

# HEAMOSTATIC DISORDERS

## HEMOSTASIS

- active process that clots blood in areas of blood vessel injury
- Main components of the hemostatic process are the **VESSEL WALL, PLATELETS, COAGULATION PROTEINS, ANTICOAGULANT PROTEINS,** AND **FIBRINOLYTIC SYSTEM.**





VASCULAR INJURY → VASOCONSTRICTION → FLOWING BLOOD COMES IN CONTACT WITH THE SUBENDOTHELIAL MATRIX → VON WILLEBRAND FACTOR (VWF) CHANGES CONFORMATION AND PROVIDES THE GLUE TO WHICH THE PLT VWF RECEPTOR BINDS → PLATS ACTIVATED → RELEASE STORAGE GRANULES (ADP), THROMBOXANE $A_2$ → TRIGGER THE AGGREGATION (BY INTERACTION OF RECEPTORS AND FIBRINOGEN) AND RECRUITMENT OF PLT → PLATELET PLUG.

- vascular injury → tissue factor exposed→ binds to factor VII → activates clotting cascade
- internalized platelet phospholipids (primarily phosphatidylserine) externalized and interact at 2 specific, rate-limiting steps in the clotting process:
  1. cofactors factor VIII (X-ase complex)
  2. factor V (prothrombinase complex).
- Thrombin (II):
  1. clots fibrinogen into fibrin
  2. activates factors V, VIII, and XI
  3. Aggregates platelets.
  4. activates factor XIII
- The stable fibrin-platelet plug is ultimately formed by clot retraction and cross linking of the fibrin clot by factor XIIIa.
- 4 clinically important anticoagulants that regulate the extension of the clotting process include:
  1. antithrombin III (AT-III), regulates factor Xa and thrombin primarily, to a lesser extent, factors IXa, XIa, and XIIa
  2. protein C inactivates factor Va and factor VIIIa
  3. protein S: a cofactor for protein C activation
  4. tissue factor pathway inhibitor (TFPI) quickly shuts down the activation of factor X by factor VII and tissue factor and shifts the activation site to factor IX
- Plasmin, generated from plasminogen by plasminogen activator, degrades the fibrin clot. regulated by plasminogen activator inhibitors and $\alpha_2$-antiplasmin
- **DISSEMINATED INTRAVASCULAR COAGULATION:** procoagulant clotting factors and anticoagulant proteins are consumed or under-produced , leaving the hemostatic system unbalanced and prone to bleeding or clotting. Ex: sepsis, severe liver disease.

## HISTORY

### HEMORRHAGIC CONDITION

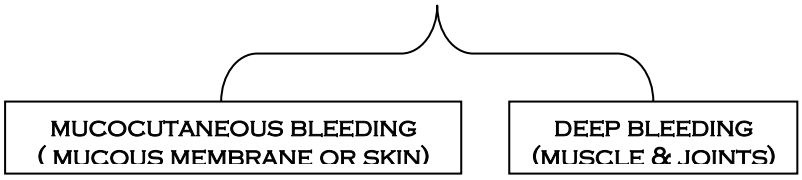
- the site or sites of bleeding
- the severity and duration of hemorrhage
- the age at onset.
- Was the bleeding spontaneous, or did it occur after trauma?
- Was there a previous personal or family history of similar problems?
- Did the symptoms correlate with the degree of injury or trauma?
- Does bruising occur spontaneously?
- Are there lumps with bruises for which there is minimal trauma?
- If the patient had previous surgery or significant dental procedures, was there any increased bleeding?
- If a child or adolescent has had surgery affecting the mucosal surfaces, such as a tonsillectomy or major dental extractions, the absence of bleeding usually rules out a hereditary bleeding disorder.
- Slow healing of superficial injuries may suggest a hereditary bleeding disorder.
- In postpubertal females, take menstrual history. as von Willebrand disease (VWD), have a fairly high prevalence, mothers and family members may have the same mild bleeding disorder and not be cognizant child's menstrual history abnormal.
- Women with mild VWD who have a moderate history of bruising frequently have a reduction of bruising in pregnancy or with oral contraceptives.
- aspirin and other NSAID drugs inhibit platelet function and increase bleeding symptoms in patients with a low platelet counts.

### THROMBATIC DISORDERS

- Outside the neonatal period, thrombotic disorders are relatively rare until adulthood
- the presence of thrombosis in the child or teenager should trigger an evaluation of the individual for a hereditary or acquired predisposition to thrombosis.
- detailed family history to evaluate for DVT, pulmonary emboli, MI, or stroke.

## PHYSICAL EXAMINATION

### HEMORRHAGIC CONDITION




- the presence of petechiae, ecchymoses, hematomas, hemarthroses, or mucous membrane bleeding.
- Patients with defects in platelet-blood vessel wall interaction (VWD or platelet function defects) usually have mucocutaneous bleeding, include:
  1. epistaxis
  2. menorrhagia
  3. petechiae, ecchymoses
  4. occasional hematomas
  5. hematuria and gastrointestinal bleeding.
- Individuals with a clotting factor deficiency, such as hemophilia (factor VIII or factor IX deficiency), have symptoms of deep bleeding into muscles and joints:
  1. hemarthroses
  2. extensive ecchymoses and hematoma formation.
- Patients with mild VWD have no abnormal findings on physical examination.

- Individuals with disorders of the collagen matrix and vessel wall may have loose joints and lax skin associated with easy bruising (Ehlers-Danlos syndrome).

### THROMBOTIC DISORDERS

- swollen, warm, tender extremities
- unexplained dyspnea or persistent "pneumonia," especially in the absence of fever (pulmonary emboli)
- varicosities and post-phlebitic changes.
- Arterial thrombi usually cause an acute, dramatic impairment of organ function, such as stroke, MI, or a painful, white, cold extremity.

## LABORATORY TESTS

1. BLEEDING TIME: assesses the function of platelets and their interaction with the vascular wall. prolongation qualitative platelet defect or VWD. bleeding usually stops within 4-8 min.
2. PLATELET COUNT: thrombocytopenia is the most common acquired cause of a bleeding diathesis in children. count of >50,000/$mm^3$ have noclinical bleeding. Thrombocytosis in children is reactive and is not associated with bleeding or thrombotic complications.
3. PT is not prolonged with deficiencies of factors VIII, IX, XI, or XII. In most laboratories, normal PT is 10-13 sec.
4. INTERNATIONAL NORMALIZED RATIO (INR) so that values can be compared from 1 laboratory or instrument to another.
5. PTT measures the initiation of clotting at the level of factor XII through sequential steps to the final clot end-point. does not measure factor VII, factor XIII, or anticoagulants.
6. THROMBIN TIME measures the final step in the clotting cascade, in which fibrinogen is converted to fibrin. 11-15 sec. Prolongation with reduced fibrinogen levels (*hypofibrinogenemia* or *afibrinogenemia*), dysfunctional fibrinogen (*dysfibrinogenemia*), heparin, DIC, uremia or fibrin split products.
7. REPTILASE TIME uses snake venom to clot fibrinogen. not sensitive to heparin and is *prolonged only by reduced or dysfunctional fibrinogen and fibrin split products*.
8. MIXING STUDIES: Normal plasma is added to the patient's plasma, and PT or PTT is repeated. Correction of PT or PTT by 1:1 mixing with normal plasma suggests deficiency of a clotting factor, because a 50% level of individual clotting proteins is sufficient to produce normal PT or PTT.

# CLOTTING FACTORS DISORDERS

## VON WILLEBRAND DISEASE

- The most common hereditary bleeding disorder
- VWD is inherited autosomally( AD>AR)
- VWD is classified on :
  1. protein is quantitatively reduced, but not absent (type 1)- The most common form.
  2. qualitatively abnormal (type 2)
  3. absent (type 3)
- functions of VWD:
  1. platelets adhere to VWF through their glycoprotein IB (GPIb) receptor.
  2. VWF serves as the carrier protein for plasma factor VIII.

## CLINICAL MANIFESTATIONS

- symptoms of **mucocutaneous hemorrhage,** including excessive bruising, epistaxis, menorrhagia, and postoperative hemorrhage, particularly after mucosal surgery.
- because others in the family may be affected with the same disorder, teenager's menstrual history is usually recognized as being abnormal,
- VWF is an acute-phase protein, stress will increase its level, patients not bleed with major stress, such childbirth, but may bleed excessively with mucosal surgery.
- Bruising symptoms may diminish during pregnancy because VWF levels may double or triple during pregnancy
- patients with VWD may have gastrointestinal telangiectasia
- type 3, or homozygous, VWD, bleeding symptoms are much more profound. may have joint hemorrhages or spontaneous CNS hemorrhages.

## LABORATORY FINDINGS

- if history is suggestive of a mucocutaneous bleeding disorder, testing should including:
  1. quantitative assay for VWF antigen
  2. testing for VWF activity (ristocetin cofactor activity)
  3. testing for plasma factor VIII activity
  4. determination of VWF structure (VWF multimers)
  5. platelet count.
- bleeding time and a long partial thromboplastin time are normal in type 1 VWD.
- type 2B disease("hyperactive" VWF=rapid clearance of VWF and platelets) or platelet-type disease (pseudo-VWD=abnormality of the GPIb receptor on platelets) may have lifelong thrombocytopenia
- Levels of VWF vary with blood type (type O < A < B < AB)

## TREATMENT

- increasing the plasma level of VWF and factor VIII
- In type 1 & some patients with type 2 , the synthetic drug DDAVP induces the release of VWF from endothelial cells.
- replacement therapy(HUMATE P):
  - ✓ type 3 and some variants of type 2
  - ✓ plasma-derived VWF containing concentrates contain factor VIII
  - ✓ 1 U/kg will increase the plasma level by 1.5%.
  - ✓ The plasma half-life of both factor VIII and VWF is 12 hr
- Avoid aspirin

## VITAMIN K DEFICIENCY

1972 SC

- Vitamin K deficiency is the most common hemorrhagic disease
- It is recommended to give 0.5-1 mg IV Vitamin K at birth
- Neonates who is breast feeded with no prophylactic vit. K are in the highest risk for hemorrhagic dz.
- Incidence 2-10 days of life.
- ICH, GI bleeding, bleeding from umbilical stump, generalized echymoses.
- Lab: ↑PT, ↑PTT, may ↓VII
- after the neonatal period is usually secondary to:
  1. a lack of oral intake of vitamin K
  2. alterations in the gut flora due to the long-term use of broad-spectrum antibiotics
  3. malabsorption of vitamin K accompany cystic fibrosis or biliary atresia reduced synthesis of vitamin K-dependent clotting factors (factors II, VII, IX, and X, and protein C and protein S).

  ✓ Prophylactic administration of water-soluble vitamin K orally is indicated in these cases (2-3 mg/24 hr for children / 5-10 mg/24 hr for adolescents and adults), or 1-2 mg IV.
- Advanced cirrhosis, synthesis of many of the clotting factors reduced so vitamin K is ineffective.
- warfarin (Coumadin) and related anticoagulants depend on interference with vitamin K, with a concomitant reduction of factors II, VII, IX, and X.
- Rat poison (superwarfarin); is a specific vitamin K antidote.
- TTT: correct nutritional disorder and malabsorbtion. In severe bleeding give: FFP + prothrombin complex concentrate (II,VII,IX,X)

## DISSEMINATED INTRAVASCULAR COAGULATION

- consumption of clotting factors, platelets, and anticoagulant proteins.
- Consequences include widespread intravascular deposition of fibrin→TISSUE ISCHEMIA AND NECROSIS+ generalized HEMORRHAGIC STATE AND HEMOLYTIC ANEMIA.
- Any life-threatening pathologic process associated with hypoxia, acidosis, tissue necrosis, shock, and/or endothelial damage may trigger DICincluding:
  1. septic shock (especially meningococcemia)
  2. incompatible blood transfusion
  3. rickettsial infection
  4. snakebite
  5. giant hemangioma
  6. acute promyelocytic leukemia

NOTE:
for activation of coagulation and fibrinolysis.
- ✓ The D-dimer = FDP test in sensitivity
- ✓ D-dimer more specific

### CLINICAL MANIFESTATIONS

- Bleeding frequently first occurs from sites of venipuncture or surgical incision.
- The skin may show petechiae and ecchymoses.
- Tissue necrosis most seen as infarction of skin, subcutaneous tissue, or kidneys.
- Anemia caused by hemolysis owing to microangiopathic hemolytic anemia.

### LABORATORY FINDINGS

- (factors II, V, and VIII, and fibrinogen) and platelets
- prolongation of PT,PTT, and thrombin times.
- The blood smear may contain fragmented, burr-, and helmet-shaped red blood cells (schistocytes).

- fibrinolytic mechanism is activated, fibrinogen degradation products (FDPs, D-dimers) appear in the blood.

### TREATMENT

- The first 2 steps in the treatment of DIC are the most critical:

1. treat the trigger that caused DIC and
2. restore normal homeostasis by correcting the shock, acidosis, and hypoxia that usually complicate DIC.

- If the underlying problem can be controlled, bleeding quickly ceases and abnormal laboratory findings improve.
- Blood components are used for replacement therapy in patients with hemorrhage.

✓ platelet infusions (for thrombocytopenia)
✓ cryo-precipitate (for hypofibrinogenemia)
✓ fresh frozen plasma (for replacement of other coagulation factors and natural inhibitors).

- heparin in DIC is limited to patients who have vascular thrombosis in association with DIC

## FACTOR VIII OR FACTOR IX DEFICIENCY (HEMOPHILIA A OR B)

- Deficiencies of factors VIII and IX are the most common SEVERE inherited bleeding disorders

### CLINICAL MANIFESTATIONS

- Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus
- 2% of neonates with hemophilia sustain intracranial hemorrhages and 30% of male infants bleed with circumcision
- With severe hemophilia, only 90% have evidence of increased bleeding by 1 yr of age
- hemophilia has a high rate of spontaneous mutation and so may go undiagnosed in the newborn.
- Obvious symptoms of easy bruising, intramuscular hematomas, and hemarthroses begin when the child "begins to cruise
- Bleeding from minor traumatic lacerations of the mouth (a torn frenulum) may persist for hr or days and may cause the parents to seek medical evaluation
- The hallmark of hemophilia is **hemarthrosis.** . The earliest joint hemorrhages appear most commonly in the ankle.
- Complain of a warm, tingling sensation in the joint as the first sign of an early joint hemorrhage.
- Repeated bleeding episodes into the same joint develop a "target" joint.
- Recurrent bleeding may then become spontaneous because of the underlying pathologic changes in the joint.
- Most muscular hemorrhages are clinically evident owing to localized pain or swelling, bleeding into the iliopsoas muscle requires specific mention.

✓ Patients may lose large blood volumes into **iliopsoas muscle** → hypovolemic shock
✓ vague area of referred pain in the groin.
✓ The hip is held in a flexed, internally rotated position due to irritation of the iliopsoas.
✓ The diagnosis is made clinically by the inability to extend the hip

- Life-threatening bleeding is by bleeding into vital structures (central nervous system, upper airway) or by exsanguination (external, gastrointestinal, or iliopsoas hemorrhage).

- Life-threatening hemorrhages require replacement therapy to achieve a level equal to that of normal plasma (100 IU/dL, or 100%).
- Patients with mild hemophilia who have factor VIII or factor IX levels of >5 IU/dL usually do not have spontaneous hemorrhages= prolonged bleeding after surgery OR moderate trauma.

## LABORATORY FINDINGS AND DIAGNOSIS

- reduced level of factor VIII or factor IX is PTT.
- In severe hemophilia, PTT is usually 2-3 times the upper limit of normal. platelet count, bleeding time, prothrom-bin time, and thrombin time are normal.
- Unless the patient has an inhibitor (ATB,heparin) to factor VIII or IX, the mixing of normal plasma with patient plasma results in correction of PTT.
- The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia
- quantitative Bethesda assay for inhibitors to measure the antibody titer as 25-35% of hemophilia patients who receive infusions of factor VIII or factor IX, a factor-specific antibody may develop , termed *inhibitors*

## GENETICS AND CLASSIFICATION

- Hemophilia occurs in approximately 1:5,000 males, with 85% having factor VIII deficiency and 10-15% having factor IX deficiency.
- mL of normal plasma has 100 IU/dL (100% activity) of each factor. term *% activity* = percentage found in normal plasma.
- The hemostatic level for factor VIII is >30-40%, and for factor IX, it is >25-30%.
- The lower limit of levels for factors VIII and IX in normal individuals is approximately 50%.
- TYPES:

1. SEVERE HEMOPHILIA <1% activity of the specific clotting factor, and bleeding is spontaneous.
2. MODERATE HEMOPHILIA levels of 1-5% and require mild trauma to induce bleeding.
3. MILD HEMOPHILIA have levels of >5%, may go many years before diagnosed, and require significant trauma to cause bleeding

- cause lyonization of the X chromosome= **some female carriers** of hemophilia A or B have sufficient reduction of factor VIII or factor IX to produce mild bleeding disorders.

## TREATMENT

- mild to moderate bleeding occurs, levels of factor VIII or factor IX must be raised to hemostatic levels in the 35-50% range.
- For life-threatening or major hemorrhages, the dose should aim to achieve levels of 100% activity.
- Calculation of the dose of recombinant factor VIII (FVIII) or recombinant factor IX (FIX) is as follows:

$$\text{Dose of FVIII (IU)} = \%\ \text{desired (rise in FVIII)} \times \text{Body weight (kg)} \times 0.5$$

$$\text{Dose of FIX (IU)} = \%\ \text{desired (rise in plasma FIX)} \times \text{Body weight (kg)} \times 1.4$$

- A concentrated intranasal form of DESMOPRESSIN ACETATE (STIMATE) can also be used to treat patients with mild hemophilia A.(synthetic vasopressin ↑ factor 8 by 4 times)

NOTE:

Deficiency of the "contact factors" (factor XII, prekallikrein, and high molecular weight kininogen) causes prolonged PTT, but no bleeding symptoms. Which are imp. Only to do the lab test. No ttt.

NOTE:

- ✓ Factor XIII has no effect on both PT and PTT
- ✓ Factor XII is asymptomatic.

NOTE:

FACTOR XI DEFICIENCY (HEMOPHILIA C)

- ✓ autosomal deficiency associated with mild to moderate bleeding symptoms
- ✓ fewer clinical symptoms in combination with longer PTT is surprising IN SEVERE CASES.
- ✓ TTT: fresh frozen plasma (FFP).

NOTE:

DEFICIENCIES IN THE FACTORS OF THE COMMON PATHWAY (FACTORS I, II, V, AND X) CAUSING PROLONGATION OF BOTH PT AND

NOTE:

FACTOR XIII DEFICIENCY (FIBRIN-STABILIZING FACTOR OR TRANSGLUTAMINASE DEFICIENCY)

- ✓ delayed hemorrhage
- ✓ mild bruising, delayed separation of the umbilical stump beyond 4 wk, poor wound healing, and recurrent spontaneous abortions in women

NOTE:

FACTOR VII DEFICIENCY

- ✓ spontaneous intracranial hemorrhage and frequent mucocutaneous bleeding.
- ✓ markedly prolonged PT but normal PTT

NOTE:

DEFICIENCY OF FACTOR V PARAHEMOPHILIA

- ✓ autosomal recessive
- ✓ mild to moderate bleeding disorder

# Platelet Function Disorders

- Bleeding time and the platelet function analyzer (PFA-100) are the only available tests to screen for abnormal platelet function.
- Bleeding time measures the interaction of platelets with the blood vessel wall and thus is affected by both platelet count and platelet function.
  - ✓ is dependent on the skill of the technician and the cooperation of the patient.
  - ✓ A normal bleeding time does not rule out mild platelet function defect in a clinically symptomatic individual.
  - ✓ Bleeding time is the only commonly available test to assess platelet-vessel wall interaction
- The PFA-100 measures platelet adhesion and aggregation in whole blood when the blood is exposed to either collagen-epinephrine or collagen-ADP.
  - ✓ More sensitive than bleeding time.
  - ✓ PFA-100 value is prolonged in VWD as well as in congenital and acquired platelet function defects.
- Both bleeding time and the PFA-100 detect moderate to severe von Willebrand disease and platelet function defects.

## Acquired Disorders of Platelet Function

- Systemic illnesses most commonly, liver disease, kidney disease (uremia), and disorders that trigger increased amounts of fibrin degradation products.
  - ✓ The most important element of management is to treat the primary illness.
  - ✓ infusions of desmopressin augmenting hemostasis and correcting bleeding time
  - ✓ transfusions of platelets and/or cryoprecipitate
- Drugs. The most commonly used drug in adults is acetylsalicylic acid (aspirin), NSAIDs, valproic acid, and high-dose penicillin.

## Congenital Abnormalities of Platelet Function

- Severe platelet function defects present with petechiae and purpura shortly after birth, especially after vaginal delivery.
- Defects in the platelet GPIb complex (the VWF receptor) or the GPIIb-IIIa complex (the fibrinogen receptor) cause *severe congenital platelet dysfunction*

### A. Bernard-Soulier syndrome

- ✓ inherited as an autosomal recessive disorder.
- ✓ absence or severe deficiency of the VWF receptor (GPIb complex) on the platelet.
- ✓ This syndrome is characterized by thrombocytopenia, with giant platelets and markedly prolonged bleeding time (>20 min).
- ✓ Platelet aggregation by ristocetin-induced test is absent as it induces the binding of VWF to platelets, but other agonists aggregation are normal.

### B. Glanzmann thrombasthenia

- ✓ this disorder is inherited in an autosomal recessive manner.
- ✓ caused by deficiency of the platelet fibrinogen receptor GPIIb-IIIa
- ✓ Prolonged bleeding time and normal platelet count.
- ✓ Platelets have normal size and morphologic features on the peripheral blood smear.
- ✓ Aggregation studies show abnormal or absent aggregation with all agonists used except ristocetin because ristocetin does not require a metabolically active platelet.

C. Dense body deficiency : absence of the granules contain ADP, ATP, $Ca^{2+}$, serotonin.

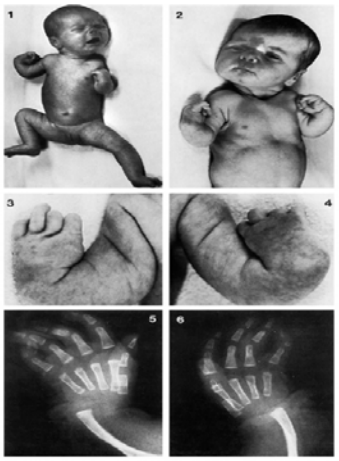
D. Gray platelet syndrome is caused by the absence of platelet α granules, resulting in platelets that appear gray on Wright stain of peripheral blood.

## DISORDERS OF THROMBOCYTOPENIA

- plt counts ↓ 150.000 mm3
- mucocutanous bleeding is the hallmark for platlets disorders
- 80.000 mm3 or less : withstand all except major truma or surgery.
- Less than 20.000 mm3 will have spontaneous bleeding
- Etiology:
  1. ↓ Plt production
  2. ↓Plt destruction
  3. sequestration

### THROMPOCYTOPENIA OF DECREASE PRODUCTION:

1. CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA
   - ✓ rare defect in hematopoiesis, manifests in the first few days to wk of life
   - ✓ Child presents with petechiae and purpura caused by profound thrombocy-topenia.
   - ✓ Bone marrow shows an absence of megakaryocytes.
   - ✓ These patients often progress to marrow failure (aplasia) over time.
   - ✓ Ttt: bone marrow transplantation
2. THROMBOCYTOPENIA-ABSENT RADIUS (TAR) SYNDROME
   - ✓ autosomal recessive disorder.
   - ✓ consists of thrombocytopenia (absence or hypoplasia of megakaryocytes)
   - ✓ Presents in early infancy with bilateral radial anomalies of variable severity, ranging from mild changes to marked limb shortening.
   - ✓ other skeletal abnormalities of the ulna, radius, and lower extremities.
   - ✓ Thumbs are present.
   - ✓ Intolerance to cow's milk formula (PRESENT IN 50%) complicate management by gastrointestinal bleeding, increased thrombocytopenia, eosinophilia, and leukemoid reaction.
   - ✓ The thrombocytopenia of TAR syndrome frequently remits over the first few yr of life.




3. APLASTIC SYNDROME 'primary disorder'
4. PANCYTOPENIA FROM BONE MARROW FAILURE (acquired)- infiltrate or aplastic.
5. CYANOTIC HEART DISEASES WITH POLYCYTHEMIA
6. VIRAL INFECTIONS: HIV, EBV, MEASLES/ Transient
7. DRUGS: heparine, quinidine, anti-convulsants, cytotoxic agents.
8. TORCH: prolonged decrease in Plt.

### THROMPOCYTOPENIA OF INCREASE DESTRUCTION :

1. IDIOPATHIC THROMBOCYTOPENIC PURPURA
   - ✓ most common cause of acute onset of thrombocytopenia in an otherwise well child

ETIOLOGY
- ✓ 1-4 wk after exposure to a common viral infection, an autoantibody directed against the platelet surface develops→ distracted in spleen (50-65%)
- ✓ Most common infectious viruses described in association with ITP= Epstein-Barr virus
- ✓ Autoimmune thrombocytopenia may be an initial manifestation of SLE, HIV infection, or rarely, lymphoma.
- ✓ Approximately 20% of patients who present with acute ITP have persistent thrombocytopenia for >**6 mo** and are said to have chronic ITP (THINK OF: SLE, HIV, type 2B and platelet-type von Willebrand disease, X-linked thrombocytopenia, WAS)

CLINICAL MANIFESTATIONS
- ✓ classic presentation of ITP is that of a previously healthy 1-4 yr old child who has sudden onset of generalized petechiae and purpura.
- ✓ Often there is bleeding from the gums and mucous membranes
- ✓ Splenomegaly, lymphadenopathy or pallor are rare.

LABORATORY FINDINGS

- ✓ Severe thrombocytopenia (platelet count <20 × $10^9$/L) is common
- ✓ platelet size is normal or increased
- ✓ hemoglobin value, white blood cell (WBC) count, and differential count should be normal.
- ✓ Hemoglobin may be decreased if there have been profuse nosebleeds or menorrhagia.
- ✓ Bone marrow examination is normal with characteristically normal or increased numbers of megakary-ocytes (do if atypical presentation- after 2 weeks of steroids).

TREATMENT

- ✓ No therapy other than education and counseling of the family and patient for patients with minimal, mild, and moderate symptoms **(80% spontaneous resolution )**
- ✓ TREATMENT WITH:
  1. IV-IG (1g/kg/d) - 1-2 days
  2. iv ANTI-D for RH+( 50-75ug/kg/dose)
  3. Prednisone (2-4mg/kg/day) for 2 WEEK

  ALL INCREASE PLT COUNTS WITHIN 2 DAYS BUT IN PRESENCE OF CONTINOUS DISTRUCTION.
- ✓ platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present
- ✓ The role of splenectomy in ITP should be reserved for 1 of 2 circumstances.
  1. The older child (≥ 4 yr) with severe ITP that has lasted >1 yr (chronic ITP)
  2. symptoms are not easily controlled with therapy
- ✓ Splenectomy is successful in inducing complete remission in 64-88% of children with chronic ITP

## 2. HEMOLYTIC-UREMIC SYNDROME

- ✓ acute disease of infancy and early childhood
- ✓ follows an episode of acute gastroenteritis, often triggered by *Escherichia coli* 0157:H7.
- ✓ signs and symptoms of hemolytic anemia, thrombocytopenia, and acute renal failure
- ✓ Sometimes neurologic symptoms.
- ✓ Thrombocytopenia= (toxin → endothelial injury→Plt activation → Plt clearance)
- ✓ elevated levels of D-dimer
- ✓ Treatment :
  1. careful fluid management and prompt appropriate dialysis.
  2. plasma-pheresis is usually reserved for patients with HUS associated with major neurologic complications.

## 3. THROMBOTIC THROMBOCYTOPENIC PURPURA

- ✓ fever, microangiopathic hemolytic anemia, thrombocytopenia, abnormal renal function, and central nervous system changes ( ACQUIRED OR CONGENITAL)
- ✓ TTP vs HUS :
  1. TTP presents in adults and occasionally in adolescents.
  2. metalloproteinase( v-WB cleavage) in TTP is low , HUS are normal= THROMBOTIC MICROANGIOPATHY
- ✓ Treatment of TTP is plasmapheresis (plasma exchange), effective in 80-95%. Corticosteroids and splenectomy are reserved for refractory cases.

4. DIC
5. THROMOTIC MICROANGIOPATHY: intravascular RBC destruction (anemia, ↓Plt, ↓Clotting factors)

## SEQUESTRATION

- ✓ Thrombocytopenia, mild leukopenia and anemia on CBC.
- ✓ etiology of splenomegaly, including infectious, inflammatory, infiltrative, neoplastic, obstructive, and hemolytic causes.

## HEMATOPOIESIS:

- Developmental hematopoiesis occurs in three anatomic stages:
  1. **Mesoblastic hematopoiesis** occurs in the yolk sac, begins between the 10th and 14th days of gestation.
  2. **Hepatic hematopoiesis** starts by 6th week of gestation. The liver remains the predominant hematopoietic organ through wk 20-24 of gestation
  3. **(myeloid) hematopoiesis** started by 12 wk. the liver production begins to diminish during the second trimester as bone marrow increases.

- ERYETHROTHROPOIETIN(EPO): is a hormone that regulates RBC production. EPO does not cross the placenta (SO maternal erythropoiesis has no effect of the fetus- stimulation or suppression).
- ✓ Antenataly produced in the liver.
- ✓ Postnataly it is produced by the kidney
- Erythropoiesis in utero is controlled by fetal erythroid growth factors.
- Fetal bone marrow space begins to develop around the 8th week post conception. Space start to enlarge by 8-10wks.
- Differentiation of RBC is regulated by:
- ✓ EPO
- ✓ IL-1
- ✓ GM-CSF

NOTE:
The zeta (ζ) chains of Hb Portland and Gower-1 are structurally similar to α chains.Both genes present in chrom. 16.

- HEMOGLOBINL: is a complex protein consists of iron containing heme & globin.
- ✓ each Hb molecule (tetramer) consists of tow pairs of polypeptide chains. with each chain having a heme group attached
- ✓ The major hemoglobin of a normal adult (Hb A), is made up of one pair of alpha (α) and one pair of beta (β) polypeptide chains, $\alpha_2\beta_2$
- ✓ The major hemoglobin in the fetus (Hb F), two alpha and two gamma globin chains, $\alpha_2\gamma_2$
- ✓ Two pairs of alleles for α & ζ chains are located on human chromosome16.
- ✓ The β, γ, δ, epsi genes are closely linked on chromosome 11.
- ✓ (RBC) mass of an embryo, fetus, child, and adult, six different hemoglobins:
  1. EMBRYONIC HEMOGLOBINS Gower-1($\zeta_2$[epsi ]$_2$), Gower-2($\alpha_2$[epsi ]$_2$), and Portland($\zeta_2\gamma_2$) - embryos of 4-8 wk gestation, the Gower hemoglobins predominate, but by the 3rd month they have disappeared.
  2. FETAL HEMOGLOBIN, Hb F ($\alpha_2\gamma_2$). Resists alkali denaturation (Kleihauer-Betke test). 8th wk ges Hb F is the predominant hemoglobin→ 6th months of ges 90% → birth 70% → 6-12 mo < 2.0%.
  3. ADULT HEMOGLOBINS,
     - Hb A($\alpha_2\beta_2$) 6th months of ges **5-10%** →at term **30%** →6-12 mo of age**>95%**
     - Hb $A_2$ ($\alpha_2\delta_2$). contains is seen only when significant amounts of Hb A are present. At birth **<1.0%** → 12 mo of age **<3.4%.**
     - Throughout life, the normal ratio of Hb A to $A_2$ is about 30:1.
  - ✓ Prenatal diagnosis is possible for all types of Hb abnormalities via chorionic villous sampling (diagnosis of major β-chain hemoglobinopathies → 16-20 wk gestation)
  - ✓ ALTERATIONS OF THE HEMOGLOBINS BY DISEASE
    - HB GROWER → trisomy 13 &15
    - HB PORTLAND→ α thalasemia
    - HB F →β thalasemia , sickle cell anemia, hemolytic, leukemia,aplastic anemia)
    - Tetramers of γ chains ($\gamma_4$ or Hb Barts) or β chains ($\beta_4$, Hb H) in α-thalassemia.
    - HB A2 increase in β thalassemia and megaloplastic anemia (B12 and folic acid), Decrease in α-thalassemia and iron deficiency anemia
- ✓ The average life span for a neonatal RBC is 60-90 days
- ✓ When neonatal RBCs are transfused into adults they have short life span but from adult donor to a neonate they have normal life span.
- ✓ ↑prematurity, remarkably shorter red cell life spans (35-50 days) are found.
- ✓ THE SHORTENED RED CELL LIFE SPAN OF THE PRETERM AND TERM NEONATE EXPLAINED BY CHARACTERISTICS SPECIFIC TO NEWBORN CELLS:
  1. a rapid decline in ***intracellular enzyme activity and ATP***;
  2. loss of membrane ***surface area*** by internalization of membrane lipids;

3. decreased levels of ***intracellular carnitine***
4. increased susceptibility of membrane lipids and proteins to ***peroxidation***
5. Increased mechanical fragility due to increased ***membrane deformability***.

## ANEMIA

- Defined as a reduction of the red blood cell (RBC) volume or hemoglobin concentration below normal values.
- Anemia can occur with normal Hb values in cases of : cyanotic cardiac or pulmonary diseases or if high affinity for oxygen is present
- Clinical manifestations depend on level of Hb, rapidity of onset, compensatory mechanisms and duration of anemia.
  - ✓ if Hb >7-8 there is little manifestations.
  - ✓ If <7 pallor appears.
- Compensatory mechanisms due to anemia:
  1. ↑cardiac output ( tachycardia)
  2. ↑oxygen extraction (increased arteriovenous oxygen difference)
  3. shunting of blood flow toward vital organs and tissues
  4. ↑concentration of 2,3-diphosphoglycerate (2,3-DPG) in the RBC→ "shift to the right" of the oxygen dissociation curve.
  5. ↑erythropoietin (EPO
- Acute anemia manifested by: tachycardia, cardiac flow murmur, poor exercise tolerance, headache, excessive sleeping, poor feeding and syncope.
- Congenital hemolytic disorders (enzyme or membrane problems) present in the first 6 months of life, associated with neonatal jaundice.
- Drug history is important in case of G6pd deficiency, bone marrow suppression, antibody mediated hemolysis)
- Physical examination:
  1. Physiological stability: tachycardia and hypotension with altered level of consciousness: bleeding.
  2. jaundice: hemolysis
  3. hepatosplenomegaly: bleeding tendency
  4. growth failure : anemia of chronic disease
- Thrombocytopenia, abnormalities in white blood cell numbers, or the presence of abnormal leukocytes → bone marrow failure (aplastic anemia, leukemia, or other malignant marrow disease).
- The most characteristic feature of hemolysis is reticulocytosis with indirect hyperbilirubinemia and increased serum lactate dehydrogenase
- Peripheral blood smear shows abnormal RBC morphology (e.g., spherocytes, sickle forms, microangiopathy) in hemolysis.
- With a ↓reticulocyte response, analysis [MCV] is useful.
- Distinguishing feature of thalassemia trait and iron deficiency is that RBC count is higher than normal along with the reduced hemoglobin and MCV.
- The anemia of renal failure is normocytic caused by reduced erythropoietin production.
- The most common cause of acquired pure red cell aplasia seen in pediatrics is transient erythroblastopenia of childhood, a normocytic anemia.
- RETICULOCYTE PRODUCTION INDEX: it is accuret interpretation of the reticulocyte count which assesses wither bone marrow responding appropriately to the degree of anemia = (reticulocyte count ×hematocrit⁄45 )÷2 ( if <2% = B12, folate, liver kidney or thyroid disease, if >2% normal marrow response = bleeding or hemolysis)
- According to the pathophysiology:
  1. ↓production of RBC( iron deficiency anemia, folate and B12 deficiency anemia, congenital hypoplastic and physiological anemia)
  2. ↑destruction(hemolysis)
  3. blood loss

NOTE:
Black children have levels about 0.5 g/dL lower than white and Asian children of perhaps in part as a result of the high incidence of α-thalassemia in blacks.

# Approach to assessing the common causes of anemia in children.

**Historical Clues in Evaluation of Anemia**

| Variable | Comments |
|---|---|
| Age | Iron deficiency rare in the absence of blood loss before 6 mo in term or before doubling birth weight in preterm infants |
| | Neonatal anemia with reticulocytosis suggests hemolysis or blood loss; with reticulocytopenia, suggests bone marrow failure |
| | Sickle cell anemia and β-thalassemia appear as fetal hemoglobin disappears (4-8 mo of age) |
| Family history and genetic considerations | X-linked: G6PD deficiency<br>Autosomal dominant: spherocytosis<br>Autosomal recessive: sickle cell anemia, Fanconi anemia |
| | Family member with early age of cholecystectomy (bilirubin stones) or splenectomy |
| | Ethnicity (thalassemia in individuals of Mediterranean origin; G6PD deficiency in blacks, Greeks, and Middle Eastern individuals) |
| | Race (β-thalassemia in individuals of Mediterranean, African, or Asian descent; α-thalassemia in blacks and those of Asian descent; SC and SS in blacks) |
| Nutrition | Cow's milk diet: iron deficiency |
| | Strict vegetarian: vitamin $B_{12}$ deficiency |
| | Goat's milk: folate deficiency |
| | Pica: plumbism, iron deficiency |
| | Cholestasis, malabsorption: vitamin E deficiency |
| Drugs | G6PD: oxidants (e.g., nitrofurantoin, antimalarials) |
| | Immune-mediated hemolysis (e.g., penicillin) |
| | Bone marrow suppression (e.g., chemotherapy) |
| | Phenytoin, increasing folate requirements |
| Diarrhea | Malabsorption of vitamins $B_{12}$ or E or iron |
| | Inflammatory bowel disease and anemia of chronic disease with or without blood loss |
| | Milk protein intolerance-induced blood loss |
| | Intestinal resection: vitamin $B_{12}$ deficiency |
| Infection | *Giardia:* iron malabsorption |
| | Intestinal bacterial overgrowth (blind loop): vitamin $B_{12}$ deficiency |
| | Fish tapeworm: vitamin $B_{12}$ deficiency |
| | Epstein-Barr virus, cytomegalovirus: bone marrow suppression, hemophagocytic syndromes |
| | *Mycoplasma:* hemolysis |
| | Parvovirus: bone marrow suppression |
| | HIV |
| | Chronic infection |
| | Endocarditis |
| | Malaria: hemolysis |
| | Hepatitis: aplastic anemia |

# Physical Findings in the Evaluation of Anemia

| System | Observation | Significance |
|---|---|---|
| Skin | Hyperpigmentation | Fanconi anemia, dyskeratosis congenita |
| | Café-au-lait spots | Fanconi anemia |
| | Vitiligo | Vitamin $B_{12}$ deficiency |
| | Partial oculocutaneous albinism | Chédiak-Higashi syndrome |
| | Jaundice | Hemolysis |
| | Petechiae, purpura | Bone marrow infiltration, autoimmune hemolysis with autoimmune thrombocytopenia, hemolytic uremic syndrome, hemophagocytic syndromes |
| | Erythematous rash | Parvovirus, Epstein-Barr virus |
| | Butterfly rash | SLE antibodies |
| Head | Frontal bossing | Thalassemia major, severe iron deficiency, chronic subdural hematoma |
| | Microcephaly | Fanconi anemia |
| Eyes | Microphthalmia | Fanconi anemia |
| | Retinopathy | Hemoglobin SS, SC disease |
| | Optic atrophy | Osteopetrosis |
| | Blocked lacrimal gland | Dyskeratosis congenita |
| | Kayser-Fleischer ring | Wilson disease |
| | Blue sclera | Iron deficiency |
| Ears | Deafness | Osteopetrosis |
| Mouth | Glossitis | Vitamin $B_{12}$ deficiency, iron deficiency |
| | Angular stomatitis | Iron deficiency |
| | Cleft lip | Diamond-Blackfan syndrome |
| | Pigmentation | Peutz-Jeghers syndrome (intestinal blood loss) |
| | Telangiectasia | Osler-Weber-Rendu syndrome (blood loss) |
| | Leukoplakia | Dyskeratosis congenita |
| Chest | Shield chest or widespread nipples | Diamond-Blackfan syndrome |
| | Murmur | Endocarditis: prosthetic valve hemolysis; severe anemia |
| Abdomen | Hepatomegaly | Hemolysis, infiltrative tumor, chronic disease, hemangioma, cholecystitis, extramedullary hematopoiesis |
| | Splenomegaly | Hemolysis, sickle cell disease, (early) thalassemia, malaria, lymphoma, Epstein-Barr virus, portal hypertension |
| | Nephromegaly | Fanconi anemia |
| | Absent kidney | Fanconi anemia |
| Extremities | Absent thumbs | Fanconi anemia |
| | Triphalangeal thumb | Diamond-Blackfan syndrome |
| | Spoon nails | Iron deficiency |
| | Beau line (nails) | Heavy metal intoxication, severe illness |
| | Mees line (nails) | Heavy metals, severe illness, sickle cell anemia |
| | Dystrophic nails | Dyskeratosis congenita |
| Rectal | Hemorrhoids | Portal hypertension |
| | Heme-positive stool | Gastrointestinal bleeding |
| Nerves | Irritable, apathy | Iron deficiency |
| | Peripheral neuropathy | Deficiency of vitamins $B_1$, $B_{12}$, and E, lead poisoning |
| | Dementia | Deficiency of vitamins $B_{12}$ and E |
| | Ataxia, posterior column signs | Vitamin $B_{12}$ deficiency |
| | Stroke | Sickle cell anemia, paroxysmal nocturnal hemoglobinuria |
| General | Small stature | Fanconi anemia, HIV, malnutrition |

# ANEMIA

## LOW RPI

### OTHER ABNORMALITIES.
aplastic anemia, leukemia

### MACROCYTIC

**MEGALOBLASTIC CHANGES**
folate or B12 deficiency or inborn error of metabolism

**NO,**
diamond blackfan anemia, pearson syndrome, congenital erythropoietic anemia

### MICROCYTIC
1. iron deficiency
2. thalssemia triat
3. hemoglobin EE dz
4. Lead poisons.

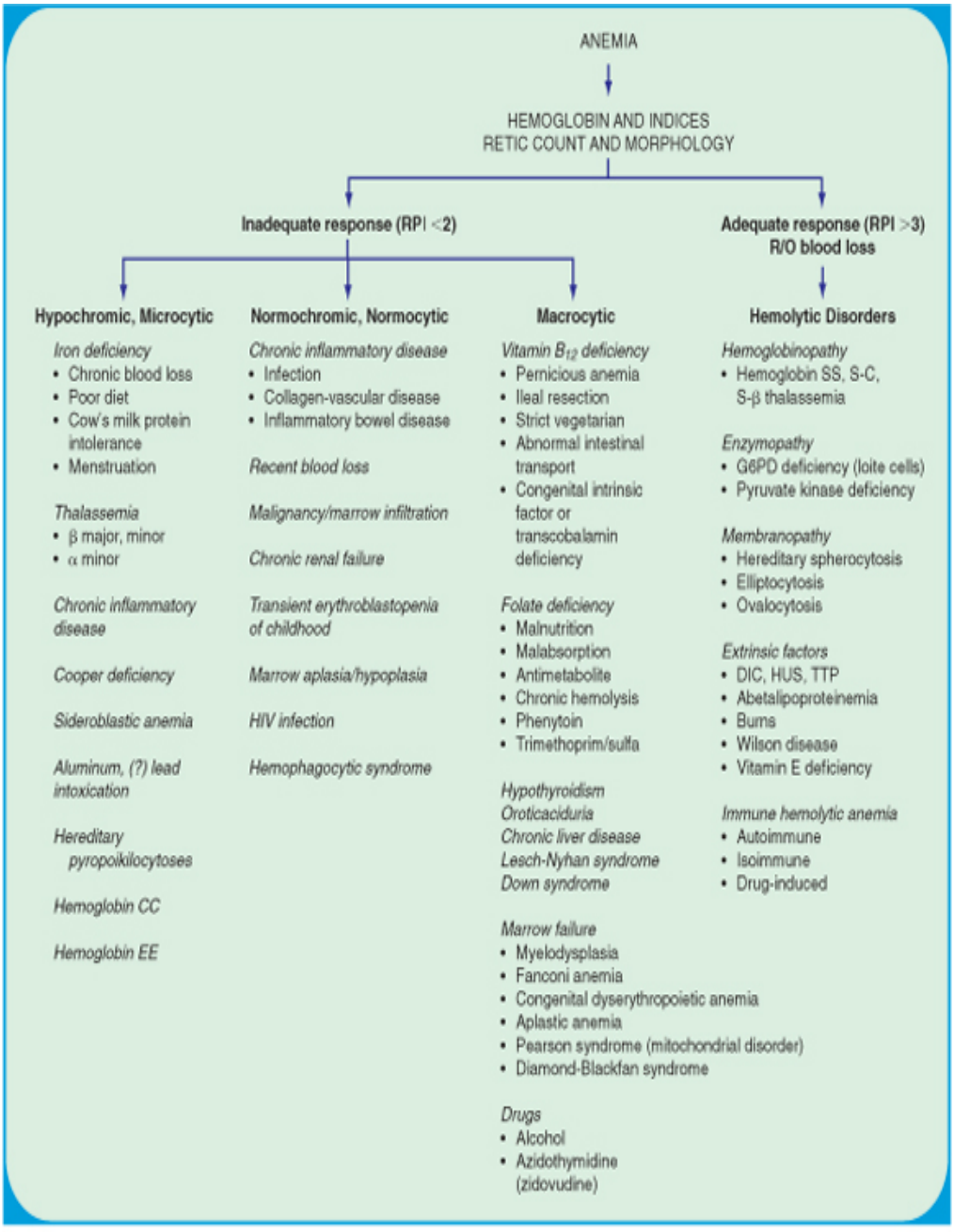
## HIGH RPI

### HEMOLYSIS OR BLEEDING.

**HYPERBILIRUBINEMIA OR INCREASE LDH ( HEMOLYSIS)**

**REVIEW PERIPHERAL BLOOD SMEAR**

1. spherocytes: hereditary sphyerocytosis, autoimmune hemolytic anemia, Wilson disease
2. sickle form( sickle cell disease or sickle – B thalassemia
3. target cells ( SC hemoglobin disease)
4. hypochromic RBC, nucleated RBC ( homozygous B thalassemia m HB E-B thalassemia
5. microangiopathy ( HUS, TTP)
6. Bite / blister cells ( G6PD deficiency)



NOTE:

- ✓ MACROCYTIC WITH MEGALOBLASTIC BONE MARROW:
  1. vitamin B12 deficiency
  2. folic acid deficiency
  3. hereditary orotic aciduria
  4. thiamin-responsive anemia
- ✓ OTHERS WITHOUT MEGALOBLASTIC (liver dz, hypothyroidism, hemolysis, chemotherapy, preleukemia)
- ✓ SPURIOUS
  1. normal newborn
  2. reticulocytosis
  3. postsplenectomy

NOTE:
MCV= age in Yrs+70
Microcytic <70 fL
Normocytic 70-100 fL
Macrocytic >100 fL

NOTE:
RDW: RBC distribution width = coeffient of RBC variations in size and shape. N= 14.
= SDof MCV/mean MCV*100

# ANEMIAS OF INADEQUATE PRODUCTION

## ACQUIRED PURE RED BLOOD CELL ANEMIAS
### (TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD)

- The most common acquired red cell aplasia occurring in children
- (TEC) is more common than congenital hypoplastic anemia.
- In previously healthy children( 6 mo - 3 yr), with most of the children older than 12 mo at onset.
- The anemia develops slowly, and marked symptoms usually develop only with severe anemia.
- THE CAUSE of this decrease in red blood cell (RBC) production is a transient immunologic suppression of erythropoiesis. It often follows a viral illness (no specific virus identified). Parvovirus B19 infections are not responsible for TEC.

### LAB RESULTS:

- Reticulocytes and bone marrow erythroid precursors are MARKEDLY DECREASED (examination of the bone marrow rarely is needed)
- neutropenia occurs in up to 20% of cases
- platelet numbers are normal or elevated, thrombocytosis presumably is caused by increased erythropoietin, which is known to have some homology with thrombopoietin.
- Mean corpuscular volume (MCV) is characteristically normal for age
- fetal hemoglobin (Hb F) levels are normal before the recovery phase.

### THERAPY:

- all children recover within 1-2 mo.
- RBC transfusions for severe anemia in the absence of signs of early recovery.
- Corticosteroid therapy is of no value in this disorder.
- Any child with presumed TEC who requires more than one transfusion should be reevaluated for another possible diagnosis.
- In rare instances, a prolonged case of apparent TEC may be caused by parvovirus-induced RBC aplasia, occurring in children with congenital or acquired immunodeficiencies.

## PHYSIOLOGIC ANEMIA OF INFANCY

- Progressive decline in hemoglobin level begins within the first week of life and persists for 6-8 wk.
- CAUSES:
  1. more oxygen available for binding to Hb → hemoglobin-oxygen saturation increases from 50 to 95%
  2. swich from fetal to adult hemoglobin → replaces high-oxygen-affinity fetal hemoglobin with lower-oxygen-affinity adult hemoglobin → deliver a greater fraction of hemoglobin-bound oxygen to the tissues

BOTH FACTORS ↓ERYTHROPOIETIN (EPO) PRODUCTION→ ERYTHROPOIESIS IS SUPPRESSED →HEMOGLOBIN LEVELS DECREASE

- Iron form degraded RBCs is stored for future Hb.
- Hb continues to decrease until tissue oxygen needs are greater than oxygen delivery → this point is between(8-12 wks) when Hb 8-11 g/dl
- Hypoxia is detected by renal or hepatic (in premature) oxygen sensors → ↑ EPO→erythropoiesis resumes.
- *Premature infants* physiologic anemia:
  - ✓ decline in hemoglobin level is both more extreme and more rapid.
  - ✓ Minimal hemoglobin levels of 7-9 g/dL commonly are reached by 3-6 wk of age, even lower is small premature infants.
  - ✓ CAUSES:
  1. blood loss as a result of sampling (iatrogenic)
  2. The erythropoietic response to anemia also is suboptimal
     - ⇒ short survival of the RBCs of premature infants (40-60 days instead of the 120 days in adults)
     - ⇒ Inadequate synthesis of EPO in response to hypoxia. (liver is the predominant source of EPO during fetal life, relative insensitivity of the hepatic oxygen sensor to hypoxia explains that)
- TTT: NO HEMATOLOGICAL PROBLEM, NO THERAPY REQUIRED beyond ensuring that the diet of the infant contains essential nutrients for normal hematopoiesis, especially folic acid and iron.

## IRON-DEFICIENCY ANEMIA

- Anemia resulting from lack of sufficient iron for synthesis of hemoglobin
- the most common hematologic disease of infancy and childhood. It is estimated that 30% of the global population suffers from IDA
- The most common hypochromic microcytic anemia.
- In term infants, anemia caused solely by inadequate dietary iron.
- Usually occurs at 9-24 mo of age.

### ETIOLOGY:

- Hemoglobin concentration of the newborn infant falls during the first 2-3 mo of life. These reclaimed stores are sufficient for blood formation in the first 6-9 mo of life.
- Delayed clamping of the umbilical cord (~2 min) in developing countries reduce the incidence of iron deficiency.
- Causes:
  1. DEFICIENT INTAKE OF IRON: cow's milk.
  2. IMPAIRED ABSORBTION OF IRON: IBD, malabsorption, postgarstrictomy, severe prolonged diarrhea.
  3. INCREASE IRON DEMAND: cyanotic heart diseases, LBW and prematurity, adolescence and pregnancy.
  4. INCREASE BLOOD LOSS: hemangioma, meckel diverticulum, peptic ulcer, polyp, hookworm infestation, milk protein-induced inflammatory colitis, cow's milk-induced colitis.

### DIETARY BASED IRON DEFICIENCY

- total body Fe : 0.5g in newborn to 5g in adult
- 0.8-1.5 mg of elemental Fe is needed daily
- Only 10% of elemental Fe is absorbed in the jejunum → daily elemental Fe required is 8-15 mg/day.
- cows milk Fe content is .75mg/L → at least 10 liters is needed daily → so infants who primarily on cows milk→ iron deficiency anemia
- BREAST FED BABIES ABSORB 50% OF IRON FROM THE BREAST MILK.

### CLINICAL MANIFESTATIONS:

- Pallor is the most important sign of iron deficiency
- IDA Can cause: GI dysfunction, impaired WBC and T cell function, cognitive deficits and poor school performance.
- PAGOPHAGIA(PICA) desire to ingest unusual substances such as ice or dirt (<7MG/DL)
- hemoglobin level falls to <5 g/Dl:

5. Irritability and anorexia are prominent ( due to alteration of iron-containing enzyme – monoamine oxidase and cytochromes).
6. Tachycardia
7. systolic murmurs
8. splenomegaly 10-15%

### LAB RESULTS:

- CBC: low MCV, low RBC, normal or slightly elevated retic count, high RDW.
- Depletion of iron storage: ferritin (serum= accurate in absence of inflammatory diseases) and hemosiderin (liver & bone marrow).
- ↓serum iron and elevated transferrin(↑TIBC= indirect measurement of transferrin)
- Elevated of free erythrocyte protoporphyrine (FEB) which are heme precursors that accumulates in iron deficiency.
- Blood film show microcytic hypochromic RBC with pikilocytosis
- Decrease activity of intracellular enzymes containing iron: catalse, cytochromes (P-450), peroxidase.
- Bone marrow: hypercellular with erythroid hyperplasia, micronormoblastic maturation, decrease hemosiderin on iron staining, normal myloid lineage. (↓ marrow sidroblast)

### TREATMENT

- Correct any causes of blood loss or underlying disorders
- Decrese intake of cows milk and use fortified formulas nad cereals
- Iron supplementation with 6mg/kg/day of elemental iron PO ×2
  - ✓ For 2 months after Hb normalization
  - ✓ Subjective improvement with decrease irritability and increase appetite within 24 hr.
  - ✓ Reticulocytosis peak at 5-7 days – increase 2-3 days.
  - ✓ Hb became normal within 4-30 days
  - ✓ Increase Hb 0.25 – 0.4 g/dl/day ( 1% of Hct)
  - ✓ Needs 1-3 months to replete the body's iron stores
  - ✓ Ferrous sulfate (20%elemental iron, ferrous gluconate 10-12%)
- If no increase of Hb within 2 weeks: ongoing blood loss, infection, poor compliance, and other causes of microcytic anemia.
- PRBC Transfusion in severe symptomatic anemia (2-3cc/kg of PRBC+/- lasix). Repeat until required Hb level is reached.
- To prevent: give iron- containing formula for bottle –fee until 12 months of age, and for breastfed after 6 months.

## MEGALOBLASTIC ANEMIAS

### FOLIC ACID DEFICIENCY

- Folates are abundant in many foods, including green vegetables, fruits, and animal organs (e.g., liver, kidney).
- Body stores of folate are limited, and mega-loblastic anemia occurs after 2-3 mo on a folate-free diet.
- megaloblastic anemia due to folate deficiency has its peak incidence at 4-7 mo of age
- affected infants with folate deficiency are irritable, have inadequate weight gain, and have chronic diarrhea.
- Folic acid deficiency accompany kwashiorkor, marasmus, or sprue.

### ETIOLOGY:

- decreased folate intake
- increased vitamin requirements (e.g., pregnancy, growth in infancy, chronic hemolysis).
  - ✓ The normal infant daily requirement is 25-35 µg/day.
  - ✓ Human breast milk, pasteurized cow's milk, and infant formulas provide adequate amounts of folic acid.
  - ✓ Goat's milk is deficient of folic acid supplementation
  - ✓ powdered milk also a poor source of folic acid.
  - ✓ Folate supplementation of at least 400 µg/day is recommended from the start of pregnancy to prevent neural tube defects
- Malabsorption due to chronic diarrheal states or diffuse inflammatory disease can lead to folate deficiency
- anticonvulsant drugs (e.g., phenytoin, primidone, phenobarbital)

- Megaloblastic anemia resulting from congenital dihydrofolate reductase deficiency .manifest in early infancy.

## LABORATORY FINDINGS

- The anemia is macrocytic (mean corpuscular volume >100 fL).
- Variations in RBC shape and size are common.
- The reticulocyte count is low
- nucleated RBCs demonstrating megaloblastic morphology often are seen in the blood.
- Neutropenia and thrombocytopenia rarely may be present
- The neutrophils are large, some with hyper-segmented nuclei.
- Normal serum folic acid levels are 5-20 ng/mL; with deficiency, levels are <3 ng/mL.
- Levels of RBC folate are a better indicator of chronic deficiency. (n= 150-600 ng/mL of packed cells).
- Levels of iron and vitamin $B_{12}$ in serum usually are normal or elevated.
- Serum activity of lactate dehydrogenase (LDH), a marker of ineffective erythropoiesis, is markedly elevated.
- The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamye-locytes) with cytoplasmic vacuolation also are seen.

## TREATMENT

- Folic acid therapy (0.5-1.0 mg/day) should be continued for 3-4 wk until a definite hematologic response has occurred.
- Maintenance therapy with a multivitamin (containing 0.2 mg of folate) is adequate.
- folate >0.1 mg can correct the anemia of vitamin $B_{12}$ deficiency but may aggravate any associated neurologic abnormalities.

## VITAMIN $B_{12}$ (COBALAMIN) DEFICIENCY

- Derived from cobalamin in food (animal sources). Humans cannot synthesize vitamin $B_{12}$.
- cobalamins → released by the acidity of the stomach → combine with R proteins and intrinsic factor (IF)→ traverse the duodenum→ pancreatic proteases break down the R proteins → IF-cobalamin absorbed in the distal ileum → In the plasma, cobalamin binds to transcobalamin II (TC-II)→carries to the liver, bone marrow, and other sites.
- TC-II enters cells by receptor-mediated endocytosis, and cobalamin is converted to active forms (methylcobalamin and adenosylcobalamin) important DNA synthesis.
- Plasma other two vitamin $B_{12}$-binding proteins, transcobalamin I and III have no specific transport role but are known to reflect vitamin $B_{12}$ tissue stores.
- Almost all vitamin $B_{12}$ in plasma is bound to TC-I and TC-III, and thus the measurement of serum $B_{12}$ concentration reflects the storage of this vitamin.
- Older children and adults have sufficient vitamin $B_{12}$ stores to last 3-5 yr.
- In young infants born to mothers with low vitamin $B_{12}$ stores, clinical signs of cobalamin deficiency become apparent in the first 6-18 months of life.

## ETIOLOGY:

- Inadequate dietary intake of vitamin (rare). is not common in kwashiorkor or infantile marasmus. Breast-fed infants whose mothers are vegans or themselves have pernicious anemia.
- Lack of IF secretion by the stomach. Congenital pernicious anemia is a rare autosomal recessive disorder due to an inability to secrete gastric IF or secretion of functionally abnormal IF.
- Impaired intestinal absorption of IF-cobalamin. inflammatory diseases such as regional enteritis or neonatal necrotizing entero-colitis, terminal ileum has been surgically removed.
- Absence of vitamin $B_{12}$ transport protein. ranscobalamin II (TC-II) deficiency is a rare cause of megaloblastic anemia due to decreased utilization of cobalamin.

## CLINICAL MANIFESTATIONS:

- weakness, fatigue, failure to thrive, or irritability.
- **pallor, glossitis, vomiting, diarrhea, and icterus.**
- **Neurologic symptoms include paresthesias, sensory deficits, hypotonia, seizures, developmental delay, developmental regression, and neuropsychiatric changes.**

## LABORATORY FINDINGS:

- The hematologic manifestations of folate and cobalamin deficiency are identical.
- The neutrophils may be large and hypersegmented.
- neutropenia and thrombocytopenia can occur, simulating aplastic anemia or leukemia.
- Serum vitamin $B_{12}$ levels are low
- Serum concentrations of METHYLMALONIC ACID AND HOMOCYSTEINE ARE ELEVATED.
- Concentrations of serum iron and serum folic acid are normal or elevated.
- Serum LDH activity is markedly increased a reflection of the ineffective erythropoiesis.
- Moderate elevations (2-3 mg/dL) of serum bilirubin levels also may be found.
- EXCESSIVE EXCRETION OF METHYLMALONIC ACID IN THE URINE (NORMAL AMOUNT <3.5 MG/24 HR) IS A RELIABLE AND SENSITIVE INDEX OF VITAMIN $B_{12}$ DEFICIENCY.

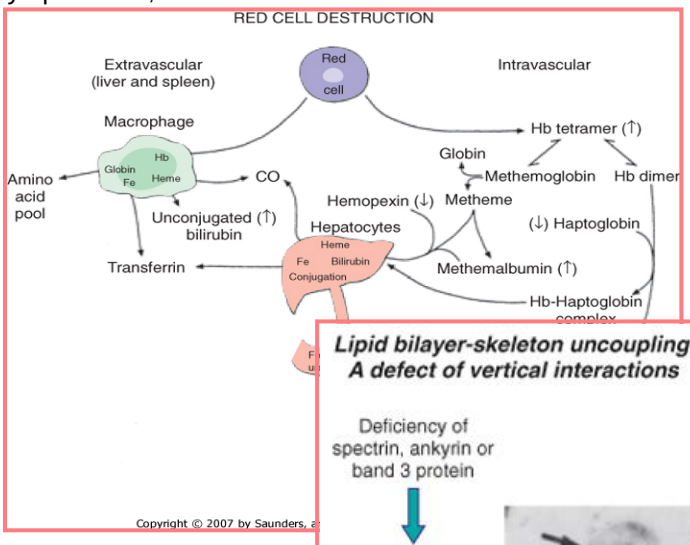
## TREATMENT:

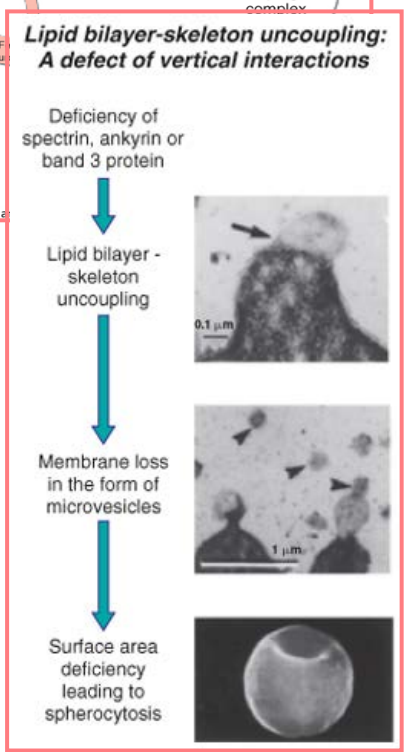
- parenteral administration of vitamin $B_{12}$ (1 mg), usually with reticulocytosis in 2-4 days
- If there is evidence of neurologic involvement, 1 mg should be injected intramuscularly daily for at least 2 wk.
- Maintenance therapy is necessary throughout a patient's life; monthly intramuscular administration of 1 mg of vitamin $B_{12}$ is sufficient.
- Oral not used due to uncertain absorption.

# HEMOLYTIC ANEMIAS

- HEMOLYSIS is defined as the premature destruction of red blood cells (RBCs).
- Normal RBC life span =110-120 days → 1% of RBCs removed daily.
- In hemolysis life span reduced to 15 days
- If destruction >> production → anemia
- Anemia + high retic = hemolysis
- Capacity of bone marrow increased up to 8 folds
- Manifestations of hemolytic anemias:

1. ERYTHROID HYPERPLASIA specially in long bones and skull, increase medullary spaces and decrease cortical thickness, resulting in Olympic faces, bone fractures. Bone marrow: increase erythroid precursors. high retic count.
2. increase INDIRECT BILIRUBIN
3. GALL STONES: as early as 3 years
4. increase free Hb in plasma and urin ( HBINEMIA & HBINURIA)
5. INCREASE METHEMALLBUMIN
6. INCREASE URINE HEMOSIDIRINE → secondary iron deficiency anemia also increase shedding of renal epithelial cells containing hemosidirine.
7. HIGH FECAL AND URINARY UROBILINOGEN
8. INCREASE CARDIAC OUTPUT
9. LOW HAPTOGLOBIN AND HEMOPEXIN with bound Hb to form complexes.
10. APLASTIC OR HYPOPLASTIC CRISES : bone marrow erythroid failure and reticulocytopenia. Rapid fall in Hb & Hct→ heart failure, hypoxia & collapse. The most common cause is parvovirus19. Last 2 weeks then resolve gradually. No effect on normal RBC.




# HEREDITARY SPHEROCYTOSIS

- Most common inherited abnormality of the red blood cell (RBC) membrane.
- Defect of the skeleton of RBCs membrane( spectrin component)
- Affected individuals may be asymptomatic, with minimal hemolysis without anemia or have severe hemolytic anemia.
- The characteristic finding is ↑number of spherocytes in the peripheral smear.
- inheritance is AD (75%), AR, new mutation or AD with reduce penetrance
- Onset: neonatal or adulthood
- Cardinal features are anemia (50%) and jaundice
- By adulthood 95% have splenomegaly
- 5% only have severe disease(ressive form)
- 30% have mild disease

## LAB FINDINGS:

- Anemia more severe in early childhood than later in life (Hb<10mg/dl)
- High retic count
- Hyperbilirubinemia in 50%
- Increase MCHC, normal MCV and MCH.
- Blood film : spherocytes in 80% +/- nucleated RBCs, normocytic hyperchromic ( normal spherocytes are <15% of RBCs)
- Gel electrophoresis is diagnostic in 80% of cases( for membrane protein)
- The definitive diagnostic test : the incubated osmotic fragility test with shows osmotic fragility.
  - ✓ Exposure of RBC to hypotonic solution leads to swelling then lyses (shyrocytes lyse more readily than normal biconcave cells.
  - ✓ RBCs incubated for 24hrs in 37 C in isoosmotic buffered salt solution to deprive them from glucose) then expose them to progressive dilutions then cells swollen and lyses.
  - ✓ A normal test result also may be found in 10-20% of patients

## COMPLICATIONS:

- Aplastic anemia: viral induced, parvovirus 19 __> severe anemia, low retic, pancytopenia ( marrow failure.
- Hyper-hemolysis: by viral illnesses, severe anemia, without marrow failure.
- Megaloblastic anemia: decrease folic acid intake with increase requirement as in all hemolytic diseases. So 1mg/day folic acid is recommended.
- Gallstones: in adolescence & adulthood but can occur as early as 3 years of age.
  - ✓ incidence: 5%<10yrs, 40-50% 10-40 yrs, 55-75% >40yrs.
- Others related to anemia: delayed growth and sexual development, frontal bossing & craniofascial features.

## MANAGEMENT

- Before 6 yrs:
  - ✓ Only 1 mg/day folic acid with regular follow up: anemia,growth,activity.
  - ✓ Partial splenectomy useful in children younger than age 5 yr
- After 6 yrs:
  - ✓ according to the severity : splenectomy with response rate 100%
  - ✓ Do not recommend splenectomy for patients whose hemoglobin values exceed 10 g/dL and whose reticulocyte percentage is <10%.
  - ✓ gallstone is an indication for splenectomy
  - ✓ Post-splenectomy: increase Hb, spherocytes & holly jolly bodies, decrease retic, osmotic fragility improves, increase possibility of sepsis.
  - ✓ **TO REDUCE SEPSIS**: pneumococcal, H influenza, meningococcal vaccination at least 2 weeks before splenectomy, prophylactic antibiotic at least 5 years (up to 18 yr of age), splenectomy not before 5 yr old.
  - ✓ If no improvement after splenectomy: accessory spleen, so do abdUS before.

# OTHER MEMBRANE DEFECTS:

- **HEREDITARY STOMATOCYTOSIS**: On stained blood film, they present a mouthlike slit in place of the circular area of central pallor. Dehydrated hereditary stomatocytosis is the most common type

- HEREDITARY ELIPTOCYTOSIS: inherited as a autosomal dominant disorder. The blood film is the most important test to establish hereditary elliptocytosis. Ttt as HS.
- PAROXYSMAL NOCTURNAL HEMOGLOBINURIA = acquired (due to complement activation) low platlets, low WBC → recurrent infections
- ACANTHOCYTOSIS: RBCs irregular circumferential pointed projections, morphologic finding is seen with alterations in the cholesterol/phospholipid ratio in liver disease and in congenital abeta-lipoproteinemia (anemia, neuromascular abnormalities, retinitis pigmentosa, malabsorption)**&**X-linked McLeod syndrome**.**

## GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

- It is loss of the protective effect of G6PDenzyme → oxidative damage of RBCs.
- responsible for 2 clinical syndromes
  1. episodic hemolytic anemia induced by infections, certain drugs or, rarely, fava beans
  2. spontaneous chronic nonspherocytic hemolytic anemia.
- Higher in Africa where malaria endemic ( PL falciparum), Mediterranean regions.
- G6PD deficiency **: X- ressive**. so females are homozygotes and males are hemizygotes
- Hetrozygotes females may be normal or have low levels depending on the extent of lionization of the X chromosome.
- Enzyme deficiency is both quantitative & qualitative
- Ezyme → production of NADPH → reduced glutathione → protects sulfhydryl group in cellular protein → protect from oxidative damage by oxygen radicals
- Symptoms develop 24-48 hr after a patient has ingested a substance that has oxidant properties.
- **Drugs with oxidant properties include aspirin, sulfonamides, and antimalarials, such as primaquine, nitrofurantoin, and naphthalene.**
- Exposure to oxidant agents →denatured Hb ( **Heinz bodies**: rapidly removed from the circulation so not seen after the first 3-4 days of illness) →irreversible damage & lyses
- Lyses most commonly occurred intravascular → Hbinuria & Hbinemia, extravascular lysis may occur →splenomegaly
- **Favism** : is acute hemolysis that precipitated by fava beans that contain vicine and convicine, characterized by :
  - ✓ unpredictability, vary from one to another & in the same patient
  - ✓ it is dose and body weight dependent
  - ✓ quality of beans : raw beans >> cooked
  - ✓ maturity of beans : young beans >>
  - ✓ the activity of vicine & covicine in the beans & intestine.
- The diagnosis depends on direct (enzyme activity in affected persons is ≤10% of normal) or indirect demonstration of reduced G6PD activity in RBCs ( ↓ NADPH formation).
- **Bite cells (cookie cells)** are seen in peripheral smear during acute hemolysis, also absent part of hemoglobin produced by phagocytosis of heinz bodies by spleen → **blister cells.**
- When hemolysis has occurred, supportive therapy may require blood transfusions.
- Recovery is the rule when the oxidant agent is discontinued.

## SICKLE CELL ANEMIA

- Hemoglobin S (Hb S) is the result of a single base pair change encodes **valine instead of glutamine** in the 6th position in the β-globin molecule.
- SICLE CELL SYNDROMES: SS diasese, S-C disease, S-B thalassemia
- hemoglobin S cells change from a normal biconcave disc (when oxygenated) to a sickled form, with resultant decreased deformability in deoxygenated conditions → forms a gel →occlusion of microvasculature → infarction, dysfunction and pain.
- This sickling phenomenon is exacerbated by hypoxia, acidosis, increased or decreased temperature, and dehydration.
- DEFINITIONS:
  1. **Sickle cell anemia,** homozygous Hb S, occurs when both β-globin genes have the sickle cell mutation. , Hb S level = 90%

2. **Sickle cell disease** compound heterozygotes where one β-globin gene mutation includes the sickle cell mutation and the 2nd β-globin other, Hb C, Hb β-thalassemia, Hb D, and Hb O Arab. Hb S is >50%.

## Clinical manifestations:

- Infants with sickle cell anemia have abnormal immune function.
- As early as 6 mo of age, some children, and by 5 yr of age, most children have functional asplenia. Bacterial sepsis is one of the greatest causes of morbidity and mortality
- the patient is susceptible to overwhelming infection by encapsulated organisms, especially *S. pneumoniae* and other pathogens.
- A patient with a sickle cell syndrome who has a temperature greater than 38.5°C (>101.5°F) must be evaluated immediately
- Current precautions to prevent infections include prophylactic daily oral penicillin begun at diagnosis (until age of 5 years) and vaccinations against pneumococcus, *H. influenzae* type b, hepatitis B virus, and influenza virus.
- The anemia of SS disease is usually a chronic, moderately severe, compensated anemia that is not routinely transfusion dependent.
- Manifestations of chronic anemia include jaundice, pallor, variable splenomegaly in infancy, a cardiac flow murmur, and delayed growth and sexual maturation.

## Clinical Manifestations of Sickle Cell Anemia

| Manifestation | Comments |
|---|---|
| Anemia | Chronic, onset 3-4 mo of age; may require folate therapy for chronic hemolysis; hematocrit usually 18-26% |
| **Aplastic crisis** | Parvovirus infection, reticulocytopenia; acute and reversible; may need transfusion |
| **Sequestration crisis** | Life threatening hyperacute decline of Hb by pooling of RBCs in the spleen and sickling within →Massive splenomegaly (may involve liver), shock; treat with transfusion |
| **Hemolytic crisis** | May be associated with G6PD deficiency,acute decrease of Hb with infections or drugs → transfusion to achieve HbS<30% |
| Dactylitis | Hand-foot swelling in early infancy |
| Painful crisis | *The most common type of vaso-occlusive*, Microvascular painful vaso-occlusive infarcts of muscle, bone, bone marrow, lung, intestines |
| Cerebrovascular accidents | Large and small vessel occlusion → thrombosis/bleeding (stroke); requires chronic transfusion to achieve HbS<30% |
| Acute chest syndrome | Acute vaso-occlusive crisis in the lung → Infection, atelectasis, infarction, fat emboli, severe hypoxemia, infiltrate, dyspnea, absent breath sounds |
| Chronic lung disease | Pulmonary fibrosis, restrictive lung disease, cor pulmonale, pulmonary hypertension |
| Priapism | Between 6-20 years, sudden painful erection→ Causes eventual impotence; treated with transfusion to achieve HbS<30%, oxygen, or corpora cavernosa-to-spongiosa shunt |
| Ocular | Retinopathy |
| Gallbladder disease | Bilirubin stones; cholecystitis |
| Renal | Hematuria, papillary necrosis, renal-concentrating defect; nephropathy |
| Cardiomyopathy | Heart failure |
| Skeletal | Osteonecrosis (avascular) of femoral or humeral head |
| Leg ulceration | Seen in older patients |
| Infections | Functional asplenia, defects in properdin system; pneumococcal bacteremia, meningitis, and arthritis; deafness from meningitis; *Salmonella* and *Staphylococcus aureus* osteomyelitis; severe *Mycoplasma* pneumonia |
| Growth failure, delayed puberty | May respond to nutritional supplements |
| Psychological | Narcotic addiction (rare), dependence unusual; chronic illness, chronic pain |

## Lab results:

- The diagnosis is made by identifying the precise amount and type of hemoglobin present using **hemoglobin electrophoresis**, **isoelectric focusing**, or **high-performance liquid chromatography**.

## Treatment:

- **Hydroxyurea**, which increases hemoglobin F, has been shown in adults and children to decrease the number and severity of vaso-occlusive events.

- **Hematopoietic stem cell transplantation** has cured many children with SCD.

## THALSSEMIA

### BETA THALASSEMIA:

- tow B genes: if one is deficient → beta thalssemia minor (triat)→ no significant hemolysis.
- Both genes → beta thalssemia major → significant hemolysis.
- Thalassemia intermedia → both genes are absents but there is milder degree of hemolysis → Hb 8-7 mg/dl but minimal or no transfusion with normal growth.
- Usually manifest at 4-12 months of age.
- Basophilic stippling can be present due to a chains presipitation
- Diagnosis baced on ↑ HbF & HbA2
- BETA THALASSEMIA MAJOR ( COOLEY ANEMIA) :
  - ✓ There is ineffective erythropiosis & shortened RBCs life span → severe anemia
  - ✓ Complications : due to hemolytic anemia ( specific faces ( frontal bossing), gallstones, chronic lung ulcers), due to iron over load ( arrhythmias, heart failure, cirrhosis, hypothyroidism, DM, delayed growth and sexual maturity)
  - ✓ Management
    1. Transfusions: should be started since age 6m-1yr to keep Hb > 10 for normal growth and development, after epiphesial closure 7-8 mg/dl is accepted.
    2. celation ( reduce iron toxicity): given with transfusion, deferoximine ( start at 3-4 yr old) – complications: deafness, color & night blindness, yersinia and mucomycosisi infections.
    3. splenectomy: indicated if : spleen very enlarged, hypersplenism, RBC requirement >200ml/kg/yr
    4. definitive cure is bone marrow transplantation → success rate is 75-80%.

### ALPHA THALASSEMIA:

- There are four genes for a :
  - ✓ one gene → silent carrier
  - ✓ tow genes → alpha thalseemia triat → no symptoms
  - ✓ three genes → HBH(4 beta) → anemia, HSM and jaundice, Heinz bodies.
  - ✓ Hemolysisi may presipetated by infection, oxidants eg. Iron, sulfonamides
  - ✓ 4 genes → HB bart (4 gamma) → hydrops fitalies → incompatabile with life ( the most severe one)
  - ✓ Diagnosis by electrophoresis → Hb bart or H.

## MISCELLANEOUS

- LEAD POISONING:
  - ✓ Hypochromic microcytic anemia
  - ✓ Most Pt have concomitant iron deficiency anemia
  - ✓ HX: pica in child who lives in old house with chipped paint or lead dust.
  - ✓ Basophilic stippling in blood smear
  - ✓ Rarely may cause hemolytic anemia
  - ✓ Exposure removal, chelation therapy, correction of iron deficiency.
- DIAMOND- BLACKFAN SYNDROME (CONGENITAL HYPOPLASTIC ANEMIA):
  - ✓ Life long disorder **,autosomal ressive**, pure red cell hypoplasia
  - ✓ newborn – 1 months, 90%< 1 yrof age.
  - ✓ **Macrocytic ,elevated HbF ,fetal I antigen is present**
  - ✓ congintial abnormalities: **short stature, web neck, cleft lip, tripharyngeal thumb**
  - ✓ late onset leukemia.
  - ✓ **50% respond to corticosteroids therapy**, if not : transfusion.
- FANCONI SYNDROME:
  - ✓ Before 10 years of age, mean 8 years.
  - ✓ **Autosomal ressive**
  - ✓ All cell lines affected- pancytopenia due to bone marrow failure.
  - ✓ **High MCV, HbF**
  - ✓ Diagnosis is based on increase chromosomal breakage after exposure to agents that damage DNA.

- ✓ Associated with**: microcephaly, absent thumb, café au lait spots, cutanous hyperpigmentation, short stature, chromosomal breaks, horseshoe or absent kidney.**
- ✓ Can develop malignancies: terminal acute leukemia 10-%.
- ✓ Treatment: androgens( complications: liver injury, liver tumors, masculinization)→ increase RBC synthesis and ↓ transfusion, corticosteroids, bone marrow transplantation.

- **DYSKERATOSIS CONGENITAL:**
  - ✓ Mean age for skin =10yrs, for anemia = 10 yrs.
  - ✓ Pancytopenia with hyperpigmentationm dystrophic nails, leukoplakia,lacremal duct stenosis.
  - ✓ X-linked ressive
  - ✓ High MCV and fetal hemoglobin
  - ✓ Treatment: androgens, splenectomy, bone marrow transplant.
- **KASABACH MERRITT SYNDROME:** RBCs damage due to exposure to nonendothelialized surfaces in gaint hemangiomas. ( waring blender syndrome in case of artificial heartvalves)
- **VITAMINE E DEFICIENCY:**
  - ✓ Cause an acquired hemolytic anemiaas result of abnormal sensitivity of membrane lipids to oxidant stress.
  - ✓ Premature with no enough supplement, severe malabsorbtion diseases ( cystic fibrosis) , transfusional iron overload ( high oxidant exposure)

## PANCYTOPENIA

- **BONE MARROW FAILURE :**
  - ✓ **features:**
    1. low reticulocyte count
    2. teardrop forms of RBCs (implying marrow replacement, not just failure),
    3. abnormal forms of leukocytes or myeloid elements less mature than band forms
    4. small platelets
    5. elevated mean corpuscular volume.
    6. a gradual process. initially one or two involved cell lines, but later progress to involvement of all three cell lines.
  - ✓ Marrow replacement: **leukemia**, **solid tumors** (especially neuroblastoma), **storage diseases**, **osteopetrosis** in infants, and **myelofibrosis**, which is rare in childhood.
  - ✓ Bone marrow aspirate and biopsy are needed for precise diagnosis of the etiology of marrow synthetic failure.
- **INCREASED DESTRUCTION:**
  - ✓ **feature**:
    1. reticulocytosis
    2. jaundice
    3. immature erythroid or myeloid elements on the blood smear
    4. large platelets
    5. increased serum bilirubin and lactic dehydrogenase.
- ✓ caused by:
  - A. **intramedullary destruction** of hematopoietic elements (myeloproliferative disorders, deficiencies of folic acid and vitamin $B_{12}$)
  - B. **peripheral destruction** of mature cells.
- ✓ The sites of peripheral destruction of blood cells are the spleen, liver and other parts of the reticuloen-dothelial system.
- ✓ **Hypersplenism** may be the result of anatomic causes, such as portal hypertension or splenic hypertrophy from:
  1. thalassemia;
  2. infections (including malaria);
  3. storage diseases, such as Gaucher disease; lymphomas; or histiocytosis.
- ✓ Splenectomy is indicated only when the pancytopenia is of clinical significance.

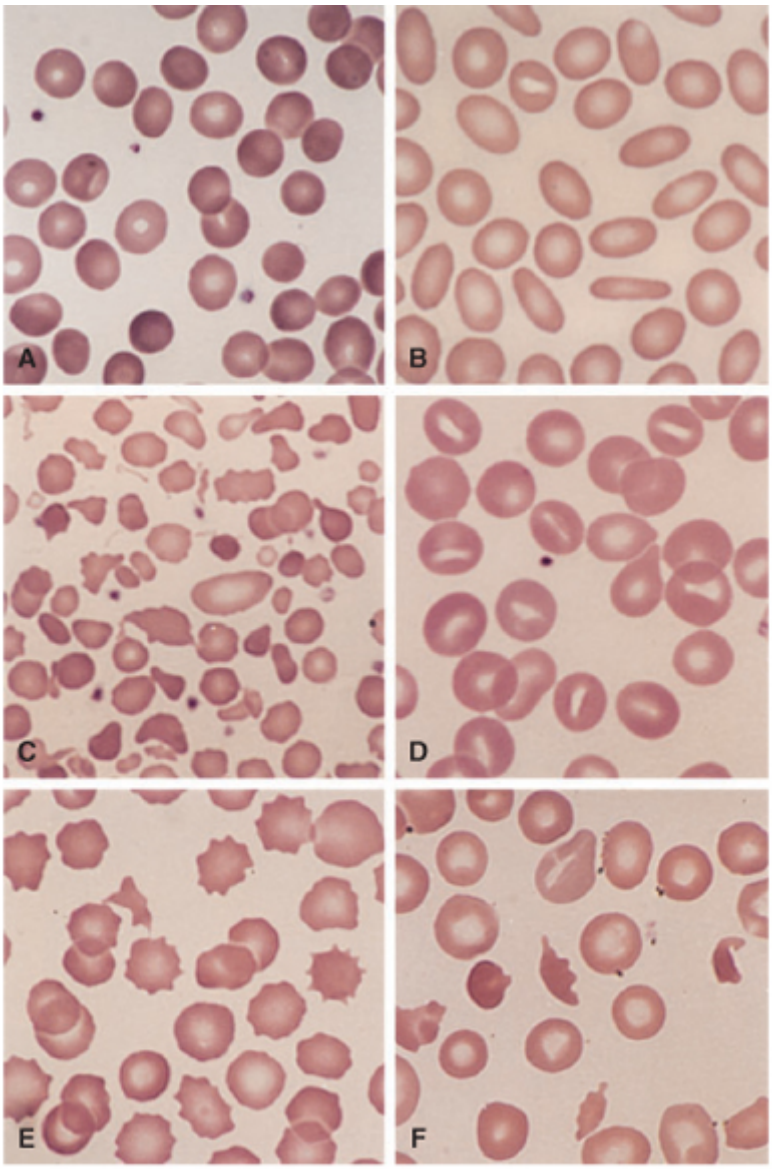
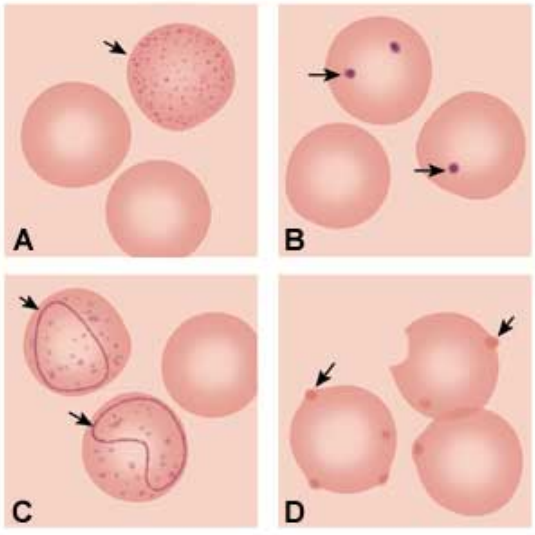





Figure 458-3 Morphology of abnormal red cells. *A*, Hereditary sphe-rocytosis; *B*, hereditary elliptocytosis; *C*, hereditary pyropoikilocytosis; *D*, hereditary stomatocytosis; *E*, acanthocytosis; *F*, fragmentation hemolysis

**Basophilic stippling**
Representing aggregated ribosomes
1. thalassemia syndromes
2. iron deficiency
3. lead poisoning




**Howell- jolly bodies**
Nuclear remnants
1. asplenia
2. pernicious anemia
3. severe iron deficiency

**Cabots ring bodies**
Nuclear remnants
1. lead toxicity
2. pernicious anemia
3. hemolytic anemias

**Heinzs bodies**
Denatured aggregated hemoglobin
1. thalassemia,
2. asplenia
3. G6PD disease
4. chronic liver disease

# Pediatrics malignances

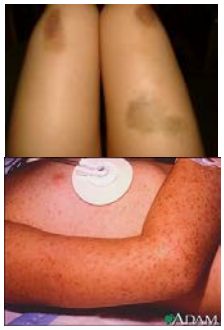
Dr. Imad dweikat

# ACUTE LYMPHOBLASTIC LEUKEMIA

- **The most common malignancy of childhood**
- Peak incidence in patients aged **2-5 years**.
- Slightly more frequent in **males**.
- The cause remains largely unknown; a small percentage of cases are associated with inherited genetic syndromes.
- The disease is more common in children with certain chromosomal abnormalities:
  1. Down syndrome
  2. Bloom syndrome
  3. ataxiatelangiectasia & SCID
  4. Fanconi syndrome
  5. Klinefelter syndrome
  6. Diamond-Blackfan anemia
  7. Turner syndrome
  8. Neurofibromatosis type 1
- Exposure to medical diagnostic radiation in utero and in childhoodh→↑ incidence of ALL
- Improvement in diagnosis and treatment have produced cure rates that now exceed 70%
- No staging system for ALL: because at time of diagnosis it is found to be disseminated out of bone marrow.

## CLINICAL MANIFESTATIONS

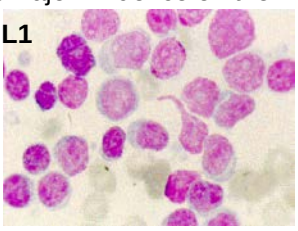
- The initial presentation of ALL usually is **nonspecific and brief**.
- Anorexia, fatigue, and irritability often are present, as is an intermittent, low-grade fever.
- Patients often have a history of an URTI in the preceding 1-2 mo.
- Bone or, less often, joint pain, particularly in the lower extremities.
- Bone pain is severe and may wake the patient at night.
- As the disease progresses, signs and symptoms of bone marrow failure become more obvious :
  1. pallor
  2. fatigue
  3. bruising
  4. epistaxis
  5. fever, which may be caused by infection.

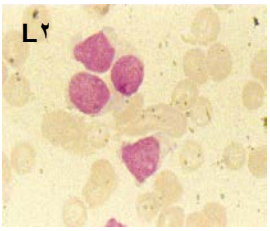


- **physical examination:**
  1. Findings reflect bone marrow failure: **pallor**, **listlessness**, **purpuric** and **petechial skin lesions**, or **mucous membrane hemorrhage**.
  2. The proliferative nature of the disease: **lymphadenopathy**, **splenomegaly**, or less commonly, **hepatomegaly**.
  3. bone or joint pain→ **tenderness over the bone or joint swelling and effusion**. with marrow involvement→ deep bone pain without elicited tenderness.
  4. leukemic involvement of the (CNS)→signs of ↑ICP : **papilledema, retinal hemorrhages,** and **cranial nerve palsies.**
  5. **Respiratory distress**: anemia, obstructive airway due to a large anterior mediastinal mass (the thymus or nodes)→most typically in : adolescent boys with T-cell ALL T-cell - has a higher leukocyte count.
- **Early pre-B-cell ALL** is the most common immunophenotype
  - ♣ onset between 1-10 yr of age.
  - ♣ The median leukocyte count at presentation is 33,000.
  - ♣ Findings:
    1. WBC <20,000 in 75% of patients
    2. thrombocytopenia in 75% of patients
    3. hepatosplenomegaly in 30-40% of patients.
    4. In all types of leukemia, CNS symptoms are seen at presentation in 5% of patients (10-20% have blasts in the CSF)
    5. Testicular (20%) and ovarian (30%) involvement, does not require a biopsy.

## LAB STUDIES:

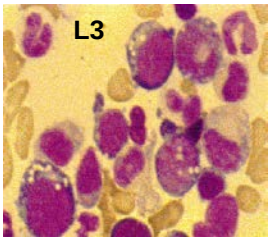
- **Basic Labs:**
  1. Peripheral smear: Circulating blasts are usually seen. Schistocytes if DIC is present
  2. Most patients have ↑(LDH), ↑uric acid level.
  3. CBC
  4. PT, PTT, Fibrinogen and D-dimers (DIC)
- **Imaging studies:**
  1. Chest radiography: For mediastinal mass
  2. Testicular ultrasound: If testes are enlarged
  3. Renal ultrasound: To assess for ( Tumor lysis syndrome )
  4. Bone and Joint radiography
- **Bone marrow:**
  - ♣ When the results of an analysis of peripheral blood suggest leukemia, a bone marrow examination should be done promptly to establish the diagnosis.
  - ♣ ALL is diagnosed when >25% of bone marrow cells are homogenous population of lymphoblasts
  - ♣ A complete morphologic, immunologic and genetic examination of the bone marrow is necessary for diagnosis of ALL
  - ♣ Staging of ALL is partly based on CSF examination. If lymphoblasts are found and the CSF leukocyte count is elevated→overt CNS or meningeal leukemia is present → worse stage and additional CNS & systemic therapy are indicated.
  - ♣ Morphology alone is usually adequate for diagnosis, but the other studies are essential for disease classification which may have a major influence on the prognosis and the choice of therapy.




## STAGING:

- **L1:** Lymphoblasts are small with scanty cytoplasm. ccounts for 85% of all cases of childhood ALL.
- L2: Cells are larger and pleomorphic with increased cytoplasm, irregular nuclear shape and prominent nucleoli
- L3: Cells have finely stippled and homogenous nuclear chromatin, prominent nucleoli and deep blue cytoplasm with prominent vacuolization. Known as **Burkitt leukemia** and is one of the most rapidly growing cancer in humans and requires a different therapeutic approach




## TREATMENT:

- **Combination Chemotherapy:**
  - ♣ Consists of remission induction, CNS therapy, and maintenance phase.
  - ♣ Different approaches based on estimated clinical risk of relapse

## PROGNOSIS:

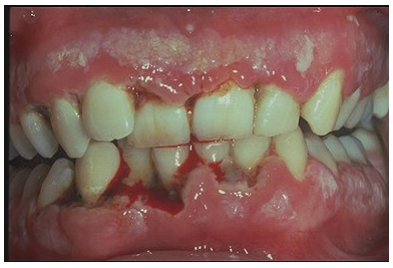
- Long term survival in most children(>80% after 5 years)
- **Poor prognostic factors:**
  1. Age < 1 year or > 10 years at diagnosis
  2. Leukocyte count > 50,000-100,000 at diagnosis
  3. Slow response to initial therapy
  4. L3 morphology
  5. Specific chromosomal abnormalities: t(9;22), t(4;11)
  6. Mediastinal mass( most commonly seen in adolescents)
  7. CNS leukemia
- **favorable characteristics:**
  1. Age 1-10 y at diagnosis
  2. leukocyte <50,000
  3. Hyperdiploidy
  4. rapid response to therapy
  5. t(12,21)

## ACUTE MYELOGENOUS LEUKEMIA

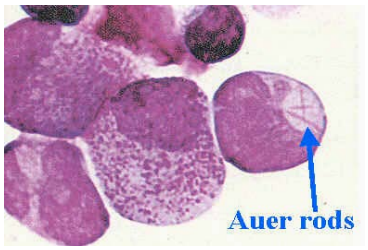
- Identified risk factors :

1. Ionizing radiation, chemotherapeutic agents (e.g., alkylating agents, epipodophyllotoxin), organic solvents.
2. Paroxysmal nocturnal hemoglobinuria.
3. Certain syndromes: Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, Shwachman-Diamond syndrome, Diamond-Blackfan syndrome,NF1.

- The characteristic feature of AML is that >30% of bone marrow cells on bone marrow aspiration or biopsy are homogeneous population of blast cells.
- The production of symptoms and signs of AML, as in ALL, is due to replacement of bone marrow by malignant cells and to secondary bone marrow failure.
- AML signs and symptoms that are uncommon in ALL, including:
  1. **subcutaneous nodules** : "blueberry muffin" lesions other causes: rubella, CMV, neonatal SLE, neuroblastoma, Hemolytic disease of the newborn, hereditary spherocytosis, .
  2. infiltration of the gingival
  3. signs and laboratory findings of **disseminated intravascular coagulation** (especially indicative of **acute promyelocytic leukemia**)
  4. **chloromas** or **granulocytic sarcomas.** typically are associated with the M2 subcategory of AML with a t(8;21) translocation. in the orbit and epidural space.
  5. **CNS symptoms** are more common in AML than ALL.
- Aggressive multiagent chemotherapy is successful inducing remission in 80% of patients.
- Here are very large, immature myeloblasts with many nucleoli. A distincitve feature of these blasts is a linear red "Auer rod" composed of crystallized granules. These findings are typical for (AML)



BLUEBERRY MUFFIN





## CHRONIC MYELOGENOUS LEUKEMIA

- clonal disorder of the hematopoietic tissue , 2-3% of all cases of childhood leukemia.
- 99% of the cases are characterized by a specific translocation, t(9;22)(q34;q11), known as the **Philadelphia chromosome.**
- The disease has been associated with exposure to ionizing radiation, but very few children with CML have a history of such exposure.
- **characterized clinically by**: initial chronic phase with ↑WBC with a predominance of mature forms but with ↑ immature granulocytes.
- Typically, the chronic phase terminates 3-4 yr after onset, when the CML moves into the accelerated or "blast crisis" phase
- "blast crisis" phase, the blood counts rise dramatically and cannot be controlled with drugs such as hydroxyurea.
- The presenting symptoms of CML are nonspecific and may include fever, fatigue, weight loss, and anorexia..
- The **spleen** often is greatly enlarged, resulting in pain in the LUQ of the abdomen.

- hyperuricemia and neurologic symptoms, which are related to increased blood viscosity with decreased CNS perfusion.
- Blood counts : mild anemia and thrombocytosis.
- The diagnosis:
  - **suggested by** increased numbers of myeloid cells with differentiation to mature forms in the peripheral blood and bone marrow
  - **Confirmed by** cytogenetic studies that demonstrate the presence of the characteristic Philadelphia chromosome.
- **BCR-ABL** gene rearrangement: translocation, characteristic of CML, also is found in a small percentage of patients with ALL or AML.
- **Imatinib mesylate:** major cytogenetics responses in over 70% of patients.
- While waiting for a response with imatinib, disabling or threatening signs and symptoms of CML can be controlled during the chronic phase with hydroxyurea, which will gradually return the leukocyte count to normal.
- Cure by allogeneic stem cell or marrow transplant, with up to 80% of children.

## HODGKIN DISEASE

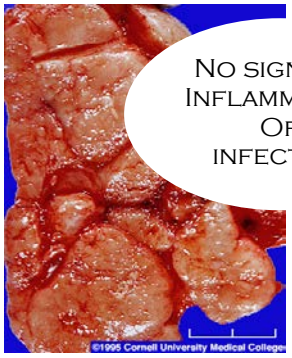
- One of the most common cancers in children.
- HD is a malignant process of the lymphoreticular system , 6% of childhood cancers.
- The role of EBV is supported by serologic studies and frequent presence of EBV genome in biopsy material.
- Increased risk with pre-existing congenital or acquired immunodeficiency. Cellular immune impairment is seen in most newly diagnosed cases.
- H.D arises in lymphoid tissues and spreads to adjacent lymph node areas.
- Hematogenous spread: Liver, spleen, bone, bone marrow and brain
- Cytokines responsible for the systemic symptoms.

### PATHOGENESIS

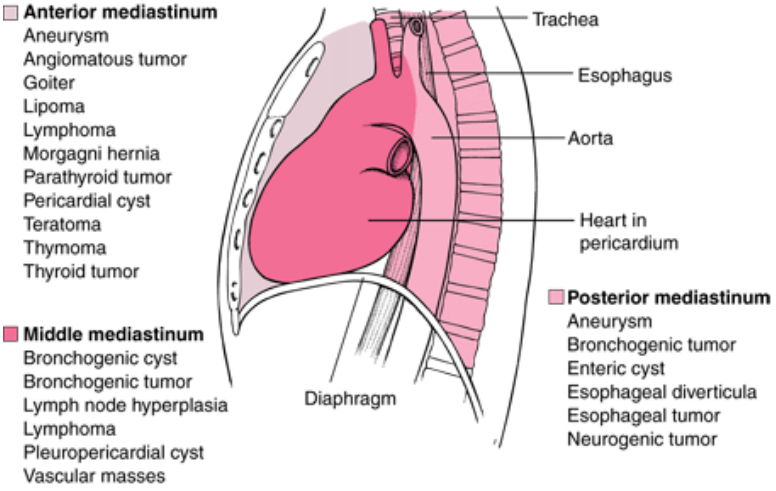
- **Reed-Sternberg cell**: large cell with multiple or multilobulated nuclei. Is the hallmark of Hodgkin disease.
- The **Rye classification system** : four major histologic subtypes:
  1. lymphocyte predominant **(LP)**
  2. lymphocyte depleted **(LD)**
  3. nodular sclerosing **(NS):** the most common subtype.
  4. mixed cellularity (**MC**)
- The prognostic significance of histologic subtypes is questioned

### CLINICAL MANIFESTATIONS

- **The most commonly** presentation: painless, non-tender, firm, rubbery, cervical or supraclavicular lymphadenopathy.
- Most patients present with some degree of mediastinal involvement.
- Clinically detectable hepatosplenomegaly rarely is encountered.
- Depending on location of nodal and extranodal disease, patients may present with:
  1. airway obstruction (dyspnea, hypoxia, cough)
  2. pleural or pericardial effusion
  3. hepatocellular dysfunction
  4. bone marrow infiltration (anemia, neutropenia, or thrombocytopenia).
- Disease presenting below the diaphragm is rare and occurs in 3% of all cases.
- **Systemic symptoms,** classified as **B symptoms** , important in staging, are:
  1. unexplained fever >39°C
  2. weight loss >10% total body weight over 3 mo
  3. drenching night sweats
- Some present as a fever of unknown origin.
- Less common: pruritus, lethargy, anorexia, or pain that worsens after ingestion of alcohol.
- **Nephrotic syndrome** is a rare but recognized presentation
- Concomitant tuberculous or fungal infections may complicate Hodgkin disease




No signs Of Inflammation Or infection




## DIAGNOSIS

- **CXR**: For mediastinal mass
- **Excisional biopsy**: FOR
  - ♣ Light microscopy
  - ♣ Immunocytochemical, molecular and cytogenetic studies
- **Staging**:
  1. CBC, ESR, Serum copper & Ferritin
  2. Chest CT scan
  3. Abdominal CT/MRI
  4. Gallium –67 scan

## TRETMENT

- Chemotherapy and radiation therapy are effective in the treatment of HD.
- Poor prognostic features include:
  1. tumor bulk
  2. stage at diagnosis
  3. presence of B symptoms

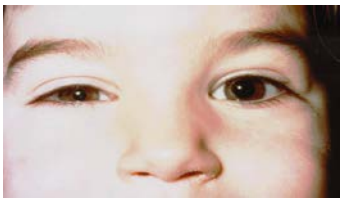
# NEUROBLASTOMA

- embryonal cancer of the peripheral sympathetic nervous system with heterogeneous clinical presentation and course.
- The third most common pediatric cancer/ALL, AML,Neuroblastoma. , accounting for about 8% of childhood malignancies.
- The most frequently diagnosed neoplasm in infants and 1/3 of neonatal malignancies
- The median age at diagnosis is 2 years.
- 90%of cases are diagnosed before 5 years of age.
- Incidence is slightly higher in boys and in whites.
- It is one of small round cell tumors. Others are:
  1. rhabdomyosarcoma
  2. Ewing sarcoma
  3. non-Hodgkin lymphoma
- Familial NB is found in 1-2% of cases

## CLINICAL MANIFESTATIONS

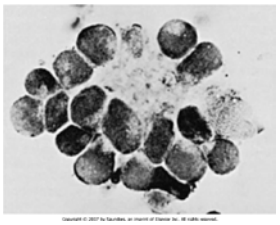
- NB can mimic many other disorders and may be difficult to diagnose.
- NB may develop at any site of sympathetic nervous system tissue.
- **Most cases of NB arise in the abdomen**, either in the adrenal gland or in retroperitoneal sympathetic ganglia.
- NB originates from cervical, thoracic, or pelvic ganglia in 30% of cases.
- Usually a firm, nodular mass , palpable in the flank or midline, causing abd. discomfort.
- On plain radiography or CT the mass often contains **calcification and hemorrhage**.
- **D/D: Wilms tumor**, another flank mass in a young child, **usually does not calcify**. More localized than neuroblastoma.
- The **most common sites of metastasis are the long bones and skull, bone marrow, liver, lymph nodes, and skin.**
- Lung metastases are rare, occurring in <3% of cases.

- Metastatic disease can be associated with myriad signs and symptoms, including:
  1. fever
  2. irritability
  3. failure to thrive
  4. bone pain
  5. bluish subcutaneous nodules
  6. orbital proptosis & periorbital ecchymoses

- Location in the superior cervical ganglion can result in **Horner syndrome.**
- Paraspinal NB can invade the neural foramina, producing symptoms of **spinal cord and nerve root compression**.
- NB can present as a **paraneoplastic syndrome** of autoimmu ne origin manifesting as ataxia or **opsomyoclonus** ("dancing eyes and dancing feet"). In such cases, the primary tumor is in the chest or abdomen, and the brain is negative for tumor.
- Some tumors produce catecholamines → increased sweating and hypertension
- some release vasoactive intestinal peptide→ secretory diarrhea.
- Children <1 yr of age also can present with a unique stage, 4S, which often includes:
  1. subcutaneous tumor nodules
  2. massive liver involvement
  3. small primary tumor without bone involvement.
- Prenatal diagnosis of NB sometimes is possible on maternal ultrasound scans.

## DIAGNOSIS

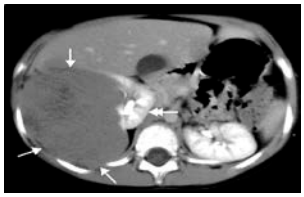


- NB usually is discovered as a mass or multiple masses on XR, CT, or MRI.
- Tumor markers, including **homovanillic acid (HVA) and vanillylmandelic acid (VMA**) in urine, ↑in 95% of cases.
- A pathologic diagnosis is established from tumor tissue obtained by biopsy.
- **Rosettes of cells** surrounding an inner mass of fibrillary material are characteristic of neuroblastoma
- Bone scan: for metastasis.

## TREATMENT

- The clinical and biologic prognostic factors currently used to determine treatment are: the age of the patient at diagnosis, stage of disease, …
- Surgery, chemotherapy, or radiation.

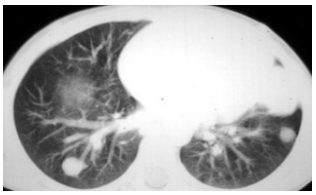
# WILMS TUMOR( NEPHROBLASTOMA )



- complex mixed embryonal neoplasm of the kidney.
- Usually occurs in children 2-5 years of age, but may occur at any age including neonates. General risk = 1%
- The second most common malignant abdominal tumor in children.
- The incidence of bilateral Wilms tumor is 7%
- 1-2% are familial, inherited as autosomal dominant: Lower age at DX = higher frequency of bilateral disease. **Congenital anomalies are absent in most families**.
- Several syndromes, chromosomal aberrations and congenital abnormalities are commonly reported in Wilms tumor.

## CINICAL MANIFISTATIONS

- Wilms tumor usually presents as incidental **abdominal mass**. Vary in size, smooth and firm, occasionally may cross the midline.
- 12-25% may present with **abdominal pain** and **vomiting**, and **hematuria**.
- **Hypertension** has been described and probably is due to renal ischemia.
- **Rapid abdominal enlargement and anemia** may occur due to bleeding into the renal parenchyma or pelvis.
- Tumor growth into the renal veins or vena cava → **embolize to heart or lungs**-DANGER.
- The genitourinary anomalies most commonly associated with Wilms tumor are hypoplasia, fusion and ectopia of the kidney, duplications of the collecting systems, hypospadias, and cryptorchidism.



- **The metastases usually involve the lungs** and occasionally the liver.

## DIAGNOSIS

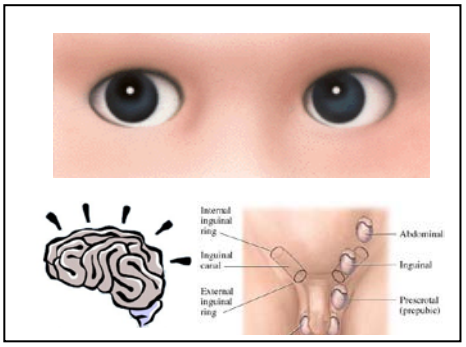
- Any abdominal mass must be considered malignant until proved otherwise
- CT/MRI confirm: Intrarenal origin, extent of tumor, involvement of IVC and integrity of the other kidney.
- Chest CT scan can identify metastases not seen on plain radiograph.
- CBC, KFT, LFT

## TREATMENT

- **Surgical resection** with inspection of patency of IVC, the other kidney & the liver and for retroperitoneal L.N for metastases
- **Chemotherapy**: Most centers utilize it and the choice depends on the stage and histology.
- **Radiotherapy** is also administered to the tumor bed
- For bilateral Wilms, chemotherapy plus unilateral nephrectomy and contralateral partial nephrectomy or bilateral partial nephrectomy

## SYNDROMES AND CONGENITAL ABNORMALITIES ARE REPORTED IN PATIENTS WITH WILMS TUMOR

### WAGR SYNDROME




- contiguous gene deletion syndrome that consists of :
  1. **W**ilms tumor
  2. **A**niridia**:** congenital underdevelopment of the eye's iris.
  3. **G**enitourinary abnormalities (cryptorchidism, streak ovaries, bicornate uterus, **ambiguous genitalia**)
  4. **R**etardation- mental.
- Patients with this syndrome have a constitutional deletion of chromosome 11p13 where the Wilms tumor gene, WT1, and the aniridia gene, PAX6, are located.

### BECKWITH-WIEDMANN SYNDROME


- characterized by:
  1. hemihypertrophy
  2. macroglossia
  3. Hypoglycemia
  4. visceromegaly
  5. 3-5% risk of developing Wilms tumor
  6. Anterior abdominal wall defects (most commonly, exomphalos).
- A variety of **11p15.5** abnormalities have been reported in patients with this syndrome, and it is postulated that a second Wilms tumor gene, WT2, is located in this region.

### DENYS-DRASH SYNDROME

- characterized by:
  1. male pseudoher-maphrodism
  2. early-onset renal failure & nephritic syndrome characterized by **mesangial sclerosis**
  3. increased risk of Wilms tumor
- Patients with this syndrome typically carry a point mutation in the WT1 gene.
- Ambiguous genitalia + generalized edema early infancy+ increase creat → DDS

### OTHER SYNDROMES:

1. Pearlman syndrome
2. Sotos syndrome
3. neurofibromatosis (von Recklinghausen disease)
4. von Willebrand disease

# IMMUNOLOGY

## ASSESSMENT

- A total of eight or more episodes of otitis media, two or more serious sinus infections, or two or more episodes of pneumonia in 1 year suggests an antibody deficiency.
- History:
  1. FTT, diarrhea, malabsorption, and fungal infections → T cell immunodeficiency.
  2. Recurrent viral infections can → T cell or NK cell deficiency.
  3. Opportunistic infections such as *Pneumocystis jirovecii* (*carinii*) → T cell disorder, such as severe combined immunodeficiency (SCID), or T cell dysfunction, as in X-linked hyper-IgM.
  4. Deep-seated abscesses and infections with *Staphylococcus aureus, Serratia marcescens,* and *Aspergillus* → neutrophil function: chronic granulomatous disease.
  5. Delayed separation of the umbilical cord, omphalitis, and periodontal disease, abscesses → leukocyte adhesion deficiency.
  6. old abscesses, eczema, and frequent fractures→ hyper-IgE syndrome.
  7. Deep-seated infections can help differentiate hyper-IgE syndrome from atopic dermatitis, which can be associated with extremely elevated levels of IgE.
  8. Onset of symptoms in the teens or 20s → common variable immunodeficiency (CVID) rather than agammaglobulinemia.
  9. The presence of associated problems such as congenital heart disease and tetany from hypocalcemia → DiGeorge syndrome.
  10. history of abnormal gait and telangiectasia on the skin→ Ataxia-telangiectasia.
  11. Atopic dermatitis → hyper-IgE syndrome and is associated
  12. Atopic dermatitis + easy bruising or a bleeding disorder → Wiskott-Aldrich syndrome.

## CLINICAL CHARACTERISTICS OF PRIMARY IMMUNODEFICIENCIES

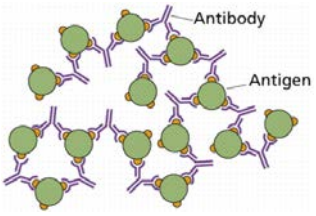
| B CELL DEFECTS |
|---|
| Recurrent pyogenic infections with encapsulated organisms: pneumococci, *Haemophilus influenzae,* and streptococci<br>Otitis, sinustitis, recurrent pneumonia, bronchiectasis, and conjunctivitis<br>Few fungal or viral infections (except enterovirus encephalitis and poliomyelitis)<br>**Decreased levels of immunoglobulins in serum and secretions**<br>**Diarrhea common**, especially secondary to infection with *Giardia lamblia*<br>Growth retardation not striking<br>Compatible with survival to adulthood unless complications occur |
| COMPLEMENT DEFECTS |
| Recurrent bacterial infections with encapsulated organisms: pneumococcus & *H. influenzae*<br>Unusual susceptibility to **recurrent gonococcal and meningococcal infections**<br>**Increased incidence of autoimmune disease (SLE)**<br>Severe or recurrent skin and respiratory tract infection |
| T CELL DEFECTS |
| Recurrent infections with less virulent or opportunistic organisms, such as fungi, mycobacteria, viruses, and protozoa<br>**Growth retardation, FTT, malabsorption, and diarrhea common**<br>Anergy<br>**Fatal reactions may occur from live virus or BCG vaccination**<br>**High incidence of malignancy**<br>Poor survival beyond infancy or childhood |
| NEUTROPHIL DEFECTS |
| **Recurrent dermatologic infections** with bacteria and fungi, such as *Staphylococcus, Pseudomonas, Escherichia coli,* and *Aspergillus*<br>Subcutaneous, lymph node, lung, and liver abscesses<br>Pulmonary infections common:abscess and pneumatocele, contributing to chronic disease<br>**Bone and joint infection common** |

## CAUSES OF SECONDARY IMMUNODEFICIENCY

| |
|---|
| **Viral Infections** |
| Measles (inhibits interleukin-12 production in macrophages) |
| Roseola (human herpesvirus-6) |
| Epstein-Barr virus (X-linked lymphoproliferative disease or Duncan syndrome) |
| Cytomegalovirus |
| HIV (destroys $CD4^+$T cells) |
| **Metabolic Disorders** |
| Diabetes mellitus |
| Malnutrition |
| Uremia |
| Sickle cell disease |
| Zinc deficiency |
| Multiple carboxylase deficiency |
| Burns |
| **Protein-Losing States** |
| Nephrotic syndrome |
| Protein-losing enteropathy |
| **Other Causes** |
| Prematurity |
| Immunosuppressive agents (e.g., corticosteroids, radiation, and antimetabolites) |
| Malignancy (leukemia, Hodgkin disease, nonlymphoid cancer) |
| Acquired asplenia |
| Periodontitis |
| Chronic (acute) blood transfusions |
| Acquired neutropenia (autoimmune, viral, or drug induced) |
| Bone marrow transplantation/graft-versus-host disease |
| Systemic lupus erythematosus |
| Sarcoidosis |

# Lymphocyte Disorders

- Lymphocytes play a major role in the adaptive immune response by providing antigen specificity and memory responses.
- Disorders that affect lymphocyte development or function result in significant immunodeficiency.
- hematopoietic stem cells → common lymphoid progenitor→T lymphocytes, B lymphocytes, and NK lymphocytes.
- B cells complete their development in the bone marrow.
- T cells develop in the thymus from bone marrow-derived precursors.
- Isolated B cell disorders → **antibody deficiency diseases**
- T cell disorders → **combined immunodeficiency** because they are necessary for:
  1. cell-mediated immunity
  2. immunity to intracellular pathogens
  3. Antibody synthesis by B cells.
- NK cells are an important component of the **innate immune response**. Kill virus-infected cells and tumor cells.




## ETIOLOGY AND CLINICAL MANIFESTATIONS

### Antibody Deficiency Diseases

- B cells synthesize antibodies can:
  1. Kill pathogens in conjunction with complement proteins
  2. facilitate uptake of pathogens by phagocytic cells
  3. Neutralize toxins secreted by pathogens.
- Disorders of B cells → ↑ encapsulated bacteria infections as antibodies are necessary for their clearance.
- A variety of defects can affect the **development or function of B cells** leading to the inability to synthesize specific antibodies.

### Agammaglobulinemia:

- Absence of B cells with subsequent absence or severe decrease in Ig levels and a total absence of specific antibody.
- **X-linked agammaglobulinemia**: (Brutons)
  - ♥ congenital immunodeficiency affects males
  - ♥ Characterized by a profound B cells deficiency → **severe hypogammaglobulinemia and absence of lymphoid tissue.**
  - ♥ The defect is caused by mutations in a gene on chromosome Xq22
  - ♥ The major consequence is the arrest of B cell development at the pre-B cell state.
  - ♥ X-linked agamma-globulinemia is more common than the autosomal recessive forms because only one copy of the gene needs to be defective to express the disease.
- Patients with agammaglobulinemia present during the first 6 -12 months of life, as maternal antibodies are waning.
- Some patients do not present with symptoms until 12 months or 3 - 5 years of age.
- These patients develop infections with *S. pneumoniae, H. influenzae, S. aureus,* and *Pseudomonas,* organisms for which antibody is an important opsonin.
- Gastrointestinal problems except for enteroviral infection and giardiasis are rare, in contrast to the frequency of gastrointestinal symptoms seen in CVID.
- agammaglobulinemia patients are susceptible to viral infections.eg: chronic enteroviral meningoencephalitis and attenuated live virus vaccine-associated poliomyelitis.

### CVID: (Common Variable ImmunoDeficiency)

- Heterogeneous disorder characterized by hypogammaglobulinemia developing after an initial period of normal immune function, most commonly in the **teens and 20s**.
- **Serum IgG < 500 mg/dL** (usually <300 mg/dL) ,**IgA levels < 10 mg/dL**, ↓ **IgM levels**.
- Antibody titers to protein antigens, such as tetanus and diphtheria, and to polysaccharide antigens, such as pneu-mococcus, are absent.
- **T cell function is variable**; decreased numbers of CD4 T cells, decreased lymphocyte proliferation to mitogens and antigens, or normal.

- B cells may be present at low or normal numbers
- Normal-sized or enlarged tonsils and lymph nodes and may have **splenomegaly**.
- CVID patients have a susceptibility to:
  1. Frequent respiratory tract infections; bronchiectasis
  2. autoimmune diseases- (RA, SLE, ITP, graves disease): hemolytic anemia, thrombocytopenia, and neutropenia
  3. GI disease: malabsorption, chronic diarrhea, liver dysfunction, *Helicobacter pylori*
  4. granulomatous disease
  5. Cancer, especially lymphoma.
- CVID is observed frequently in families with IgA deficiency.
- The gene defects leading to CVID are unknown (AR, AD).
- D/D that must be excluded first:
  1. hypogammaglobulinemia secondary to immunoglobulin loss (intestinal loss)
  2. hypogammaglobu-linemia associated with thymoma.
  3. X-linked agammaglobulinemia
  4. X-linked lymphoproliferative disease
  5. hyper-IgM syndrome.

## SELECTIVE IGA DEFICIENCY

- Defined as **serum IgA levels < 5 -10 mg/dL** accompanied by normal or increased levels of other immunoglobulins.
- It occurs in 1 in 500 individuals- the most common.
- Many patients with selective IgA deficiency are asymptomatic.
- In others, associated with:
  1. recurrent sinopulmonary infections
  2. $IgG_2$ subclass deficiency
  3. food allergy
  4. autoimmune disease
  5. Celiac disease.
- IgA deficiency occurs in families→ autosomal inheritance.
- seen in families with CVID.
- The genes for IgA deficiency reside in the MHC class III on chromosome 6.

## IgG SUBCLASS DEFICIENCY

- Occurs when the level of antibodies in ≥1 of the four IgG subclasses is selectively decreased, while total IgG levels are normal or only slightly decreased.
  1. **$IgG_1$**: most prevalent of the IgG subclasses, deficiency → hypogammaglobulinemia.
  2. **$IgG_2$**: **the most common of these deficiencies** and often is associated with IgA deficiency, ataxia-telangiectasia, and reduced capacity to produce antibody against polysaccharide antigens.
  3. **$IgG_3$**: associated with recurrent infections.
  4. **IgG4**: not considered to be clinically significant.
- Inability to synthesize specific antibody titers to protein or polysaccharide antigens → recurrent infections.

## TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY

- **Temporary** condition characterized by **delayed immunoglobulin production**.
- The pathogenesis of this disorder is unknown= prolongation of the physiologic hypogammaglobu-linemia of infancy.
- The normal Ig nadir at 6 months of age is accentuated, with Ig levels < 200 mg/dL.
- B and T cells are present, and antibodies can be synthesized to protein antigens, such as diphtheria and tetanus toxoid.
- Immunoglobulin levels remain diminished throughout the first year of life, but increase to normal, age-appropriate levels by 2 to 4 years of age
- low levels may persist longer.
- The incidence of sinopulmonary infection is increased in some patients.
- This diagnosis suspected if hypogammaglobulinemia is associated with normal antibody titers to protein antigens.

- The transient nature of this disorder cannot be confirmed, however, until immunoglobulin levels return to the normal range.

### Antibody deficiency syndrome

- Inability to synthesize specific antibody to poly-saccharide antigens, such as to the 23-valent pneumo-coccal vaccine.
- characterized by recurrent infections with normal immunoglobulin levels and normal lymphocyte numbers and subsets
- The pathogenesis of this disorder is unknown
- The lack of specific antibody titers →recurrent infections.

## Combined Immunodeficiency Diseases

### Hyper-IgM syndrome

- Classified under antibody deficiency diseases or B cell disorders.
- **X-linked hyper-IgM: The most common form** of hyper-IgM, is a combined immunodeficiency disease, with deficient T cell function.
- Hyper-IgM syndrome is characterized by:
  1. failure of Ig isotype switching from IgM & IgD to IgG, IgA, or IgE
  2. lack of memory responses
- Patients have **normal or ↑ levels of IgM with ↓ or absent IgG, IgA, IgE.**
- Immunoglobulin isotype switching allows a B cell to maintain antigen specificity while altering immunoglobulin function.
- Other forms of AR hyper-IgM: restricted to B cells and present with a failure of Ig isotype switching **without abnormality in T cell priming** → antibody disorder and not a combined immunodeficiency.
- May have small lymph nodes with no germinal centers,or lymphadenopathy and large germinal centers.
- All patients have a susceptibility to sinopulmonary infections
- The hyper-IgM phenotype is found in an X-linked disorder associated with ectodermal dysplasia , with a different susceptibility to infection: meningitis & atypical mycobacteria.

### SCID

- Characterized by a profound lack of T cell function and B cell dysfunction resulting from the gene defect itself or secondary to lack of T cell function .
- SCID can result from any specific genetic mutation that interferes with T cell development in the thymus or T cell function in the periphery.
- **X-linked SCID**
  - ♥ the most common form of SCID
  - ♥ caused by mutations in the gene on chromosome Xq13.1 coding for the common gamma chain of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors.
  - ♥ Affected patients have:
    1. no T cells or NK cells in the peripheral blood
    2. normal numbers of B cells
    3. Immunoglobulin levels are low or undetectable
    4. Lymph nodes and tonsils are absent.
  - ♥ The defect in T cell and NK cell development results from a failure of signaling via the IL-7 and IL-15 receptors
- **Autosomal recessive SCID**:
  - ♥ Results from defects in signaling molecules, such as

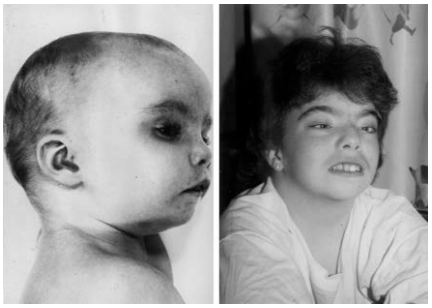
1. Janus tyrosine kinase 3 (Jak3), which signals downstream of the common gamma chain: T cells and NK cells are absent, B cells normal numbers not functional.
2. ZAP-70 kinase, marked decrease in CD8 T cells with normal numbers of CD4 T cells that are not functional.

- **Omenn syndrome**:
  - ♥ Mutations in *RAG1* or *RAG2* that preserve limited function result in, a variant form of autosomal recessive SCID with no T cells or B cells present.

- characterized by:
  1. exfoliative erythroderma
  2. lymphadenopathy
  3. hepatosplenomegaly
  4. marked eosinophilia
  5. elevated serum IgE
  6. Impaired T cell function.

- **Bare lymphocyte syndrome**
  - Results from absence of either MHC class I or MHC class II molecules.
  - Lymphoid tissue and B cells may be present in normal amounts
  - CD4 T cells are decreased or absent in class II deficiency, CD8 cells are decreased or absent in class I deficiency.
- All patients with ADA or purine nucleoside phosphorylase deficiency SCID have lymphopenia and loss of immune function over time (**Nezelof syndrome-late onset**).
- **Clinical manifestations** of SCID:
  1. failure to thrive
  2. severe bacterial infection in the first month of life
  3. chronic candidiasis
  4. infection with *P. jirovecii* (*carinii*) and other opportunistic organisms
  5. intractable diarrhea
  6. Skin disease similar to eczema, related to GVHD from engraftment of maternal lymphocytes, which is not fatal.
  7. Susceptible to fatal GVHD, from lymphocytes in blood transfusions→ should receive irradiated blood products.

## DiGeorge syndrome



- Inherited in AD, AR, X-linked fashions.
- dysmorphogenesis of the 3ed & 4th pharyngeal pouches→hypoplasia of the thymus (where T cells must mature) →T cell deficiency .
- Pathological hallmarks include conotruncal abnormalities and absence or hypoplasia of thymus and parathyroid glands (hypoparathyroidism).
- characteristic diagnostic marker, most of del22 patients have long tapered fingers.(skeletal anomalies)
- Most, but not all, patients represent a subset of patients with a field defect on chromosome **22**q11.2, including:
  1. **velocardiofacial syndrome**
  2. **CATCH 22 syndrome** (**c**ardiac anomalies, **a**bnormal facies, **t**hymic hypoplasia, **c**left palate, and **h**ypocalcemia).

> **Note:**
> **Facies :** hypertelorism, micrognathia, short philtrum, fish-mouth, antimongoloid slant, and telecanthus + short palpebral fissures.
> **Otolaryngic**: low-set ears, defective pinna; cleft palate; velopharyngeal insufficiency.

- DiGeorge syndrome is classically characterized by:
  1. hypocalcemic tetany(60%)
  2. conotruncal and aortic arch anomalies (e.g., interrupted aortic arch type B, **TOF**: most common, and truncus arteriosus)
  3. Increased infections.
- The diagnosis of CATCH 22 is established by fluorescent in situ hybridization with a DNA probe to detect deletions in chromosome 22q11.2.
- Most patients have partial immune defects with low T cell numbers and function that improve with age.
- A congenital heart defect is the main cause of morbidity and mortality.
- Severe T cell deficiency is rare, but results in SCID (lack of T cell and B cell function).

## Wiskott-Aldrich syndrome:

- **X-linked disorder** in early infancy characterized by:
  1. thrombocytopenia
  2. eczema
  3. defects in cell-mediated and humoral immunity
  4. predisposition to lymphoproliferative disease.

- It is caused by mutations of the gene Xp11.22 coding for the Wiskott-Aldrich syndrome protein, expressed in lymphocytes, platelets, and monocytes.
- Mutation Result in:
  1. ↑ IgE and IgA, ↓IgM
  2. poor responses to polysaccharide antigens
  3. waning T cell function
  4. profound thrombo-cytopenia.
- Opportunistic infections and autoimmune cytopenias :problematic in older children.
- **Isolated X-linked thrombocytopenia** results from mutations of the identical gene.
- Prognosis:
  1. One third of patients with Wiskott-Aldrich syndrome die as a result of **hemorrhage**
  2. Two thirds die as a result of **recurrent infection** caused by bacteria, CMV, *P. jirovecii* (*carinii*), or herpes simplex virus.
- Bone marrow or stem cell transplantation has corrected the immunologic and hematologic problems in some patients.

## Ataxia-telangiectasia: AR

- Patients have **cutaneous and conjunctival telangiectasias** and **progressive cerebellar ataxia** with degeneration of Purkinje cells.
- Caused by the *ATM* (ataxia-telangiectasia, mutated) gene on chromosome **11**q22.3.
- **↓ IgA, ↓ IgE, ↓$IgG_2$ subclass (variable severity), variably depressed T cell function.**
- Ataxia-telangiectasia cells are exquisitely sensitive to irradiation.
- **Leukemias**, **lymphomas**, **diabetes** may be present, and **sexual maturation is delayed**.
- There is no uniformly effective therapy for this disease
- antimicrobial therapy and IVIG replacement therapy may be helpful.

## Chronic mucocutaneous candidiasis: AR

- Characterized by chronic or recurrent candidal infections of the mucous membranes, skin and nails. 3-5 years.
  1. normal antibody production
  2. decreased or absent lymphocyte proliferation
  3. Delayed skin reactivity to *Candida*.
- Patients do not respond to topical antifungal therapy and must be treated with oral antifungal agents.
- In most patients, an autoimmune endocrine disorder, such as **hypoparathyroidism** and **Addison disease**, develops by early adulthood.
- **Autoimmune hemolytic anemia**, also have been reported.

## X-linked lymphoproliferative disease

- Defect in immune responsiveness to Epstein-Barr virus (EBV).
- Boys with this disease are normal, until they become infected with EBV (infectious mononucleosis), which is **fatal in 80% of patients**.
- The disease is caused by a mutation in the gene called *SH2D1A* at chromosome Xq25, which codes for protein that inhibits signal in proliferating T cells.
- In EBV infection→ **extensive expansion of CD8 T cells→hepatic necrosis→ death**.
- Boys who survive the EBV infection have significant **hypogammaglobulinemia** , with **aplastic anemia** and **lymphoma**.
- Treatment of the acute EBV infection: prednisone, acyclovir, VP-16 and anti-CD20 monoclonal antibody.
- IVIG for hypogammaglobulinemia is indicated.
- Bone marrow transplantation has prevented disease progression.

## Hyper-IgE syndrome

- characterized by:
  1. Markedly **elevated serum IgE levels**
  2. **rash** that resembles atopic dermatitis
  3. **eosinophilia**
  4. **staphylococcal abscesses** of the skin, lungs, joints, and viscera.

- Infections with *H. influenzae, Candida,* and *Aspergillus* may occur.
- These patients have **coarse facial features**, **osteopenia, Failure to shed 1st teeth.**
- May have **giant pneumatoceles** in the lungs after staphylococcal pneumonias.
- serum IgG, IgA, and IgM concentrations are near-normal but humoral immune responses to specific antigens are reduced, as is cell-mediated immunity.
- Long-term treatment with antistaphylococcal medications is indicated, and IVIG therapy may be helpful.

## TREATMENT

- All blood products to be transfused need to be irradiated and ascertained to be CMV negative because lymphocytes present in blood products can cause fatal **GVHD** in SCID.
- CMV is fatal in an immunodeficiency patient undergoing bone marrow transplantation.
- Live viral vaccines need to be withheld from patients and household members because patients with T cell deficiency or agammaglobulinemia are susceptible to infection from it.
- Patients with milder forms of antibody deficiency diseases may benefit from **vaccination** with protein-conjugated polysaccharide vaccines to *H. influenzae* type b and *S. pneumoniae* (seven-valent), with postvaccination titers assayed at least 1 month later.
- **Antibiotic prophylaxis** : once-daily trimethoprim-sulfamethoxazole or amoxicillin 1/2 the therapeutic dose, if Pt haven't a severe antibody deficiency or complicated infection.
- **Immunoglobulin replacement therapy** with IVIG is a lifesaving therapy for patients with severe antibody deficiency diseases.
  - ♥ provides passive immunity against common infectious microorganisms
  - ♥ Reduces the frequency and severity of infection in most patients with antibody deficiency diseases.
  - ♥ IVIG is indicated in patients with:
    1. antibody deficiency diseases: agammaglobulinemia,hyper-IgM syndrome, others
    2. combined immunodeficiency diseases
    3. patients with infections requiring hospitalization, especially in ICUs
    4. infections that affect growth, development, or hearing and speech development
    5. Patients who have failed antibiotic prophylaxis.
  - ♥ IVIG is administered at a dose =400- 500 mg/kg every 3 to 4 weeks.
  - ♥ IVIG therapy should be monitored by regularly measuring trough IgG levels, antibody titers to *H. influenzae* type b, and, most importantly, the clinical course.
  - ♥ **Complications of IVIG** therapy include:
    1. Transfusion reactions with chills, fever, and myalgia, prevented by pretreatment with antihistamine and antipyretic and by slower rate of infusion.
    2. Headache - aseptic meningitis, in the first 24 hours, responds to ibuprofen.
    3. Allergic reactions occur in patients with absent IgA if the patient develops IgE antibodies to the IgA present in IVIG. (No problem if with detectable serum IgA levels or no synthesize of any antibodies).
    4. Allergic reactions are rare and should
    5. The risk for transmission of infectious agents is low, but the potential remains.
- Therapy for severe T cell disorders is stem cell transplantation, from an HLA-matched sibling.
- **GVHD**, in which the transplanted cells initiate an immune response against the host tissues, is the main complication of bone marrow transplantation.
- **Examine diarrheal stools for *Giardia* and *Clostridium difficile***
- Prenatal diagnosis is possible for all immunodeficiency diseases with an identified gene defect.

# NEUTROPHIL DISORDERS

- Neutrophils play **important roles in immunity and wound healing**.
- The major function of neutrophils is to ingest and kill pathogens.
- Neutrophil disorders result from:
  1. Deficient cell numbers
  2. Defective chemo-taxis
  3. Defective function.
- Patients with neutrophil disorders are susceptible to infections with *S. aureus,* certain fungi, and gram-negative bacteria.
- present with:
  1. mucous membrane infections (gingivitis)
  2. abscesses in the skin and viscera
  3. lymphadenitis
  4. poor wound healing
  5. delayed umbilical cord separation
  6. absence of pus.
- Neutrophils develop by the action of -stimulating factors: stem cell factor, granulocyte - monocyte colony-stimulating factor (GM-CSF), G-CSF, IL-3.
- **Chemotactic factors**, including the complement fragment C5a, IL-8, and bacterial formylated peptides.
- Neutrophils kill ingested pathogens by enzymes found in granules or by activation of oxygen radicals.

## ETIOLOGY AND CLINICAL MANIFESTATIONS

### DISORDERS OF NEUTROPHIL NUMBERS

- The normal neutrophil count varies with age.
- **Neutropenia** is defined as an absolute neutrophil count (ANC) less than 1500/mm$^3$ for white children 1 year old or older.
- Neutropenia may be caused by decreased marrow production or peripheral neutrophil destruction.
- Neutropenia characterized as
  1. **mild neutropenia,** with an ANC of 1,000-1,500/µL.
  2. **moderate neutropenia,** with an ANC of 500-1,000/µL.
  3. **severe neutropenia,** with an ANC <500/µL.
- The effect of neutropenia depends on its severity.
  - ♥ The increased susceptibility to infection is minimal until the ANC is < 1000/mm$^3$
  - ♥ Most patients do well with an.
  - ♥ ANC > 500/mm$^3$: localized infections are more common than generalized bacteremia.
  - ♥ Serious bacterial infections are common with an ANC less than 200/mm$^3$.
  - ♥ patients ANC ranges from 100 -500/mm$^3$ have ↑frequency of infections, particularly respiratory infections: major problem is the slow resolution of the infections.
- Neutropenia may be congenital or acquired.
- The major types of infection associated with neutropenia are:
  1. cellulites
  2. gingivitis
  3. pharyngitis
  4. pneumonia
  5. enteritis (typhlitis)
  6. abscesses (cutaneous or perianal)
  7. lymphadenitis
- The sites of the infection usually are colonized heavily with normal bacterial flora that becomes invasive in the presence of neutropenia.
- **Drugs Associated with Neutropenia**
  1. Cytotoxic drugs
  2. Phenytoin, Carbamazepine
  3. Chloramphenicol Sulfonamides Penicillins Trimethoprim-sulfamethoxazole

4. Gold salts Penicillamine
5. Indomethacin
6. Cimetidine, Methyldopa

- Infections Associated with Neutropenia
  1. **Bacterial:** Typhoid-paratyphoid, Brucellosis, Neonatal sepsis, Meningococcemia, Tuberculosis, Congenital syphilis
  2. **Viral:** Measles, Hepatitis B, HIV, Rubella, CMV,EBV, Influenza
  3. **Rickettsial:** Rocky Mountain spotted fever, Typhus

## Mechanisms of Neutropenia

| |
|---|
| **Abnormal Bone Marrow** |
| ***Marrow Injury*** **:** Drugs( idiosyncratic, cytotoxic), Radiation, Chemicals( DDT, benzene) , Hereditary, Immune-mediated( T and B cell and immunoglobulin) , Infection( HIV, hepatitis B) ,Infiltrative processes(tumor, storage disease) |
| ***Maturation Defects*****:** Folic acid deficiency , Vitamin $B_{12}$ , Glycogen storage disease type Ib , Shwachman-Diamond syndrome, Organic acidemias, Clonal disorders: congenital, Cyclic neutropenia |
| **Peripheral Circulation** |
| *Pseudoneutropenia: Shift to Bone Marrow* : Hereditary ,Severe infection |
| *Intravascular*:<br>Destruction: neonatal isoimmune, autoimmune, hypersplenism.<br>Leukoagglutination: lung, after cardiac bypass surgery |
| **Extravascular Mechanisms** |
| Increased use: severe infection, anaphylaxis |
| Destruction: antibody-mediated, hypersplenism |

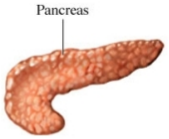
## Congenital neutropenia

- Caused by an inadequate production of cells.

## Severe congenital neutropenia (Kostmann syndrome)

- Inherited as an autosomal recessive disorder and may present in infancy.
- The peripheral blood shows an impressive mono-cytosis.
- Endogenous G-CSF levels are increased; nevertheless, exogenous G-CSF produces a rise in the neutrophil count.
- Treatment: G-**CSF**.
- **Acute myeloid leukemia** has developed in a few Pt survived into adolescence.
- Bone marrow transplantation may be curative.

## Shwachman-Diamond syndrome




- **Severe congenital neutropenia** that may be either persistent or cyclic
- An **autosomal recessive syndrome** of **pancreatic insufficiency** accompanying **bone marrow dysfunction**.
- **panmyeloid disorder** in which neutropenia is the most prominent manifestation.
- Common complications of neutropenia: **gingivitis**, if severe → alveolar bone destruction.
- Patients may become **edentulous at an early age**.
- **Metaphyseal dysostosis** and **dwarfism**.
- Treatment: G-**CSF**.

## Benign congenital neutropenia

- Functional diagnosis for patients with significant neutropenia in whom major infectious complications do not develop.
- These disorders: sporadic or familial and in some instances are transmitted as AD .

### SCID IN RETICULAR DYSGENESIS

- Severe congenital neutropenia
- Disorder of hematopoietic stem cells affecting all lineages.

### CYCLIC NEUTROPENIA

- stem cell disorder in which all marrow elements cycle
- autosomal dominant, recessive, or sporadic disorder
- The only clinically significant abnormality is neutropenia, because of the short half-life of neutrophils in the blood (6 to 7 hours) compared with plts (10 days) & RBCs(120 days).
- The usual cycle is 21 days: neutropenia lasting 4 to 6 days + monocytosis & eosinophilia.
- Clinical manifestations: present at the time of neutropenia:
  1. stomatitis or oral ulcers
  2. pharyngitis
  3. lymphadenopathy
  4. fever
  5. cellulites
  6. Severe, debilitating bone pain -when the neutrophil count is low.
- Cyclic neutropenia responds to G-CSF with a reduced number of days of neutropenia and an overall increase in neutrophil numbers.

### OTHERS:

### NEONATAL NEUTROPENIA:

- Neutropenia is common in stressed neonates.
  1. any major illness, including asphyxia.
  2. Maternal conditions, such as hypertension and eclampsia.
  3. Secondary to depletion of bone marrow stores. May due to Infectious processes

### ISOIMMUNE NEUTROPENIA

- occurs in neonates and is the result of transplacental transfer of maternal antibodies to fetal neutrophil antigens.
- The mother is sensitized to specific neutrophil antigens on fetal leukocytes that are inherited from the father and are not present on maternal cells.
- Isoimmune neonatal neutropenia is a transient process.
- Cutaneous infections are common, whereas sepsis is rare.
- Early treatment of infection while the infant is neutropenic is the major goal of therapy.
- IVIG decrease the duration of neutropenia.

### AUTOIMMUNE NEUTROPENIA

- Develops early in childhood (5 to 24 months old) and often persists for prolonged periods.
- Neutrophil autoantibodies may be IgG, IgM, IgA, or a combination of these.
- the condition resolves in 6 months to 4 years.
- most patients respond to G-CSF.
- autoimmune neutropenia **rarely** may be an early manifestation of systemic lupus erythematosus or rheumatoid arthritis.
- The marrow in autoimmune neutropenia and SLE shows myeloid hyperplasia except that if antibody is directed against myeloid precursors, it reveals hypoplasia.

## DISORDERS OF NEUTROPHIL MIGRATION

- Neutrophils adhere to endothelium and migrate to areas of inflammation by the interaction of membrane proteins called *integrins* and *selectins* with endothelial cell adhesion molecules.
- A hallmark of defects in neutrophil migration is the absence of pus at sites of infection.
- The presence of neutrophils in abscesses or other sites of infections rules out a chemotactic defect.

### Leukocyte adhesion deficiency type I (LAD-I)

- Transmitted as an autosomal recessive trait.
- infants lacking the $\beta_2$ integrin CD18
- exhibit the condition early in infancy with:
  1. failure of separation of the umbilical cord (often 2 months after birth)
  2. omphalitis
  3. sepsis
  4. The neutrophil count > 20,000/$mm^3$ because of failure of the neutrophils to adhere to vascular endothelium and to migrate out of blood to the tissues.
  5. severe gingivitis
- Cutaneous, respiratory, and mucosal infections occur.
- Sepsis usually leads to death in early childhood.
- Bone marrow transplantation may be lifesaving.

### Leukocyte adhesion deficiency type II (LAD-II)

- Results from a general defect in fucose metabolism → absence of sialylated Lewis X blood group on the surface of neutrophils & other leukocytes→ impairment of neutrophil rolling along the vascular wall (the first step in neutrophil migration into tissues and sites of infection).

### Hyper-IgE syndrome

- characterized by:
  1. eczema
  2. hyperimmunoglobulinemia E
  3. extrinsic chemotactic defect
  4. absent T cell and B cell responses to antigens
  5. Recurrent **cold boils** (characteristically caused by *S. aureus*) that do not become markedly red or drain .

## Disorders of Neutrophil Function

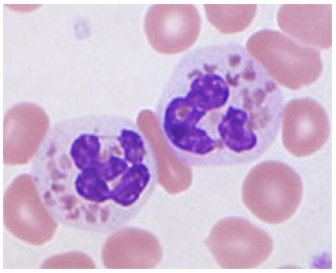
- Defects in neutrophil function are relatively rare inherited disorders
- Associated with a marked susceptibility to bacterial and fungal infection.

### CGD

- rare disorder of white blood cells
- Inability to activate the "respiratory burst," the catalytic conversion of molecular oxygen to superoxide ($O_2^-$)→ defective intracellular killing of bacteria and intracellular pathogens by neutrophils and macrophages.
- inability to kill catalase-positive pathogens, such as:
  1. *S. aureus*
  2. enteric gram-negative bacteria *(Salmonella, Proteus, Klebsiella, Escherichia coli, Serratia marcescens, Burkholderia cepacia)*
  3. fungi *(Aspergillus fumigatus, Candida albicans, Torulopsis glabrata)*.
- The $gp91^{phox}$ gene is located on Xp21.1 , the more common form of the disease because only one copy of the gene needs to be defective to be expressed in males.
- The other gene defects are inherited in an autosomal recessive manner
- Severe forms of **glucose-6-phosphate dehydrogenase deficiency** result in CGD (involved in the production of superoxide).
- Patients characteristically have:
  1. lymphadenopathy
  2. hypergammaglobulinemia
  3. hepatosplenomegaly
  4. dermatitis
  5. failure to thrive
  6. anemia
  7. chronic diarrhea
  8. abscesses

9. Infections: chronic bronchitis, and in the middle ear, gastrointestinal tract, skin, urinary tract, lymph nodes, liver, and bones.
10. Granulomas may obstruct the pylorus or ureters.

## CHÉDIAK-HIGASHI SYNDROME



- Abnormality of secondary granules: caused by a mutation in a cytoplasmic protein (CHS1) involved in organellar protein trafficking, resulting in fusion of the primary and secondary granules in neutrophils.
- autosomal recessive disorder
- **Giant granules** are present in many cells: lymphocytes, platelets, and melanocytes.
- Patients have **partial oculocutaneous albinism**.
- **defective neutrophil and NK cell function**, leading to recurrent and sometimes fatal infections with streptococci and staphylococci.
- Most patients progress to an accelerated phase associated with EBV infection and characterized by a **lymphoproliferative syndrome** with:
  1. generalized lymphohistiocytic infiltrates
  2. fever
  3. jaundice
  4. hepatomegaly
  5. adenopathy
  6. pancytopenia.

## LABORATORY DIAGNOSIS

- The evaluation of a neutropenic child depends on:
  1. associated clinical abnormalities, such as signs of infection
  2. family history
  3. medication history
  4. age of the patient
  5. cyclic or persistent nature of the condition
  6. signs of bone marrow infiltration (malignancy or storage disease)
  7. Evidence of involvement of other cell lines.
- Neutropenia is **confirmed by CBC** and differential.
- A **bone marrow aspirate and biopsy** : determine if the neutropenia is due to a failure of production in the bone marrow, infiltration of BM, or loss of neutrophils in the periphery.
- **Antineutrophil antibodies** → autoimmune neutropenia.
- Neutrophil chemotactic defects can be excluded by the presence of neutrophils at the site of infection.
- The **Rebuck skin window** is a 4-hour in vivo test for neutrophil chemotaxis that is not performed routinely by most laboratories.
- **Flow cytometry** for presence of adhesion molecules→leukocyte adhesion defects, CGD.
- CGD can be diagnosed by **nitroblue tetrazolium** test→ soluble yellow dye is reduced to an insoluble blue compound in activated neutrophils that have generated oxygen radicals.
- **Light microscopy** of neutrophils for the presence of giant granules can help diagnose Chédiak-Higashi syndrome.
- The presence of an elevated **IgE level**, especially in association with poor antibody and T cell responses to antigens, suggests hyper-IgE syndrome.

## DIFFERENTIAL DIAGNOSIS

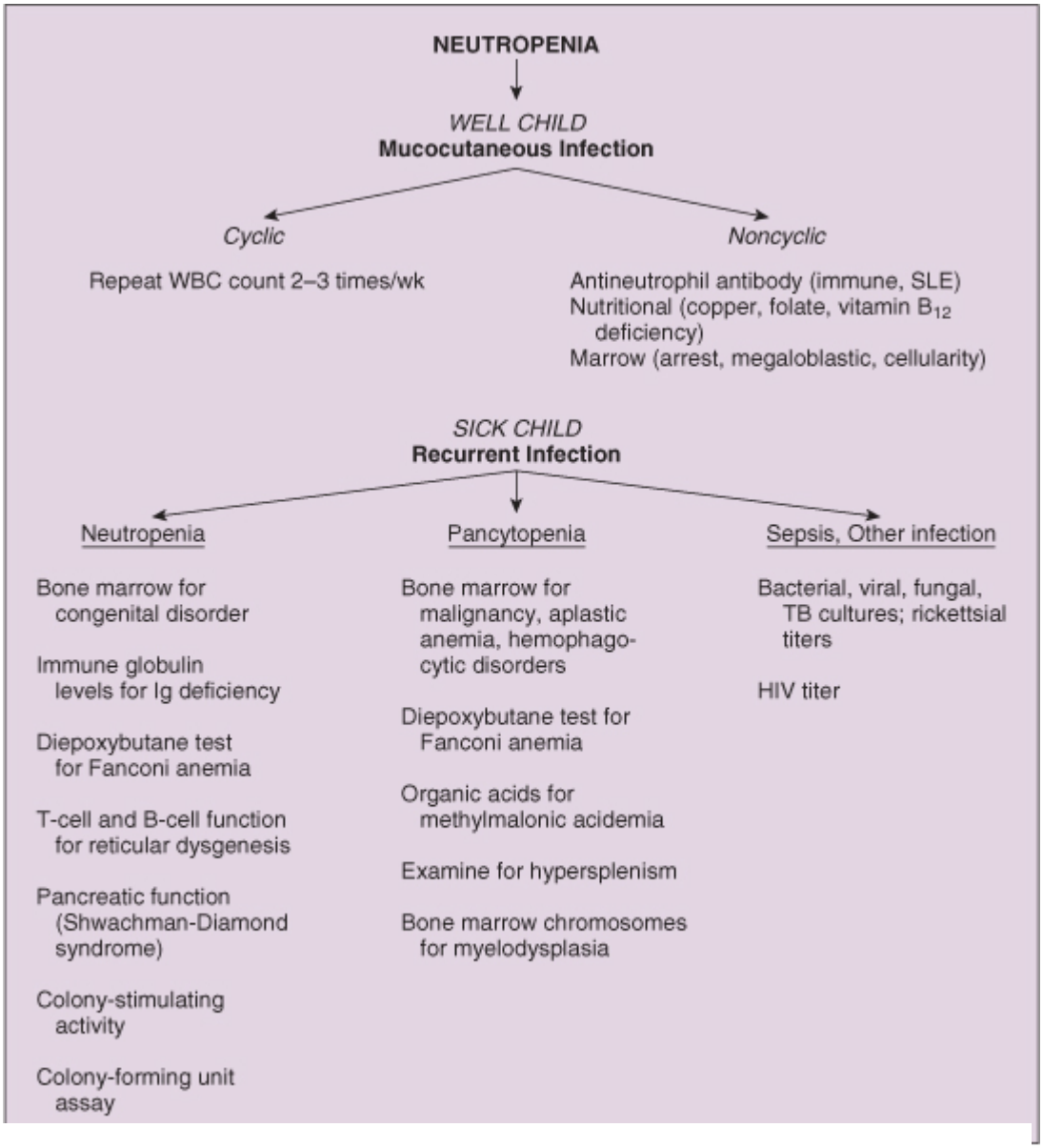
- Neutropenia can result from bone marrow infiltration from malignancy or from a storage disease.
- The differential diagnosis of autoimmune neutropenia includes:
  1. systemic lupus erythematosus
  2. rheumatoid arthritis (Felty syndrome)
  3. immunodeficiency
  4. drug-induced neutropenia.
- Atopic dermatitis can be associated with elevated IgE levels and superficial skin infections, but not with deep-seated infections and abscesses.

## TREATMENT

- Therapy for neutropenia depends on the underlying cause.
- Patients with severe bacterial infections require broad-spectrum antibiotics
- the resolution of neutropenia during an infection is a good prognostic sign.
- Most patients with severe congenital neutropenia or autoimmune neutropenia respond to therapy with **G-CSF**.
- **Granulocyte transfusion** for life-threatening infection; the results → disappointing.
- Chronic mild neutropenia not associated with immunosuppression : antimicrobial treatment of soft tissue infections, which caused by *S. aureus* or group A streptococci.
- Frequent courses of antibiotics, including trimethoprim-sulfamethoxazole prophylaxis, and surgical débridement of infections are required in **CGD**.
- *A. fumigatus* can cause serious infection in CGD, moldy hay, decomposing compost, and other nests of fungi must be avoided.
- The frequency of infection in CGD ↓ by **recombinant interferon-γ SC** 3/ week.
- Stem cell transplantation lifesaving in CGD, LAD-1, and Chédiak-Higashi syndrome.

## PROGNOSIS AND PREVENTION

- interferon-γ has improved the prognosis of CGD, bone marrow transplantation is the only mode of therapy that can reverse the poor prognosis of severe neutrophil defects.
- prenatal diagnosis and genetic counseling are possible for all known gene mutations.



# COMPLEMENT

- The **complement system** consists of several plasma and membrane proteins that function in the innate immune response and in adaptive immunity by complementing antibody-mediated immunity.
- **Complement proteins** can kill pathogens with or without antibody, opsonize pathogens to facilitate their uptake by phagocytes, or mediate inflammation.
- Disorders of the complement predispose to:
  1. recurrent infection
  2. autoimmunity
  3. angioedema
- **Deficiency of Complement and Associated Disease**
  1. SLE: C(1-6),C3b receptor.
  2. pneumococcal infection: C1
  3. Meningococcal: C(5,6,9),Properdin,factorH.
  4. gonococcal: C5-8.
  5. GN: C(1,2,3,5),FactorH
  6. Raynaud phenomenon: C7
  7. JRA: C2
  8. pyogenic infection:C4
  9. Familial Mediterranean fever: C5a inhibitor
  10. Hereditary angioedema: C1 inhibitor
- Disorders of complement proteins can result from inherited deficiency or can be secondary to increased consumption.
- The consequences of decreased complement depend on the affected factor
- **Deficiencies of early components** of the classic pathway, C1, C2, or C4, are not associated with severe infections, C2 deficiency present with milder recurrent infections.
- Patients with C1, C2, or C4 deficiency are susceptible to autoimmune diseases, especially systemic lupus erythematosus.
- **Deficiency of properdin, C3, or the terminal components** :
  - ◇ Predisposes patients to severe recurrent infections.
  - ◇ Especially with encapsulated organisms : *S. pneumoniae* and *H. influenzae* type b.
  - ◇ Deficiency of one of the terminal components predisposes patients to infection with *Neisseria meningitidis* or *Neisseria gonorrhoeae*.
- 40% of patients presenting with recurrent neisserial infections→ Complement deficiency.
- Deficiency of mannose-binding lectin (MBL) is associated with an increased frequency of bacterial infections, including sepsis.
- **hereditary angioedema**
  - ◇ The disorder is inherited as an autosomal dominant disease
  - ◇ results from a heterozygous deficiency of C1-inhibitor leading to serum levels less than 30% of normal values.
  - ◇ Some mutations (type II hereditary angioedema) result in normal or elevated antigenic levels of C1-inhibitor but defective function.
  - ◇ characterized by recurrent episodes of nonpruritic angioedema lasting 48 to 72 hours.
  - ◇ occurring spontaneously or after minor trauma, stress, or anxiety.
  - ◇ The mechanism by which angioedema occurs in C1-inhibitor deficiency is not known.
  - ◇ Angioedema can occur in any tissue.
    1. Abdominal edema → acute abdominal pain
    2. edema of the upper airway can be life-threatening and may → tra-cheostomy.
  - ◇ An acquired form of angioedema results from autoanti-bodies to C1-inhibitor in lymphoid malignancies or autoimmune disorders, but is uncommon in childhood.

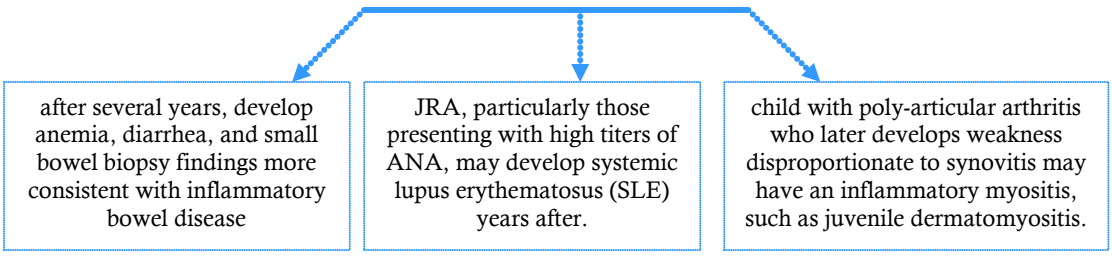
# Rheumatic Diseases of Childhood (Connective Tissue Diseases, Collagen Vascular Diseases)

# APPROACH TO RHEUMATIC DISEASES

- Rheumatic diseases result from autoimmune processes that lead to inflammation of target organs.
- Vasculitis is a component of many rheumatic diseases and is the prominent element of Henoch-Schönlein purpura (HSP) and Kawasaki disease (KD
- The classic rheumatic diseases of children include juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), and juvenile dermatomyositis (JDM).
- rheumatic diseases must be considered for a wide range of presenting complaints as they effect on many organs.
- **OVERLAP SYNDROMES (MIXED CONNECTIVE TISSUE DISEASE)** with manifestations fulfilling criteria for more than one rheumatic disease.
- **UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE** in which manifestations strongly suggest but do not meet diagnostic criteria for a specific rheumatic disease.
- DEFINITIONS:
  - ✓ **ENTHESITIS** is inflammation at the insertion of a ligament to a bone.
  - ✓ **SEROSITIS**, inflammation of serosal linings, such as pleuritis, pericarditis, or peritonitis, gives rise to chest pain, shortness of breath, or abdominal pain.
  - ✓ **MYOSITIS**, inflammation of the muscle, may lead to symptoms of muscle pain, weakness, or difficulty performing tasks of daily living.
  - ✓ **VASCULITIS**, inflammation of the blood vessels, of small vessels deep in the papillary dermis leads to nonspecific symptoms of rash (**petechiae, purpura**) and edema; involvement of medium-sized vessels results in a **circumscribed tender nodule.**
- Because specific diagnostic tests are not available, it is essential to exclude nonrheumatic diseases causing similar symptoms (malignant and infectious etiologies).
- Early diagnosis of rheumatic disease may not always be possible because specific diagnostic manifestations may take months or, rarely, even years to develop after the initial presentation. *Interval repeated clinical evaluations and review of the differential diagnosis is necessary in these circumstances.*

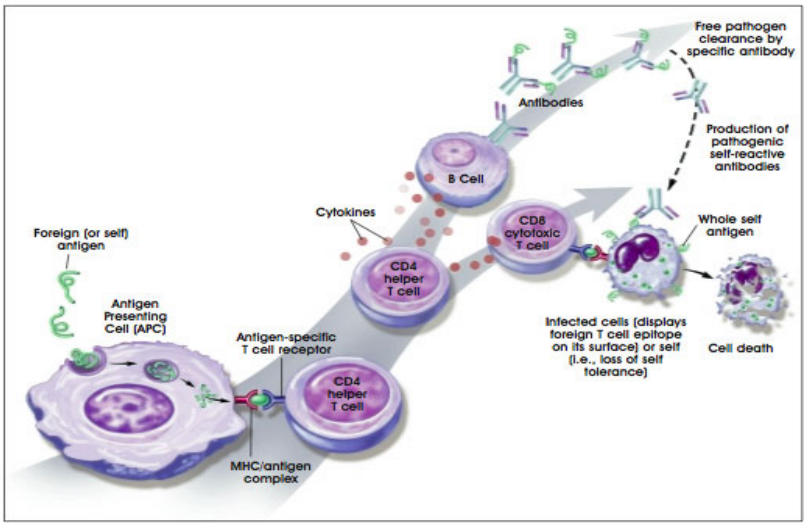
EXAMPLE:

A CHILD MEETING DIAGNOSTIC CRITERIA FOR JUVENILE RHEUMATOID ARTHRITIS (JRA)




## ETIOLOGY AND PATHOGENESIS

- The immune system normally responds to viruses, bacteria, and other non-self molecules but does not mount reactions to self molecules.
- This property of **tolerance** to self is lost in rheumatic diseases= **autoimmune responses.**
- Two possible explanations:
  1. similarity between foreign and self molecules that are recognized by immune cells, particularly T lymphocytes
  2. viral or other infections that incite, exaggerate, or prolong otherwise self-limited immune responses
- Certain genetic factors, such as specific HLA alleles, may influence susceptibility to developing disease




FOREIGN ANTIGENS → ENTER THE GROOVE OF THE HLA MOLECULE ON THE SURFACES OF ANTIGEN-PRESENTING CELLS → T LYMPHOCYTES RECOGNIZE THEM → ACTIVATE OTHER CELLS SUCH AS MACROPHAGESM& B LYMPHOCYTES& PRODUCE INFLAMMATORY CYTOKINES ( TNF-α, IL-1 ,IL-6) → TISSUE DAMAGE

- IL-6 and other cytokines bind to neuronal receptors in the central nervous system, causing fever
- IL-6 and other cytokines interfere with osteoblastic activity, resulting in osteopenia.
- cytokines appear to induce neuroendocrine pathways to produce cortisol, which suppresses cellular and humoral immunity → amplify autoimmune responses.
- The increased incidence of some rheumatic diseases in females may be attributable to the property of female sex hormones to augment cellular immune responses.

## CLINICAL MANIFESTATIONS

- Symptoms Suggestive of Rheumatic Diseases

| SYMPTOM | RHEUMATIC DISEASES | SOME POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS |
|---|---|---|
| FEVERS | Systemic JRA | Malignancies, infections, inflammatory bowel disease, periodic fever syndromes |
| ARTHRALGIA | JRA, SLE, rheumatic fever, juvenile dermatomyositis, scleroderma | Hypothyroidism, trauma, reactive arthritis, endocarditis, other infections |
| WEAKNESS | Juvenile dermatomyositis | Muscular dystrophies, other myopathies |
| MALAR RASH | SLE | Photosensitivity dermatitis, Fifth disease |
| CHEST PAIN | JRA, SLE (with associated pericarditis or costochondritis) | Costochondritis (isolated), rib fracture, viral pericarditis |
| BACK PAIN | JRA, spondyloarthropathy | Vertebral microfracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis |

- Morning stiffness may be reported by children with JRA or postinfectious reactive arthritis.
- Facial rashes in children with joint complaints or weakness suggest lupus or dermatomyositis.
- Raynaud phenomenon may be a primary disorder, or it can be a presenting complaint of children with scleroderma, lupus, and overlapping rheumatic syndromes.
- Weakness can result from muscular dystrophies, viral myositis, and inflammatory myopathies, of which juvenile dermatomyositis is the most common.

- Monoarticular arthritis near the site of trauma may suggest nonrheumatic disease, such as hemarthrosis, a torn meniscus, or osteochondritis.
- Abnormal gait is associated with many orthopedic problems, such as Legg-Calvé-Perthes disease, as well as JRA.
- Foreign travel, enteric illness in the family, or exposure to reptile pets may lead to reactive arthritis after an enteric infection.
- Tick exposure raises the possibility of Lyme arthritis.
- Fever is not specific for rheumatic diseases, and evaluation for infections or malignancies is necessary.
  - ✓ high, spiking fevers returning to or below baseline are typical of systemic JRA
  - ✓ A hectic fever, or fever without periodicity or pattern, is commonly found in vasculitides such as KD, but also occurs in children with underlying infection.
  - ✓ Many other rheumatic illnesses cause low-grade fevers -never exceeding 38.5-.
  - ✓ fevers persist despite an unremarkable evaluation, the autoinflammatory **periodic fever syndromes** should be considered

## PHYSICAL EXAMINATION

- repeated examinations are important to detect new manifestations.
- Lack of normal movement on the examination table may be a result of muscle weakness, arthritis, central nervous system disease, or skeletal abnormality.
- Weight loss or decreased growth velocity may reflect malnutrition from inflammatory bowel disease.
- A pericardial friction rub with orthopnea may occur with pericarditis from lupus or systemic JRA.
- Persisting oral mucosal lesions are found in lupus and Behçet disease
- swollen tongue or lips, raises the possibility of Kawasaki disease, Stevens-Johnson syndrome, and scarlet fever.
- Conjunctival injection could be episcleritis of lupus, conjunctival inflammation of Kawasaki disease, or uveitis.

**NOTE:**
The joint examination can detect arthritis, which can be infectious, rheumatic, or secondary to trauma.

- All children with joint symptoms should be asked about muscle weakness, which is characteristic of dermatomyositis and mixed connective tissue disease.
- The neurologic examination can identify focal deficits resulting from intracranial or intraspinal lesions as well as muscle weakness.
- Pain to palpation along the long bones or ribs is not typical for rheumatic diseases, but raises the possibility of leukemia or neuroblastoma.
- **Arthritis** is evident by either joint swelling or the combination of pain and limited motion.
- **Arthralgia,** or pain in a joint with full range of motion, is seen in trauma, psychogenic arthralgia, immune complex diseases, or early rheumatic disease that cannot yet be specifically diagnosed.

**NOTE:**
**Growing pains** are common in children between *4 and 8 yr* of age, are usually bilateral over the anterior thigh or calf or behind the knee, and are *intermittent*. Children with growing pains have *a normal physical examination and normal laboratory tests.*

- ERYTHEMA NODOSUM:

✓ Is rash characterized by pretibial tender erythematous nodules found in the deep dermis and subcutaneous tissue, is a hypersensitivity reaction resulting from certain infections, inflammatory diseases or drugs.

✓ Lesions evolve from erythematous to bluish, may sometimes be flat, and, in severe cases, may be found along the entire length of the legs and rarely involve the feet or arms.

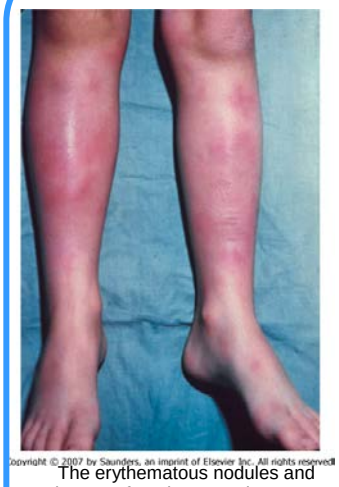
✓ New crops of nodules may develop over several weeks

✓ CAUSES:

1. INFECTIONS: group A streptococcus pharyngitis, tuberculosis, *Yersinia,* histoplasmosis, and coccidioidomycosis

2. INFLAMMATORY DISEASES: inflammatory bowel disease, sarcoidosis, and spondyloarthropathy.
3. DRUGS: sulfonamides, phenytoin, or oral contraceptive agents.

- ✓ Erythema nodosum is sometimes accompanied by fever, D/D:
  1. Cellulitis
  2. insect bites
  3. thrombophlebitis
  4. fungal skin infections
- ✓ It resolves with effective treatment of the underlying etiology.
- ✓ Supportive treatment for severe pain includes bed rest, elevation of the legs, and analgesics.





The erythematous nodules and plaques of erythema nodosum are present over both shins. The skin overlying the lesions is red, smooth, and shiny. The nodules are usually tender.

## LABORATORY FINDINGS

- The erythrocyte sedimentation rate (ESR) and C reactive protein are useful to screen for infectious and rheumatic diseases.
  - ✓ A normal ESR value does not exclude rheumatic disease
  - ✓ Infections typically lead to transiently increased ESR
- The ANA test is a screening test (antibodies against nuclear constituents)
- ✓ A positive titer (≥1 : 80) is a nonspecific reflection of increased lymphocyte activity.
- ✓ Positive ANA tests are found in :
  1. Rheumatic diseases
  2. Idiopathic thrombocytopenic purpura
  3. Crohn disease
  4. Chronic autoimmune hepatitis
  5. Graves disease
  6. Leukemia or lymphoma.
  7. Drugs (anticonvulsant medications (phenytoin, ethosuximide) and antiarrhythmic agents (procainamide) )
  8. Malaria and some parasitic infections.

**Specific Antinuclear Antibodies and Associated Diseases**

| ANTIGEN | DISEASE |
|---|---|
| Histone | Drug-induced lupus |
| Ribonucleoprotein | Sjögren syndrome, scleroderma, polymyositis, MCTD |
| Pm-Sc1 | Sclerodermatomyositis |
| Sc1 | Scleroderma |
| Sm | Systemic lupus erythematosus |
| Ro/SSA (Robert) | Sjögren syndrome, congenital heart block, annular erythema |
| La/SSB (lane) | SLE,Sjögren syndrome |

- ✓ Children with a positive ANA who have non-rheumatic diseases may sometimes develop lupus or overlapping rheumatic syndromes.
- Levels of total hemolytic complement ($CH_{50}$), C3, and C4 are characteristically decreased in active lupus and vasculitis syndromes.
- The complete blood count :normochromic, normocytic anemia of chronic disease.
- Immune activation may be reflected by elevated levels of
  1. immune complexes
  2. serum immunoglobulins
  3. neopterin (a macrophage product)
  4. von Willebrand factor antigen (a molecule found on the surface of vascular endothelium).
- Lactate dehydrogenase levels may be elevated in rheumatic diseases as a result of cell turnover, and marked elevations raise the possibility of *malignancy*.
- Thyroid function studies for hypothyroidism, which cause musculoskeletal symptoms.
- Decreased albumin and serum protein seen in nephrosis or inflammatory bowel disease.
- Bone scans or MRI can detect early osteomyelitis or malignancy. reveal abnormalities of JRA, dermatomyositis, and sarcoidosis, and exclude nonrheumatic abnormalities.
- Echocardiography distinguish patients with rheumatic carditis from those with Kawasaki disease or pericarditis resulting from systemic lupus erythematosus or systemic JRA.

# JUVENILE RHEUMATIC ARTHRITIS

## ETIOLOGY

- The most common chronic rheumatologic disease of childhood is JRA**(juvenile chronic arthritis),** prevalence of **1 : 1000.**
- It is **autoimmune disease** of unknown etiology
- Possible external triggers include viruses (parvovirus B19, rubella, Epstein-Barr virus), host hyperreactivity to specific self antigens (type II collagen), and enhanced T-cell reactivity to bacterial or mycobacterial heat shock proteins.
- The synovitis of JRA is characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the subsynovial tissues.
- The manifestation of this group of illnesses is the presence of chronic **synovitis**.
  - ✓ The synovium becomes thickened and hypervascular with infiltration by lymphocytes
  - ✓ lymphocytes with inflammatory cytokines can be found in the synovial fluid.
  - ✓ The inflammation leads to the production and release of tissue proteases and collagenases.
  - ✓ if left untreated can lead to tissue destruction, particularly of the articular cartilage and eventually the underlying bony structures.
- **Pannus formation,** which is an inflammatory exudate over the synovial lining, occurs in advanced uncontrolled disease and results in progressive erosion of articular cartilage and contiguous bone**.**

## EPIDEMIOLOGY

- The disease has two peaks (1 to 3 years and 8 to 12 years) but JRA can occur in any age group.
- Girls are affected more commonly than boys, particularly with respect to the **pauciarticular form** of the illness.

## CLINICAL PRESENTATION

**Criteria for the Classification of JRA**

| |
|---|
| Age at onset: <16 yr |
| Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joints |
| Duration of disease: ≥6 wk |
| Onset type defined by type of articular involvement in the 1st 6 mo after onset: |
| Polyarthritis: ≥5 inflamed joints |
| Oligoarthritis: ≤4 inflamed joints |
| Systemic disease: arthritis with a characteristic intermittent fever |
| Exclusion of other forms of juvenile arthritis |

- JRA can be divided into three subtypes:

1. pauciarticular
2. polyarticular
3. systemic onset

- Chronic arthritis typically presents with swelling of the joint and effusion.
- the onset of the arthritis is slow, the actual joint swelling is often noticed by the child or parent acutely, such as after an accident or fall, and can be confused with trauma (although traumatic effusions are rare in children).
- Morning stiffness and gelling also can occur in the joint and, if present, can be followed in response to therapy.

**Features of Juvenile Rheumatoid Arthritis Subgroups**

| Feature | PAUCIARTICULAR | POLYARTICULAR | SYSTEMIC ONSET |
|---|---|---|---|
| No. joints | <5 | ≥5 | Varies, usually ≥5 |
| Types of joints | Medium to large | Small to medium | Small to medium |
| Gender predominance | F > M (especially in younger children) | F > M | F = M |
| Systemic features | None | Some constitutional | Prominent |
| Uveitis | +++ | + | + |
| ANA positivity | ++ | + | - |
| RF positivity | - | + (in older children with early onset RA) | - |
| Outcomes | Excellent, >90% complete remission | Good, >50% complete remission, some risk for disability | Variable, depends on extent of arthritis |

- In children, owing to the presence of an active growth plate, it may be possible to find **bony abnormalities** of the surrounding bone. In a lower extremity joint, a leg length discrepancy may be appreciable if the arthritis is asymmetric.
- All children with chronic arthritis are at risk for chronic **iridocyclitis** (anterior uveitis)
- There is an association with:

✓ HLA-DR5, HLA-DR6, and HLA-DR8 and uveitis.

✓ positive **antinuclear antibody (ANA)** and chronic uveitis.

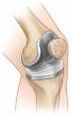
✓ young girls, with pauciarticular JRA and a positive ANA are at highest risk, with an incidence of uveitis of 80%.

- The uveitis associated with JRA can be asymptomatic until the point of visual loss, so it is an indication for slit- lamp ophthalmic exam.

## PAUCIARTICULAR JUVENILE RHEUMATOID ARTHRITIS

- Pauciarticular JRA is defined as the presence of arthritis in fewer than five joints within the first 6 months from diagnosis.
- This is the most common form of JRA (approximately 50% of cases)
- The arthritis is found in medium-sized to large joints, with *the knee being the most common joint* involved followed by the ankle and the wrist.
- It is unusual for small joints, such as the fingers or toes, to be involved.
- Involvement of the hip is almost never a presenting sign of JRA.
- Children with pauciarticular JRA not show any evidence of systemic inflammation.

| PAUCIARTICULAR TYPE I | PAUCIARTICULAR TYPE II |
|---|---|
| 45% | 5% |
| 80% females | 90% males |
| Early childhood | Late childhood |
| Large joints | Large joints |
| ANA 50% | ANA Neg. |
| HLA- B27 0% | HLA- B2 75% |
| Prognosis as spondyloarthritis | Prognosis as spondyloarthritis |

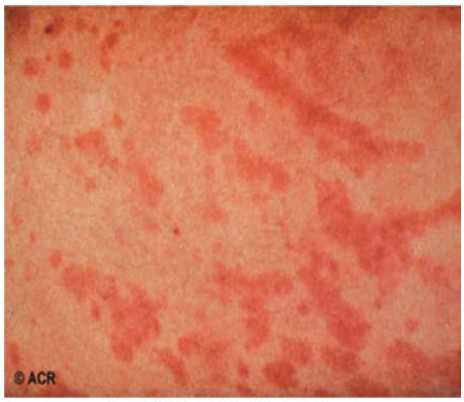


## POLYARTICULAR JUVENILE RHEUMATOID ARTHRITIS

- Polyarticular JRA describes children with arthritis in ≥5 joints within the first 6 months of diagnosis and accounts for about 40% of cases.
- As many as 20-40 joints may be affected in the more severely involved child.
- Children with polyarticular JRA tend to have symmetric arthritis, which can affect any joint, but typically involves the small joints of the hands, feet, ankles, wrists, and knees.
- The cervical spine can be involved, leading to fusion of the spine over time. with a risk of atlantoaxial subluxation and potential neurologic sequelae
- **Rheumatoid nodules** on the extensor surfaces of the elbows and over the Achilles tendons, while unusual, are associated with a more severe course.
- **Micrognathia** reflects chronic temporomandibular joint disease.
- polyarticular disease can present with evidence of systemic inflammation, including malaise, low-grade fever, growth retardation, anemia of chronic disease, and elevated markers of inflammation.
- Differ from the other group by the presence of a positive **rheumatoid factor ( positive in 15% of JRA)**
- Rheumatoid factor-positive polyarticular JRA most likely represent a subgroup with true adult rheumatoid arthritis.
- Polyarthritis with positive RF have > 50% severe arthritis, more than systemic onset which 30% only.

## SYSTEMIC-ONSET JUVENILE RHEUMATOID ARTHRITIS

- A small subgroup of patients (approximately 10%) with juvenile arthritis present with **systemic inflammation** rather than arthritis.
- The arthritis of JRA follows the systemic inflammation by 6 weeks to 6 months.
- characterized by a recurring spiking fever with temperatures to ≥39°C, sometimes followed by mildly hypothermic temperatures for ≥2 wk, once or twice a day.
- Each febrile episode is frequently accompanied by evanescent **salmon-colored lesions**
  - ✓ a characteristic faint, erythematous, macular rash
  - ✓ linear or circular
  - ✓ 2-5 mm in size
  - ✓ distributed in groups with a linear distribution
  - ✓ most commonly over the trunk and proximal extremities .
  - ✓ is not pruritic.
  - ✓ Its most diagnostic feature is its transient nature, with a group of lesions usually lasting <1 hr.
  - ✓ The **Koebner phenomenon** is cutaneous hypersensitivity to superficial trauma resulting in a localized recurrence of the rash, is suggestive, but not diagnostic, of systemic-onset disease.
  - ✓ Heat, such as a warm bath, also evokes a reappearance of the rash.

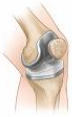




- Internal organ involvement also occurs.
  - ✓ Serositis, ex. pleuritis and pericarditis (50% of cases)
  - ✓ Hepatosplenomegaly (70% of children)
- Laboratory findings also show the inflammation, with elevated ESR, CRP, WBC count, and platelet counts and anemia.
- The arthritis is typically polyarticular in nature and can be extensive and resistant to treatment, placing these children at highest risk for long-term disability.

## LABORATORY AND IMAGING STUDIES

- Most children with pauciarticular JRA may have no laboratory abnormalities.
- Children with polyarticular and systemic-onset disease commonly show Laboratory abnormalities characteristic of inflammation include:



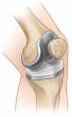
- ✓ elevated erythrocyte sedimentation rate (ESR)
- ✓ elevated C-reactive protein (CRP)
- ✓ Leukocytosis
- ✓ Thrombocytosis
- ✓ anemia of chronic disease,
- indicators for leukemia include a low WBC count or platelet count, instead of elevated values, or significantly lower hemoglobin than would be expected with anemia of chronic disease alone.
- Elevated ANA titers are present in 40-85% of children with oligoarticular or polyarticular JRA, but are unusual in children with systemic-onset disease.
- All patients with pauciarticular JRA should have an **ANA** to help identify patients at higher risk for uveitis.
- Rheumatoid-factor (RF) seropositivity may be associated with:
- ✓ onset of polyarticular involvement in an older child (≈8%)
- ✓ development of rheumatoid nodules
- ✓ poor overall prognosis with eventual functional disability.
- Both ANA and RF seropositivity occur in association with viral infections, particularly Epstein-Barr virus.
- Older children and adolescents with polyarticular disease should have a **rheumatoid factor** performed to identify children with early onset adult rheumatoid arthritis.
- Diagnostic **arthrocentesis** may be necessary to exclude suppurative arthritis in children who present with acute onset of monarticular symptoms.
- ✓ The synovial fluid WBC count less than 50,000 to 100,000/$mm^3$
- ✓ predominantly lymphocytes, not neutrophils as in suppurative arthritis
- ✓ negative Gram stain and culture .
- **The most common radiologic finding in the early stages of JRA is a normal bone x-ray.**
- **periarticular osteopenia is most commonly found**.
- Erosions of bony articular surfaces may be a late finding.
- Abnormalities of skeletal growth become most prominent during the pubertal growth spurt and in postpubertal children (Tanner stages IV-V) and lead osteopenia.

## DIFFERENTIAL DIAGNOSIS

- Although a presumptive diagnosis of systemic-onset JRA can be established for a child during the systemic phase, a definitive diagnosis is not possible until arthritis develops.
- Children must be younger than 16 years old at time of onset of disease; the diagnosis of JRA does not change when the child becomes an adult.
- Because there are so many other causes of arthritis, these disorders need to be excluded before providing a definitive diagnosis of JRA.
- The acute arthritides can affect the same joints as JRA, but have a shorter time course.
- All of the pediatric spondyloarthropathies (associated with spinal involvement and enthesitis)can present with peripheral arthritis before other manifestations and initially may be diagnosed as JRA.

### Comparison of Juvenile Rheumatoid Arthritis and Spondyloarthropathies

| **Clinical Manifestations** | **JRA** | **JAS** | **PsA** poststreptococcal arthritis | **IBD** |
|---|---|---|---|---|
| Gender predominance | **F** | M | Equal | Equal |
| Peripheral arthritis | **+++** | + | ++ | + |
| Back symptoms | **-** | +++ | + | ++ |
| Family history | **-** | ++ | ++ | + |
| ANA positivity | **++** | - | - | - |
| HLA-B27 positivity | **-** | ++ | - | + |
| RF positivity | **+ (in early-onset JRA)** | - | - | - |
| Extra-articular manifestations | **Systemic symptoms (systemic-onset JRA)** | Enthesopathy | Psoriasis, nail changes | Bowel symptoms |
| Eye disease | **Anterior uveitis** | Iritis | Posterior uveitis | Anterior uveitis |



## TREATMENT

- **NSAIDs** are the first choice in the treatment of JRA. Naproxen℞, sulindac℞, ibuprofen℞, indomethacin℞.
- Aspirin℞ products, the mainstay of arthritis treatment in the past because of concerns about Reye syndrome, and the convenience of twice daily rather than four times daily dosing.
- **Systemic corticosteroid medications**, it is used as **bridging therapy** until other medications take effect in:

✓ severe systemic-onset JRA with internal organ involvement
✓ active arthritis leading to inability to ambulate.

- **Second-line medications**, such as **hydroxychloroquine** and **sulfasalazine℞.**
- **Methotrexate**, orally or SC, safest, most efficacious, and least toxic of the currently available second-line agents for initial adjunctive therapy with an NSAID. Methotrexate can cause bone marrow suppression and hepatotoxicity; regular monitoring can minimize these risks.
- For patients who do not respond to NSAIDs, second-line medications, or methotrexate, can use agents that control arthritis by blocking the cytokine TNF-α. **etanercept**℞ and **infliximab**℞,

## COMPLICATIONS

- Complications with JRA result primarily from the **loss of function of an involved joint** secondary to joint contractures or bony fusion or loss of joint space.
- anterior uveitis result in posterior synechiae, cataracts, and band keratopathy, and result in blindness.
- **macrophage activation syndrome,** a rare and occasionally fatal complication of systemic JRA

✓ The acute development of a profound anemia associated with thrombocytopenia(≤262 × $10^9$/L) or leukopenia(≤4.0 ×$10^9$/L) , Elevated levels of aspartate aminotransferase (>59 U/L),Hypofibrinogenemia (≤2.5 g/L) ,with a high, spiking fever, lymphadenopathy, and hepatosplenomegaly
✓ Other abnormal laboratory findings in S-JIA-associated MAS:erythrocyte sedimentation rate fall, increased bilirubin, presence of fibrin degradation products, hypertriglyceridemia, low sodium levels, decreased albumin, and hyperferritinemia.
✓ bone marrow biopsy demonstrating hemophagocytosis
✓ Emergency treatment with high-dose intravenous pulse methylprednisolone, cyclosporine.

## PROGNOSIS

- The prognosis of JRA is **excellent**, with an overall 85% complete remission rate.
- poorer prognosis:
  1. Systemic-onset disease
  2. positive rheumatoid factor
  3. poor response to therapy
  4. the presence of erosions on x-ray .
- Children with pauciarticular JRA uniformly tend to do well, whereas children with polyarticular disease and systemic-onset disease constitute most children with functional disability.

# SYSTEMIC LUPUS ERYTHEMATOSUS

## ETIOLOGY

- SLE is a multisystem disorder of unknown etiology characterized by the production of large amounts of **circulating autoantibodies**.
- This antibody production due to loss of T lymphocyte control on B lymphocyte activity, leading to hyperactivity of B lymphocytes, which leads to nonspecific and specific antibody and autoantibody production.
- These antibodies form immune complexes, which can get trapped in the microvasculature, leading to inflammation and ischemia.
- Autoantibodies (ANA, anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RNP, antiphospholipid antibody: in descending order of prevalence) may precede the onset of SLE by 9 yr, suggesting a presymptomatic state of autoimmunity.
- HLA types (HLA-B8, HLA-DR2, and HLA-DR3) occur with increased frequency among patients with lupus.

## EPIDEMIOLOGY

- Approximately 5% of SLE presents in childhood, mostly around puberty.
- SLE is rare in children younger than 9 years old.
- Lupus has been diagnosed in the 1st yr of life.
- Female predominance varies from 4 : 1 before puberty to 8 : 1 afterward.
- The overall prevalence of SLE in the pediatric population is 10 to 25 per 100,000.

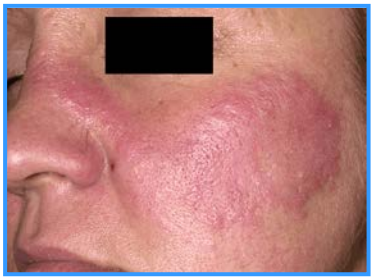
## CLINICAL MANIFESTATIONS

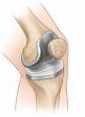
- Patients with SLE can present in acute or chronic manner.

**Presenting Manifestations of Systemic Lupus Erythematosus**

| TARGET ORGAN | MANIFESTATIONS |
|---|---|
| Constitutional | Fatigue, anorexia, weight loss, prolonged fever, lymphadenopathy |
| Musculoskeletal | Arthralgias, arthritis |
| Skin | Malar rash, discoid lesions, livedo reticularis, vasculitis |
| Renal | Glomerulonephritis, hypertension, nephrotic syndrome, renal failure |
| Cardiovascular | Pericarditis (cardiac tamponade).valvular thickening and verrucous endocarditis (Libman-Sacks disease). |
| Neurologic | Seizures, psychosis, stroke, cerebral venous thrombosis, pseudotumor cerebri, aseptic meningitis, chorea, global cognitive deficits, mood disorders, transverse myelitis, peripheral neuritis (mononeuritis multiplex) |
| Pulmonary | Pleuritic pain, pulmonary hemorrhage, Pneumonitis |
| Hematologic | Coombs-positive hemolytic anemia, anemia of chronic disease, thrombocytopenia, leukopenia |
| Gastrointestinal | Pancreatitis,Mesenteric,arteritismSerositis,Hepatomegaly,Hepatitis (chronic lupoid),Splenomegaly |
| Reproduction | Repeat spontaneous abortions, Neonatal lupus erythematosus, Congenital heart block |
| Laboratory | Elevated ESR and CRP; decreased C3 or C4; positive ANA and anti-double-stranded DNA antibodies |

- Skin disease findings:
  1. MALAR "BUTTERFLY" RASH: common raised, erythematous rash on the cheeks, across the bridge of the nose, on the forehead, and chin, but spars the nasolabial folds.33% of pediatrics SLE onset. No scaring. Precipitated by sun- exposure.
  2. PHOTOSENSITIVITY: problematic during the summer months
  3. DISCOID LUPUS, is an inflammatory process that leads to disruption of the dermal-epidermal junction, cause scarring and loss of pigmentation in the affected area. If occurs in the scalp, alopecia ensues. Only 2-3% of all DLE occurs in childhood.





4. RAYNAUD PHENOMENON, not specific for SLE
5. LIVEDO RETICULARIS.
6. OTHERS: erythematous macular eruptions (particularly on fingers, palms, and soles), purpura, sub-acute psoriasiform or annular skin lesions, bullous or urticarial lesions, and alopecia.

- MOUTH AND NASAL SORES resulting from mucosal ulceration are a common complaint in patients with SLE. can lead to ulceration and perforation of the nasal septum.
- LYMPHADENOPATHY AND SPLENOMEGALY are common findings in SLE. Because of reticuloendothelial system stimulation (axillary lymphadenopathy can be a sensitive indicator of disease activity)
- SEROSITIS with chest pain and pleural or pericardial friction rubs or frank effusion.
- RENAL INVOLVEMENT is one of the most serious manifestations of SLE and is common in pediatric SLE,
  - ✓ occurring in 50% to 70% of children.
  - ✓ range from microscopic proteinuria or hematuria to gross hematuria, nephrotic syndrome, and renal failure.
  - ✓ Hypertension or the presence of edema should clue to the risk of lupus renal disease.
- ARTHRALGIAS AND ARTHRITIS is rarely deforming and typically involves the small joints of the hands, although any joint may be involved.
- MYALGIAS OR FRANK MYOSITIS, with muscle weakness and muscle fatigability.
- CNS, leading to symptoms ranging from symptoms, such as poor school performance and difficulty concentrating, to seizures, psychosis, and stroke.
- The occurrence of arterial or venous thrombosis suggesting antiphospholipid antibody syndrome, associated with :
  - ✓ recurrent fetal loss
  - ✓ livedo reticularis
  - ✓ thrombo-cytopenia
  - ✓ Raynaud phenomenon

## LAB AND DIAGNOSIS

- SLE is a multisystem disease, it can be difficult to diagnosis early in the disease course.
- Elevated ANA titers are often present in children with active lupus. is an excellent screening tool
- Levels of anti-double-stranded DNA, which are more specific for lupus, often reflect the degree of serologic disease activity.
- total hemolytic complement ($CH_{50}$), C3, and C4 are decreased in active disease and provide a second measure of disease activity.
- Serum levels of Anti-Smith antibody, found specifically in patients with lupus, *does not measure disease activity.*
- Hypergammaglobulinemia is common but nonspecific
- The **lupus anticoagulant,** found in ⅔ of patients, is associated with antiphospholipid antibodies.
  - ✓ reacts with the cardiolipin used in the serologic test for syphilis and may result in a false-positive test
  - ✓ reacts with the phospholipid reagent used in the partial thromboplastin time (PTT), causing an elevated result.
  - ✓ associated with increased incidence of deep venous thrombosis and neurologic disease including stroke and psychosis.

**NOTE:**
SLE antibodies indicate renal involvements are:
- ✓ Double-stranded DNA
- ✓ Sm (Smith)

- DRUG-INDUCED LUPUS:
  - ✓ is a lupus-like disease that is precipitated by exposure to certain drugs ( anticonvulsants, sulfonamides, and antiarrhythmic agents)
  - ✓ The finding of antihistone antibodies suggests antigenic similarities between these drugs and histone proteins leading to cross-reactive immune reactions.
  - ✓ The typical symptoms: fever, rash, and pleuropericardial disease typically abate with discontinuation of the drug.
  - ✓ The serum complement usually remains normal
  - ✓ complications, including renal disease, are rare

- Criteria have been developed for the diagnosis of SLE .The presence of 4 of 11 of these criteria has 98% sensitivity and 97% specificity for SLE.

**Criteria for Diagnosis of Systemic Lupus Erythematosus***

| |
|---|
| **Physical Signs** |
| ✓ Malar (butterfly) rash |
| ✓ Discoid lupus |
| ✓ Photosensitivity |
| ✓ Oral and nasopharyngeal ulcers |
| ✓ Nonerosive arthritis (≥2 joints with effusion and tenderness) |
| ✓ Pleuritis *or* pericarditis (serositis) |
| ✓ Seizures *or* psychosis in absence of metabolic toxins or drugs |
| **Laboratory Data** |
| ✓ *Renal Disease (Nephritis)* |
| Proteinuria (>500 mg/24 hr,>3-plus (+++) if quantitation not performed) *or* |
| Cellular casts (red blood cell, hemoglobin, granular, tubular, or mixed) |
| ✓ *Hematologic Disease* |
| Hemolytic anemia with reticulocytosis *or* |
| Leukopenia (<4000 on 2 occasions) *or* |
| Lymphopenia (<1500 on 2 occasions) *or* |
| Thrombocytopenia (<100,000/$mm^3$) |
| **Serologic Data** |
| ✓ Positive anti-dsDNA *or* Positive anti-Sm *or* |
| Evidence of presence of antiphospholipid antibodies |
| 1. IgG or IgM anticardiolipin antibodies *or* |
| 2. Lupus anticoagulant *or* |
| 3. False-positive VDRL for >6 mo |
| ✓ Positive ANA in absence of drugs known to induce lupus |

**NOTE:**
Peritonitis is not in SLE criteria.

## TREATMENT

- **Corticosteroids** are the **mainstay of treatment** for SLE..
- ✓ systemic disease are often started on 1-2 mg/kg/24 hr of oral prednisone in divided daily doses.
- ✓ When complement levels increase to within the normal range, the dose is carefully tapered to the lowest effective dose.
- **NSAIDs** have been used to treat the arthralgias and arthritis associated with SLE. are used with caution because patients with lupus are more susceptible to hepatotoxicity.
- **Hydroxychloroquine** is used for:
- ✓ treatment of lupus skin disease, such as discoid lupus
- ✓ reduce the risk of thromboembolic disease and lowers lipid levels.
- ✓ maintenance therapy
- ✓ longer periods of wellness between flares of disease
- ✓ decreased numbers of flares.
- For lupus nephritis or cerebritis,**Cyclophosphamide**℞is used. It shows significant decreased rates of progression to renal failure.
- For patients who are not able to tolerate the tapering of their corticosteroids, the use of **steroid-sparing agents**, such as azathioprine℞ or methotrexate may be indicated.

sun has been shown to lead to flares of the disease.

- Worse prognoses are seen in patients with severe lupus nephritis or cerebritis, with risk of chronic disability or progression to renal failure.
- patients benefit from supplementation with **calcium and vitamin D** to reduce the risk of osteoporosis that may result from prolonged cortico-steroid use.
- Patients with thrombosis and antiphospholipid antibodies or a lupus anticoagulant should receive anticoagulant medication at least until lupus is in remission. The length of therapy is controversial. Low molecular weight heparin is the anticoagulant of choice.
- renal biopsy for staging can help determine whether an immunosuppressive agent such as cyclophosphamide needs to be added to a corticosteroid regimen.

EXCELLENT PROGNOSIS
- ❖ **Class I** :minimal mesangial change without proteinuria or hematuria.
- ❖ **Class II**:mesangial proliferation.

- **Class III (focal proliferative glomerulonephritis)** shows involvement of <50% of glomeruli having focal, segmental proliferation of cells near capillaries with necrosis and lymphocytic infiltration, and is often associated with chronic renal disease.
- **Class IV (diffuse segmental or global proliferative glomerulonephritis)** exhibits a majority of each glomeruli affected by cellular infiltration, mesangial cellular proliferation, and crescent formation corresponding to scarring, with increased risk for developing end-stage renal disease in adulthood; intravenous pulse cyclophosphamide can decrease this risk.
- **Class V disease (membranous glomerulonephritis)** shows thickened capillary walls on light microscopy and subepithelial deposits on electron microscopy along the basement membrane. associated with proteinuria
- **Class VI** is advanced sclerosing nephritis and demonstrates diffuse, chronic damage suggesting progression to renal failure.

## COMPLICATIONS AND PROGNOSIS:

- the 5-yr survival rate is >90%.
- Long-term complications include **avascular necrosis** owing to corticosteroid use, infections, and myocardial infarction.
- **accelerated atherosclerosis**, based not only on prolonged cortico-steroid use, but also on the disease.
- Secondary infections with opportunistic organisms are the leading cause of mortality.

## NEONATAL LUPUS

- Lupus in newborns results from maternal transfer of IgG auto-antibodies, usually anti-Ro/SSA or anti-La/SSB, between the 12th and 16th wk of gestation.
- Only a small percentage of offspring of mothers with autoantibodies to Ro and/or La develop disease.
- Symptoms usually derive from a single organ, although multiple organ involvement may

✓ congenital heart block
✓ cutaneous lesions, occur after ultraviolet exposure at about 6 wk of life and last 3-4 mo ,on the face and scalp,25% of rashes scar.
✓ Hepatitis
✓ thrombocytopenia
✓ neutropenia
✓ pulmonary and neurologic disease.

- Treatment is supportive.
- CHB is permanent and often requires cardiac pacing, either after birth or antenatally.
- Even infants of asymptomatic mothers with lupus may have slightly prolonged PR intervals.
- Cardiomyopathy is a rare serious sequel.
- NEONATAL ONSET MULTISYSTEM INFLAMMATORY DISEASE: (D/D)

✓ a rare syndrome characterized by *fever, rash, arthropathy, chronic meningitis, seizures, uveitis, and lymphadenopathy.*
✓ resulting from defective IL-1 regulation in the innate immune system
✓ Anakinra, an IL-1 antagonist, has been very successful in the treatment of a small cohort of these patients

# JUVENILE DERMATOMYOSITIS

## INFLAMMATION ISOLATED TO SKIN AND MUSCLES

- the most common of the pediatric inflammatory myopathies
- have characteristic rash and proximal symmetric muscle weakness that is often responsive to the immunosuppressive therapy.

## ETIOLOGY

- The etiology of JDM is unknown, but it is characterized by activation of T and B lymphocytes, leading to vasculitis affecting small vessels of skeletal muscle, with immune complex deposition and subsequent inflammation of blood vessels and muscle.
- JDM has been documented to follow:
  1. infections (infection 3 mo before disease onset is obtained in most affected children )
  2. allergic reactions
  3. sun exposure

## EPIDEMIOLOGY

- JDM is a ***rare*** disease, with an incidence of less than 0.1 : 100,000.
- JDM peak incidence between ages ***4 and 10 years.***
- more common in ***girls*** than boys.

## CLINICAL MANIFESTATIONS

### WHERE IN THE BODY:

- Affects *the proximal muscles*, particularly the hip and shoulder girdles, and the abdominal and neck muscles.

### COURSE OF ILLNESS:

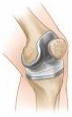
- Dermatomyositis tends to present in a slow, progressive fashion with insidious onset
- Some children can present in an acute fashion.

### SYMPTOMS:

- ✓ low-grade fevers
- ✓ fatigue and malaise
- ✓ rash
- ✓ progressive muscle weakness
- ✓ Difficulty climbing steps, getting out of chairs, and getting off the floor.
- ✓ difficulty swallowing
- ✓ joint pain

### SIGNS:

- ✓ positive GOWER SIGN : needing to lean on legs while getting up from the ground.
- ✓ In severe cases, the patient is not able to sit up from a supine position or even lift the head off the examination table.
- ✓ VOICE SOUND NASAL AND DIFFICULTY SWALLOWING: If muscles of the upper airway and pharynx are involved
- ✓ skin rash is the first symptom in 50% of cases, and concomitantly with weakness in 25% of cases.
- ✓ The classic **JDM rash** (SHAWL SIGN)hyperpigmentation and telangiectasia of the skin, followed by atrophy occur on exposed skin, such as the extensor surfaces of the arm, the V of the neck, or the upper part of the back
- ✓ HELIOTROPE DISCOLORATION of the eyelids. may cross the bridge of the nose, in a mask-like distribution, and involve the ears as well
- ✓ GOTTRON PAPULES Scaly, red plaques, classically are found across the knuckles, but can be found on the extensor surfaces of any joint.
- ✓ PERIUNGUAL ERYTHEMA AND DILATED NAIL-FOLD CAPILLARIES**.**
- ✓ Less commonly, cutaneous vasculitis, with inflammation, erythema, and skin breakdown.
- ✓ At some point in their illness, 15% of patients with JDM develop arthritis. The arthritis commonly affects *small joints*, but can occur in any joint.
- ✓ Raynaud phenomenon
- ✓ hepatomegaly, and splenomegaly.



## LABORATORY AND IMAGING STUDIES

- JDM has no evidence of systemic inflammation, with a normal blood count and ESR, indicating inflammation isolated to the muscle and skin.
- Evidence of myositis can be identified in 98% of children with active JDM by elevated **serum muscle enzymes**, including: (Serum levels are in the normal range for the 1st 4-5 mo after disease onset):
  1. aspartate aminotransferase,
  2. alanine aminotransferase,
  3. creatine phosphokinase,
  4. aldolase,
  5. lactate dehydrogenase.
- There may be a Coombs-negative anemia
- Antinuclear antibody (ANA) with a speckled pattern (unknown specificity) is present in >80% of children.
- Pm/Scl Antibodies identify a subgroup of myopathies with a protracted disease course, often complicated by pulmonary interstitial fibrosis, tachycardia, conduction abnormalities, and elevated troponin levels.
- **Electromyography(EMG)** and **muscle biopsy** can be used to document the myositis.
- **MRI** *is a noninvasive means of showing muscle inflammation*.

## DIFFERENTIAL DIAGNOSIS

- *Diagnosis of JDM is based on the presence of documented muscle inflammation in the setting of classic rash.*

1. polymyositis is rare in children, they should have a muscle biopsy to exclude other causes of muscle weakness, such as *muscular dystrophy*, particularly boys.
2. *postinfectious myositis*
3. *other myopathies.*

**Criteria for Diagnosis of Juvenile Dermatomyositis* (4of 5)**

| | |
|---|---|
| 1. | Rash typical of dermatomyositis |
| 2. | Symmetric proximal muscle weakness |
| 3. | Elevated muscle enzymes (SGOT, SGPT, LDH, CPK, and aldolase) |
| 4. | EMG abnormalities typical of dermatomyositis (fasciculations, needle insertion irritability, and high-frequency discharges) |
| 5. | Positive muscle biopsy specimen with chronic inflammation |
| 6. | |

## TREATMENT

- Systemic corticosteroids are the cornerstone of therapy for JDM.
- In severe or refractory cases, it may be necessary to use *cyclosporine* (Immunosuppressives) ℞ or *cyclophosphamide* (Disease modifying antirheumatic drugs- cytotoxic)℞.
- IVIG as adjunctive therapy.
- *Hydroxychloroquine or dapsone*℞ (is bactericidal as well as bacteriostatic against *Mycobacterium leprae/* primary treatment for Dermatitis herpetiformis) has been used for the skin manifestations; they ***do not*** significantly affect the muscle disease.
- Exposure to the sun worsens the cutaneous manifestations, but also exacerbates the muscle disease; sunlight may lead to flare.

## COMPLICATIONS

1. **calcinosis** :The most serious complication of JDM .

✓ consequence of chronic inflammation, Dystrophic calcification occur in the skin and soft tissues in any area of the body

✓ Range from mild to extensive (**calcinosis universalis**).

- ✓ Are associated with increased morbidity and mortality. They are present at diagnosis in about 25% of children with JDM.
- ✓ They may drain a white, cheesy material and resolve, or serve as a nidus for infection, *most frequently staphylococcal*, progress to septicemia and death.
- ✓ Aggressive immunosuppressive therapy at the time of diagnosis decrease frequency of calcinosis.
- ✓ it seems to occur more commonly in children who have had:
    - A. cutaneous vasculitis,
    - B. prolonged disease activity,
    - C. Delays in onset of therapy.

2. **Gastrointestinal perforation and gastrointestinal bleeding :**JDM patients who develop vasculitis are at risk for it.
3. **lipoatrophy and insulin resistance**:

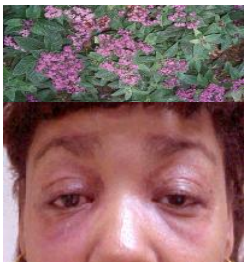
- ✓ in >10% of chronic JDM cases. It
- ✓ is characterized by:
    1. loss of subcutaneous fat on the extremities
    2. hypermuscular appearance
    3. acanthosis nigricans
    4. weakened abdominal muscles resulting in a potbelly appearance
    5. Abnormal glucose and lipid metabolism. which can progress to frank type 2 diabetes, control of insulin resistance leads to improvement in muscle disease.
    6. Girls may lose their menses; sterility may result if the onset of JDM is before puberty.. In these patients,

4. Aspiration pneumonia is a frequent major complication associated with unrecognized impairment in swallowing fluids.

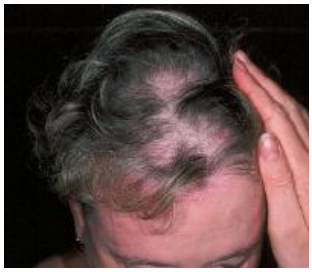
## PROGNOSIS

- The outcomes in patients with JDM depend greatly on:
  a. the extent of muscle disease
  b. the time between disease onset and initiation of therapy.
- JDM follows one of three clinical courses:
    1. uniphasic course, in which patients are treated and improve without significant sequelae.
    2. chronic recurrent course: poor response to therapy+ loss of function.
    3. chronic progressive course, poor response to therapy + loss of function.
- Patients who ultimately develop calcinosis also are at risk for chronic loss of mobility depending on the extent of calcium deposition.

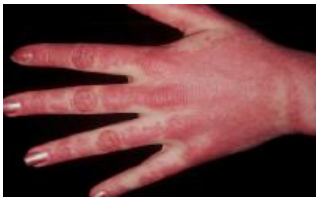
**NOTE:**
The association of polymyositis with malignancy is seen in adults and not in children.



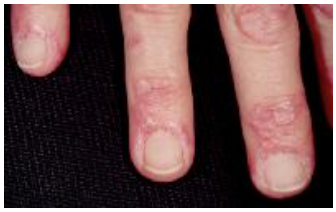
**THE HELIOTROPE RASH** IS A PATHOGNOMONIC CUTANEOUS FEATURE OF DERMATOMYOSITIS.



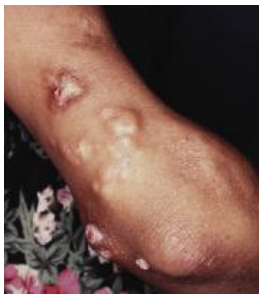
**A DIFFUSE ALOPECIA** WITH A SCALY SCALP DERMATOSIS.



**PHOTODISTRIBUTION OF DERMATOMYOSITIS**
**COLLODION**
. NOTE THE SPARING OF THE INTERDIGITAL WEB SPACES.



**GOTTRON PAPULES** AND **NAIL FOLD TELANGIECTASIA**



**CALCINOSIS** .HE HAD ACTIVE DERMATOMYOSITIS 15 YEARS PRIOR TO THE TIME OF THIS PHOTOGRAPH.

# KAWASAKI DISEASE

## INFANTILE POLYARTERITIS NODOSA
## MUCOCUTANEOUS LYMPH NODE SYNDROME

## ETIOLOGY

- KD is a vasculitis of unknown etiology that is characterized by multisystem involvement and inflammation of small to ***medium-sized arteries***(predominantly) with resulting aneurysm formation.
- strongly supported to be an infectious origin
- Kawasaki disease has recurred in families when previously affected parents have children who develop the disease.

## EPIDEMIOLOGY

- the highest frequency is in Japan.
- The incidence in the U.S. is approximately 6 per 100,000 children younger than age 5 years.
- KD most commonly occurs in children younger than age 5=80%, with a peak between ages 2 and 3 years, and is rare in children older than age 7.
- A seasonal variability has been described with a peak between February and May(2-5)

## CLINICAL MANIFESTATIONS

- **Aneurysmal involvement of the coronary arteries is the most important manifestation of KD.**
- The clinical course of KD can be divided into three phases

### ACUTE PHASE

- The acute phase of KD lasts 1 to 2 weeks.
- marked by sudden onset of a high, **hectic fever** (≥40°C) without an apparent source.

✓ The duration of fever without treatment is generally 1-2 wk, but it may persist for 3-4 wk.

✓ Prolonged fever is prognostic for the development of coronary artery disease.

- followed by **conjunctival erythema** -The conjunctivitis is bilateral and nonsuppurative-; mucosal changes, including dry, **cracked lips** and a **strawberry tongue**.
- **Cervical lymphadenopathy** is found in 70% of children and should be greater than 1.5 cm in diameter for the purposes of diagnosis.
- swelling of the hands and feet.
- **A rash**, vary in appearance, occurs in 80% of children with KD ,particularly in the inguinal area and on the chest. (maculopapular, erythema multiforme, or scarlatiniform)
- **Perineal desquamation** is common in the acute phase.
- Extreme **irritability** is prominent, especially in infants.
- **arthritis,** particularly of medium-sized to large joints, can arise.
- **Abdominal pain** ,**hydrops of the gallbladder** and **CSF pleocytosis**,
- **Carditis** in the acute phase manifested by tachycardia, SOB, or overt CHF.
- **Giant coronary artery aneurysms**, rare, can appear during this phase. most commonly in very young children.

### SUBACUTE PHASE

- lasts <u>until</u> the fourth week
- characterized by **gradual resolution of fever** (if untreated) and other symptoms.
- **Periungual desquamation** of the fingers and toes begins 1-3 wk after the onset of illness and may progress to involve the entire hand and foot
- **The platelet count**, previously normal or slightly elevated, increases to a significant degree (often >1 million/$mm^3$).
- This phase heralds the onset of **coronary artery aneurysms**, which appear in the subacute and convalescent phases, and pose the highest risk of sudden death.
- Risk factors for development of coronary artery aneurysms include:

1. prolonged fever,
2. prolonged elevation of inflammatory parameters such as the ESR,
3. age younger than 1 year,
4. male gender.
5. laboratory values at presentation

- ✓ low hemoglobin or platelet levels
- ✓ high neutrophil and band counts
- ✓ Hyponatremia
- ✓ low albumin and age-adjusted serum IgG levels.

**NOTE:**
Beau lines are deep grooved lines that run from side-side on fingernail.
Causes: infection, trauma, coronary occlusion, hypocalcaemia, skin disease, diabetes, chemotherapy malnutrition.

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## CONVALESCENT PHASE

- begins with the disappearance of clinical symptoms and continues until the ESR returns to normal
- usually 6 to 8 weeks after the onset of illness.
- Beau lines of the fingernails may appear during this phase

## LABORATORY AND IMAGING STUDIES

- In the acute phase, inflammatory parameters are elevated, including :
  1. WBC count (with neutrophilia and immature forms)
  2. platelet count
  3. the ESR (often >80 mm/hr).
- Hypoalbuminemia, Hyponatremia, Elevated serum transaminases, Leukocytosis in synovial fluid
- It is particularly important to exclude other causes of fever, notably infection.
  1. blood culture.
  2. urine culture.
  3. chest x-ray.
  4. A lumbar puncture (may show pleocytosis)
- Tests of hepatobiliary function may be abnormal.
- Greatly elevated platelet counts develop during the subacute phase.
- two-dimensional echocardiograms identifie The development of coronary artery aneurysms ( acute phase, at 2 to 3 weeks, and at 6 to 8 weeks).

**NOTE:**
The is no specific lab test for KD diagnosis
.

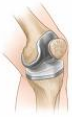
## DIFFERENTIAL DIAGNOSIS

- The diagnosis of KD is based on the presence of fever for more than 5 days without an identifiable source and the presence of 4/5 of other clinical criteria.

**Criteria for Diagnosis of Kawasaki Disease**

| FEVER OF ≥5 DAYS' DURATION ASSOCIATED WITH AT LEAST 4* OF THE FOLLOWING 5 CHANGES |
|---|
| ✓ **Bilateral nonsuppurative conjunctivitis (**injection without exudates**)** |
| ✓ One of more **of mucous membranes changes** in upper respiratory tract<br>1. including diffuse injection of oral and pharyngeal mucosa<br>2. dry fissured lips<br>3. injected lips<br>4. "strawberry" tongue |
| ✓ One or more **changes of the extremities**:<br>1. including peripheral erythema, peripheral edema (acute phase)<br>2. periungual desquamation, and generalized desquamation (subacute phase) |
| ✓ **Polymorphous rash,** primarily truncal |
| ✓ **Cervical lymphadenopathy** >1.5 cm in diameter, usually unilateral. |

- ATYPICAL KD: if only three clinical criteria + coronary artery aneurysms.



## TREATMENT

- **IV immunoglobulin (IVIG)** 2 g/kg over 10-12 hr orally until 14th illness day - is the mainstay of therapy for KD, unknown mechanism of action.
- **Aspirin** :
  - ✓ **anti-inflammatory doses** (80 to 100 mg/kg/day divided every 6 hours) in the acute phase.
  - ✓ When the fever has resolved for at least 48 hours, the dose of aspirin is decreased to **antithrombotic doses** (3 to 5 mg/kg/day as a single dose).
  - ✓ This dose is continued through the subacute and convalescent phases until echo. fails to show the presence of coronary artery aneurysms.
- **Corticosteroids** are **rarely** used in KD ( not like other vascultitis)
  - ✓ acute phase if active carditis is apparent
  - ✓ children with persistent fever after two doses of IVIG.
  - ✓ With therapy, the CRP normalizes much more quickly than the ESR, which will often increase immediately after IVIG therapy.

## COMPLICATIONS

- There are few long-term complications of KD because most cases resolve without sequelae.
- Sudden cardiac death from coronary artery aneurysm.
- Myocardial infarction caused by stenosis of a coronary artery at the site of an aneurysm.

## PROGNOSIS

- Other than the risk for persistent coronary artery aneurysms, KD has an **excellent** prognosis
- Coronary artery aneurysms develop in up to 25% of untreated patients in the 2nd-3rd wk of illness
- IVIG reduces the prevalence of coronary artery disease from 20% to 25% in children treated with aspirin alone to 2% to 4% in children treated with IVIG and aspirin in the first 10 days of illness.

.

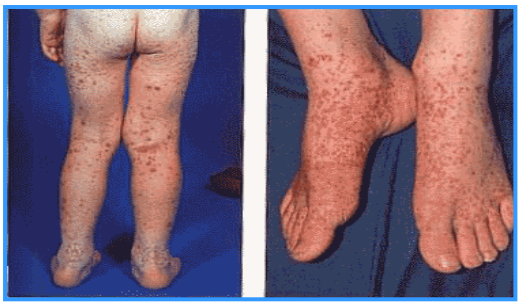
| Complications of Kawasaki Disease |
|---|
| Coronary artery thrombosis |
| Coronary artery aneurysms |
| Peripheral artery aneurysm |
| Peripheral gangrene |
| Congestive heart failure |
| Myopericarditis |
| valvular regurgitation |
| Irritability |
| Arthritis |
| Sterile pyuria (urethritis) |
| Thombocytosis (late) |
| Diarrhea |
| Pancreatitis |
| Hydrops of gallbladder |
| Hepatic dysfunction |
| Aseptic meningitis |
| Sensorineural hearing loss |
| Raynaud phenomenon |
| Anterior uveitis (mild) |

# HENOCH-SCHÖNLEIN PURPURA
## ANAPHYLACTOID PURPURA

## ETIOLOGY
- HSP is a vasculitis of unknown etiology characterized by inflammation of small blood vessels with associated leukocytic infiltration of tissue, hemorrhage, and ischemia.
- The immune complexes associated with HSP are predominantly composed of IgA, raising the suggestion that this illness may be allergy mediated.
- HSP is associated with group A streptococcal infection, but no causal association has been proved.
- often follows an upper respiratory tract infection.

## EPIDEMIOLOGY
- HSP is the most common systemic vasculitis of childhood and of nonthrombocytopenic purpura, with an incidence of 13 per 100,000 children.
- most cases occurring between 2 and 8 yr of age
- Males are affected twice as frequently as females
- most frequently in the winter months.

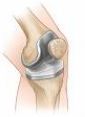
## CLINICAL MANIFESTATIONS
- HSP is characterized by rash, arthritis, gastrointestinal or renal vasculitis.
- Low-grade fever and fatigue are present in more than half of affected children.
- The hallmark of HSP is the rash of **PALPABLE PURPURA**
  - ✓ caused by small vessel inflammation in the skin leading to extravasation of blood into the surrounding tissues.
  - ✓ IgA often is deposited in the lesions.
  - ✓ begin as small macules or urticarial lesions, but rapidly progresses to purpura with areas of ecchymosis.
  - ✓ classically found in dependent areas, below the waist on the buttocks and lower extremities.
  - ✓ accompanied by edema, particularly of the calves and dorsum of the feet and the scalp and scrotum or labia.
  - ✓ last from 3-10 days, and may appear at intervals that vary from a few days to as long as 3-4 mo.
  - ✓ In <10% of children, recurrences of the rash may not end until as late as a 1yr.



- **ARTHRITIS** occurs in ⅔ of children with HSP, most commonly the ankles and knees.
  - ✓ effusions are serous, not hemorrhagic, in nature and resolve after a few days without residual deformity or articular damage.
- Edema and damage to the vasculature of the **GASTROINTESTINAL TRACT** may also lead to (50%):
  1. intermittent abdominal pain ( colicky)
  2. peritoneal exudates
  3. enlarged mesenteric lymph nodes
  4. segmental edema
  5. hemorrhage into the bowel
  6. 50% patients= occult heme-positive stools, diarrhea (±blood), or hematemesis.
  7. Intussusception, suggested by an empty right lower abdominal quadrant, currant jelly stools, complete obstruction or infarction with bowel perforation. Ttt: hydrostatic reduction during a contrast study vs. surgical intervention.

**NOTE:**
Palpable purpura can occur in meningococcemia if there are pre-existing coagulation abnormalities such as factor V Leiden, protein S, or protein C deficiency

- **PANCREATITIS**, and **ORCHITIS**.
- **RENAL INVOLVEMENT** :Most cases of glomerulonephritis occur within the first few months of presentation occurs in 25-50% of children and manifest with:
  1. hematuria
  2. proteinuria



3. nephritis or nephrosis
4. acute renal failure
5. chronic hypertension
6. end-stage renal disease .

- Others:
  1. HEPATOSPLENOMEGALY and LYMPHADENOPATHY may also be present during active disease.
  2. NEUROLOGICAL INVOLVEMENS: seizures, encephalopathy,, mononeuropathies ,paresis, or coma.
  3. rheumatoid-like nodules
  4. cardiac and eye involvement
  5. pulmonary or intramuscular hemorrhage.

**NOTE:**

ACUTE HEMORRHAGIC EDEMA (AHE)

- ✓ ≤2 yr of age that may be confused with HSP.
- ✓ fever; tender edema of the face, scrotum, hands, and feet; and ecchymosis (usually larger than the purpura of HSP) on the face and extremities .The trunk is spared.
- ✓ urinalysis is normal.
- ✓ The younger age, nature of the lesions, absence of other organ involvement, and biopsy may help distinguish AHE from HSP

## LABORATORY AND IMAGING STUDIES (neither specific nor diagnostic)

- HSP show evidence of systemic inflammation with elevated ESR, CRP, and WBC count.
- The platelet count is the most important test because HSP is characterized by nonthrombocytopenic purpura with a normal, or even high, platelet count.

THE PRESENCE OF NORMAL PLATELET NUMBERS DIFFERENTIATES HSP FROM OTHER CAUSES OF PURPURA THAT ARE ASSOCIATED WITH THROMBOCYTOPENIA, SUCH AS AUTOIMMUNE THROMBOCYTOPENIA, SLE, OR LEUKEMIA.

- urine urinalysis for evidence of hematuria, and serum BUN and creatinine to evaluate renal function.
- Stool for occult blood.
- 50% of patients have elevated concentrations of IgA as well as IgM
- negative for antinuclear antibodies (ANAs), antibodies to nuclear cytoplasmic antigens (ANCAs), and rheumatoid factor.
- radiologic investigation? Gut perforation.
- Definitive diagnosis of vasculitis is confirmed by biopsy
- Renal biopsy may show mesangial deposition of IgA and occasionally IgM, C3, and fibrin.

## DIFFERENTIAL DIAGNOSIS

- The diagnosis of HSP is based on the presence of 2/4 criteria - 87.1% sensitivity and 87.7% specificity.

### CRITERIA FOR DIAGNOSIS OF HENOCH-SCHÖNLEIN PURPURA

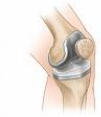
| Criteria | Definition |
|---|---|
| PEDIATRIC age group | Age ≤20 years at onset of symptoms |
| Palpable PURPUR | Raised, palpable hemorrhagic skin lesions in the absence of thrombocytopenia |
| BOWEL angina | Diffuse abdominal pain or the diagnosis of bowel ischemia |
| Diagnostic BIOPSY | Histologic changes showing granulocytes in the walls of arterioles or venules |

2P

2B

## TREATMENT

- Therapy for HSP is **supportive**.
- A short-term course of nonsteroidal anti-inflammatory drugs (**NSAIDs**) can be administered for the acute arthritis.
- Use of systemic **corticosteroids**
- ✓ A typical dosing regimen is PREDNISONE℞, 1 mg/kg/day for 1 to 2 weeks followed by a taper schedule.
- ✓ children with gastrointestinal disease.
- ✓ Acute nephritis typically is treated with **corticosteroids**, require more aggressive immunosuppressive therapy.



## COMPLICATIONS

- Most cases of HSP are uniphasic in nature, lasting 3 to 4 weeks, then resolving completely.
- The **rash can wax and wane**, however, for 1 year after HSP, and parents should be warned regarding possible recurrences.
- The arthritis of HSP does not leave any permanent joint damage, and it does not typically recur.
- ***Renal involvement rarely*** *may lead to acute renal failure.*

## PROGNOSIS

- The prognosis of HSP is EXCELLENT.
- Patients with HSP renal disease (elevated BUN, persistent high-grade protein-uria) are at highest risk for long-term complications, such as hypertension or renal insufficiency.
- There is a long-term risk of progression to end-stage renal disease in less than 1% of children with HSP.
- The rare patients who develop end-stage renal disease may require renal transplantation. HSP may recur in the transplanted kidney.

# MISCELLANEOUS

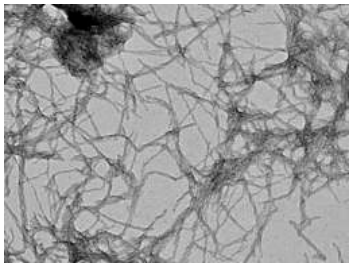
## AMYLOIDOSIS

- Amyloidosis comprises a group of diseases characterized by extracellular deposition of insoluble, fibrous amyloid proteins in various body tissues.

## EPIDEMIOLOGY

- AL amyloidosis is extremely rare in children and usually occurs in persons of middle age or older.
- Only AA amyloidosis affects children in appreciable numbers,
  1. FMF
  2. juvenile rheumatoid arthritis (JRA)
  3. ankylosing spondylitis
  4. inflammatory bowel disease
  5. chronic infections such as tuberculosis
  6. cystic fibrosis
  7. systemic lupus erythematosus
  8. juvenile dermatomyositis.

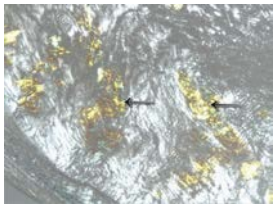
} LESS COMMON



## PATHOGENESIS

- AMYLOID MATERIAL = microscopic protein fibrils ( heterogeneous,20 different types) + serum amyloid P ( nonfibrillar component)
- Amyloid fibril deposition result in no apparent consequences vs. organ dysfunction.
- The nomenclature of amyloidoses is based on biochemical analysis
  1. AL amyloidosis: The most common type of amyloidosis in the United States.
     - ✓ composed of monoclonal immunoglobulin light-chain
     - ✓ was known as idiopathic or myeloma-associated amyloidosis
  2. AA amyloidosis (secondary or reactive amyloidosis) : is the most common serious complication of FMF ( THE MOST ONE OCCURS IN CHILDREN)
     - ✓ amyloid A protein
     - ✓ (FMF), chronic infection, and chronic inflammatory diseases
  3. TTR amyloidosis:.Amyloid conditions associated with aging
     - ✓ fibril protein of the transport protein transthyretin (TTR) .
     - ✓ (Alzheimer disease) & rare autosomal dominant forms of amyloidoses
- The AA protein isolated from AA amyloidosis →fragment of serum amyloid A (SAA)→ SAA is an acute-phase reactant→ Chronic inflammation elevated levels of SAA→ a precursor to the fibril formation of AA amyloidosis.

**NOTE:**
amyloid followed by the abbreviation for the type of fibril protein.



- The factors responsible for determining the site of amyloid deposition in any form of amyloidosis are unknown.
- Amyloid composed of eosinophilic material: stains with Congo red dye , *polarized light demonstrates the pathognomonic apple-green birefringence*, seen by hematoxylin and eosin (H&E)-staining.

## CLINICAL MANIFESTATIONS

- Various patterns of organ dysfunction
- Clinical symptoms usually begin >10 yr after the onset of inflammatory disease.
- The diagnosis is usually established when disease is far advanced.
- The most common clinical presentation of AA amyloidosis is RENAL DYSFUNCTION ( proteinuria → nephrotic syndrome → eventual renal failure).
- Involvement of THE GASTROINTESTINAL SYSTEM (chronic diarrhea, gastrointestinal bleeding, abdominal pain, malabsorption)
- ANEMIA, HEPATOMEGALY, and SPLENOMEGALY.

## DIAGNOSIS

- BY BIOPSY demonstrating amyloid fibril proteins in affected tissues.
  - Renal biopsies are contraindicated because of potential bleeding.
  - The liver and spleen are not suitable sites for biopsy.
  - Biopsy sites : rectal mucosa, gingival tissue, and abdominal fat aspirate
- A method of microradiographic scintigraphy using serum amyloid P component a tool for the diagnosis +monitoring of the status of amyloidosis.

## TREATMENT

- The primary means of treatment of AA amyloidosis is aggressive management of the underlying inflammatory or infectious disease
- Colchicine is effective in controlling the attacks of FMF and also in preventing the development of amyloidosis
- JRA respond to chlorambucil
- Anti-tumor necrosis factor-α (TNF-α) therapy, with etanercept or infliximab, reducing proteinuria in patients with AA amyloidosis secondary to inflammatory arthritides.

## COMPLICATIONS AND PROGNOSIS

- End-stage renal failure is the underlying cause of death in 40-60% of cases of amyloidosis
- median survival time from diagnosis of 2-10 y

**NOTE:**

COGAN SYNDROME
ocular inflammation+ vestibuloauditory abnormalities+ systemic vasculitis

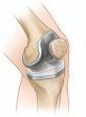
**NOTE:**

- LARGE VESSEL VASCULITIS:
  1. Takayasu arteritis
  2. Giant cell arteritis
  3. Cogan syndrome
  4. Behçet disease
- MEDIUM-VESSEL VASCULITIDES
  1. Classic and Cutaneous polyarteritis nodosa
  2. Kawasaki disease
  3. Rheumatoid vasculitis
  4. Primary angiitis of the l CNS
- OTHERS ARE SMALL VESSEL DISEASES

**NOTE:**

**Churg-Strauss syndrome** is a vasculitis (ANCA-ASSOCIATED) . D/D:WG.

1. chronic sinus lesions
2. history of asthma
3. circulating eosinophilia
4. eosinophilic cutaneous vasculitis
5. not associated with destructive upper airway disease



# OTHER TYPES OF VASCULITIS

| TYPE OF VASCULITIS | TAKAYASU ARTERITIS | POLYARTERITIS NODOSA | WEGENER GRANULOMATOSIS |
|---|---|---|---|
| DEFINITION | **PULSELESS DISEASE,** is a chronic of large vessels (aorta and its major branches). | necrotizing vasculitis affecting small- and medium-sized arteries.<br>segmental effect | necrotizing granulomatous<br>small vessel<br>Resp. tract (upper & lower) & kidneys. |
| EPIDEMIOLOGY | 3ed most common child-hood vasculitis in the world after HSP and KD<br>F2.5 : M1 ratio<br>⅓ onset <age 20 yr. | PAN rarely in kids<br>F=M<br>mean age of 9 yr<br>Chronic HbB, parvovirus TB,IM, CMV,URTI | mean age at dx 6 yr<br>F 3: M 1.<br>predominates in whites |
| CLINICAL FINDINGS | prepulseless phase: (night sweats, anorexia, weight loss, fatigue, myalgia, and arthritis→ hypertension.<br>pulseless phase* systemic symptoms more in children than adults:(splenomegaly, erythema nodosum, malar rash, erythema induratum. dilated cardiomyopathy, myocarditis, pericarditis, aortitis, aortic regurgitation Uveitis<br>associated: interstitial lung disease, UC, RA, and polymyositis | fever ,Weight loss<br>mesenteric arterial = abd. Pain<br>Renovascular = HTN hematuria,proteinuria<br>skin : purpura,edema, linear erythema & palpable,painful nodules along artery<br>CNS: peripheral neuropathy,CVA TIA,<br>Cardiac :MI,HF arrhythmias perimyocarditis<br>arthritis, myalgias. | fever, malaise, wt loss, myalgia, arthralgia.<br>Resp. tract 87% subglottic stenosis hemoptysis & dyspnea<br>kidneys 53%, GN late.<br>joints 53%<br>eyes 53% conjunctival ,corneal lesions,uveitis invasive orbital pseudotumor<br>skin 53% ulcers, palpable purpuric nodules<br>sinuses 35% cough, congestion, and nasal discharge & deformity<br>CNS 12%. Cranial & peripheral neuropathy, intracranial,granulomas |
| DIAGNOSIS | characteristic bruit over carotid or subclavian art.<br>↓ or absent radial pulses<br>confirmed by angiography, (dilated aortic arch + aneurysmal dilatation & stenosis of large vessels) | characteristic of vasculitis on biopsy(necrotizing arteritis) or angiography<br>Angiography : areas of aneurysmal dilatation, at branch points or segmental stenosis | suspected :severe sinusitis + pulmonary granulomas or renal nephritis.<br>The diagnosis confirmed<br>1. anti-PR3 ANCAs<br>2. biopsy :necrotizing granulomatous angiitis on pulmonary, sinus, renal. |
| LAB RESULTS | ESR >60 mm/hr<br>microcytic hypochromic A.<br>leukocytosis<br>polyclonal hypergamma-globulinemia in ⅓ | elevated ESR is often the earliest finding.<br>anemia and leukocytosis<br>Hypergammaglobulinemia<br>↑ LE :hepatitis B, adults | ↑ESR, CRP,WBC, Plt in ¾<br>Anemia<br>PR3-ANCA (IgG) |
| TREATMENT | surgical excision of the predominant lesions<br>Prednisone(PO/IV) +others. | Oral & IV corticosteroids ± PO,IV cyclophosphamide. | PO&IV corticosteroids and cyclophos-phamide |
| PROGNOSIS | 50% achieve remission after the 1st course therapy<br>¼ of cases never remission<br>5-yr mortality 35%<br>The most fearful comp. is arterial aneurysm rupture | renal Dz, the 1-yr survival 73% & 5-yr survival 60% | Enlarging granulomas disrupt local anatomy:<br>1. Intrasinus : orbit<br>2. ear :unilateral deafness.<br>Chronic GN →ESRD<br>subglottic stenosis |


REFERENCES:

- Nelson textbook, 18th edition
- Essentials of pediatrics, 5th edition

# Infections

# CHILDHOOD VACCINATION

BY: DR. A. LATEEF AL-KHATEEB

- **Immunobiologics:** (immunizing agents) used for immunization or therapy
  1. Antigens: e.g. vaccines & toxoids
  2. Antibodies: e.g. Immunoglobulins & antitoxins
- **Immunization:** providing artificial immunity by an immunobiologic. passive or active.
- **Vaccination:** (vaccinia = small pox virus vaccine) : administration of any vaccine or toxoid
- Vaccination is not necessarily lead to immunity which may be partial, complete or Non.
- **Vaccine:** suspension of live attenuated microrganism (viral, bacterial) or inactivated (killed)
  1. **Live vaccines** → single dose → life long immunity *(booster doses may be needed)*
  2. **Killed vaccines**: multiple & booster doses are needed.
- Local mucus membrane immunity (secretory IgA) is more provided by live vaccines than killed ones e.g. OPV > IPV
- **Toxoid:** non-toxic (modified) bacterial toxin, but still immunogenic (can induce antitoxin antibody formation.) e.g. tetanus & diphtheria toxoids
- **Immunoglobulins (Ig):** Antibody containing solutions from human source for passive immunization (IM, IV). Either specific or non-specific. don't transfer infectious diseases
- **Antitoxin:** solution of antibodies, from animal serum ↓ risk of hypersensitivity & serum sickness. E.g. diphtheria antitoxin & botulinum antitoxin
- IPV is given before OPV in the schedule to stimulate immunity before giving OPV, so decreasing the possibility of OPV associated paralytic polio.

## CONSTITUENTS OF VACCINES

1. **Main antigen:**
   - ◇ Bacteria, virus, toxoid.
   - ◇ live attenuated or killed inactivated
2. **Suspending fluids:**
   - ◇ Simple: sterile water, saline.
   - ◇ Complex: containing proteins like serum proteins, egg proteins or cell culture antigens, all are derived from the medium in which the vaccine is produced**.**
3. **Preservatives**, stabilizers & antibiotics:

◇ Inhibit bacterial growth in cultures or to stabilize the antigen or antibodies, e.g. mercurial (thiamersal), phenols, neomycin, albumin, glycin→ can produce allergy in the recipient.

4. **Adjuvants:**

◇ e.g Aluminum hydroxide in toxoids & HB vaccine in order to enhance immunogenicity by prolonging antigen absorption.

### ROUTINE IMMUNIZATION SCHEDULE JERUSALEM-MAKASSED HOSPITAL-

| VACCINE | BIRTH | 1 MO | 2 MO | 4 MO | 6 MO | 12 MO | 18 MO | 24 MO | (4-6Y) | 7 YR |
|---|---|---|---|---|---|---|---|---|---|---|
| HBV | HBV | HBV2 | | | HBV3 | | | | | |
| EIPV | | IPV1 | IPV2 | | IPV3 | | | | | |
| OPV | | — | OPV1 | OPV2 | OPV 3 | | | OPV4 | | |
| DTP | | DTP 1 | DTP2 | DTP3 | DTP4 | | | — | TD | TD |
| HIB ++ | | HIB 1 | HIB 2 | HIB 3 | HIB 4 | | | | | |
| MMR | | | | | MMR1 | | | MMR2 | | |
| HAV-HAVRIX | | | | | | HAV1 | HAV2 | | | |

## NOTES:

- DT: Diphtheria-Tetanus Toxoid, pediatric use <7 yr if pertussis is contraindicated
- Td: Diphtheria-Tetanus Toxoid for adult use & children >= 7 yr, smaller dose
- DTP or TD booster doses at 4-6yr then Td every 10 yr.
- If the mother is HbsAg positive give the infant HBIG plus vaccine within 12 hr of delivery.
- Hib Can be given in combination with DTP & IPV in one vaccine

- Vercilla recommended age in USA: 12-18 months. In preadolescent assessment if <13 years 1 dose, if >13 years 2 doses.

## Administration of Vaccines - General Instructions

1. Precautions should be taken to minimize spread of diseases.
2. The person giving vaccines should be immunized against HBV, mumps, rubella, influenza, tetanus, & diphtheria.
3. Hand washing before & after each patient (gloves are not required).
4. Sterile & disposable syringes & needles are used, separate syringe and needle for each injection.
5. Don't mix vaccines, inject in separate sites & via the suitable route (oral, S.C,IM,I.D).
6. The buttocks should not be used for active or passive vaccination due to risk of sciatic nerve injury & possibility of inappropriate injection (S.C, IM,or deep IM). But can be used for passive immunization if large volumes of Ig are given.
7. Vomiting of oral vaccines (OPV) if occurs within 5-10 min→ repeat the dose.
8. Follow the instructions of the manufacturer regarding dose, route storage & handling of vaccines.

## Spacing between immunobiologics

1. Administration of more than one dose of antigen is to produce adequate antibody response. Booster doses (reinforcement) are used to maintain protection.
2. *There is a minimum interval between doses but no maximum interval,* (longer duration between doses doesn't reduce the final antibody response). Interruption between doses doesn't require reinstitution of the series. Shorter duration between doses decreases antibody response.
3. Simultaneous administration of vaccines: it is as safe and effective as if given separately. Vaccines can be given on the same day but not at the same site.
4. Live vaccines affect the results of PPD test (tuberculin test), so PPD test should be done on the same day of vaccination or 4-6 weeks later.

- Vaccines that are not affected by simultaneous administration of Ig
  1. Inactivated killed vaccines
  2. OPV & yellow fever vaccines
- seronegative women to rubella should be vaccinated immediately after delivery even if they received anti-D or blood products.

| Indication | Before MMR (mon) |
|---|---|
| Tetanus(TIG) | 3 |
| Hepatitis A(IG): | |
| ◇ Contact prophyl. | 3 |
| ◇ Travel | 3 |
| Hepatitis BIG | 3 |
| Rabies (HRIG) | 4 |
| Varicella (VZIG) | 5 |
| Measles (IG): | |
| ◇ Normal contact | 5 |
| ◇ Immunodef. | 6 |
| Blood transfusion: | |
| ◇ RBCs: -washed | 0 |
| ◇ adenine-saline | 3 |
| ◇ Packed RBCs | 6 |
| ◇ Whole blood | 6 |
| ◇ Plasma/platelet | 7 |
| Immunodeficiency | 8 |
| Treatment of: | |
| ◇ ITP | 8 |
| ◇ ITP | 10 |
| Kawasaki disease | 11 |

## Response to vaccines

- Antibodies after vaccination may be of any type: IgG, IgM, IgA
- Latent period:
  A. Primary response: after First dose→onset 7-10 days, peak 2-6wk, early IgM later IgG
  B. Secondary response after subsequent doses, rapid onset= 4-5 days (memory cells = T-cell dependent immunity)
- Polysaccharide antigens in vaccines:
  A. Un-conjugated: e.g. pneumococcal vaccines produce **T-cell independent immune response** and secondary response is absent so repeated vaccination is unnecessary except after 5-10 yr if indicated (waned immunity).
  B. Conjugated: (linked to protein) e.g conjugated H. influenza or pneumococcal vaccines→ primary and secondary imm. response can revaccinate with primary and booster doses.
- Unnecessary to measure serum level of Ig to detect response.

## LIVE VACCINES

| | | |
|---|---|---|
| OPV | Live virus 3 serotypes | Oral |
| BCG | Live bacteria (Bacillus of Calmette & Guerin) | I.D/Percutan. |
| MMR/M,M,R | Live virus, combined or separated | SC |
| VARICELLA | Live vaccine | SC |
| YELLOW FEVER | Live virus | SC |
| ADENOVIRUS | Live virus | Oral |

## KILLED, INACTIVATED VACCINES

| | | |
|---|---|---|
| Td/TD | Inactivated toxins | IM |
| DTP<br>DTaP,acellular | Toxoids & inactivated whole bacteria<br>Toxoids & inactivated bact. components | IM<br>IM |
| eIPV | Enhanced inactiv. Virus 3 serotypes | S.C,IM |
| HAV | Hepatitis A vaccine, Inactive viral antigen | |
| HBV | Hepatitis B vaccine, Inactive viral antigen | IM |
| Hib conjugate | Hemophilus influenza type b (bacterial polysaccharide conjugated to protein) | IM |
| Pneumococcal (PCV7,23-PS) | Bacterial polysach.conjug. to protein (PCV7) or alone(23-PS) | IM/SC |
| Influenza | Inactiv. Virus or virus components | IM |
| Rabies(HDCV) | Inactiv. virus, human deployed cell vaccine | IM/I.D |

## PASSIVE IMMUNIZATION (IMMUNE GLOBULINS & ANTITOXINS)

| IMMUNOBIOLOGIC | TYPE | INDICATIONS |
|---|---|---|
| Diphtheria Antitoxin | Specific equine Abs. | Diphtheria |
| Tetan.imm.glob.(TIG) | Specific human Abs. | Tetan. treatment |
| HBIG (Hepatitis B) | Specific human Abs. | Post-exposure prophy. |
| HRIG (Rabies) | Specific human Abs. | Post-exposure prophy. |
| VZIG(Varicella zoster) | Specific human Abs. | Post-exposure prophyl. |
| Immune globulin IV | ***Pooled*** human Abs. (non-spedific) | ◇ Abs deficiency disorders<br>◇ ITP, Kawasaki. |
| Immune globulin (IG) | ***Pooled*** human Abs. (non-spedific) | ◇ Hep. A:pre-post exposure<br>◇ Measles(post- exposure)<br>◇ Rubella (Post-exposure) |
| -Botulinum Antitoxin<br>-CMV –IGIV | Specific equine Abs.<br>Specific human Abs. | Treatment of botulism<br>Prophyl. In B.M.& Kidn. transplant |

## POST EXPOSURE IMMUNIZATION

**RUBELLA (not absolute indication):-**

- ◇ Ig if given within 7- 8 days of exposure e.g. in pregnant susceptible women
- ◇ Congenital rubella may not be prevented

**MEASLES:** Ig if given within 6 days of exposure may prevent or modify infection.
**TETANUS**Ig (TIG) & toxoid)
**RABIES**: Ig & vaccine:
**HEPATITIS A**: Ig

HEPATITIS B:

- HBIG +/- vaccine

| TYPE OF EXPOSURE | HBIG | VACCINE |
|---|---|---|
| **1- Perinatal:** | Within 12hr after birth (as soon as possible), repeat at 3mo if vacc. not given | Within 7 days after birth, repeat at 1& 6mo of age |
| **2- Sexual:** | Single dose within 14 days; repeat at 3mo if contact is still +ve & vacc. not given | Yes, for contact of HbsAg carriers & homosexuals |

- Check infant's serology at 9mo:
  - ✓ If HbsAg & Anti-HBs are neg→ give dose of vaccine
  - ✓ If HbsAg is positive: → Prophylaxis has failed, consider as carrier.
  - ✓ If anti-HBs is positive→ Successful vaccination

| **3- Percutaneous:** | HBIG | VACCINE |
|---|---|---|
| **a-HbsAg +ve:** | Within 24hr | -Initiate vaccine or booster if immunized previously |
| **b-Unknown:** | | |
| ◇ high risk source: e.g. acute hepatitis | -Within 24 hr. repeat in 1mo if source is positive & vaccine not given | -If source is +ve: as above |
| ◇ intermediate risk: | -*IG* within 24hr, -HBIG if source +ve, repeat in 1mo if vacc. not given | -If source +ve: as above |
| ◇ low risk: | -Treatment is optional, if decide to treat give *IG* | -If source positive: as above |

- HBIG (hepatitis B immunoglobulin), Dose: Perinatal: 0.5ml IM , Sexual or percutan.: 0.06 ml/kg IM
- In Percutaneous, If contact is vaccinated & has protective Ab. level→ no treatment
- Intermediate-risk:
  - ◇ Blood of immigrants from endemic areas
  - ◇ Residents of custodial institutions
  - ◇ Hemodialysis patients
  - ◇ Users of illicit drugs
  - ◇ Homosexuals

## VACCINATION IN CERTAIN SITUATIONS

### PREMATURES

- Regardless of birth weight or gestational age they are vaccinated at the same chronological age. ***(don't reduce, delay or divide doses)***
- **Exceptions:**
  1. OPV should be delayed until discharge from NICU ( risk of cross infection)
  2. HBV is not given until Wt is >=2 Kg/ or >1mo old & acceptable wt
  3. If mother is HBsAg positive give vaccine and immunoglobulin (HBIG) within 12 hr of delivery regardless of birth weight. (if < 2kg give 4doses instead of 3)

### BREAST FEEDING

- No contraindications for both the mother and the baby.

### PEGNANCY

- Live vaccines are contraindicated

- Check all for HBsAg, tetanus immunity, rubella serology & polio
- Contraindicated vaccine to House-hold contacts: MMR,Var,. Precautions in OPV

### IMMUNO-DEFICIENCY

- Live vaccines are in general contraindicated for the patient and his household contacts
- Exceptions:
  1. MMR & BCG are NOT contraindicated for household contacts ( transmission risk is low)
  2. MMR is NOT contraindicated for HIV patients (risk of wild measles is >>> risk of vaccine associated measles).

### HEMOPHILIA & COAGULOPATHIES

- Increased Risk of HIV infection & HBV
- IM injections are hazardous:
  - ◇ Give vaccines after factor replacement
  - ◇ use fine needles
  - ◇ apply firm pressure for few minutes

## SIDE EFFECTS, PRECAUTIONS & CONTRAINDICATIONS

- Side effects: Local- Systemic OR Mild- severe
- The most common animal protein in vaccines is egg protein e.g. in influenza, measles, mumps, and yellow fever vaccines, these are contraindicated only in anaphylaxis to egg.
- Neomycin: e.g. IPV, MMR, Varicella or any combination containing one of them, contraindicated in anaphylaxis to neomycin
- Thimerasol (mercurial) e.g in DTP, DT, Hib, HBV, influenza vaccines. In most of recipients there is no reaction
- Streptomycin: IPV
- Baker's yeast: -HBV
- Gelatin: in varicella and MMR
- DTP + POLIO COMBINATION
  1. Anaphylaxis within 24 hr
  2. Encephalopathy (or encephalitis) within 3days
  3. Shock – collapse within 3 days
  4. hypotonia - hyporesponsive collapse within 3 days
  5. Residual seizure disorder →no limit
  6. Any acute complication or sequelae of above → no limit
- MMR, DT, TD, TT:
  1. Anaphylaxis → 24hr
  2. Encephalopathy or encephalitis→15 days for MMR & 3 days for others
  3. Residual seizure→ no limit
  4. Any acute complication or sequela→ no limit
- OPV
  1. Paralytic polio in immunodeficients →30 days
  2. Paralytic polio in immunodeficients or community case→ 6 mo.
  3. Any acute complication →no limit
- eIPV
  1. Anaphylaxis →24hr
  2. Any acute complication → no limit

## GENERAL CONTRAINDICATIONS FOR *ALL* VACCINES

1. Anaphylactic reaction to vaccine or its constituents
2. Moderate or severe illness +/-fever

- **Contraindications of DTP / DTaP:**
  - A. **Absolute contraindications***:* Encephalopathy within 7 days of a previous dose.
  - B. **Relative contraindications (Precautions):**
    1. Fever 0f >= 40.5 within 48 hr
    2. Shock-like state or collapse within 48 hr (hypotonia, hyporesponsiveness episode)

3. Persistent inconsolable crying lasting >=3hr within 48hr of vaccine
4. Seizures within 3 days of a previous dose of DTP

## NOT CONTRAINDICATIONS

1. Mild to moderate local reaction (soreness, redness, swelling)
2. Mild acute illness +/- low grade fever
3. Current antibiotic therapy
4. Convalescence of disease
5. Prematurity
6. Recent exposure to infectious disease
7. History of allergy (personal/family)

## TETANUS IMMUNO-PROPHYLAXIS

- PASSIVE IMMUNIZATION
  - ◇ Give TIG 3,000 – 6,000 U IM (part of it into wound)
  - ◇ If TIG is not available, give equine antitoxin after testing for hypersensitivity. Dose: 3,000 –5,000 U for susceptible wounds & 50,000 – 100,000 U for clinical illness. (2,000 IV & rest IM).
- IN WOUND MANAGEMENT:
  - ◇ Parenteral penicillin or tetracycline MAY be given for 10- 14days .
  - ◇ Tetanus Prune wounds
    1. Contaminated wounds with soil saliva, feces, dirt,----
    2. Puncture wounds
    3. Avulsions
    4. Crushing
    5. Burns
    6. Frostbites

| PREVIOUS TETANUS IMMUNIZATION UNCERTAIN OR < 3 DOSES | CLEAN MINOR WOUND | TETANUS PRUNE WOUND |
|---|---|---|
| | Td only | Td +TIG within 3 days |
| 3 DOSES | Td (4th dose) | Td(4th dose) |
| > 3 DOSES | Td if last dose > 10 years | Td if last dose > 5 years |

## INDICATIONS FOR PNEUMOCOCCAL VACCINE

- **Routine or universal use vaccination**
  - ◇ Type of vaccine: Heptavalent pneumococcal conjugate vaccine *(PCV7)*
  - ◇ Age: =<23 mo.: at 2,4,6 and 12-15 mo.
  - ◇ The number of doses is reduced if the age of the child is ≥ 7 mo.
- **High-risk patients**
  - ◇ Type of vaccine: PCV7or 23-valent pneuomococcal polysaccharide Vaccine *(23-PS vaccine)*
  - ◇ Age: 24 – 59 mo for PCV7 (2 doses if not previously vaccinated) , ≥24 mo for 23-PS vaccine
  - ◇ They are:
    1. Sickle cell anemia
    2. Functional or anatomic asplenia
    3. Nephrotic syndrome or renal failure
    4. Immunosupression: HIV, Chemotherapy, Malignancy, Organ transplant, -
    5. Cerebrospinal fluid leak: e.g. basal skull fracture, --
- **Antibiotic prophylaxis against pneumococcus**
    1. In children with asplenia + sickle cell anemia,
    2. Age: can be discontinued after 5 yrs of age IF(both):
       A. Child has not experienced invasive pneumococcal infection

B. Child has received recommended pneumococcal vaccination

## Evaluating the Febrile Patient with a Rash(viral exanthem )
## Dr.Mutaz soltan

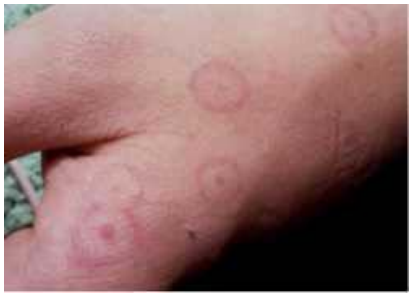
- The differential diagnosis for febrile patients with a rash is extensive.
- Potential causes include :
  1. Infectious: viruses, bacteria, spirochetes, rickettsiae,
  2. Medication
  3. Rheumatologic diseases

### History :

- Details about the rash should include:
  1. site of onset
  2. rate and direction of spread
  3. presence or absence of pruritus
  4. temporal relationship of rash and fever**.**
- *The time of year* .
- Drug ingestion .
- Contact with ill persons .
- Immunization
- Immunocompetence of the patient .

### Physical Examination :

- Evaluating the patient's vital signs and general appearance.
- Assessment triad of febrile patient: general aberrance, circulation(color),breathing.
- Signs of toxicity, adenopathy, oral, genital or conjunctival lesions, hepatosplenomegaly, evidence of excoriations or tenderness, and signs of nuchal rigidity or neurologic dysfunction.
- The rashes:
  1. **Macule:** Circumscribed area of change in normal skin color, with no skin elevation or depression; may be any size.
  2. **Papule**: Solid, raised lesion up to 0.5 cm in greatest diameter.
  3. **Vesicle**: Circumscribed, elevated, fluid-containing lesion < 0.5 cm in greatest diameter.
  4. **Pustule**: vesicle containing purulent fluid of variable character.
  5. **Nodule**: Deep-seated, roundish lesion, <1.5 cm in diameter, can involve the epidermal, dermal, and/or subcutaneous tissue.
  6. **Plaque**: A palpable elevated lesion > 1 cm in diameter.
  7. **Purpura**: Papular or macular non blanching lesions that are due to extravasation of red blood cells.(Petechiae & ecchymosis)
  8. **Wheals** (urticaria): Irregularly elevated skin due to dermal edema, erythematous with sharp borders but not stable. Could be confused with erythema migrans.
- **Erythema multiforme (EM)**:



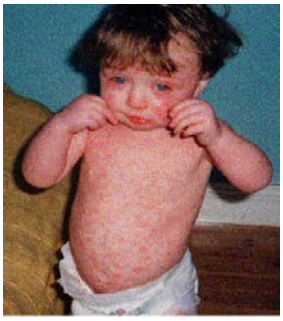
- ♥ Erythematous macules or plaques
- ♥ usually asymptomatic
- ♥ symmetrically distributed "target" lesions, typically involve the palms, soles, mucous membranes, extensor surfaces of the upper limbs. (Dermal & epidermal)
- ♥ Causes of EM
  1. Idiopathic >50 %
  2. Contact reactions
  3. Drugs
  4. Endocrine factors
  5. Infections
  6. Physical (Sunlight, X-ray therapy).
- **Erythema nodosum :**

- Painful red nodular lesions found symmetrically on the lower extremities, appear to be pigmented.
- Causes:
  1. infectins: GAS,EBV, Fungus, TB
  2. idiopathic
  3. IBD
- **Exanthems and association:**
  - palatal petechial lesions → Rubella and EBV
  - hand, foot, & mouth syndrome → Coxsackie virus
  - strawberry tongue → Scarlet fever, Kawasaki syndrome
  - Koplik's spots → Measles

## VIRAL EXANTHEMS

- viral infection causing skin rash
- Viral exanthems are mostly associated with self-limited diseases.
- In many cases an accurate diagnosis cannot be made on the basis of morphology alone.

## MEASLES

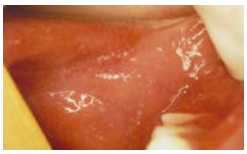


- measles virus : single-stranded RNA virus of the family paramyxoviridae .
- It is acute communicable disease
- One antigenic type is known.

INFECTIVITY: (respiratory: air born droplets)

- Contagious: 9-10 days after exposure (beginning of the prodrome )- from 1 to 2 days before symptoms (about 5 days before onset of rash) to 4 days after the appearance of the rash.
- Isolation is recommended for 7 days after exposure to 5 days after the rash.

EPIDEMIOLOGY :



- One of the highly contagious diseases.
- Before immunization : peak incidence is 5-10 years , now it is reported in preschool unimmunized children and in previously immunized young adult .
- Transplacental immunty lasts for 4-6 months.

IT HAS 3 STAGES :

- Incubation : (10-12 days )
- Prodromal ( catarrhal ): for 3-5 days
  - 3 C's(cough , coryza , conjunctivitis )
  - Koplik's spots (pathognomonic ) : grayish white dotes over the buccal mucosa that last 12 to 24 hours
  - Fever ( low grade)
- Skin rash for 2-3 days, *maculopapular with high fever*, Measles spreads more slowly than rubella, as entire body involved by day 3. Start at hair line→ face→neck →extremities. It may be petechial or hemorrhagic (**black measles**).

DIAGNOSIS:

- Clinical picture
- Tissue cx , AB titer , measles IgM (appear within 1 to 2 days of the rash and persist for 1 to 2 months)
- Leukopenia is characteristic.
- **Warthin-Finkeldey cells:** The characteristic histologic finding, the presence of large, multinucleated giant.
- The conjunctiva may reveal a characteristic transverse line of inflammation along the eyelid margin (**Stimson line**).
- Cervical lymphadenitis, splenomegaly, and mesenteric lymphadenopathy with abdominal pain may be noted.
- ***All cases should be reported***.

COMPLICATIONS:

1. diarrhea ( the most common)
2. seizures (with or without fever)
3. Otitis media.
4. Pneumonia
5. Myocarditis.
6. Encephalitis 1/800 reported cases:CSF reveals an increased protein, a lymphocytic pleocytosis, and normal glucose levels.
7. SSPE(subacute sclerosing panencephalitis): late neurologic complication , 8 to 10 years after measles.

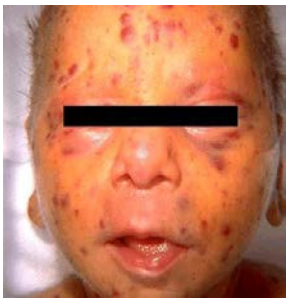
IMMUNIZATION:

- Active: live attenuated virus given with mumps and rubella (MMR) at 12-15 months( because Passive immunity may interfere with effective vaccination until 12 to 15 months of age). Second dose at school entry (not a booster dose but reduces the primary vaccine failure rate, which is 5% or less).
- **postexposure prophylaxis** : vaccine, within 72 hours of exposure, or immunoglobulin within 6 days of exposure.
- Contraindications to measles vaccine include:
  1. immunocompromised states :congenital immunodeficiency, severe HIV infection, leukemia, lymphoma, cancer therapy, corticosteroids (≥2 mg/kg/day for ≥14 days)
  2. pregnancy
  3. recent administration of Ig (3 to 11 months depending on dose).
- MMR vaccination is recommended:
  1. HIV-infected persons who do not have evidence of severe immunosuppression (low age-specific total CD4 T lymphocyte count or a low CD4 T lymphocyte count as a percentage of total lymphocytes)
  2. children with cancer in remission / not received chemotherapy in previous 3 months,
  3. Children who previously have received immunosuppressive doses of corticosteroids but who have not received corticosteroids in the previous month.

TREATMENT:

- supportive
- vitamin A :reduce morbidity and mortality in developing countries , recommended in :
- Children 6months -2 yrs hospitalized for measles
- Immunodeficiency
- Malnutrition
- Signs of vitamin A deficiency (**eye**: *xerophthalmia*, Bitot spots, conjunctivitis, keratomalacia leading to blindness, **skin**: keratinization of mucous membranes and skin, **immune**: impaired resistance to infection)
- IV ribavirin may be beneficial in severe infections.
- Deaths most frequently result from bronchopneumonia or encephalitis

## RUBELLA ( GERMAN MEASLES)
## (3-DAY MEASLES)



- Common communicable disease caused by rubella virus which is single-stranded RNA virus.

EPIDEMIOLOGY :

- Spread by oral droplets or transplacental.
- Before vaccine peak incidence 5-14 yrs now most cases in susceptible adults.
- Transplacental immunity for 6 months .
- Single attack: usually permanent immunity although reinfection may occur

CLINICAL MANIFISTATIONS :

- IP 2-3 weeks.
- Prodromal stage of mild catarrhal illness .The most caracteristic sign is *enlargment of the retro auricular , posteriocervical and post occipital LN .*
- Enanthem of the soft palate (rose spots ) in 20% = **Forchheimer spots**"petechia" .
- Rapid evolution of pin point maculopapular rash *with mild fever*.

- most contagious from 2 days before until 5 to 7 days after onset of the rash.
- Other manifestations of rubella include:
  1. mild pharyngitis
  2. conjunctivitis
  3. FAHM
  4. Polyarthritis, usually of the hands, especially among older women
  5. Paresthesias and tendinitis

**DIAGNOSIS :**

- Clinical picture
- Antibodies titer.
- The WBC count usually is normal or low
- thrombocytopenia rarely occurs.

**IMMUNIZATION :**

- Active &Passive

**CONGENITAL RUBELLA COMMON MANIFESTATIONS :**

1. Maternal infection during the first trimester results in fetal infection in more than 90% of cases with a generalized vasculitis.
2. Intrauterine growth retardation .
3. Cataract
4. deafness
5. Myocarditis
6. PDA
7. Skin lesions
8. Infants with congenital rubella may shed virus in nasopharyngeal secretions and urine for longer than 1 year after birth and may transmit the virus to susceptible contacts.

**PREVENTION :**

- Avoid exposure
- Determine immune status to rubella in all women in child bearing age.
- Management after exposure of pregnant woman :
- Determine immunization status:
  - If immune …reassure
  - Not immuned abortion or passive immunization if not accepted.

## ROSEOLA INFANTUM (EXANTHEM SUBITUM )

- Acute febrile illness caused by human herpesvirus (HHV) type 6 (in younger infant) and
- in 10% to 30% of cases by HHV-7.
- HHV-6 & HHV-7 are large, enveloped double-stranded DNA viruses(herpesvirus family)

**EPIDEMIOLOGY :**

- Peak incidence is ***6-12 months*** , it is a disease of infancy.
- Infection is around the year .more in late spring
- Most newborn are seropositive till the age of 6 months.

**CLINICAL MANIFESTATIONS:**

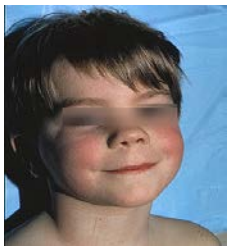
- Most children with roseola are irritable and appear toxic.
- Sudden high fever with no focus sometimes with seizure
- Seizure occurs in 5-10% of cases, *responsible for 1/3 of febrile seizure in infants.*
- On the third day fever resolve and rash appear ( maculopapular and it remains for 3 days)
- Pattern of high fever for 3 to 5 days without significant physical findings followed by onset of rash with absence of fever is ***characteristic***.
- Encephalitis with roseola is characterized by mild pleocytosis (30 to 200 cells/$mm^3$) with mononuclear cell predominance, ↑protein concentration, & normal glucose concentration.

**DIAGNOSIS:**

- Viral isolation and Ab titer
- The diagnosis can be confirmed by serologic testing showing a fourfold rise in acute and convalescent sera..

Treatment is symptomatic.

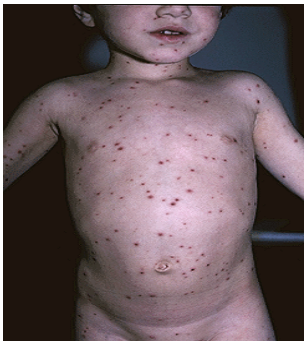
## Erythema infectiosum (5th disease )



- Benign self limiting illness of childhood (3 - 12 years of age ) caused by parvovirus B19 which is a single-stranded DNA virus .
- The virus is transmitted by respiratory secretions and by blood product transfusions.
- parvovirus B19 is linked to the aplastic crises in chronic hemolytic disease .
- primary infection in pregnancy. causes fetal anemia & hydrops fetalis
- Erythema infectiosum is manifested by rash, low-grade or no fever, and occasionally pharyngitis and mild conjunctivitis.
- The hallmark of the disease is the erythematous facial flushing (slapped cheeks) and then spread to the trunk and extremities.
- The rash appears in three stages:
  1. erythematous cheeks, appearing as a **"slapped cheek" rash** with circumoral pallor.
  2. erythematous symmetric, maculopapular, truncal rash appears 1 to 4 days later
  3. later fades as central clearing takes place, giving a distinctive **lacy, reticulated rash** that lasts 2 to 40 days (mean 11 days).
- The rash resolves spontaneously.
- Can present as rheumatic syndrome in adults.
- Diagnosis is usually clinically.
- Serologic tests showing antibody response to parvovirus, especially the presence of specific IgM antibody to parvovirus, are diagnostic.

## Chickenpox (varicella )

- An acute infectious disease of childhood caused by Varicella –Zoster virus which is DNA virus of the human herpesvirus group.



Pathology:

- Varicella begins with mucosal inoculation of virus transferred by resp secretions or
- by direct contact of skin lesions.
- IP 10-21 days .
- After this primary infection VZV become latent in the dorsal root ganglion cells. Its reactivation causes herpes zoster infection

Epidemiology :

- 90-95% of individual acquire infection in the childhood.
- Annual epidemics in winter and spring.
- It is contagious from 24-48 hrs before rash and until all lesions are crusted (3-7) days.
- Transmission is by direct contact, droplet, and air.
- **Zoster** is a recurrence of latent VZV.

Clinical features:

- Prodromal symptoms of fever, malaise, and anorexia may precede the rash by 1 day.
- The characteristic rash appears initially as small red papules that rapidly progress to nonumbilicated, oval, "teardrop" vesicles on an erythematous base.
- The fluid progresses from clear to cloudy, and the vesicles ulcerate, crust, and heal.
- New crops appear for 3 to 4 days, usually beginning on the trunk followed by the head, the face, and, less commonly, the extremities.
- There may be a total of 100 to 500 lesions, with all forms of lesions being present at the same time.
- Lesions also may be present on mucous membranes.
- Pruritus is universal and marked.
- Lymphadenopathy may be generalized.
- ***Rash: erythematous macules …vesicles …crusts; lesions of different generations.***

Diagnosis

- Infection can be confirmed by:

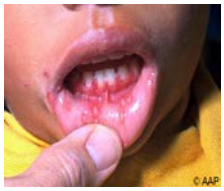
1. detection of varicella-specific antigen in vesicular fluid by immunofluorescence using monoclonal antibodies
2. Demonstration of a fourfold antibody increase of acute and convalescent sera.

- D/D: **Eczema herpeticum**, or **Kaposi varicelliform eruption**, is a localized, vesicular eruption caused by HSV that develops on skin that is affected by eczema or trauma.

TREATMENT:

- Symptomatic
- Antiviral therapy( acyclovir)
  1. Older children > 13 yrs ( more complications as encephalitis & pneumonia).
  2. Secondary household cases
  3. Hx of chronic cutaneous, cardiopulmonary disorders, Renal failure or DM
  4. Children taking intermittent oral or inhaled steroid therapy ( mandatory in immuno-compromised)
  5. Children taking chronic salicylates
- Thrombocytopenia and hemorrhagic lesions or bleeding also may occur, known as **varicella gangrenosa**.
- Reye syndrome may follow varicella; aspirin use is **contraindicated** during varicella infection.
- VARCILLA VACCINE: Live, attenuated, recommended in all children between 12 & 15 mo of age, 2nd dose at age 4 to 6yr.

## HERPES SIMPLEX VIRUS



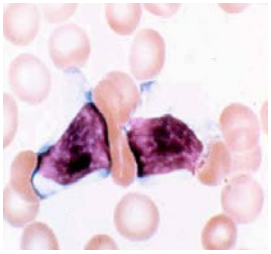
- Often asymptomatic.
- Primary infection of HSV 1
- Gingivostomatitis.
- Herpes labialis is the most common presentation of HSV-1 infection and generally represents HSV-1 reactivation.
- Treatment of herpes gingvostomatitis:

1. Topical or oral analgesics, IV rehydration, mouth rinses.
2. In more severe cases→ oral opiates may be required.
3. Antiseptics →drying lesions & dec risk of super infection.
4. ACYCLOVIR

## INFECTIOUS MONONUCLEOSIS :

- An acute infectious disease of childhood and adolescent caused by Epistien-Barr virus (EBV) which is a DNA virus a member of herpesviridae.
- EBV infects 95% of world's population, transmitted by oral secretions (kissing disease )
- The incubation period is **30-50 days**
- Majority of primary EBV infection in infants and children are asymptomatic.
- In older children: prodromal symptoms followed by increasing fever and sore throat.

PHYSICAL FINDINGS



1. splenomegaly
2. Generalized lymphadenopathy
3. hepatomegaly (less common )
5. maculopapuler rash in 3-15%

DIAGNOSIS :

- Clinical picture
- Blood film :atypical lymphocytes ( activated T lymphocytes with ↓nuclear-cytoplasm ratio ) ≥ 20% of peripheral blood film with atypical lymphocytes.
- Heterophile antibody test: sensitive in only up to 50% of cases in children < 4 yrs.
- Specific EBV antibodies.
- Avoid amoxicillin & penicillin → maculopulpar rash.

NO SPECIFIC TREATMENT AND THE PROGNOSIS IS EXCELLENT .

## Entervirus infections

- Enteroviruses are a large group of viral agents that inhibit the intestinal tract and responsible for frequent human illnesses .
- They are RNA viruses belonging to the picornaviridae family .the major subgroups are coxsackieviruses, echoviruses and polioviruses .
- The nonpolio enteroviruses are a common cause of large variety of skin manifestations in the summer and fall they are the leading cause of exanthems .
- Echovirus type 9 → nonspecific febrile illness , aseptic meningitis and exanthem
- Coxsackievirus A 16 →hand foot mouth syndrome (الحمى القلاعية)

## Other deferential diagnosis:

- Kawasaki disease
- Henoch–Schonlein purpura (HSP)

  The classic tetrad of HSP
  1. Palpable purpura, 100%
  2. Arthritis/ arthralgia, 75%
  3. Abdominal pain, 20-30%
  4. Renal disease, 21-54%

# Croup (Laryngotracheobronchitis)

## ETIOLOGY

- Croup ( laryngotracheobronchitis) is the **most common infection of the middle respiratory tract** ( viral infection of glotic and subglotic region).
- Parainfluenza (75%) (types 1, 2, and 3) and RSV are the most common causes of croup.
- Males>females.
- Laryngotracheal airway inflammation → mucosal edema and inflammation →small decrease in diameter → increases airway resistance→ increases the work of breathing
- stridor characteristic of croup: During inspiration→ the walls of the subglottic space are drawn together→aggravating the obstruction → stridor.
- **Clinical Features of Laryngotracheal Respiratory Tract Infections**

| Feature | Epiglottitis | Bacterial Tracheitis | croup | Spasmodic Croup |
|---|---|---|---|---|
| Viral prodromal illness | - | + | ++ | - |
| Mean age | 3-4 yr (25% <2 yr) | 4-5 yr | 6-36 mo (60% <24 mo) | 6-36 mo (60% <24 mo) |
| Onset of illness | Acute (6-24 hr) | Acute (1-2 days) | Gradual (2-3 days) | Sudden (at night) |
| Fever | + | + | ± | - |
| Toxicity | + | ++ | - | - |
| stridor | Mild | Harsh | Harsh | Harsh |
| Drooling, neck hyperextension | ++ | + | - | - |
| Cough | - | ++ | ++ | ++ |
| Sore throat | ++ | ± | ± | - |
| + blood culture | + | ± | - | - |
| Leukocytosis | + | + | - | - |
| Recurrence | - | - | + | ++ |
| Hospitalization and ET intub. | Frequent | Frequent | Rare | Rare |

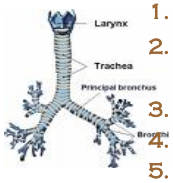
## EPIDEMIOLOGY

- Croup is most common in children 6 months to 3 years old
- peak in fall and early winter.
- Episodes typically follow a common cold.

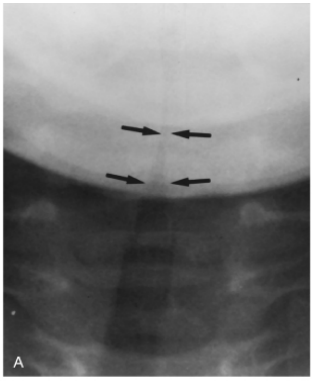
- Symptomatic reinfection is common; reinfections are usually mild.

## CLINICAL MANIFESTATIONS

- The manifestations of croup are:
  1. hoarseness
  2. inspiratory stridor: harsh, high-pitched respiratory sound produced by turbulent airflow that is usually inspiratory, but may be biphasic; it is a sign of upper airway obstruction.
  3. Cough: harsh, that is described as **barking** or **brassy** in quality.
  4. low-grade fever
  5. respiratory distress (develop slowly or quickly) = Signs of upper airway obstruction
  6. Wheezing if there is lower airway involvement.
- Symptoms aggravate by agitation and crying. Worse at night.
- **Differential Diagnosis of Stridor**




| INFECTIONS | NONINFECTIOUS CONDITIONS |
|---|---|
| CROUP | Foreign body aspiration |
| Epiglottitis | Angioneurotic edema |
| Bacterial tracheitis | Spasmodic croup , Vocal cord paralysis |
| Pharyngitis | Ingestion of caustic or hot fluid |
| Parapharyngeal abscess | Trauma, smoke inhalation |
| Laryngeal papillomatosis | **Laryngomalacia** , **Hypocalcemia** |
| Laryngopharyngeal diphtheria | **Congenital subglottic stenosis** |
| Extrinsic inflammatory mass compressing the trachea (e.g., TB) | Extrinsic mass compressing the trachea (cystic hygroma, **hemangioma**, vascular malformation) |




## LABORATORY AND IMAGING STUDIES

- THE DIAGNOSIS OF CROUP USUALLY IS ESTABLISHED BY CLINICAL MANIFESTATIONS.
- **steeple sign:** the diagnostic subglottic narrowing of croup seen by AP X-ray.
- Leukocytosis is uncommon and suggests epiglottitis or bacterial tracheitis.
- rapid tests (PCR or antigen) : for parainfluenza viruses and RSV , influenza & adenoviruses.

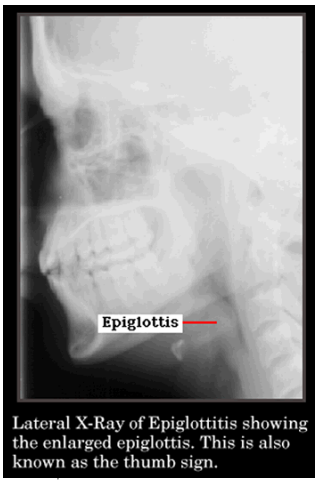
## DIFFERENTIAL DIAGNOSIS

- Think of other causes as (subglottic stenosis or hemangioma) and so the need for direct laryngoscopy if:

1. Stridor in infants younger than 4 months old
2. persistence of symptoms for more than 1 week

### EPIGLOTTITIS

- Typically, in children 1 to 5 years old
- A medical emergency because of the risk of sudden airway obstruction.
- Hib is historically the principal causative agent, but immunization has reduced Hib infections markedly. Now strep and staph become more common.
- Clinical manifestations:
  1. Stridor is common (sudden onset and rapid progression)- late finding suggest near complete obstruction.
  2. high fever
  3. muffled rather than hoarse voice
  4. dysphagia
  5. drooling of secretions
  6. refusal to eat or drink
  7. refusal to sleep
  8. (**sniffing position**) : preference for sitting, head held forward , the mouth open & the jaw thrust forward



Lateral X-Ray of Epiglottitis showing the enlarged epiglottis. This is also known as the thumb sign.

- **Thumb sign**:Lateral neck x-ray reveals thickened and bulging epiglottis and swelling of the aryepiglottic folds.
- ***The diagnosis is confirmed by*** *direct observation of the inflamed and swollen supraglottic structures and swollen, cherry-red epiglottitis, which should be performed only in the operating room with a competent surgeon and anesthesiologist prepared to place an endotracheal tube or less often to perform a tracheostomy.*
- Epiglottitis requires endotracheal intubation to maintain the airway and antibiotic therapy ( after taking cultures give IV ceftriaxon or cefuroxim for 7-10 days)
- Clinical recovery is rapid, and most children can be extubated safely within 48 to 72 hours.

## BACTERIAL TRACHEITIS

- is a rare but serious super-infection of the trachea that may follow viral croup
- mean age: 4-5 yr
- most commonly caused by ***S. aureus***.
- Symptoms include high fever with cough and stridor, RD.
- It is clinical diagnosis mainly.
- The diagnosis requires :
  1. visualization of the middle airway
  2. Culture of the thick mucopurulent subglottic debris.
- Chest X-ray: patchy infiltrations, subglotic narrowing with rough tracheal column.
- Treatment includes endotracheal intubation and antibiotic therapy.

## SPASMODIC CROUP

- Sudden onset of croup symptoms, usually at night, but without an URT predrome.
- recurrent and severe but usually are of short duration.
- Spasmodic croup has a milder course than viral croup and responds to relatively simple therapies, such as exposure to cool or humidified air.
- + family history.
- The etiology is not well understood but may be allergic, psychogenic or GERD.

## TREATMENT

- Most can managed at home safely (mainstay of treatment is airway management) = current recommendation is to provide cool mist.
- Administration of aerosolized racemic (D- and L-) or L-epinephrine reduces subglottic edema by α-adrenergic vasoconstriction, temporarily producing marked clinical improvement.
  - Dose: 0.25-0.75 ml/kg 2.25% epinephrine / max <4years= 2.5 ml & >4years = 5ml with N/S nebulizer
  - The peak effect is within 10 to 30 minutes, but fades within 2 hours.
  - A rebound effect may occur, with worsening of symptoms.
  - Aerosol treatment can be repeated q 20 minutes (for 1 to 2 hours) in severe cases.
  - Children receiving aerosol treatment should be hospitalized or observed for at least 2 to 3 hours because of the risk of rebound.
  - Indications:
    1. moderate- severe stridor at rest
    2. need for intubation
    3. respiratory distress
    4. hypoxia
- Oral or IM dexamethasone in mild /moderate croup reduces the need for hospitalization and shortens hospital stays. (dose: 0.6mg/kg IM injection – lower effective dose = 0.15 mg/kg dexamethazone, 2mg nebulized budisonide has the same effect)
- Children should be kept as calm as possible to minimize forceful inspiration.
  - One useful calming method is for a child with croup to sit in the parent's lap.
  - Sedatives should be used cautiously and only in the ICU.

- ♥ Cool mist administered by tent or facemask may help prevent drying of the secretions around the larynx.

- Hospitalization often is required for children with:
  1. progressive stridor
  2. severe stridor
  3. stridor at rest
  4. respiratory distress
  5. hypoxia and cynosis
  6. depressed mental status
  7. need for reliable observation
- Subsidence of symptoms may indicate improvement or fatigue and impending respiratory failure.

## COMPLICATIONS

- The most common complication of croup is viral pneumonia, which occurs in 1% to 2% of children with croup.
- Parainfluenza pneumonia and secondary bacterial pneumonia are more common among immuno-compromised persons.

## PROGNOSIS

- excellent prognosis.
- Illness lasts 5 days.
- There is no vaccine for parainfluenza or RSV.

# PHARYNGITIS

## ETIOLOGY

- Infectious agents cause pharyngitis ( 60% viral).
  1. Group A streptococci (*Streptococcus pyogenes*) are gram-positive, nonmotile cocci.
  2. Group C beta-hemolytic streptococcus; *Arcanobacterium haemolyticum,* which is a hemolytic, gram-positive rod; and *Francisella tularensis,* the gram-negative coccobacillus that is the cause of tularemia.
  3. *Chlamydophila pneumoniae,* strain TWAR.
  4. *M. pneumoniae*
  5. *S. aureus*, Hib, and *S. pneumoniae* : their role in causing pharyngitis is unclear.
  6. adenoviruses, more likely than other viruses to cause pharyngitis as prominent symptom
  7. Rhinoviruses, more likely to cause pharyngitis as a minor part of an illness that primarily features other symptoms, such as rhinorrhea or cough.
  8. EBV (mononucleosis), enteroviruses (herpangina), and primary HIV infection

**MAJOR MICROBIAL CAUSES OF ACUTE PHARYNGITIS**

| AGENT | SYNDROME OR DISEASE |
|---|---|
| Group A streptococcus **15-30%** (*Streptococcus pyogenes*) | Pharyngitis, tonsillitis |
| Group C streptococcus | Pharyngitis, tonsillitis |
| Other (e.g., *Corynebacterium diphtheriae*) | Pharyngitis, laryngitis |
| Rhinoviruses (>100 types) **20%** | Common cold |
| Coronaviruses (≥4 types) | Common cold |
| Adenoviruses (types 3, 4, 7, 14, 21) | Pharyngoconjunctival fever, acute respiratory disease |
| Herpes simplex viruses (types 1& 2) | Gingivitis, stomatitis, pharyngitis |
| Parainfluenza viruses (types 1-4) | Common cold, croup |
| Influenza viruses (types A and B) | Influenza |

## EPIDEMIOLOGY

| | |
|---|---|
| Epstein-Barr virus | Mononucleosis |
| **Unknown 40%** | |

- Sore throat is the primary symptom in one third of Infections of the upper respiratory tract.
- Streptococcal pharyngitis:
  - ◇ uncommon before 2 to 3 years of age,
  - ◇ peak 4-7 years
  - ◇ Incidence ↑in young school-age children, then ↓in late adolescence and adulthood.
  - ◇ Streptococcal pharyngitis occurs with a peak during the winter and spring.
- Viral infections spread via close contact with an infected person & peak in winter and spring.

## CLINICAL MANIFESTATIONS

- The inflammation of pharyngitis causes :
  1. fever
  2. sore throat
  3. dysphagia
  4. cough
- If involvement of the tonsils is prominent: **tonsillitis** or **tonsillopharyngitis**

### STREPTOCOCCAL PHARYNGITIS

- The onset of is rapid and associated with:
  1. prominent sore throat
  2. Moderate to high fever.
  3. Headache
  4. nausea, vomiting
  5. abdominal pain
- **Most suggestive symptoms**: 5-15yrs, acute pharyngitis, fever, no URTI.
- The pharynx is red, and the tonsils are enlarged and covered with a yellow, blood-tinged exudate.
- petechiae or "doughnut-shaped" lesions on the soft palate and posterior pharynx, and the uvula red, stippled, and swollen.
- **The most suggestive physical finding**= diffuse tonsilar redness+tonsiles pillars+petechial mottling of soft palat.
- The anterior cervical lymph nodes are enlarged and tender to touch.
- The clinical spectrum of disease is broad and many children present with only mild pharyngeal erythema without consular exudate or cervical lymphadenitis.

### SCARLET FEVER:

- the stigmata of scarlet fever:

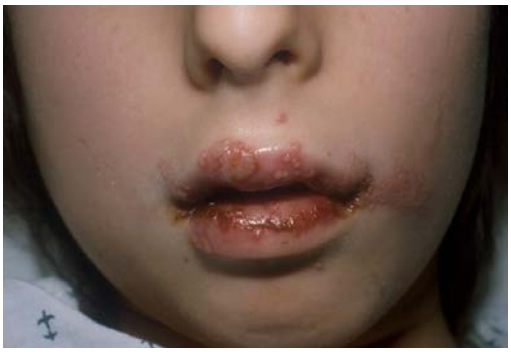
1. circumoral pallor,
2. strawberry tongue,
3. fine diffuse erythematous macular-papular rash.

- The tongue initially has a white coating, but red and edematous lingual papillae later project through this coating, producing a **white strawberry tongue**.
- When the white coating peels off, the resulting **red strawberry tongue** is a beefy red tongue with prominent papillae.

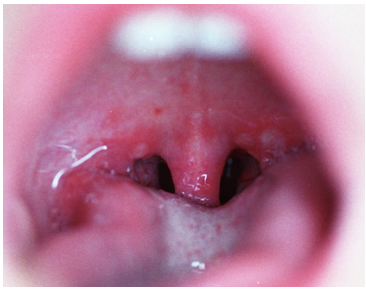
### VIRAL PHARYNGITIS

- onset of is typically more gradual, and symptoms more often include :
  1. rhinorrhea
  2. cough
  3. diarrhea.
- **Gingivostomatitis** is characteristic of HSV-1 and occurs in children 1 to 5 years old, with the highest incidence from 9 to 36 months of age.
  - ◇ Transmitted by direct contact with draining mucosal lesions or asymptomatic shedding.
  - ◇ The incubation period of oral HSV illness is 7 days (range 2 to 25 days).

- Primary HSV infection is more severe than recurrent illness.
- Clinical features of primary HSV gingivostomatitis include :
  1. high fever
  2. poor intake of liquid and solid food,
  3. dehydration
  4. malaise
  5. stinging mouth pain
  6. drooling
  7. fetid breath
  8. oropharyngeal vesicular lesions
  9. lymphadenopathy



- Grouped lesions on an erythematous base are present around the stomal opening , on the tongue, gums, lips, oral mucosa and the soft & hard palate.
- The lesions crusted and heal without scarring within 5 to 10 days, may last 3 wks.
- Primary infection is accompanied by fever and tender lymphadenopathy, which are often absent with recurrent disease.
- **herpes labialis**: Limited involvement to only a portion of the vermilion, characteristic of recurrent illness than primary HSV infection.



- **Herpangina** is an enteroviral infection with major symptoms of sudden onset of:
  1. high fever
  2. malaise & myalgia
  3. sore throat and dysphagia
  4. conjunctivitis
  5. headache
  6. backache
  7. vomiting & poor intake
  8. drooling.
  - The oral lesions of herpangina classically : one or more small, tender, papular, or pinpoint vesicular lesions on an erythematous base scattered over the soft palate, uvula, fauces, and tongue.
  - These vesicles enlarge from 1 to 2 mm to 3 to 4 mm over 3 to 4 days, rupture, and produce small, punched-out ulcers that persist for several days.

## LABORATORY EVALUATION

- The principal challenge is to distinguish pharyngitis caused by group A streptococci from pharyngitis caused by nonstreptococcal (usually viral) organisms.
- A rapid streptococcal antigen test or a throat culture or both are often performed to improve diagnostic precision and who are to benefit from antibiotic therapy of streptococcal disease.
- WBC count, ESR, and CRP not routinely recommended.
- CBC in infectious mononucleosis show a predominance of atypical lymphocytes.
- **Throat culture is the diagnostic "gold standard" for establishing the presence of streptococcal pharyngitis.**
- A proportion of positive cultures reflect streptococcal carriage, but not the etiology of the acute pharyngitis.

## DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of infectious pharyngitis includes :
  1. retropharyngeal abscesses (*S. aureus,* streptococci, anaerobes),
  2. diphtheria (if unimmunized),
  3. peritonsillar abscesses (with quinsy sore throat or unilateral tonsil swelling caused by streptococci, anaerobes, or, rarely, *S. aureus*),
  4. epiglottitis.
  5. neutropenic mucositis (leukemia, aplastic anemia),

6. thrush (candidiasis secondary to T cell immune deficiency),
7. auto-immune ulceration (SLE, Behçet disease),
8. Kawasaki disease pharyngitis.

- Pharyngitis is often a prominent feature of EBV-associated mononucleosis.
- Membranous exudate: diphtheria, IM
- Gonoccocal pharyngeal infections are asymptomatic.
- **Vincent infection** or **trench mouth** is a fulminant form of **acute necrotizing ulcerative gingivitis** with synergistic infection with certain spirochetal organisms, notably *Treponema vincentii,* with anaerobic *Selenomonas* and *Fusobacterium*.
- **Vincent angina** : virulent form of anaerobic pharyngitis where in gray pseudomembranes are found on the tonsils= **false diphtheria**.
- **Noma( cancrum oris** or **gangrenous stomatitis)** : related in pathophysiology to Vincent infection, but typically begins as a focal gingival lesion and rapidly progresses to gangrene and consequent destruction of bone, teeth, and soft tissues.
  - ◊ Mortality rates of 70% to 90% occur in the absence of prompt surgical intervention.
  - ◊ Associated with infection by *Borrelia vincentii* and *Fusobacterium nucleatum*.
  - ◊ Noma related to severe malnutrition or to immunodeficiency states.
- **Ludwig angina** is a mixed anaerobic bacterial cellulitis of the submandibular and sublingual regions.
  - ◊ odontogenic in origin, typically spreading from a periapical abscess of the second or third mandibular molar.
  - ◊ associated with tongue piercing.
  - ◊ A propensity for rapid spread, glottic and lingual swelling→ airway obstruction makes prompt intervention imperative.
- **(PFAPA)** syndrome: **periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis** is a rare cause of recurrent fever in children.
  - ◊ aphthae are painful solitary vesicular lesions in the mouth.
  - ◊ The fevers begin at a young age (usually <5 years old).
  - ◊ Episodes last 5 days; duration is shorter with treatment with oral prednisone.
  - ◊ There is a mean of 28 days between episodes.
  - ◊ Episodes are unresponsive to NSAIDs or antibiotics.
  - ◊ The syndrome resolves in some children, whereas symptoms persist in other children.
  - ◊ Long-term sequelae do not develop.

## TREATMENT

- Even if untreated, most episodes of streptococcal pharyngitis resolve over a few days.
- antimicrobial therapy accelerates clinical recovery by 12 to 24 hours.
- The major benefit of antimicrobial therapy is the prevention of **acute rheumatic fever** .
- treatment instituted within 9 days of illness is virtually 100% successful in preventing rheumatic fever.Because the incubation period of acute rheumatic fever is long (1 to 3 wks),
- Antibiotic therapy should be started immediately in children with :
  1. positive rapid test for group A streptococcus
  2. scarlet fever
  3. symptomatic pharyngitis whose siblings are ill with documented streptococcal pharyngitis
  4. symptomatic pharyngitis and a past history of rheumatic fever or a recent history of rheumatic fever in a family member,
  5. Symptomatic pharyngitis who are living in an area experiencing an epidemic of acute rheumatic fever or poststreptococcal glomerulonephritis.
- antimicrobial agents to treat streptococcal pharyngitis .

1. Penicillin: narrow spectrum, inexpensive, few adverse effects. orally 3-4/day for a full 10 days.oral amoxicillin is preferred over oral penicillin.
   - ◊ single IM dose of benzathine penicillin, painful,provides adequate blood levels for >10d
   - ◊ For patients allergic to penicillins, erythromycin is the drug of choice.

2. oral first-generation cephalosporins: as good as, or better than, penicillin in eradicating the streptococci as:
   - ◇ staphylococci or anaerobes in the pharynx produce β-lactamase→ inactivates penicillin and reduces its efficacy.
   - ◇ These other drugs are more effective in eradicating streptococcal carriage.

- Children with recurrent episodes of pharyngitis with throat cultures positive for group A streptococcus → alternative antibiotic to treat pharyngeal flora producing β-lactamase ( responsible for the recurrences) → amoxicillin-clavulanate or clindamycin ( effective regimen for eliminating streptococcal carriage).
- Patients with primary herpetic gingivostomatitis : early treatment with oral acyclovir.
- Antimicrobial prophylaxis with daily oral penicillin prevents recurrent streptococcal infections and is rec-ommended only to prevent recurrences of rheumatic fever.

## COMPLICATIONS AND PROGNOSIS

- Pharyngitis caused by streptococci or respiratory viruses usually resolves completely.
- The complications of group A streptococcal pharyngitis include :
  1. local suppurative complications, such as parapharyngeal abscess.
  2. nonsuppurative complications, such as acute rheumatic fever & acute postinfectious GN.
- Viral respiratory tract infections, including influenza A, adeno-viruses, parainfluenza type 3, & rhinoviruses→ predispose to bacterial middle ear infections.

# MENINGITIS

## ETIOLOGY

- **Meningitis**: inflammation of the leptomeninges caused by bacteria, viruses or rarely fungi.
- **aseptic meningitis**= viral meningitis, but a similar picture seen with:
  1. infectious organisms (Lyme disease- borrelia bugdorferi, TB,Syphilis)
  2. parameningeal infections (brain abscess, epidural abscess, venous sinus empyema)
  3. chemical exposure (**NSAIDs**, IV Ig)
  4. autoimmune disorders
- The organisms commonly causing bacterial meningitis before the availability of current conjugate vaccines were Hib, *S. pneumoniae,* and *N. meningitidis*.
- The bacteria causing neonatal meningitis are the same as the bacteria that cause neonatal sepsis.
- Staphylococcal meningitis occurs in patients who have had neurosurgery or penetrating head trauma
- Viral meningitis:
  - ♥ caused most commonly by entero-viruses ( usually last 2-4 days, may improve after lumbar puncture):
    1. coxsackieviruses
    2. echoviruses
    3. polioviruses ( if unvaccinated)
  - ♥ Other viruses: HSV, EBV, CMV, lymphocytic choriomeningitis virus, and HIV.
  - ♥ Enteroviruses and arboviruses are the principal causes of meningoencephalitis.
  - ♥ Mumps virus is a common cause of viral meningitis in unvaccinated children.

| AGE | MOST COMMON | LESS COMMON |
|---|---|---|
| NEONATAL | Group B streptococci | Staphylococcus aureus |
| | Escherichia coli | Coagulase-negative staph. |
| | Klebsiella | Enterococcus faecalis |
| | Enterobacter | Citrobacter diversus |
| | | Salmonella |
| | | Listeria monocytogenes |
| | | Pseudomonas aeruginosa |
| | | Haemophilus influenzae types a, b, c, d, e, f, and nontypable |
| >1 MO | Streptococcus pneumoniae **( with highest rate of commplicatons)** | H. influenzae type b **( in areas without vaccine)** |
| | Neisseria meningitidis | Group A streptococci |
| | | Gram-negative bacilli |
| | | L. monocytogenes |

## EPIDEMIOLOGY

- bacterial meningitis is highest among **children <1 year of age**.
- Risk factors:
  1. Genetic factors
  2. acquired or congenital immunodeficiencies
  3. hemoglobinopathies ex. sickle cell disease, functional or anatomic asplenia.

4. Crowding.
5. CSF leak resulting from congenital anomaly or after a basilar skull fracture especially caused by *S. pneumoniae*.
6. Low birth weight, PROM, chorioamionitis.

> **NOTE:**
> **Most common 3 symptoms:**
> 1. vomiting.
> 2. lethargy
> 3. fever
>
> ♥ headache: if old age.

## CLINICAL MANIFESTATIONS

- Preceding upper respiratory tract symptoms are common.
- Rapid onset is typical of *S. pneumoniae* and *N. meningitidis*.
- Indications of meningeal inflammation include ( symptoms) :
  1. headache
  2. irritability
  3. nausea & vomiting
  4. nuchal rigidity
  5. lethargy
  6. photophobia
  7. Fever (95%)( in bacterial = high fever / in lyme dz = low grade fever)
- Signs:
  1. Young infants: **irritability**, **restlessness**, **depressed mental status**, and **poor feeding** as signs of meningeal inflammation.
  2. Children >I year of age: **Kernig sign** (flexion of the hip 90 degrees with subsequent pain with extension of the leg), and **Brudzinski sign** (involuntary flexion of the knees and hips after passive flexion of the neck while supine→signs of meningeal irritation are positive**.**
  3. others: Focal neurologic signs, seizures, arthralgia, myalgia, petechial or purpuric lesions(with rapid onset in N. Meningitis), erythema migrans (lyme disease),sepsis, shock, and coma.
  4. increased intracranial pressure complaints are:
     1. headache
     2. diplopia
     3. vomiting
     4. bulging fontanel in infants
     5. Ptosis,
     6. sixth nerve palsy
     7. anisocoria,
     8. bradycardia with HTN
     9. apnea
     10. Papilledema (uncommon)

> **NOTE:**
> - **N. meningitides:** C5-9 terminal complement
> - **H. influenzae:** humeral immunity deficiency.

## LABORATORY AND IMAGING STUDIES

- If bacterial meningitis is suspected, a lumbar puncture should be performed **( diagnostic)**
- A lumbar puncture should be avoided in the presence of :
  1. cardiovascular instability
  2. Signs of ↑ ICP other than bulging fontanel → risk of herniation.
  3. skin infection over skin site of LP
  ♥ Thrombocytopenia is a relative contraindication for LP.
- Bacterial meningitis is characterized by:
  1. neutrophilic pleocytosis
  2. moderately to markedly elevated protein
  3. low glucose.
- Viral meningitis is characterized by:
  1. mild to moderate lymphocytic pleocytosis
  2. normal or slightly elevated protein
  3. normal glucose
- **CSF should be cultured** for bacteria and, fungi, viruses, and mycobacteria.
- **PCR** : diagnose enteroviruses and HSV(more sensitive & rapid than viral culture)

- **CBC**:Leukocytosis is common.
- **Blood cultures** are positive in 90% of cases.
- **electroencephalogram (EEG)** may confirm an encephalitis component.

**CSF Findings in Various CNS Disorders:**

## DIFFERENTIAL DIAGNOSIS

- Many disorders show signs of meningeal irritation & ↑ ICP including :
  1. encephalitis
  2. hemorrhage
  3. rheumatic diseases
  4. malignancies
  5. malignant HTN
  6. hypoxia/anoxia
  7. drug intoxication
- Seizures are associated with meningitis, encephalitis, and intracranial abscess or brain edema, cerebral infarction or hemorrhage, or vasculitis.

| CONDITION | PRESSURE | WBC (/µL) | PROTEIN (MG/DL) | GLUCOSE (MG/DL) | COMMENTS |
|---|---|---|---|---|---|
| NORMAL | 50-180 mm $H_2O$ | <4; 60-70% lymphocytes, 30-40% monocytes, 1-3% neutrophils | 20-45 | >50 or 75% blood glucose | |
| ACUTE BACTERIAL MENINGITIS | elevated | 100-60,000+; a few thousand; PMNs predominate | 100-500 | Depressed compared with blood glucose; usually <40 | Organism may be seen on Gram stain and recovered by culture |
| PARTIALLY TREATED BACTERIAL MENINGITIS | Normal or elevated | 1-10,000; PMNs ,mononuclear cells predominate if pretreated for extended period | >100 | Depressed or normal | Organisms may be seen; pretreatment may render CSF sterile in pneumococcal and meningococcal disease, but antigen may be detected |
| TUBERCULOUS MENINGITIS | elevated; low if CSF block in advanced stages | 10-500; PMNs early ,lymphocytes and monocytes predominate later | 100-500; may be higher in presence of CSF block | <50 usual; decreases with time if treatment not provided | Acid-fast organisms may be seen on smear; organism can be recovered in culture or by PCR; PPD, chest x-ray positive |
| FUNGAL | elevated | 25-500; PMNs early; mononuclear cells predominate later | 20-500 | <50; decreases with time if treatment not provided | Budding yeast may be seen; organism recovered in culture; India ink preparation or antigen positive in cryptococcal disease |
| VIRAL MENINGITIS OR MENINGOENCEPHALITIS | Normal or slightly elevated | PMNs early; mononuclear cells predominate later; rarely more than 1000 cells. | 20-100 | Generally normal; may be depressed to 40 in some viral diseases (15-20% of mumps) | Enteroviruses may be recovered from CSF by appropriate viral cultures or PCR; HSV by PCR |
| ABSCESS | Normal or elevated | 0-100 PMNs unless rupture into CSF | 20-200 | Normal | Profile may be completely normal |

### CLINICAL NOTES BY DR. IMAD:

- Every 500 RBC: ↑ 1 WBC,↑ 0.5 protein.
- So if CSF contain 100.000 RBC with protein 140 → 100.000/500× 0.5 = 100 → 100-140 =40 ( normal CSF protein)
- CSF culture and gram stain are not change if traumatic LP was happened
- Neonates have as many as 30 leukocytes/$mm^3$ (usually <10), but older children <5 leukocytes/$mm^3$ in the CSF/both → a predominance of lymphocytes or monocytes.
- Plz memorize partial treated bacterial meningitis.

## TREATMENT

- Treatment of bacterial meningitis focuses on sterilization of the CSF by antibiotics ( effective + cross BBB) and maintenance of adequate cerebral and systemic perfusion.
- If suspected bacterial meningitis give: 3ed generation cephalosporins ( cefotaxime or ceftriaxon) in meningitis dose – the highest dose. As no H.Inf or N.M were reported to be resistant.
- If suspect S*. pneumoniae:* cefotaxime (or ceftriaxone) *plus* vancomycin (relatively resistant to penicillin or cephalosporins – in some places up to 60%)
- *N. meningitidis* and *H. influenzae* types *a -f*: Cefotaxime or ceftriaxone only.
- Infants <2 months of age: add ampicillin to cover the possibility of *Listeria monocytogenes*.
- In H. influenza : antibiotic → bacteria lyses → release toxic metabolites → affect hearing ( so give steroids before antibiotic to prevent inflammation – proven to H. inf but can be given in case of N.M or Strep.
- Duration of treatment:
  1. 10 -14 days for *S. pneumoniae*
  2. 7 -10 days for *H. influenzae*
  3. 5 -7 days for *N. meningitides*
- **Initial Antimicrobial Therapy by Age for Presumed Bacterial Meningitis**

**NOTE:**
**Best empirical therapy:**
3ed generation cephalosporins + vancomycin
(Gram -) (Gram +)

| AGE | RECOMMENDED TREATMENT | ALTERNATIVE TREATMENTS |
|---|---|---|
| NEWBORNS (0-28 days) | Cefotaxime or ceftriaxone plus ampicillin with or without gentamicin | Gentamicin plus ampicillin |
| | | Ceftazidime plus ampicillin |
| INFANTS AND TODDLERS (1 mo-4 yr) | Ceftriaxone or cefotaxime plus vancomycin | Cefotaxime or ceftriaxone plus rifampin |
| CHILDREN AND ADOLESCENTS (5-13 yr) & ADULTS | Ceftriaxone or cefotaxime plus vancomycin | Ampicillin plus chloramphenicol? Don't use… |

## COMPLICATIONS

- Include:
  1. SIADH: necessitates balancing the need for fluid administration for hypotension and hypoperfusion.
  2. seizures
  3. strike
  4. cerebral and cerebellar herniation
  5. transverse myelitis
  6. ataxia
  7. thrombosis of dural venous sinuses
- CT or MRI detects subdural effusions with *S. pneumoniae* &Hib meningitis. Most are asymptomatic &do not need drainage unless associated with ↑ ICP or focal neurologic signs.
- Persistent fever (n= 5-7 days, if >10 days as in 10% of pts) think of:
  1. infective or immune complex-mediated pericardial or joint effusions
  2. thrombophlebitis
  3. drug fever
  4. nosocomial infection
  5. intracranial viral infection
  6. secondary bacterial infection
- A repeat lumbar puncture is not indicated for fever in the absence of other signs of persistent CNS infection.

## PROGNOSIS

- the mortality rate for bacterial meningitis in children is significant:
  - ♥ 25% for *S. pneumoniae,*
  - ♥ 15% for *N. meningitidis,*
  - ♥ 8% for Hib.

- 35%, particularly after pneumococcal infection→deafness, seizures, learning disabilities, blindness, paresis, ataxia, or hydrocephalus.
- All patients with meningitis should have hearing evaluation.
- Poor prognosis is associated with:
  1. young age < 6 months
  2. delayed antibiotic treatment
  3. seizures ( only after 4th day)
  4. coma at presentation
  5. shock
  6. low or absent CSF WBC count with visible bacteria on Gram stain of the CSF
  7. immunocompromised status.
- Rarely, **relapse** occurs 3 to 14 days after treatment from parameningeal foci or resistant organisms.
- **Recurrence** indicate an immunologic or anatomic defect.

## PREVENTION

- Routine **immunizations** against Hib and *S. pneumoniae* are recommended for children beginning at 2 months of age.
- Vaccines against *N. meningitidis* are recommended for young adolescents and college freshmen as well as military personnel and travelers to highly endemic areas.
- Close contacts: who stay with the index case more than 24 hrs/ week.
- **Chemoprophylaxis** :(rifampin/ red body secretions, ciprofloxacin, or ceftriaxone )
  1. *N. meningitidis* :close contacts and the index case
  2. Hib close contacts and the index case
  3. No for *S. pneumoniae*
- Immunization:
  1. Hib immunize all < 4 years who are not fully immunized or partial immunized
  2. N. *meningitidis*: immunize all close contact never mind the age.
  3. *S. pneumoniae*: vaccine not developed yet.
- *S. pneumoniae* cases can be stay in the ward as its very rare to be transmitted by respiration.

# URINARY TRACT INFECTION

## ETIOLOGY

- UTIs include **:**
  1. **cystitis** (infection localized to the bladder),
  2. **pyelonephritis** (infection of the renal parenchyma, calyces, and renal pelvis),
  3. **Renal abscess**: intrarenal or perinephric.
- The urinary tract and urine are normally sterile.
- *E. coli* ascending from bowel flora =90% of 1st infection & 75% of recurrent infections.
- *90%* of nephritogenic *E. coli* possess P-fimbriae→facilitates adherence to uroepithelial cells.
- Other bacteria: Klebsiella*, Proteus, Enterococcus,* and *Pseudomonas.*
- *Staphylococcus saprophyticus* in some children and in sexually active adolescent girls.
- **Acute urethral syndrome** ( **postcoital urethritis)** occurs 12 to 72 hours after sexual intercourse*)* the chief causes are *S. saprophyticus, C. trachomatis,* and *E. coli* .

## EPIDEMIOLOGY

### FEMALE TO MALE RATIO :

- 5% of girls and 1% of boys have a UTI by 11 years of age.
- The lifetime incidence of UTI in females is about 30% and only 1% in males.
- *75% of infants <3 months with bacteriuria are male***,** congenital obstruction: posterior urethral valve / 10% 3-8 months are males

- *>1 year* → UTI in healthy children usually is seen in girls.

## RISK FACTORS:

1. A short urethra predisposes girls to UTI.
2. Uncircumcised male infants (<1 year old) are at 5-fold to 12-fold increased risk for UTI.
3. Obstruction to urine flow and urinary stasis is the major risk factor ,result from :
   - ◇ anatomic abnormalities
   - ◇ megaureter
   - ◇ extrinsic compression
   - ◇ pregnancy
   - ◇ ureteropelvic junction obstruction
   - ◇ indwelling urinary catheter
   - ◇ nephrolithiasis
   - ◇ renal tumor
4. Vesicoureteral reflux, primary (70% of cases) or secondary to urinary tract obstruction→ chronic infection and renal scarring.
5. hygiene
6. neurological bladder
7. pinworms infections "vermicularis" : itching and discomfort
8. voiding dysfunction and toilet training
9. constipation
10. encorporesis and incontinence

◇ **immune compromised state is not a risk factor**

## CLINICAL MANIFESTATIONS

- The symptoms and signs of UTI vary markedly with age.
  - A. neonates:
    1. failure to thrive
    2. feeding problems
    3. Vomiting
    4. diarrhea
    5. Direct hyperbilirubinemia ( prolonged neonatal jaundice)
  - B. Infants 1 month to 2 years old:
    1. feeding problems
    2. failure to thrive
    3. diarrhea
    4. vomiting
    5. unexplained fever
    6. irritability
  - C. 2 years of age→ the classic signs of UTI:
    1. urgency
    2. dysuria
    3. frequency
    4. abdominal pain
    5. Enuresis

**NOTE:**
**If unexplained fever:**
1. urine analysis in all cases
2. urine culture : all females < 2 years, all males <12months, abnormal UA, high clinical suspition.

- Rare to have convulsions with UTI .
- The symptoms may masquerade as gastrointestinal illness with "colic," irritability, and screaming periods.
- The presence of UTI should be suspected in:
  1. all **infants** and young children with **unexplained fever**
  2. all ages with fever
  3. Congenital anomalies of the urinary tract.

## LABORATORY AND IMAGING STUDIES

- The diagnosis of UTI requires a culture of the urine.
  - ◇ Urine samples for urinalysis should be examined promptly (within 20 minutes) or refrigerated until cultured

- ◇ A voided urine sample with greater than $10^5$ cfu/mL of a single organism has a 95% positive correlation with positive culture by suprapubic aspiration.
- ◇ Urine obtained by midstream, clean-catch technique (for older children and adolescents) is considered significant with bacterial growth >100,000 cfu/mL;
- ◇ urine obtained by catheter is considered significant with bacterial growth > 10,000 cfu/mL
- ◇ urine obtained by suprapubic aspiration is significant with bacterial growth of one organism or >100 cfu/mL. for staph. Epidermis / use if < 6 months , less pelvic bladder.

- Perineal bags for urine collection are prone to contamination and are not recommended for urine collection for culture( good negative, if positive = not reliable) , positive if :
  1. circumcised male
  2. single antigen
  3. ↑ 100,000
  4. abnormal UA
- For infants and young children with unexplained fever urine specimen should be obtained by catheterization or suprapubic percutaneous aspiration.
- Urinalysis= **pyuria** (leukocyturia of >10 WBC/$mm^3$) → infection, but also is consistent with:
  1. urethritis
  2. vaginitis
  3. nephrolithiasis
  4. glomerulonephritis
  5. interstitial nephritis.
- **Leukocyte esterase dipstick test** has poor sensitivity (50%) for pyuria
- **Urinary nitrate dipstick test** has poor sensitivity (30%) for bacterial counts >$10^5$ cfu/mL.
- for anatomic and functional assessment of the urinary tract:
  1. Ultrasonography: do in all Pts, detect 30% scarring, 30% pyelonephritis, R/O obstruction, anatomic abnormality or perinephric abcess.
  2. VCUG: best imaging study for determining the presence or absence of vesicoureteral reflux. All males, all females, febrile UTI. Even at the 5th day can be done.
  3. radionuclide cystography
  4. renal nucleotide scans (DMSA scan): operator dependant and expensive, most sensitive to detect renal scarring, can detect pyelonephritis, use when: pyelonephritis uncertain , 4 months after treatment & if VUR is present
  5. CT or MRI: pyelonephritis

## DIFFERENTIAL DIAGNOSIS

- The diagnosis of a UTI is confirmed by a positive culture of bacteria in the urine.
- upper UTI is associated more frequently with bacteremia and with anatomic abnormalities .
- Fever and abdominal pain may occur with either lower or upper UTI.
- upper tract involvement:
  1. high fever
  2. costovertebral tenderness
  3. high ESR
  4. leukocytosis
  5. bacteremia
- findings of limited value in localizing the site of the UTI to the upper tract:
  1. WBC casts
  2. inability to concentrate urine maximally
  3. presence of antibody-coated bacteria detected by immunofluorescence
  4. $\beta_2$-microglobulin excretion or ratios

- D/D:
  1. sepsis
  2. enteritis
  3. appendicitis

4. mesenteric lymphadenitis
5. pneumonia
6. hypersensitivity to soaps or detergents
7. vaginitis

## TREATMENT

- Empirical therapy: symptomatic children & all children with a urine culture confirming UTI.
- Neonates with UTI are treated for 10 -14 days with IV antibiotics because of the higher rate of bacteremia.
- Older children with acute cystitis are treated for 7 to 14 days with an oral antibiotic(TMP-SMZ & nitrofurontoin)
- MEDICATIONS THAT CAN BE USED
  1. amoxicillin Increasing bacterial resistance has limited the usefulness of It.
  2. TMP-SMZ: resistance to this drug is increasing.
  3. Oral 3ed-generation cephalosporins (cefixime℞ cefpodoxime) :effective but expensive.
- Parental treatment indications: ( complet 14 days by oral ATB according to the culture)
  1. acute pyelonephritis
  2. systemic toxcicity(chills and high fever):IV cefotaxime & gentamicin (or another aminoglycoside).
  3. <1 year old
  4. not compliant
- admission if:
  1. ill looking
  2. vomiting
  3. <1year ( increase risk of urosepsis)
  4. dehydration

## COMPLICATIONS

- **Bacteremia** occurs in 2% to 5% of episodes of pyelonephritis and is more likely in infants than in older children.
- Focal renal abscesses are an uncommon complication.
- Renal scarring as late complications (10-20%)
- HTN 25%
- CRF5%
- Recurrent UTI 50'% ( risk factors are four F: female, first year UTI, fetus>child, faults"abnormalities"

## PROGNOSIS

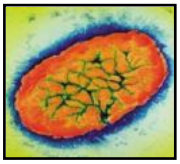
- Relapse rate of UTI is 25% to 40%, with most relapses occurring within 2 to 3 weeks of treatment. So periodic screening is important ( 1m- 6m- 12m- annually)
- Follow-up urine cultures should be obtained 1 to 2 weeks after completing therapy to document sterility of the urine and because many relapses are asymptomatic.
- Grade 1 to 3 reflux resolves at a rate of about 13% per year for the first 5 years, then at a rate of 3.5% per year.
- Grade 4 to 5 reflux resolves at a rate of about 5% per year.
- Bilateral reflux resolves more slowly than unilateral reflux.

## PREVENTION

- Primary prevention is achieved by promoting good perineal hygiene
- managing underlying risk factors for UTI, such as:
  1. chronic constipation
  2. encopresis " the event must take place for at least 6 months, the chronologic and mental age of the child must be at least 4 years."
  3. Daytime and nighttime urinary incontinence.

- Secondary prevention of UTI with antibiotic prophylaxis given once daily is directed toward preventing recurrent infections**.**
  - ◇ Drugs: 1st generation ceph., nitrofurantoin (least used, best result – as need special preparations/ not used in pyelonephritis as no good renal paranchymal consentration/ SE: G6PD hemolysis)
  - ◇ Indications:
    1. VUR
    2. recurrent UTI ( > 2, 6 months )
    3. one episode of pyelonephritis in infant < 1 year
    4. urinary stasis
    5. obstruction
    6. neurogenic bladder
    7. waiting for imaging
- Acidification of the urine with cranberry juice is not recommended as the sole means of preventing UTI in children at high risk.

# PERTUSSIS SYNDROME




## ETIOLOGY

- Caused by *Bordetella pertussis*.
- Classic pertussis,( **whooping cough syndrome)** is caused by *B. pertussis,* a gram-negative pleomorphic bacillus with fastidious growth requirements.
- other organisms, including *Bordetella parapertussis,* :causes milder illness that is not affected by *B. pertussis* vaccination.
- *B. pertussis* and *B. parapertussis* infect only humans and are transmitted by coughing.
- Asymptomatic carriage is rare.
- ***Adenoviruses*** have been associated with the pertussis syndrome.

## EPIDEMIOLOGY

- The mean incubation period is 6 days.
- Patients are most contagious during the earliest stage.

## CLINICAL MANIFESTATIONS

- Classic pertussis is the syndrome seen in infants beyond the neonatal period -school age.
- The progression of the disease is divided into:
  - ◇ **Catarrhal stage** is marked by nonspecific signs (injection, ↑nasal secretions, and low-grade fever) last 1 to 2 weeks.
  - ◇ **Paroxysmal stage** is the most distinctive stage of pertussis It lasts 2 to 4 weeks.
    1. Coughing in **paroxysms** during expiration, causing children to lose their breath. need to dislodge plugs of necrotic bronchial epithelial tissues and thick mucus.
    2. **Whoop,** characteristic. The forceful inhalation against a narrowed glottis that follows this paroxysm of cough produces
    3. Post-tussive emesis is common.
  - ◇ **Convalescent stage** is marked by gradual resolution of symptoms over 1 to 2 weeks.

| Catarrhal stage 1-2 weeks | paroxysmal stage 2-4 weeks | convalescent stage 1-2 weeks |
|---|---|---|
| LGF, NASAL CONG | WHOOP, COUGH & POST-TUSSIVE EMESIS (WHOOPING COUGH) | RESOLUTION |

- The disease typically lasts 6 to 8 weeks; residual cough may persist for months, especially with physical stress or respiratory irritants.
- Young infants may not display the classic pertussis syndrome→first signs :episodes of apnea→ more likely to have CNS damage as a result of hypoxia& to have secondary bacterial pneumonia.
- Adolescents and adults with pertussis present with a prolonged bronchitic illness that often begins as a nonspecific URTI. Adults do not have a whoop with the cough.

## LABORATORY AND IMAGING STUDIES

- Characteristic feature of pertussis in patients beyond the neonatal age is an abnormally high absolute number and relative percentage of lymphocytes in the peripheral blood. ,
  - ◇ **lymphocytosis** is found in 75% to 85%, in young infants the rate is much less.
  - ◇ The WBC count increase from 20,000 cells/$mm^3$ to more than 50,000 cells/$mm^3$
  - ◇ Consisting mostly of mature lymphocytes.
- The diagnosis depends on isolation of *B. pertussis,* during the early phases of illness by culture of nasopharyngeal swabs
- Direct fluorescent antibody staining to detect the organism is technically difficult, dependent on the skills of the technologist, and has low specificity.
- PCR.
- Available serologic tests are not useful
- Physical and radiographic signs of segmental lung atelectasis especially during the paroxysmal stage.
- Perihilar infiltrates are common and are similar to what is seen in viral

## TREATMENT

- **Erythromycin, given early in the course of illness,** eradicates nasopharyngeal carriage of organisms within 3 to 4 days.
- erythromycin has been associated rarely with pyloric stenosis in the neonatal period but still recommended because of the seriousness of pertussis at this age.
- Azithromycin and clarithromycin can be given for a shorter duration and are associated with fewer gastrointestinal adverse effects.
- Treatment is not effective in the paroxysmal stage. but Pertussis-specific immunoglobulin may be effective in reducing the symptoms of this stage.
- Patients should be isolated from susceptible individuals (especially infants) for 4 weeks, especially until 5-7 days of antibiotic therapy is completed.

## COMPLICATIONS

- Major complications :
  1. hypoxia & apnea
  2. pneumonia:most frequent complication is pneumonia caused by *B. pertussis* itself or resulting from secondary bacterial infection from *S. pneumoniae,* Hib, and *S. aureus*.
  3. Atelectasis may develop secondary to mucous plugs.
  4. seizures& encephalopathy
  5. The force of the paroxysm → pneumomediastinum, pneumothorax, or interstitial or subcutaneous emphysema; epistaxis; hernias; and retinal and subconjunctival hemorrhages.
  6. Malnutrition
  7. Otitis media and sinusitis

## PREVENTION

- Active immunity: by acellular pertussis vaccine+ toxoids of tetanus and diphtheria=(DTaP).
  - ◇ Pertussis vaccine has an efficacy of 70% to 90%.

- ◇ The acellular vaccines contain one or more antigens isolated from *B. pertussis,* such as pertussis toxin, pertactin, or filamentous hemagglutinins.

- Close contacts:
  A. <7 years old who have received four doses of vaccine should receive a booster dose of DTaP, unless a booster dose has been given within the preceding 3 years+ macrolide antibiotic.
  B. >7 years old :prophylactic macrolide antibiotic for 10 to 14 days, but not the vaccine.

# THE COMMON COLD

## ETIOLOGY

- The common cold(rhinitis) is a viral infection with prominent symptoms of :
  1. rhinorrhea
  2. nasal obstruction
  3. lacking systemic manifestations (absent or mild fever)
- More correctly termed **rhinosinusitis** cause usually involves the sinus mucosa.
- The viruses primarily associated with colds are **rhinoviruses** and less commonly coronaviruses.
- Other viruses: RSV, influenza viruses, parainfluenza viruses, and adenoviruses.
- Viral infection of the nasal epithelium → acute inflammatory response → mucosal infiltration by inflammatory cells and release of inflammatory cytokines → symptoms.

## EPIDEMIOLOGY

- Colds peak incidence from early fall through late spring.
- Young children have an average of 6 to 7 colds each year.
- 10% to 15% of children have at least 12 colds each year.
- The annual number of colds decreases with age, to 2 to 3 colds each year by adulthood.
- Children in out-of-home daycare during the first year of life have 50% more colds than children cared for only at home.
- Transmitted by 3 touts:
  1. large particles droplets
  2. small particles aerosols
  3. secretions
- immune response in general : 1$^{st}$ day IgA is found in nasal secretions, within days nasal secretions contain IgG, after 1 week serum IgG & IgM are detected in 80% of Pts
- 20% do not acquire serum antibodies to specific rhinoviruses.

## CLINICAL MANIFESTATIONS

- Common cold symptoms typically develop *1 to 3 days after viral infection* and include
  1. nasal obstruction
  2. rhinorrhea,
  3. sore or "scratchy" throat
  4. occasional non-productive cough
- Colds persist about 1 week, 10% last 2 weeks.
- There is often a change in the color or consistency of nasal secretions, which *is not indicative of sinusitis or bacterial superinfection.*
- Examination of the nasal mucosa reveals swollen, erythematous nasal turbinates.

**NOTE:**

**The pharyngeal lesions pattern:**

- **Eythema alone**: rhino, para inf,RSV, inf, Rota
- **Follicular**: adenovirus, enterovirus
- **Vesicular or ulcerative**: HSV, enterovirus.

## LABORATORY AND IMAGING STUDIES

- Laboratory studies are not helpful.
- nasal smear for eosinophils may be useful in the evaluation for allergic rhinitis.

## DIFFERENTIAL DIAGNOSIS

- Rhinorrhea is a frequent manifestation of infection and allergic disease.
- **The differential diagnosis includes:**
  1. allergic rhinitis
  2. foreign body (unilateral nasal discharge)
  3. sinusitis: >2yrs. Duration >10days.
  4. pertussis
  5. streptococcal nasopharyngitis
  6. Wegener granulomatosis
  7. choanal atresia or stenosis
  8. CSF fistula
  9. diphtheria
  10. congenital syphilis (with "snuffles")
  11. nasopharyngeal malignancy
- **Allergic rhinitis is characterized by:**
  4. absence of fever
  5. eosinophils in the nasal discharge
  6. allergic shiners
  4. nasal polyps
  5. transverse crease on the nasal bridge
  6. Pale, edematous, nasal turbinate mucosa

## TREATMENT

- There is no specific therapy for the common cold.
- Antibacterial therapy *is not beneficial* for the common cold.
- Acetaminophen & ibuprofen reduce symptoms of sore throat & fever.
- Topical or oral adrenergic agents may be used as nasal decongestants.
- Cough suppressants and expectorants are unnecessary & not been shown to be beneficial.
- Topical adrenergic agents, such as xylometazoline, oxymetazoline, or phenylephrine, are available as intranasal drops or nasal sprays, not approved for use in children <2 years old.
  - ◇ Prolonged use → **rhinitis medicamentosa**, a rebound effect that causes the sensation of nasal obstruction when the drug is discontinued.
  - ◇ Oral adrenergic agents are less effective than the topical preparations and are associated with systemic effects, such as CNS stimulation, hypertension, and arrhythmias.
- First-generation antihistamines reduce rhinorrhea by 25% to 30%, which seems to be related to the anticholinergic effect rather than the antihistaminic properties.
  - ◇ Second-generation or "nonsedating" antihistamines have no effect on common cold symptoms.
  - ◇ The major adverse effect associated with the use of antihistamines is sedation
- Rhinorrhea also treated with ipratropium bromide, a topical anti-cholinergic agent that produces an effect comparable to antihistamines but is not associated with sedation.
  - ◇ The most common adverse effects of ipratropium are nasal irritation and bleeding.
- RSV Ig is used in high risk Pts for lower respiratory tract infections.
- Vitamin C, guaifenesin, and inhalation of warm, humidified air are no more effective than placebo.
- The benefit of zinc lozenges or sprays has been inconsistent.
- No role of IFN is found in common cold.

## COMPLICATIONS AND PROGNOSIS

- complications include :
  1. otitis media :the most common complication (5% to 20%)
  2. bacterial sinusitis, considered if rhinorrhea or daytime cough persists without improvement for at least 10 to 14 days or if severe signs of sinus involvement develop, such as fever, facial pain, or facial swelling
  3. exacerbation of asthma

## PREVENTION

- good hand washing and avoiding contact with infected persons.
- No significant effect of vitamin C for prevention of the common cold has been confirmed.

# BRONCHIOLITIS

## ETIOLOGY

- **Bronchiolitis** is first-time wheezing with a viral respiratory infection.

- Acute bronchiolitis = respiratory tract inflammation with swelling of small bronchioles → airway obstruction → inadequate expiratory airflow.
- Bronchiolitis is life-threatening.
- CAUSES:
  1. ***RSV is the primary cause***
  2. human metapneumovirus
  3. parainfluenza viruses
  4. influenza viruses
  5. adenoviruses
  6. rhinoviruses
  7. *M. pneumoniae* (infrequently).
- Viral bronchiolitis is extremely contagious, spread by:
  1. Hand carriage of contaminated secretions = the most frequent mode of transmission.
  2. coughing aerosols

## EPIDEMIOLOGY

- 50% of children experience bronchiolitis during the first 2 years of life
- Peak age at 2 to 6 months.
- The incidence falls rapidly between the ages of 1 and 5 years
- 10% of healthy children with bronchiolitis and wheezing require hospitalization.
- Boys > girls in a ratio of 1.5: 1.

## CLINICAL MANIFESTATIONS

- if caused by RSV → IP= 4 - 6 days.
- Bronchiolitis classically presents as a progressive respiratory illness that is similar to the common cold in its early phase with cough, coryza, and rhinorrhea → progresses over 3 to 7 days to noisy, raspy breathing and audible wheezing.
- low-grade fever with irritability, which may reflect the increased work of breathing.
- young infants infected with RSV may have apnea as the first sign of infection.
- Physical signs of bronchiolar obstruction include:
  1. prolongation of the expiratory phase of breathing
  2. intercostal retractions & suprasternal retractions
  3. Air trapping with hyperexpansion of the lungs.
  4. During the wheezing phase, percussion of the chest : only hyperresonance.
  5. Auscultation: diffuse wheezes and crackles throughout the breathing cycle.
  6. grunting and cyanosis ( more severe disease)

## LABORATORY AND IMAGING STUDIES

- Routine laboratory tests are not required to confirm the diagnosis.
  1. mild leukocytosis 12,000 - 16,000/μL frequent but not specific
  2. Assess gas exchange in severe cases.
  3. Pulse oximetry is adequate for monitoring O2 sat (visual evaluation –poor assessment)
  4. Regular visual assessments and cardiorespiratory monitoring of infants are necessary because respiratory failure may develop precipitously in very tired infants.
  5. Antigen tests (usually by immunofluorescence or ELISA) of nasopharyngeal secretions for RSV, para-influenza viruses, influenza viruses, and adenoviruses **are the most sensitive tests to confirm the infection**.
  6. Rapid viral diagnosis also is performed by PCR
  7. The chest radiograph shows :
     1. hyperexpansion of the lungs( increased lung radiolucency and flattened or depressed diaphragms)
     2. lungs may appear normal or ↑ density→ viral pneumonia or localized atelectasis.
- The or may show areas

## DIFFERENTIAL DIAGNOSIS

- Differentiate asthma from bronchiolitis by physical examination may be impossible, the major differential factors are:

| BRONCHIOLITIS | ASTHMA |
|---|---|
| fever | No fever, unless a RTI is the trigger for the asthma attack |
| first year of life | older children |
| no history (personal or family) of asthma | history (personal or family) of asthma |

- Other Wheezing deferential diagnosis:
  1. foreign body in the airway : A focal area on radiography that does not inflate or deflate
  2. congenital airway obstructive lesion
  3. Cystic fibrosis: poor growth, chronic diarrhea, and a positive family history.
  4. exacerbation of BPD
  5. pneumonia
  6. **Cardiogenic asthma**, confused with bronchiolitis in infants, is wheezing associated with pulmonary congestion secondary to left-sided heart failure.
  7. GERD: chronic or recurrent & history of frequent emesis.

## TREATMENT

- supportive therapy, including:
  1. monitoring
  2. control of fever
  3. good hydration
  4. upper airway suctioning
  5. Oxygen administration (by nasal cannula is often, with intubation and ventilatory assistance for respiratory failure or apnea).
- Indications for hospitalization include:
  1. young age (<6 months old)
  2. moderate to marked respiratory distress (sleeping RR >50 to 60 breaths/min)
  3. hypoxemia ($P_O2$ <60 mm Hg or oxygen saturation <92% on room air)
  4. apnea
  5. inability to tolerate oral feeding
  6. lack of appropriate care available at home
  7. High-risk children with bronchiolitis should be considered.
- Children with chronic lung disease such as BPD, hemodynamically significant cyanotic and acyanotic congenital heart disease, neuromuscular weakness, or immunodeficiency are at increased risk of severe, potentially fatal disease.
- Temporary use of bronchodilators improve wheezing and respiratory distress in infants and young children as outpatients.( modest, short-lived, and do not reduce hospitalization)

## COMPLICATIONS

- Most hospitalized children show marked improvement in 2 to 5 days with supportive treatment alone.
- There may be tachypnea and hypoxia after admission, progressing to respiratory failure requiring assisted ventilation.
- **Apnea is a major concern for very young infants with bronchiolitis.**

## PROGNOSIS

- Most cases of bronchiolitis resolve completely
- Minor abnormalities of pulmonary function & bronchial hyperreactivity may persist for years.
- Recurrence is common, tends to be mild, and should be treated similarly to the first episode.

- The incidence of asthma higher for children hospitalized for bronchiolitis as infants, but it is unclear whether this is causal or if children prone to having asthma are more likely to be hospitalized when they develop bronchiolitis.
- Mortality rate=1% to 2%, highest among infants with preexisting cardiopulmonary or immunologic impairment.

## PREVENTION

- Monthly injections of **palivizumab**, an RSV-specific monoclonal antibody, initiated just before the onset of the RSV season confers some protection from severe RSV disease.
- Palivizumab is indicated for :
  1. some infants< 2 years old with chronic lung disease (bronchopulmonary dysplasia)
  2. very low birth weight infants
  3. infants with hemodynamically significant cyanotic and acyanotic CHD.

# PNEUMONIA

## ETIOLOGY

- **Pneumonia** : infection of the lower respiratory tract that involves the airways and parenchyma with consolidation of the alveolar spaces.
- **Lower respiratory tract infection**: : bronchitis, bronchiolitis or pneumonia or any combination of the three, which may be difficult to distinguish clinically.
- **Pneumonitis**: lung inflammation ± consolidation.
- **Lobar pneumonia** : "typical" pneumonia localized to one or more lobes of the lung in which the affected lobe or lobes are completely consolidated.
- **Atypical pneumonia** : patterns other than lobar pneumonia.
- **Bronchopneumonia** : inflammation of the lung that is centered in the bronchioles and leads to the production of a mucopurulent exudate that obstructs some of these small airways and causes patchy consolidation of the adjacent lobules.
- **Interstitial pneumonitis** : inflammation of the interstitium, which is composed of the walls of the alveoli, the alveolar sacs and ducts, and the bronchioles. characteristic of acute viral infections, but also may be a chronic process.
- host defenses:
  1. mucus secreted by the goblet cells caught Airway contaminants
  2. Cilia on epithelial surfaces, composing the **ciliary elevator system**, beat synchronously to move particles upward toward the central airways and into the throat, where they are swallowed or expectorated.
  3. neutrophils from blood and tissue macrophages ingest and kill microorganisms.
  4. IgA secreted into the upper airway fluid protects against invasive infections
- The infectious agents that commonly cause community-acquired pneumonia vary by age.
  - ◇ in infants The most common causes is RSV.
  - ◇ children <5 years old : RSV, para-influenza viruses, influenza viruses, adenoviruses).
  - ◇ children > 5:*M. pneumoniae* and *S. pneumoniae*.
  - ◇ **atypical pneumonia**: the principal causes are *M. pneumoniae* and *C. pneumoniae*.
  - ◇ Hantavirus cardiopulmonary syndrome : by Sin Nombre virus, which is carried by *Peromyscus maniculatus* (the deer mouse) and transmitted to humans by aerosolized rodent excreta.
  - ◇ *Legionella pneumophila* (legionnaires' disease) is a rare cause of pneumonia in children.
  - ◇ infants 1 to 3 months of age: *Chlamydia trachomatis* and *Mycoplasma hominis, Ureaplasma urealyticum*, and CMV → similar respiratory syndrome ( subacute onset of an **afebrile pneumonia** with cough and hyperinflation as the predominant signs)
  - ◇ Causes of pneumonia in immunocompromised persons: gram-negative enteric bacteria, mycobacteria (*M. avium* complex), fungi (aspergillosis, histoplasmosis), viruses (CMV), and *Pneumocystis jirovecii* (*carinii*).
  - ◇ Pneumonia in patients with cystic fibrosis: *S. aureus* in infancy and *P. aeruginosa* or *Burkholderia cepacia* in older patients.

## EPIDEMIOLOGY

- Risk factors for lower respiratory tract infections include:
  1. gastroesophageal reflux
  2. neurologic impairment (aspiration)
  3. immunocompromised states
  4. anatomic abnormalities of the respiratory tract
  5. residence in residential care facilities for handicapped children, and hospitalization, especially in an ICU or requiring invasive procedures.
- Recurrent pneumonia: >2times/year ( investigate)

**NOTE:**
Indications for admission:
1. age<6 months
2. multible lobar pneumonia
3. vomiting & dehydration
4. severe RD/Need O2
5. not tolerate PO ATB
6. immunocompromised
7. Sickle cell anemia
8. toxic appearance

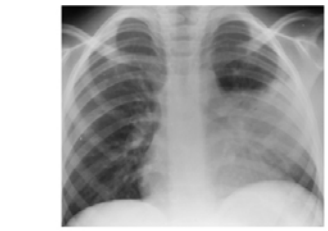
## CLINICAL MANIFESTATIONS

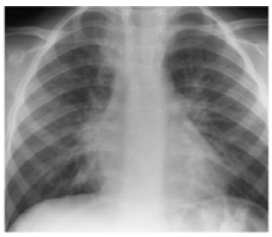
- Age is a determinant in the clinical manifestations of pneumonia.
  - ◇ Neonates may have fever only with subtle or no physical findings of pneumonia.
  - ◇ older infants and children have **Fever**, **chills**, **tachypnea**, **cough**, **malaise**, **pleuritic chest pain**, **retractions**, and **apprehension**, because of difficulty breathing or SOB
- tachypnea is the most common constant clinical manifestations in infant
- **Viral pneumonias**: **cough**, **wheezing**, or **stridor**; **fever** is less prominent than bacterial.
  - ◇ The chest x-ray: diffuse, streaky infiltrates of bronchopneumonia
  - ◇ the WBC count : normal or mildly elevated, with a predominance of lymphocytes.
- **Bacterial pneumonias**: higher **fever**, **chills**, **cough**, **dyspnea**, and **auscultatory findings of lung consolidation**.
  - ◇ The chest x-ray: lobar consolidation (or round pneumonia) & pleural effusion (10%- 30%).
  - ◇ The WBC count is elevated (>20,000/$mm^3$) with a predominance of neutrophils.
- **Afebrile pneumonia** in young infants is characterized by **tachypnea**, **cough**, **crackles** on auscultation, and often **concomitant chlamydial conjunctivitis**.
  - ◇ WBC count typically shows mild eosinophilia
  - ◇ Chest X-ray: hyperinflation
- All significant pneumonias have localized **crackles** and **decreased breath sounds**
- **pleural effusion** has dullness to percussion.

## LABORATORY AND IMAGING STUDIES

- The upper respiratory tract bacterial flora is not an accurate reflection of the causes of lower respiratory tract infection, and good quality sputum is rarely obtainable from children.
- In healthy children without life-threatening disease, invasive procedures to obtain lower respiratory tissue or secretions usually are not indicated.
- **Serologic tests** are not useful for the most common causes of bacterial pneumonia.
- **The WBC count**:
  - ◇ viral pneumonias : normal or mildly elevated, with a predominance of lymphocytes.
  - ◇ bacterial pneumonias the WBC count (>20,000/$mm^3$) with a predominance of neutrophils.
  - ◇ *C. trachomatis* pneumonia of infant: Mild eosinophilia is characteristic.
- **Blood cultures** positive in 10% to 20% of bacterial pneumonia and are considered to be confirmatory of the cause of pneumonia if positive.
- **Urinary antigen tests** for *L. pneumophila* (legionnaires' disease).
- viral and mycoplasmal lower respiratory disease: **Cultures of upper respiratory secretions or serologic tests** with paired sera are relatively accurate for the diagnosis.
- **pneumolysin-based PCR** test: aid in diagnosis of pneumococcal pneumonia.
- CMV and enterovirus: culture from nasopharynx, urine, or bronchoalveolar lavage fluid.
- *M. pneumoniae* : if cold agglutinins are present in peripheral blood samples; this may be confirmed by *Mycoplasma* IgM or more specifically PCR.
- The diagnosis of *M. tuberculosis* is established by **TSTs** and analysis of sputum or gastric aspirates by culture, antigen detection, or PCR.

- The need to establish an etiologic diagnosis of pneumonia is greater for patients who are:
  1. ill enough to require hospitalization
  2. immunocompromised
  3. recurrent pneumonia,
  4. pneumonia unresponsive to empirical therapy.
- methods of obtaining material for microbiologic diagnosis:
  1. bronchoscopy with bronchoalveolar lavage and brush mucosal biopsy,
  2. needle aspiration of the lung
  3. open lung biopsy
- When there is effusion or empyema→ **thoracentesis** ( diagnostic and therapeutic).
- **Gram stain and culture**
  - ◇ The pleural fluid should be cultured for bacteria, mycobacteria, fungi, and viruses.
  - ◇ If the fluid is grossly purulent, removal reduces the patient's toxicity and associated discomfort and may facilitate more rapid recovery.
  - ◇ If accumulation is large, removal improves pulmonary mechanics & gas exchange.
- **Frontal and lateral radiographs** are required to localize the diseased segments and to visualize adequately infiltrates behind the heart or the diaphragmatic leaflets.
- Characteristic radiographic findings of pneumonia:
  - ◇ May be normal in early pneumonia, with appearance of an infiltrate during the treatment phase of the disease when edema fluid is greater.
  - ◇ Bacterial pneumonia characteristically shows lobar consolidation, or a round pneumonia, with pleural effusion in 10% to 30% of cases.
  - ◇ Viral pneumonia characteristically shows diffuse, streaky infiltrates of bronchopneumonia.
  - ◇ Atypical pneumonia, such as with *M. pneumoniae* and *C. pneumoniae,* shows increased interstitial markings or bronchopneumonia.
  - ◇ Hilar lymphadenopathy is uncommon with bacterial pneumonia, but may be a sign of tuberculosis, histoplasmosis, or malignant neoplasm.
  - ◇ S.aureus → unilaternal bronchopneumonia→ area of necrosis→Lung abscesses, pneumatoceles, and empyema (common in: boys, <1yr and GI manifistations)




- Decubitus views or ultrasound assess size of pleural effusions and whether they are freely mobile.
- CT evaluates serious disease, pleural abscesses, bronchiectasis, and delineating effusions.

## DIFFERENTIAL DIAGNOSIS

### INSPECTION:

- **Mucosal congestion and inflammation** of the upper airway suggest a viral infection.
- **signs of respiratory distress** include Tachypnea, flaring of the alae of the nose, intercostal and subcostal retractions, and grunting.
- Generalized or peripheral **cyanosis** indicates hypoxia with severe diffuse or multilobular pneumonia or a large pleural effusion.
- With a young infant, **apneic spells** may be the first sign of pneumonia.
- Asymmetry or shallow breathing may be due to splinting from pain.

### PERCUSSION :

- **Low diaphragms by percussion** indicate air trapping, which is common in asthma, but also frequently accompanies viral lower respiratory infections.
- Poor diaphragmatic excursion may indicate hyperexpanded lungs or an inability for expansion because a large consolidation is causing poor lung compliance.
- **Hyperexpansion** may push the diaphragm and liver downward.
- **Dullness** to percussion may be due to lobar or segmental infiltrates or pleural fluid.

### AUSCULTATION:

- the presence of localized **crackles**, **rhonchi**, and **wheezes** may help one to detect and locate pneumonia.
- **Distant breath sounds** may indicate a large, poorly ventilated area of consolidation or pleural fluid.
- Pneumonia must be differentiated from **other acute lung diseases**, including:
  1. lung edema caused by heart failure,
  2. allergic pneumonitis, and aspiration,
  3. autoimmune diseases, such as rheumatoid disease and SLE.
- Radiographically, pneumonia must be differentiated from:
  1. lung trauma
  2. contusion
  3. hemorrhage
  4. foreign body obstruction
  5. irritation from subdiaphragmatic inflammation

## TREATMENT

- Therapy for pneumonia includes supportive and specific treatment.
- *S. pneumoniae* Pneumonia presents a problem because of increasing antibiotic resistance.
- pneumococcal meningitis, presumed pneumococcal pneumonia can be treated with high-dose penicillin or cephalosporin, even with high-level penicillin resistance.
- Vancomycin used if the isolate shows high-level resistance and the patient is severely ill.
- Infants 4 to 18 weeks old with afebrile pneumonia most likely have infection with *C. trachomatis,* and erythromycin℞ is the recommended treatment.
- Severe pneumonia + malnutrition: give zinc.

| PATHOGEN | RECOMMENDED TREATMENT |
|---|---|
| *Streptococcus pneumoniae*[T] | Ceftriaxone, cefotaxime, penicillin G or V |
| Group A streptococcus | Penicillin G |
| Group B streptococcus | Penicillin G |
| *Haemophilus influenzae* type b | Ceftriaxone, cefotaxime, amoxicillin, or ampicillin |
| *Mycoplasma pneumoniae* | Erythromycin, clarithromycin or azithromycin |
| Gram (-) aerobic bacilli (except *P.aeruginosa*) | Cefotaxime (or ceftriaxone) ± aminoglycoside |
| *P. aeruginosa* | Ceftazidime ± aminoglycoside |
| *Staphylococcus aureus* | Nafcillin or oxacillin |
| *Chlamydophila pneumoniae* | Erythromycin, azithromycin or clarithromycin |
| *Chlamydia trachomatis* (afebrile pneumonia) | Erythromycin, azithromycin or clarithromycin |
| Herpes simplex virus | Acyclovir |

## COMPLICATIONS

- Bacterial pneumonias frequently cause **parapneumonic effusion** or, if grossly purulent, an **empyema**. Large effusions usually restrict breathing and require drainage.
- **pneumatocele**, or air pocket.
- **bronchiectasis** and increased risk for recurrent infection.
- **lung abscess**.
  - ◇ uncommon in children, caused by aspiration or infection behind an obstructed bronchus.
  - ◇ The most commonly involved sites : **posterior segments of the upper lobes** and the **superior segments of the lower lobes**, drain in recumbent position .
  - ◇ Anaerobic bacteria predominate, along with various streptococci, *E. coli, Klebsiella pneumoniae, P. aeruginosa,* and *S. aureus*.

- ◇ Chest X-ray or CT scan : cavitary lesion, with an air-fluid level, surrounded by parenchymal inflammation.
- ◇ If the cavity communicates with the bronchi, organisms may be isolated from sputum.
- ◇ bronchoscopy indicated to exclude a foreign body and obtain microbiologic specimens.
- ◇ Lung abscesses antimicrobial ttt: clindamycin℞, penicillin G, or ampicillin-sulbactam.

## PROGNOSIS

- Most children recover from pneumonia rapidly and completely.
- The radiographic abnormalities take 6 to 8 weeks to return to normal.
- In a few children, pneumonia may persist longer than 1 month or may be recurrent. must be investigated further, such as :
  1. with TST,
  2. sweat chloride determination for cystic fibrosis,
  3. serum immunoglobulin and IgG subclass determinations,
  4. bronchoscopy to identify anatomic abnormalities or foreign body,
  5. barium swallow for gastroesophageal reflux.
- **bronchiolitis obliterans:** Severe adenovirus pneumonia→subacute inflammatory process→ small airways are replaced by scar tissue→ reduction in lung volume and lung compliance.
- **Swyer-James syndrome** : **unilateral hyperlucent lung**, **focal** sequela of severe necrotizing pneumonia in which all or part of a lung has increased translucency radiographically and linked to adenovirus type 21.

# INFECTIVE ENDOCARDITIS

## ETIOLOGY

- **Infective endocarditis** : infection on the heart endothelial surface, including the heart valves.
- **endocarditis equivalent**: Infections on the endothelial surface of blood vessels
- **vegetations**: The infectious endothelial lesions, occur on the valve leaflets. Composed of microorganisms trapped in a fibrin mesh that extends into the bloodstream.
- High doses of antibiotics are required for an extended period of treatment, Because antibiotics must reach the organisms by passive diffusion through the fibrin.
- **Viridans streptococci** : the principal causes in children with CHD without previous surgery.
- ***S. aureus* and coagulase-negative staphylococci** : assume greater prominence after cardiac surgical procedures and with prosthetic cardiac and endovascular material.

## EPIDEMIOLOGY

- Infective endocarditis among children is primarily a complication of congenital heart disease.
- High-risk cardiac lesions include:
  1. VSD
  2. PDA
  3. TOF
  4. aortic valve abnormalities: AS &AR
  5. Transposition of the great vessels.
- The risk is increased after dental and oral procedures or instrumentation or surgical procedures of the **respiratory tract, genitourinary tract, or gastrointestinal tract.**
- Rheumatic heart disease is a **rare risk factor.**
- Neonatal endocarditis associated with the use of central vascular catheters and surgery.
- **Endocarditis is a sporadic disease in children** with no geographic predisposition and little gender or socioeconomic predisposition.

## CLINICAL MANIFESTATIONS

- The most common early symptoms of infective endocarditis are nonspecific and include fever, malaise, and weight loss.

- The subtle and nonspecific findings for children with congenital heart disease and for unexplained illness after dental or surgical procedures→ obtain blood cultures.
- Endocarditis is usually a subacute, slowly progressive disorder
- Acute endocarditis is often due to *S. aureus* and may resemble sepsis.
- SYMPTOMS:
  1. Fever & Chills
  2. Malaise
  3. Anorexia or weight loss
  4. Chest pain
  5. Dyspnea
  6. Arthralgia & Myalgia
  7. Focal neurologic deficit (aseptic meningitis)
- SIGNS:
  1. **Fever**
  2. Tachycardia
  3. New or changed murmur
  4. Heart failure
  5. **Splenomegaly**
  6. Petechia
  7. Embolic phenomena (Osler nodes, Roth spots, Janeway lesions, splinter hemorrhages, conjunctival hemorrhages)
  8. Clubbing ( uncommon)

## LABORATORY STUDIES AND IMAGING

- **The key to diagnosis** : continuous bacteremia or less often fungemia by culturing the blood.
- Multiple blood cultures are performed before initiating antibiotic therapy.
  - ◇ Three separate venipunctures for blood culture represent near-maximal sensitivity (about 95%) in patients who have not been treated recently with antibiotics.
  - ◇ Patients who have been treated with antibiotics→ additional cultures performed.
  - ◇ 10% to 15% endocarditis cases are culture-negative (Despite adequate blood culture)
- Echocardiography: endocardial and valvular vegetations measuring ≥2 mm.
- Transesophageal echocardiography often unnecessary in children.
- **Laboratory Findings Associated with Infective Endocarditis in Children:**
  1. Positive blood culture
  2. Elevated ESR, CRP
  3. CBC: Anemia & Leukocytosis
  4. Positive rheumatoid factor
  5. **Hematuria**
  6. Echocardiographic evidence of vegetation

- DUKE CLINICAL CRITERIA FOR DIAGNOSIS OF INFECTIVE ENDOCARDITIS

| |
|---|
| ***Pathologic Criteria*** |
| 1. *Microorganisms by culture or histologic findings* in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess<br>2. *Pathologic lesion-vegetation or intracardiac abscess present*, confirmed by histologic findings showing active endocarditis |
| CLINICAL CRITERIA (2 MAJOR CRITERIA OR 1 MAJOR AND 3 MINOR CRITERIA OR 5 MINOR CRITERIA) |
| ***Major Criteria*** |
| 1. **Blood culture positive for infective endocarditis** |
| A. Typical microorganisms from two separate Blood cultures:<br>◇ Viridans streptococci,* *Streptococcus bovis*, HACEK (***H****aemophilus aphrophilus*, ***A****ctinobacillus actinomycetemcomitans*, ***C****ardiobacterium hominis*, ***E****ikenella corrodens*, and ***K****ingella kingae*)<br>◇ Community-acquired *Staphylococcus aureus* or *Enterococcus* in the absence of a primary focus<br>B. Persistently positive blood culture result, defined as:<br>◇ recovery of a microorganism consistent with endocarditis from blood cultures drawn >12 hr apart |

| |
|---|
| ◊ All of 3 or a majority of ≥4 separate blood culture specimens, with first & last drawn at least 1 hr apart |
| 2. **Evidence of endocardial involvement** : Echocardiogram positive for infective endocarditis |
| 1. Oscillating intracardiac mass on valve or supporting structures *or* in path of regurgitant jets *or* on implanted material in the absence of an alternative anatomic explanation,<br>2. Abscess<br>3. New partial dehiscence of prosthetic valve<br>4. New valvular regurgitation (increase or change in preexisting murmur not sufficient) |
| ***Minor Criteria*** |
| 1. **Predisposition-predisposing heart condition *or* IV drug use** |
| 2. **Fever ≥38°C (≥100.4°F)** |
| 3. **Vascular phenomena-**major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions |
| 4. **Immunologic phenomena-**glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor |
| 5. **Microbiologic evidence**-positive blood culture result, but not meeting major criteria as noted previously† *or* serologic evidence of active infection with organism consistent with infective endocarditis |
| 6. **Echocardiogram-**consistent with infective endocarditis, but not meeting major criteria |
| POSSIBLE INFECTIVE ENDOCARDITIS |
| Findings consistent with infective endocarditis that fall short of "definite" but not "rejected" |
| REJECTED **, one of :** |
| 1. Firm alternate diagnosis for manifestations of endocarditis<br>2. Resolution of manifestations of endocarditis with antibiotic therapy for ≤4 days<br>3. No pathologic evidence of endocarditis at surgery or autopsy after antibiotic therapy of ≤4 days |

## TREATMENT

- Multiple blood cultures should be obtained before initiating antibiotic therapy.
- With subacute disease, it is recommended to await results of blood cultures to confirm the diagnosis and to treat according to the susceptibility of the isolate.
- Empirical antibiotic therapy may be started for acutely ill persons.
- Treatment of a culture-positive case is directed against the particular bacterium using bactericidal antibiotics continued for **4 to 8 weeks**.
- Infective carditis from viridans streptococci can be treated with penicillin G for 4 weeks.
- Surgery is indicated or if there is:
  1. medical treatment is unsuccessful
  2. persistent bacteremia
  3. unusual pathogen (fungal endocarditis)
  4. abscess of the valve annulus or of the myocardium
  5. rupture of a valve leaflet
  6. valvular insufficiency with refractory heart failure
  7. recurrent serious embolic complications
  8. Refractory prosthetic valve disease.

## COMPLICATIONS

- The major complications of infective endocarditis are:
  - A. direct damage to the heart and heart valves
    1. regurgitation with vegetations
    2. actual defects in the leaflets resulting from embolization of the leaflet tissue
    3. abscess of the valve ring
    4. myocardial abscess
  - B. Distant complications secondary to sterile and septic emboli from vegetations
    1. Cerebral abscesses or aneurysms → strokelike picture
    2. Splenic abscesses → fatal bleeding

## PROGNOSIS

- The outcome of infective endocarditis caused by the most common organisms is good. cure rate > 90%.
- The cure rate for *Enterococcus* endocarditis 75% - 90%.
- The course of *S. aureus* endocarditis may acute and severe, cure rate = 60% - 75%.
- The prognosis for endocarditis caused by gram-negative bacilli and rarer organisms is poor.
- **Fungal endocarditis has the poorest prognosis, cure rate 50%.**

## PREVENTION

- Surgical repair of congenital heart disease reduces the risk for endocarditis.
- In patients with preexisting endothelial or endocardial lesions, prophylactic antibiotics before:
  1. invasive dental procedures in which the gingivae are cut
  2. colonoscopy
  3. urinary tract instrumentation in patients who have bacteriuria.
- The antibiotic regimen to prevent endocarditis:
  1. dental or respiratory procedures : oral amoxicillin 1 hour before the procedure.
  2. GI or GU manipulation: oral amoxicillin or IV ampicillin & gentamicin.
- The recommendation is for high-risk patients, such as patients with prosthetic heart valves, systemic-to-pulmonary shunts, or previous endocarditis.
- Clindamycin is indicated for most patients allergic to penicillin.
- Prolonged or continuous antibiotic prophylaxis is not recommended.

# OCULAR INFECTIONS

## ETIOLOGY

### ACUTE CONJUNCTIVITIS, OR RED EYE

- Is usually a bacterial or viral infection of the eye characterized by a rapid onset of symptoms that persists for a few days.
- The most common causes of bacterial conjunctivitis are nontypable *H. influenzae, S. pneumoniae,* and *M. catarrhalis*
  - ◇ Other causes: *N. gonorrhoeae* and *P. aeruginosa,* which is associated with extended-wear soft contact lenses.
- Viral conjunctivitis most commonly is caused by adenoviruses, which are the cause of epidemic keratoconjunctivitis, less frequently by coxsackieviruses and other enteroviruses.
- NEONATAL CONJUNCTIVITIS, OR OPHTHALMIA NEONATORUM, is purulent conjunctivitis during the first 10 days of life, usually acquired during birth.
  - ◇ in order of decreasing prevalence, silver nitrate is used for gonococcal prophylaxis, *C. trachomatis.*
  - ◇ common bacterial causes of conjunctivitis, *E. coli,* other gram-negative enteric bacilli, and *N. gonorrhoeae*.
  - ◇ Neonatal conjunctivitis can occur as a part of perinatal HSV infection.
- **Manifestations of Acute Conjunctivitis in Children**

| | BACTERIAL | VIRAL |
|---|---|---|
| **cause** | *Haemophilus influenzae* (usually nontypable) *Streptococcus,pneumoniae Moraxella catarrhalis* | Adenoviruses type 8, 19 Enteroviruses Herpes simplex virus |
| **Incubation** | 1-3 days | 1-14 days |
| **Symptoms** | | |
| Photophobia | Mild | Moderate to severe |
| Blurred vision | Common with discharge | If keratitis is present |
| Foreign body sensation | Unusual | Yes |
| **Signs** | | |
| Discharge | Purulent discharge | Watery discharge |

| | | |
|---|---|---|
| Palpebral reaction | Papillary response | Follicular response |
| Preauricular LN | Unusual for acute (<10%) | More common (20%) |
| Chemosis | Moderate | Mild |
| Hemorrhagic conjunctivae | Occasionally with *Streptococcus* or *Haemophilus* | Frequent with enteroviruses |
| Treatment (topical) | Polymyxin B-trimethoprim *or* sulfacetamide 10% *or* erythromycin | Adenovirus: self-limited<br>Herpes simplex virus: trifluridine 1% solution *or* vidarabine 3% ointment; ophthalmologic cons. |
| End of contagious period | 24 hr after start of effective treatment | 7 days after onset of symptoms |

### KERATITIS

- Inflammation of the cornea, is not commonly associated with conjunctivitis, but does occur with *N. gonorrhoeae,* HSV, and adenovirus infections.

### BLEPHARITIS

- Associated with staphylococcal infections, seborrhea, and meibomian gland dysfunction.
- The child complains of photophobia, burning, irritation, and a foreign body sensation that causes the child to rub the eyes.
- Eyelid hygiene with an **eyelid scrub** routine is the initial step in treatment.

### HORDEOLA

- acute suppurative nodular inflammatory lesions of the eyelids associated with pain and redness.
- **External hordeola** or **styes** occur on the anterior eyelid, in the Zeis glands, or in the lash follicles and usually are caused by staphylococci.
- **Internal hordeola** occur in the meibomian glands, may be infected with staph. or sterile.
- **chalazion** If the meibomian gland becomes obstructed, the gland secretions accumulate.
- Hordeola usually respond spontaneously to local treatment measures, but may recur.

### DACRYOCYSTITIS

- infection or inflammation of the lacrimal sac, which is usually obstructed.
- most commonly caused by *S. aureus* or coagulase-negative staphylococci.
- A mucopurulent discharge can be expressed with gentle pressure on the nasolacrimal sac.
- Treatment requires probing of the nasolacrimal system to establish communication.

### ENDOPHTHALMITIS

- emergent, sight-threatening infection that usually follows trauma, surgery, or hematogenous spread from a distant focus.
- Causative organisms include coagulase-negative staphylococci, *S. aureus*, *S. pneumoniae, B. cereus,* and *Candida albicans.*
- Examination is difficult because of severe blepharospasm and extreme photophobia.
- A hypopyon and haze may be visible on examination.

## EPIDEMIOLOGY

- Conjunctivitis is common in young children, especially if in contact with other children with conjunctivitis.
- Predisposing factors for bacterial infection include:
  1. nasolacrimal duct obstruction
  2. sinus disease
  3. ear infection
  4. allergic children who rub their eyes frequently.
- Conjunctivitis occurs in 1% to 12% of neonates.
- A mild to moderate chemical conjunctivitis commonly is present from 24 to 48 hours of age in most newborns who receive ophthalmic silver nitrate as gonococcal prophylaxis.

- Neonatal acquisition of *C. trachomatis* occurs in approximately 50% of infants born vaginally to infected mothers.
- In infants with perinatal acquisition of *C. trachomatis,* the risk of chlamydial :
  1. conjunctivitis, called **inclusion conjunctivitis**, is 25% to 50%
  2. pneumonia is 5% to 20%.

## CLINICAL MANIFESTATIONS

- Symptoms include:
  1. redness
  2. discharge
  3. matted eyelids
  4. mild photophobia.
- Physical examination findings:
  1. chemosis
  2. injection of the conjunctiva
  3. edema of the eyelids.
- Corneal involvement suggests gonococcal or herpetic infection. Herpetic corneal lesions appear as dendritic or ameboid ulcers or, more commonly, in recurrent infection, as a deep keratitis.
- Unilateral conjunctivitis with ipsilateral otitis media is often caused by nontypable *H. influenzae*.
- *N. gonorrhoeae* causes severe conjunctivitis with profuse purulent discharge.
- Chlamydial conjunctivitis may appear 3 days to 6 weeks after delivery, but usually occurs in the second week of life. There is mild to moderate inflammation with purulent discharge issuing from one or both eyes.

## LABORATORY AND IMAGING STUDIES

- Cultures are not routinely obtained because bacterial conjunctivitis is usually self-limited or responds quickly to antibiotic treatment.
- Gram stain and culture of neonatal conjunctivitis must be obtained, if gonococcal conjunctivitis is suspected.

## DIFFERENTIAL DIAGNOSIS

- Distinguishing bacterial from viral conjunctivitis by presentation and appearance is difficult
- Vesicular lid lesions, if present, suggest the diagnosis of HSV.
- The differential diagnosis of bacterial and viral conjunctivitis includes:
  1. allergic conjunctivitis
  2. chemical conjunctivitis (contaminated eye solutions)
  3. blepharitis
  4. keratitis
  5. contact lens use
  6. foreign body
  7. nasolacrimal duct obstruction
  8. eye rubbing
  9. corneal abrasion
  10. Kawasaki syndrome
  11. anterior uveitis (iridocyclitis) associated with JRA, Behçet disease, & IBD

## TREATMENT

- The lids neede warm compresses to remove the accumulated discharge.

### ACUTE BACTERIAL CONJUNCTIVITIS

- self-limited, but topical antibiotics significantly hasten resolution.
- Antibiotics are instilled between the eyelids four times a day until the discharge subsides, and the chemosis resolves.

- Recommended treatment includes:
  1. Topical ciprofloxacin solution
  2. trimethoprim-polymyxin B solution
  3. sulfacetamide 10% solution
  4. erythromycin ointment.
  5. single dose of ceftriaxone (25 to 50 mg/kg IV or IM; max. dose is 125 mg): Gonococcal ophthalmia neonatorum & newborns to mothers with untreated gonorrhea
  6. oral erythromycin for 14 days: Chlamydial conjunctivitis, partly to reduce the risk of subsequent chlamydial pneumonia.

## PROGNOSIS AND COMPLICATIONS

- The prognosis for bacterial and viral conjunctivitis is excellent.
- The major complication is keratitis, which can lead to ulcerations and perforation.
- This complication is uncommon except with *N. gonorrhoeae* infection.
- Complications of neonatal conjunctivitis are uncommon except with *N. gonorrhoeae* & HSV.
- Chlamydial conjunctivitis may progress in infants to chlamydial pneumonia, which typically develops from 4 to 12 weeks of age.

## PREVENTION

- Careful hand washing is important to prevent spread of conjunctivitis.
- Bacterial conjunctivitis is considered contagious for 24 hours after initiating effective treatment.
- All infants should receive prophylaxis for gonococcal ophthalmia neonatorum whether delivered vaginally or by CS, as soon as possible after delivery. silver nitrate 1% . causes a chemical conjunctivitis .Alternative methods (less irritating):
  1. erythromycin 0.5% ointment
  2. tetracycline 1% ointment

| CONDITION | ETIOLOGY | SIGNS AND SYMPTOMS | TREATMENT |
|---|---|---|---|
| **Bacterial conjunctivitis** | *Haemophilus influenzae, Haemophilus aegyptius, Streptococcus pneumoniae Neisseria gonorrhoeae* | Mucopurulent unilateral or bilateral discharge, normal vision, photophobia Conjunctival injection and edema (chemosis); gritty sensation | Topical antibiotics, parenteral ceftriaxone for gonococcus, *H. influenzae* |
| **Viral conjunctivitis** | Adenovirus, ECHO virus, coxsackievirus | As above; may be hemorrhagic, unilateral | Self-limited |
| **Neonatal conjunctivitis** | *Chlamydia trachomatis,* gonococcus, chemical (silver nitrate), *Staphylococcus aureus* | Palpebral conjunctival follicle or papillae; as above | Ceftriaxone for gonococcus and oral erythromycin for *C. trachomatis* |
| **Allergic conjunctivitis** | Seasonal pollens or allergen exposure | Itching, incidence of bilateral chemosis (edema) greater than that of erythema, tarsal papillae | Antihistamines, steroids, cromolyn |
| **Keratitis** | Herpes simplex, adenovirus, *S. pneumoniae, S. aureus, Pseudomonas, Acanthamoeba,* chemicals | Severe pain, corneal swelling, clouding, limbus erythema, hypopyon, cataracts; contact lens history with amebic infection | Specific antibiotics for bacterial/fungal infections; keratoplasty, acyclovir for herpes |
| **Endophthalmitis** | *S. aureus, S. pneumoniae, Candida albicans,* associated surgery or trauma | Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze | Antibiotics |
| **Anterior uveitis (iridocyclitis)** | JRA, Reiter syndrome, sarcoidosis, Behçet disease, IBD | Unilateral/bilateral; erythema, ciliary flush, irregular pupil, iris adhesions; pain, photophobia, small pupil, poor vision | Topical steroids, plus therapy for primary disease |
| **Posterior uveitis (choroiditis)** | Toxplasmosis, histoplasmosis, *Toxocara canis* | No signs of erythema, decreased vision | Specific therapy for pathogen |
| **Episcleritis /scleritis** | Idiopathic autoimmune disease (e.g., SLE, Henoch-Schönlein purpura) | Localized pain, intense erythema, unilateral; blood vessels bigger than in conjunctivitis; scleritis may cause globe perforation | Episcleritis is self-limiting; topical steroids for fast relief |

| | | | |
|---|---|---|---|
| **Foreign body** | Occupational or other exposure | Unilateral, red, gritty feeling; visible or microscopic size | Irrigation, removal; check for ulceration |
| **Blepharitis** | *S. aureus, Staphylococcus epidermidis,* seborrheic, blocked lacrimal duct; rarely molluscum contagiosum, *Phthirus pubis, Pediculus capitis* | Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins | Topical antibiotics, warm compresses |
| **Dacryocystitis** | Obstructed lacrimal sac: *S. aureus, H. influenzae,* pneumococcus | Pain, tenderness, erythema and exudate in areas of lacrimal sac (inferomedial to inner canthus); tearing (epiphora); possible orbital cellulitis | Systemic, topical antibiotics; surgical drainage |
| **Dacryoadenitis** | *S. aureus, Streptococcus,* CMV, measles, EBV, enteroviruses; trauma, sarcoidosis, leukemia | Pain, tenderness, edema, erythema over gland area (upper temporal lid); fever, leukocytosis | Systemic antibiotics; drainage of orbital abscesses |
| **Orbital cellulitis (postseptal cellulitis)** | Paranasal sinusitis: *H. influenzae, S. aureus, S. pneumoniae,* streptococci<br>Trauma: *S. aureus* | Rhinorrhea, chemosis, vision loss, painful extraocular motion, proptosis, ophthalmoplegia, fever, lid edema, leukocytosis | Systemic antibiotics, drainage of orbital abscesses |
| | Fungi: *Aspergillus, Mucor* if immunodeficient | | |
| **Periorbital cellulitis (preseptal cellulitis)** | Trauma: *S. aureus,* streptococci<br>Bacteremia: pneumococcus, streptococci, *H. influenzae* | Cutaneous erythema, warmth, normal vision, minimal involvement of orbit; fever, leukocytosis, toxic appearance | Systemic antibiotics |

# OSTEOMYELITIS

## ETIOLOGY

- pediatric osteomyelitis Syndromes, include:
  1. **acute hematogenous osteomyelitis**, accompanied by bacteremia
  2. **subacute focal disease**, follows local inoculation by penetrating trauma / No associated systemic symptoms.
  3. **chronic osteomyelitis**, the result of an untreated or inadequately treated bone infection.
- bone infections occur almost exclusively in the **metaphysic** in children beyond the newborn period and without hemoglobinopathies,
  - ◇ in children with sickle cell disease occur in the diaphyseal portion of the long bones, as a consequence of antecedent focal infarction.
  - ◇ < 1 year old, the capillaries perforate the epiphyseal growth plate, permitting spread of infection across the epiphysis that can lead to suppurative arthritis.
  - ◇ In older children, the infection is contained in the metaphysis because the vessels no longer cross the epiphyseal plate.
- **Causes:**
  - ◇ **S. aureus is responsible for most skeletal infections**
  - ◇ ***S. aureus* is the most common cause of chronic osteomyelitis.**
  - ◇ *Haemophilus influenzae* type b* diminished since introduction of conjugate vaccine
  - ◇ **Neonates**: Group B streptococcus and *S. aureus* are the major causes.
  - ◇ **S**ickle cell disease osteomyelitis caused by ***S**almonella* and ***S**. aureus.*
  - ◇ *Pasteurella multocida* osteomyelitis : cat or dog bites.
  - ◇ ambulatory persons who sustain **puncture wounds** of the foot : Subacute focal bone infections caused by *P. aeruginosa* and *S. aureus*.
  - ◇ puncture wounds through sneakers, which harbor *Pseudomonas* : associated strongly with *Pseudomonas* **chondritis**
- **Multifocal recurrent osteomyelitis** is a poorly understood syndrome characterized by recurrent episodes of fever, bone pain, and radiographic findings of osteomyelitis; no pathogen has been confirmed as the cause of this syndrome.

## EPIDEMIOLOGY

- Osteomyelitis occur at any age, most common in children **3 -12 years** old.

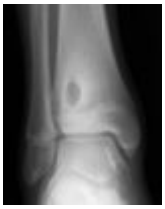
- **boys** twice > girls.
- **Hematogenous osteomyelitis is the most common form in infants and children.**
- penetrating trauma or peripheral vascular disease Osteomyelitis is more common in adults.

## CLINICAL MANIFESTATIONS

- The most common presenting complaints are:
  1. focal pain,
  2. point tenderness, warmth, erythema, swelling, over the bone
  3. Decreased use of the affected extremity (**pseudoparalysis**).
- Fever, anorexia, irritability, and lethargy may accompany the focal findings.
- Muscle spasm may make the extremity difficult to examine.
- The adjacent joint space may be involved in young children.
- Usually only one bone is involved.
  - ◇ **The femur, tibia, or humerus is affected in two thirds of patients.**
  - ◇ hands or feet bones 15% of cases.
  - ◇ Flat bone infections, including the pelvis, 10% of cases.
- *Vertebral osteomyelitis* : insidious onset, vague symptoms, backache, spinal cord compression, and little associated fever or systemic toxicity.
- *Patients with osteomyelitis of the pelvis* present with fever, limp; vague abdominal, hip, groin, or thigh pain.

## LABORATORY AND IMAGING STUDIES

- The presence of leukocytosis is unusual.
- Elevated acute phase reactants, ESR and CRP, are sensitive but nonspecific Serial determinations are helpful in monitoring the course of the illness and response to treatment.
- Direct subperiosteal or metaphyseal needle aspiration is the **definitive procedure for establishing the diagnosis of osteomyelitis.**
- Plain radiographs.
  - ◇ **loss of the periosteal fat line**: is the earliest radiographic finding of acute systemic osteomyelitis, at about 9 days
  - ◇ **Periosteal elevation** and **periosteal destruction** are later findings.
  - ◇ **Brodie abscess** is a subacute intraosseous ( in bone) abscess that does not drain into the subperiosteal space and is classically located in the distal tibia.
  - ◇ **Sequestra**, or portions of avascular bone that have separated from adjacent bone, covered with a thickened sheath, an involucrum (**hallmarks of chronic osteomyelitis**)
- Others:
  - ◇ **MRI**, which is sensitive to the inflammatory changes in the marrow even during the earliest stages of osteomyelitis.
  - ◇ **Technetium-99m bone** scans are useful for evaluating multifocal disease.
  - ◇ **Gallium-67 scans** are often positive if the technetium-99m bone scan is negative.



## DIFFERENTIAL DIAGNOSIS

1. infectious arthritis
2. cellulitis
3. fasciitis
4. discitis
5. trauma
6. juvenile rheumatoid arthritis
7. malignancy

## COMPLICATIONS

- Complications of acute osteomyelitis are uncommon and usually arise because of inadequate or delayed therapy.

- Young children → suppurative arthritis.
- Vascular insufficiency, which affects delivery of antibiotics, and trauma are associated with higher rates of complications.

## TREATMENT

- Initial antibiotic therapy for osteomyelitis is based on knowledge of the likely organism for the age of the child, Gram stain of bone aspirate, and associated diseases.
- Initial therapy should be with an antibiotic, such as **oxacillin**, **nafcillin**, or **clindamycin**.
- **Vancomycin** : methicillin-resistant *S. aureus* is suspected.
- sickle cell disease *(Salmonella*).: **cefotaxime** and **ceftriaxone**
- Antibiotics are administered for a minimum of **4 - 6 weeks**.
- There is usually a response to IV antibiotics (↓fever and pain) within 48 hours. If not:
  1. indicates that surgical drainage
  2. unusual pathogen may be present.
- Surgical drainage is indicated if :
  1. sequestrum is present
  2. chronic or atypical diease
  3. hip joint is involved
  4. Spinal cord compression is present.

| Common Pathogens | Recommended Treatment |
|---|---|
| **Acute Hematogenous Osteomyelitis** | |
| *Staphylococcus aureus* | Nafcillin (*or* oxacillin) *or* cefazolin |
| *Streptococcus pneumoniae* | Penicillin G *or* ceftriaxone (*or* cefotaxime) *or* vancomycin (based on susceptibilities) |
| Group A streptococcus | Penicillin G |
| *Haemophilus influenzae* type b* | Ceftriaxone (*or* cefotaxime) |
| **Subacute Focal Osteomyelitis** | |
| *Pseudomonas aeruginosa* (puncture wound osteomyelitis) | Ceftazidime *or* piperacillin-tazobactam *and* an aminoglycoside ( amikasin & gentamicine) |
| *S. aureus* | Nafcillin (*or* oxacillin) *or* cefazolin |

## PROGNOSIS

- Hematogenous osteomyelitis has an excellent prognosis if treated promptly and if surgical drainage is performed when appropriate.
- **poorest outcome** is in neonates and in infants with involvement of the hip or shoulder joint.
- Retarded growth is more common among neonates.
- Recurrent infection occurs in 4% of acute infections despite adequate therapy.
  - ◇ 25% of these fail to respond to extensive surgical débridement and prolonged antimicrobial therapy→ bone loss, sinus tract formation, and amputation.

## PREVENTION

- The value of oral prophylactic antibiotics for prevent osteomyelitis after penetrating injury is unknown (oral **cephalosporin** or **amoxicillin-clavulanate** provides coverage for *S. aureus*)
- An oral **fluoroquinolone**, which provide coverage for *P. aeruginosa,* e an alternative for persons 18 years old or older.

# Infectious Arthritis

## ETIOLOGY

- **Infectious arthritis** (**suppurative or septic arthritis):** is a serious bacterial infection of the joint space

- Occurs most commonly in children < 5 years old and adolescents.
- results from:
  1. hematogenous dissemination
  2. contiguous spread of infection from surrounding soft tissues
  3. direct inoculation into the joint (penetrating trauma)
- The bacteria causing infectious arthritis are similar to bacteria causing osteomyelitis
- Lyme disease causes arthritis as part of the late disease.
- **Reactive arthritis** : immune-mediated synovial inflammation, after bacterial or viral infection.
  - ◇ Typically symmetric and polyarticular and involves the large joints, especially the hips.
  - ◇ Had a preceding episode of gastroenteritis or urethritis.
  - ◇ Reactive arthritis of the hip joints in children 3 - 6 years old→ **Toxic synovitis** or **transient synovitis** of the hip.

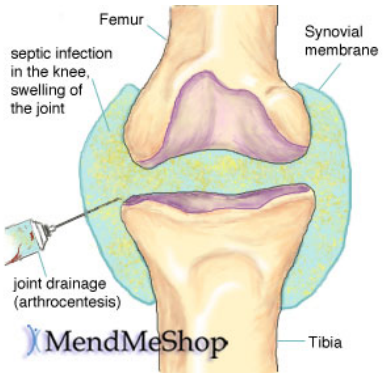
## CLINICAL MANIFESTATIONS

- The typical features of suppurative arthritis include:
  1. erythema, warmth, swelling, and tenderness over the affected joint
  2. palpable effusion
  3. decreased range of movement.
- The onset : sudden or insidious
- **The lower extremity joints are most often involved:** knees: **40%,** hips: 20**%**, ankle: **14%.**

- symptoms noted only when the joint is moved, such as:
  1. during a diaper change
  2. if parents become aware of decreased voluntary movement (**pseudoparalysis**) of limb.
  3. Toddlers may have a limp.
- In septic arthritis of the hip, the lower limb held in external rotation and flexion to minimize pain from pressure on the joint capsule.
  - ◇ The knee and elbow joints are held in flexion.
- The arthritis of **disseminated gonococcal infections** includes:
  - ◇ Reactive and suppurative forms of arthritis in early and late gonococcal disease.
  - ◇ With untreated genital gonococcal infection→gonococcemia (high prevalence) manifests as a febrile illness with polyarticular, symmetric arthritis and rash, known as the **arthritis-dermatitis syndrome**. (Bacterial cultures of the synovium = sterile) .
  - ◇ Monarticular arthritis of large, weight-bearing joints develops days to weeks later. (Cultures of affected synovial fluid = pathogen).
  - ◇ A history of febrile illness antedating the development of monarticular arthritis characterizes late gonococcal arthritis.

## LABORATORY AND IMAGING STUDIES

- **Leukocytosis**
- **elevated ESR and CRP**
- **Arthrocentesis and analysis of the effusion**: the test of choice for rapid diagnosis of infectious arthritis.
- **Blood or joint cultures** : positive in 70% to 85% of cases.
- Because of the bacteriostatic effects of synovial fluid→ Joint fluid with characteristics of pyogenic infection, negative cultures in 30% of patients.
- Adolescents with acute infectious arthritis: urethral, cervical, rectal, and pharyngeal examination and cultures for *N. gonorrhoeae*.
- Gram stain, acid-fast stain, and KOH preparation for fungi → informative even if the cultures are negative.
- **Plain radiographs** add little information to the physical findings:
  1. swelling of the joint capsule
  2. widened joint space
  3. Displacement of adjacent normal fat lines.



- **Radionuclide scans** are of limited use( technetium-99m bone scans) : exclude concurrent bone infection, either adjacent or distant from the infected joint.
- **Ultrasound** : the diagnostic procedure of choice for evaluation of hip suppurative infections .
- **MRI** : distinguishing joint infections from cellulitis or deep abscesses.

## DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of infectious arthritis:
  1. **Other infectious diseases**: Lyme disease, osteomyelitis, suppurative bursitis, fasciitis, myositis, cellulitis, and soft tissue abscesses
  2. **Rheumatoid disorders** :JRA, Kawasaki syndrome, HSP
  3. **Rheumatic fever**
  4. **Crohn disease**
  5. **Trauma**
- Psoas muscle abscess often presents with fever and pain on hip flexion and rotation.
- The presence of symmetric or multiple joint involvements often excludes infectious arthritis.
- **Suppurative bursitis** with *S. aureus* occurs most often in older boys and men and is a consequence of trauma or, less commonly, a complication of bacteremia.

| Condition | Appearance | WBC (µg/L) | Neutr. (%) | Mucin Clot | ΔGlucose (mg/dL) synovial fluid - serum | Comment |
|---|---|---|---|---|---|---|
| **Normal** | Clear, yellow | 0-200 | <10 | Good | 0 | - |
| **Trauma** | Clear, turbid, hemorrhagic | 50-4,000 (600) | <30 | Good | 0 | Common in hemophilia |
| **SLE** | Clear or slightly turbid | 0-9,000 (3,000) | <20 | Good - fair | 0 | LE cell positive, ↓complement |
| **reactive arthritis (Reiter synd, IBD)** | Turbid | 250-80,000 (19,000) | >70 | Poor | 30 | Decreased complement |
| **Pyogenic infection** | Turbid | 10,000-250,000 (80,000) | >90 | Poor | 50-90 | + culture, + Gram stain |
| **Tuberculosis** | Turbid | 2,500-100,000 (20,000) | >60 | Poor | 40-70 | + culture, PPD, and acid-fast stain |
| **Lyme arthritis** | Turbid | 500-100,000 (20,000) | >60 | Poor | 70 | History of tick bite. erythema migrans |

## TREATMENT

- Initial antibiotic therapy for infectious arthritis is based on knowledge of the likely organism for the age of the child and the Gram stain of joint fluid.
- Suppurative arthritis of the hip joint or shoulder joint necessitates prompt surgical drainage.
- These joints are ball-and-socket joints with insertion of the joint capsule below the epiphysis: the increased pressure in the joint space → affects adversely the vascular supply to the head of the femur or humerus→ ischemic injury and necrosis.
- Infections of the knee may be treated with repeated arthrocenteses + IV antibiotics.
- Antibiotics:
  1. Initial therapy for neonates : nafcillin and cefotaxime, with activity against *S. aureus,* group B streptococcus, and aerobic gram-negative rods.
  2. Initial therapy for children 3 months to 5 years old should include antibiotics such as cefotaxime or ampicillin-sulbactam with activity against *S. aureus* and Hib.
  3. Confirmed methicillin-susceptible *S. aureus* infections are treated with nafcillin or oxacillin
  4. methicillin-resistant *S. aureus* infections are treated with vancomycin or clindamycin

- The duration of therapy depends on clinical resolution of fever and pain and ↓ ESR.
- Infection with virulent organisms, ex: *S. aureus,* necessitates treatment for at least 21 days.
- Oral agents with excellent activity against *S. aureus* to complete therapy include:
  1. cephalexin
  2. amoxicillin-clavulanate
  3. dicloxacillin
  4. clindamycin
  5. ciprofloxacin (in persons ≥18 years old)
- **Recommended Antibiotic Therapy for Infectious Arthritis in Children**

| | Common Pathogens | Recommended Treatment |
|---|---|---|
| Infants (<2 mo) | Group B streptococcus | Ampicillin *plus* aminoglycoside |
| | *Escherichia coli* | Cefotaxime (*or* ceftriaxone) *plus* aminoglycoside |
| | *Klebsiella pneumoniae* | Cefotaxime (*or* ceftriaxone) *plus* aminoglycoside |
| | *Staphylococcus aureus* | Nafcillin (*or* oxacillin), vancomycin |
| Older infants and children | *S. aureus* | Nafcillin (*or* oxacillin), vancomycin |
| | *Streptococcus pneumoniae* | Penicillin G *or* cefotaxime (*or* ceftriaxone) *or* vancomycin (based on susceptibilities) |
| | Group A streptococcus | Penicillin G |
| | *Kingella kingae* | Penicillin G *or* nafcillin (*or* oxacillin) |
| | *Hib* | Cefuroxime (*or* cefotaxime *or* ceftriaxone) |
| Disseminated gonococcal | *Neisseria gonorrhoeae* | Ceftriaxone |

## COMPLICATIONS

- The major complication is loss of joint function resulting from damage to the articular surface.
- The highest incidence of these complications occurs with hip infections, presumably as a result of ischemic injury to the head of the femur.
- The high incidence of suppurative arthritis with adjacent osteomyelitis in neonates places the epiphyseal growth plate at high risk for growth abnormalities with loss of longitudinal bone growth → limb shortening. (40% to 50%).

## PROGNOSIS

- The prognosis in infants and children is excellent.
- The poorest outcome is for infectious arthritis of the hip or shoulder.

# SINUSITIS

## ETIOLOGY

- **Sinusitis** is a suppurative infection of the paranasal sinuses and often complicates the common cold and allergic rhinitis.
- Development of paranasal sinuses:
  1. ethmoid sinuses are present and the only pneumatized at birth.
  2. The maxillary presents at birth become pneumatized at 4 years of age.
  3. The sphenoid sinuses are present by 5 years of age.
  4. The frontal sinuses begin to develop at 7 years of age and completle develop at adolescence.
- The ostia draining the sinuses are narrow (1 to 3 mm) → drains into the middle meatus in the **ostiomeatal complex**.
- The mucociliary system maintains the sinuses as normally sterile.
- mucosal edema resulting from a viral rhinosinusitis(common cold) → Obstruction to mucociliary flow → impedes sinus drainge → bacterial proliferation.
- Bacteria causing sinusitis include :
  1. *S. pneumoniae*
  2. nontypable *H. influenzae*
  3. *Moraxella catarrhalis*
  4. less commonly *S. aureus,* other streptococci, and anaerobes.

- Indwelling nasogastric and nasotracheal tubes predispose to nosocomial sinusitis, which is often caused by gram-negative bacteria (*Klebsiella* and *Pseudomonas*).
- Antibiotic therapy predisposes to infection with antibiotic-resistant organisms.
- Sinusitis in neutropenic and immunocompromised persons may be caused by *Aspergillus* and the Zygomycetes (e.g., *Mucor, Rhizopus*).
- **risk factors :**
  1. The common cold :major predisposing factor at all ages.
  2. cystic fibrosis
  3. immunodeficiency ,HIV infection
  4. nasogastric or nasotracheal intubation
  5. immotile cilia syndrome
  6. nasal polyps
  7. nasal foreign body

## CLINICAL MANIFESTATIONS

- Clinical manifestations most commonly include:
  1. persistent, mucopurulent, unilateral or bilateral rhinorrhea
  2. nasal stuffiness
  3. cough, especially at night.
- Less common symptoms include a nasal quality to the voice, halitosis, facial swelling, facial tenderness and pain, and headache.
- **Sinusitis may exacerbate asthma.**

## LABORATORY AND IMAGING STUDIES

- Culture of the nasal mucosa is not useful.
- **Sinus aspirate culture** is the **most accurate diagnostic method** but is not practical or necessary.
- **Transillumination**: show evidence of fluid, difficult to perform in children and is not reliable.
- **Plain film and CT** :
  1. sinus clouding
  2. mucosal thickening
  3. air-fluid level.
- Abnormal radiographic findings are not diagnostic of sinusitis
  1. CT and MRI frequently show abnormalities, including air-fluid levels, in the sinuses of asymptomatic persons.
  2. Abnormal radiographic findings do not differentiate infection from allergic disease.
  3. normal radiographs have high negative predictive value for bacterial sinusitis.

## DIFFERENTIAL DIAGNOSIS ( CLINICAL)

- The diagnosis usually is based on history and physical findings for longer than 10 to 14 days without improvement or increased severity of symptoms compared with the common cold.

## TREATMENT

- Amoxicillin continued for 7 days after resolution of symptoms is recommended for treatment of uncomplicated sinusitis.
- Alternative antibiotics for penicillin-allergic patients include:
  1. cefuroxime axetil
  2. cefpodoxime
  3. clarithromycin
  4. azithromycin.
- treatment with high-dose amoxicillin-clavulanate is recommended:
  1. For children at increased risk for resistant bacteria (antibiotic treatment in the preceding 1 to 3 months, daycare attendance, age <2 years)
  2. for children who fail to respond to initial therapy with amoxicillin within 72 hours,.
- Failure to respond to this regimen necessitates referral to an otolaryngologist.

## COMPLICATIONS

- Complications include:
  1. orbital cellulites
  2. epidural or subdural empyema
  3. brain abscess
  4. dural sinus thrombosis
  5. osteomyelitis of the outer or inner table of the frontal sinus (**Pott puffy tumor**)
  6. Meningitis
- These complications managed with: sinus drainage + broad-spectrum IV antibiotics.
- Sinusitis exacerbates bronchoconstriction in asthmatic patients.

### ORBITAL CELLULITIS:

- Serious complication of sinusitis in adolescents that follows spread of bacteria into the orbit through the wall of the infected sinus.
- It typically begins as ethmoid sinusitis and spreads through the lamina papyracea, which is a thin, bony plate that separates the medial orbit and the ethmoid sinus.
- Orbital involvement → subperiosteal abscess, proptosis, ophthalmoplegia, cavernous sinus thrombosis, and vision loss.
- Manifestations of orbital cellulitis include:
  1. orbital pain
  2. Proptosis
  3. chemosis
  4. ophthalmoplegia and limited extraocular muscle motion
  5. diplopia
  6. reduced visual acuity.
- Disorders to be considered in the differential diagnosis:
  1. periorbital cellulitis
  2. rhabdomyosarcoma
  3. neuroblastoma
  4. Wegener granulomatosis
  5. inflammatory pseudotumor of the orbit
  6. zygomycosis (mucormycosis)
  7. aspergillosis
  8. trichinosis.
- The diagnosis of orbital cellulitis is confirmed by a CT scan of the orbit, which determines the extent of orbital infection and the need for surgical drainage.
- Therapy for orbital cellulitis involves broad-spectrum IV antibiotics, such as oxacillin and ceftriaxone.

### PRESEPTAL CELLULITIS (PERIORBITAL CELLULITIS) :

- preseptal (anterior to the palpebral fascia) or periorbital space Infection.
- occurs in children < 3 years old
- children do not have proptosis or ophthalmoplegia.
- usually is associated with a skin lesion or trauma
- usually is caused by *S. aureus* or group A streptococcus.

## PROGNOSIS

- >50% of children with acute bacterial sinusitis recover without any antimicrobial therapy.
- Fever and nasal discharge should improve dramatically within 48 hours of initiating treatment for sinusitis.
- Persistent symptoms suggest another etiology.

# OTITIS MEDIA

## ETIOLOGY

- **Otitis media** is suppurative infection of the middle ear cavity.
- pharyngitis, or hypertrophied adenoids ➔ blocked normal patency of the eustachian tube → Bacteria gain access to the middle ear / Air trapped in the middle ear is resorbed→ creating negative pressure in this cavity → facilitating reflux of nasopharyngeal bacteria ➔infected middle ear effusion.
- The bacterial pathogens are:
  1. *S. pneumoniae*
  2. nontypable *H. influenzae*
  3. *M. catarrhalis*
  4. less frequently, group A streptococcus.
- Viruses, including rhinoviruses and RSV, are recovered alone or as copathogens in 20% to 25% of patients.

## EPIDEMIOLOGY

- 1/3 of office visits to pediatricians are Diseases of the middle ear.
- The peak incidence of acute otitis media is in the second 6 months of life.
- By the first birthday, 62% of children experience at least one episode.
- Few first episodes occur after 18 months of age.
- Otitis media is more common in boys and in patients of lower socioeconomic status.
- There is increased incidence of otitis media in certain high-risk populations, such as children with HIV, cleft palate, and trisomy 21.

- The major risk factors for acute otitis media are:
  1. young age
  2. bottle-feeding as opposed to breastfeeding
  3. drinking a bottle in bed
  4. parental history of ear infection
  5. the presence of a sibling in the home (especially a sibling with a history of ear infection)
  6. sharing a room with a sibling
  7. passive exposure to tobacco smoke from parental smoking
  8. increased exposure to infectious agents (daycare)
- **Recurrent otitis media** (otitisprone): the presence of ≥6 acute otitis media episodes in the first 6 years of life (12% of children) ESPICALLY with Craniofacial anomalies and immunodeficiencies but most children are healthy.

## CLINICAL MANIFESTATIONS

- In infants, the most frequent symptoms of acute otitis media are nonspecific and include fever, irritability, and poor feeding.
- In older children and adolescents, acute otitis media usually is associated with fever and **otalgia** (acute ear pain).
- Acute otitis media also may present with **otorrhea**, after spontaneous rupture of the tympanic membrane.

## LABORATORY AND IMAGING STUDIES

- CBC and ESR are not useful in the evaluation of otitis media.
- Tympanometry: Measurements of the resulting tympanogram correlate well with the presence or absence of middle ear effusion.
- Acoustic reflectometry as a screening test for acute otitis media should be followed by examination with pneumatic otoscopy when abnormal reflectometry is identified.
- **Bacteria recovered from the nasopharynx do not correlate with bacteria isolated by tympanocentesis.**
- Tympanocentesis and culture of the middle ear exudate is required for accurate identification of bacterial pathogens, may be useful in:
  1. neonates

2. immunocompromised patients
3. Patients not responding to therapy.

## DIFFERENTIAL DIAGNOSIS

- The hallmark of otitis media is the presence of effusion in the middle ear cavity.
- **Pneumatic otoscopy**, is a standard for clinical diagnosis.
- The tympanic membrane of the normal, air-filled middle ear has much greater compliance than if the middle ear is fluid-filled.
- With acute otitis media, the tympanic membrane is characterized by:
  1. hyperemia, or red color rather than the normal pearly gray color, but it can be pink, white, or yellow
  2. a full to bulging position
  3. with poor mobility to negative and positive pressure
  4. The light reflex is lost
  5. the middle ear structures are obscured and difficult to distinguish
  6. A hole in the tympanic membrane or purulent drainage confirms perforation.
- bullae may present on the lateral aspect of the tympanic membrane, which characteristically are associated with severe ear pain.
- The major difficulty is differentiation of acute otitis media from **otitis media with effusion**, which also is referred to as **chronic otitis media**.
  - ◇ Acute otitis media is accompanied by signs of acute illness, such as fever, pain, and upper respiratory tract inflammation.
  - ◇ Otitis media with effusion is the presence of effusion without any of the other signs and symptoms.

## TREATMENT

- **The recommended first-line therapy for most children with acute otitis media is amoxicillin (80 to 90 mg/kg/day in two divided doses).**
- Failure of initial therapy with amoxicillin at 3 days suggests infection with:
  1. β-lacta-mase-producing *H. influenzae*
  2. *M. catarrhalis*
  3. relatively or highly resistant *S. pneumoniae*.
- Recommended next-step treatments include:
  1. high-dose amoxicillin-clavulanate (amoxicillin 80 to 90 mg/kg/day)
  2. cefuroxime axetil
  3. cefdinir
  4. ceftriaxone (50 mg/kg intramuscularly in one to three daily doses).especially for children < 3 years old with vomiting that precludes oral treatment.
- Tympanocentesis: for patients who are difficult to treat or who do not respond to therapy, but this is not a routine procedure.
- Acetaminophen and ibuprofen are recommended for fever.
- Decongestants or antihistamines are **not effective** alone or when combined with antibiotics.

## COMPLICATIONS

- The complications of otitis media are:
  1. chronic effusion
  2. hearing loss
  3. cholesteatoma (masslike keratinized epithelial growth)
  4. petrositis
  5. intracranial extension (brain abscess, subdural empyema, or venous thrombosis),
  6. mastoiditis.

### ACUTE MASTOIDITIS

- Suppurative complication of otitis media with inflammation and potential destruction of the mastoid airspaces.
- The disease progresses from a periostitis to an osteitis with mastoid abscess formation.

- Posterior auricular tenderness and swelling and erythema, in addition to the signs of otitis media, are present.
- The pinna is displaced downward and outward.
- Radiographs or CT scan of the mastoid reveals clouding of the air cells, demineralization, or bone destruction.
- The bacteria that cause acute otitis media are those responsible for acute mastoiditis.
- Treatment includes IV antibiotics and drainage if the disease has progressed to abscess formation.
- reasonable indicator of need for intervention with insertion of pressure equalization tubes:
  1. children at developmental risk
  2. frequent episodes of recurrent acute otitis media
  3. 3 months of persistent effusion with significant bilateral hearing loss

## PROGNOSIS

- **Otitis media with effusion** is the **most frequent** sequela of acute otitis media and occurs most frequently in the first 2 years of life.
- **Persistent middle ear effusion** may last for many weeks or months in some children.
- **Conductive hearing loss** assumed to be present with persistent middle ear effusion; the loss is mild to moderate and often is transient or fluctuating.
- **Glue ear**: the presence of a viscous, gluelike effusion , produced when the chronically inflamed middle ear mucosa produces an excess of mucus, retained for prolonged periods, because the normal clearance of the middle ear cavity is absent.

## PREVENTION

- Continue exclusive breastfeeding.
- NO children taking a bottle to bed.
- The home should be a smoke-free environment.
- Pneumococcal vaccine (↓otitis media by 6%) and influenza vaccine
- Children at high-risk for recurrent acute otitis media → antimicrobial prophylaxis = Amoxicillin (20 to 30 mg/kg/day) or sulfisoxazole (50 mg/kg/day) given once daily at bedtime for 3 to 6 months or longer.

# OTITIS EXTERNA

## ETIOLOGY

- Otitis externa "**swimmer's ear**": inflammation and exudation in the external auditory canal in the absence of other disorders, such as otitis media or mastoiditis.
- **The most common bacterial pathogen is P. aeruginosa**, swimming in pools or lakes.
- Otitis externa develops in 20% of children with tympanostomy tubes, associated with *S. aureus, S. pneumoniae, M. catarrhalis, Proteus, Klebsiella,* and anaerobes.
- Coagulase-negative staphylococci and *Corynebacterium* = external canal normal flora.
- **Malignant otitis externa** is caused by *P. aeruginosa* in immuno-compromised persons and adults with diabetes.

## EPIDEMIOLOGY

- Otitis externa is a frequent complaint in summer, in contrast to otitis media, which occurs primarily in colder seasons in association with viral URTI.
- Disruption of the integrity of the cutaneous lining of the ear canal and local defenses predisposes to otitis externa as:
  1. cleaning of the auditory canal
  2. swimming
  3. diving

## CLINICAL MANIFESTATIONS

- the characteristic clinical findings of otitis externa:

1. Pain
2. tenderness
3. aural discharge

- Fever is notably absent & Hearing is unaffected.
- **Valuable diagnostic criterion**: Tenderness with movement of the pinnae, especially the tragus, and with chewing. not present in otitis media.
- Inspection:
  1. The lining of the auditory canal is inflamed with mild to severe erythema and edema.
  2. Scant to copious discharge from the auditory canal, often obscuring the tympanic membrane.
- **malignant otitis externa:**
  - ◇ The most common symptoms are:
  1. severe ear pain
  2. tenderness on movement of the pinna
  3. drainage from the canal
  4. Facial nerve palsy
  - ◇ the most common physical findings are:
  1. swelling and granulation tissue in the canal
  2. discharge from the external auditory canal

## LABORATORY AND IMAGING STUDIES

- The diagnosis of uncomplicated otitis externa: clinical symptoms and physical examination
- *In malignant otitis externa, an elevated ESR is a constant finding.*
- diagnostic imaging studies, such as **CT or MRI** : requires for documentation of the extent of involvement with
- **Cultures** are required to identify the etiologic agent, which is usually *P. aeruginosa,* and the antimicrobial susceptibility.

## DIFFERENTIAL DIAGNOSIS

- **Otitis media with tympanic perforation** and discharge into the auditory canal may be confused with otitis externa, particularly in infants in whom it may be difficult to clear the discharge.
- **Tuberculous otitis media** is marked by a chronic, painless aural discharge, further suggested by skin testing and chest x-ray.
- **Malignancies** : rare in children, but may occur with discharge, unusual pain, or hearing loss.

## TREATMENT

- The most widely used topical otic preparations contain a combination of an aminoglycoside, such as neomycin and polymyxin B, with a topical corticosteroid.
- There are theoretical risks of ototoxicity with neomycin and polymyxin B, which should be avoided in the presence of tympanic perforation.
- Topical **quinolone** antibiotic drops (ciprofloxacin, ofloxacin) are more popular despite the cost. They are active against *S. aureus* and gram-negative bacteria, including *P. aeruginosa*.
- None of these antibiotics has any antifungal activity.
- Local therapy with acetic acid preparations (2%) restore the acid pH of the auditory canal is usually effective. have indirect antibacterial and antifungal effects by acidification.
- Fungi such as *Aspergillus, Candida,* occasionally are isolated from the external ear. (? normal flora or cause of inflammation). local therapy and restoration of normal pH as for bacterial otitis externa are sufficient.
- **Tympanostomy tube otorrhea** is best treated with quinolone otic drugs because they are considered less likely to be ototoxic.
- **Malignant otitis externa** is treated by IV antimicrobials with activity against *P. aeruginosa*:
  1. expanded-spectrum penicillin (mezlocillin, piperacillin-tazobactam)
  2. cephalosporin (ceftazidime, cefepime) + aminoglycoside.

## COMPLICATIONS AND PROGNOSIS

- Acute otitis externa usually resolves without complications within 1 to 2 days of treatment.
- Persistent pain, severe or iaccompanied by fever → other conditions.
- Malignant otitis externa frequently is accompanied by complications.
  - ◇ Invasion of the bones of the base of the skull may cause cranial nerve palsies, such as facial nerve palsy.
  - ◇ mortality of 15% to 20% occurs in adults with malignant otitis media.
  - ◇ Relapses within the first year after treatment are common.

## PREVENTION

- vigorous cleaning of an asymptomatic auditory canal should be avoided.
- Drying the auditory canals with acetic acid (2%), (rubbing alcohol) after swimming may be used prophylactically to prevent the maceration that may facilitate bacterial invasion.
- Often underwater gear, such diving equipment, must be avoided to prevent recurrency.
- There is no role for prophylactic otic antibiotics.

# ACUTE GASTROENTERITIS

## ETIOLOGY & EPIDEMIOLOGY

- **Acute enteritis or acute gastroenteritis → diarrhea**: abnormal frequency and liquidity of fecal discharges. Could be viral, bacterial, or parasitic causes.
- Diarrhea is caused by many different infectious or inflammatory processes that directly affect enterocyte secretory and absorptive functions.
  1. *Vibrio cholerae, E. coli* heat-labile toxin, VIP-producing →↑ cyclic AMP levels.
  2. *Shigella* toxin, congenital chloridorrhea→ secretory diarrhea by affecting ion channels.
- **Mechanisms of Diarrhea**

| PRIMARY MECHANISM | DEFECT | STOOL EXAMINATION | EXAMPLES | COMMENT |
|---|---|---|---|---|
| **Secretory** | ↓absorption, ↑ secretion: electrolyte transport | Watery, normal osmolality; osmols = 2 × ($Na^+$ + $K^+$) | Cholera, toxigenic *E.coli;* carcinoid, VIP, neuroblastoma , congenital CL diarrhea, *Clostridium difficile,* cryptosporidiosis (AIDS) | Persists during fasting; bile salt malabsorption ↑ intestinal water secretion; no stool leukocytes |
| **Osmotic** | Maldigestion, transport defects, ingestion of unabsorbable solute | Watery, acidic, + reducing substances; ↑osmolality; osmosis > 2 × ($Na^+$ + $K^+$) | Lactase deficiency, glucose-galactose malabsorption, lactulose ,laxative abuse | Stops with fasting, increased breath hydrogen with carbohydrate malabsorption, no stool leukocytes |
| **Motility** | | | | |
| ↑motility | Decreased transit time | Loose to normal-appearing stool, stimulated by gastrocolic reflex | Irritable bowel syndrome, thyrotoxicosis, postvagotomy dumping syndrome | Infection also may contribute to increased motility |
| ↓ motility | Defect in neuro-muscular units, stasis (bacterial overgrowth) | Loose to normal-appearing stool | Pseudo-obstruction, blind loop | Possible bacterial overgrowth |
| **Mucosal inflammation** | Inflammation, ↑mucosal surface area and/or colonic reabsorption, ↑motility | Blood and increased WBCs in stool | Celiac disease, *Salmonella, Shigella,* amebiasis, *Yersinia, Campylobacter,* rotavirus enteritis | Dysentery = blood, mucus, and WBCs |

- Diarrhea is a major cause of childhood mortality in the developing world.
- Some organisms are spread :

| ORGANISMS | VIRULENCE PROPERTIES |
|---|---|
| **Viruses** | |

1. person to person
2. animal to human
3. contaminated food or water
4. Many spread by multiple routes

- Viral causes of gastroenteritis in children:
  1. rotaviruses
  2. caliciviruses (including the noroviruses),
  3. astroviruses
  4. enteric adenoviruses (serotypes 40 and 41).

| | |
|---|---|
| Rotaviruses | Damage to microvilli |
| Caliciviruses | Mucosal lesion |
| Astroviruses | Mucosal lesion |
| Enteric adenoviruses (serotypes 40 and 41) | Mucosal lesion |

## ROTAVIRUS

- invades the epithelium and damages villi of the upper small intestine
- In severe cases involves the entire small bowel and colon.
- The most frequent cause of diarrhea during the winter months.
- Vomiting last 3 to 4 days, and diarrhea may last 7-10 days.
- Dehydration is common in younger children.
- Primary infection with rotavirus in infancy more severe than later in life.

## TYPHOID FEVER" ENTERIC FEVER"

- Caused by *Salmonella typhi* and Salmonella *paratyphi* /gram negative rods.
- The incubation period is 7-14 days (range 3 - 60 days).
- The typhoid bacillus infects humans only
- chronic carriers are responsible for new cases.
- Cause prolonged fever, inconsistent presence of diarrhea, and extraintestinal manifestations (rash, cervical LAP, seizures, ultered mental statues, ↓vision).
- Characterized by bacteremia & fever precede the final enteric phase.
- blood cultures are + early , stool cultures + after the secondary bacteremia.
- There is fever, headache, and abdominal pain that worsen over 48 to 72 hours with nausea, ↓appetite, and constipation over the first week.
- If untreated, the disease persists for 2 to 3 weeks marked by significant weight loss and occasionally hematochezia or melena.
- Drug of choise: IV ceftriaxone
- Bowel perforation is a common complication in adults, but is rare in children.

## NONTYPHOIDAL *SALMONELLA*

- Produce diarrhea by invading the intestinal mucosa.
- Transmitted by contact with infected animals (chickens, pet iguanas, other reptiles, turtles) or from contaminated food products, such as dairy products, eggs, and poultry.
- **Chronic carriers**, serve as reservoirs and sources of continuous spread.
- Carriers often have **cholelithiasis**.
- A large inoculum, of 1000 to 10 billion organisms, is required because *Salmonella* are killed by gastric acidity.
- The incubation period =6 - 72 hours, usually < 24 hours.

## SHIGELLA DYSENTERIAE

- Cause disease by producing **Shiga toxin**, either alone or combined with tissue invasion.
- The incubation period is 1-7 days; infected adults shed organisms for 1 month.
- Infection is spread by person-to-person contact or by the ingestion of contaminated food with 10 to 100 organisms.
- The **colon** is selectively affected.
- **High fever + seizures + diarrhea.**

- Antibiotic treatment is bacteriologic cure in 80% after 48 hours, reducing the spread of the disease→oral third-generation cephalosporin (ceftriaxone, cefixime, cefpodoxime) or a fluoroquinolone for persons ≥18 years .

## E. COLI

- Only certain strains of *E. coli* produce diarrhea.
- *E. coli* strains associated with enteritis are classified by the mechanism of diarrhea:
  1. Enteropathogenic (E**P**EC), produce disease by liberating toxins that induce upper small intestinal secretion and limit absorption. in newborn nurseries and in daycare centers.
  2. Enterotoxigenic (E**T**EC), produce **heat-labile (cholera-like) enterotoxin**, **heat-stable enterotoxin**, or both. That induces upper small intestinal secretion and limit absorption.causes 40% - 60% of **traveler's diarrhea**.
  3. Enteroinvasive (E**I**EC), invades the colonic mucosa, producing mucosal damage with acute inflammation, similar to *Shigella*.
  4. Entero-hemorrhagic (E**H**EC), especially the *E. coli* O157:H7, produce a **Shiga-like toxin** → hemorrhagic colitis (bloody diarrhea) and most cases of **HUS,** associated with contaminated food, (unpasteurized fruit juices and undercooked beef).
  5. Enteroaggregative (E**A**EC).
- Antibiotic treatment of *E. coli* enteritis is indicated for:
  1. infants < 3 months old with EPEC
  2. patients who remain symptomatic.
  - ♥ not recommended for *E. coli* O157:H7 or HUS because release of toxin may precipitate or worsen the course of HUS.

## CAMPYLOBACTER JEJUNI

- Accounts for 15% of bacterial diarrhea.
- spread by person-to-person contact and contaminated water and food(poultry,milk, cheese).
- The organism invades the mucosa of the jejunum, ileum, and colon→enterocolitis.
- Most patients recover spontaneously before the diagnosis is established.
- Treatment with erythromycin, azithromycin or ciprofloxacin (for persons > 18 years old) initiated within 5 days of the onset of illness speeds recovery and reduces the duration of the carrier state.

## YERSINIA ENTEROCOLITICA

- self-limited, lasting 3 days - 3 weeks.
- Transmitted by pets and contaminated food.
- Infants and young children characteristically have a diarrheal disease.
- Older children have acute lesions of the terminal ileum or acute mesenteric lymphadenitis mimicking appendicitis or Crohn disease.
- Arthritis, rash, and spondylopathy.
- The efficacy of antibiotic treatment is questionable, but children with septicemia or focal infection, such as mesenteric lymphadenopathy→TMP-SMZ; gentamicin or cefotaxime.

## CLOSTRIDIUM DIFFICILE

- causes ***C. difficile*-associated diarrhea**,antibiotic-associated diarrhea secondary to its toxin.
- The organism produces spores that spread from person to person
- *C. difficile*-associated diarrhea follow exposure to any antibiotics, classically : **clindamycin**
- Treatment of *C. difficile* (pseudomembranous colitis) includes discontinuation of the antibiotic and, if diarrhea is severe, oral metronidazole or vancomycin.

## AMEBIASIS

- occurs in warmer climates, and is common among infants in daycare centers
- *E. histolytica* infects the colon; amebae may pass through the bowel wall and invade the liver, lung, and brain.

- Diarrhea is of acute onset, bloody, and contains WBCs.
- The diagnosis is based on identification of the organism in the stool.
- Serologic tests are useful for diagnosis of extraintestinal amebiasis;amebic hepatic abscess.
- treated with metronidazole followed by a luminal agent, such as iodoquinol.

### G. LAMBLIA

- Transmitted by ingestion of cysts, either from contact with an infected individual or from food or freshwater or well water contaminated with infected feces.
- The organism adheres to the microvilli of the duodenal and jejunal epithelium.
- characteristic of giardiasis:
  1. Insidious onset of progressive anorexia
  2. nausea & weight loss
  3. gaseousness & abdominal distention
  4. watery diarrhea
  5. secondary lactose intolerance
- Giardiasis diagnosed by identifying trophozoites or cysts in stool; less often a duodenal aspirate or biopsy of the duodenum or upper jejunum is needed.
  - ◇ *Giardia* is excreted intermittently; three specimens are required.
  - ◇ The Entero-Test is a nylon string affixed to a gelatin capsule, which is swallowed.
  - ◇ After several hours, the string is withdrawn and duodenal contents are examined for *G. lamblia* trophozoites.
- The treatment of *G. lamblia* is with albendazole, metronidazole**,** furazolidone or quinacrine.

### CRYPTOSPORIDIUM

- Causes mild, **watery diarrhea** in immunocompetent persons that resolves without treatment.
- It produces severe, prolonged diarrhea in persons with AIDS.
- No specific treatment is recommended for *Cryptosporidium* in otherwise healthy persons.
- azithromycin or paromomycin and octreotide in persons with HIV/AIDS

## CLINICAL MANIFESTATIONS

- Gastroenteritis accompanied by systemic findings, ex: fever, lethargy, and abdominal pain.
- Viral diarrhea is characterized by:
  1. watery stools, with no blood or mucus
  2. Vomiting present
  3. dehydration may be prominent
  4. low grade Fever
- **Dysentery** is diarrhea involving the colon and rectum, with blood and mucus, foul smelling, and fever (GI bleeding may be significant).
  1. *Shigella*
  2. nontyphoidal *Salmonella*
  3. EIEC, EHEC
  4. *E. histolytica* (**amebic dysentery**)
  5. *C. jejun*
  6. *Y. enterocolitica*
- **Enterotoxigenic disease** is caused by agents that produce enterotoxins, such as *V. cholerae* and ETEC:
  1. Fever is absent or only low grade.
  2. Diarrhea involves the ileum with watery stools without blood or mucus and lasts 3 to 4 days with four to five loose stools per day.
- A chief consideration in management of diarrhea is to assess the **degree of dehydration**.

## LABORATORY AND IMAGING STUDIES

- CBC, electrolytes, BUN, creat, and urinalysis for specific gravity as an indicator of hydration.

- **Stool analysis** for mucus, blood, and leukocytes, which indicate colitis.
  - ◇ Positive fecal leukocyte: invasive or cytotoxin-producing organism, such as *Shigella, Salmonella, C. jejuni,* and invasive *E. coli*.
  - ◇ Minimal fecal leukocytes: Shiga toxin-producing *E. coli* and *E. histolytica*.
  - ◇ Negative for blood and WBCs, and there is no history to suggest contaminated food ingestion, a viral etiology is most likely.
- Rapid diagnostic test for rotavirus in stool should be performed, especially during the winter.
- **Stool cultures** are recommended for patients with:
  1. fever, profuse diarrhea, and dehydration
  2. if HUS is suspected.
- Stool evaluation for parasitic agents should be considered for acute dysenteric illness or in protracted cases of diarrhea in which no bacterial agent is identified.
- Positive blood cultures are uncommon with bacterial enteritis except
  1. *S. typhi* (typhoid fever)
  2. nontyphoidal *Salmonella*
  3. *E. coli* enteritis in very young infants.

## DIFFERENTIAL DIAGNOSIS

- Diarrhea can be caused by :
  1. infection
  2. toxins
  3. gastrointestinal allergy ex. allergy to milk or its components
  4. malabsorption defects
  5. inflammatory bowel disease
  6. celiac disease
  7. acute diseases, such as intussusception and acute appendicitis
  8. Heavy metals that leach into canned food or drinks
  9. Ingestion of preformed enterotoxins produced by bacteria, such as *S. aureus* and *Bacillus cereus*. Short incubation period→ vomiting & cramps ±diarrhea.
- Many noninfectious causes of diarrhea produce chronic diarrhea (>14 days)→ require tests for malabsorption or invasive studies, including endoscopy and small bowel biopsy.
- The most common parasitic food-borne causes: ***C. parvum*** and ***Cyclospora cayetanensis***.

## TREATMENT

- Most infectious causes of diarrhea in children are self-limited.
- Management of viral and most bacterial causes of diarrhea is primarily supportive and consists of correcting dehydration and ongoing fluid and electrolyte deficits.
  - ◇ Hyponatremia is common, and hypernatremia is less common.
  - ◇ Metabolic acidosis from losses of bicarbonate in stool, lactic acidosis resulting from malabsorption or shock
  - ◇ Phosphate retention resulting from transient prerenal-renal insufficiency.
- **Antibiotic treatment is recommended for only some bacterial and parasitic causes.**
  - ◇ Antibiotic treatment of *Salmonella* only for patients with:
    1. *S. typhi* (typhoid fever) and sepsis
    2. bacteremia with signs of systemic toxicity
    3. metastatic foci
    4. age < 3 months with nontyphoidal salmonella
  - ◇ *Vibrio cholerae*: Tetracycline, doxycycline℞, TMP-SMZ

## COMPLICATIONS

- The major complication of gastroenteritis is dehydration and the cardiovascular compromise that can occur with severe hypovolemia.
- Intestinal abscesses can form with *Shigella* and *Salmonella* infections, especially typhoid fever, leading to intestinal perforation, which is a life-threatening complication.

- Severe vomiting associated with gastroenteritis →esophageal tears or aspiration.

## PROGNOSIS

- At least 10% of patients who have typhoid fever shed *S. typhi* for about 3 months, and 4% become chronic carriers.
- The risk of becoming a chronic carrier is low in children.
- Ciprofloxacin is recommended for **adult** carriers with persistent *Salmonella* excretion.

## PREVENTION

- Only two vaccines for the prevention of diarrheal diseases are available.
  a. Three types of typhoid vaccines recommended onlu for travelers to endemic areas:
     1. oral live attenuated vaccine (Ty 21a);
     2. parenteral killed whole cell vaccine
     3. Parenteral capsular polysaccharide vaccine (Vi CPS).
  b. Rotavirus vaccine / association with intussusception.

# VIRAL HEPATITIS

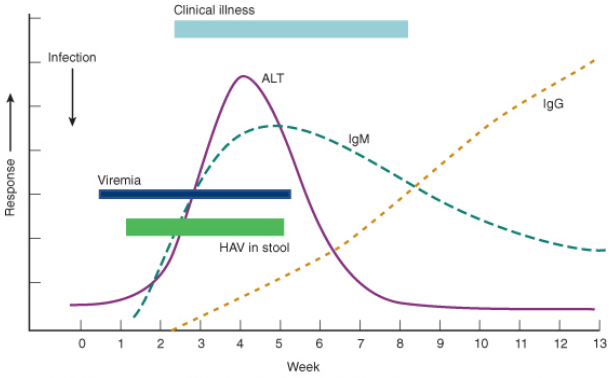
## ETIOLOGY AND EPIDEMIOLOGY

- *Hepatitis*: infections with predominantly hepatic involvement.
- Hepatitis A, B, C, D, and E viruses cause hepatitis with jaundice and elevated transaminases
- Hepatitis A virus (HAV) is transmitted by the fecal-oral route and is highly infectious.
- Hepatitis B and C viruses (HBV, HCV) are less infectious under ordinary circumstances, but can be transmitted in:
  1. infected blood products and body fluids.
  2. vertically from mother to child.
  3. sexual contact, especially homosexual activity and with multiple partners.
- The incidence of new infections has declined 10-fold since routine immunization 1990
- Transmission is decreasing since testing of blood products for HBV and HCV
- still occurs in children by vertical transmission (HBV) in 5% of pregnancies of infected mothers and in adolescents engaging in high-risk sexual behavior or IV drug use.

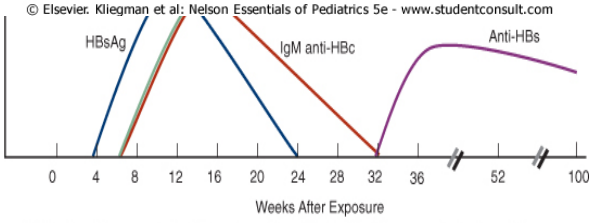
## CLINICAL MANIFESTATIONS

### HAV:

- Average incubation period of 30 days.
- Most cases are self-limited and relatively minor
- Rare cases can manifest as fulminant liver failure.
- Symptoms tend to diminish as the jaundice peaks, heralding recovery.
- HAV is diagnosed by detection of antibodies to the virus. IgM antibodies are detectable early in infection, usually before the onset of clinical illness.









### HBV:

- Incubation period of 1-3 months.

- A prodrome of malaise, fatigue, low-grade fever, and arthralgias → jaundice, pruritus, nausea, and vomiting.
- In some cases, the prodromal illness resembles serum sickness, with prominent migrating polyarticular arthritis, urticaria, macropapular rash, and GN.
- Prodromal symptoms subside as active hepatitis begins.
- As with HAV, young children may not develop clinical hepatitis.
- The incidence of chronic infection is inversely proportional to age. Infants infected in the perinatal period usually develop chronic illness. In older children and adults, the incidence of chronic infection is less than 10%.
- HBV infection is detectable early in the illness by the presence of hepatitis B early antigen (HBeAg) and hepatitis B surface antigen (HBsAg).
- With recovery, cleared HBsAg & HBeAg, and anti-HBs antibody is detected.
- In acute and chronic HBV, antibody to the hepatitis B core protein (anti-HBc) is detectable as IgM at the onset of symptoms and persists as IgG for years afterward.
- If the infection persists as chronic HBV, HBsAg and HBeAg persist, and **anti-HBs antibodies do not appear.**

HCV :

- Incubation period is 6 - 7 weeks.
- Clinical manifestations are absent early in the course, with fatigue, jaundice, and other signs of liver injury occurring later.
- In contrast to other viral hepatitides, hepatitis C becomes chronic in 80% of cases.
- the chronic infection is characterized by slow progression to cirrhosis in 20% of cases, over 30 years.
- A higher incidence and more rapid progression are seen with concurrent liver injury caused by HIV, HBV, alcohol, and fatty liver.
- Acute HCV infection is best diagnosed by HCV RNA in the blood by PCR.
- Within 2 to 3 months of infection, anti-HCV antibodies appear.
- Most cases result in chronic infection→ characterizic:presence of anti-HCV and HCV RNA.

### Laboratory and Imaging Studies

- Tests give an idea of the degree of liver injury and adequacy of hepatocellular synthetic function.
  1. Transaminases (alanine aminotransferase, aspartate aminotransferase)
  2. serum total and direct bilirubin
  3. serum albumin
  4. blood clotting (prothrombin time, partial thromboplastin time)

### Treatment

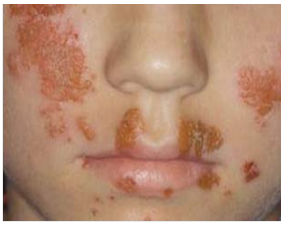
- There is **no specific treatment** for HAV.
- HBV is treated only when transaminases are elevated because response to treatment in individuals without hepatic inflammation is poor. **interferon alfa + DNA polymerase-inhibiting agents lamivudine and adefovir**.
- HCV is best treated by a combination of **interferon alfa + ribavirin**.
- Not like HBV, persistent ↑ transaminases is not associated with ↑efficacy of HCV treatment. Determine HCV genotype before therapy → response to treatment corresponds well to it.

## SUPERFICIAL BACTERIAL INFECTIONS

### Impetigo

- TYPES:

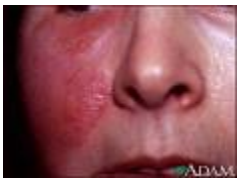
1. **Nonbullous or crusted impetigo**: caused mostly by *S. aureus,* occasionally, group A strep. Begins as a single erythematous papulovesicule → one or many honey-colored, crusted lesions weeping serous drainage.
2. **Bullous impetigo** is an uncommon variant with thin-walled (0.5 to 3 cm) bullae, with erythematous margins resembling second-degree burns, and is associated with *S. aureus* phage type 71.



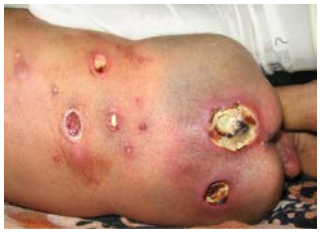
- **most common bacterial skin infection in children**
- Impetigo most frequently occurs on the face, around the nares and mouth, and extremities.
- Fever is uncommon.
- The **diagnosis** by the clinical appearance alone, without the need for culture.
- Recommended **treatment** is topical 2% mupirocin or oral antibiotics.
- Disseminated lesions or that's around the eyes or that are not amenable to topical therapy are treated with oral antibiotics with good activity against *S. aureus,* such as cephalexin.
- **Streptococcal impetigo is associated with ↑risk for poststreptococcal GN but not acute rheumatic fever**
- Antibiotic treatment for streptococcal impetigo may not ↓ the risk for poststreptococcal GN, but ↓ spread of nephritogenic strains to close contacts.
- Children with impetigo should remain out of school or daycare until 24 hours of antibiotic therapy has been completed

## CELLULITIS

- **Cellulitis** is infection involving the subcutaneous tissues and the dermis.
- Caused by *S. aureus,* group A streptococcus, *S. pneumoniae*.
- Hib cellulitis, especially of the face, was common before routine vaccination for Hib.
- Typically presents with indurated, warm, and erythematous macules with indistinct borders that expands rapidly.
- Additional manifestations commonly include:
  1. fever
  2. lymphangitis
  3. regional lymphadenitis
  4. Less often bacteremia → secondary foci and sepsis.
- **Erysipelas**: superficial variant of cellulitis usually caused by group A streptococcus that involves only the dermis.
  - ◇ The rapidly advancing lesions are tender, are bright red in appearance, have sharp margins, and have an "orange peel" quality.



- Aspiration of the leading edge of the cellulitis reveals positive Gram stain and culture in a few cases.
- Blood cultures are recommended.
- Empirical antibiotic treatment is recommended with a first-generation cephalosporin (cefazolin, cephalexin).
- Hospitalization and initial IV antibiotic treatment is recommended for:cellulitis of the face, hands, feet, or perineum or with lymphangitis.
- **Ecthyma**: caused by group A streptococcus and complicates impetigo. Characterized by a lesion with a rim of erythematous induration Arround an eschar, if removed→ shallow ulcer.
- **Ecthyma gangrenosum** is a serious skin infection that occurs in immuno-compromised persons that results from hematogenous spread of septic emboli to the skin.
  - ◇ Classically, caused by *P. aeruginosa* or other gram-negative organisms or *Aspergillus*.
  - ◇ The lesions begin as purple macules that undergo central necrosis to become exquisitely tender, deep, punched-out ulcers 2 to 3 cm in diameter with a dark necrotic base, raised red edges, and sometimes a yellowish green exudate.
  - ◇ Fever usually is present.



- **Necrotizing fasciitis** is the most extensive form of cellulitis and involves the deeper subcutaneous tissues and fascial planes

- ◇ may progress to **myonecrosis**, with involvement of the underlying muscle.
- ◇ It usually is caused by *S. aureus* and group A streptococcus alone or in combination with anaerobic organisms, such as *Clostridium perfringens*.
- ◇ Risk factors include immunodeficiency, recent surgery or trauma, and varicella infection.
- ◇ The lesions progress rapidly with raised or sharply demarcated margins.
- ◇ Subcutaneous gas formation confirms anaerobic infection.
- ◇ MRI delineates the extent of deep tissue involvement.
- ◇ Necrotizing fasciitis is a medical emergency, associated with systemic toxicity and shock.
- ◇ Treatment includes surgical débridement of all necrotic tissues and IV antibiotics, such as clindamycin plus cefotaxime or ceftriaxone, with or without an aminoglycoside.

# HIV AND AIDS

## ETIOLOGY

- The cause of AIDS is HIV, a single-stranded RNA virus of the retrovirus family
- HIV-1 causes 99% of all human cases. HIV-2, which is less virulent.
- HIV infection is a continuously progressive process with a variable period of clinical latency before development of AIDS-defining conditions.
- **Horizontal transmission** of HIV is by unprotected heterosexual or homosexual contact and IV drug use. Transmission by contaminated blood and blood products .
- **Vertical transmission** of HIV from mother to infant may occur transplacentally in utero, during birth, or by breast-feeding. Risk factors for perinatal transmission include:
  5. prematurity
  6. rupture of membranes more than 4 hours
  7. High maternal circulating levels of HIV at delivery.
- Perinatal transmission ↓from 25% to < 8% with antiretroviral treatment of the mother before and during delivery and postnatal treatment of the infant.
- Breastfeeding by HIV-infected mothers ↑ the risk of vertical transmission by 50% to 100%.
- In untreated infants, the mean incubation interval for development of an AIDS-defining condition after vertical transmission is 5 months (range 1 to 24 months)
- Incubation period after horizontal transmission = 7 to 10 years.

## CLINICAL MANIFESTATIONS

- In adolescents and adults, primary infection results in the **acute retroviral syndrome**, which develops after an incubation period of 2 to 6 weeks and consists of :
  1. fever
  2. malaise
  3. weight loss
  4. pharyngitis
  5. lymphadenopathy
  6. maculopapular rash.
- The risk of opportunistic infections & AIDS-defining conditions is related to ↓ CD4 T cells.
- Initial symptoms with vertical transmission vary and may include:
  1. failure to thrive
  2. neurodevelopmental delay
  3. lymphadenopathy
  4. hepatosplenomegaly
  5. chronic or recurrent diarrhea
  6. interstitial pneumonia
  7. oral thrush
- Manifestations that are more common in children than adults with HIV infection include:
  1. recurrent bacterial infections
  2. lymphoid hyperplasia
  3. chronic parotid swelling
  4. lymphocytic interstitial pneumonitis

5. Earlier onset of progressive neurologic deterioration.

- Pulmonary manifestations of HIV infection are common and include *P. jirovecii* (*carinii*) pneumonia, which can present early in infancy as a primary pneumonia characterized by:
  1. fever
  2. hypoxia
  3. tachypnea
  4. retractions
  5. ↑serum LDH

## LABORATORY AND IMAGING STUDIES

- HIV infection can be diagnosed definitively by 1 month of age and in virtually all infected infants by 6 months of age using viral diagnostic assays (RNA PCR, DNA PCR, or virus culture).
- Maternal antibodies may be detectable until 12 to 15 months of age, and a positive serologic test is not considered diagnostic until 18 months of age.
- HIV DNA PCR is the preferred virologic method for diagnosing HIV infection during infancy and identifies 96% at 28 days.
- HIV RNA PCR has 100% sensitivity by 2 to 3 months of age.
- HIV culture is complicated and not routinely performed.
- HIV infection of an infant is confirmed if virologic tests are positive on 2 separate occasions.
- Loss of HIV antibody + no HIV DNA PCR confirms "absence of HIV infection".
- Persistence of HIV antibody at older than 18 months of age → HIV infection.

## COMPLICATIONS

- Pneumococcal sepsis is common
- *P. jirovecii* (*carinii*) pneumonia is treated with high-dose TMP-SMZ and corticosteroids.
- Oral and GI candidiasis is common in children and responds to imidazole therapy.
- VZV infection may be severe and should be treated with acyclovir or other antivirals.
- Recurrent HSV infections also may require antiviral prophylaxis.
- Other common infections : toxoplasmosis, CMV, EBV, salmonellosis, and tuberculosis.
- Children and adults with HIV are prone to malignancie:
  1. non-Hodgkin lymphomas, with the gastrointestinal tract being the most common site.
  2. Leiomyosarcomas are the second most common tumors among HIV-infected children.
  3. Kaposi sarcoma, caused by HHV-8, is distinctly rare in children with HIV.

# BRUCELLA

- *Brucella abortus* (cattle), *B. melitensis* (goat/sheep), *B. suis* (swine), and *B. canis* (dog) are the most common organisms responsible for human disease.
- small, aerobic, non-spore-forming, nonmotile, gram-negative coccobacillary bacteria .
- Routes of infection for these organisms include:
  1. inoculation through cuts or abrasions in the skin
  2. inoculation of the conjunctival sac of the eye
  3. inhalation of infectious aerosols
  4. ingestion of contaminated meat or dairy products.
- Brucellosis is a systemic illness, diagnose in children with history of animal or food exposure.
- Symptoms can be acute or insidious in nature and are usually nonspecific, beginning 2-4 wk after inoculation.
- **the classic triad** : fever, arthralgia/arthritis, and hepatosplenomegaly
- Some present as a fever of unknown origin.
- Other associated symptoms:
  1. abdominal pain,vomiting & diarrhea
  2. headache
  3. rash
  4. night sweats

5. cough & pharyngitis

- The bones and joints frequently are involved, with the sacroiliac joint as well as the hips, knees, and ankles being the most common.
- Invasion of the nervous system occurs in only about 1% of cases.
- Neonatal and congenital infections with these organisms have also been described.
- thrombocytopenia, neutropenia, anemia, or pancytopenia may occur.
- A definitive diagnosis is by recovering the organisms in the blood, bone marrow, or others.
- Isolation of the organism still may require as long as 4 wk from a blood culture sample.
- The serum agglutination test (SAT) is the mostly used and detects antibodies against *B. abortus, B. melitensis,* and *B. suis* but not *B. canis* → lacks the smooth lipopolysaccharide.
- No single titer is ever diagnostic, most patients with acute infections have titers of ≥1 : 160.
- enzyme immunoassay : the most sensitive method for detecting *Brucella* antibodies.
- Doxycycline is the most useful antimicrobial agent + Rifampin or Gentamicin

## Principles of Antibacterial Therapy

| DRUG (TRADE NAMES, FORMULATIONS) | INDICATIONS (MECHANISM OF ACTION) AND DOSING | COMMENTS |
|---|---|---|
| **Amikacin sulfate** IV over 30-60 min. **Gentamicin Tobramycin** | Aminoglycoside : active against gram-negative bacilli (*E.coli, Klebsiella, Proteus, Enterobacter, Serratia, Pseudomonas).* | Anaerobes, *Streptococcus* (*S. pneumoniae*) are resistant. ototoxicity ,nephrotoxicity. eliminated renally. |
| **Neomycin sulfate.** | Aminoglycoside used for topical application or orally before surgery to decrease gastrointestinal flora (nonabsorbable) and hyperammonemia. | abdominal cramps, diarrhea, rash. ototoxicity and nephrotoxicity if absorbed. |
| **Amoxicillin** Capsule: 250, 500 mg. | Penicillinase-susceptible β-lactam: gram-positive pathogens except *Staphylococcus, Salmonella, Shigella, Neisseria, E. coli,* and *Proteus mirabilis.* | Rash, diarrhea, abdominal cramping. Drug eliminated renally. *Drug interaction:* Probenecid. |
| **Amoxicillin-clavulanate** Augmentin. Children: 20-45 mg/kg *2 PO. 80-90 mg/kg/24 hr PO for otitis media. | β-Lactam (amoxicillin) and β-lactamase inhibitor (clavulanate) ↑amoxicillin activity against pencillinase-producing bacteria. *S. aureus* (not methicillin-resistant organism), *Streptococcus, Haemophilus influenzae, Moraxella catarrhalls, E. coli, Klebsiella, Bacteroides fragilis.* | diarrhea, rash. Drug eliminated renally..Higher dose active against penicillin tolerant /resistant *S. pneumoniae.* |
| **Nafcillin sodium** | Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci. | β-Lactam safety profile (rash, eosinophilia), phlebitis; painful given IM; *Adverse effect:* Neutropenia. |
| **Oxacillin sodium** | Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci. | *Cautions:* (rash, eosinophilia). Moderate oral bioavailability (35-65%). renally eliminated. *Adverse effect:* Neutropenia. |
| **Penicillin G** | Penicillin active against most gram-positive cocci; *S. pneumoniae* (resistance is increasing), group A streptococcus, and some gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*). | *Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with marked renal disease. renally eliminated. |
| **Penicillin G, benzathine Bicillin.** Injection. | Long-acting repository form of penicillin effective in the treatment of infections responsive to persistent, low penicillin concentrations (1-4 wk), e.g., group A streptococcus pharyngitis, rheumatic fever prophylaxis. | *Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy. Administer by IM injection only. renally eliminated. |
| **Ampicillin-sulbactam** | β-Lactam (ampicillin) β-lactamase inhibitor (sulbactam) enhances ampicillin activity against penicillinase-producing bacteria: *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, E. coli, Klebsiella, B. fragilis.* | *Cautions:* diarrhea, rash. Drug eliminated renally. *Note:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae.* |

| | | |
|---|---|---|
| **Azithromycin** | Azalide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Mycoplasma, Legionella, C. trachomatis.*<br>Group A Streptococcus pharyngitis: 12 mg/kg/24 hr PO for 5 days.Uncomplicated *C. trachomatis* infection: single 1 g dose PO. | *Note:* very long half-life permitting once-daily dosing. No metabolic-based drug interactions (unlike erythomycin and clarithromycin), limited gastrointestinal distress. |
| **Cephalexin** Keflex **Cefadroxil,Cephradine Cefazolin**. | 1st generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella,* and *Proteus.* | *Caution:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. |
| **Cefotetan disodium** Injection. | 2nd generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus,* and *Bacteroides.* Inactive against *Enterobacter.* | Highly protein-bound, poor CNS penetration; β-Lactam safety profile (rash, eosinophilia), disulfiram-like reaction with alcohol. Renally eliminated (~20% in bile). |
| **Cefoxitin sodium**. Injection. | 2nd generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus,* and *Bacteroides.* Inactive against *Enterobacter.* | *Cautions:* Poor CNS penetration; β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Painful given intramuscularly. |
| **Cefaclor** Capsule: 250, 500 mg. | 2nd generation cephalosporin active against *S. aureus, Streptococcus* including *S. pneumoniae, H. influenzae, E. coli, Klebsiella,* and *Proteus.* | *Cautions:* β-Lactam safety profile (rash, eosinophilia) with high incidence of serum sickness. Renally eliminated. |
| **Cefprozil Cefuroxime** Zinacef. | 2nd generation cephalosporin active against *S. aureus, Streptococcus, H. Influenzae, E. coli, M. catarrhalis, Klebsiella,* and *Proteus.* | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. |
| **Cefixime** | 3rd generation cephalosporin active against *Streptococcus, H. influenzae, M. catarrhalis, N. gonorrhoeae, S. marescens,* and *P. vulgaris.* No antistaphylococcal or antipseudomonal activity. | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. |
| **Cefoperazone sodium** Injection. | 3rd generation cephalosporin active against many gram-positive and gram-negative pathogens. | weak antipseudomonal activity. hepatically eliminated in bile.Disulfiram-like reaction with alcohol. |
| **Cefotaxime sodium** Claforan. Injection. | 3rd generation cephalosporin active against gram-positive and gram-negative pathogens. No antipseudomonal activity. | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. 2.2 mEq sodium/ gram. |
| **Cefpodoxime proxetil** | 3rd generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, N. gonorrhoeae, E. coli, Klebsiella,* and *Proteus.* No antipseudomonal activity. Uncomplicated gonorrhea: 200 mg PO as single-dose therapy. | β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. Increased bioavailability with food. |
| **Ceftriaxone sodium** Rocephin. Injection. | 3rd generation cephalosporin active against gram-positive and gram-negative pathogens. No antipseudomonal activity. Very potent and β-lactamase stable. | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Eliminated via kidney (33-65%) and bile; can cause sludging. Long half-life.. |
| **Cefepime** Maxipime. Injection. | Expanded-spectrum, 4th generation cephalosporin active against many gram-positive and gram-negative pathogens, including many multi-drug-resistant pathogens. | *Adverse events:* Diarrhea, nausea, vaginal candidiasis<br>*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. |
| **Cefdinir** | Extended-spectrum, semi-synthetic cephalosporin. | *Cautions:* ↓ in renal dz (crea. clearance <60 mL/min). |
| **Clarithromycin**. | Macrolide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Legionella, Mycoplasma,* and *C. trachomatis.* | Adverse events less than erythromycin; GI upset, dyspepsia, nausea, cramping. |
| **Erythromycin** | Bacteriostatic macrolide antibiotic most active against gram-positive organisms, *Corynebacterium diphtheriae,* and *Mycoplasma pneumoniae.* May also be used to promote gastrointestinal motility and improve feeding intolerance in preterm infants. | Motilin agonist → abdominal cramping, nausea, vomiting, diarrhea. Associated with hypertrophic pyloric stenosis in young infants. |
| **Ofloxacin** | Quinolone antibiotic for treatment of conjunctivitis or corneal ulcers (ophthalmic solution); and otitis externa and chronic suppurative otitis media (otic solution) caused by susceptible gram-positive, gram-negative, anaerobic bacteria, or *Chlamydia trachomatis.* | *Adverse events:* Burning, stinging, eye redness (ophthalmic solution), dizziness with otic solution if not warmed. |
| **Chloramphenicol** | Broad-spectrum protein sythesis inhibitor active against gram-positive and gram-negative bacteria, *Salmonella,* vancomycin-resistant *Enterococcus* | *Cautions:* **Gray-baby syndrome** (from too-high dose in neonate), bone marrow suppression aplastic anemia (monitor |

| | | |
|---|---|---|
| | *faecium, Bacteroides, Mycoplasma, Chlamydia,* and *Rickettsia; Pseudomonas* resistant. | hematocrit, free serum iron). |
| **Clindamycin** Administer slow IV over 30-60 min. | Protein synthesis inhibitor active against most gram-positive aerobic and anaerobic cocci except *Enterococcus.* | Diarrhea, nausea, C. difficile-associated colitis, rash. Topically active as an acne treatment. |
| **Co-trimoxazole** (trimethoprim-sulfamethoxazole; TMP-SMZ) | Antibiotic combination with sequential antagonism of bacterial folate synthesis with broad antibacterial activity: *Shigella, Legionella, Nocardia, Chlamydia, Pneumocystis carinii.* | Sulfonamide skin reactions: rash, erythema multiforme, Stevens-Johnson syndrome, nausea, leukopenia. Renal and hepatic elimination; reduce dose in renal failure. |
| **Demeclocycline** **Doxycycline** | Tetracycline active against most gram-positive cocci except Enterococcus, many gram-negative bacilli, anaerobes, *Borrelia burgdorferi* (Lyme disease), *Mycoplasma,* and *Chlamydia.* | *Cautions:* Teeth staining, possibly permanent (if administered <8 yr of age) prolonged use: DI, nausea photosensitivity, vomiting, diarrhea, superinfections. |
| **Meropenem** | Carbapenem antibiotic active against broad-spectrum gram-positive cocci and gram-negative bacilli including *P. aeruginosa* and anerobes. | *Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem. 80%renal remove. |
| **Metronidazole** Flagyl: IV over 30-60 min. | Highly effective in the treatment of infections due to anaerobes. | Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol. ↓hepatic Dz. |
| **Nitrofurantoin** | Effective in the treatment of lower urinary tract infections caused by gram-positive and gram-negative pathogens. | *Cautions:* Vertigo, dizziness, rash, jaundice, interstitial pneumonitis. Do not use: moderate-severe renal dz |
| **Sulfadiazine** | Sulfonamide antibiotic primarily indicated for the treatment of lower urinary tract infections due to *E. coli, P. mirabilis,* and *Klebsiella.*Toxoplasmosis, Rheumatic fever prophylaxis | Rash,**Stevens-Johnson syndrome** , nausea, leukopenia, crystalluria. Renal & hepatic elimination; avoid use with renal disease. |
| **Sulfisoxazole** **Sulfamethoxazole** | Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections due to susceptible bacteria. | Rash,**Stevens-Johnson syndrome** , nausea, leukopenia, crystalluria. Renal & hepatic elimination; avoid use with renal disease. |
| **Trimethoprim** | Folic acid antagonist effective in the prophylaxis and treatment of *E. coli, Klebsiella, Proteus mirabilis,* and *Enterobacter* urinary tract infections; *P. carinii* pneumonia. | Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash. |
| **Vancomycin** Infuse IV over 45-60 min. | Glycopeptide antibiotic active against most gram-positive pathogens including *Staphylococcus* (including methicillin-resistant *S. aureus* and coagulase-negative staphylococci), *S. pneumoniae* including penicillin-resistant strains, *Enterococcus* (resistance is increasing), and *Clostridium difficile*-associated colitis | Ototoxicity and nephrotoxicity. Flushing (**red-man syndrome**) associated with rapid IV infusions, fever, chills, phlebitis (central line is preferred). Renally eliminated. |

## NOTES:

- Cephalosporins: bactericidal, disrupt synthesis of bacterial wall layers, each newer generation → gram +
  - **1st generation**: cephalexin, cefadroxil,cefadine, cefalordine, cefazolin, cefaglycine.
  - **2nd generation**: cefaclor, cefonicid, cefuroxime (PO:zinnat, IV:zinacef), ceftin, cefprozil.
  - **3ed generation**: cefperazone, ceftazidime, ceftriaxonem ceftaxime, cefixime, ceftamet, cefmenoxime.
  - **4th generation**: cefpime, cefozopran, cefpriome, cefquinome,
- Cephalosporine against pseudomonas: ceftazidime, cefsulodin, cefpiramide, ceftriaxone, cefmenxime.
- Macrolides: inhibit protein synthesis ( erythromycin, azithromycin, clarithromycin), DOC: atypical bacteria, SE: most common GI ubset, rash.
- Aminoglycosides (Gentamicin, Amikacin): bactericidal, again gram (-), not absorbed orally, SE: ototoxicity, nephrotoxicity, peripheral neuritis.
- Deep seted infections as infective endocarditis give: PencillinG
- DOC for staph.aureus is cloxa "IV flucacillin"
- Tetracycline indications: Brucella & Ricktsial infection.

# Digestive system

# ORAL CAVITY

## EFFECTS OF SYSTEMIC DISEASE ON THE ORAL CAVITY

- anticholinergic properties→ ↓saliva production → ↑ **dental caries and parotitis**.
- Tetracyclines taken before the eruption of the permanent teeth →**stain the enamel**.
- Excessive fluoride in vitamin preparations or in drinking water → **mottled teeth**.
- **Gingival hypertrophy** , caused by:
  1. cyclosporine
  2. phenytoin
  3. calcium channel blockers**.**
- GER → **enamel erosion and caries**.
- Neonatal hyperbilirubinemia →bluish black **discoloration of the deciduous teeth**.
- Renal failure →**mottled enamel of the permanent teeth**.
- Congenital syphilis → marked **abnormalities in the shape of teeth** (incisors & molars).
- CD and Behçet disease → **oral ulcers**.
- Peutz-Jeghers syndrome & Addison disease→ **lips & buccal mucosa pigmentation** .
- immunodeficiency and diabetes → **Candidiasis**.
- Leukemic infiltrates → **gum hyperplasia and bleeding**
- Treatment of neoplastic conditions → **severe mucositis**.
- Lymphoma→ may present as **mass lesions of the buccal cavity**.
- *Osteogenesis imperfecta* → **abnormal dentin** and risk of **caries**.
- *ectodermal dysplasias* → **malformed or missing teeth**.
- Pierre Robin syndrome → **micrognathia and cleft palate**.
- Disorders resulting in facial dysmorphism → **dental malocclusion** & mandibular function:
  1. mandibulofacial dysostosis
  2. Crouzon syndrome
  3. conditions associated with dwarfism

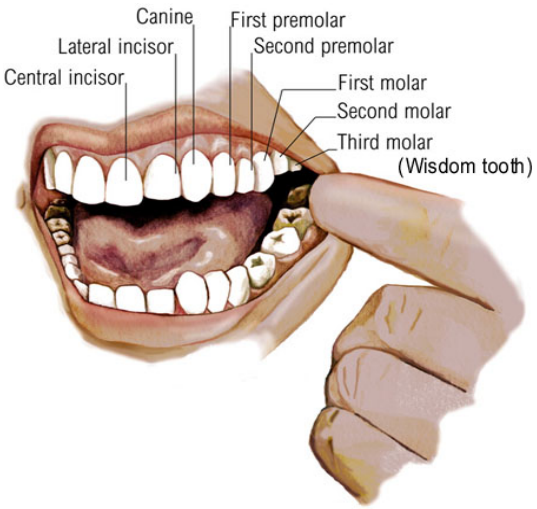
## DECIDUOUS AND PRIMARY TEETH

- Most infants are born without teeth.
- *Natal teeth* : present at birth, are supernumerary, and poorly attached. No treatment is necessary except if they are causing difficulties with feeding or injuries to the tongue.
- **The lower central incisors are the first to erupt**→the upper central incisors→ lateral incisors→first molars→ bicuspids.
- **Delayed eruption** occurs in association with:
  1. hypopituitarism
  2. hypothyroidism
  3. Gaucher disease
  4. Down syndrome
  5. osteopetrosis
  6. cleidocranial dysplasia
  7. rickets.
- **Deciduous teeth** begin to be replaced by the permanent teeth at around age **6 years**.
- The sequence of replacement is similar to that of the appearance of deciduous teeth.

**NOTE:**
No. of deciduous teeth= 20 tooth
No. of permanent teeth= 32 tooth

### TIME OF ERUPTION OF THE PRIMARY AND PERMANENT TEETH

| | PRIMARY, AGE (MO) | | PERMANENT, AGE (YR) | |
|---|---|---|---|---|
| TOOTH TYPE | UPPER | LOWER | UPPER | LOWER |
| Central incisor | 6 ± 2 | 7 ± 2 | 7-8 | 6-7 |
| Lateral incisor | 9 ± 2 | 7 ± 2 | 8-9 | 7-8 |
| Cuspids | 18 ± 2 | 16 ± 2 | 11-12 | 9-10 |
| First bicuspids | - | - | 10-11 | 10-12 |
| Second bicuspids | - | - | 10-12 | 11-12 |
| First molars | 14 ± 4 | 12 ± 4 | 6-7 | 6-7 |
| Second molars | 24 ± 4 | 20 ± 4 | 12-13 | 11-13 |
| Third molars | - | - | 17-21 | 17-21 |



# DENTAL CARIES

## ETIOLOGY

- Dental caries, "cavities," : result of interactions between: the tooth enamel+ dietary carbohydrates+ oral flora.
- ↑susceptibility if the enamel is abnormal or hypoplastic.
- ***Streptococcus mutans***: adhere to and colonize the teeth, survive at low pH, and produce acids during fermentation of carbohydrates → dental caries.
- The diet has a significant role.
- "**bottle mouth**," or **baby bottle caries**: condition results from the practice of allowing an infant to have a bottle in the mouth for prolonged periods, especially during sleep, and with sweet beverages or milk in the bottle→ allows bacteria to have continuous substrate for acid production → destruction of multiple teeth, especially the upper incisors.
- Sticky sweet foods, candies, also offer a mechanism for prolonged presence of carbohydrate at the surface of the tooth.

## EPIDEMIOLOGY AND TREATMENT

- Risks : lack of dental care and poor socioeconomic status (developing countries).
- Baby bottle caries are seen in 50% to 70% of low-income infants.
- Treatment of caries is with dental restorative surgery.
- When not properly treated, dental decay results in inflammation and infection of the dental pulp and alveolar bone→ abscess and facial space infections.

## PREVENTION

- **Avoiding inappropriate use of bottles and excessive sweets** is a commonsense remedy for baby bottle caries.
- **Oral hygiene** offers some protection, but young children (<8 years old) do not have the ability to brush their own teeth adequately; brushing should be done by the parents.
- **Fluoride supplementation** of community water supplies to a concentration of 1 ppm is highly effective in reducing dental caries.
- Excessive fluoride supplementation causes fluorosis, a largely cosmetic defect of chalky white marks and brown staining of the teeth.

# CLEFT LIP AND PALATE

## EPIDEMIOLOGY

- 1 in 700 infants.
- *The combined cleft lip/palate type has a male predominance.*
- Clefting occurs with two possible patterns: isolated soft tissue cleft palate or cleft lip with or without associated clefts of the hard palate.
- *Isolated cleft palate is associated with a higher risk of other congenital malformations.*

## ETIOLOGY

- Cleft lip is due to hypoplasia of the mesenchymal tissues + subsequent failure of fusion.
- There is a strong genetic component; the risk is higher in children with affected first-degree relatives.
- Monozygotic twins are affected with only 60% concordance, suggesting other nongenomic factors.
- Environmental factors during gestation also increase risk, including:
  1. *drugs (phenytoin, valproic acid, thalidomide),*
  2. maternal alcohol and tobacco use
  3. dioxins and other herbicides
  4. possibly high altitude

## CLINICAL MANIFESTATIONS

- Cleft lip can be unilateral or bilateral and associated with cleft palate and defects of the alveolar ridge and dentition
- creating problems with speech and swallowing
- Feeding is a significant problem

### TREATMENT

- squeeze-bottle feedings, special nipples, nipples with attached shields to seal the palate, and gastrostomy in severe cases.
- *Surgical closure of the cleft lip is usually done by 3 months of age.*
- Closure of the palate follows, usually before 1 year of age.

### COMPLICATIONS

- Speech is nasal as a result of the cleft palate.
- Frequent episodes of otitis media are common

## TEETHING

### CLINICAL MANIFESTATIONS

- the most common symptoms observed
  1. Fussiness
  2. sleep disturbance
  3. gum inflammation
  4. drooling
- Fevers, diarrhea, and a multitude of other complaints have been popularly blamed on teething without justification.

### TREATMENT: conservatively

- Nonpharmacologic management includes the use of rubbery teething toys that help the child "chew" the tooth through the gums, teething biscuits, and even frozen bananas.
- Pharmacologic management:
  1. Topical anesthetics can be used in small amounts with good effect.
  2. acetaminophen or NSAIDs to reduce pain or inflammation may be helpful.
- There is no evidence that bronchitis, ear infections, or pulmonary infections are causally related to teething.

## THRUSH

### EPIDEMIOLOGY

- Oropharyngeal *Candida albicans* infection is common.
- acquired in the birth canal or from the environment.
- Persistent infection is common in breastfed infants as a result of colonization or infection of the mother's nipples.
- Thrush in normal older patients suggest the possibility of :
  1. immunodeficiency
  2. broad-spectrum antibiotic
  3. diabetes
- Common conditions associated with severe thrush:
  1. innate immunodeficiency
  2. AIDS
  3. anti-transplant rejection drug therapy
  4. cancer chemotherapy

### CLINICAL MANIFESTATIONS

- Thrush as white plaques, with a "fuzzy" appearance, on oral mucous membranes.
- Oropharyngeal candidiasis is sometimes painful (especially if associated with esophagitis) and can interfere with feeding.
- When scraped with a tongue depressor, the plaques are difficult to remove, and the underlying mucosa is inflamed and friable.
- Clinical diagnosis is adequate, but may be confirmed by fungal culture or potassium hydroxide smear.

### TREATMENT

- Topical nystatin or azole anti-fungal agents. Nystatin therapy is started first, but treatment response is slow and often incomplete.

- Fluconazole & itraconazole, orally, have a systemic effect and an excellent response rate.
- When the mother's breasts are infected and painful→ treating her at the same time.
- Because thrush is self-limited in newborns, withholding therapy in asymptomatic infants and treating only persistent or severe cases is a reasonable approach.

# ESOPHAGUS AND STOMACH

## GASTROESOPHAGEAL REFLUX

### ETIOLOGY AND EPIDEMIOLOGY

- GER: effortless retrograde movement of gastric contents upward into the esophagus or oropharynx.
- In infancy, GER is not always an abnormality.
- **Physiologic GER** ("spitting up") is normal in infants < 8 -12 months old.
- 50% of all infants are reported to spit up at 2 months of age.
- Infants who regurgitate stomach contents meet the criteria for physiologic GER so long as they maintain adequate nutrition and have no signs of respiratory or peptic complications.
- Factors involved in GER include:
  1. liquid diet
  2. horizontal body position
  3. short, narrow esophagus
  4. small, noncompliant stomach
  5. frequent, relatively large volume feedings
  6. immature lower esophageal sphincter (LES)
- most stop spitting up by 9- 12 months of age, As infants grow they:
  1. spend more time upright
  2. eat more solid foods
  3. longer and larger diameter esophagus
  4. larger and more compliant stomach
  5. Lower caloric needs per unit of body weight.

### CLINICAL MANIFESTATIONS

- The presence of GER is easy to observe in an infant who spits up.
- In older children, the refluxate is kept down by reswallowing.
- GER may be suspected by associated symptoms, such as:
  1. heartburn
  2. cough
  3. dysphagia (trouble swallowing)
  4. wheezing
  5. aspiration pneumonia
  6. hoarse voice
  7. failure to thrive
  8. recurrent otitis media or sinusitis
- In severe cases of esophagitis, there may be laboratory evidence of anemia and hypoalbuminemia secondary to esophageal bleeding and inflammation.
- **Pathologic GER** is diagnosed after 18 months of age or if there are complications, such as esophagitis, respiratory symptoms, or failure to thrive, in younger infants.
- In older children, normal protective mechanisms against GER include :
  1. antegrade esophageal motility
  2. tonic contraction of the LES
  3. the geometry of the gastroesophageal junction.
- Abnormalities that cause GER in older children and adults include :
  1. reduced tone of the LES
  2. transient relaxations of the LES
  3. esophagitis (which impairs esophageal motility)
  4. increased intra-abdominal pressure as cough (asthma or cystic fibrosis)
  5. hiatal hernia.

- When esophagitis develops as a result of acid reflux, esophageal motility and LES function are impaired further, creating a cycle of reflux and esophageal injury.

## Laboratory and Imaging Studies

- Effortless regurgitation is sufficient for clinical Dx.
- Indication of diagnostic studies are :
  1. persistent symptoms
  2. complications
  3. possibility of GER in the absence of regurgitation
- A child with recurrent pneumonia, chronic cough, or apneic spells without overt emesis may have occult GER.
- Diagnostic studies are:
  1. **Barium upper GI series**: R/O gastric outlet obstruction, malrotation, or other anatomic contributors to GER. negative barium study does *not* R/O GER.
  2. **24-hour esophageal pH probe monitoring**, uses a pH electrode placed transnasally into the distal esophagus, with continuous recording of esophageal pH. Data gathered for 24 hours→ number and temporal pattern of acid reflux analyzed.
  3. **esophageal impedance monitoring**, records the migration of electrolyte rich gastric fluid in the esophagus.
  4. **Endoscopy** : rule out esophagitis, esophageal stricture, and anatomic abnormalities.

## Treatment

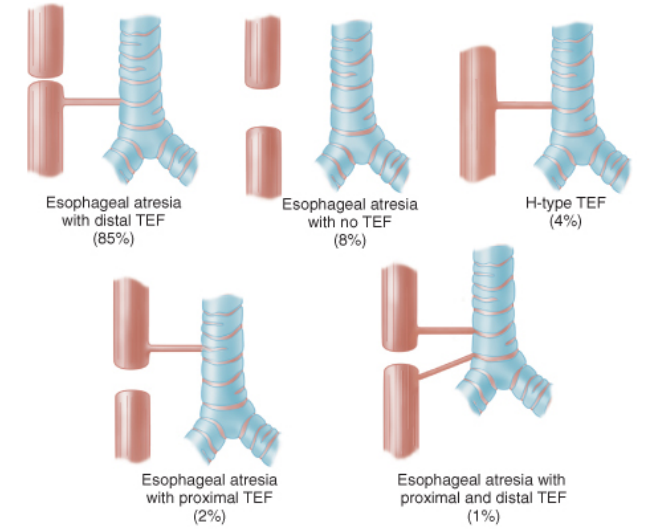
- healthy young infants ("well-nourished, happy spitters"), *no treatment*, other than a towel on the shoulder of the caretaker.
- infants with complications of GER, pharmacologic therapy with a **proton-pump inhibitor.**
- **Prokinetic drugs**, such as metoclo-pramide, may be helpful by enhancing gastric emptying and increasing LES tone, but are seldom very effective.
- Severe symptoms persist despite medication, or if life-threatening aspiration → Fundoplication procedures, such as the Nissen operation.
- When In children with a severe neurologic defect who cannot tolerate oral or gastric tube feedings, feeding jejunostomy is considered as an alternative to fundoplication.

### Treatment of Gastroesophageal Reflux

| Therapies | Comments |
|---|---|
| **Conservative Therapies** | |
| Towel on caregiver's shoulder | Cheap, effective. Useful only for physiologic reflux |
| Thickened feedings | Reduces number of episodes, enhances nutrition |
| Smaller, more frequent feedings | Can help some. Be careful not to *underfeed* child |
| Avoidance of tobacco smoke & alcohol | Always a good idea. May help reflux symptoms |
| Abstaining from caffeine | Inexpensive, offers some benefit |
| Positional therapy-upright in seat, elevate head of crib or bed | Prone positioning with head up is helpful, but *not* for young infants due to risk of SIDS |
| **Medical Therapy** | |
| Proton-pump inhibitor | Effective for heartburn and esophagitis |
| $H_2$ receptor antagonist | Reduces heartburn, less effective for healing esophagitis |
| Metoclopramide | Enhances stomach emptying and LES tone. Real benefit is often minimal |
| **Surgical Therapy** | |
| Nissen or other fundoplication procedure | For life-threatening or medically unresponsive cases |
| Feeding jejunostomy | Useful in child requiring tube feeds. Delivering feeds downstream eliminates GERD |

# ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

## ETIOLOGY AND EPIDEMIOLOGY





- The esophagus & trachea develop in close proximity to each other during 4- 6 wks of fetal life.
- Defects in the mesenchyme separating these two structures result in (TEF)
- Often in association with other anomalies (renal, heart, spine, limbs).
- This defect occurs in about 1: 3000 live births.
- TEF is *not thought to be a genetic defect* because concordance between monozygotic twins is poor.

## CLINICAL MANIFESTATIONS

- The most common forms of TEF occur with esophageal atresia.
- The "H-type" TEF without atresia is uncommon, as is esophageal atresia without TEF .
- Associated defects include the **VACTERL** association:
  1. **v**ertebral anomalies (70%)
  2. **a**nal atresia (imperforate anus) (50%)
  3. **c**ardiac anomalies (30%)
  4. **TEF** (70%)
  5. **r**enal anomalies (50%)
  6. **l**imb anomalies (polydactyly, forearm defects, absent thumbs, syndactyly) (70%).
- A **single artery umbilical cord** is often present at birth.
- Infants with esophageal atresia have a history of **polyhydramnios** and exhibit drooling and have mucus and saliva bubbling from the nose and mouth.
- Patients with a TEF are vulnerable to ***aspiration pneumonia***.
- If TEF is suspected→ delay the first feeding until a diagnostic study is performed.

## LABORATORY AND IMAGING STUDIES

- The simplest test for TEF is to attempt gently to place a 10F or larger tube via the mouth into the stomach. The passage of the tube is blocked at the level of the atresia.
- Confirmation is by chest x-ray with the tube coiled in the esophageal pouch. Air can be injected through the tube to outline the atretic pouch.
- Don't use Barium because of extreme risk of aspiration, but a tiny amount of dilute water-soluble contrast can be given carefully, then aspirated when the defect is clearly shown.

## TREATMENT AND PROGNOSIS

- The treatment of TEF is surgical.
- A thoracotomy provides access to the mediastinum via extrapleural dissection. The fistula is divided and ligated. The esophageal ends are approximated and anastomosed.
- In some cases, primary anastomosis cannot be performed because of a long gap between the proximal and distal esophagus→ pulling up the stomach, elongating the esophagus by myotomy, and simply delaying esophageal anastomosis and providing continuous suction to the upper pouch and allowing for growth.

## COMPLICATIONS

- The surgically reconstructed esophagus is not normal and is prone to:
  1. poor motility
  2. GER
  3. anastomotic stricture
  4. recurrent fistula
  5. leakage
- The trachea also is malformed; tracheomalacia is common.

# CAUSTIC INJURIES AND PILL ULCERS

## ETIOLOGY AND EPIDEMIOLOGY

- In adolescents, caustic ingestion injuries are usually the result of suicide attempts.
- In toddlers, the accidental ingestion of household cleaning products is common.
- Lye-based drain cleaners, especially liquid products, cause the worst injuries because they are swallowed easily and liquefy tissue rapidly.
- Granular products are less likely to cause esophageal injury during accidental exposures because they burn the tongue and lips and often are expelled before swallowing.
- Full-thickness burns can occur in seconds.
- **Pill ulcers** occur when certain medications (tetracyclines and NSAIDs) are swallowed without sufficient liquids, allowing prolonged direct contact of the pill with the esophageal mucosa.

## CLINICAL MANIFESTATIONS

- *immediate and severe mouth pain*.
- The child cries out, drools, spits, and usually drops the container immediately.
- *Burns of the lips and tongue are visible almost immediately*.
- These burns clearly indicate the possibility of esophageal involvement, although esophageal injury can occur in the absence of oral burns.
- Symptoms may not be present
- Evaluation by endoscopy is indicated with any significant history of caustic ingestion.
- Pill injury causes severe *chest pain* and often *prominent odynophagia* (painful swallowing) and *dysphagia*.

## LABORATORY AND IMAGING STUDIES

- A **chest x-ray** should be obtained to rule out aspiration and to inspect for mediastinal air.
- **The child should be admitted to the hospital and given IV fluids until endoscopy.**
- Most endoscopists perform the initial endoscopy soon after injury, when the patient has been stabilized.
- The true extent of burns may not be endoscopically apparent immediately, but delayed endoscopy can increase the risk of perforation.
- The extent of injury and severity of the burn should be carefully determined.
- Risk of subsequent esophageal strictures is related to the degree of burn and whether the injury is circumferential.

## TREATMENT

- A nasogastric tube can be placed over a guidewire at the time of the initial endoscopy to provide a route for feeding and to stent the esophagus.
- Systemic steroid use does not always reduce the risk of stricture.
- Broad-spectrum antibiotics should be prescribed if infection is suspected.

## COMPLICATIONS

- Esophageal strictures, if they occur, usually develop within 1 to 2 months and are treated with balloon dilation. The risk of perforation during dilation is significant.
- When esophageal destruction is severe, surgical reconstruction of the esophagus using stomach or intestine may be necessary.

# ESOPHAGEAL FOREIGN BODIES

## ETIOLOGY AND EPIDEMIOLOGY

- Young children often place nonfood items in their mouths. When these items are swallowed, they may become lodged in the upper esophagus at the thoracic inlet.
- ***The most common objects are coins*.**
- Smaller coins may pass harmlessly into the stomach, where they rarely cause symptoms.
- Predisposing factors to food impactions are Children with:
  1. prior history of esophageal atresia
  2. with poor motility secondary to GER
  - ♣ Seldom occur in the normal esophagus.

## Clinical Manifestations

- Some children are asymptomatic.
- Most exhibit some degree of ***drooling, food refusal, or chest discomfort***.
- Older children can *point to the region* of the chest where they feel the object to be lodged.
- *Respiratory symptoms* tend to be minimal, but cough present, when the esophagus is completely blocked by a large object, such as a piece of meat presses on the trachea.

## Diagnosis

- Plain **chest and abdominal radiographs** should be taken when foreign body ingestion is suspected. Metallic objects are easily visualized.
- A plastic object often can be seen if the child is given a small amount of dilute x-ray contrast material to drink.
- **endoscopy** is probably safer and more definitive.

## Treatment

- **Endoscopy** is necessary in most cases to remove an esophageal foreign body.
- Various devices can be used, depending on object size, shape, and location. Coins usually are grasped with a special-purpose forceps and removed. Nets, baskets, and snares also are available.
- Whenever objects that may threaten the airway are being recovered, endoscopy should be performed with endotracheal intubation and under general anesthesia.

## Complications

- Sharp objects may **lacerate or perforate the esophagus**; smooth objects present for a long time also may result in perforation.
- Corrosive objects, such as zinc-containing pennies and disc batteries, can cause considerable local tissue injury and esophageal perforation.

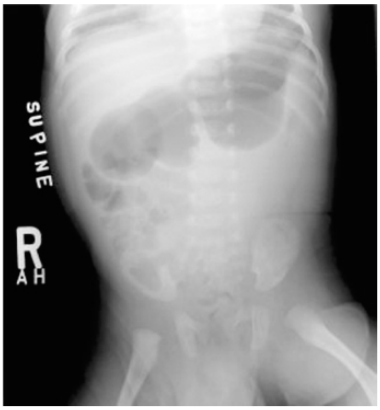
# PYLORIC STENOSIS

## Etiology and Epidemiology

- ***Acquired condition*** caused by hypertrophy and spasm of the pyloric muscle, resulting in gastric outlet obstruction.
- Its cause is unknown, but it seems that a *deficiency in inhibitory neuronal signals*, mediated by nitric oxide, is likely.
- occurs in 6- 8 per 1000 live births
- 5:1 male predominance
- more common in first-born children.

## Clinical Manifestations

- Infants with pyloric stenosis *typically begin vomiting during the first month of life,* but onset of symptoms may be delayed.
- The emesis becomes increasingly more frequent and forceful as time passes.
- Vomiting in pyloric stenosis differs from spitting up because of its extremely forceful and often projectile nature.
- The vomited material never contains bile because the gastric outlet obstruction is proximal to the duodenum.
- Affected infants are ravenously(نهم) hungry early in the course of the illness, but become more lethargic with increasing malnutrition and dehydration.
- The stomach becomes massively enlarged with retained food and secretions, and gastric **peristaltic waves** are often visible in the left upper quadrant.
- A hypertrophied pylorus (the "olive") may be palpated.
- As the illness progresses, very little of each feeding is able to pass through the pylorus, and the child becomes progressively thinner and more dehydrated.



## Laboratory and Imaging Studies

- Repetitive vomiting of gastric contents → loss of hydrochloric acid→ classic laboratory finding = **hypochloremic hypokalemic metabolic alkalosis**
- elevated BUN secondary to dehydration.
- Jaundice with **unconjugated hyperbilirubinemi**a.
- abdominal x-rays typically show a huge stomach and diminished or absent gas in the intestine.
- Ultrasound examination of the pylorus shows marked elongation and thickening of the pylorus .
- A barium upper GI series is obtained whenever doubt about the diagnosis exists; this shows a **"string sign"** caused by barium moving through an elongated, constricted pyloric channel.

## Treatment

- IV fluid and electrolyte resuscitation followed by surgical pyloromyotomy.
- Before surgery, dehydration and hypochloremic alkalosis must be corrected, generally with an initial normal saline fluid bolus followed by infusions of half-normal saline containing 5% dextrose and potassium chloride when urine output is observed.
- **Pyloromyotomy**: small incision is made, usually directly over the pylorus or at the umbilicus, and the pyloric muscle is incised longitudinally to release the constriction. Care is taken not to cut into the mucosa itself.

# PEPTIC DISEASE

## Etiology and Epidemiology

- Acid-related injury can occur in the esophagus, stomach, or duodenum.
- ***Helicobacter pylori*** is responsible for >50% of ulcers in the stomach and the duodenum in adults→ plays significant lesser role in childhood ulcer disease.
- Risk factors for *H. pylori* : low socioeconomic status and poor sanitation→ highest incidence in developing countries.
- **Nonulcer dyspepsia** includes upper abdominal symptoms (pain, bloating, nausea, early satiety) in the absence of gastric or duodenal ulceration.*not* associated with *H. pylori* infection of the stomach.
- GER allows acidic gastric contents to injure the esophagus→ **esophagitis**.
- Esophagitis is characterized by retrosternal and epigastric burning pain and is best diagnosed by endoscopy.

### Risk Factors for Peptic Ulcer Disease

| |
|---|
| ***Helicobacter pylori* infection** |
| **Drugs** |
| NSAIDs, including aspirin |
| Tobacco use |
| Bisphosphonates |
| Potassium supplements |
| **Family history** |
| **Sepsis** |
| **Head trauma** |
| **Burn injury** |
| **Hypotension** |

## Clinical Manifestations

- burning epigastric and retrosternal pain strongly suggests esophagitis.
- With duodenal ulcers, pain typically occurs several hours after meals and often awakens patients at night. Eating tends to relieve the pain.
- Gastric ulcers differ in that pain is commonly aggravated by eating, resulting in weight loss.
- GI bleeding from either can occur.
- Many patients report significant symptom relief with antacids or acid blockers.

## Laboratory and Imaging Studies

- Whenever symptoms are localized to the upper abdomen or the retrosternal region, upper GI endoscopy is indicated.
- Empirical therapy with a proton-pump inhibitor may be considered, but has the risk of not diagnosing the underlying condition.
- The possibilities of IBD, anatomic abnormality such as malrotation, pancreatitis, and biliary disease should be ruled out by appropriate testing when suspected .
- Testing for *H. pylori* should be performed by biopsy during every endoscopy.
- If endoscopy is not done,noninvasive tests for infection with reasonable accuracy include:
  1. *H. pylori* antibodies
  2. $^{13}C$ urea breath tests (urea is metabolized into $^{13}CO_2$ by the organism)
  3. stool *H. pylori* antigen tests.

## PEPTIC ULCER, SYMPTOMS, AND CLINICAL INVESTIGATION

| Syndrome and Associated Symptoms | Clinical Investigation |
|---|---|
| **Peptic Ulcer Disease** | |
| **"Alarm" symptoms** | Endoscopy-mandatory with alarm symptoms |
| 1. Weight loss | Test for *Helicobacter pylori* |
| 2. Hematemesis | CBC, ESR, amylase, lipase, abd US |
| 3. Melena, heme-positive stools | |
| 4. Chronic vomiting | |
| 5. Microcytic anemia | |
| 6. Nocturnal pain | |
| Other symptoms-same as for esophagitis and nonulcer dyspepsia | |

### TREATMENT

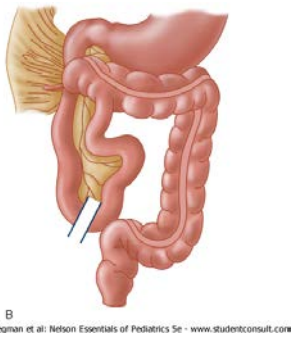
- If *H. pylori* is present in association with ulcers, it should be treated with a multidrug regimen: twice daily for 1-2 weeks:

  **omeprazole +2 of (clarithromycin, metronidazole, amoxicillin)**
- Other proton-pump inhibitors may be substituted when necessary.
- Bismuth compounds are effective against *H. pylori* and can be considered.
- In North America, only the subsalicylate salt is available, the use of which raises some concerns about Reye syndrome and potential salicylate toxicity.
- Tetracycline is useful in adults, but should be avoided in children .
- In the absence of *H. pylori,* esophagitis and peptic ulcer disease are treated with a proton-pump inhibitor, which yields higher rates of healing than $H_2$ receptor antagonists.
- Gastric and duodenal ulcers heal in 4- 8 weeks in 80% of patients.
- Esophagitis requires 4 - 5 months of proton-pump inhibitor treatment for optimal healing.

# INTESTINAL TRACT

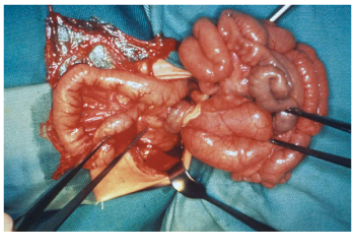
## MIDGUT MALROTATION

### ETIOLOGY AND EPIDEMIOLOGY





- During early fetal life, the midgut is attached to the yolk sac and loops outward into the umbilical cord.
- at 10 weeks' gestation, the bowel reenters the abdomen and rotates counterclockwise around the superior mesenteric artery until the cecum arrives in the right lower quadrant.
- The duodenum rotates behind the artery and terminates at the **ligament of Treitz** in the left upper quadrant.
- The base of the mesentery becomes fixed along a broad attachment posteriorly, running from the cecum to the ligament of Treitz.
- When rotation is incomplete or otherwise abnormal= "malrotation".
- Incomplete rotation occurs when the cecum stops near the right upper quadrant, and the duodenum fails to move behind the mesenteric artery; this results in an extremely narrow mesenteric root that makes the child susceptible to midgut **volvulus**.
- It is common for abnormal mesenteric attachments (Ladd bands) to extend from the cecum across the duodenum, causing partial obstruction.




### CLINICAL MANIFESTATIONS

- 60% of children with malrotation present with symptoms of **bilious vomiting during the first month of life**. The remaining 40% present later in infancy or childhood.
- The emesis initially may be due to obstruction by Ladd bands without volvulus.
- When midgut volvulus occurs, the venous drainage of the gut is impaired, and congestion results in ischemia, pain, tenderness, and often bloody emesis and stools.
- The bowel undergoes ischemic necrosis, and the child may appear septic.

- Physicians caring for children must be alert to the possibility of volvulus in patients with vomiting and fussiness or abdominal pain.

### Laboratory and Imaging Studies

- **Plain abdominal x-rays** : show evidence of obstruction.
- **Abdominal ultrasound** : show evidence of malrotation.
- **upper GI series** :shows the absence of a typical duodenal "C-loop," with the duodenum instead remaining on the right side of the abdomen.
- When doubt exists about the normalcy of the duodenal course, the contrast material can be followed until it reaches the cecum.
- Abnormal placement of the cecum on follow-through (or by contrast enema) **confirms the diagnosis**.
- Laboratory studies are non-specific, showing evidence of dehydration, electrolyte loss, or evidence of sepsis.
- **A decreasing platelet count is a common indicator of bowel ischemia.**

### Treatment: surgical

- The bowel is untwisted, and Ladd bands and other abnormal membranous attachments are divided.
- The mesentery is spread out and flattened against the posterior wall of the abdomen by moving the cecum to the left side of the abdomen.
- Sutures may be used to hold the bowel in position, but postoperative adhesions tend to hold the mesentery in place, resulting in a broad attachment and eliminating the risk of recurrent volvulus.
- Necrotic bowel is resected and at times results in short gut syndrome.

## INTESTINAL ATRESIA

### Etiology and Epidemiology

- Developmental defect of congenital partial or complete blockage of the intestine.
- Occurs in 1 : 1500 live births.
- Atresia occurs in several forms.
  A. One or more segments of bowel may be missing completely
  B. may be varying degrees of obstruction caused by webs or stenosis
  C. may be obliteration of the lumen in cordlike bowel remnants.
- The end result is obstruction with upstream dilation of the bowel and small, disused intestine distally.
- When obstruction is complete or high grade, bilious vomiting and abdominal distention are present in the newborn period.
- In lesser cases, as in "windsock" types of intestinal webs, the obstruction is partial, and symptoms are more subtle.

### Clinical Manifestations

- Intestinal atresia presents in the neonatal period with a history of :
  1. poly-hydramnios
  2. abdominal distention
  3. bilious vomiting
- If intestinal perforation is present, peritonitis and sepsis are inevitable.

### Laboratory and Imaging Studies

- abdominal x-rays may localize the area of atresia and identify evidence of perforation, such as free air or calcifications typical of meconium peritonitis.
- Duodenal atresia appears as a double-bubble sign (gas in the stomach and enlarged proximal duodenum), with no gas distally.
- Atresias of the distal intestine are characterized by longer segments of dilated, air-filled bowel.
- Contrast studies are helpful if plain films are not sufficient.
- Atresia may be a complication of **meconium ileus** associated with cystic fibrosis.

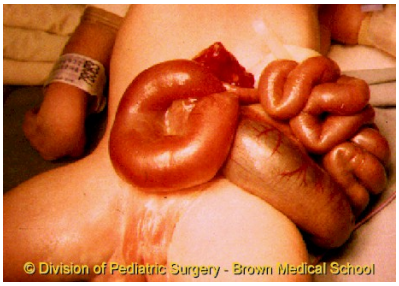
- Laboratory evaluation for **cystic fibrosis** is indicated in cases of small bowel atresia.
- Other laboratory studies should be measured to identify dehydration, pancreatitis, and other complications are not specific for atresia: CBC, serum electrolytes, liver functions, and amylase

### TREATMENT

- The treatment of intestinal atresia is surgical, preceded by adequate stabilization of the patient.
- IV fluids, nasogastric suction, and broad-spectrum antibiotics should be given.

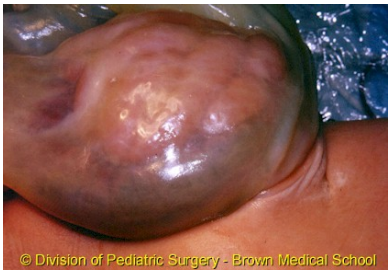
## OTHER CONGENITAL DISORDERS

### GASTROSCHISIS:



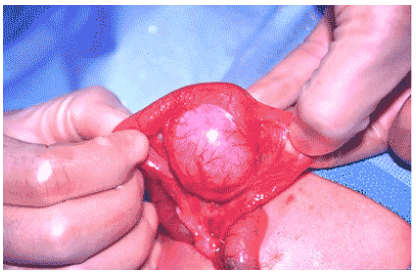

- abdominal wall defect not involving the umbilicus, through which intestinal contents have herniated.
- the bowel is not covered by peritoneum or amniotic membrane.
- As a result, prolonged contact with the amniotic fluid typically causes a thick, exudative covering (a "peel") on the exposed bowel.
- **Gastroschisis is not associated with extraintestinal anomalies**, but segments of intestinal atresia are common.
- After surgical reduction of the defect, return of normal bowel function may be slow and requires prolonged parenteral nutrition for infants with long atretic segments (short bowel syndrome) and infants with a thick peel.

### OMPHALOCELE




- abdominal wall defect at the umbilicus caused by failure of the intestine to return to the abdomen during fetal life.
- The bowel remains within the umbilical cord and is covered by peritoneum and amniotic membranes.
- This defect is associated with other congenital anomalies, especially:
  1. cardiac defects
  2. **Beckwith-Wiedemann syndrome** (somatic overgrowth, hyperinsulinemic hypoglycemia, risk for Wilms tumor)
  3. intestinal complications.
- Treatment is surgical closure, which sometimes must be performed in stages to fit the bowel into a congenitally small abdominal cavity.

### DUPLICATION CYSTS

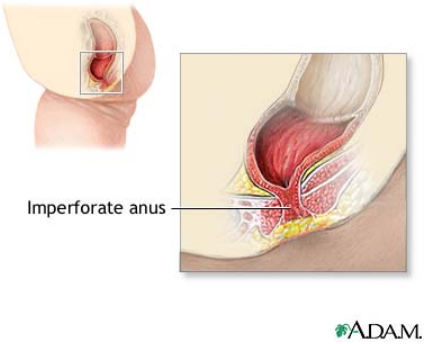


- Abnormal fluid-filled structures lined with intestinal or gastric mucosa.
- They are found within the mesentery and lie adjacent to normal bowel.
- These cysts do not communicate with the adjacent bowel lumen.
- some cysts may cause symptoms in early infancy or grow slowly for years, eventually causing problems secondary to:
  1. perforation
  2. bowel obstruction
  3. intussusception
  4. volvulus.
- Diagnosed by ultrasound, CT scan, or contrast studies.
- Treatment is surgical excision.

### ANORECTAL MALFORMATIONS

- Including imperforate anus and its variants, are embryologic defects recognized at birth by the absence of a normal anal opening.
- Evaluation of these infants should include observation for emergence of meconium from the urethra or fistulas on the perineum.
- A urinary catheter should be placed if urinary distention is present.
- In low lesions, a fistulous opening that drains meconium is present on the perineum.
- Low lesions commonly are associated with fistulization between the bowel and bladder, vagina, or urethra.

- Lateral x-rays show the defect level and show gas in the bladder caused by a fistula.
- These children are treated initially by colostomy to divert the fecal flow, with subsequent anogenital reconstruction.
- The internal sphincter muscle is functionally absent in high lesions, and continence after repair is difficult to achieve.
- **All** children with imperforate anus require MRI of the lumbosacral spinal cord because of high incidence of **tethered spinal cord**.
- Urologic dysfunction is common and should be evaluated appropriately.




## HIRSCHSPRUNG DISEASE

- Motility defect caused by failure of ganglion cell precursors to migrate into the distal bowel during fetal life.
- The aganglionic distal segment does not exhibit normal motility and is functionally obstructed secondary to spasm.
- 75% of cases, the involved segment is limited to the **rectosigmoid**, but total colonic involvement is seen in 8%.
- Rarely, long segments of small bowel also are aganglionic.
- "Ultrashort" segment involves only a few centimeters of distal rectum.
- Hirschsprung disease typically presents in the newborn period with failure to pass meconium by 24 hours of age.
  - ♣ 95% of normal infants pass stool spontaneously by this age
  - ♣ 95% of infants with Hirschsprung disease do not.
- Symptoms of distal bowel obstruction occur with distention and bilious vomiting.
- **Abdominal distention** is present in most cases.
- If diagnosis is not made quickly→ **enterocolitis**, associated with a high rate of mortality.
- Diagnosis is based on examination and one or more diagnostic studies.
  - ♣ **Digital rectal examination** reveals an empty rectum that clenches around the examiner's finger, giving the impression of an elongated sphincter. When the finger is withdrawn, a powerful gush of retained stool is expelled.
  - ♣ **A deep rectal biopsy** specimen obtained surgically or by using a suction biopsy instrument. When no ganglion cells are shown in the submucosal plexus, accompanied by nerve trunk hyperplasia, the diagnosis is certain.
  - ♣ **Barium enema** and **anorectal manometry** may be used before biopsy, but false-negative and false-positive results can occur.
- **Treatment:**
  - ♣ Therapy is surgical.
  - ♣ When the bowel is markedly distended or inflamed, an initial colostomy is performed above the aganglionic segment, followed weeks later by definitive repair procedure.
  - ♣ **The transanal pull-through** excises the aganglionic bowel and creates a primary colorectal anastomosis without laparotomy. considered in patients with uncomplicated involvement limited to the rectosigmoid region.

## MECKEL DIVERTICULUM

- Remnant of the fetal omphalomesenteric duct and is an outpouching of the distal ileum
- present in 1% to 2% of the population.
- Although most diverticula are asymptomatic throughout life, some cause:
  1. massive, painless GI bleeding.
  2. Ectopic gastric tissue within causes ulceration of mucosa in the adjacent ileum.
  3. lead point for intussusception or may enable twisting (volvulus) of neighboring bowel around its vascular supply.
  4. Diverticulitis mimics appendicitis.
- Diagnosis may be made in most cases by:
  1. technetium scan (Meckel scan)
  2. ultrasound and barium enteroclysis
  3. surgical or laparoscopic investigation
- The treatment is surgical excision.

# CELIAC DISEASE

## ETIOLOGY AND EPIDEMIOLOGY

- Celiac disease, or celiac sprue, is an injury to the mucosa of the proximal small intestine caused by the ingestion of **gluten** (a toxic protein component) from wheat, rye, & barley.
- Rice does not contain toxic gluten and can be eaten freely.
- Intolerance is permanent.
- Genetic predisposition:100% concordance in monozygotic twins.
- Environmental factors play a role.
- In its severe form, celiac disease causes malabsorption and malnutrition.
- Diagnosis was based on the presence of typical symptoms, followed by small bowel biopsy.
- The availability of more sensitive and specific serologic testing has revealed a "celiac iceberg" of many pts with few or no symptoms who have early attenuated or latent dz.
- 1 in 250 persons in the U.S. have celiac disease, only few were diagnosed.
- The disease is seen in association with selective IgA deficiency, DM, JRA, Thyroiditis, Addison ds, DM & down syndrome .
- Secondary malignancy is a risk in long standing celiac disease
- The most common period of presentation is 6 month to 2 years.

## CLINICAL MANIFESTATIONS

- **Classical celiac disease** is dominated by symptoms and sequelae of gastrointestinal malabsorption .
- **Celiac disease with atypical symptoms**.
  - **Silent celiac disease** refers to individuals who are asymptomatic but have a positive serologic test and villous atrophy.
  - **Latent celiac disease** is defined by a positive serology but no villous atrophy on biopsy .
- Celiac disease should be considered in any child with chronic abdominal complaints.
- Symptoms can begin at any age when gluten-containing foods are given.
- classic symptoms:
  1. Diarrhea
  2. abdominal bloating
  3. failure to thrive
  4. irritability
  5. decreased appetite
  6. ascites caused by hypoproteinemia
  7. clubbing
- Constipation is found in a few patients, probably because of reduced intake.
- extraintestinal manifestations:
  1. dermatitis herpetiformis
  2. intensely pruritic rash
  3. Iron deficiency anemia
  4. unexplained short stature
  5. delayed puberty, infertility, recurrent fetal loss.
  6. osteoporosis
  7. vitamin deficiencies
  8. protein calorie malnutrition
  9. recurrent aphthous stomatitis
  10. elevated transaminases
- Children may be minimally symptomatic or may be severely malnourished.
- A careful inspection of the child's growth curve and determination of reduced subcutaneous fat and abdominal distention are crucial.

## LABORATORY AND IMAGING STUDIES

- Serologic markers: IgA antiendomysial antibody & IgA tissue transglutaminase antibody. Also Antibodies for gliadin ,reticulin,
  - IgA deficiency is common in celiac disease→ total serum IgA also must be measured to document the accuracy of these tests.

- ♣ In the absence of IgA deficiency, either test yields a **sensitivity & specificity of 95%.**
- An endoscopic **small bowel biopsy** is essential to confirm the diagnosis and should be performed while the patient is still taking gluten.
  - ♣ The biopsy specimen shows various degrees of villous atrophy (short or absent villi), mucosal inflammation, crypt hyperplasia -deepened, and ↑intraepithelial lymphocytes. Histological conformation is mandatory.
  - ♣ When there is any question about response to treatment, a repeat biopsy specimen may be obtained several months later.
- Mild elevations of the transaminases are common and should normalize with dietary therapy.
- **Who should be tested for celiac disease?**
  1. Individuals with gastrointestinal symptoms
  2. Individuals without other explanations for signs and symptoms such as persistent elevations of transaminases, short stature, delayed puberty, iron-deficiency anemia, recurrent fetal loss, and infertility should be tested .
  3. Populations at higher risk for celiac disease. Symptomatic individuals in these populations should be tested for celiac disease .

### TREATMENT

- Treatment is complete elimination of gluten from the diet. changes occur in one weak of therapy.
- Consultation with a dietitian experienced in celiac disease is helpful, as is membership in a celiac disease support group.
- Starchy foods that are safe include rice, soy, tapioca, buckwheat, potatoes, & (pure) oats.
- Most patients respond clinically within a few weeks with weight gain, improved appetite, and improved sense of well-being.
- Histologic improvement lags behind clinical response, requiring several months to normalize.

## INFLAMMATORY BOWEL DISEASE

### EPIDEMIOLOGY AND ETIOLOGY

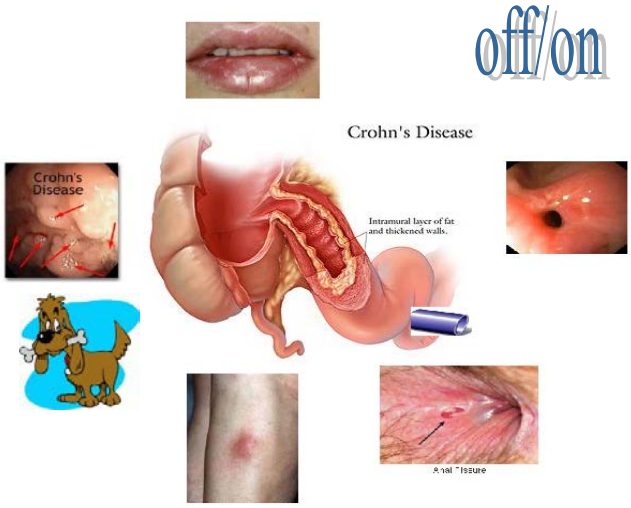
- The peak incidence of IBD in children is in the second decade of life
- higher risk if there is a family history of IBD.
- Environmental factors seem to play a role
- It is possible that viral infections can initiate the inflammatory process.
- Smoking doubles the risk of CD and halves the risk for UC.

### CLINICAL MANIFESTATIONS:

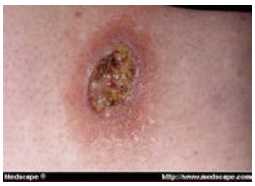
- *UC involves only the colon, whereas CD can include the entire gut from mouth to anus.*
- **Colitis** from either condition results in:
  - ♣ diarrhea with blood, and mucus in the stool
  - ♣ urgency
  - ♣ *tenesmus* : ensation of incomplete emptying after defecation.
  - ♣ in severe cases, awakens from sleep to pass stool
  - ♣ **Toxic megacolon** is a life-threatening complication characterized by:
    1. fever
    2. abdominal distention and pain
    3. massively dilated colon
    4. anemia
    5. low serum albumin owing to fecal protein losses
- **Small bowel involvement** in CD is associated with:
  1. loss of appetite
  2. crampy postprandial pain
  3. poor growth
  4. delayed puberty
  5. anemia and lethargy
  6. Severe CD may cause partial or complete small bowel obstruction.

## COMPARISON OF CROHN DISEASE AND ULCERATIVE COLITIS

| FEATURE | CD | UC |
|---|---|---|
| 1. Rectal bleeding | Sometimes | Usual |
| 2. **Abdominal mass** | Common | Rare |
| 3. **Perianal disease** | Common | Rare |
| 4. **Ileal involvement** | Common | None (backwash ileitis) |
| 5. **Strictures** | Common | Unusual |
| 6. **Fistula** | Common | Very rare |
| 7. **Skip lesions** | Common | Not present |
| 8. **Transmural involvement** | Usual | Not present |
| 9. Crypt abscesses | Variable | Usual |
| 10. **Intestinal granulomas** | Common | Rarely present |
| 11. Risk of cancer* | Increased | Greatly increased |
| 12. **Erythema nodosum** | Common | Less common |
| 13. **Mouth ulceration** | Common | Rare |
| 14. **Osteopenia at onset** | Yes | **No** |
| 15. Autoimmune hepatitis | Rare | Yes |
| 16. 1Sclerosing cholangitis | Rare | Yes |




- Extraintestinal manifestations of UC occur in a few patients and may include primary sclerosing cholangitis, arthritis, **uveitis**, and **pyoderma gangrenosum**
- Perineal abnormalities, including skin tags and fistulas, distinguishing CD from UC.
- Other extraintestinal manifestations of CD include arthritis, **erythema nodosum**, and **uveitis** or iritis.


PYODERMA GANGRENOSUM

### LABORATORY AND IMAGING STUDIES

- **Anemia** and **elevated platelet counts** are typical.
- Testing for abnormal serum antibodies can be helpful in diagnosing IBD and in discriminating between the colitis of CD and UC ( but not absolute ).
  1. **Anti-*Saccharomyces cerevisiae* antibody (ASCA)** is present in most CD patients and is uncommon in UC.
  2. **Atypical perinuclear staining by antineutrophil cytoplasmic antibody (p-ANCA)** is found in about 66% of UC patients and in only a few CD cases.
  3. anti-OmpC, directed against an *Escherichia coli* membrane protein. Found in some UC and CD patients, rare in non-IBD
- **upper GI series with small bowel follow-through**
- **Colonoscopy** is preferred over contrast enema because biopsy specimens can be obtained and because visual features can be diagnostic.is needed to detect small bowel involvement.

| CD | UC |
|---|---|
| Ulcerations much larger with a linear, branching, or aphthous appearance; skip areas present. | diffuse carpeting of the distal or entire colon with tiny ulcers and loss of haustral folds. no skip areas. |

- **Upper endoscopy** cannot evaluate the jejunum and ileum, but is more sensitive than contrast studies in identifying proximal CD involvement.
- **The capsule endoscope**, swallowed device that can visualize the entire small bowel, is potentially useful to visualize subtle small bowel disease.

### TREATMENT

#### CROHN DISEASE

- Inflammation in CD typically responds less well to aminosalicylates; oral or IV steroids are more important in inducing remission.

- To avoid the need for repetitive steroid therapy, immunosuppressive drugs, either azathioprine or 6-mercaptopurine, are started soon after diagnosis
- CD is difficult to control may be treated with methotrexate or with agents that block the action of tumor necrosis factor-α. **Infliximab** is the most effective such drug.
- antibodies that inhibit WBC migration or action, such as natalizumab, also show promise.
- surgery is not curative in CD, its use must be limited, and the length of bowel resection must be minimized.

### Ulcerative Colitis

- aminosalicylate drugs, which deliver **5-aminosalicylic acid** (5-ASA) to the distal gut.
- aminosalicylates (sulfasalazine, mesalamine, olsalazine, and balsalazide)
- Sulfasalazine is the least expensive
- When aminosalicylates alone cannot control the disease, steroid therapy may be required to induce remission.
- An immunosuppressive drug, such as **6-mercaptopurine** or **azathioprine**, is useful to spare excessive steroid use in difficult cases.
- Surgical colectomy with ileoanal anastomosis is an option for unresponsive severe disease or electively to end chronic symptoms and to reduce the risk of colon cancer, which is high in patients with UC.

## APPENDICITIS

### Etiology and Epidemiology

- Appendicitis is the most common surgical emergency in childhood.
- The incidence peaks in the late teenage years, 5% of cases children < 5 years old.
- There is a slight male predominance.
- Appendicitis begins with obstruction of the lumen:
  1. most commonly by fecal matter (fecalith)
  2. secondary to hyperplasia of lymphoid tissue associated with viral infections
  3. neoplastic tissue, commonly an appendiceal carcinoid tumor.
- Trappe bacteria proliferate→invade appendiceal wall → inducing inflammation and secretion.
- The obstructed appendix becomes engorged, its blood supply is compromised→ruptures.
- The entire process is rapid, with appendiceal rupture occurring within 48 hours of the onset of symptoms.

### Clinical Manifestations

- Classic appendicitis begins with **visceral pain**, localized to the periumbilical region.
- Nausea and vomiting occur soon after, triggered by the appendiceal distention.
- As the inflammation begins to irritate the parietal peritoneum adjacent to the appendix, **somatic pain** fibers are activated, and the pain localizes to the right lower quadrant.
- Examination of the patient reveals:
  1. tender right lower quadrant
  2. Voluntary guarding is present initially→ rigidity→ rebound tenderness with rupture and peritonitis.
- These classic findings may not be present, especially in young children, if the appendix is retrocecal, covered by omentum, or in another unusual location.
- When classic history and physical examination findings are present, the patient is taken to the operating room.
- When doubt exists, imaging is helpful to rule out complications (right lower quadrant abscess, liver disease) and other disorders, such as mesenteric adenitis and ovarian or fallopian tube disorders.
- If the workup is negative but some doubt remains, the child should be admitted to the hospital for close observation and serial examinations.

### Laboratory and Imaging Studies

- The history and examination are often enough to make the diagnosis, but laboratory and imaging studies are helpful when the diagnosis is uncertain

- A WBC count greater than 10,000/mm$^3$ is found in 89% of patients with appendicitis and 93% with perforated appendicitis.
- The specificity of an elevated WBC count is low.
- Urinalysis is done to rule out urinary tract infection
- chest x-ray rules out pneumonia masquerading as abdominal pain.
- Amylase, lipase, and liver enzymes are done to look for pancreatic or liver and gallbladder disease.
- The plain abdominal x-ray may reveal a calcified fecalith, which strongly suggests the diagnosis.
- When these studies are inconclusive, CT scan or abdominal ultrasound is indicated → enlarged, thick-walled appendix with surrounding fluid. A diameter > 6 mm is diagnostic.

### Treatment

- Treatment of appendicitis is surgical.
- Simple appendectomy is curative if performed before perforation.
- With perforation, a course of postoperative IV antibiotics is required: Broad-spectrum coverage is necessary to cover the mixed bowel flora.

## MILK AND SOY PROTEIN INTOLERANCE (ALLERGIC COLITIS)

### Etiology and Epidemiology

- Dietary proteins are a common cause of intestinal inflammation with rectal bleeding in infants.
- The most commonly implicated agents are cow's milk and less often soy proteins.
- Symptoms can appear from 1-2 weeks of age to 12 months.

### Clinical Manifestations

- appear **healthy**
- **streaks of bloody mucus in their stools**
- no abdominal tenderness or distention and no vomiting→ if there are present think of intussusception or volvolus
- **some severe anemia**
- Some develop intestinal protein loss produces **edema** & a **protein-losing enteropathy**.
- D/D: anal fissure. Careful examination of the anus is essential.

### Laboratory and Imaging Studies

- Most children are diagnosed clinically and treated empirically.
- No blood test is particularly helpful
  1. CBC = iron deficiency anemia.
  2. Peripheral eosinophilia
  3. diagnosis can be confirmed safely and easily by rectal mucosal biopsy; this shows eosinophilic inflammation of the mucosa.
  4. the Visual findings at proctoscopy usually include: mucosal friability **& lymphoid hyperplasia** → a lumpy, "mosquito-bitten" appearance to the rectal mucosa.

### Treatment

- Infants who are bottle-fed should be switched to a **hydrolyzed protein formula** (e.g., Nutramigen, Pregestamil, or Alimentum).
- Breastfed infants may continue breastfeeding, but the mother should restrict soy and dairy products from her diet.
- Visible blood in the stools typically resolves within a few days, although occult blood persists for several weeks.
- For infants with persistent bleeding, an amino acid-based formula is necessary.
- Nearly all of these infants lose their sensitivity to the offending protein **by 1 year of age.**
- Treatment of iron deficiency also is indicated

## INTUSSUSCEPTION

### Etiology and Epidemiology

- Intussusception is the "telescoping" of a segment of proximal bowel (the intussusceptum) into downstream bowel (the intussuscipiens).
- Most cases occur in infants 1- 2 years old.
- There is a slight male predominance.
- In infants < 2 years old, nearly all cases are idiopathic. Viral-induced lymphoid hyperplasia may produce a lead point in these children.
- In young children, **ileocolonic** intussusception is common; the ileum invaginates into the colon, beginning at or near the ileocecal valve.
- When pathologic lead points are present, the intussusception may be ileoileal, jejunoileal, or jejunojejunal

## Clinical Manifestations

1. sudden onset of **crampy abdominal pain**
2. the **infant's knees draw up**
3. the infant cries out & exhibits pallor with a colicky pattern every 15 to 20 minutes.
4. **Feedings are refused**.
5. **bilious vomiting** becomes prominent if progresses, and obstruction becomes prolonged and the dilated, fatigued intestine generates less pressure and less pain.
6. Third space fluid losses and **"currant jelly" stools** result.
7. **lethargy**.
8. **A sausage-shaped mass** caused by the swollen, intussuscepted bowel may be palpable in the right upper quadrant or epigastrium.

- The intussuscepted bowel moves further into the downstream intestine by its native motility→ the mesentery is pulled →becomes stretched and compressed→ venous outflow from the intussus-ceptum is obstructed→ leading to edema, weeping of fluid, and congestion with bleeding.

## Laboratory and Imaging Studies

*Direct demonstration of bowel-within-bowel*

- Abdominal ultrasound: A simple and direct way.
- Pneumatic or contrast enema under fluoroscopy is the most direct and potentially useful way to show and **treat** intussusception.
- pneumatic reduction vs hydrostatic reduction
  1. Success is bit higher than with barium =90% if done when symptoms have been present for < 24 hours.
  2. The pneumatic enema has the additional advantage over barium of not preventing subsequent radiologic studies, such as upper GI series or CT scan

## Treatment

- **IV catheter**
- **nasogastric tube**
- **fluid resuscitation** to correct the severe dehydration (vomiting and third space losses)
  - ♣ Ultrasound may be performed before the fluid resuscitation is complete
- **pneumatic or hydrostatic reduction**
  - ♣ If is successful, the child should be admitted to the hospital for overnight observation of possible recurrence (risk is 5%- 10%).
  - ♣ If reduction is not complete, emergency surgery is required.

# Liver Diseases

Dr Mutaz Sultan

- The estimated incidence of neonatal liver disease is 1 in 2500 live births.
- Early recognition is imp in neonate &infants because a delay may have a negative effect.
- Reasons of delay of referral of infants with liver disease.
  1. Lack of F.U of neonatal jaundice.
  2. Failure to fractionate S.bilirubine.
  3. Inadequate inv of hemorrhagic disease.

4. Misdiagnosis of cholestasis as human milk jaundice.
5. False security due to fall in S.bil or presence of pigmented stool.

- DDX of neonatal cholistasis :
  - ♣ Extrahepatic ; biliary atresia or cholydochal cyst.
  - ♣ Intrahepatic ;
    1. Paucity of bile duct : syndromic or non syndromic .
    2. No paucity of bile ducts: idiopathic neonatal hepatitis, metabolic and infections .

## HISTORY & SIGNS OF LIVER DISEASE.

- Neonates and infants :
  - ♣ Jaundice in any infant after 2wks should raise the suspicion of liver disease & bil should be fractionated.
  - ♣ Perinatal Hx: Maternal fever or signs of infection suggest sepsis & UTI.
  - ♣ Pigmented stool is against biliary atresia.
  - ♣ males,LBW & with intrafamilial recurrence→Idiopathic neonatal hepatitis.
  - ♣ Biliary atresia is more in females &normal WT.
  - ♣ Family history: suggest inherited disorder (tyrosinemia,byler disease-progressive familial intrahepatic cholestasis-).
  - ♣ Dietary changes .
- Older child :
  - ♣ History of fever ,anorexia, vomiting ,& abd pain suggest hepatitis A(acute onset ). Hepatitis A usually is anecteric in children<5 yrs.
  - ♣ Drug Hx :INH, sulpha, NSAID.
  - ♣ Confusion or coma suggests liver failure or metabolic Ds leading to hypoglycemia& hyperammonemia or a combination.
  - ♣ Female teenager with jaundice & acne ,intermittent arthritis may have autoimmune hepatitis.
  - ♣ Patient with immune deficiency & jaundice may have CMV, or EBV infection.
  - ♣ Enlarged kidneys suggest cong hepatic fibrosis .
  - ♣ History of IBD suggest primary sclerosing cholangitis .

**NOTE:**
**Ray syndrome:** "aspirin + vircella virus"
1. ↑liver enzymes
2. hypoglycemia
3. encephalopathy

**Hereditary fructose intolerance:**
1. HSM
2. hypoglycemia
3. jaundice

## PHYSICAL EXAMINATION :

- Hepatomegaly & jaundice are the most common signs.
  - ♣ Hepatomegaly often is the only manifestation of liver Ds,liver span is useful at initial presentation & for F.U.The mean span : 5 cm at 1wk to 6-7cm at adolescence .
  - ♣ False hepatomegaly?
  - ♣ Impressive hepatomegaly in isolation with minimal liver dysfunction suggests congenital hepatic fibrosis.
- If the spleen is enlarged many causes of portal Htn or storage Ds should be suspected.
  - ♣ Massive HSM may indicate storage Ds or malignancy .
- In neonates who suffer cong infection = microcephaly,chorioretinitis ,purpera & LBW.
- Dysmorphic features,Alagille usually have characteristic faces(beaked nose, high forehead),heart murmur ,posterior emberyotoxone on eye exam.
- Pruritus is a sign of obst liver Ds & may present with irritability.
- Ascites due to :
  1. Decreased plasma colloid osmotic pressure
  2. Increased capillary hydrostatic pressure
  3. Abn renal Na retention
- Signs of chronic liver disease more common in adult:
  - ♣ Spider angioma: due to altered estrogen metabolism.Most prominent on face & chest.
  - ♣ Palmer erythema : may be due to vasodilatation .
- Portal Htn : elevation of portal pressure above 10-12 mmHg. It is the main complication of cirrhosis.
  - ♣ Variceal hemorrhage ; a complication of portal Htn .

- Hepatorenal syndrom: It is a functional renal failure in patients with end stage liver Ds ,the hallmark is intense renal vasoconstriction .

## USEFUL SIGNS AND SYMPTOMS

- **Fever:** viral infection , systemic illness , hepatic abscess .
- **Vomiting / diarrhea**: Reye and reye like syndrome, fatty acid oxidation defect, GSD and other metabolic disease.
- **Distinctive odor**: organic acidemia .
- **Neurologic deterioration**: lipidosis , zellweger syndrome ,MPS and Wilson disease .
- **Skin findings** ( purpura , papular acrodermatitis ): TORCH infection and viral hepatitis .
- **Eye findings** ( cataract,chorioretinitis, Kayser flisher ring, post embryotoxon ) :TORCH, Wilson, Alagille .
- **Dysmorphic features** :storage diseases and Alagille .
- **Microcephaly** : cong infection .
- **Recurrent chest infection** : Cystic fibrosis .

## LAB EVALUATION

- **Bilirubin T&D**: Bilirubin fractionation is imp in any infant > 2wks with jaundice.
  - ♣ Unconjugated bilirubinemia makes liver Ds unlikely but may need to be evaluated for hemolysis ,thyroid dysfunction&cong disorder of bilirubin metabolism(Crigler Najjar).
  - ♣ When conjugated bil is > 15% of total bil it should be considered abn & evaluated immediately .
- **Aminotransferase activity**: ALT(SGPT)& AST(SGOT) are the most sensitive tests for hepatocytic necrosis. Slight abn values may be associated with cholestasis.
  - ♣ A high levels suggest drug toxicity, hypoxia\shock & viral hepatitis
  - ♣ these levels do not have any prognostic sign .
  - ♣ ↓values in the presence of a shrinking liver, rising PT&PTT & bil is ominous sign.

> NOTE:
> **Zinc deficiency:** ↓Ca ↓Phos. ↓AP
> **Rickets;**↓Ca ↓Phos. ↑ AP

- **Alkaline phosphatase** :
  - ♣ localized primarily to the canalicular membrane of the liver cells, elevated (AP) usually indicate obstruction.
  - ♣ AP is found in other tissues: bone,kidney &small intestine .
  - ♣ High AP values normally are found in children during period of accelerated growth .
  - ♣ Bone pathology is suspected in high AP values not associated with high GGT.
  - ♣ Chronically low AP may mean low zinc level.
- **Gamma-glutamyl transferase (GGT)**: found in small bile ductule epithelium of the liver. Also present in pancreas ,spleen, brain, breast small intestine & kidney.
  - ♣ GGT level is helpful in elucidating the origin of elevated AP .
- **Albumin:** It is normally low in neonate (2.5 gm\dl) reaching adult level after several months (3.5gm\dl ) . Low albumin is a late finding in liver disease.
- **Ammonia:** The liver plays a major role in its elimination .
  - ♣ Hyperammonemia & encephalopathy are classical finding of liver failure .
- **Prothrombin time:** deficiency of factor V & vit K dependant factors(II,VII,IX,X) may occur in patient with sever liver Ds .
  - ♣ If prolonged PT is a result of cholestasis, parenteral vit K should correct coagulopathy
  - ♣ No matter what the cause prolonged PT is a serious sign in liver Ds
- **Urinanalysis:**
  - ♣ Conjugated bil is excreated in urine & may appear before jaundice.
  - ♣ Urobilinogen is seen in hepatocellular damage because of decreased liver uptake.
- Serum glucose, ketones, lactic acid, amino acid, uric acid& urine organic acid when metabolic defect is suspected.
- **Liver biopsy** :
  - ♣ can be used for:
    1. Histological Dx in neonatal cholestasis, chr active hepatitis, metabolic liver Ds, intrahepatic cholistasis(paucity of bile ducts),cong hepatic fibrosis, undefined portal Ht .
    2. enzyme analysis.

3. Stored material such as iron& copper.

- ♣ Percutaneous approach needle biopsy is easily done infant & children.
- ♣ Contraindication:
  1. Prolonged PT or thrombocytopenia .
  2. Suspicion of vascular , cystic or infectious lesion in the path of the needle .
  3. Sever ascites .

- **Imaging studies:**
  1. Abd US : liver size, liver texture, cystic & noncystic parenchymal lesion(1cm), presence or absence of GB, stones, doppler for hepatic & portal blood flow .
  2. CT or MRI may be superior for small focal lesion as tumors.
  3. Radionuclide scanning: helpful in young infant to distinguish biliary atresia from neonatal hepatitis. Biliary atresia is diagnosed by cholangiography (intraoperative)

# CHOLESTASIS

## ETIOLOGY AND EPIDEMIOLOGY

- Cholestasis is defined as reduced bile flow
- characterized by elevation of the conjugated, or direct, bilirubin fraction.
- Neonatal jaundice that is secondary to unconjugated hyperbilirubinemia is the result of immature hepato-cellular excretory function or hemolysis, which increases the production of bilirubin.
- Emphasis must be placed on the rapid diagnosis of treatable disorders, especially biliary atresia and metabolic disorders, such as galactosemia or tyrosinemia.

| CONJUGATED HYPERBILIRUBINEMIA | | | | | |
|---|---|---|---|---|---|
| OBSTRUCTIVE | INFECTIOUS | METABOLIC | TOXIC | IDIOPATHIC (MOST COMMON) | AUTOIMMUNE |
| Alagille syndrome | Hepatitis(A,B,C,D,E,G) | Byler disease | TPN | Idiopathic neonatal hepatitis | Autoimmune chronic hepatitis |
| Non-sy paucity of BD | CMV, UTI(gram –) | Wilson syndrome | Acetaminophen | Familial benign recurrent cholestasis | Sclerosing cholangitis |
| Biliary atresia | HS type 1,2,6 | A1-antitrypsin deficiency | Iron | Aagenaes syndrome( cholestasis+lymphedema) | Graft vs. host dz |
| Choledochal cyst | EBV | Galactosemia | salicylates | Shock | |
| Cholelithiasi | Coxsackie virus | tyrosinemia | Ethanol, phenytoin | Cholestasis with hypopituitarism | |
| Tumor/neuplsia | ECHO virus | Niemann-Pick dz | halothane | Familial erythrophagocytic lymphochistiocytosis | |
| BD stenosis | Measles, vericella | Gaucher dz | Valproic- acid | | |
| BD- mucous plug | Syphilis, bacterial sepsis. | Zellwenger syndrome | Estradiol, methldopa | | |
| Congenital hepatic fibrosis | Human parvovirus B19 | Cystic fibrosis | | | |

## CLINICAL MANIFESTATIONS

- Cholestasis is caused by many different disorders, the common characteristic of which is **cholestatic jaundice**.
- **Clinical features of several of the most common causes are :**

**EXTRAHEPATIC BILIARY ATRESIA** (biliary atresia) :

- jaundice is not evident immediately at birth, develops in the first week or two of life.
- The reason is that extrahepatic bile ducts are usually present at birth, but are then destroyed by an idiopathic inflammatory process.
- infants do not initially appear ill.
- The liver injury progresses rapidly to cirrhosis.

- Symptoms of portal hypertension :splenomegaly, ascites, muscle wasting & poor weight gain are evident by a few months of age.
- If surgical drainage is not performed successfully early in the course (ideally by 2 months), progression to liver failure is inevitable.

Birth→ ( 1-2weeks) jaundice → cirrhosis( PHTN) → (2months) liver failure

## NEONATAL HEPATITIS

- Characterized by an ill-appearing infant with an enlarged liver and jaundice.

**ill+ hepatomegaly+ jaundice = NH**

- There is no specific diagnostic test, but if **liver biopsy** is performed, the presence of **hepatocyte giant cells is characteristic**.
- Hepatobiliary scintigraphy typically shows slow hepatic uptake with eventual excretion of isotope into the intestine.
- good prognosis overall, with spontaneous resolution occurring in most.
- **D/D:** Cytomegalovirus and syphilis must be ruled out.

## $\alpha_1$-ANTITRYPSIN DEFICIENCY

- presents with clinical findings indistinguishable from neonatal hepatitis.
- Only 20% of all infants with the genetic defect exhibit neonatal cholestasis.
- Of these affected infants, 30% go on to have severe chronic liver disease resulting in cirrhosis and liver failure.
- the leading metabolic disorder requiring **liver transplantation**.

## ALAGILLE SYNDROME

- Characterized by chronic cholestasis with the unique liver biopsy finding of paucity (few) of bile ducts in the portal triads.
- Associated abnormalities in some (syndromic) types include :


1. **peripheral pulmonic stenosis** or other cardiac anomalies
2. hypertelorism with deep-set eyes
3. prominent forehead
4. pointed chin
5. butterfly vertebrae
6. defect of the limbus (*posterior embryotoxon*).

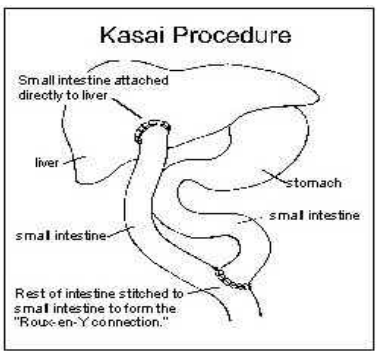
- Cholestasis is variable but is usually lifelong and associated with **hypercholesterolemia** and **severe pruritus**.
- Progression to end-stage liver disease is uncommon. Good prognosis.
- Liver transplantation sometimes is performed electively to relieve severe and uncontrollable pruritus.

## LABORATORY AND IMAGING STUDIES

- Imaging studies also are performed early to rule out biliary obstruction and other anatomic lesions that may be surgically treatable.
- When necessary to rule out biliary atresia or to obtain prognostic information, liver biopsy is a final option.

## TREATMENT

- Treatment of extrahepatic biliary atresia is the surgical **Kasai procedure**.
  - ♣ the damaged bile duct remnant is removed and replaced with a roux-en-Y loop of jejunum.
  - ♣ must be performed before 3 months of age to have the best chance of success.
  - ♣ Even so, the success rate is low; many children require liver transplantation.



- Some metabolic causes of neonatal cholestasis
  - ♣ treatable by dietary manipulation (galactosemia) or medication (tyrosinemia)
  - ♣ all affected patients require supportive care. includes: fat-soluble vitamin supplements.
  - ♣ formula containing medium-chain triglycerides, which can be absorbed without bile salt-induced micelles.
  - ♣ Choleretic agents, such as ursodeoxycholic acid and phenobarbital, may improve bile flow in some conditions.

# FULMINANT LIVER FAILURE

## ETIOLOGY AND EPIDEMIOLOGY

- defined as severe liver disease with onset of hepatic encephalopathy within 8 weeks after initial symptoms, in the absence of chronic liver disease.

### CAUSES OF FULMINANT LIVER FAILURE IN CHILDHOOD

| |
|---|
| **Metabolic**: Neonatal hemochromatosis, Galactosemia, Wilson disease, Bile acid synthesis disorders Electron chain transport defects, Disorders of fatty acid oxidation, Hereditary fructose intolerance |
| **Cardiovascular:** Shock, hypotension, Congestive heart failure,Budd-Chiari syndrome |
| **Infectious**:Echovirus, Coxsackievirus, Adenovirus, Parvovirus, CMV, Sepsis, Herpes simplex |
| **Neoplastic**: Acute leukemia, Lymphoproliferative disease |
| **Toxic**: Acetaminophen, Valproic acid, Phenytoin, Isoniazid, Halothane, *Amanita* mushrooms |

## CLINICAL MANIFESTATIONS

- **Respiratory compromise** occurs as severity of the failure increases and requires early institution of ventilatory support.
- **Hypoglycemia** resulting from impaired glycogenolysis and gluconeogenesis must be prevented.
- Renal function is impaired, and **frank renal failure**, or **hepatorenal syndrome** (characterized by low urine output, azotemia, and low urine sodium content).
- **Ascites** develops secondary to hypoalbuminemia and disordered regulation of fluid and electrolyte homeostasis.
- Increased risk of **infection** occurs and may cause death.
- **Esophageal varices** may cause significant **hemorrhage**
- **hypersplenism** from portal hypertension produce **thrombocytopenia**.

## LABORATORY AND IMAGING STUDIES

- **Coagulation tests and serum albumin** are used to follow hepatic synthetic function.
  - ♣ These tests are confounded by administration of blood products and clotting factors.
  - ♣ In addition to monitoring prothrombin time and partial thromboplastin time, many centers measure factor V serially as a sensitive index of synthetic function.
- Renal function tests, electrolytes, serum ammonia, blood counts, and urinalysis also should be followed.
- In the setting of acute liver failure, liver biopsy may be indicated to ascertain the nature and degree of injury and estimate the likelihood of recovery.
  - ♣ In the presence of coagulopathy, biopsy must be done using a transjugular or surgical approach.

## TREATMENT

- Treatment of acute liver failure is supportive
- The definitive lifesaving therapy is liver transplantation

### TREATMENT OF FULMINANT LIVER FAILURE

| | |
|---|---|
| **Hepatic encephalopathy** | Avoid sedatives |
| | Lactulose via nasogastric tube-start with 1-2 mL/kg/day, adjust dose to yield several loose stools per day |
| | Enemas if constipated |
| | Mechanical ventilation if stage III or IV |

| | |
|---|---|
| **Coagulopathy** | Fresh frozen plasma only if active bleeding, monitor coagulation studies frequently |
| | Platelet transfusions as required |
| **Hypoglycemia** | IV glucose supplied with ≥10% dextrose solution, electrolytes as appropriate |
| **Ascites** | Restrict fluid intake to 50%-60% maintenance |
| | Restrict sodium intake to 0.5-1 mEq/kg/day |
| | Monitor central venous pressure to maintain adequate intravascular volume (avoid renal failure) |
| **Renal failure** | Maintain adequate intravascular volume, give albumin if low |
| | Diuretics |
| | Vasoconstrictors |
| | Dialysis or hemofiltration |
| | Exchange transfusion |

# CHRONIC LIVER DISEASE

## ETIOLOGY AND EPIDEMIOLOGY

- Chronic liver disease in childhood is characterized by the development of cirrhosis and its complications and by progressive hepatic failure.
- Causative conditions may be congenital or acquired.
  - ♣ Major congenital disorders leading to chronic disease include:
    1. biliary atresia
    2. tyrosinemia
    3. untreated galactosemia
    4. $\alpha_1$-antitrypsin deficiency.
  - ♣ In older children:
    1. HBV, HCV
    2. autoimmune hepatitis
    3. Wilson disease
    4. primary sclerosing cholangitis
    5. cystic fibrosis
    6. biliary obstruction secondary to choledochal cyst.

## CLINICAL MANIFESTATIONS

- Chronic liver disease is characterized by the consequences of portal hypertension, impaired hepatocellular function, and cholestasis.
- **Portal hypertension** caused by cirrhosis results in risk of GI bleeding, ascites, and reduced hepatic blood flow.
- **Ascites** develops as a result of weeping of a high-pressure ultrafiltrate from the surfaces of the viscera and is at risk of infection (spontaneous bacterial peritonitis)
- The spleen enlarges secondary to impaired splenic vein outflow, causing excessive scavenging of platelets and WBCs→ susceptibility to bleeding and infection.
- **Impaired hepatocellular function** is associated with:
  1. coagulopathy unresponsive to vitamin K
  2. low serum albumin
  3. elevated ammonia
  4. **hepatic encephalopathy**.
- Malaise develops and contributes to poor nutrition, leading to muscle wasting and other consequences.
- debilitating pruritus and deepening jaundice
- reduced excretion of bile acids impairs absorption of fat calories and fat-soluble vitamins
- Deficiency of vitamin K impairs production of clotting factors II, VII, IX, and X and increases the risk of bleeding.
- Vitamin E deficiency leads to hematologic and neurologic consequences .

## TREATMENT

- survival depends on transplantation.

- When transplantation is not possible or is delayed, palliative procedures, such as portosystemic shunts, can be considered.
  - ♣ Transjugular intrahepatic portosystemic shunt has an expandable stent placed between the hepatic vein and a branch of the portal vein within the hepatic parenchyma. performed using catheters inserted via the jugular vein
  - ♣ All portosystemic shunts carry increased risk of hepatic encephalopathy.

## WILSON DISEASE

- neurodegenerative disease of copper metabolism.
- In 1912, Wilson first described it as a familial disorder associated with neurological symptoms and cirrhosis.
- Characterized by abnormal storage of copper in the liver, leading to hepatocellular injury, CNS dysfunction, and hemolytic anemia.
- autosomal recessive trait caused by mutations in the ***ATP7B*** gene on chromosome 13. The encoded protein of this gene functions as an ATP-driven copper pump.
- Defective mobilization of copper from lysosomes in liver cells for excretion into bile is the basis for the multiorgan damage in patients with Wilson disease.
- The incidence is 1/500,000–100,000 births.

### DIAGNOSIS

- Diagnosis is made by identifying:
  1. ↓ serum levels of ceruloplasmin: **The best screening test.**
  2. ↑24-hour urine copper excretion (> 100 mg/d)
  3. presence of Kayser-Fleischer rings in the iris
  4. evidence of hemolysis**:** Coombs-negative acute intravascular hemolysis
  5. elevated hepatic copper content
     - ♣ This test is regarded as **standard for diagnosis of Wilson disease**.
     - ♣ A liver biopsy with sufficient tissue reveals levels of > 250 mcg/g of dry weight (normally <10µg/g dry weight).
- Genetic diagnosis: Linkage analysis has been used in family studies for presymptomatic testing
  - ♣ > 100 mutations have been identified, making diagnosis by DNA mutational analysis a difficult task unless a proband mutation is known.
- Serum copper level may be elevated in early Wilson disease, and urinary copper excretion (<40µg/ day) is increased to > 100µg/day, often up to 1,000µg or more per day.
- In equivocal cases, the response of urinary copper output to chelation may be of diagnostic help; after a 1-g oral d-penicillamine, patients excrete 1,200–2,000µg/24hr.

### PATHOPHYSIOLOGY

- The mechanisms responsible for copper homeostasis in older children reach maturity by 2 yr of age.
- The wilsonian trait may be expressed after this time, but Wilson disease is not clinically manifested before age 5 yr.
- Defective mobilization of copper from lysosomes in liver cells for excretion into bile is the basis for the multiorgan damage in patients with Wilson disease.
- copper accumulates in the liver, brain, kidney, and cornea .
- The mechanism of liver damage in Wilson disease is oxidant injury to the hepatocyte mitochondria, which is the target organelle in copper-induced toxicity.

### CLINICAL PRESENTATION

- Seldom occurs before age 3 years.
- Mutations that completely destroy gene function are associated with an onset of disease symptoms as early as 2–3 yr of age**.**
- Milder mutations can be associated with neurologic symptoms or liver disease as late as 50 yr of age.
- The younger the patient, the more likely hepatic involvement will be the predominant manifestation. After 20 yr of age, neurologic symptoms predominate.

- Kayser-Fleischer rings may be absent in young patients with liver disease but are **always present** in patients with neurologic symptoms.
- Hepatic presentations include:
  1. appearance of jaundice
  2. asymptomatic hepatomegaly
  3. spider hemangiomas
  4. portal hypertension and its consequences
  5. cirrhosis
  6. chronic active hepatitis
  7. fulminant hepatic failure.
- Neurologic abnormalities may predominate, including:
  1. intention tremor
  2. dysarthria
  3. dystonia
  4. decline in school performance
  5. worsening handwriting
  6. psychiatric disturbances
- One study describes 4 distinct diagnostic categories based on patients' major neurologic findings (Walshe, 1984).
  1. The **parkinsonian** patients (45%)
  2. The pseudosclerotic patients (24%)
  3. The patients in the dystonic group (15%)
  4. The patients in the choreic group (11%)
- Anemia may be the first noted symptom.
- Unusual manifestations include arthritis and endocrinopathies, such as hypoparathyroidism.
- Renal
  - ♣ Fanconi syndrome,
  - ♣ Urolithiasis, found in16% of patients with Wilson disease.

## TREATMENT

- The mainstay of therapy for Wilson disease is pharmacologic treatment with chelating agents.
- Lifelong, uninterrupted chelation therapy is necessary in all patients with Wilson disease.
  1. Penicillamine: adults 1g/day*2 before meals , < 10 yr :0.5–0.75g/day
  2. Trientine(Trien, TETA) at a dose of 0.5–2g/24hr
  3. Zinc sulfate: adjuvant or maintenance therapy owing to its unique ability to impair the gastrointestinal absorption of copper. 25 to 50mg *3
- Diet therapy
  - ♣ restrict copper intake to less than 1mg/day. Foods such as liver, shellfish, nuts, and chocolate should be avoided.
  - ♣ if the copper content of the water exceeds 0.1mg/L, it may be necessary to demineralize the water.
- liver transplantation is a potentially curative treatment of Wilson disease.
  - ♣ Transplantation is primarily reserved for treatment of patients with fulminant liver failure or end-stage liver cirrhosis.
- Urinary copper levels become normal with continued d-penicillamine, with marked improvement in hepatic & neurologic function & disappearance of Kayser-Fleischer rings.
- Toxic effects of penicillamine are uncommon and consist of:
  1. hypersensitivity reactions (Goodpasture syndrome, SLE, polymyositis)
  2. interaction with collagen and elastin
  3. deficiency of zinc
  4. aplastic anemia
  5. nephrosis
  6. antimetabolite of vitamin B6 .
- Adequate therapy must be continued for life to prevent liver and CNS deterioration.

## AUTOIMMUNE HEPATITIS

- Immune-mediated liver injury may be primary or occur in association with other autoimmune disorders, such as IBD or SLE.
- **Diagnosis** :
  1. elevated serum total IgG
  2. the presence of an autoantibody, most commonly antinuclear, anti-smooth muscle, or anti-liver-kidney microsomal antibody.
  3. Liver biopsy specimen shows the presence of a plasma cell-rich portal infiltrate with piecemeal necrosis.
- **Treatment** : corticosteroids initially, with addition of immunosuppressive drug after remission is achieved.
- Many patients require lifelong immunosuppressive therapy, but some may be able to stop medications after several years under careful monitoring for recurrence.

## PRIMARY SCLEROSING CHOLANGITIS

- Occurs by itself or more often in association with **UC**.
- **Overlap syndrome** = Primary Sclerosing Cholangitis**+** autoimmune hepatitis.
- **ANCA** is present in many cases.
- Diagnosis is by **liver biopsy** and **cholangiography**, generally performed as ERCP.
  - ♣ inflammation and fibrosis surrounding bile ducts in biopsy specimens
  - ♣ Varying degrees of segmental stricturing of larger bile ducts by cholangiography.
- Treatment :
  1. **ursodiol**, slow progression and improves indices of hepatic injury,dilation of major biliary strictures during ERCP
  2. **liver transplantation** for end-stage liver disease.

## STEATOHEPATITIS

- *nonalcoholic fatty liver disease* or *nonalcoholic fatty hepatitis.*
- characterized by the presence of macrovesicular fatty change in hepatocytes on biopsy.
- Varying degrees of inflammation and portal fibrosis may be present.
- This disorder occurs in obese children, sometimes in association with insulin-resistant (type 2) diabetes and hyperlipidemia.
- **Steatohepatitis**= obese Children± type 2 diabetes+ ↑liver enzymes + no other identifiable liver disease.
- Treatment :
  1. diet and exercise
  2. Vitamin E may have some benefit.
  3. control blood glucose and hyperlipidemia and promote weight loss.
- In general, the rate of progression to end-stage liver disease is slow.

# PANCREATIC DISEASE

## PANCREATIC INSUFFICIENCY

### ETIOLOGY AND EPIDEMIOLOGY

- The cause of inadequate pancreatic digestive function:
  1. **cystic fibrosis:** 95% of PI cases.
  2. Shwachman-Diamond syndrome
  3. Pearson syndrome
  4. severe malnutrition

### CLINICAL MANIFESTATIONS

1. bulky, foul-smelling stools each day
2. visible oil or fat in stool.
3. (typically) voracious appetites because of massive malabsorption of calories from fat, complex carbohydrates, and proteins.
4. Failure to thrive

- testing should be performed to rule out conditions such as: celiac disease & IBD

### LABORATORY AND IMAGING STUDIES

- Testing of pancreatic function is difficult.
  1. Direct enzyme measurement in aspirated pancreatic juice technically difficult.
  2. Stools teste for the presence of maldigested fat→ poor fat digestion.
     - ♣ qualitative assessment of fat absorption (fecal Sudan stain)
     - ♣ semiquantitative measurement (72-hour fecal fat)
  3. Test presence of pancreatic enzymes in the stool. **fecal elastase-1** the most accurate method of assessment. Resistant to digestion, easy to measure by immunoassay. ↓fecal elastase-1 concentration correlates well with the presence of PI.

### TREATMENT

- Replacement of missing pancreatic enzymes is the best available therapy.
- Pancreatic enzymes are available as enzyme powder, which can be:
- Excessive use must be avoided as high doses (>6000 U/kg/meal) cause colonic fibrosis.
  - ♣ In infants, **2000 - 4000 U of lipase/120 mL** of formula.
  - ♣ In children < 4 years old, **1000 U/kg/meal**.
  - ♣ older children, **500 U/kg/meal** is usual.
- $H_2$ receptor antagonists or PPIs increase the efficacy of pancreatic enzymes by enhancing their release from the microspheres and reducing inactivation by acid.

## ACUTE PANCREATITIS

### ETIOLOGY AND EPIDEMIOLOGY

- The exocrine pancreas produces numerous proteolytic enzymes, including trypsin, chymotrypsin, and carboxypeptidase.
  - ♣ Produced as inactive proenzymes to protect the pancreas from autodigestion.
  - ♣ Trypsin is activated after leaving the pancreas by enterokinase, an intestinal brush border enzyme.
  - ♣ After activation, trypsin cleaves other proteolytic proenzymes into their active states.
  - ♣ Protease inhibitors found in pancreatic juice inhibit early activation of trypsin.
- Pancreatitis occurs when digestive enzymes are activated inside the pancreas.
- Triggers for acute pancreatitis differ between adults and children.
  - ♣ In the adult patient, most episodes are related to alcohol abuse or gallstones.
  - ♣ In children, most cases are idiopathic.
- Some cases are caused by:
  1. drugs
  2. hypertriglyceridemia
  3. biliary microlithiasis
  4. trauma
  5. Viral infection
  6. Collagen vascular disorders
  7. parasite infestations

### CLINICAL MANIFESTATIONS

- Acute pancreatitis presents with rapid onset of **severe epigastric pain**, radiate to the back, aggravated by eating.The patient moves frequently to find a position of comfort.
- **Nausea and vomiting** occur in most cases.
- Severe pancreatitis can lead to hemorrhage, visible as ecchymoses in the flanks (Grey Turner sign) or periumbilical region (Cullen sign).
- Rupture of a minor pancreatic duct can lead to development of a pancreatic pseudocyst, characterized by persistent severe pain and tenderness and a **palpable mass**.
- With necrosis and fluid collections, patients experiencing severe pancreatitis are prone to infectious complications, clinician must be alert for **fever and signs of sepsis**.

### LABORATORY AND IMAGING STUDIES

- Acute pancreatitis can be surprisingly difficult to diagnose.
- Elevations in total serum amylase or lipase support the diagnosis.
  - ♣ These pancreatic enzymes are released into the blood during pancreatic injury.

- As acute pancreatitis progresses, the amylase level tends to decline faster than lipase, making the latter a good choice for diagnostic testing late in the course of the disease.

- Because enzyme levels are not 100% sensitive or specific, imaging studies are important for the diagnosis of pancreatitis.
  - Ultrasound is capable of detecting edema and should be performed as part of the overall diagnostic approach. edema is present in all but the mildest cases.
  - CT scan allows complete visualization of the gland.
  - Ultrasound and CT also can be used to monitor for the development of **pseudocysts** and for evidence of ductal dilation secondary to obstruction.

### Treatment

1. If a predisposing etiology is found, such as a drug reaction or a gallstone obstructing the sphincter of Oddi, this should be specifically treated.
2. the old maxim of "rest the gland" is accomplished by:
   - prohibiting oral intake
   - use of an acid-blocking drug
   - (except in mild cases) nasogastric suction.
3. Fluid resuscitation because of vomiting and third space losses.
4. Pain relief should be provided
   - avoiding morphine because of its tendency to cause spasm of the sphincter of Oddi.
   - Meperidine is the traditional narcotic of choice, but neurotoxicity of its metabolites limits long-term high-dose use
   - fentanyl is used frequently.
5. Nutritional support should be provided early in the course because the patient may be NPO for extended periods.
   - Feedings administered downstream from the duodenum via a nasojejunal tube are generally well tolerated.
   - If this is not possible, parenteral nutrition is an option.
   - Fewer complications and more rapid recovery occur with jejunal feedings compared with parenteral nutrition.
6. if the patient is febrile, has extensive pancreatic necrosis, or laboratory evidence of infection→ broad-spectrum antibiotic, such as imipenem, is the best choice.

## CHRONIC PANCREATITIS

### Etiology and Epidemiology

- Defined as **recurrent or persistent attacks of pancreatitis**, which have resulted in irreversible morphologic changes in pancreatic structure.
- Pancreatic exocrine insufficiency and diabetes mellitus may result.
- Most patients have discrete attacks of acute symptoms occurring repeatedly, but chronic pain may be present.
- The causes of chronic pancreatitis include **hereditary pancreatitis** and milder phenotypes of **cystic fibrosis** associated with pancreatic sufficiency.
- Familial disease is caused by one of several known mutations in the trypsinogen gene. These mutations inhibiting feedback inhibition of trypsin digestion. Genetic testing is available.
- Genetic testing for cystic fibrosis can be performed, but must include screening for the less common mutations associated with pancreatic sufficiency.

### Clinical Manifestations

- Children with chronic pancreatitis initially present with recurring attacks of acute pancreatitis.
- Injury to the pancreatic ducts predisposes these children to continued attacks owing to scarring of small and large pancreatic ducts, stasis of pancreatic secretions, stone formation, and inflammation.
- Loss of pancreatic exocrine and endocrine tissue over time can lead to exocrine and endocrine deficiency.

- > 90% of the pancreatic mass must be destroyed before exocrine deficiency becomes clinically apparent; this is a late complication that does not occur in all cases.
- Chronic pain is a serious problem in most affected individuals.
- These patients have many episodes; many do not require hospitalization.

### Laboratory and Imaging Studies

- Monitoring should include looking for consequences of chronic injury, including diabetes mellitus and compromise of the pancreatic and biliary ducts.
- Pancreatic and biliary imaging has been accomplished by ERCP.
- ERCP offers the possibility of therapeutic intervention to remove gallstones, dilate strictures, and place stents to enhance flow of pancreatic juice.
- Magnetic resonance cholangiopancre-atography is an alternative to ERCP.
- Plain abdominal x-rays may show pancreatic calcifications.
- Diagnostic testing for the etiology of chronic pancreatitis should include genetic testing for hereditary pancreatitis and cystic fibrosis and sweat chloride determination.

### Treatment

- Treatment is largely supportive.
- Potential but unproven therapies include;
  1. daily pancreatic enzyme supplements
  2. octreotide (somatostatin) to abort early attacks
  3. low-fat diets
  4. daily antioxidant therapy
- Interventional ERCP to dilate large strictures and remove stones and surgical pancreatic drainage procedures to decompress dilated pancreatic ducts by creating a side-to-side pan-creaticojejunostomy may have some value.

## Peritonitis

### ETIOLOGY AND EPIDEMIOLOGY

- The peritoneum consists of a single layer of mesothelial cells that covers all intra-abdominal organs.
  - ♣ The portion that covers the abdominal wall is derived from the underlying somatic structures and is innervated by somatic nerves.
  - ♣ The portion covering the viscera is derived from visceral mesoderm and is innervated by nonmyelinated visceral afferents.
- Peritonitis causes:
  1. usually by infection
  2. exogenous irritants introduced by penetrating injuries or surgical procedures
  3. radiation
  4. endogenous irritants, such as meconium.
- Infectious peritonitis can be:
  - ♣ acute complication of intestinal inflammation and perforation, as in appendicitis
  - ♣ secondary to contamination of preexisting ascites associated with renal, cardiac, or hepatic disease.
- In this setting, when there is no other intra-abdominal source, it is referred to as **spontaneous bacterial peritonitis**. usually due to pneumococcus & less often to *E. coli.*

### CLINICAL MANIFESTATIONS

- Peritonitis is characterized on examination by marked abdominal tenderness.
- Rebound tenderness also generally is quite pronounced.
- The patient tends to move very little owing to intense peritoneal irritation and pain.
- Fever is not always present, and absence of fever should not be regarded as contradictory to the diagnosis.
- Patients who are taking corticosteroids for an underlying condition, such as nephrotic syndrome, are likely to have little fever and reduced tenderness.

## LABORATORY AND IMAGING STUDIES

- An elevated WBC count, ESR, and CRP suggest infection.
- In children older than 5 years, appendicitis is the leading cause.
- Total serum protein, albumin, and urinalysis to rule out nephrotic syndrome.
- Liver function tests should be performed to rule out chronic liver disease causing ascites.
- The best way to diagnose suspected peritonitis is to sample the peritoneal fluid with a needle or catheter (paracentesis).
  - ♣ Peritoneal fluid in spontaneous bacterial peritonitis has a high neutrophil count of > 250 cells/$mm^3$.
  - ♣ Others: amylase (to rule out pancreatic ascites), culture, albumin, and lactate dehydrogenase concentration.
  - ♣ For culture, a large sample of fluid should be placed into aerobic and anaerobic blood culture bottles immediately on obtaining the sample.

## TREATMENT

- Peritonitis caused by an intra-abdominal surgical process, such as appendicitis or a penetrating wound, must be managed surgically.
- Spontaneous bacterial peritonitis should be treated with a broad-spectrum antibiotic with good coverage of resistant pneumococcus and enteric bacteria.
  - ♣ Cefotaxime is generally effective as initial therapy while awaiting culture and sensitivity results.
  - ♣ Anaerobic coverage with metronidazole should be added whenever a perforated viscus is suspected.

# M ALABSORBTION

DR MUTAZ SULTAN

- Malabsortive syndroms are conditions that cause insuffecient assimilation of ingested nutrients either due maldigestion or malabsorption
- Classification of malabsorption
  1. Impaired intraluminal digestion
  2. Intestinal malabsorption
  3. Fermentation

## MALABSORPTION DUE TO IMPAIRED INTRALUMINAL DIGESTION :

1. CF .
2. Schwachman syndrome
3. Isolated lipase deficiency
4. Impaired bile synthesis
5. Billiary obstruction
6. Interrupted enterohepatic circulation :Crohns disease, Ileal resection .
7. Congenital trypsinogen or enterokinase deficiency .

## INTESTINAL MALABSORPTION

1. Celiac disease
2. Cow's milk allergy
3. Giardia infestation
4. Post enteritis syndrome
5. Immunodeficiency syndromes
6. Crohns disease
7. Short bowl syndrome
8. Autoimmune enteropathy
9. Cong microvillous atrophy
10. Selective transport defect

## MALABSORPTION DUE TO FERMENTATION

1. Disacharidase deficiency:
   - ♣ Lactase deficiency ( cong and $2^{nd}$).
   - ♣ Sucarase isomaltase deficiency
2. Monosacharide malabsorption:
   - ♣ Glocose – galactose malabsorption .

- ♣ Fructose malabsorption .
- In the primary forms the small intestine has normal structure .

## CLINICAL MANIFISTATIONS:

- Many disorders of malabsorption are inherited .
- Careful history of time of onset of symptoms and the relation to diet is important .
- Congenital disorders may present from birth, others present after introducing specific food
- Malabsorption may present as watery diarrhea, acidic diarrhea or steotorrhea .
- normal stool does not rule out malabsorption .
- Frequency, looseness, quantity of stool are helpful .
- Color is rarely informative .
- Growth pattern is imp .
- Signs of malnutrition:lethargy ,decreased S.C tissue,ms waisting,edema,clubbing and depigmentation of skin and hair
- Common symptoms of malabsorbtion:
  1. Chronic diarrhea .
  2. Wt loss or slowed growth
  3. Abdominal distention
  4. Decreased turgor
  5. Vomiting
  6. Anemia
  7. Edema
  8. 2nd vitamin deficiency

## LAB FINDINGS:

- Stool for fat:most useful screening test,6-8 and more is abnormal .
- Positive test should be confirmed with 72hr fecal fat test. Premature infant absorbe 65%_75% of dietery fat,older children absorbe>95%of dietary fat .
- steatorhea is most prominent with pancreatic insufficiency which is indication of sweat test .
- Blood test for pancreatic enz& hormons(limited value).Trypsinogen is good screening test
- Measurement of CHO in the stool by using reagent for reducing substances .+2 & highier raises the possibility of CHO malabsorption .
- Excess CHO in stool leads to acidic flautulance & abd distention.Stool ph <5.6 suggest CHO malabsorption (CHO fermented in the colon to lactic acid & short chain fatty acid).
- H breath test can be used to asses CHO malabsorption
- Protein loss can,t be evaluated directly.
- Low albumin level may result from difficult assimilation of dietary protein or other cause.
- Spot stool for alpha antitrypsin for diagnosis of protein loosing enteropathy.
- Specific nutrient measurement:.iron,folate,B12,ca
- Microbiology:stool for giardia &HIV.
- Small bowl biopsy: for celiac, abetalipoprotenemia& lymphangectasia .
- Hematological: microcyts, macrocyts, neutropenia .

# The Cardiovascular System

# ASSESSMENT

## HISTORY

- Heart disease in children =combination of genetic and environmental causes.
- The **prenatal history** : evidence of a maternal infection:
  - ♥ early in pregnancy (possibly teratogenic)
  - ♥ Later in pregnancy (causing myocarditis or myocardial dysfunction in infants).
- A **maternal history** of medication, drug, or alcohol use or excessive smoking may contribute to cardiac and other systemic findings.
- **Growth** is an extremely valuable sign of cardiovascular health.
  - ♥ Infants with **congestive heart failure (CHF)** grow poorly, with weight being more significantly affected than height and HC.
- CHF present with:
  1. **fatigue** or **diaphoresis** with feeds
  2. **fussiness**
  3. **tachypnea** and **dyspnea**
  4. **feeding is difficult and prolonged**
  5. **easy fatigability**, **shortness of breath** on exertion, and **orthopnea**(Older children)
  6. **Exercise intolerance**: by asking how well children keep up playing with their friends or in physical education class.
  7. Before diagnosis of CHF, patients may have been diagnosed **with recurrent "pneumonia," "bronchitis," wheezing, or asthma.**
- A history of a heart **murmur** is important, but many well children have a normal or innocent heart murmur at some time in their life.
- Other cardiac symptoms include cyanosis, palpitations, chest pain, syncope, and near-syncope.
- A review of systems for possible systemic diseases or congenital malformation syndromes that may cause cardiac abnormalities.
- A history of drug use is important in older children and adolescents
- **Family history** for:
  1. early atherosclerotic heart disease
  2. congenital heart disease
  3. sudden unexplained deaths
  4. thrombophilia
  5. rheumatic fever
  6. hypertension
  7. hypercholesterolemia

### CARDIAC MANIFESTATIONS OF SYSTEMIC DISEASES

| Systemic Disease | Cardiac Complications |
|---|---|
| Hunter-Hurler syndrome | Valvular insufficiency, heart failure, hypertension |
| Fabry disease | Mitral insufficiency, coronary artery disease with myocardial infarction |
| Pompe disease | Short P-R interval, cardiomegaly, heart failure, arrhythmias |
| Friedreich ataxia | Cardiomyopathy, arrhythmias |
| Duchenne dystrophy | Cardiomyopathy, heart failure |
| Juvenile rheumatoid arthritis | Pericarditis |
| Systemic lupus erythematosus | Pericarditis, Libman-Sacks endocarditis, congenital AV block |
| Marfan syndrome | Aortic and mitral insufficiency, dissecting aortic aneurysm |
| Homocystinuria | Coronary thrombosis |
| Kawasaki disease | Coronary artery aneurysm, thrombosis, myocardial infarction, myocarditis |
| Lyme disease | Arrhythmias, myocarditis, heart failure |
| Graves disease (hyperthyroidism) | Tachycardia, arrhythmias, heart failure |
| Tuberous sclerosis | Cardiac rhabdomyoma |
| Neurofibromatosis | Pulmonic stenosis, coarctation of aorta |

## PHYSICAL EXAMINATION

- Information regarding the cardiovascular status can be gained by observation and **inspection**, which is supplemented by **palpation** and **auscultation**.
- The examination starts with vital signs: heart rate, respiratory rate, and blood pressure.
- The normal **heart rate** varies with age and activity.
  - ♥ Tachycardia :
    1. anemia
    2. dehydration
    3. shock
    4. heart failure
    5. dysrhythmia.
  - ♥ Bradycardia :
    1. normal finding in patients with high vagal tone (athletes)
    2. atrioventricular block.
- The **respiratory rate** ↑:
  1. left-to-right shunt
  2. pulmonary venous congestion.
- The normal **blood pressure** also varies with age.
  - ♥ A properly sized cuff: bladder width 90% of the arm circumference and a length that is 80% to 100% of the arm circumference.
  - ♥ initially, blood pressure in the right arm is measured. If elevated, measurements in the left arm and leg are indicated → coarctation of the aorta.
- The **pulse pressure**
  - ♥ Systolic pressure – diastolic pressure = < 50 mm Hg or half the systolic pressure.
  - ♥ A wide pulse pressure is seen with:
    1. aortopulmonary connections (PDA, truncus arteriosus)
    2. arteriovenous malformations
    3. aortic insufficiency
    4. relative intravascular volume depletion (anemia, vasodilation with fever or sepsis).
  - ♥ A narrow pulse pressure is seen with:
    1. pericardial tamponade
    2. aortic stenosis
    3. CHF
- Many chromosomal abnormalities and syndromes associated with cardiac defects have dysmorphic features or failure to thrive.
- Skin color must be assessed for **cyanosis** and pallor. Perioral cyanosis is a common finding in pale infants or when infants and toddlers become cold.
- Chronic arterial desaturation results in **clubbing** of the fingernails and toenails.
- Inspection of the chest may reveal asymmetry or a prominent left precordium suggesting chronic cardiac enlargement.
- Pulses should be assessed for rate, regularity, intensity, symmetry, and timing between upper and lower extremities.
- The presence of a good pedal pulse effectively rules out coarctation of the aorta if the right arm blood pressure is normal.
- The precordium should be assessed for apical impulse, **point of maximum impulse**, hyperactivity, and presence of a **thrill**.
- Abdominal palpation is primarily for assessment of liver and spleen size.
  - ♥ The liver size provides a good assessment of intravascular volume and is enlarged with systemic venous congestion.
  - ♥ splenomegaly: rarely with heart failure, infective endocarditis.

## Congenital Malformation Syndromes Associated with Congenital Heart

| Syndrome | Cardiac Features |
|---|---|
| Trisomy 21 (Down syndrome) | Endocardial cushion defect, VSD, ASD, PDA |
| Trisomy 18 | VSD, ASD, PDA, PS |
| Trisomy 13 | VSD, ASD, PDA, dextrocardia |
| XO (Turner syndrome) | Coarctation of aorta, aortic stenosis |
| CHARGE association (*c*oloboma, *h*eart, *a*tresia choanae, *r*etardation, *g*enital and *e*ar anomalies) | TOF, aortic arch and conotruncal anomalies* |
| 22q11 (DiGeorge) syndrome | Aortic arch anomalies, conotruncal anomalies* |
| VACTERL association† (*v*ertebral, *a*nal, *c*ardiac, *t*racheo*e*sophageal, *r*adial, *r*enal, *l*imb anomalies) | VSD |
| Congenital rubella | PDA, peripheral pulmonic stenosis, mitral regurgitation (in infancy) |
| Marfan syndrome | Dilated and dissecting aorta, aortic valve regurgitation, mitral valve prolapse |
| Williams syndrome | Supravalvular aortic stenosis, peripheral pulmonary stenosis |
| Infant of diabetic mother | Hypertrophic cardiomyopathy, VSD, conotruncal anomalies |
| Holt-Oram syndrome | ASD, VSD |
| Asplenia syndrome | Complex cyanotic heart lesions, anomalous pulmonary venous return, dextrocardia, single ventricle, single AV valve |
| Polysplenia syndrome | Azygos continuation of inferior vena cava, pulmonary atresia, dextrocardia, single ventricle |
| Fetal alcohol syndrome | VSD, ASD |
| Ellis-van Creveld syndrome | Single atrium |
| Zellweger syndrome | PDA, VSD, ASD |
| Fetal hydantoin syndrome | TGA, VSD, TOF |
| | |

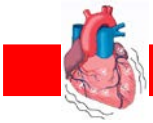
*Conotruncal-tetralogy of Fallot, pulmonary atresia, truncus arteriosus, transposition of great arteries.

# Heart Sounds

## Abnormal Second Heart Sound

| |
|---|
| **Single $S_2$** |
| Pulmonary hypertension (severe) |
| One semilunar valve (aortic atresia, pulmonary atresia, truncus arteriosus) |
| Malposed great arteries (*d*-TGA, *l*-TGA) |
| Severe aortic stenosis |
| **Widely split $S_2$** |
| Increased flow across valve (ASD, PAPVR) |
| Prolonged flow across valve (pulmonary stenosis) |
| Electrical delay (right bundle branch block) |
| Early aortic closure (severe mitral regurgitation) |
| **Paradoxically split $S_2$** |
| Severe aortic stenosis |
| **Abnormal intensity of $P_2$** |
| Increased in pulmonary hypertension |
| Decreased in severe pulmonary stenosis, tetralogy of Fallot |

- **$S_1$** = closure of the mitral and tricuspid valves, is usually single, and is best heard at the lower left sternal border or apex, if a split $S_1$ is heard: normal, ejection click or $S_4$.
- **$S_2$**= closure of the aortic and pulmonary valves.$S_2$ normally split with inspiration and be single with expiration.
- $S_3$ is heard in early diastole and is related to rapid ventricular filling. It is best heard at the LLSB or apex, normal sound. A loud $S_3$ =dilated ventricles.



- $S_4$ occurs late in diastole just before $S_1$. It is best heard at the LLSB/apex and is associated with decreased ventricular compliance. It is rare and is always abnormal.

## CLICKS

- A click implies a valvular abnormality or dilated great artery
- Ejection or mid-systolic in timing.
- A mid-systolic click is associated with mitral valve prolapse.
- **Ejection clicks** early in systole.
  - ♥ Pulmonary ejection clicks are best heard at the left upper sternal border and vary in intensity with respiration.
  - ♥ Aortic clicks are louder at the apex, left mid-sternal border, or right upper sternal border. They do not vary with respiration.

## MURMURS

- Murmurs should be classified as **systolic**, **diastolic**, or **continuous** .
- **Ejection murmurs** are crescendo-decrescendo with a short time between $S_1$ and the onset of the murmur (isovolumic contraction).
  1. aortic stenosis
  2. pulmonic stenosis
  3. atrial septal defects (ASDs)
  4. coarctation of the aorta
- **Holosystolic murmurs** have onset with $S_1$, and there is flow during isovolumic contraction. heard with:
  1. ventricular septal defects (VSDs)
  2. mitral regurgitation
  3. tricuspid regurgitation
- A "late regurgitant" murmur may be heard after the mid-systolic click in mitral valve prolapse.
- Ejection murmurs usually are best heard at the base of the heart, whereas holosystolic murmurs are louder at the lower left sternal border and apex.
- Pulmonary ejection murmurs radiate to the back and axilla, whereas aortic ejection murmurs radiate to the neck.
- Early diastolic murmurs occur when there is regurgitation through the aortic or pulmonary valves.
- Mid-diastolic murmurs are heard when there is increased flow across the mitral or tricuspid valves (VSD, ASD), or when there is anatomic stenosis at these valves.
- The intensity or loudness of a heart murmur is graded I - VI .

### HEART MURMUR INTENSITY

| | |
|---|---|
| Grade I | Very soft, heard in quiet room with cooperative patient |
| Grade II | Easily heard but not loud |
| Grade III | Loud but no thrill |
| Grade IV | Loud with palpable **thrill** |
| Grade V | Loud with thrill, audible with stethoscope at 45-degree angle |
| Grade VI | Loud with thrill, audible with stethoscope off chest 1 cm |

***Continuous murmurs**:*

- heard when there is flow throughout the entire cardiac cycle and are abnormal with one common exception, the **venous hum**
- A PDA is the most common abnormal continuous murmur.
- Continuous murmurs can also be heard with coarctation of the aorta when collateral vessels are present.

***Normal physiologic or innocent murmurs***

- common, occurring in at least 80% of normal infants and children at some time in life.
- called *benign, functional, vibratory,* and *flow murmurs*.
- These normal murmurs are heard most often during the first 6 months of life, from 3 to 6 years of age, and in early adolescence.

- Characteristic findings of innocent murmurs include:
  1. the quality of the sound
  2. lack of significant radiation
  3. significant alteration in the intensity of the murmur with positional changes
  4. the cardiovascular history and examination are otherwise normal.
- The presence of symptoms, including failure to thrive or dysmorphic features, should make one more cautious about diagnosing a "normal" murmur.
- Diastolic, holosystolic, late systolic, and continuous (except for the venous hum) murmurs and the presence of a thrill are not normal.

## Normal or Innocent Heart Murmurs

| Murmur | Timing/Location/Quality | Usual Age |
|---|---|---|
| Still murmur/vibratory murmur | Systolic ejection murmur | 3-6 yr |
| | LLSB or between LLSB and apex | |
| | Grade I-III/VI | |
| | Vibratory, musical quality | |
| | Intensity decreases in upright position | |
| **Venous hum** | Continuous murmur | 3-6 yr |
| | Infraclavicular region (right > left) | |
| | Grade I-III/VI | |
| | Louder in upright position | |
| | Changes with compression of jugular vein or turning head | |
| Carotid bruit | Systolic ejection murmur | Any age |
| | Neck, over carotid artery | |
| | Grade I-III/VI | |
| Adolescent ejection murmur | Systolic ejection murmur | 8-14 yr |
| | LUSB | |
| | Grade I-III/VI | |
| | Usually softer when upright position | |
| | Does not radiate to back | |
| Peripheral pulmonic stenosis | Systolic ejection murmur | Newborn-6 mo |
| Murmur of infancy | Axilla and back, LUSB/RUSB | |
| | Grade I-II/VI | |
| | Harsh, short, high frequency | |

# PERICARDITIS

- Pericarditis is inflammation of the parietal and visceral surfaces of the pericardium.

## ETIOLOGY

- It is most often **viral** in origin.
- A bacterial etiology is rare, ***S. aureus*** **and** ***Streptococcus pneumoniae*** are the most likely bacterial causes. causes a much more serious and symptomatic pericarditis
- Pericarditis is associated with:
  1. **collagen vascular diseases**, such as rheumatoid arthritis.
  2. **uremia**
  3. **Postpericardiotomy syndrome** is common form of pericarditis follows heart surgery.

### ETIOLOGY OF PERICARDITIS AND PERICARDIAL EFFUSION

| IDIOPATHIC (PRESUMED VIRAL) INFECTIOUS AGENTS |
|---|
| *Bacteria* |
| Group A streptococcus *Staphylococcus aureus* |
| *Viral*† |
| Coxsackievirus (group A, B), Hepatitis B |
| Echovirus, Herpes simplex, Herpes zoster |
| Mumps, Epstein-Barr, Cytomegalovirus, Influenza |
| *Fungal:* Histoplasma capsulatum |
| *Parasitic* |
| Toxoplasma gondii, Entamoeba histolytica, Schistosomes |
| **COLLAGEN VASCULAR-INFLAMMATORY AND GRANULOMATOUS DISEASES** |
| Rheumatic fever, Mixed connective tissue disease, Reiter syndrome, IBD,SLE (idiopathic and drug-induced),Wegener granulomatosis,RA,Kawasaki disease,Scleroderma,Dermatomyositis,Stevens-Johnson syndrome |
| **TRAUMATIC** |
| Cardiac contusion (blunt trauma),Penetrating trauma,Postpericardiotomy syndrome,Radiation |
| **CONTIGUOUS SPREAD** |
| Pleural disease,Pneumonia,Aortic aneurysm (dissecting) |
| **METABOLIC** |
| Hypothyroidism,Uremia,Gaucher disease,Chylopericardium,Fabry disease |
| **NEOPLASTIC** |
| Primary Contiguous (lymphoma),Metastatic Infiltrative (leukemia) |
| **OTHERS** |
| Drug reaction,Pancreatitis,After myocardial infarction,Heart failure,Hemorrhage (coagulopathy),Biliary-pericardial fistula,Thalassemia |

## CLINICAL MANIFESTATIONS

- The symptoms of pericarditis depend on the amount of fluid in the pericardial space and how fast it accumulates.The faster, the sooner the pt is hemodynamically compromised.
- symptoms:
  1. Chest pain (worsened if lying down or with inspiration)
  2. Patient assumes sitting position
  3. Dyspnea & Malaise
- Signs:
  - *Nonconstrictive*:
    1. Fever, Tachycardia
    2. Friction rub (accentuated by inspiration, body position)
    3. Enlarged heart by percussion and x-ray examination
    4. Distant heart sounds
  - *Tamponade* : *As above*, *plus*:
    1. Distended neck veins
    2. Hepatomegaly
    3. Pulsus paradoxus (>10 mm Hg with inspiration)
    4. Narrow pulse pressure ,Weak pulse
    5. poor peripheral perfusion

- *Constrictive Pericarditis*:
  1. Distended neck veins
  2. Kussmaul sign (inspiratory increase of jugular venous pressure)
  3. Distant heart sounds
  4. Pericardial knock
  5. Hepatomegaly
  6. Ascites, Edema
  7. Tachycardia.

## IMAGING AND LABORATORY STUDIES

- ***Echocardiography*** is the most specific and useful diagnostic test .
- **A chest x-ray** reveals cardiomegaly. A large effusion creates a rounded, globular cardiac silhouette.
- **The ECG** shows tachycardia, elevated ST segments, and changes in the QRS complex.
- **blood tests** & **diagnostic testing of pericardial fluid :** identify The causative organism.

### LABORATORY EVIDENCE OF PERICARDITIS

| Test | Evidence Seen |
|---|---|
| ECG | Elevated ST segments, T wave inversion (late), tachycardia, reduced QRS voltage, electrical alternans (variable QRS amplitudes) |
| Chest radiograph | Cardiomegaly ("water bottle heart") |
| Echocardiogram | Pericardial fluid |
| Pericardiocentesis | Gram and acid-fast stains, culture, PCR (virus, bacteria, mycobacteria, fungus), cytology, cell count, glucose, protein, pH |
| Blood tests | ESR, viral titers, ANA, ASO titers, EBV titers |

## TREATMENT

- **Pericardiocentesis** is indicated for:
  1. treatment of hemodynamically significant effusions
  2. provides valuable information regards to the etiology of the pericarditis.
- There is no specific treatment for viral pericarditis other than **anti-inflammatory medications**.

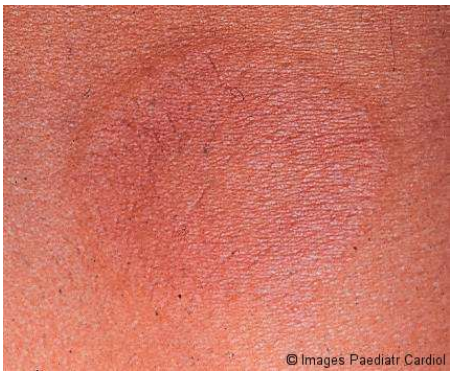
# RHEUMATIC FEVER

## ETIOLOGY AND EPIDEMIOLOGY

- most common in children 6 - 15 years old.
- It is due to an immunologic reaction that is a delayed sequela of group A betahemolytic streptococcal infections of the pharynx
- A family history of rheumatic fever and lower socioeconomic status are additional factors.

## CLINICAL MANIFESTATIONS

- Acute rheumatic fever is diagnosed using the **revised Jones criteria**, which consist of clinical and laboratory findings.
  - The presence of either two **major criteria** or one major and two **minor criteria**, along with evidence of an antecedent **streptococcal infection** confirm the diagnosis e.g.:
    1. scarlet fever
    2. positive throat culture
    3. elevated antistreptolysin O or other antistreptococcal antibodies
- The infection often precedes the presentation of rheumatic fever by 2 to 6 weeks.
- Streptococcal antibody tests, such as the antistreptolysin O titer, are the most reliable laboratory evidence of prior infection.
- **Arthritis** is the **most common major manifestation**. It involves the large joints and is migratory.
- Arthralgia cannot be used as a minor manifestation if arthritis is used as a major manifestation.
- **Carditis** occurs in 50% of pts.
  1. Tachycardia
  2. new murmur (mitral or aortic regurgitation)
  3. pericarditis
  4. cardiomegaly
  5. **Signs of CHF**



- **Erythema marginatum**, a serpiginous, nonpruritic, and evanescent rash, uncommon, occurs on the trunk, and is brought out by warmth.
- **Subcutaneous nodules**: predominantly with chronic or recurrent dz. firm, painless, non-pruritic, mobile nodules, on the extensor surfaces of large and small joints, scalp & spine.
- **Chorea** (Sydenham chorea or St. Vitus dance) consists of neurologic and psychiatric signs. It also is uncommon and often presents long after the infection.

### MAJOR CRITERIA IN THE JONES SYSTEM FOR ACUTE RHEUMATIC FEVER

| SIGN | COMMENTS |
|---|---|
| 1. **Polyarthritis** | Common; swelling, limited motion, tender, erythema |
| | Migratory; involves large joints but rarely small or unusual joints, such as vertebrae |
| 2. **Carditis** | Common; pancarditis, valves, pericardium, myocardium |
| | Tachycardia greater than explained by fever; new murmur of mitral or aortic insufficiency; Carey-Coombs mid-diastolic murmur; heart failure |
| 3. **Chorea (Sydenham disease)** | Uncommon; presents long after infection has resolved; more common in females; antineuronal antibody positive |
| 4. **Erythema marginatum (10%)** | Uncommon; pink macules on trunk and proximal extremities, evolving to serpiginous border with central clearing; evanescent, elicited by application of local heat; nonpruritic |
| 5. **Subcutaneous nodules** | Uncommon; associated with repeated episodes and severe carditis; present over extensor surface of elbows, knees, knuckles, and ankles or scalp and spine; firm, nontender |

MINOR CRITERIA :

1. fever ( [38.2°C - 38.9°C])
2. leukocytosis
3. ↑ESR/CRP
4. arthralgias
5. Prolonged P-R interval
6. previous rheumatic fever


## TREATMENT AND PREVENTION

- Management of acute rheumatic fever consists of :
  1. **benzathine penicillin** to eradicate the betahemolytic streptococcus,
  2. anti-inflammatory therapy with **salicylates** after the diagnosis is established
  3. **bed rest**.
- **Long-term penicillin prophylaxis**, preferably with IM benzathine penicillin G, 1.2 million U every 28 days, is required. Oral regimens for prophylaxis are not as effective.

## PROGNOSIS

- acute rheumatic fever depends on the degree of permanent cardiac damage.
- Cardiac involvement may resolve completely, especially if it is the first episode and the prophylactic regimen is followed.
- The severity of cardiac involvement worsens with each recurrence of rheumatic fever.

# CONGESTIVE HEART FAILURE

## ETIOLOGY AND EPIDEMIOLOGY

- As the preload (fiber length, left ventricular filling pressure or volume) increases, the myocardial performance (stroke volume and wall tension) increases up to a point (the normal Starling curve).
- Heart rate is another important determinant of cardiac work because the cardiac output equals stroke volume times the heart rate.
- CHF is defined as the pathophysiologic state in which the heart is unable to pump blood at a rate commensurate with the body's metabolic needs (oxygen delivery).
- may be due to:
  1. Change in **myocardial contractility** → low cardiac output
  2. **abnormal loading conditions** being placed on the myocardium.
     - ♥ **afterload** (pressure overload, such as with aortic stenosis, pulmonary stenosis, or coarctation of the aorta)
     - ♥ **preload** (volume overload, such as in VSD, PDA, or valvular insufficiency)

- **Volume overload is the most common cause** of CHF in children.

## ETIOLOGY OF HEART FAILURE

| |
|---|
| **Fetus** |
| Severe anemia (hemolysis, fetal-maternal transfusion, hypoplastic anemia) |
| SVT,VT ,Complete heart block |
| Atrioventricular valve insufficiency |
| High-output cardiac failure (AV malformation, teratoma) |
| **Premature Neonate** |
| Fluid overload |
| PDA, VSD |
| Cor pulmonale (BPD) |
| **Full-Term Neonate** |
| Asphyxial cardiomyopathy |
| AV malformation (vein of Galen, hepatic) |
| Left-sided obstructive lesions (coarctation of aorta, hypoplastic left heart, critical aortic stenosis) |
| Transposition of great arteries |
| Large mixing cardiac defects (single ventricle, truncus arteriosus) |
| Viral myocarditis |
| Anemia |
| SVT ,Complete heart block |
| **Infant-Toddler** |
| Left-to-right cardiac shunts (VSD) , Postoperative repair of congenital heart disease |
| Hemangioma (arteriovenous malformation) |
| Anomalous left coronary artery |
| Metabolic cardiomyopathy |
| Acute hypertension (hemolytic-uremic syndrome) |
| SVT |
| Kawasaki disease |
| **Child-Adolescent** |
| Rheumatic fever ,Viral myocarditis , Endocarditis |
| Acute hypertension (glomerulonephritis) |
| Thyrotoxicosis, Arrhythmias |
| Hemochromatosis-hemosiderosis |
| Cancer therapy (radiation, doxorubicin) |
| Sickle cell anemia |
| Cor pulmonale (cystic fibrosis ,Chronic upper airway obstruction) |
| Unrepaired or palliated congenital heart disease |
| Cardiomyopathy |

- In the **first weeks of life**, CHF is most commonly due to an **excessive afterload** .
- CHF presenting around 2 months of age is usually due to increasing left-to-right shunts of congenital heart defects as the pulmonary vascular resistance decreases.
- Acquired heart disease, such as myocarditis & cardiomyopathy, can present at any age.

## CLINICAL MANIFESTATIONS

- Clinical presentation of CHF in infants includes:
  1. poor feeding
  2. failure to thrive
  3. tachypnea
  4. diaphoresis with feeding
- Older children may present with :
  1. shortness of breath
  2. easy fatigability
  3. edema
- The physical examination findings depend on whether pulmonary venous congestion, systemic venous congestion, or both are present.

- ♥ Tachycardia, a gallop rhythm, and thready pulses may be present with either cause.
- ♥ If left-sided failure is predominant, tachypnea,orthopnea,wheezing,Pulmonary edema .
- ♥ If right-sided failure is present, hepatomegaly, edema, distended neck veins

## IMAGING STUDIES

- **chest radiography**, are not specific, absence of cardiomegaly on a chest x-ray R/O CHF.
- **An echocardiogram** assesses the heart chamber sizes, measures myocardial function accurately, and diagnoses congenital heart defects when present.

## TREATMENT OF HEART FAILURE

| Therapy | Mechanism |
|---|---|
| **General Care** | |
| Rest | Reduces cardiac output |
| Oxygen | Improves oxygenation in presence of pulmonary edema |
| Sodium, fluid restrictions | Decreases vascular congestion; decreases preload |
| **Diuretics** | |
| Furosemide | Salt excretion by ascending loop of Henle; reduces preload; afterload reduced if hypertension improves; may also cause venodilation |
| Combination of distal tubule and loop diuretics | Greater sodium excretion |
| **Inotropic Agents** | |
| Digitalis | Inhibits membrane $Na^+$, $K^+$-ATPase and increases intracellular $Ca^{2+}$, improves cardiac contractility, increases myocardial oxygen consumption |
| Dopamine | Releases myocardial norepinephrine plus direct effect on β-receptor, may increase systemic blood pressure; at low infusion rates, dilates renal artery, facilitating diuresis |
| Dobutamine | $\beta_1$-receptor agent; often combined with dopamine |
| Amrinone/milrinone | Nonsympathomimetic, noncardiac glycosides with inotropic effects; may produce vasodilation |
| **Afterload Reduction** | |
| Hydralazine | Arteriolar vasodilator |
| Nitroprusside | Arterial and venous relaxation; venodilation reduces preload |
| Captopril/enalapril | Inhibition of angiotensin-converting enzyme; reduces angiotensin II production |
| **Other** | |
| Mechanical counterpulsation | Improves coronary flow, afterload |
| Transplantation | Removes diseased heart |
| Extracorporeal membrane oxygenation | Bypasses heart |
| Carvedilol | β-blocking agent |

- Initial treatment is directed at improving myocardial function and optimizing preload and afterload.
- Long-term therapy is usually **digoxin** and diuretics.
- Depending on the etiology of failure, afterload reduction frequently is added.
- Long-term therapy with **β-blockers** is beneficial.

# CARDIAC DYSARHYTHMIAS

## ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

- Cardiac dysrhythmias are uncommon in pediatrics, but may be caused by:
  1. infection and inflammation
  2. structural lesions
  3. metabolic abnormalities
  4. intrinsic conduction abnormalities
- Many pediatric dysrhythmias are normal variants that do not require treatment or even further evaluation.

- **Sinus rhythm** originates in the sinus node and has a normal axis P wave (upright in leads I and AVF) preceding each QRS complex.
- sinus bradycardia and sinus tachycardia are defined based on age.
- **Sinus arrhythmia** is a common finding in children
  - ♥ Represents a normal variation in the heart rate associated with breathing.
  - ♥ The heart rate increases with inspiration and decreases with expiration, producing a recurring pattern on the ECG tracing.
  - ♥ does not require further evaluation or treatment.

## Etiology of Arrhythmias

| **Drugs** |
|---|
| Intoxication (cocaine, tricyclic antidepressants, and others) |
| Antiarrhythmic agents (proarrhythmic agents [quinidine]) |
| Sympathomimetic agents (caffeine, theophylline, ephedrine, and others) |
| Digoxin |
| **Infection and Postinfection** |
| Endocarditis |
| Lyme disease |
| Diphtheria |
| Guillain-Barré syndrome |
| Rheumatic fever |
| **Metabolic-Endocrine** |
| Cardiomyopathy |
| Electrolyte disturbances (↓↑$K^+$, ↓↑$Ca^{2+}$, ↓$Mg^{2+}$) |
| Uremia |
| Thyrotoxicosis |
| Pheochromocytoma |
| Porphyria |
| Mitochondrial myopathies |
| **Structural Lesions** |
| Mitral valve prolapse |
| Ventricular tumor |
| Ventriculotomy |
| Pre-excitation and aberrant conduction system (Wolff-Parkinson-White syndrome) |
| Congenital heart defects |
| Arrhythmogenic right ventricle (dysplasia) |
| **Other Causes** |
| Adrenergic-induced |
| Prolonged Q-T interval |
| Maternal SLE |
| Idiopathic |
| Central venous catheter |

## Atrial Dysrhythmias

- A **wandering atrial pacemaker** :
  - ♥ change in the morphology of P waves with variable P-R interval & normal QRS.
  - ♥ This is a benign finding, requiring no further evaluation or treatment.
- **Premature atrial contractions:**
  - ♥ Relatively common prenatally and in infants.
  - ♥ A premature P wave, with abnormal axis consistent with its ectopic origin, is present.
  - ♥ The premature atrial activity may be:
    1. blocked (no QRS following it)
    2. conducted normally (normal QRS present)
    3. Conducted aberrantly (a widened, altered QRS morphology).
- Premature atrial contractions are usually benign and, if present around the time of delivery, often disappear during the first few weeks of life.

- **Atrial flutter** & **atrial fibrillation** are uncommon dysrhythmias in pediatrics
  1. after surgical repair of complex congenital heart disease
  2. myocarditis
  3. drug toxicity.
- **Supraventricular tachycardia** (SVT) :
  - ♥ the most common symptomatic arrhythmia in pediatric patients.
  - ♥ The rhythm is a rapid, regular rate with a narrow complex QRS.
  - ♥ SVT in infants is 280-300 beats/min with slower rates for older children & adolescents.
  - ♥ The tachycardia has an abrupt onset and termination.
  - ♥ In a child with a structurally normal heart, most episodes are relatively asymptomatic other than a pounding heart beat.
  - ♥ If there is structural heart disease or the episode is prolonged (>12 hours), there may be alteration in the cardiac output and development of symptoms of CHF.
  - ♥ most patients with SVT have structurally normal hearts and normal baseline ECGs,
  - ♥ some children have **Wolff-Parkinson-White syndrome** or pre-excitation as A cause

## VENTRICULAR DYSRHYTHMIAS

- **Premature ventricular contractions** :
  - ♥ less common than premature atrial contractions in infancy but more common in older children and adolescents.
  - ♥ not preceded by a P wave, and the QRS complex is wide and bizarre.
  - ♥ benign and require no treatment If:
    1. the heart is structurally normal
    2. the premature ventricular contractions are singleton, uniform in focus, and disappear with increased heart rate.
  - ♥ Any deviation from this presentation, ex: history of syncope or a family history of sudden death, requires further investigation and treatment with antiarrhythmic drugs.
- **Ventricular tachycardia**:
  - ♥ defined as three or more consecutive premature ventricular contractions
  - ♥ relatively rare in pediatric patients.
  - ♥ usually is a sign of serious cardiac dysfunction or pathology.
  - ♥ Rapid rate ventricular tachycardia results in decreased cardiac output and cardiovascular instability.
  - ♥ Treatment in symptomatic patients is synchronized cardioversion.
  - ♥ Medical management with lidocaine or amiodarone may be appropriate in a conscious asymptomatic patient.

### CLASSIFICATION OF DRUGS FOR ANTIARRHYTHMIA

| CLASS | ACTION | EXAMPLES |
|---|---|---|
| **I** | Depresses phase o depolarization (velocity of upstroke of action potential); **sodium channel blockers** | |
| | **Ia** Prolongs QRS complex and Q-T interval | **Quinidine**, **procainamide**, disopyramide |
| | **Ib** Significant effect on abnormal conduction | **Lidocaine**, mexiletine, **phenytoin**, tocainide |
| | **Ic** Prolongs QRS complex and P-R interval | Flecainide, propafenone, moricizine |
| **II** | **β blockade**, slows sinus rate, prolonged P-R interval | Propranolol, atenolol, acebutolol |
| **III** | Prolonged action potential; prolonged P-R, Q-T intervals, QRS complex; **sodium and calcium channel blocker** | Bretylium, **amiodarone**, **sotalol** |
| **IV** | **Calcium channel blockade**; reduced sinus and AV node pacemaker activity and conduction; prolonged P-R interval | Verapamil and other calcium channel blocking agents |

## HEART BLOCK

- **First-degree heart block** is the presence of a prolonged P-R interval. It is asymptomatic and when present in otherwise normal children requires no evaluation or treatment.
- **Second-degree heart block** :
  - ♥ When not all of the P waves are followed by a QRS complex.

- Mobitz type I (also known as *Wencke-bach*) : characterized by a progressive prolongation of the P-R interval until a QRS is dropped. not progress to other forms of heart block & require no evaluation or treatment in otherwise normal children.
- Mobitz type II : when the P-R interval does not change, but a QRS is intermittently dropped. may progress to CHB and may require pacemaker placement.
- **Third-degree heart block**, which may be congenital or acquired, is present when there is no relationship between the atrial and ventricular activity.
    1. **Congenital complete heart block** is associated with maternal collagen vascular disease (SLE) or congenital heart disease.
    2. **The acquired form** most often occurs after cardiac surgery.

## TREATMENT

- Most atrial dysrhythmias require no intervention.
- In patients with a complaint of palpitations, it is important to document heart rate and rhythm during their symptoms before considering therapeutic options.
- Treatment of SVT depends on presentation and symptoms.
    - Acute treatment of SVT in infants usually consists of **vagal maneuvers**, such as application of cold (ice bag) to the face.
    - IV **adenosine** usually converts the dysrhythmia because the atrioventricular node forms a part of the reentry circuit in most patients with SVT.
    - In patients with cardiovascular compromise at the time of presentation, **synchronized cardioversion** is indicated using 1 to 2 J/kg.
- Ongoing pharmacologic management with either **digoxin** or a **β-blocker** is usually the first choice.
- digoxin is contraindicated in patients with Wolff-Parkinson-White syndrome.

### ARRHYTHMIAS IN CHILDREN

| Type | ECG Characteristics | Treatment |
|---|---|---|
| SVT | Rate >200 beats/min (180-320 beats/min); abnormal atrial rate for age; ventricular rate may be slower because of AV block; P waves usually present and are related to QRS complex; normal QRS complexes unless aberrant conduction is present | Increase vagal tone (bag of ice water to face, Valsalva maneuver); adenosine; digoxin; sotalol; electrical cardioversion if acutely ill; catheter ablation |
| Atrial flutter | Atrial rate usually 300 beats/min, with varying degrees of block; sawtooth flutter waves | Digoxin, sotalol, cardioversion |
| Premature ventricular contraction | Premature, wide, unusually shaped QRS complex, with large inverted T wave | None if normal heart and if premature ventricular contractions disappear on exercise; lidocaine, procainamide |
| Ventricular tachycardia | ≥3 Premature ventricular beats; AV dissociation; fusion beats, blocked retrograde AV conduction; sustained if >30 sec; rate 120-240 beats/min | Lidocaine, procainamide, propranolol, amiodarone, cardioversion |
| Ventricular fibrillation | No distinct QRS complex or T waves; irregular undulations with varied amplitude and contour, no conducted pulse | Nonsynchronized cardioversion |
| Complete heart block | Atria and ventricles have independent pacemakers; AV dissociation; escape-pacemaker is at atrioventricular junction if congenital | Awake rate <55 beats/min in neonate or <40 beats/min in adolescent or hemodynamic instability requires permanent pacemaker |
| First-degree heart block | Prolonged P-R interval for age | Observe, obtain digoxin level if on therapy |
| Mobitz type I (Wenckebach) second-degree heart block | Progressive lengthening of P-R interval until P wave is not followed by conducted QRS complex | Observe, correct underlying electrolyte or other abnormalities |
| Mobitz type II second-degree heart block | Sudden nonconduction of P wave with loss of QRS complex without progressive P-R interval lengthening | Consider pacemaker |
| Sinus tachycardia | Rate <240 beats/min | Treat fever, remove sympathomimetic drugs |

# CONGENITAL HEART DISEASE

## ETIOLOGY AND EPIDEMIOLOGY

### CLASSIFICATION OF CONGENITAL CARDIAC DEFECTS

| | Shunting | | |
|---|---|---|---|
| **Stenotic** | *Right→Left* | *Left→Right* | **Mixing** |
| Aortic stenosis | Tetralogy | PDA | Truncus |
| Pulmonic stenosis | Transposition | VSD | TAPVR |
| Coarctation of the aorta | Tricuspid atresia | ASD | HLH |

HLH, hypoplastic left heart syndrome; TAPVR, total anomalous pulmonary venous return.

- Congenital heart disease occurs in 8 per 1000 births.
- Congenital heart defects can be divided into three broad pathophysiologic groups:
  1. **left-to-right shunts**
  2. **right-to-left shunts**
  3. **obstructive stenotic lesions**
- Acyanotic congenital heart disease includes:
  1. **left-to-right shunts** resulting in an increase in pulmonary blood flow
  2. **obstructive lesions**, which usually have normal pulmonary blood flow

## ACYANOTIC CONGENITAL HEART DISEASE

### VENTRICULAR SEPTAL DEFECT

#### ETIOLOGY AND EPIDEMIOLOGY

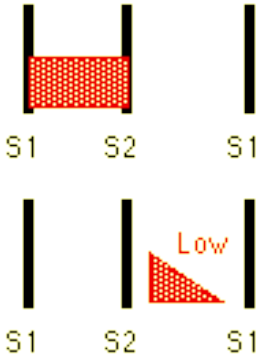
- The ventricular septum is a complex structure , divided into four components.
  1. **muscular septum** : largest component.
  2. **endocardial cushion**: The inlet or posterior septum.
  3. **The subarterial or supracristal septum** comprises conotruncal tissue.
  4. The **membranous septum** : below the aortic valve and is relatively small.
- VSDs occur when any of these components fails to develop normally.
- **the most common congenital heart defect**, 25% of all congenital heart disease.
- **Perimembranous VSDs** are the most common of all VSDs (67%).
- prognostically and in approach to repair the location of the VSD is important.
- physiologically, the amount of flow crossing a VSD depends on the size of the defect and the pulmonary vascular resistance.
- Even large VSDs are not symptomatic at birth because the pulmonary vascular resistance is normally elevated at this time (increase in the pulmonary arterioles media + relative polycythemia).
- As the pulmonary vascular resistance decreases over the **first 6 to 8 weeks of life** → amount of shunt ↑→ symptoms develop
- A left-to-right shunt at the ventricular level has 3 hemodynamic consequences:
  1. increased LV volume load→ LV dilatation and then hypertrophy→ increase pulmonary venous pressure → **raises** pulmonary capillary pressure→ increase pulmonary interstitial fluid→ pulmonary edema
  2. excessive pulmonary blood flow
  3. reduced systemic cardiac output
- The natural history has a wide spectrum, ranging from spontaneous closure to congestive heart failure (CHF) to death in early infancy.
- Spontaneous closure frequently occurs in children, usually occurs by the age of 2 years. Closure is uncommon after 4 years of age. Closure is most frequently observed in muscular defects (80%).
- Patients are at risk for infective endocarditis, but small muscular VSDs pose no other adverse possibilities.

> **NOTE:**
> The increase in pulmonary venous pressure is not seen with an ASD because LA pressures are low, as blood can readily exit it through the atrial communication

#### CLINICAL MANIFESTATIONS

- The size of the VSD affects the clinical presentation.

- Small VSDs, with little shunt, are often
  1. Asymptomatic
  2. a loud murmur.
- Moderate - large VSDs result in pulmonary over circulation and CHF, presenting as
  1. fatigue,
  2. diaphoresis with feedings
  3. poor growth.




- The typical physical finding with a VSD is:
  1. **pansystolic murmur** heard best at the lower left sternal border.
  2. **mid-diastolic murmur** at the apex. As larger shunts result in increased flow across the mitral valve.
  3. splitting of $S_2$ & intensity of $P_2$ depend on pulmonary artery pressure.

### IMAGING STUDIES

- ECG and chest x-ray findings depend on the size of the VSD.
  - Small VSDs may have normal studies.
  - Larger VSDs cause volume overload to the left side of the heart resulting in ECG findings of left atrial and ventricular enlargement and hypertrophy.
- A chest radiograph may reveal:
  - cardiomegaly, enlargement of the left ventricle
  - Increase in the pulmonary artery silhouette and increased pulmonary blood flow.
  - **Increased flow** or **increased pulmonary vascular resistance** →Pulmonary hypertension → right ventricular enlargement and hypertrophy.

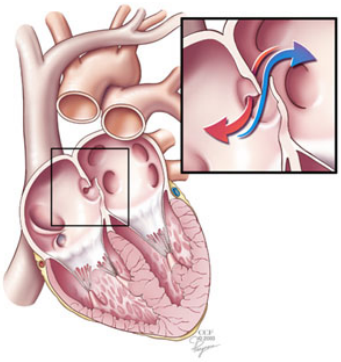
### TREATMENT

- 35% of all VSDs close spontaneously.
- Small VSDs usually close spontaneously.
- if they do not close:
  - surgical closure may not be required
  - **prophylactic antibiotics** are needed to prevent subacute bacterial endocarditis.
- moderate to large VSDs includes **:**
  - Initial treatment of **diuretics** and **digoxin**
  - closure of the defect if poor growth or pulmonary hypertension despite therapy
- Most VSDs are closed in **surgery**, but some VSDs, especially muscular defects, can be closed with **devices** placed at cardiac catheterization.

## ATRIAL SEPTAL DEFECT

### ETIOLOGY AND EPIDEMIOLOGY

- septum grows toward the endocardial cushions to divide the atria. **Failure of septal growth or excessive reabsorption** of tissue leads to ASDs.
- ASDs represent 10% of all congenital heart defects.
  1. **secundum defect**, hole in the region of the foramen ovale, the most common ASD.
  2. **primum ASD**, located near the endocardial cushions, may be part of a complete atrioventricular canal defect, but can be present with an intact ventricular septum.
  3. **sinus venosus defect** :the least common ASD is, may be associated with anomalous pulmonary venous return.



### CLINICAL MANIFESTATIONS

- Regardless of the site of the ASD, the pathophysiology and amount of shunting depend on the size of the defect and the relative compliance of the right and left ventricles.
- Even with large ASDs and significant shunts, infants and children are rarely symptomatic.
  1. A prominent left precordium with a **right ventricular impulse** at the left lower sternal border often can be palpated.
  2. A soft (grade I - II) **systolic ejection murmur** in the region of the right ventricular outflow tract

3. **fixed split $S_2$** (owing to overload of the right ventricle with prolonged ejection into the pulmonary circuit) are often audible.
4. Mid-diastolic murmur: larger shunt, at left lower sternal border as a result of the increased volume passing across the tricuspid valve.

### IMAGING STUDIES

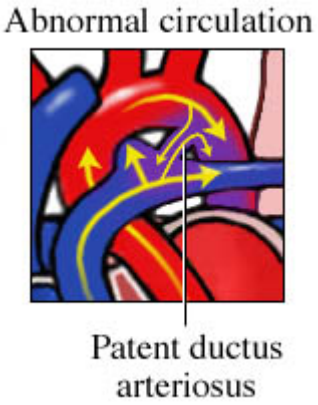
- ECG and chest x-ray findings reflect the **increased blood flow** through the right atrium, right ventricle, pulmonary arteries, and lungs.
- **The ECG** may show **right axis deviation** and **right ventricular hypertrophy**.
- **A chest radiograph** shows:
  1. cardiomegaly
  2. right atrial enlargement
  3. prominent pulmonary artery

### TREATMENT

- Medical management is rarely indicated
- **prophylaxis** for subacute bacterial endocarditis is warranted for nonsecundum ASDs.
- If a significant shunt is still present at around 3 years of age, **closure** is recommended.
- Many secundum ASDs can be closed with an ASD **closure device** in the catheterization laboratory.
- Primum and sinus venosus defects require **surgical closure**.

## PATENT DUCTUS ARTERIOSUS

### ETIOLOGY AND EPIDEMIOLOGY




- The ductus arteriosus allows blood to flow from the pulmonary artery to the aorta during fetal life.
- Failure of the normal closure of this vessel results in a PDA .
- With a falling pulmonary vascular resistance after birth, left-to-right shunting of blood and increased pulmonary blood flow occur.
- Excluding premature infants, PDAs = 5%-10% of congenital heart disease.

### CLINICAL MANIFESTATIONS

- Symptoms depend on the amount of extra blood flow to the lungs.
- The magnitude of the shunt, which can be similar to a VSD, depends on:
  1. the size of the PDA (including diameter, length, and tortuosity)
  2. pulmonary vascular resistance
- Patients with small PDAs are asymptomatic.
- Moderate to larger shunts produce the symptoms of CHF as the pulmonary vascular resistance decreases over the first 6 to 8 weeks of life.
- The physical examination depends on the size of the shunt.
  1. **widened pulse pressure** is often present due to the runoff of blood into the pulmonary circulation during diastole.
  2. **continuous machine-like murmur** can be heard at the left infraclavicular area, and a thrill may be palpable. radiates along the pulmonary arteries and is often well heard over the left back.
  3. Larger shunts with increased flow across the mitral valve may result in a mid-diastolic murmur at the apex and a **hyperdynamic precordium**.
  4. Splitting of $S_2$ and the intensity of the $P_2$ depend on the pulmonary artery pressure. ↑ pulmonary pressures →↑ intensity of $P_2$ .

### IMAGING STUDIES

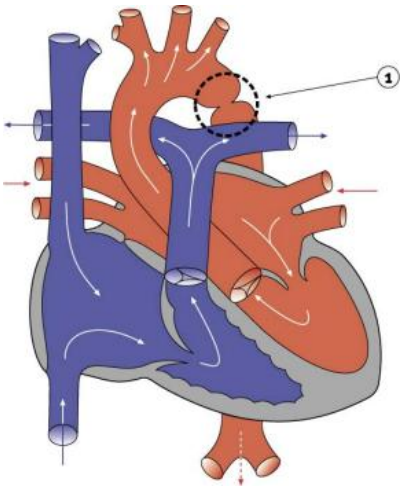
- ECG and chest x-ray findings are normal with small PDAs.
- Moderate to large shunts may result in a **full pulmonary artery silhouette** and **increased pulmonary vascularity**.
- ECG findings vary from normal to evidence of left ventricular hypertrophy.
- If pulmonary hypertension is present, there is also right ventricular hypertrophy.

### TREATMENT

- Spontaneous closure of a PDA after a few weeks of age is **uncommon** in full-term infants.
- Moderate and large PDAs may be managed initially with **diuretics** and **digoxin** but eventually requires closure.

- Closure of small PDAs also is recommended because of the **risk of subacute bacterial endocarditis.**
- Most PDAs can be closed in the catheterization laboratory by either **coil embolization** or a **PDA closure device**.

## COARCTATION OF THE AORTA




### ETIOLOGY AND EPIDEMIOLOGY

- Coarctation of the aorta occurs in 10% of all congenital heart defects.
- It is almost always **juxtaductal** in position.
- During development of the aortic arch, the area near the insertion of the ductus arteriosus fails to develop correctly, resulting in a narrowing of the aortic lumen.

### CLINICAL MANIFESTATIONS

- Timing of presentation depends primarily on the severity of obstruction and associated cardiac defects.
- Infants presenting with coarctation of the aorta frequently have hypoplastic aortic arches, abnormal aortic valves, and VSDs.
- They may be **dependent on a patent ductus** to provide flow to the descending aorta. Symptoms develop when the aortic ampulla of the ductus closes.
- Less severe obstruction causes no symptoms because blood flow into the descending aorta is not dependent on the ductus.
- Symptoms, including: (may develop before 2 weeks of age)
  1. poor feeding
  2. respiratory distress
  3. shock
- Classically the **femoral pulses** are weaker and delayed compared with the radial pulses.
  - ♥ The blood pressure in the lower extremities is lower than that in the upper extremities.
  - ♥ If cardiac function is poor, these differences may not be apparent until appropriate resuscitation is accomplished.
- There may be no murmur, but an **$S_3$** is usually present.
- Older children presenting with coarctation of the aorta are usually asymptomatic, although there may be :
  1. a history of **leg discomfort** with exercise
  2. headache
  3. epistaxis
  4. Decreased or absent lower extremity pulses
  5. **hypertension** (upper extremity)
  6. murmur may be present
- The murmur of coarctation is typically best heard in the left interscapular area of the back.
- If significant collaterals have developed, continuous murmurs may be heard throughout the chest.
- An abnormal aortic valve is present 50% of the time, causing a systolic ejection click and systolic ejection murmur of aortic stenosis.

### IMAGING STUDIES

- *The ECG* and *chest x-ray* show evidence of right ventricular hypertrophy in infantile coarctation with marked **cardiomegaly** and **pulmonary edema**.
- In older children, the ECG and chest x-ray usually show left ventricular hypertrophy and a mildly enlarged heart.
- **Rib notching** may also be seen in older children (>8 years old) with large collaterals.
- *Echocardiography* shows:
  1. the site and degree of coarctation
  2. presence of left ventricular hypertrophy
  3. aortic valve morphology and function
  4. associated lesion

### TREATMENT

- Management of an infant presenting with cardiac decompensation includes:
  1. IV infusions of **prostaglandin $E_1$** (chemically opens the ductus arteriosum)
  2. inotropic agents
  3. diuretics
- **Balloon angioplasty** has been done, especially in critically ill infants
- **surgical repair** of the coarctation is most commonly performed.

## PULMONARY STENOSIS

### ETIOLOGY

- Pulmonary stenosis accounts for 10% of all congenital heart disease
- **valvular**, **subvalvular**, or **supravalvular** in nature.
- The valve develops early in gestation as the truncus arteriosus develops.
- Pulmonary stenosis results from:
  1. the failure of the development of the three leaflets of the valve
  2. insufficient resorption of infundibular tissue
  3. insufficient canalization of the peripheral pulmonary arteries.

### CLINICAL MANIFESTATIONS

- Regardless of the site of obstruction, symptoms depend on the degree of obstruction present.
- Infants and children with mild pulmonary stenosis are asymptomatic.
- Moderate to severe stenosis results in **exertional dyspnea** and easy **fatigability**.
- Newborns with severe stenosis may be more symptomatic and even cyanotic because of right-to-left shunting at the atrial level.
- Pulmonary stenosis causes a **systolic ejection murmur** at the second left intercostal space ($P_2$), which radiates to the back. A **thrill** may be present.
- $S_2$ may be widely split with a quiet pulmonary component.
- **right ventricular hypertrophy** with more severe pulmonary stenosis results in impulse at the left lower sternal border.
- Valvular stenosis may result in a **click** that varies with respiration.
- Murmurs of **peripheral pulmonary stenosis** vary with the location of the lesions.
- The systolic ejection murmur is heard distal to the obstruction along the course of blood flow in the pulmonary circulation.

### IMAGING TESTS

- **ECG and chest x-ray** findings are normal in mild stenosis.
  - ♥ Moderate to severe stenosis results in **right axis deviation** and **right ventricular hypertrophy**.
  - ♥ The heart size is usually normal on chest x-ray, although the main pulmonary artery segment may be prominent because of **poststenotic dilation**.
- **Echocardiography** provides assessment of:
  1. site of stenosis
  2. valve morphology
  3. degree of hypertrophy
  4. Estimate of the pressure gradient.

### TREATMENT

- Valvular pulmonary stenosis does not progress, especially if it is mild.
- **Balloon valvuloplasty** is usually successful in reducing the gradient to acceptable levels for more significant or symptomatic stenosis.
- **Surgical repair** is required if balloon valvuloplasty is unsuccessful or when subvalvular (muscular) stenosis is present.
- **Subacute bacterial endocarditis prophylaxis** is recommended for appropriate indications.

## AORTIC STENOSIS

### ETIOLOGY AND EPIDEMIOLOGY

- **Valvular**, **subvalvular**, or **supravalvular aortic stenosis** represents 5% of all congenital heart disease.
- lesions result from failure of development of the three leaflets or failure of resorption of tissue around the valve.

### CLINICAL MANIFESTATIONS

- Symptoms depend on the degree of stenosis.
- Mild to moderate obstructions cause no symptoms.
- More severe stenosis results in symptoms of:
  1. easy fatigability
  2. exertional chest pain
  3. syncope.
- Infants with critical aortic stenosis may present with symptoms of CHF.
- A **systolic ejection murmur** is heard at the right second intercostal space along the sternum and radiating into the neck. thrill may be present at the right upper sternal border or in the suprasternal notch.
- **systolic ejection click** often is heard.
- The aortic component of $S_2$ may be decreased in intensity.

### IMAGING STUDIES

- ECG and chest x-ray findings are normal with mild degrees of stenosis.
- **Left ventricular hypertrophy** develops with moderate to severe stenosis and is detected on the ECG and chest x-ray.
- **Poststenotic dilation** of the ascending aorta or aortic knob may be seen on chest radiographs.
- Echocardiography shows the site of stenosis, valve morphology, and presence of left ventricular hypertrophy and allows estimate of the pressure gradient.

### TREATMENT

- The degree of stenosis frequently **progresses with growth**.
- Aortic insufficiency often develops or progresses.
- Serial follow-up with echocardiography is indicated because of the likelihood of progressive obstruction.
- **Balloon valvuloplasty** is usually the first interventional procedure for significant stenosis. It is not as successful as pulmonary balloon valvuloplasty and has a higher risk of significant valvular insufficiency.
- **Surgical management** is necessary when balloon valvuloplasty is unsuccessful, or significant valve insufficiency develops.
- **Subacute bacterial endocarditis prophylaxis** is indicated throughout the child's life.

## CYANOTIC CONGENITAL HEART DISEASE

### ETIOLOGY

- Cyanotic congenital heart disease occurs when some of the systemic venous return crosses from the right heart to the left and goes back to the body without going through the lungs (**right-to-left shunt**).
- **Cyanosis**, the visible sign of this shunt, occurs when 5 g/100 mL of reduced hemoglobin is present in systemic blood.
  - ♥ The patient's hemoglobin level determines the presentation of clinical cyanosis.
  - ♥ polycythemic patient appears cyanotic with a lower percentage of reduced hemoglobin.
  - ♥ patient with anemia requires a higher percentage of reduced hemoglobin for the recognition of cyanosis.
- The most common cyanotic congenital heart defects are the 5 "Ts":
  1. tetralogy of Fallot
  2. transposition of the great arteries
  3. tricuspid atresia

4. truncus arteriosus
5. total anomalous pulmonary venous return

- mixing congenital heart defects can present with cyanosis depending on how much pulmonary blood flow is present.

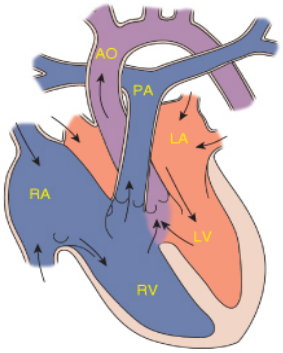
## CATEGORIES OF PRESENTING SYMPTOMS IN THE NEONATE

| SYMPTOM | PHYSIOLOGIC CATEGORY | ANATOMIC CAUSE | LESION |
|---|---|---|---|
| **Cyanosis with respiratory distress** | Increased pulmonary blood flow | Transposition | *d*-Transposition with or without associated lesions |
| **Cyanosis without respiratory distress** | Decreased pulmonary blood flow | Right heart obstruction | Tricuspid atresia, Ebstein anomaly , Pulmonary atresia, Pulmonary stenosis, Tetralogy of Fallot |
| **Hypoperfusion** | Poor cardiac output | Left heart obstruction | Total anomalous pulmonary venous return with obstruction, Aortic stenosis ,Hypoplastic left heart syndrome |
| | Poor cardiac function | Normal anatomy | Cardiomyopathy, Myocarditis |
| **Respiratory distress with desaturation (not visible cyanosis)** | Bidirectional shunting | Complete mixing | Truncus arteriosus, AV canal Complex ,single ventricle (including heterotaxias) without pulmonary stenosis |
| **Respiratory distress with normal saturation** | Left-to-right shunting | Simple intracardiac shunt | ASD, VSD, PDA, Aortopulmonary window, AVM |

ASD, atrial septal defect; AV, atrioventricular; AVM, arteriovenous malformation; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

# TETRALOGY OF FALLOT

## ETIOLOGY AND EPIDEMIOLOGY




- **The most common cyanotic congenital heart defect**,10% of all congenital heart defects .
- Anatomically, there are four structural defects:
  1. **VSD**
  2. **pulmonary stenosis**
  3. **overriding aorta**
  4. **right ventricular hypertrophy**
- Tetralogy of Fallot is believed to be due to abnormalities in the septation of the truncus arteriosus into the aorta and pulmonary arteries that occur early in gestation (3 - 4 weeks).
- The VSD is large
- the pulmonary stenosis is most commonly subvalvular or infundibular
- ***Causes:***
  1. CATCH 22 (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia).
  2. DiGeorge syndrome
  3. branchial arch abnormalities.
  4. Fetal hydantoin syndrome
  5. Fetal carbamazepine syndrome
  6. Fetal alcohol syndrome
  7. Maternal phenylketonuria (PKU) birth defects

## CLINICAL MANIFESTATIONS

- The degree of cyanosis depends on the amount of pulmonary stenosis.
- Cyanosis develops within the first few years of life
- Infants initially may be acyanotic.
- First presentation may include poor feeding, fussiness, tachypnea, and agitation
- **pulmonary stenosis murmur** is the usual initial abnormal finding.Systolic ejection murmur .
- More cyanotic patients have greater obstruction and a **soft**er murmur.

- An acyanotic patient with TOF (pink tet) has a **long, loud**, systolic murmur with a thrill along the RVOT.
- If the pulmonary stenosis is more severe, the amount of right-to-left shunting at the VSD increases and the patient becomes more **cyanotic**.
- **single $S_2$** (Pulmonic valve closure not heard)
- May have a bulging left hemithorax+ Right ventricular predominance on palpation .
- **right ventricular impulse** at the left sternal border are typical findings (heave)
- **hypoxic ("Tet") spells**:
  - ♥ sudden, increased subpulmonic stenosis
  - ♥ they are usually progressive.
  - ♥ During a spell, the child typically becomes restless and agitated and may cry inconsolably.
  - ♥ **Hyperpnea** occurs with gradually increasing cyanosis and loss of the murmur.
  - ♥ In severe spells, prolonged **unconsciousness** and **convulsions**, **hemiparesis**, or **death** may occur.
- Independent of hypoxic spells, patients with tetralogy are at increased risk for **cerebral thromboembolism and cerebral abscesses** from their right-to-left intracardiac shunt.

### Imaging Studies

- **The ECG** has **right axis deviation** and **right ventricular hypertrophy**.
- **The classic chest x-ray** finding is a **boot-shaped heart** created by the small main pulmonary artery and upturned apex secondary to right ventricular hypertrophy.
- **Echocardiography** shows the anatomic features, including the levels of pulmonary stenosis, and provides quantification of the degree of stenosis.
- Coronary anomalies, specifically a left coronary artery crossing the anterior surface of the right ventricular outflow tract, are present in 5% of patients with tetralogy of Fallot.

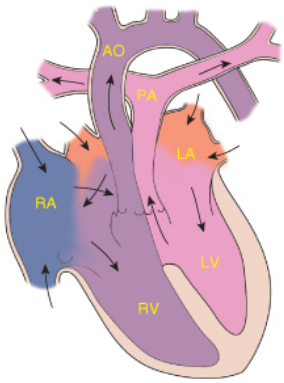
### Treatment

- The natural history of tetralogy of Fallot is progression of pulmonary stenosis and cyanosis.
- Treatment of hypoxic spells consists of:
  1. **oxygen** administration
  2. placing the child in the **knee-chest position** (to increase venous return),
  3. giving **morphine sulfate** ℞ (to relax the pulmonary infundibulum and for sedation)
  5. **α-adrenergic agonist** (phenylephrine) to crease systemic vascular resistent.
  6. If spells are frequent, **β-adrenergic antagonists** (propranolol) ↓muscular spasm.
- **Complete surgical repair** with closure of the VSD and removal or patching of the pulmonary stenosis can be performed in infancy.
- **palliative shunt surgery** between the subclavian artery and pulmonary artery is performed for complex forms of TOF with more complete repair at a later time.
- **Subacute bacterial endocarditis prophylaxis** is indicated.

## TRANSPOSITION OF THE GREAT ARTERIES

### Etiology and Epidemiology

- Although **dextroposed transposition of the great arteries** represents only about 5% of congenital heart defects.
- **The most common cyanotic lesion to present in the newborn period.**
- In dextroposed transposition, the aorta arises from the right ventricle, anterior and to the right of the pulmonary artery, which arises from the left ventricle.
- This transposition results in desaturated blood returning to the right heart and being pumped back out to the body, while well-oxygenated blood returning from the lungs enters the left heart and is pumped back to the lungs.



- Without mixing of the two circulations, death occurs quickly.
- Mixing can occur at the atrial (patent foramen ovale/ASD), ventricular (VSD), or great vessel (PDA) level.

### Clinical Manifestations

- A history of **cyanosis** is always present, although it may not be profound and depends on the amount of mixing.
- **Quiet tachypnea** and a **single $S_2$** are typically present.
- If the ventricular septum is intact, there may be no murmur.
- Children with transposition and a large VSD have improved intracardiac mixing.
- They may present with signs of CHF.
- The heart is hyperdynamic, with palpable left and right ventricular impulses.
- A loud VSD murmur is heard.

### Imaging Studies

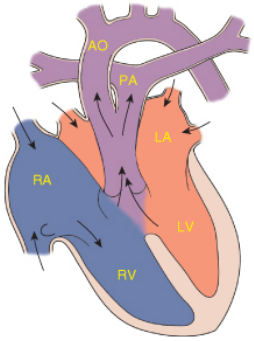
- ECG findings typically include **right axis deviation** and **right ventricular hypertrophy**.
- The chest x-ray reveals **increased pulmonary vascularity**, and the cardiac shadow is classically **an egg on a string** created by the narrow superior mediastinum.
- Echocardiography shows the transposition of the great arteries, the sites and amount of mixing, and any associated lesions.

### Treatment

- Initial medical management includes **prostaglandin $E_1$** to maintain ductal patency.
- If the infant remains significantly hypoxic on prostaglandin therapy, a **balloon atrial septostomy** is performed to improve mixing between the two circulations.
- Complete surgical repair is most often an **arterial switch**; the atrial switch is rarely done. performed within the first 2 weeks of life, when the left ventricle still can maintain a systemic pressure.

## TRUNCUS ARTERIOSUS

### Etiology and Epidemiology




- Truncus arteriosus occurs in less than 1% of all cases of congenital heart disease.
- It results from the failure of septation of the truncus, which normally occurs during the first 3- 4 weeks of gestation.
- Anatomically a single arterial trunk arises from the heart with a large VSD immediately below the truncal valve.
- The pulmonary arteries arise from the single arterial trunk either as a single vessel that divides or individually from the arterial trunk to lungs.

### Clinical Manifestations

- Varying degrees of **cyanosis** depend on the amount of pulmonary blood flow.
- If not diagnosed at birth, the infant may develop signs of **CHF** as pulmonary vascular resistance decreases.
- The signs include t**achypnea** and **cough**.
- Peripheral pulses are usually bounding as a result of the diastolic runoff into the pulmonary arteries.
- A **single $S_2$** is due to the single valve.
- There may be a systolic ejection click.
- there is often a **systolic murmur** at the left sternal border.

### Imaging Studies

- ECG findings include **combined ventricular hypertrophy** and **cardiomegaly.**
- **Increased pulmonary blood flow** is usually seen on chest x-ray. Pulmonary arteries may appear displaced.
- Echocardiography defines the anatomy, including the VSD, truncal valve function, and origin of the pulmonary arteries.

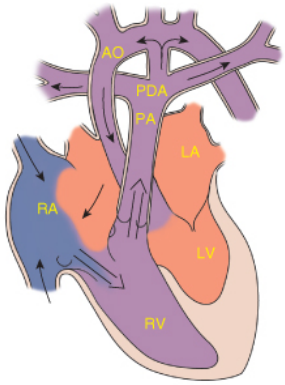
### Treatment

- Medical management is usually needed and includes **anticongestive medications.**
- **Surgical repair** includes VSD closure and placement of a conduit between the right ventricle and pulmonary arteries.

# HYPOPLASTIC LEFT HEART SYNDROME

## ETIOLOGY AND EPIDEMIOLOGY

- Hypoplastic left heart syndrome accounts for 1% of all congenital heart defects
- **the most common cause of death from cardiac defects in the first month of life.**
- Hypoplastic left heart syndrome occurs when there is failure of development of the mitral or aortic valve or the aortic arch.
- A small left ventricle that is unable to support normal systemic cir culation is a central finding of hypoplastic left heart syndrome, regardless of etiology.
- Associated degrees of hypoplasia of the ascending aorta and aortic arch are present.
- Left-to-right shunting occurs at the atrial level.




## CLINICAL MANIFESTATIONS

- After delivery, the infant is dependent on right-to-left shunting at the ductus arteriosus for systemic blood flow.
- As the ductus arteriosus constricts, the infant becomes critically ill with signs and symptoms of **CHF** from excessive pulmonary blood flow and obstruction of pulmonary venous return.
- Pulses are diffusely weak or absent.
- $S_2$ is single and loud.
- There is usually no heart murmur.
- Cyanosis may be minimal, but **low cardiac output** gives a grayish color to the cool, mottled skin.

## IMAGING STUDIES

- ECG findings include **right ventricular hypertrophy** with **decreased left ventricular forces**.
- The chest x-ray reveals **cardiomegaly** (with right-sided enlargement) and pulmonary venous congestion or pulmonary edema.
- Echocardiography shows the small left heart, the degree of stenosis of the aortic and mitral valves, the hypoplastic ascending aorta, and the adequacy of left-to-right atrial flow.

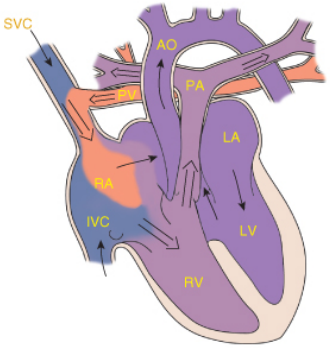
## TREATMENT

- Medical management includes **prostaglandin $E_1$** to open the ductus arteriosus, **correction of acidosis**, and ventilatory and blood pressure support as needed.
- **Surgical repair** is staged with the first surgery (Norwood procedure) done in the newborn period.
- Subsequent procedures create a systemic source for the pulmonary circulation (bidirectional Glenn and Fontan procedures), leaving the right ventricle to supply systemic circulation.
- There have been and continue to be many modifications to all three stages of the surgical repair.

# TOTAL ANOMALOUS PULMONARY VENOUS RETURN

## ETIOLOGY AND EPIDEMIOLOGY

- Accounts for 1% of congenital heart disease.
- Disruption of the development of normal pulmonary venous drainage during the third week of gestation results in one of four abnormalities.
- Anatomically, all of the pulmonary veins fail to connect to the left atrium and return abnormally via the right heart.
- They may have **supracardiac**, **cardiac**, **infracardiac**, or **mixed drainage**.
- An atrial level communication is necessary for systemic cardiac output and survival.




## CLINICAL MANIFESTATIONS

- The most important determinant of presentation is the presence or absence of **obstruction** to the pulmonary venous drainage.

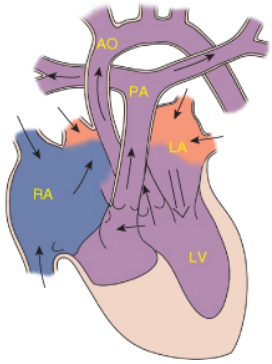
- Infants without obstruction have minimal cyanosis and may be asymptomatic.
- The pulmonary blood flow creates a **continuous murmur** and reenters the right atrium and right ventricle.
- There is a hyperactive **right ventricular impulse** with a **widely split $S_2$** (owing to increased volume ejected from the right ventricle)
- **systolic ejection murmur** at the left upper sternal border.
- Growth is relatively poor.
- Infants with **obstruction** present with cyanosis, marked tachypnea and dyspnea, and signs of right heart failure including hepatomegaly.
- The obstruction results in little, if any, increase in right ventricular volume.
- There may be no murmur or changes in $S_2$.

### IMAGING STUDIES

- For infants without obstruction, the ECG is consistent with **right ventricular volume overload**.
- Cardiomegaly with increased pulmonary blood flow is seen on chest x-ray.
- Infants with obstructed veins have **right axis deviation** and **right ventricular hypertrophy** on ECG.
- On chest x-ray, the heart is normal or mildly enlarged with varying degrees of pulmonary edema that can appear similar to hyaline membrane disease or pneumonia.
- Echocardiography shows the volume-overloaded right heart, right-to-left atrial level shunting, and common pulmonary vein including site of drainage and degree of obstruction.

### TREATMENT

- At **surgery**, the common pulmonary vein is opened into the left atrium, and there is ligation of any vein or channel that had been draining the common vein.




## TRICUSPID ATRESIA

### ETIOLOGY AND EPIDEMIOLOGY

- accounts for 2% of all congenital heart defects
- The absence of the tricuspid valve results in a **hypoplastic right ventricle**.
- All systemic venous return must cross the atrial septum into the left atrium.
- The presence of a PDA or VSD also is necessary for pulmonary blood flow and survival.

### CLINICAL MANIFESTATIONS

- Infants with tricuspid atresia are usually **severely cyanotic** and have a **single $S_2$**.
- If a VSD is present, there may be a murmur.
- A diastolic murmur across the mitral valve may be audible.
- Frequently there is no significant murmur.

### IMAGING STUDIES

- The ECG shows **left ventricular hypertrophy** and a **superior QRS axis** (between 0 and -90 degrees).
- The chest x-ray reveals a normal or mildly enlarged cardiac silhouette with **decreased pulmonary blood flow**.
- Echocardiography shows the anatomy, associated lesions, and source of pulmonary blood flow.

### TREATMENT

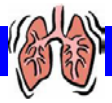
- Management initially depends on the presence of a VSD and the amount of blood flow across the VSD to the lungs.
- If there is no VSD, or it is small, prostaglandin $E_1$ is used to maintain pulmonary blood flow until surgery.
- Surgery is staged with:
  1. an initial subclavian artery-to-pulmonary shunt (**Blalock-Taussig procedure**)
  2. followed by a two-stage procedure (**bidirectional Glenn** and **Fontan procedure**), which directs systemic venous return directly to the pulmonary arteries.

## EXTRACARDIAC COMPLICATIONS OF CYANOTIC CONGENITAL HEART DISEASE

| PROBLEM | ETIOLOGY | THERAPY |
|---|---|---|
| Polycythemia | Persistent hypoxia | Phlebotomy |
| Relative anemia | Nutritional deficiency | Iron replacement |
| CNS abscess | Right-to-left shunting | Antibiotics, drainage |
| CNS thromboembolic stroke | Right-to-left shunting or polycythemia | Phlebotomy |
| Gingival disease | Polycythemia, gingivitis, bleeding | Dental hygiene |
| Gout | Polycythemia, diuretic agents | Allopurinol |
| Arthritis, clubbing | Hypoxic arthropathy | None |
| Pregnancy | Poor placental perfusion, poor ability to increase cardiac output | Bed rest |
| Infectious disease | Associated asplenia, DiGeorge syndrome | Antibiotics |
| | Fatal RSV pneumonia with pulmonary hypertension | Ribavirin, RSV immune globulin |
| Growth | Failure to thrive, increased oxygen consumption, decreased nutrient intake | Treat heart failure; correct defect early |

## BACTERIAL ENDOCARDITIS

- Antimicrobial prophylaxis is not indicated for :
  3. isolated secundum ASD
  4. repaired secundum ASD
  5. VSD 6 months after patch placement
  6. divided and ligated PDA 6 months after repair.
- The antibiotic regimen to prevent endocarditis during dental or respiratory procedures is **oral amoxicillin**.
- Preventive treatment for gastrointestinal or genitourinary manipulation includes **oral amoxicillin or parenteral ampicillin and gentamicin.** The latter recommendation is for high-risk patients, such as patients with:
  1. prosthetic heart valves
  2. systemic-to-pulmonary shunts
  3. Previous endocarditis.
- **Clindamycin** is indicated for most patients allergic to penicillin.



# RESPIRATORY DISEASES

## CHOANAL ATRESIA

- This is the most common congenital anomaly of the nose
- Frequency = 1/7,000 live births.
- It consists of a unilateral or bilateral bony (90%) or membranous (10%) septum between the nose and the pharynx
- Most cases are a combination of bony and membranous atresia.
- 50% of affected infants have other congenital anomalies, more in bilateral cases.
- **CHARGE syndrome** one of the more common anomalies associated with it:
  1. **C**oloboma: in one of the structures of the eye
  2. **H**eart disease
  3. **A**tresia choanae
  4. **R**etarded growth and development or CNS anomalies or both
  5. **G**enital anomalies or hypogonadism or both,
  6. **E**ar anomalies or deafness or both.

### CLINICAL MANIFESTATIONS

- Newborn infants have a variable ability to breathe through their mouths, so nasal obstruction does not produce the same symptoms in every infant.
- If unilateral, may be asymptomatic for a prolonged period, often until the 1st respiratory infection( unilateral nasal discharge or persistent nasal obstruction)
- If bilateral , difficulty with mouth breathing make vigorous attempts to inspire, often suck in their lips, and develop cyanosis →Distressed children → cry → relieves the cyanosis and become calmer, only to repeat the cycle after closing their mouths.
- Those who are able to breathe through their mouths at once experience difficulty when sucking and swallowing, becoming cyanotic when they attempt to feed.

### DIAGNOSIS

- inability to pass a firm catheter through each nostril 3-4 cm into the nasopharynx.
- The atretic plate may be seen directly with fiberoptic rhinoscopy.
- The anatomy is best evaluated by using high-resolution CT .

### TREATMENT

- Initial treatment consists of prompt placement of an oral airway, maintaining the mouth in an open position, or intubation.
- In bilateral cases, intubation or, less often, tracheotomy may be indicated.
- If the child is free of other serious medical problems, operative intervention is considered in the neonate.
- transnasal repair is the treatment of choice with the introduction of small magnifying endoscopes and smaller surgical instruments and drills.
- Stents are usually left in place for weeks after the repair to prevent closure or stenosis.
- Operative correction of unilateral obstruction may be deferred for several yr.
- Mitomycin C help prevent the development of granulation tissue and stenosis.

## NASAL POLYPS

### ETIOLOGY

- Nasal polyps are benign pedunculated tumors formed from edematous, usually chronically inflamed nasal mucosa.
- They commonly arise from the ethmoidal sinus and present in the middle meatus.
- maxillary antrum polyps can extend to the nasopharynx (**antrochoanal polyp**) represent 4-6% of all nasal polyps in the general population, but 33% in the pediatric population.
- Large or multiple polyps can completely obstruct the nasal passage.
- The polyps originating from the ethmoidal sinus are usually smaller and multiple, as compared with the large and usually single antro-choanal polyp.
- **Cystic fibrosis is the most common childhood cause of nasal polyposis** (Suspected in any child <12 yr old with nasal polyps) ( 30% of children with CF)
- Nasal polyposis is associated with chronic sinusitis and allergic rhinitis.
- **Samter triad**, nasal polyps + aspirin sensitivity + asthma.

## CLINICAL MANIFESTATIONS

- Obstruction of nasal passages is prominent= hyponasal speech and mouth breathing.
- Profuse unilateral mucoid or mucopurulent rhinorrhea.
- glistening, gray, grapelike masses squeezed between nasal turbinates & the septum.

## TREATMENT

- Local or systemic decongestants are not usually effective in shrinking the polyps, although they may provide symptomatic relief from the associated mucosal edema.
- Intranasal steroid sprays, and systemic steroids, may provide some shrinkage of nasal polyps with symptomatic relief and have proved useful in children with cystic fibrosis .
- Polyps should be removed surgically if:
  1. Complete obstruction
  2. uncontrolled rhinorrhea
  3. deformity of the nose appears
  4. Antrochoanal polyps: these types are not associated with any other disease process→ recurrence rate is low.

# TONSILS AND ADENOIDS

## ANATOMY

- **Waldeyer ring** consists of lymphoid tissue that surrounds the opening of the oral and nasal cavities into the pharynx and includes:
  1. the palatine tonsils
  2. the pharyngeal tonsil or adenoid
  3. lymphoid tissue surrounding the eustachian tube orifice in nasopharynx lateral walls
  4. the lingual tonsil at the base of the tongue
  5. scattered lymphoid tissue throughout the remainder of the pharynx
- **Palatine tonsil**: Lymphoid tissue located between the palatoglossal fold (anterior tonsillar pillar) and the palatopharyngeal fold (posterior tonsillar pillar), separated from the surrounding pharyngeal musculature by a thick fibrous capsule.
- **Adenoid**: is a single aggregation of lymphoid tissue that occupies the space between the nasal septum and the posterior pharyngeal wall. A thin fibrous capsule separates it from the underlying structures.
- **lingual tonsil**: Lymphoid tissue at the base of the tongue .

## NORMAL FUNCTION

- 65% of the lymphocytes that make up the lymphoid tissue of Waldeyer ring are B lymphocytes, the remainder being either T lymphocytes or plasma cells.
- The immunologic role of the tonsils and adenoid is to induce secretory immunity and to regulate the production of the secretory Ig.
- tonsils and adenoid are in a position to provide primary defense against foreign matter.
- tonsillar crypts are lined with squamous epithelium and have a concentration of lymphocytes at their bases.
- Lymphoid tissue of Waldeyer ring is most immunologically active between 4 and 10 yr of age, with a decrease after puberty.
- No major immunologic deficiency has been demonstrated after removal of either or both of the tonsils and adenoid.

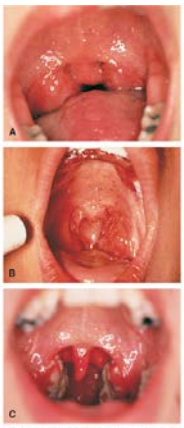
## PATHOLOGY & CLINICAL MANIFESTATIONS

### ACUTE INFECTION

- Most episodes of acute pharyngotonsillitis are caused by viruses.
- Group A β-hemolytic streptococcus (GABHS) is the most common cause of bacterial infection in the pharynx.
- Oral candidiasis can occur in immunocompromised patients or children who have been treated chronically with antibiotics or inhaled steroids.
- Symptoms of GABHS infection include:
  1. odynophagia, dysphagia ,referred otalgia
  2. dry throat

3. headache, malaise
4. fever and chills
5. muscular aches
6. enlarged cervical nodes.

- Signs include:
  1. dry tongue
  2. erythematous enlarged tonsils
  3. tonsillar or pharyngeal exudates
  4. palatine petechiae
  5. enlargement and tenderness of the jugulodigastric lymph nodes




## CHRONIC INFECTION

- The tonsils and adenoid can be chronically infected by multiple microbes, which may include a high incidence of β-lactamase-producing organisms.
- Both aerobic species, such as streptococci and *Haemophilus influenzae,* and anaerobic species, such as *Peptostreptococcus, Prevotella,* and *Fusobacterium,* predominate.
- The tonsillar crypts can accumulate desquamated epithelial cells, lymphocytes, bacteria, and other debris, causing cryptic tonsillitis.
- With time cryptic plugs →calcify into tonsillar concretions or tonsillolith.
- Children with chronic or cryptic tonsillitis present with:
  1. halitosis
  2. chronic sore throats
  3. foreign body sensation
  4. history of expelling foul-tasting and smelling cheesy lumps.
- Examination reveals tonsils of any size and, frequently, contains copious debris in crypts.
- Because the organism is not usually GABHS, streptococcal culture is negative.

## AIRWAY OBSTRUCTION

- Both the tonsils and adenoid are a major cause of upper airway obstruction in children.
- Airway obstruction,typically manifested in sleep-disordered breathing, including:
  1. obstructive sleep apnea
  2. obstructive sleep hypopnea
  3. upper airway resistance syndrome.
- Daytime symptoms of airway obstruction, due to adenotonsillar hypertrophy, include:
  1. chronic mouth breathing
  2. nasal obstruction
  3. hyponasal speech
  4. hyposmia
  5. decreased appetite
  6. poor school performance
  7. symptoms of right-sided heart failure (rare).
- Nighttime symptoms consist of:
  1. loud snoring
  2. choking & gasping
  3. sleep talking
  4. frank apneas
  5. restless sleep & abnormal sleep positions
  6. somnambulism
  7. night terrors & diaphoresis
  8. enuresis
- Large tonsils are typically seen on examination, although the absolute size may not be indicative of the degree of obstruction.
- The size of the adenoid tissue can be demonstrated on a lateral neck radiograph or with flexible endoscopy.
- Other signs that can contribute to airway obstruction include the presence of a craniofacial syndrome or hypotonia.

### TONSILLAR NEOPLASM

- Rapid enlargement of one tonsil is highly suggestive of a tonsillar malignancy, typically lymphoma in children.
- tonsillar malignancy= The rapid unilateral enlargement of a tonsil+systemic signs of night sweats, fever, weight loss+ lymphadenopathy.
- if the tonsil appears grossly abnormal → tonsillar malignancy.

## TREATMENT

### MEDICAL MANAGEMENT

- Because co-pathogens such as staphylococci or anaerobes can produce β-lactamase that can inactivate penicillin, the use of cephalosporins or clindamycin may be more efficacious in the treatment of chronic throat infections.
- Children with cryptic tonsillitis may be able to express tonsillolith or debris manually with either a cotton-tipped applicator or a water jet.
- Chronically infected tonsillar crypts can be cauterized using silver nitrate.

### TONSILLECTOMY

- Tonsillectomy alone is usually performed for **recurrent or chronic pharyngotonsillitis**.
- Indications for surgery remain uncertain
- One criteria is:
  1. 7 or more throat infections treated with antibiotics in the preceding yr
  2. 5 or more throat infections treated in each of the preceding 2 yr
  3. 3 or more throat infections treated with antibiotics in each of the preceding 3 yr.
- The American Academy of Otolaryngology-Head and Neck Surgery offers guidelines of 3 or more infections of tonsils and/or adenoids per yr despite adequate medical therapy
- Tonsillectomy is effective in ↓ infections and symptoms of chronic tonsillitis
- In resistant cases of **cryptic tonsillitis**, tonsillectomy may be curative.
- Rarely, tonsillectomy indicated for **biopsy** of a unilaterally enlarged tonsil to exclude a neoplasm or to treat **recurrent hemorrhage from superficial tonsillar blood vessels**.
- Tonsillectomy has not been shown to offer clinical benefit over conservative treatment in children with mild symptoms.

### ADENOIDECTOMY

- Adenoidectomy alone indicated for :
  1. **chronic nasal infection** (chronic adenoiditis)
  2. **chronic sinus infections** that have failed medical management
  3. **recurrent bouts of acute otitis media**
  4. management of patients with nasal obstruction, chronic mouth breathing, and loud snoring suggestive of **sleep-disordered breathing**.
  5. children in whom **upper airway obstruction is suspected of causing craniofacial or occlusive developmental abnormalities.**

### TONSILLECTOMY AND ADENOIDECTOMY

- The criteria for both tonsillectomy and adenoidectomy for recurrent infection are **the same as those for tonsillectomy alone.**
- major indication for performing both procedures together is **upper airway obstruction secondary to adenotonsillar hypertrophy** that results in:
  1. sleep-disordered breathing
  2. failure to thrive
  3. craniofacial or occlusive developmental abnormalities
  4. speech abnormalities
  5. rarely, cor pulmonale.

## COMPLICATIONS

### ACUTE PHARYNGOTONSILLITIS

- The 2 major complications of untreated GABHS infection are post-streptococcal glomerulonephritis and acute rheumatic fever .

## PERITONSILLAR INFECTION

- Peritonsillar infection can occur as either cellulitis or a frank abscess in the region superior and lateral to the tonsillar capsule .
- usually occur in children with a history of recurrent tonsillar infection
- polymicrobial, including both aerobes and anaerobes.
- presenting symptoms: **Unilateral throat pain, referred otalgia, drooling, and trismus**.
- The affected tonsil is displaced down and medial by swelling of the anterior tonsillar pillar and palate.
- The diagnosis of an abscess can be confirmed by CT or by needle aspiration
- the contents of which should be sent for culture

## RETROPHARYNGEAL SPACE INFECTION

- Infections in the retropharyngeal space develop in the lymph nodes that drain the oropharynx, nose, and nasopharynx.

## PARAPHARYNGEAL SPACE INFECTION

- Tonsillar infection can extend into the parapharyngeal space, causing fever, neck pain, stiffness, swelling of the lateral pharyngeal wall and neck on the affected side.
- The diagnosis is confirmed by contrast medium enhanced CT.
- treatment : IV antibiotics and external incision and drainage if abscess is demonstrated.
- **Lemierre syndrome**: Septic thrombophlebitis of the jugular vein, presents with fever, toxicity, neck pain and stiffness, and respiratory distress due to multiple septic pulmonary emboli and is a complication of a parapharyngeal space or odontogenic infection from ***Fusobacterium necrophorum.***
- Concurrent Epstein-Barr virus mononucleosis can be a predisposing event before the sudden onset of fever, chills, and respiratory distress in an adolescent patient.
    - ◊ Treatment: high-dose IV antibiotics (ampicillin-sulbactam, clindamycin, penicillin, or ciprofloxacin) and heparinization.

## CHRONIC AIRWAY OBSTRUCTION

- Although rare, children with chronic airway obstruction from enlarged tonsils and adenoids can present with cor pulmonale.
- The effects of chronic airway obstruction and mouth breathing on facial growth remain a subject of controversy.
- Studies of chronic mouth breathing, both in humans and animals, have shown changes in facial development, including prolongation of the total anterior facial height and a tendency toward a retrognathic mandible, the so-called adenoid facies.
- Adenotonsillectomy may reverse some of these abnormalities. Other studies have disputed these findings.

## TONSILLECTOMY AND ADENOIDECTOMY

- Bleeding may occur in the immediate postoperative period or be delayed after separation of the eschar.
- tongue and soft palate Swelling → acute airway obstruction ( 1st few hours after surgery)
- Children with underlying hypotonia or craniofacial anomalies are at greater risk of suffering this complication.
- Dehydration from odynophagia is not uncommon in the 1st postoperative week.
- Rare complications include velopharyngeal insufficiency, nasopharyngeal or oropharyngeal stenosis, and psychologic problems.

## DISEASES ASSOCIATED WITH RECURRENT, PERSISTENT, OR MIGRATING LUNG INFILTRATES BEYOND THE NEONATAL PERIOD

1. **Asthma**
2. **Repeated aspiration**
3. **Foreign body**
4. **Sickle cell disease**
5. **Cystic fibrosis**
6. **Congenital infection:** CMV, Rubella ,Syphilis
7. **Acquired infection**

- Cytomegalovirus, HIV,Other viruses
- Tuberculosis,*Chlamydia Mycoplasma, Ureaplasma* Pertussis, *Pneumocystis carinii*
- Fungal organisms

8. **Inadequately treated bacterial infection**
9. **Congenital anomalies**:

- Lung cysts , Pulmonary sequestration ,Bronchial stenosis ,
- Vascular ring, Congenital heart disease with large left-to-right shunt

10. **Aspiration**

- Pharyngeal incompetence (e.g., cleft palate)
- Laryngotracheoesophageal cleft
- TEF, GERD
- Foreign body
- Lipid aspiration

11. **Immunodeficiency, phagocytic deficiency**

- Humoral, cellular, combined immunodeficiency states
- Chronic granulomatous disease and related phagocytic defects
- Complement deficiency states

12. **Allergy-hypersensitivity**

- Pulmonary hemosiderosis (cow's milk-related, other)
- Asthma
- Hypersensitivity pneumonitis (allergic alveolitis)

13. **Primary ciliary dyskinesia (Kartagener syndrome)**
14. **Other bronchiectases**
15. **Sarcoidosis**
16. **Neoplasms (primary, metastatic)**
17. **Interstitial pneumonitis and fibrosis**

- Usual
- Lymphoid (AIDS)
- Genetic disorders of surfactant synthesis, secretion
- Desquamative
- Acute (Hamman-Rich)

18. **Alveolar proteinosis**
19. **Pulmonary lymphangiectasia**
20. **α1-Antitrypsin deficiency**
21. **Drug-induced, radiation-induced inflammation and fibrosis**
22. **Collagen-vascular diseases**
23. **Eosinophilic pneumonias**
24. **Visceral larva migrans**
25. **Histiocytosis**
26. **Leukemia**

## LARYNGOMALACIA

- the **most common congenital laryngeal anomaly**
- The **most frequent cause of stridor in infants and children**.

### CLINICAL MANIFESTATIONS

- 60% Of congenital laryngeal anomalies in children with stridor.
- **stridor** : inspiratory, low pitched, and exacerbated by any exertion (crying, agitation, feeding), supine position, and viral infections of the upper airway.
- Stridor results from the collapse of supraglottic structures inward during inspiration.
- Symptoms usually appear in the first 2 wk of life and increase in severity for up to 6 mo.
- Gradual improvement can begin at any time.
- Laryngopharyngeal reflux is commonly associated with laryngomalacia.

### DIAGNOSIS

- The diagnosis is **confirmed by flexible laryngoscopy** in the office.
- if work of breathing is moderate- severe, airway films and chest radiographs is indicated.
- If associated dysphagia, a contrast swallow study and esophagogram is indicated.
- Because 15-60% of infants with laryngomalacia have synchronous airway anomalies, complete bronchoscopy is undertaken for patients with moderate to severe obstruction.

### TREATMENT

- Expectant observation for most infants because most symptoms resolve spontaneously.
- Laryngopharyngeal reflux is managed aggressively.
- endoscopic supraglottoplasty for few patients who have severe obstruction (patients with apparent life-threatening events, cor pulmonale, cyanosis, failure to thrive)

## PNEUMOTHORAX

### ETIOLOGY

- Pneumothorax is the accumulation of air in the pleural space that may result from external trauma or from leakage of air from the lungs or airways.
- **Spontaneous pneumothoraces** : occur in teenagers and young adults, more commonly in tall, thin males and smokers.
- Predisposing conditions include:
  1. mechanical ventilation
  2. asthma
  3. CF
  4. trauma
  5. disorders of collagen (**Marfan syndrome**)
  6. idiopathic subpleural bullae (common and often bilateral)
  7. exertion with a Valsalva maneuver.

### CLINICAL MANIFESTATIONS

- The symptoms of pneumothorax often begin while the patient is at rest (if spontaneous).
- Symptoms are:
  1. pain
  2. dyspnea
  3. cyanosis.
- If the air leak communicates with the mediastinum, subcutaneous emphysema may become apparent.
- Physical findings include:
  1. decreased breath sounds
  2. tympanitic percussion note
  3. signs of mediastinal shift
  4. subcutaneous crepitus.
- If the amount of air collection is small, few or no physical signs of pneumothorax present.
- Symptoms may progress rapidly if the air in the pleural space is under pressure (known as **tension pneumothorax**), with death resulting if the tension is not relieved.

## DIAGNOSTIC STUDIES

- The diagnosis is confirmed by chest radiograph.
- In infants, transillumination of the chest wall may help in the rapid diagnosis of pneumothorax.

## TREATMENT

- Intervention depends on the amount of intrapleural air and the nature of the underlying disease.
- Small (<20%) pneumothoraces often resolve spontaneously.
- Inhaling high concentration $O_2$ for 12 to 24 hours can speed reabsorption.
- Larger pneumothoraces (and tension pneumothoraces) necessitate immediate drainage.
- In an emergency situation, a simple needle aspiration may suffice, but placement of a chest tube may be required for resolution.
- Sclerosing the pleural surfaces to obliterate the pleural space (pleurodesis) may benefit patients with recurrent pneumothoraces.

# PLEURAL EFFUSION

## ETIOLOGY

- Fluid accumulates in the pleural space
- whenever the local hydrostatic forces pushing fluid out of the vascular space exceed osmotic forces, pulling fluid back into the vascular space.
- The underlying causes of pleural effusion are:
  1. inflammation or infection of the pleura
  2. congestive heart failure
  3. hypoproteinemia
  4. obstruction of lymphatic drainage
  5. malignancy
  6. collagen vascular disease.
- Infection producing a reactive **parapneumonic effusion** or a more serious purulent **empyema** is the most common cause of pleural effusion in children.
- Empyema often is caused by:
  1. *Streptococcus pneumoniae*
  2. group A streptococci
  3. *S. aureus*
  4. rarely by *Mycobacterium tuberculosis, Mycoplasma,* or adenovirus.
- Anaerobic bacteria produce empyema associated with aspiration pneumonia and dental, lung, or subdiaphragmatic abscesses.
- *H. influenzae* frequently causes parapneumonic effusion but is rare in immunized populations.

## Clinical Manifestations

- Pleural effusion heralded by pain, dyspnea, and signs of respiratory insufficiency resulting from compression of the underlying lung.
- Physical findings include:
  1. tachypnea
  2. dullness to percussion
  3. decreased breath sounds
  4. mediastinal shift
  5. decreased tactile fremitus
- The diagnosis is **confirmed radiographically**.
- Decubitus views, ultrasonography, or CT may help to determine size, location, and presence or absence of loculations of fluid.

## DIAGNOSTIC STUDIES

- **Thoracentesis** can help establish the cause of the effusion and exclude infection.
- The diagnostic culture yield of thoracentesis is low, however, in children with obvious infection who have received antibiotics for greater than 24 hours.

- In the absence of inflammation, transudate pleural fluid :
  1. low specific gravity (<1.015)
  2. protein content (<2.5 g/dL)
  3. low lactic dehydrogenase activity (<200 IU/L)
  4. low cell count with few polymorphonuclear cells (a transudate).
- exudative pleural effusions ( inflammation) :
  1. high specific gravity
  2. high protein (>3 g/dL)
  3. lactic dehydrogenase (>250 IU/L) content
  4. low pH (<7.2)
  5. low glucose (<40 mg/dL) level
  6. high cell count with many polymorphonuclear leukocytes.

### TREATMENT

- Therapy is directed at the underlying condition causing the effusion and at relief of the mechanical consequences of the fluid collection.
- small effusions, especially if they are transudative, no drainage therapy is required.
- For large effusions, drainage with a **chest tube**, especially if the fluid is purulent (empyema), is often needed.
- In cases of empyema and parapneumonic effusion, in which drainage is complicated by a loculated pleural collection, **video-assisted thoracoscopic surgical débridement** is useful and may reduce morbidity and length of hospital stay.
- small - moderate parapneumonic effusions can be managed conservatively with IV antb.
- If the underlying condition is treated successfully, the prognosis for pediatric patients with pleural effusions, including empyema, is excellent.

## CYSTIC FIBROSIS

- Cystic fibrosis (CF) is an inherited multisystem disorder of children and adults,
- It is the most common life-limiting recessive genetic trait among whites.
- Characterized chiefly by obstruction and infection of airways and by maldigestion and its consequences.
- A dysfunction of epithelialized surfaces is the predominant pathogenetic feature.
- CF is the cause of:
  1. severe chronic lung disease in children
  2. most exocrine pancreatic insufficiency in early life.
  3. salt depletion
  4. nasal polyposis
  5. pansinusitis
  6. rectal prolapse
  7. pancreatitis
  8. cholelithiasis
  9. insulin-dependent hyperglycemia.
  10. failure to thrive
  11. cirrhosis or other forms of hepatic dysfunction.

### GENETICS

- CF occurs most frequently in white populations of northern Europe, North America, and Australia/New Zealand.
- CF is inherited as an autosomal recessive trait.
- The CF gene codes for a protein of 1,480 amino acids called the *CF transmembrane regulator (CFTR).*
- CFTR is expressed largely in epithelial cells of:
  1. airways
  2. the GI tract (the pancreas and biliary system)
  3. the sweat glands
  4. the genitourinary system.

- > 1,500 CFTR polymorphisms are associated with the CF
- The most prevalent mutation of CFTR is the deletion of a single phenylalanine residue at amino acid 508 (ΔF508).
- W1282X mutation occurs in 60% of Ashkenazi Jews .
- Mutations categorized as "severe" (ΔF508) are associated almost uniformly with pancreatic insufficiency.
- Several mutations are found in patients with normal sweat chloride concentrations.
- Occurrence of liver disease cannot be predicted by CFTR genotype.

## PATHOGENESIS

- Four long-standing observations are of fundamental pathophysiologic importance:
  1. failure to clear mucous secretions
  2. paucity of water in mucous secretions
  3. elevated salt content of sweat and other serous secretions
  4. chronic infection limited to the respiratory tract.
- greater negative potential difference across the respiratory epithelia of CF patients than across the respiratory epithelia of control subjects.
- The postulated epithelial pathophysiology in airways involves an inability to secrete salt and secondarily to secrete water in the presence of excessive reabsorption of salt and water.
- The proposed outcome is insufficient water on the airway surface to hydrate secretions.
- Desiccated secretions become more viscous and elastic (rubbery) and are harder to clear by mucociliary and other mechanisms.
- Altered mucus rheology can be aggravated by low $HCO_{3-}$ and a more acidic pH.
- These secretions are retained and obstruct airways, starting with those of the smallest caliber, the bronchioles.
- **Airflow obstruction at the level of small airways is the earliest observable physiologic abnormality of the respiratory system.**
- It is plausible that similar pathophysiologic events take place in the pancreatic and biliary ducts (and in the vas deferens), leading to desiccation of proteinaceous secretions and obstruction.
- sweat gland duct cells absorb rather than secrete chloride, salt is transported to the skin surface; chloride and sodium levels are↑ .
- Chronic infection in CF is limited to the airways.
- explanation for infection is a sequence of events starting with failure to clear inhaled bacteria → persistent colonization → inflammatory response in airway walls.
- An alternative hypothesis : abnormal CFTR →creates a proinflammatory state or amplifies the inflammatory response to initial viral infections.
- Inflammatory events occur 1st in small airways, perhaps because clearance more difficult from these regions.
- Chronic bronchiolitis and bronchitis are the initial lung manifestations, but after months to years, structural changes in airway walls produce bronchiolectasis and bronchiectasis.
- Several inflammatory products, including proteases, contribute to the mucus hypersecretion that is characteristic of chronic airway disease.
- high prevalence of airway colonization with *Staphylococcus aureus* (infant) , *Pseudomonas aeruginosa* & *Burkholderia cepacia* (older)

| **RESPIRATORY** |
|---|
| Bronchiectasis, bronchitis, bronchiolitis, pneumonia |
| Atelectasis |
| Hemoptysis |
| Pneumothorax |
| Nasal polyps |
| Sinusitis |
| Reactive airway disease |
| Cor pulmonale |
| Respiratory failure |
| Mucoid impaction of the bronchi |
| Allergic bronchopulmonary aspergillosis |
| **GASTROINTESTINAL** |
| Meconium ileus, meconium plug (neonate) |
| Meconium peritonitis (neonate) |
| Distal intestinal obstruction syndrome (non-neonatal obstruction) |
| Rectal prolapse |
| Intussusception |
| Volvulus |
| Fibrosing colonopathy (strictures) |
| Appendicitis |
| Intestinal atresia |
| Pancreatitis |
| Biliary cirrhosis (portal hypertension: esophageal varices, hypersplenism) |
| Neonatal obstructive jaundice |
| Hepatic steatosis |
| Gastroesophageal reflux |
| Cholelithiasis |
| Inguinal hernia |
| Growth failure (malabsorption) |
| Vitamin deficiency states (vitamins A, K, E, D) |
| Insulin deficiency, symptomatic hyperglycemia, diabetes |
| Malignancy (rare) |
| **OTHER** |
| Infertility |
| Delayed puberty |
| Edema-hypoproteinemia |
| Dehydration-heat exhaustion |
| Hypertrophic osteoarthropathy-arthritis |
| Clubbing |
| Amyloidosis |
| Diabetes mellitus |

## PATHOLOGY

- Eccrine sweat glands and parotid salivary glands, including ducts, are not involved pathologically, despite abnormalities in the electrolyte content of their secretory product.
- The earliest pathologic lesion in the lung is that of **bronchiolitis**

- With time, mucus accumulation and inflammation extend to the larger airways (**bronchitis**).
- With longstanding disease, evidence of airway destruction such as **bronchiolar obliteration, bronchiolectasis,** and **bronchiectasis** becomes prominent.
- Bronchiectatic cysts and emphysematous bullae or subpleural blebs are frequent with advanced lung disease, the upper lobes being most commonly involved.
- These enlarged air spaces may rupture and cause pneumothorax.
- Interstitial disease is not a prominent feature.
- True emphysema occurs but is not a general pathologic finding.
- Bronchial arteries are enlarged and tortuous→ **hemoptysis** in bronchiectatic airways.
- Small pulmonary arteries eventually display medial hypertrophy, which would be expected in **secondary pulmonary hypertension**.
- **paranasal sinuses** are uniformly filled with secretions containing inflammatory products, and the epithelial lining show hyperplastic and hypertrophied secretory elements.
- The **pancreas** is small, may cystic, and often difficult to find at postmortem examination.
- 85-90%, the lesion progresses to complete or almost complete disruption of acini and replacement with fibrous tissue and fat.
- Foci of calcification may be seen on radiographs of the abdomen.
- The islets of Langerhans contain normal appearing β cells, although they may begin to show architectural disruption by fibrous tissue in the 2nd decade of life.
- The **intestinal tract** shows only minimal changes.
- Esophageal and duodenal glands are often distended with mucous secretions.
- Concretions may form in the appendiceal lumen or cecum.
- Crypts of the appendix and rectum may be dilated and filled with secretions.
- **Focal biliary cirrhosis** secondary to blockage of intrahepatic bile ducts is uncommon in early life, although it is responsible for occasional cases of prolonged neonatal jaundice.
- found in 25% or more of patients at postmortem examination.
- Infrequently, this process proceeds to symptomatic multilobular biliary cirrhosis that has a distinctive pattern of large irregular parenchymal nodules and interspersed bands of fibrous tissue.
- 30% : fatty infiltration of the liver, in some cases despite apparently adequate nutrition.
- hepatic congestion frequently secondary to cor pulmonale.
- The gallbladder : hypoplastic and filled with mucoid material and often contains stones.
- Atresia of the cystic duct and stenosis of the distal common bile duct may occur.
- **Cervix glands** are distended with mucus, copious amounts collect in cervical canal.
- Endocervicitis prevalent in teenagers and young women.
- >95% of males, the body and tail of the epididymis, the vas deferens, and the seminal vesicles are obliterated or atretic.
- **Generalized amyloidosis** has been reported rarely

## CLINICAL MANIFESTATIONS

### RESPIRATORY TRACT

- Cough is the most constant symptom of pulmonary involvement.
- At first, the cough may be dry and hacking, but eventually it becomes loose and productive.
- In older patients, the cough is most prominent on arising in the morning or after activity.
- Expectorated mucus is usually purulent.
- Some patients remain asymptomatic for long periods or seem to have prolonged but intermittent acute respiratory infections.
- may acquire a chronic cough in the 1st weeks of life &have pneumonia repeatedly.
- Extensive bronchiolitis is attended by wheezing, which is a frequent symptom during the 1st years of life.
- As lung disease slowly progresses, exercise intolerance, shortness of breath, and failure to gain weight or grow are noted.
- Cor pulmonale, respiratory failure, and death eventually supervene unless lung transplantation is accomplished.

- A few mutations (**R117H**) may substantially or even fully spare the lungs.
- **Male gender** and **exocrine pancreatic sufficiency** are associated with a slower rate of pulmonary function decline.
- **physical findings** include:
  1. increased anteroposterior diameter of the chest
  2. generalized hyperresonance
  3. scattered or localized coarse crackles
  4. digital clubbing
  5. Expiratory wheezes, especially in young children.
  6. Cyanosis is a late sign.
- Common pulmonary complications include: (beyond the 1st decade of life)
  1. atelectasis
  2. hemoptysis
  3. pneumothorax
  4. cor pulmonale
- Even though the paranasal sinuses are virtually always opacified radiographically, acute sinusitis is infrequent.
- **Nasal polyps** are most troublesome between 5 and 20 yr of age.

## INTESTINAL TRACT

- **meconium ileus** the ileum is completely obstructed by meconium
  - 15-20% of newborn infants with CF.
  - The frequency is greater (≈30%) among siblings born subsequent to a child with meconium ileus .
  - Abdominal distention, emesis, and failure to pass meconium appear in the 1st 24-48 hr of life.
  - Abdominal radiographs show dilated loops of bowel with air-fluid levels and, frequently, a collection of granular, "ground-glass" material in the lower central abdomen.
- Rarely, **meconium peritonitis** results from intrauterine rupture of the bowel wall and can be detected radiographically by the presence of peritoneal or scrotal calcifications.
- **Meconium plug syndrome** occurs with increased frequency in infants with CF but is less specific than meconium ileus.
- **distal intestinal obstruction syndrome or meconium ileus equivalent**: Ileal obstruction with fecal material occurs in older patients, causing cramping abdominal pain and abdominal distention.
- > 85% of affected children show evidence of maldigestion from exocrine **pancreatic insufficiency.**
- Symptoms : frequent, bulky, greasy stools and failure to gain weight even when food intake appears to be large.
- 40% of patients display nutritional failure by the criterion of weight/height less than the 10th percentile.
- Characteristically, stools contain readily visible droplets of fat.
- typical physical signs : protuberant abdomen, ↓muscle mass, poor growth, and delayed maturation.
- Excessive flatus may be a problem.
- A number of mutations are associated with preservation of some exocrine pancreatic function, including **R117H** and **3849 + 10 kb C >**T.
- Virtually all individuals homozygous for ΔF508 have pancreatic insufficiency.
- Less common , **intussusception**, fecal impaction of the cecum with an asymptomatic right lower quadrant mass, and epigastric pain owing to duodenal inflammation.
- **Acid or bile reflux with esophagitis** symptoms is common in older children and adults.
- **Subacute appendicitis and periappendiceal abscess** have been encountered.
- **rectal prolapse** occurs much less frequently as the result of earlier diagnosis and initiation of pancreatic enzyme replacement therapy.
- **hypoproteinemia** with anasarca appears in malnourished infants, especially if children are fed soy-based preparations.

- **vitamin E deficiency:** Neurologic dysfunction (dementia, peripheral neuropathy) and hemolytic anemia**.**
- **Hypopro-thrombinemia** owing to vitamin K deficiency may result in a bleeding diathesis.
- Clinical manifestations of other fat-soluble vitamin deficiencies: decreased bone density and night blindness, Rickets is rare.

### Biliary Tract

- liver dysfunction is most often detected in the 1st 15 yr of life ( 30% of cases).
- Liver disease occurs independent of genotype but is associated with meconium ileus and pancreatic insufficiency.
- **Biliary cirrhosis** : symptomatic in only 2-3% of patients: icterus, ascites, hematemesis from esophageal varices, and evidence of hyper-splenism.
- **Steatosis**: A neonatal hepatitis-like picture and massive hepatomegaly .
- Biliary colic secondary to **cholelithiasis** may occur in the 2nd decade or later.

### Pancreas

- exocrine pancreatic insufficiency
- **insulin-dependent diabetes**: 8 % of 11-17 yr old patients and 18% of 18-24 yr olds.
- Ketoacidosis usually does not occur, but eye, kidney, and other vascular complications have been noted in patients living ≥10 yr after the onset of hyperglycemia.
- **Recurrent acute pancreatitis** occurs in individuals who have residual exocrine pancreatic function and may be **the sole manifestation of two CFTR mutations**.

### Genitourinary Tract

- **delayed Sexual development** by an average of 2 yr.
- > 95% of males are **azoospermic** because of failure of development of Wolffian duct structures, but sexual function is generally unimpaired.
- The incidence of **inguinal hernia, hydrocele,** and **undescended testis** is higher.
- **secondary amenorrhea**, especially with exacerbations of pulmonary disease.
- **Cervicitis** and accumulation of tenacious mucus in the cervical canal have been noted.
- The **female fertility rate is diminished**.
- Pregnancy is generally tolerated well by women with good pulmonary function but may accelerate pulmonary progression in those with moderate or advanced lung problems.

### Sweat Glands

- Excessive loss of salt in the sweat predisposes young children to salt depletion episodes, especially during episodes of gastroenteritis and during warm weather.
- These children present with **hypochloremic alkalosis.**
- parents notice salt "frosting" of the skin or a salty taste when they kiss the child.
- A few genotypes (**3849 + 10 kb C >T**) are associated with normal sweat chloride values.

## DIAGNOSIS AND ASSESSMENT

### Diagnostic Criteria for Cystic Fibrosis (CF)

| |
|---|
| Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary) or |
| A history of CF in a sibling or |
| A positive newborn screening test |
| PLUS |
| **Laboratory evidence for CFTR dysfunction:** |
| Two elevated sweat chloride concentrations obtained on separate days or |
| Identification of two CF mutations or |
| An abnormal nasal potential difference measurement |

## THE SWEAT TEST

- The standard approach to diagnosis.
- A 3 mA electric current is used to carry pilocarpine into the skin of the forearm and locally stimulate the sweat glands.
- For reliable results, 75 mg - 100 mg of sweat should be collected.
- Testing is difficult in the 1st 2 wk of life because of low sweat rates but is recommended any time after the 1st 48 hrs of life.
- More than 60 mEq/L of chloride in sweat is diagnostic of CF when 1 or more other criteria are present.
- Threshold levels of 40 mEq/L for infants have been suggested.
- In healthy adults, the sweat chloride values increase slightly, but a value of 60 mEq/L still adequately differentiates CF from other conditions.
- False-negative test results may be encountered in children with:hypoproteinemic edema
- false-positive results can occur when testing is performed on skin affected by eczema or contaminated with skin creams or lotions.
- Non-CF conditions associated with positive sweat test:
  1. untreated adrenal insufficiency
  2. ectodermal dysplasia
  3. hereditary nephrogenic diabetes insipidus
  4. G6PD
  5. hypothyroidism
  6. hypoparathyroidism
  7. familial cholestasis
  8. pancreatitis
  9. mucopolysaccharidoses
  10. fucosidosis
  11. malnutrition

## DNA TESTING

- Several commercial laboratories test for 30-80 of the most common CFTR mutations.
- This testing identifies ≥90% individuals who carry 2 CF mutations.
- Some children with typical CF manifestations have 1 or no detectable mutations by this methodology.
- Some laboratories perform comprehensive mutation analysis, screening for all of the >1,500 identified mutations.

## OTHER DIAGNOSTIC TESTS

- The finding of increased potential differences across nasal epithelium.
- The loss of this difference with topical amiloride application, and the absence of a voltage response to a β-adrenergic agonist → confirm diagnosis in patients with equivocal or normal sweat chloride values.

## PANCREATIC FUNCTION

- Exocrine pancreatic dysfunction is clinically apparent in many patients.
- Measurement of fat balances with a 3 day stool collection provides a reliable measure.
- Quantitation of elastase-1 activity in a fresh stool sample is a useful screening test.
- Measurement of immunoreactive trypsinogen in serum, used for newborn screening, also reliably distinguishes patients with CF, with and without pancreatic insufficiency.
- yearly monitoring with a modified 2 hr (OGTT) after 10 yr of age.

## RADIOLOGY

- Pulmonary radiologic findings suggest the diagnosis but are not specific.
- Hyperinflation of lungs occurs early .
- With advanced disease, impressive hyperinflation with markedly depressed diaphragms, anterior bowing of the sternum, and a narrow cardiac shadow are noted.
- bronchiectasis : Bronchial thickening and plugging and ring shadows ,appear 1st in the upper lobes.

- Nodular densities, patchy atelectasis, and confluent infiltrate follow.
- Hilar lymph nodes may be prominent.
- with advanced disease: Cyst formation, extensive bronchiectasis, dilated pulmonary artery segments, and segmental or lobar atelectasis.
- Many children with normal lung function have bronchiectasis by CT, indicating that this imaging modality is sensitive to early lung changes.
- Radiographs:paranasal sinuses → panopacification + failure of frontal sinus development.
- Fetal US may suggest ileal obstruction with meconium early in the 2nd trimester, but this finding is not predictive of meconium ileus at birth.

## PULMONARY FUNCTION

- Standard pulmonary function studies are not obtained until 4-6 yr of age, by which time many patients show the typical pattern of obstructive pulmonary involvement.
- The findings of obstructive airway disease and modest responses to a bronchodilator are consistent with the diagnosis of CF at all ages.
- Restrictive changes, characterized by declining total lung capacity and vital capacity, correlate with extensive lung injury and fibrosis and are a late finding.
- Some patients reach adolescent or adult life with normal pulmonary function and without evidence of overinflation.

## MICROBIOLOGIC STUDIES

- The finding of *S. aureus* or *P. aeruginosa or B. cepacia* on culture of the lower airways (sputum) strongly suggests a diagnosis of CF.
- Failure of respiratory symptom flares to respond to usual antibiotics triggers testing for **mycoplasma and viruses**.
- **Fiberoptic bronchoscopy** is used to gather lower respiratory tract secretions of infants and young children who do not expectorate.

## HETEROZYGOTE DETECTION AND PRENATAL DIAGNOSIS

- Termination of pregnancy is a less popular option because the clinical course is not predictable and expected longevity now approaches 4 decades on average.

## NEWBORN SCREENING

- Most newborns with CF can be identified by determination of **immunoreactive trypsinogen** and limited **DNA testing** on blood spots, coupled with **confirmatory sweat analysis.**
- This screening test is ≈95% sensitive.
- Newborn diagnoses can prevent early nutritional deficiencies and improve long-term growth, and may spare cognitive function.
- *There is as yet no compelling evidence that early diagnosis improves pulmonary outcome and, therefore, survival*.

## TREATMENT

- **Pulmonary Therapy**: object is to clear secretions from airways and to control infection
- **Inhalation Therapy**
  - Aerosol therapy is used to deliver medications and hydrate the lower respiratory tract.
  - Metered-dose inhalers can deliver some agents such as bronchodilators and corticosteroids, with a spacer for younger children.
  - The basic aerosol solution is **0.9% saline**.
  - with reactive airways, **albuterol** or other β agonists are added.
  - β Agonists decrease $PaO_2$ acutely by increasing ventilation-perfusion mismatch.
  - if resistant to oral antibiotics or when the infection is difficult to control at home, aerosolized antibiotics: reduce symptoms, improve pulmonary function, no hospitalization
  - **Human recombinant DNase** (2.5 mg), once daily aerosol dose, improves pulmonary function, decreases numbers of pulmonary exacerbations, and promotes a sense of well-being in patients who have moderate disease and purulent secretions.

- mucolytic agent, ***N*-acetyl-cysteine**, is toxic to ciliated epithelium, and repeated administration should be avoided.
- Hypertonic saline aerosols are reported to increase mucus clearance and improve pulmonary function. Benefit is variable and inferior to DNase.

- **Airway Clearance Therapy**
  - This treatment usually consists of chest percussion combined with postural drainage
  - cough clears mucus from large airways, but chest vibrations move secretions from small airways where expiratory flow rates are low.
  - **Chest physical therapy (PT)** useful with CF because they accumulate secretions in small airways first, even before the onset of symptoms.
  - cessation of chest PT in children with mild to moderate airflow limitation results in deterioration of lung function within 3 wk.
  - Chest PT is recommended 1-4 times a day, depending on severity of lung dysfunction.
- **Antibiotic Therapy**
  - Antibiotics are the mainstay of therapy designed to control progression of lung infection.
  - The goal is to reduce the intensity of endobronchial infection and to delay progressive lung damage.
  - Antibiotic treatment varies from intermittent short courses of 1 antibiotic to nearly continuous treatment with 1 or more antibiotics.
  - Dosages for some antibiotics are often 2 - 3 times the amount recommended for minor infections because patients with CF have:
    1. more lean body mass
    2. higher clearance rates for many antibiotics than do other individuals
    3. difficult to achieve effective drug levels of many antimicrobials in RT secretions.
  - The quinolones are the only broadly effective oral antibiotics for *Pseudomonas* infection, but resistance emerges rapidly.
  - Long-term therapy with azithromycin times a week has been shown to improve lung function in patients with chronic *P. aeruginosa* infection.
  - Tetracycline : avoided in children <9 yr of age.
  - *P. aeruginosa* and other gram-negative organisms are resistant to all oral antibiotics.
  - Inhaled tobramycin 300 mg twice daily on alternate months for 6 mo- *Pseudomonas*
  - progressive or unrelenting symptoms and signs despite intensive home measures, intravenous antibiotic therapy is indicated. -usually advisable to extend the period of treatment to at least 14 days.
  - Permanent intravenous access can be provided for long-term or frequent courses of therapy in the hospital or at home.

| ROUTE | ORGANISMS | AGENTS |
|---|---|---|
| ORAL | *Staphylococcus aureus* | Dicloxacillin<br>Linezolid<br>Cephalexin<br>Clindamycin<br>Amoxicillin-clavulanate |
| | *Haemophilus influenzae* | Amoxicillin |
| | *Pseudomonas aeruginosa* | Ciprofloxacin |
| | *Burkholderia cepacia* | Trimethoprim-sulfamethoxazole |
| | Empirical | Azithromycin<br>Erythromycin |
| IV | *S. aureus* | Nafcillin<br>Vancomycin |
| | *P. aeruginosa* | **Amikacin**<br>**Aztreonam**<br>**Carbenicillin**<br>**Cefipime**<br>**Ceftazidime**<br>**Imipenem-cilastatin**<br>**Meropenem**<br>**Netilmicin**<br>**Piperacillin**<br>**Piperacillin-Tazobactam**<br>**Tobramycin**<br>**Ticarcillin**<br>**Ticarcillin-clavulanate** |
| | *B. cepacia* | Chloramphenicol<br>Meropenem |
| AEROSOL | | Tobramycin (inhaled) |

# ASTHMA

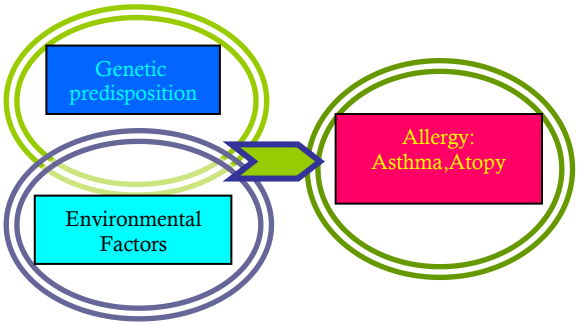
DR. ABDULLATEEF AL KHATEEB

## DEFINITION:

- Chronic inflammatory disease of the airways resulting in episodic airflow obstruction.
- It is the most common childhood chronic disease
- **Clinically** : has symptoms of intermittent wheezing, cough, dyspnea, and chest tightness,
- **Physiologically** has airway obstruction.
- **Pathologically** has (due to) inflammation.
- It is characterized by:
  1. hyper-responsiveness of airways to several allergic (provocative) stimuli (exposures)
  2. Reversibility of obstruction: spontaneous or by therapy
- TYPES OF ASTHMA:
  1. **Chronic asthma**: (**the most common type**) Associated with allergy. Persists into later childhood and adulthood.
  2. **Recurrent wheezing in early childhood**: triggered by respiratory viral infections.
  3. **Third type:** occurs in females who have obesity & early-onset puberty
  4. **Occupational asthma**: in adults more than children. Seen in farms and farm-type animals in the home.
- asthma prevalence of & mortality have been increased in the last two decades. Why??

## PATHOLOGY

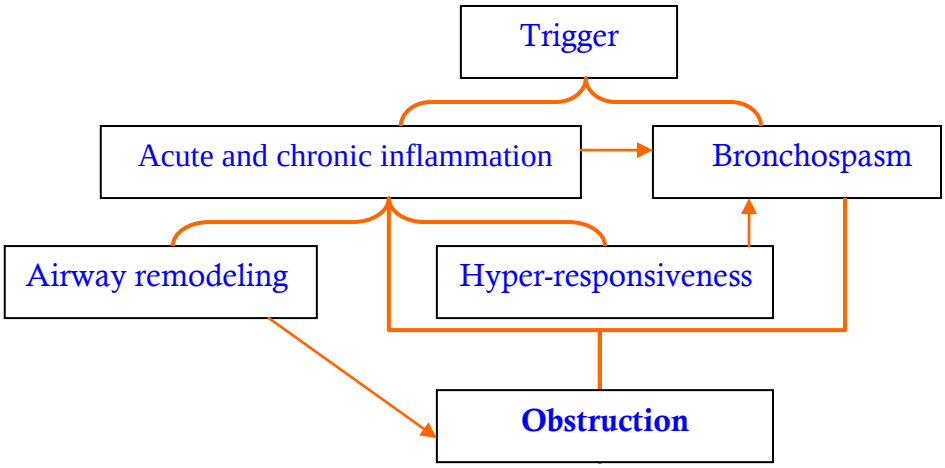
- **The obstruction is produced by:**
  1. Broncho-constriction
  2. Mucous membrane edema
  3. Mucus over-secretion
  4. Desquamation (epithelial damage)
  5. Inflammation (cellular infiltrates):
     - In children it is acute & reversible
     - In adults it is chronic & *irreversible*
  6. Remodeling of airways In chronic cases: hypertrophy of smooth muscles & hyperplasia of mucus glands, thickening of basement membrane, and subepithelial collagen deposition.
- All of the above are produced by allergic stimuli called triggers of asthma
- **Triggers of Asthma:**
  1. Allergens: Seasonal (pollens), Perennial (dust mites, animal fur, molds, insects e.g. cockroaches)
  2. Infections: Mostly Viral, Rarely others, e.g. colds, sinusitis, bronchitis,
  3. Airway irritants: *Cigarettes (Active or passive),* air pollution, wood smoke, perfumes, sprays, paints odors, cleaning agents, ozone.
  4. Exercise: sustained, in cold air →exercise induced bronchospasm (EIB)
  5. Cold or dry air & changes in weather
  6. Medications & chemicals: Aspirin, NSAIDs, beta-blockers.
  7. Food: soy proteins, food additives & preservatives: Na metabisulfite & tartrazine
  8. Stress: emotional factors: laughing (**mirth triggered asthma**), hyperventilation




## ETIOLOGY:

A. **Inheritance & genetic factors in asthma**
   - More than 22 loci on 15 autosomal chromosomes are linked to asthma, e.g. IL-4 gene clusters on chromosome 5
   1. **Multi-factorial inheritance***:* so **:**
      - If One parent is affected→ **25%** risk of asthma
      - If Both parents are affected→ risk is **50%**
      - Monozygotic twins are highly concordant regarding liability to bronchospasm on exercise, Dizygotic twins are less concordant
   2. **Genetic variations in receptors** for asthma medications results in variations in response. (i.e. polymorphism in drugs receptors)

## ASTHMA PATHOGENESIS

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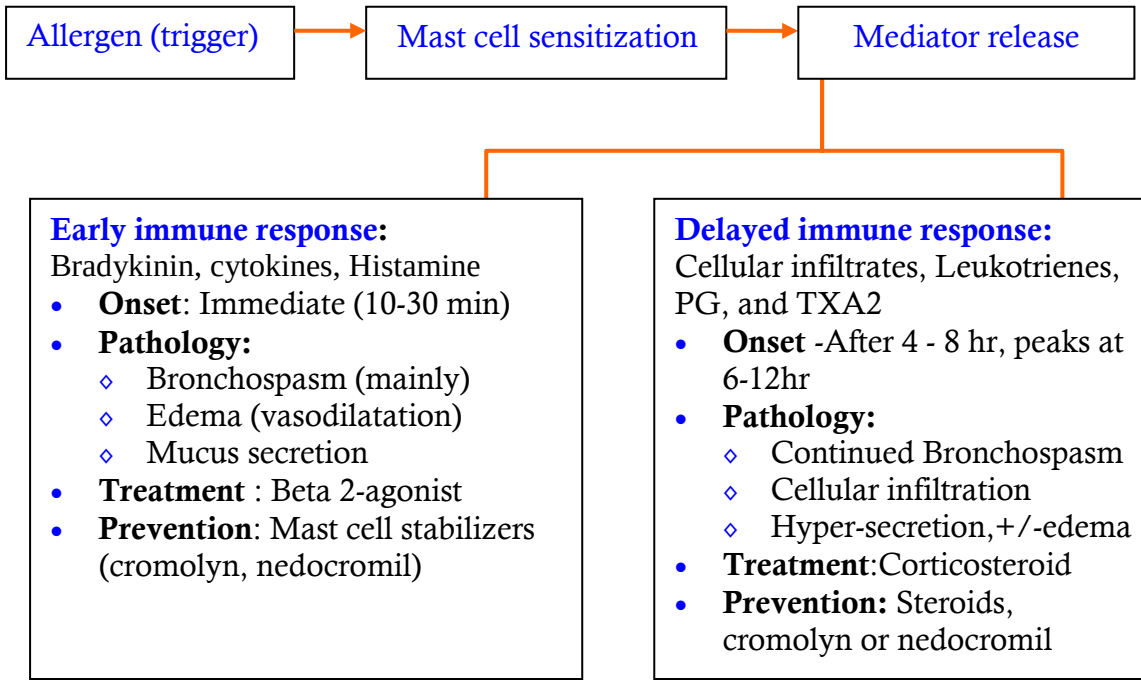
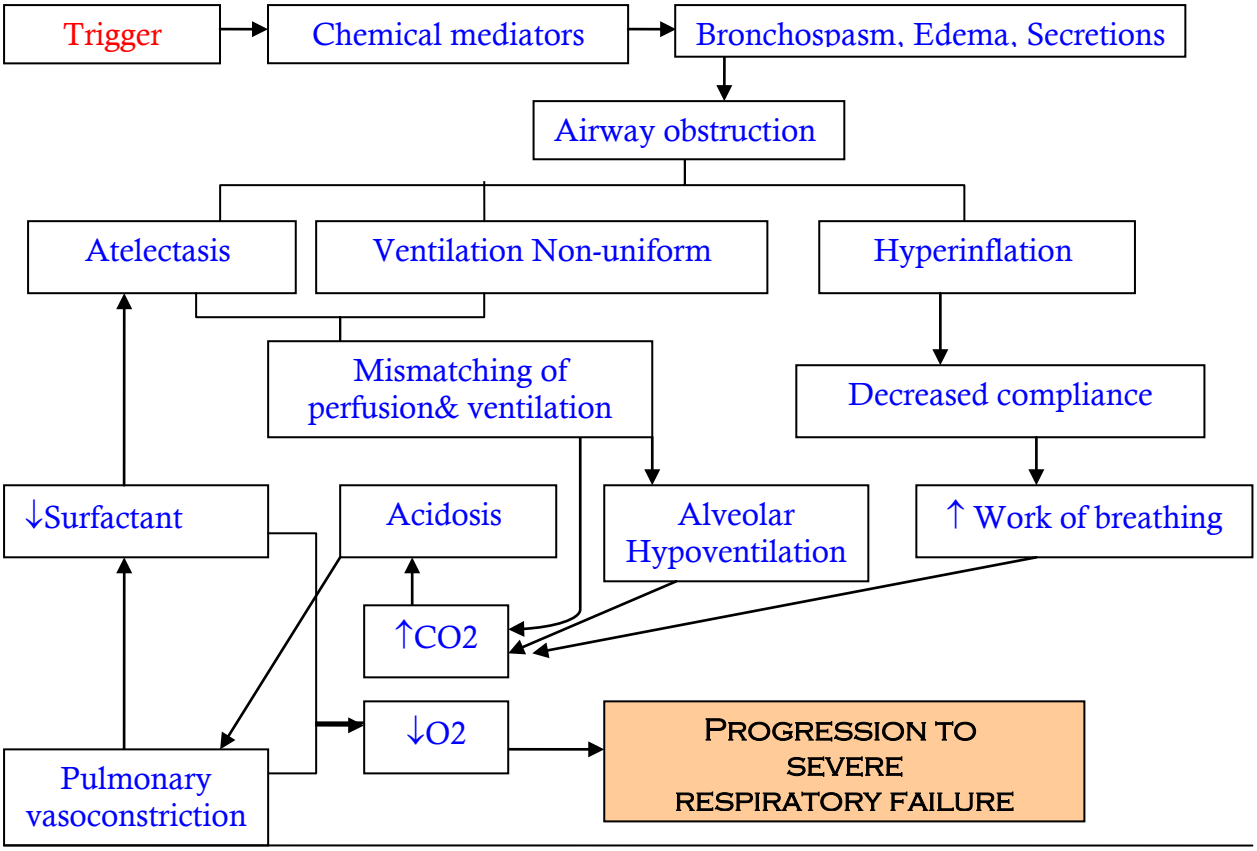



| TYPE OF ASTHMA | EXTRINSIC | INTRINSIC |
|---|---|---|
| ENVIRONMENTAL ALLERGEN | Yes | No |
| SERUM IgE | High | Normal |
| SKIN TESTS | Positive | Negative |




B. **Environmental factors**
   1. **Infectious causes**: the most important are Viruses: by common respiratory viruses e.g. RSV (the most common and important virus), the more the severe is the injury the more likely the asthma persists.
      A. in early life: RSV + Parainfluenza
      B. In older ages: Rhinoviruses + Influenza
      - **Mechanism**: vagal stimulation or IgE response: e.g. RSV IgE
      - RSV unmask asthma in predisposed patient (if 1st episode triggered by RSV)
   2. **Allergen exposure**: leads to sensitization to the same allergen and to other irritant exposures.
      - Perennial exposure is a major factor for degree of severity.
      - Allergen elimination → control of asthma
   3. **Tobacco smoke**
   4. **Air pollutants** (ozone, sulfur dioxide).
   5. **Dry and cold air**
   6. **Strong odors**
   - some of these triggers only produce bronchospasm without inflammation

C. **Autonomic Factors**
   - Vagal stimulation→ Broncho-constriction
   - Histamine & Leukotrienes → Broncho-constriction (directly or by vagal stimulation)
   - Adenosine ( locally produced in airways) → Broncho-constriction
   - VIP → Broncho-dilation
   - Catecholamines → Broncho-dilation

D. **Endocrine Factors**
   - Menses & pregnancy : may ↑severity of asthma
   - Asthma may start with menopause
   - Thyrotoxicosis may worsen asthma
   - Asthma may improve or subside at puberty

E. **Psychological factors**
   - Asthma may be triggered with laughing or crying
   - Asthma may lead to behavioral & emotional problems

## EPIDEMIOLOGY

- Boys 10-15%, Girls 7-10%
- 10% of children & 5% of adults
- Prepubertal age: Boys > Girls, ratio 2:1***Postpubertal age: Boys = Girls
- Adulthood onset asthma: females > males

IN USA:

- 12% of children experience asthma (~5 millions< 18 yr)
- Asthma is the most common cause of childhood emergency visits, hospitalizations, & missed school days
- Death from asthma is uncommon in children, many of these deaths are preventable.
- In blacks morbidity and mortality is x3, but prevalence is slightly increased, (16 vs 13%)

WORLDWIDE:

- 80% of asthmatics have onset before 6 yr of age, 100% by 7-8yr of age
- Asthma prevalence is increasing inspite improvement in management & medical therapy.
- Variations in prevalence from country to another and also from urban (more prevalent) to rural areas (less prevalent).

| RISK FACTORS FOR OCCURRENCE OF ASTHMA (INCREASED PREVALENCE) | |
|---|---|
| 1. Poverty<br>2. Large family size<br>3. Parental smoking<br>4. Birth Wt < 2.5 Kg<br>5. Maternal age < 20 Yr<br>6. Black race | 1. Small home size<br>2. Intense allergic exposure<br>3. Frequent respiratory infections in early childhood<br>4. Less than optimal parenting |

EARLY CHILDHOOD RISK FACTORS FOR PERSISTENT ASTHMA

1. **Atopic dermatitis**
2. **Allergic rhinitis**
3. **Food allergy**
4. **Inhalant allergen sensitization**
5. Pneumonia
6. Bronchiolitis requiring hospitalization
7. Parental asthma
8. Wheezing apart from colds
9. Male gender
10. Low birth weight
11. Environmental tobacco smoke exposure

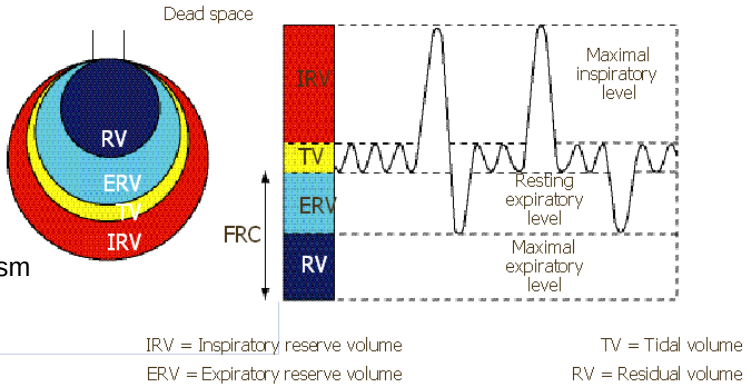
- the first four are major risk factors
- **Food allergy and Asthma (GERD)**
  - ◇ Ingested food allergen protein
    - A. Trans-epithelial absorption Membrane cell transporter →Reflux route to lung.
    - B. Aspiration and arolization of ingested material →inhalation rout to lung
  - ◇ **These results indicate that anti-GER treatments may provide significant benefits for asthmatic children with coexisting GER.**

NOTE:
TRIAD ASTHMA: Rare in children, seen in adults & consists of:
1. asthma
2. sinusitis/nasal polyposis
3. hypersensitivity to aspirin and other NSAIDs

## CLINICAL ASPECTS OF ASTHMA

ONSET:

- Acute:
  - ◇ develops in few minutes
  - ◇ due to bronchospasm of large airways
  - ◇ examples: pollens, smoke, drugs,--
- Insidious:
  - ◇ develops over days
  - ◇ due to inflammation, &↑ mucus, +/- spasm
  - ◇ examples: viral infections



## CLINICAL MANIFESTATIONS

- According to severity of attack: we may have: *Tachypnea, retraction, wheezing, cough, accessory muscle use,----*
  1. Wheezing +/- cough or <u>cough alone</u> ( night cough)
  2. Dyspnea: (shortness of breathing); difficult walking or talking
  3. Abdominal pain, vomiting,
  4. Palpable liver &spleen (overinflation)
  5. Low grade fever (work of breathing)
  6. Profuse sweating
  7. Pulsus paradoxus (drop in systolic BP during inspiration)
- **In chronic asthma:**
  - ◇ Barrel-shaped chest deformity
  - ◇ Harrison sulcus
  - ◇ ***Rarely*** digital clubbing: usually late manifestation in older ages, if seen in children other diagnoses are possible like ***cystic fibrosis***
- Subtle symptoms: fatigue, ↓physical activity, sleepiness
- Auscultation: wheezing, rhonchi, rales, ↓air entry (unilateral or regional)

## CLINICAL DIAGNOSIS OF ASTHMA:

- **The presence of any of these is <u>suggestive</u> of asthma**
  1. Recurrent episodes of wheezing (≥ 3 attacks), +/- cough → highly suggestive
  2. Clinical improvement after therapy with *drugs* that are specific for asthma,
  3. Positive family history of *asthma or atopy*
  4. Episodes are caused by *specific environmental triggers* e.g. allergen exposure, exercise, viral infection→<u>*environmental history is essential in dx and ttt*</u>
  5. Symptoms worsen at *night & early* morning
- Normal chest exam does not exclude asthma
- **Consider asthma if any of the following signs or symptoms are present:**
  1. Frequent episodes of wheezing: > once a month
  2. Activity-induced cough or wheeze
  3. Cough particularly at night during periods without viral infections
  4. Absence of seasonal variation in wheeze
  5. Symptoms that persist after age 3
  6. Symptoms occur or worsen in the presence of:
     - ◇ Animals with fur
     - ◇ Aerosol chemicals
     - ◇ Changes in temperature
     - ◇ Domestic dust mites
     - ◇ Drugs (aspirin, beta blockers)
     - ◇ Exercise
     - ◇ Pollen
     - ◇ Respiratory (viral) infections
     - ◇ Smoke
     - ◇ Strong emotional expression
  7. The child's colds repeatedly "go to the chest" or take more than 10 days to clear up
  8. Symptoms improve when asthma medication is given

## LABORATORY TESTS: (HELPFUL, NOT DIAGNOSTIC)

1. **Eosinophilia** in the blood or sputum
2. **IgE serum level**: may be increased
3. **Allergy skin testing** & RAST to determine specific allergen
4. **Chest X-RAY:**
   - ◇ **Findings:** Variable: often normal, hyperinflation, atelectasis, peribronchial thickening, pneumothorax
   - ◇ **Indications:**
     - A. In the first attack of asthma to R/O other diagnosis
     - B. In recurrent attacks **IF:**
       1. Patient is febrile
       2. H.R >160/min
       3. Tachypnea >60/min
       4. Suspicion of pneumothorax
       5. Localized findings on chest exam, e.g. localized breathing or ↓air entry
5. **Blood Gases:**
   - ◇ Hypoxia (low PaO2)
   - ◇ PaCO2: Early low → normal → high.

- Normal PaCO2 in a tachypneic patient is an ominous sign = impending respiratory failure
- pH: **Early respiratory alkalosis → Mixed respiratory & metabolic acidosis**

6. **Pulmonary function tests:**
   - A. **Lung volumes:**
     - Decreased VC & FVC
     - Increased TLC, RV, & FRC
   - B. **Airway flow:**
     - Decreased PEF (PFR), FEV1, FEF25-75%

## PULMONARY FUNCTION TESTS :

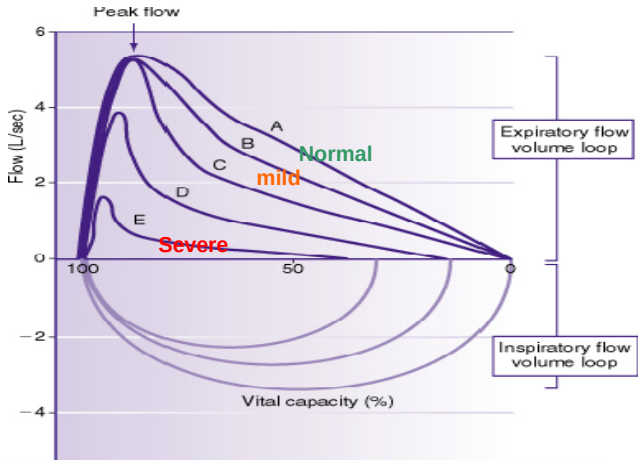
1. **Spirometry:**
   - Measures lung volumes and airflow during forced expiration.
   - **It is the gold standard measure of airflow in asthmatics**
   - A. ↓FEV1 as a percentage of predicted norms
   - B. ↓FEV1/FVC, if < 80% = significant airway obstruction
   - C. Bronchodilator response (B-agonist nebulizer)→ improvement in FEV1 ≥ 15%

### SPIROMETRIC FLOW-VOLUME LOOPS

A. is an expiratory flow-volume loop of a Non-asthmatic, without airflow limitation.

B. expiratory flow-volume loops in asthmatic Patients with mild degree of airflow limitation

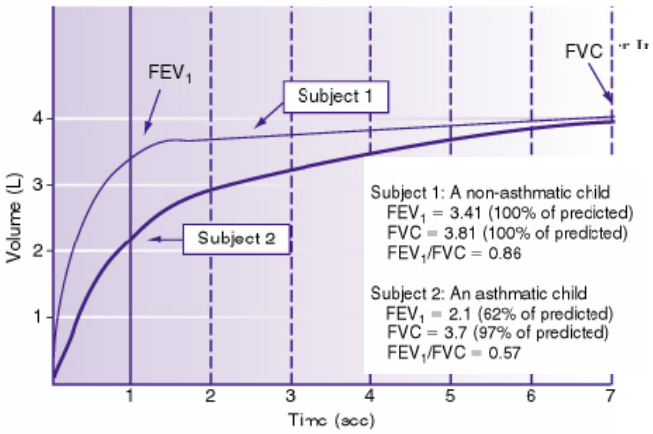
E. expiratory flow-volume loops in asthmatic patients with severe degree of airflow limitation




- Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping."

### SPIROMETRIC VOLUME-TIME CURVES

- The FEV1 is the volume of air exhaled in the 1st second of a forced expiratory effort.
- The FVC is the total volume of air exhaled during a forced expiratory effort.
- Subject 2's FEV1 and FEV1/FVC ratio are smaller than subject 1's, demonstrating airflow obstruction.
- Subject 2's FVC is very close to expected.




2. **Bronchoprovocative tests**: to test airway hyper-responsiveness.
   - **Principle:** Asthmatic airways are hyper-responsive → have ↑sensitivity to inhaled methacholine, histamine, cold dry air.
   1. methacholine inhalation: At least 15% decrease of FEV1. rarely used.
   2. exercise challenge test
      - running 6-8min→ At least 15% worsening of FEV1
      - Identify patients with exercise induced bronchospasm (EIB)
      - In non-asthmatics FEV1 improves by 5-10%
      - Dangerous in high risk asthmatics→ sever attack
3. **peak expiratory flow: (PEF)**
   - simple and inexpensive, for home use
   - Started by measuring the best PEF for the patient morning and evening for several weeks to practice the technique.
   - take the best of three conescutive readings

**NOTE:**
**Spirometry**:
- Airflow limitation
  1. Low FEV1
  2. FEV1/FVC ratio < 0.8
- Bronchodilator response (inhaled β2-agonist) ↑FEV1 ≥12%*
- Exercise challenge ↓FEV1 ≥15%*

**Peak flow** morning-to-afternoon variation ≥20%*

* Main criteria consistent with asthma

- morning to evening variation ≥ 20% is consistent with asthma

## DIFFERENTIAL DIAGNOSIS OF CHILDHOOD ASTHMA

A. **UPPER RESPIRATORY TRACT CONDITIONS**
   1. Allergic & Chronic rhinitis*
   2. Sinusitis*
   3. Adenoidal or tonsillar hypertrophy
   4. Nasal foreign body

B. **MIDDLE RESPIRATORY TRACT CONDITIONS**
   1. Laryngotracheobronchomalacia*
   2. Laryngotracheobronchitis (e.g., pertussis) *
   3. Laryngeal web, cyst or stenosis
   4. Vocal cord dysfunction*
   5. Vocal cord paralysis
   6. TEF
   7. Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
   8. Foreign body aspiration*
   9. Chronic bronchitis from environmental tobacco smoke exposure*
   10. Toxic inhalations

C. **LOWER RESPIRATORY TRACT CONDITIONS**
   1. Bronchopulmonary dysplasia or chronic lung disease of preterm infants
   2. Viral bronchiolitis*
   3. GER*
   4. Bronchiolitis obliterans
   5. Interstitial lung diseases
   6. Causes of bronchiectasis:
      - ◇ Cystic fibrosis
      - ◇ Immune deficiency
      - ◇ Allergic bronchopulmonary mycoses (e.g., aspergillosis)
      - ◇ Chronic aspiration
      - ◇ Immotile cilia syndrome, (primary ciliary dyskinesia)
   7. Hypersensitivity pneumonitis
   8. Pulmonary eosinophilia, Churg-Strauss vasculitis
   9. Pulmonary hemosiderosis
   10. TB
   11. Pneumonia
   12. Pulmonary edema (e.g., congestive heart failure)
   13. Medications associated with chronic cough: Acetyl cholinesterase inhibitors ,β-Adrenergic antagonists

## PROGNOSIS

| SEVERITY | % OF ASTHMATICS | FINDINGS BETWEEN ATTACKS | % AFFECTED AS ADULTS |
|---|---|---|---|
| **Mild** | 75% | Normal | **15%** moderate |
| **Moderate** | 20% | 40 % Has low PFR+/-chest deformity | **60%**<br>◇ 35% Mod<br>◇ 25% sever |
| **Sever** | <5% | > 50%has low PFR +/-chest deformity | **95%**<br>◇ 40% mod<br>◇ 50% sever |

# DDx of wheezing

| Diseases associated with wheezing | Clinical features |
|---|---|
| 1. **Asthma syndrome** | -Episodic recurrent illness<br>-Environmental trigger<br>-Responds to specific treatment |
| 2. **Bronchiolitis** | -First episode during epidemic<br>-Under 2 yr old<br>-Viral URTI: Low grade fever, rhinorrhea. |
| 3. **Gastro-esophageal reflux, recurrent aspiration** | -Associated with feeding<br>-Tachypnea, fatigue, apnea, FTT<br>Regurgitation,+/- vomiting<br>-Swallowing dysfunction |
| 4. **Foreign body aspiration** | Sudden onset of cough/choking in previously healthy infant<br>-Unilateral findings |
| 5. **Cystic fibrosis, immunodeficiency**, | Steatorrhea, diarrhea<br>-Failure to thrive<br>-Chronic/recurrent infections |
| 6. **Bronchopulmonary dysplasia** | History of: prematurity, mechanical ventilation, & prolonged O2 therapy |
| 7. **Upper airway anomalies:** Tracheomalacia, great arteries anomalies | Positional changes<br>-Stridor |
| 8. **Cardiac: heart failure** | -Murmur, Gallop,Hepatomegaly<br>-FTT |
| 9. **Pertussis/tuberculosis** | Active disease in family member or community. Compressing L.N in TB |
| 10. **Vasculitis, Hypersensitivity diseases:**<br>1. Aspirgillosis:<br>2. Churg-Strauss syndrome:<br>3. Periarteritis nodosa: | -Marked eosinophilia, serum IgE<br>-Eosinophilia, angitis, granulomas<br>-Eosinophilia, Multisystemic: renal, lung, nerves |

## Risk Factors associated with SEVER ASTHMATIC ATTACK (Potentially fatal episode) → increased mortality

**History:**
- ◇ Chronic steroid dependency
- ◇ Prior IC admission
- ◇ Recurrent ER visits in last 48 hr
- ◇ Frequent ER visits > 3/yr
- ◇ Frequent hospitalization >2/yr
- ◇ Poor compliance
- ◇ Underestimation, under-treatment
- ◇ Sudden onset of distress

**Physical examination:**
- ◇ Pulsus paradoxus >20mmHg
- ◇ Hypotension, tachypnea, H.R
- ◇ Cyanosis, 1-2 word dyspnea
- ◇ Lethargy, Agitation,
- ◇ Retraction of chest
- ◇ Silent chest with sever distress =(poor gas exchange)

**Laboratory tests:**
- ◇ Hypercabnia
- ◇ Hypoxia on Oxygen
- ◇ FEV1 or PEF < 30% expected, no improvement 1 hr after aerosol therapy
- ◇ X-Ray: Air leak

**Therapy:**
- ◇ Overuse of aerosol
- ◇ Delayed use of systemic steroids
- ◇ Sedation
- ◇ Delayed admission

## TREATMENT

### MANAGEMET OF ASTHMA

1. **pharmacologic & non-pharmacologic**
2. **Evaluation of the acute episode** :Mild, Moderate, Severe
3. **Relievers** (quick-relief medications): They work fast to treat attack or relieve symptoms
4. **Controllers:** Prophylactic Medications (long-term preventive medications): They prevent symptoms & attack from starting.
5. Asthma is a chronic inflammatory disorder of the airways, So ***anti-inflammatory agents*** particularly *inhaled corticosteroids* are the *most effective* long term preventive medications.
6. **Classify severity of asthma disease** (Mild, Moderate, Sever) before using controllers
7. **Stepwise approach:**
   A. Classify severity
   B. Gain control
   C. Go step up if control is not achieved or sustained
   D. Go step down if control is sustained for at least 3 months
   E. Follow gradual stepwise reduction to the least necessary drug or dose

### LINES OF TREATMENT IN ASTHMA

#### A) PHARMACOLOGIC TREATMENT

1. **Bronchodilators**: Beta 2-agonists(short acting ,long acting),Aminophylline, Anti-cholinergic drugs.
2. **Anti-inflammatory agents**: Steroids: Topical (inhaled) or systemic, Cromone( Cromolyn Sodium, Nedocromil: in > 12 Yr old)
3. Alternative drugs: (steroid sparing agents):
   1. Anti-leukotriens: montelukast, zafirlukast , pranlukast, 5-lipooxygenase inhibitors (zileuton)
   2. Ketotifen
   3. Methotrexate
   4. Cyclosporin A
   5. Gold
   6. Dapson
4. **MgSO4 iv**

### LEUKOTRIENE MODIFIERS

1. Montelukast – Singulair: Child:Not approved, 600 mg qid.
2. Zafirlukast – Accolate: Child:10 mg bid, Adult:20 mg bid
3. Zileuton – Zyflo: Child:5 mg once/day, Adult:10 mg once/day

- **mode of action**
  1. leukotriene receptor antagonists: Montelukast and zafirlukast.
  2. Inhibition of leukotrienes synthesis: Zileuton
- **Leukotrienes*:***
  1. Increase migration of eosinophils,
  2. Increase production of mucus and edema of the airway wall, and
  3. Cause bronchoconstriction

### INHALED BETA2-ADRENERGIC AGONIST, LONG-ACTING

- Salmeterol
  1. (Serevent): metered-dose inhaler , (21µg/pufff) =1-2 puffs q12h
  2. (Serevent Diskus): dry-powder inhaler, (50 µg/inhalation) =1 inhalation q12h
- Twice-daily inhalation of salmeterol has been effective for maintenance treatment in combination with inhaled corticosteroids and may be especially useful in patients with nocturnal symptoms*.*

### INHALED GLUCOCORTICOIDS DAILY DOSAGE GUIDELINES

- The NAEPP guidelines recommend starting with higher inhaled glucocorticoid doses and "stepping down" the dose as asthma control improves*.*

## B) Non-Pharmacologic treatment

- Environmental control: Identify & avoid triggers
- Immunotherapy
- Education: patient, family, teacher, --

## Practical points in management of *acute* asthma

1. Don't forget **Oxygen:**
   - It relieves tachypnea even if saturation is normal
   - Give it with nebulized beta-agonist to avoid treatment induced hypoxemia: (* Beta-agonist & aminophylline → pulmonary vasodilatation & ↑COP→ventilation / perfusion mismatching → hypoxemia)
2. **Epinephrine** is ***now rarely*** used
3. **Beta 2-agonist aerosols** are now the treatment of choice for acute bronchospasm and prevention of EIA
4. The addition of **aminophylline to beta 2-agonist** has little (if any) benefit , but it may be helpful in:
   - Very sever obstruction e.g. status asthmaticus
   - Patients receiving less than optimal B-2-agonists
     -Adding it → increase side effects
     -Take its serum level, *1mg/kg → inc. serum level by 1mg/L*
     -Consider factors that affect its metabolism.
5. **Steroids (systemic):** they are added:
   - In Steroid dependent asthmatics
   - If Steroids are given recently (last 6 months)
   - In Unresponsiveness to initial treatment in acute episodes
   - In Sever episodes
   - If patient is admitted to the hospital
   - When you decided to send patient home in border line cases (short courses, used in many cases)
   - *Most patients in acute episodes require therapy with systemic corticosteroids to resolve symptoms and prevent relapse*
   - Benefits of steroids:
     1. Reverse tachyphylaxis to B-2-agonists
     2. Hasten resolution, (anti-inflammatory)
     3. Reduce relapses & re-hospitalization

## Management of Acute Asthma Attack

## Hospital care

### Initial assessment: **(Mild, Moderate or Sever episode)**

1. History
2. P.E: Auscultation, Resp. rate, Heart rate, Accessory muscle use, PEF, FEV1, O2 sat, ABG, other tests as indicated

### Initial treatment:

- Inhaled short-acting beta2 agonist: one dose / 20min →1hr.(0.15mg/kg = 0.03ml/kg)
- Oxygen→ saturation ≥95%
- Systemic steroids if:
  - no immediate response
  - patient recently took systemic steroids
  - episode is sever

### Repeat assessment:

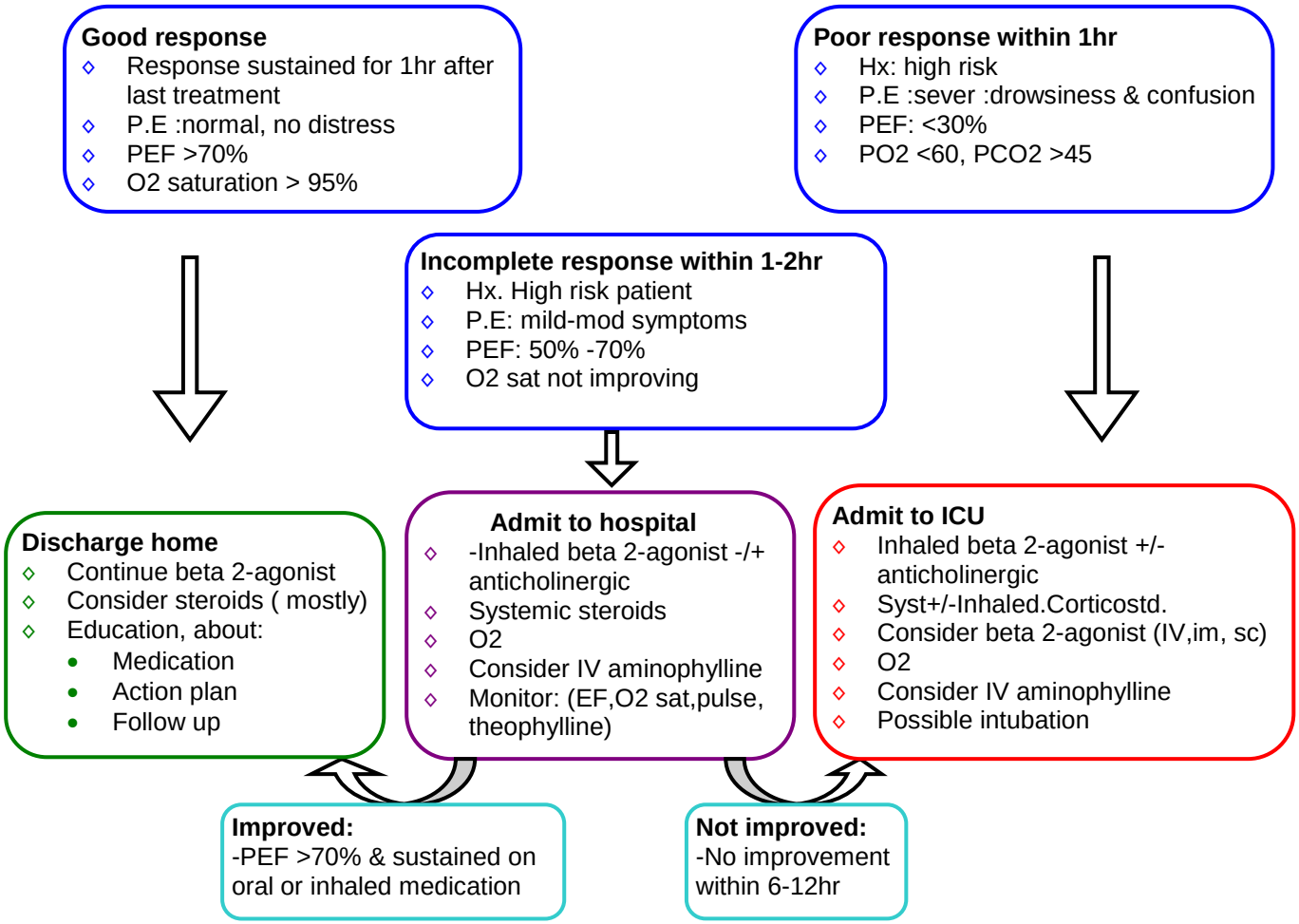
### P.E, PEF, others

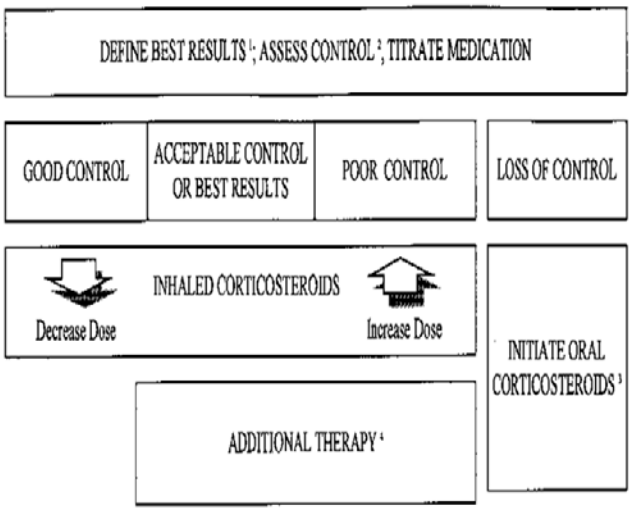
**Moderate Episode**:

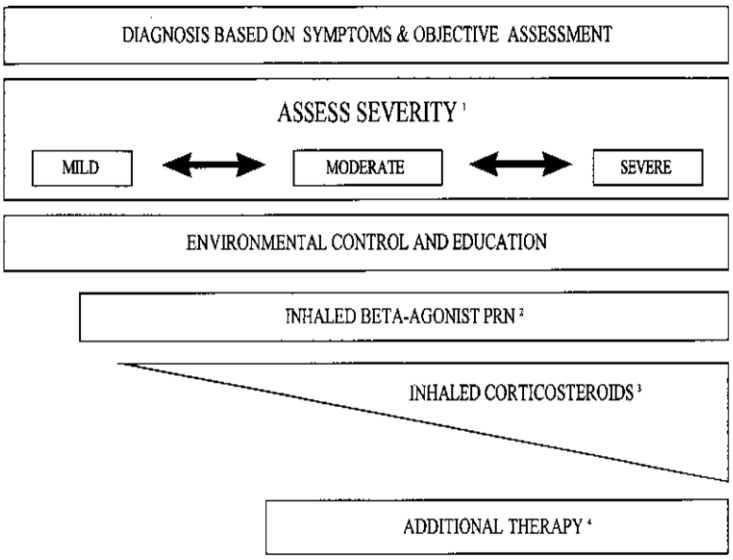
- PEF 60-80% predicted/personal best
- P.E: moderate symptoms, accessory muscle use.
- Treatment:
  1. Inhaled beta2-agonist/1hr
  2. Consider steroids
  3. Continue for 1-3hr, provided there is improvement

**Sever Episode:**

- PEF < 60%, predicted/personal best
- P.E: sever symptoms at rest, retraction
- Hx.: High-risk patient
- No improvement after initial therapy
- Treatment:
  1. Inhaled beta2-agonist hourly or continuous +/- inhaled anticholinergic
  2. Oxygen
  3. Systemic steroids
  4. Consider parenteral beta2-agonist (iv, im, sc)
- Hospitalization should be considered if the PEF remains < *70%* of predicted
- Patients **candidates for *intubation*** who exhibit:
  - PEFR less than **50%** of predicted
  - increasing pCO2 level
  - declining mental status






## Pharmacotherapy for Asthma Based on Disease Classification

| Classification | Long-term controllers | Quick-relievers |
|---|---|---|
| **Mild intermittent:**<br>-Daytime symp=<2/d<br>-Nocturnal symp=2/mo<br>-PEF =>80%, varibility <20% | NO anti-inflammatory medications | Short-acting beta2 agonist as needed |
| **Mild persistent:**<br>-Daytime >2/d<br>-Nocturnal > 2/mo<br>-PEF =>80%, variab 20-30% | -Low-dose inhaled corticosteroid or<br>-cromolyn sodium (Intal) or<br>-nedocromil (Tilade) or<br>-leukotriene modifiers (=>2yr old) | Short-acting beta2 agonist as needed |
| **Moderate persistent:**<br>-Daytime daily<br>-Night >1/week<br>-PEF>60 - <80%,variab >30% | -Low - Medium-dose ICS<br>plus a long-acting bronchodilator<br>(long-acting beta2 agonist) if needed<br>-medium dose ICS +/- antileukotr | Short-acting beta2 agonist as needed |
| **Severe persistent:**<br>-Continuous symp<br>-Frequent night symp<br>-PEF =<60%,variability >30% | High-dose inhaled corticosteroid plus a long-acting bronchodilator and systemic corticosteroid if needed | Short-acting beta2 agonist as needed |

NOTE:
**This chapter plus Dr.Imad sheet about 'Tuberculosis in children'**

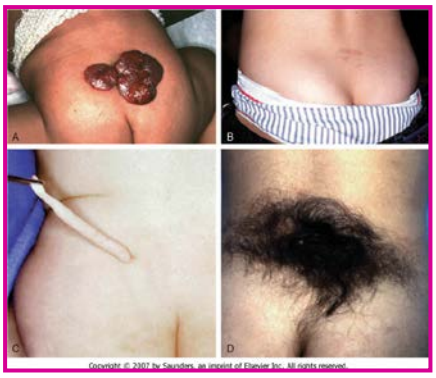
# Neurology

# CONGENITAL ANOMALIES OF THE CENTRAL NERVOUS SYSTEM

## NEURAL TUBE DEFECTS (DYSRAPHISM)

- Failure of the neural tube to close spontaneously between the 3rd and 4th wk of in utero development.
- neural tube factors, including hyperthermia, drugs, malnutrition, chemicals, maternal obesity or diabetes, and genetic determinants (mutations in folate-responsive or folate-dependent pathways)
- The major neural tube defects include:
  1. spina bifida occulta
  2. meningocele
  3. myelomeningocele
  4. encephalocele
  5. anencephaly
  6. dermal sinus
  7. tethered cord
  8. syringomyelia
  9. diastematomyelia
  10. lipoma involving the conus medullaris and/or filum terminale.
- In the 3rd wk of embryonic development, the neural tube is formed**.**
- Normally, the rostral end of the neural tube closes on the 23rd day and the caudal neuropore closes by the 27th day of development.
- Failure of closure of the neural tube allows excretion of fetal substances (α-fetoprotein [AFP], acetylcholinesterase) into the amniotic fluid, serving as biochemical markers for a neural tube defect.
- Prenatal screening of maternal serum for AFP in the 16th-18th wk of gestation is an effective method for identifying pregnancies at risk for fetuses with neural tube defects in utero.

### SPINA BIFIDA OCCULTA



- Anomaly consists of a midline defect of the vertebral bodies without protrusion of the spinal cord or meninges.
- Most individuals are asymptomatic and lack neurologic signs, and the condition is usually of no consequence.
- patches of hair, a lipoma, discoloration of the skin, or a dermal sinus in the midline of the lower back suggests a more significant malformation of the spinal cord
- A spine roentgenogram in simple spina bifida occulta shows a defect in closure of the posterior vertebral arches and laminae, typically involving L5 and S1
- Spina bifida occulta is associated with developmental abnormalities: syringomyelia, diastematomyelia, and a tethered cord.( **occult spinal dysraphism**) = usually with cutaneous manifestations.
- **dermoid sinus** a small skin opening, which leads into a narrow duct, sometimes indicated by protruding hairs, a hairy patch, or a vascular nevus.
  - ✓ Dermoid sinuses occur in the midline at the lumbosacral region or occiput.
  - ✓ Dermoid sinus tracts may pass through the dura,act as conduit for spread of infection.

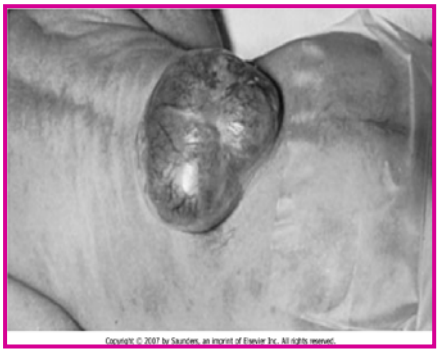
### MENINGOCELE

- When the meninges herniate through a defect in the posterior vertebral arches.
- The spinal cord is usually normal and assumes a normal position in the spinal canal
- There may be tethering, syringomyelia, or diastematomyelia.
- A fluctuant midline mass that may transilluminate occurs along the vertebral column, usually in the lower back.
- Most meningoceles are well covered with skin and pose no threat to the patient.
- roentgenograms, ultrasonography, and MRI

- Urologic evaluation, by cystometrogram (CMG), will identify those children with neurogenic bladder who are at risk for renal deterioration.
- Those patients with leaking cerebrospinal fluid (CSF) or a thin skin covering should undergo immediate surgical treatment to prevent meningitis.
- A CT scan of the head is recommended for children with a meningocele because of the association with hydrocephalus in some cases.
- An **anterior meningocele** projects into the pelvis through a defect in the sacrum.
  - ✓ Symptoms of constipation and bladder dysfunction develop due to the increasing size of the lesion.
  - ✓ Female patients may have associated anomalies of the genital tract, including a rectovaginal fistula and vaginal septa.
  - ✓ Plain roentgenograms demonstrate a defect in the sacrum
  - ✓ CT scanning or MRI outlines the extent of the meningocele.

## MYELOMENINGOCELE

- the most severe form of dysraphism involving the vertebral column and occurs
- Incidence ≈1/4,000 live births.
- The cause of myelomeningocele is unknown
- Genetic predisposition exists; the risk of recurrence after one affected child increases to 3-4% and increases to ≈10% with two previous abnormal pregnancies.
- Folate is intricately involved in the prevention and etiology of NTDs.
- Maternal periconceptional use of folic acid supplementation reduces
- 50%. (before conception - least the 12th wk of gestation) - 0.4mg of folic acid daily, if high-risk =4mg of folic acid daily 1mo before the time of the planned conception
- May be located anywhere along the neuraxis, but the lumbosacral region accounts for at least 75% of the cases.
- The extent and degree of the neurologic deficit depend on the location of the myelomeningocele, as well as the associated lesions.
  - ✓ A lesion in the low sacral region causes bowel and bladder incontinence associated with anesthesia in the perineal area but with no impairment of motor function.
  - ✓ the midlumbar region typically have a saclike cystic structure covered by a thin layer of partially epithelialized tissue
    - ♦ Remnants of neural tissue are visible beneath the membrane, which may occasionally rupture and leak CSF.
    - ♦ Produce lower motor neuron signs due to abnormalities and disruption of the conus medullaris.
    - ♦ flaccid paralysis of the lower extremities, an absence of deep tendon reflexes, a lack of response to touch and pain, and a high incidence of lower extremity deformities (clubfeet, subluxation of the hips).
    - ♦ Constant urinary dribbling and a relaxed anal sphincter may be evident.

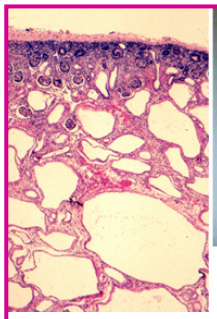


  - ✓ increasing neurologic deficit as the myelomeningocele extends higher into the thoracic region
  - ✓ In the upper thoracic or the cervical region usually have a very minimal neurologic deficit and, in most cases, do not have hydrocephalus.
- HYDROCEPHALUS IN ASSOCIATION WITH A TYPE II CHIARI DEFECT develops in at least 80% of patients with myelomeningocele.
  - ✓ the lower the deformity in the neuraxis (sacrum), the less likely is the risk of hydrocephalus.
  - ✓ Ventricular enlargement may be indolent and slow growing or may be rapid:
    - ♦ Bulging anterior fontanel, dilated scalp veins, setting-sun appearance of the eyes, irritability, and vomiting, increased head circumference.
    - ♦ About 15% of infants with hydrocephalus and Chiari II malformation develop symptoms of hindbrain dysfunction (difficulty feeding, choking, stridor, apnea, vocal cord paralysis, pooling of secretions, and spasticity of the upper extremities) if untreated→ death.
    - ♦ This **Chiari crisis** is due to downward herniation of the medulla and cerebellar tonsils through the foramen magnum.

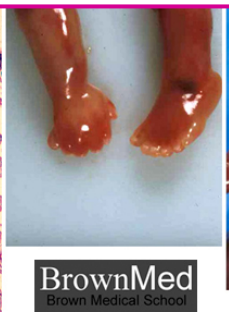
- **Surgery** is often done within a day or so of birth but can be delayed for several days (except when there is a CSF leak)
- After repair of a myelomeningocele, most infants require a **shunting procedure** for hydrocephalus.
- reassessment of the **genitourinary system** (regularly catheterize a neurogenic bladder → low residual volume and bladder pressure →t prevents UTI and reflux leading to pyelonephritis, hydronephrosis, and bladder damage)
- **incontinence of fecal matter** is common → fecal impaction and/or megacolon
- the mortality rate is ≈10-15%, and most deaths occur before age 4yr
- At least 70% of survivors have normal intelligence
- Renal dysfunction is one of the most important determinants of mortality.

## ENCEPHALOCELE

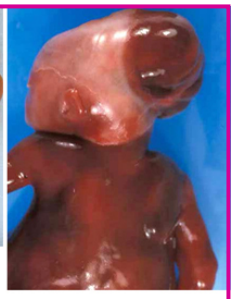
- Two major forms of dysraphism affect the skull, resulting in protrusion of tissue through a bony midline defect( **cranium bifidum)**
  1. CRANIAL MENINGOCELE consists of a CSF-filled meningeal sac only
  2. CRANIAL ENCEPHALOCELE contains the sac plus cerebral cortex, cerebellum, or portions of the brainstem.
- The cranial defect occurs most commonly in the occipital region at or below the inion, but in certain parts of the world, frontal or nasofrontal encephaloceles are more prominent
- Are at increased risk for developing hydrocephalus due to aqueduct stenosis, Chiari malformation, or the Dandy-Walker syndrome.
- Examination: small sac with a pedunculated stalk or a large cystlike structure that may exceed the size of the cranium.
- Investigations:
  1. A plain roentgenogram of the skull and cervical spine → anatomy of the vertebrae.
  2. Ultrasonography → the contents of the sac.
  3. MRI or CT further → the spectrum of the lesion.
- MECKEL-GRUBER SYNDROME is a rare autosomal recessive condition
  1. occipital encephalocele
  2. cleft lip or palate
  3. microcephaly
  4. microphthalmia
  5. abnormal genitalia
  6. polycystic kidneys
  7. polydactyly
- Perinatal diagnosis:
  1. maternal serum α-fetoprotein levels
  2. ultrasound measurement of the biparietal diameter , identification of the encephalocele itself.
- PROGNOSIS:
  1. cranial meningocele → good prognosis
  2. encephalocele : at risk of visual problems, microcephaly, mental retardation, seizures.
  3. cranial encephalocele and hydrocephalus have the poorest prognosis.



Polycystic kidney disease




polyductyly



encephalocele

## ANENCEPHALY

- a large defect of the calvarium, meninges, and scalp associated with a rudimentary brain, which results from failure of closure of the rostral neuropore, the opening of the anterior neural tube.
- recurrence risk is ≈4% and increases to 10% if a couple has had two previously affected pregnancies.
- 50% of cases of anencephaly have associated polyhydramnios.
- Most infants die within several days of birth

### NOTE:

- ✓ **Lissencephaly:** no brain sulcation, seizure +developmental retardation, chromosomal
- ✓ **Schizenecephaly**: symmetrical bilateral cleft extend from cerebral cortex to ventricles, severe mental and motor retardation.
- ✓ **Holoprosenecephalus**: failure of cerebral vesicle to divide, associated with midline fascial defects: hypotolerism, cleft lip, cleft palate. isolated or chromosomal.

# MICROCEPHALY

- Head circumference that measures more than three standard deviations below the mean for age and sex.
- main groups:
  1. primary (genetic) microcephaly : associated with a specific genetic syndrome, familial and autosomal dominant microcephaly,
  2. secondary (nongenetic) microcephaly: large number of noxious agents that affect a fetus in utero or an infant during periods of rapid brain growth( 1st 2yr of life)
- Family history for additional cases of microcephaly or disorders affecting the nervous system.
- The head circumference of each parent and sibling should be recorded.
- INV:
  1. mother's serum phenylalanine level should be determined. High phenylalanine serum levels in an asymptomatic mother can produce marked brain damage in an otherwise normal nonphenylketonuric infant.
  2. karyotype if a chromosomal syndrome is suspected or if the child has abnormal facies, short stature, and additional congenital anomalies.
  3. MRI is useful in identifying structural abnormalities of the brain
  4. CT scanning is useful to detect intracerebral calcification.
  5. fasting plasma and urine amino acid analysis
  6. serum ammonia determination
  7. *t*oxoplasmosis, *r*ubella, *c*ytomegalovirus, and *h*erpes simplex (TORCH) titers as well as HIV testing of the mother and child; and a urine sample for the culture of cytomegalovirus.

| CAUSES | CHARACTERISTIC FINDINGS |
|---|---|
| PRIMARY (GENETIC) | |
| 1. Familial (autosomal recessive)- microcephaly vera | • severely mentally retarded and prominent seizures. Typical appearance with slanted forehead, prominent nose and ears |
| 2. Autosomal dominant | • Nondistinctive facies, upslanting palpebral fissures, mild forehead slanting, and prominent ears<br>• Normal linear growth, seizures readily controlled, and mild or borderline mental retardation |
| 3. Syndromes | |
| Down (21-trisomy) | • Abnormal rounding of occipital and frontal lobes and a small cerebellum |
| Edward (18-trisomy) | • Low birthweight, microstomia, micrognathia, low-set malformed ears, prominent occiput, rocker-bottom feet, flexion deformities of fingers, congenital heart disease |
| Cri-du-chat (5 p-) | • Round facies, prominent epicanthic folds, low-set ears, hypertelorism, and characteristic cry<br>• No specific neuropathology |
| Cornelia de Lange | |
| Rubinstein-Taybi | |

| | |
|---|---|
| Smith-Lemli-Opitz | • Low birthweight, marked feeding problems |
| **SECONDARY (NONGENETIC)** | |
| 1. **Radiation** | • Microcephaly and mental retardation most severe if exposure before 15th wk of gestation |
| 2. **Congenital infections** | |
| Cytomegalovirus | • Small for dates, petechial rash, hepatosplenomegaly, chorioretinitis, deafness, mental retardation, and seizures<br>• Central nervous system calcification and microgyria |
| Rubella | • Growth retardation, purpura, thrombocytopenia, hepatosplenomegaly, congenital heart disease, chorioretinitis, cataracts, and deafness |
| Toxoplasmosis | • Purpura, hepatosplenomegaly, jaundice, convulsions, hydrocephalus, chorioretinitis, and cerebral calciffication |
| 3**. Drugs** | |
| Fetal alcohol | • Growth retardation, ptosis, absent philtrum and hypoplastic upper lip, congenital heart disease, feeding problems |
| Fetal hydantoin | • Growth delay, hypoplasia of distal phalanges, inner epicanthic folds, broad nasal ridge, and anteverted nostrils |
| 4. Meningitis/encephalitis | • Cerebral infarcts, cystic cavitation, diffuse loss of neurons |
| 5. Malnutrition | • Controversial cause of microcephaly |
| 6. Metabolic | • Maternal DM and maternal hyperphenylalaninemia |
| 7. Hyperthermia | • Significant fever during 1st 4-6 wk has been reported to cause microcephaly, seizures, and facial anomalies<br>• Further studies showed no abnormalities with maternal fever |
| 8. Hypoxic-ischemic encephalopathy | • Initially diffuse cerebral edema; late stages characterized by cerebral atrophy |

## PRIMARY CRANIOSYNOSTOSIS

- Craniosynostosis is defined as premature closure of the cranial sutures and is
- Classified:
  1. **Primary craniosynostosis** : closure of one or more sutures due to abnormalities of skull development
  2. **secondary craniosynostosis** results from failure of brain growth and expansion
- Incidence of primary craniosynostosis approximates 1/2,000 births

**NOTE:**

SECONDARY CAUSES:

- ✓ Metabolic disorders (hyperthyroidism ,Mucopolysaccharidosis
- ✓ Malformations (holoprosencephaly, microcephaly, shunted hydrocephalus, encephalocele)
- ✓ valproic acid, phenytoin

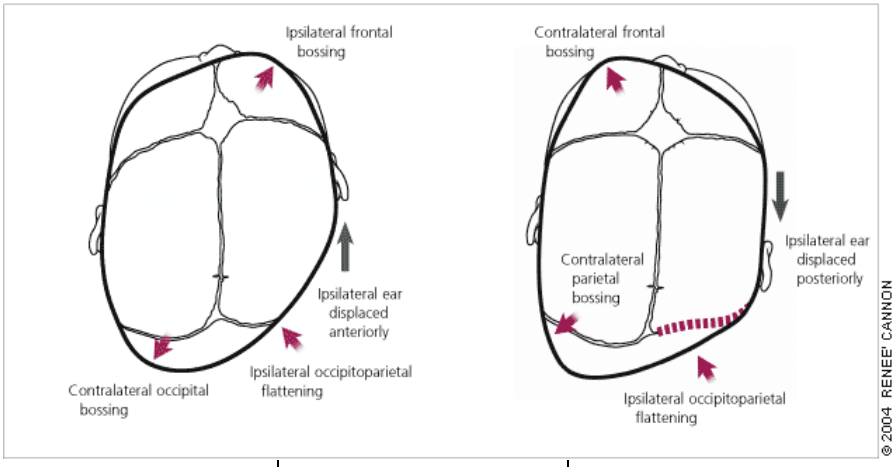
- The cause is unknown in the majority of children, genetic syndromes account for 10-20% of cases.
- Most cases are evident at birth and are characterized by a skull deformity
- FORMS:

1. SCAPHOCEPHALY:
   - ✓ The most common form of craniosynostosis.
   - ✓ Premature closure of the sagittal suture produces a long and narrow skull
   - ✓ Associated with a prominent occiput, a broad forehead, and a small or absent anterior fontanel.
   - ✓ The condition is sporadic, more common in males 80%
   - ✓ Causes difficulties during labor because of cephalopelvic disproportion.
   - ✓ Does not produce increased ICP or hydrocephalus, normal neurologic examination
2. **Frontal plagiocephaly**:
   - ✓ the next most common form of craniosynostosis
   - ✓ Result of premature fusion of a coronal and sphenofrontal suture.
   - ✓ Characterized by unilateral flattening of the forehead, elevation of the ipsilateral orbit and eyebrow, and a prominent ear on the corresponding side.
   - ✓ The condition is more common in females
   - ✓ Surgical intervention produces a cosmetically pleasing result.
3. **Occipital plagiocephaly**:
   - ✓ most often a result of positioning during infancy – need positional maneuvers only
   - ✓ more common in an immobile or handicapped child
   - ✓ Fusion or sclerosis of the lambdoid suture cause unilateral occipital flattening and bulging of the ipsilateral frontal bone.
4. **Trigonocephaly:**
   - ✓ Rare form of craniosynostosis due to premature fusion of the metopic suture.
   - ✓ a keel-shaped forehead and hypotelorism
   - ✓ At risk for associated developmental abnormalities of the forebrain.
5. **Turricephaly** :
   - ✓ Cone-shaped head due to premature fusion of the coronal and often sphenofrontal and frontoethmoidal sutures.
6. **kleeblattschädel deformity:**
   - ✓ skull resembles a cloverleaf.
   - ✓ Affected children have very prominent temporal bones, and the remainder of the cranium is constricted.
   - ✓ Hydrocephalus is a common complication

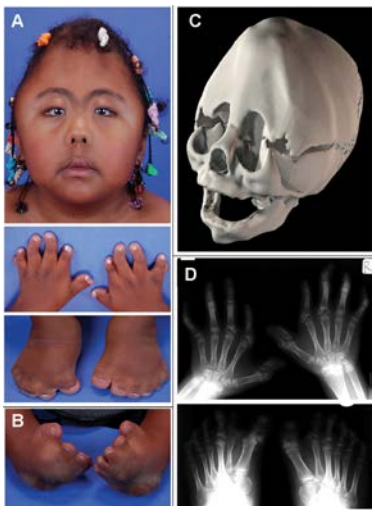
- THE MOST PREVALENT GENETIC DISORDERS ASSOCIATED WITH CRANIOSYNOSTOSIS:
  1. **Crouzon syndrome**: inherited as an autosomal dominant trait. The shape of the head most often is brachycephaly. The orbits are underdeveloped, and ocular proptosis is prominent. Hypoplasia of the maxilla and orbital hypertelorism are typical facial features.
  2. **Apert syndrome:** sporadic condition,may AD. associated with premature fusion of multiple sutures,The facies tend to be asymmetric, eyes are less proptotic than in Crouzon syndrome. *Apert syndrome is characterized* by syndactyly of the 2nd, 3rd, and 4th fingers, which may be joined to the thumb and the 5th finger also occur in the feet. All patients have progressive calcification and fusion of the bones of the hands, feet, and cervical spine.
  3. **Carpenter syndrome** :autosomal recessive, klee-blattschädel skull deformity. Soft tissue syndactyly of the hands and feet is always present, and mental retardation is common.
  4. **Chotzen syndrome** is characterized by asymmetric craniosynostosis and plagiocephaly. *The condition is the most prevalent of the genetic syndromes* and is inherited as an autosomal dominant trait. facial asymmetry, ptosis of the eyelids, shortened fingers, syndactyly of the 2nd and 3rd fingers.
  5. **Pfeiffer syndrome** is most often associated with turricephaly. The eyes are prominent and widely spaced, and the thumbs and great toes are short and broad. Partial soft tissue syndactyly may be evident. Most cases appear to be sporadic.

- TREATMENT:
  - ✓ Premature fusion of only one suture rarely causes a neurologic deficit → the sole indication for surgery is child's cosmetic appearance
  - ✓ when two or more sutures are prematurely fused, Neurologic complications, including hydrocephalus and increased ICP may occur→operative intervention is essential.
  - ✓ The best time to intervene is when the infant is between 3-9 months of age (less than 1 year).
  - ✓ Infants with increased intracranial pressure require urgent decompression.

NOTE:

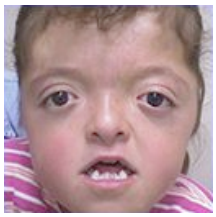



| DIFFERENCES | DEFORMATIONAL PLAGIOCEPHALY | LAMBDOID SYNOSTOSIS |
|---|---|---|
| POSTERIOR BOSSING | absent | contralateral and parietal |
| FRONTAL BOSSING | Ipsilateral, prominent | absent or contralateral |
| IPSILATERAL EAR | anterior displacement | displaced posteriorly toward the fused suture |

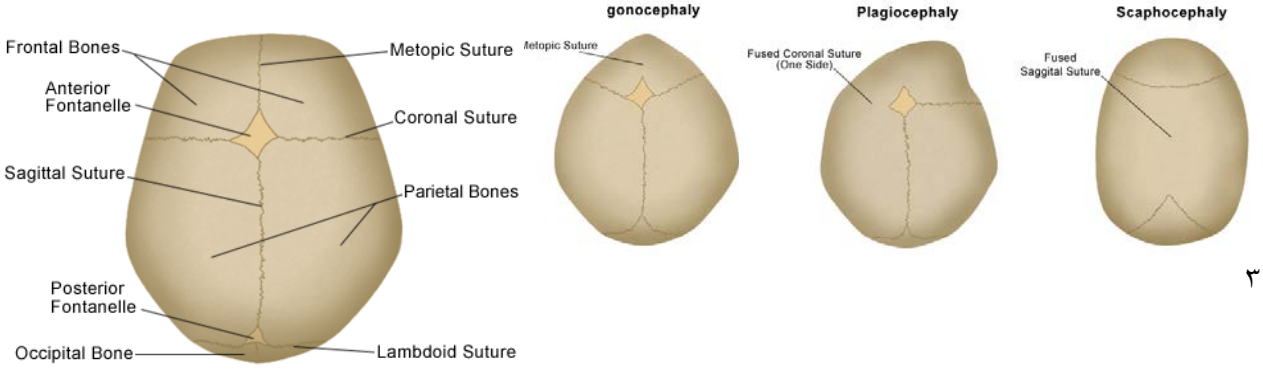



**Carpenter syndrome**

**Crouzon syndrome**



**Apert syndrome**

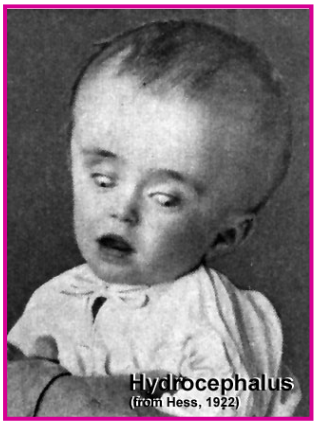


# HYDROCEPHALUS:

- **CFS:**

✓ Formed primarily in the ventricular system by the choroid plexus, which is situated in the lateral, 3rd, and 4th ventricles.
✓ most CSF is produced in the lateral ventricles, ≈25% originates from extrachoroidal sources( BRAIN CAPILLARIES)
✓ Adrenergic system ↓ CSF production, cholinergic nerves↑ the normal CSF production.
✓ The total volume of CSF: 50mL in an infant and 150mL in an adult.
✓ CSF flows from the lateral ventricles → foramina of Monro →the 3rd ventricle→ aqueduct of Sylvius→ 4th ventricle→ paired lateral foramina of Luschka and the midline foramen of Magendie → cisterns at the base of the brain→ over the convexities of the cerebral hemispheres→ absorbed by arachnoid villi.

- HYDROCEPHALUS:
  1. **obstructive** or **non-communicating hydrocephalus:** obstruction within the ventricular system
     ✓ *Most commonly in children because of an abnormality of the aqueduct stenosis(* sex-linked recessive or infectious- intrauterine infections &mumps ) *or a lesion in the 4th ventricle.*
     ✓ OTHERS: posterior fossa brain tumors,Dandy-Walker malformation, Chiari malformation,
  2. **nonobstructive** or **communicating hydrocephalus:** obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi.
     ✓ most commonly follows a subarachnoid hemorrhage
     ✓ OTHERS: leukemic infiltrates, Pneumococcal and tuberculous meningitis




- CLINICAL FEATURES:
  ✓ In an infant:
  1. accelerated rate of enlargement of the head is the most prominent sign
  2. the anterior fontanel is wide open and bulging
  3. the scalp veins are dilated
  4. The forehead is broad
  5. the setting-sun eye sign.
  6. Long-tract signs: brisk tendon reflexes, spasticity, clonus (particularly in the lower extremities), and Babinski sign.

  ✓ In an older child:
  1. Irritability, lethargy, poor appetite, and vomiting are common to both age groups
  2. Headache is a prominent symptom in older patients.
  3. A gradual change in personality and a deterioration in academic productivity.
  4. Increase velocity of head circumference growth.
  5. Macewen sign: skull Percussion produce cracked pot sound → sutures separation
  6. occiput: flat → Chiari malformation, prominent → Dandy-Walker malformation.
  7. Papilledema, abducens nerve palsy, and UMN are apparent in most cases.
- Multiple café-au-lait spots and other clinical features of neurofibromatosis point to aqueductal stenosis as the cause of hydrocephalus.
- TYPE II CHIARI MALFORMATION is characterized by progressive hydrocephalus with a myelomeningocele.
- DANDY-WALKER MALFORMATION consists of triad: complete or partial agenesisi of vermis, cystic dilatation of the 4$^{th}$ ventricle, enlarged posterior fossa. 90% of patients have hydrocephalus. managed by shunting the cystic cavity.
- **D/D:**
  1. **Hydranencephaly** : The cerebral hemispheres are absent or represented by membranous sacs with remnants of cortex dispersed over the membrane.
  2. **Familial megalencephaly**: autosomal dominant trait , characterized by delayed motor milestones and hypotonia , normal or near-normal intelligence. # parents' head circumference for diagnosis.
  3. **megalencephaly**. Ex: lysosomal diseases (Tay-Sachs, mucopolysaccharidoses), the aminoacidurias (maple syrup urine disease), leukodystrophies, genatics causes( cerebral gigantism (sotos syndrome) and neurofibromatosis/ + Mental R.)

4. **thickened cranium** : chronic anemia, rickets, osteogenesis imperfecta, and epiphyseal dysplasia.

- **Treatment**:
  - ✓ Therapy for hydrocephalus depends on the cause.
  - ✓ Medical management, acetazolamide and furosemide, provide temporary relief by ↓rate of CSF production.
  - ✓ Most cases of hydrocephalus require extracranial shunts,ex: ventriculoperitoneal shunt. The major complications of shunting are :
    1. occlusion (characterized by headache, papilledema, emesis, mental status changes)
    2. bacterial infection (fever, headache, meningismus), *Staphylococcus epidermidis*

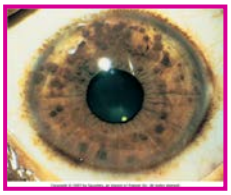
# NEUROCUTANEOUS DISORDERS

DERMATOLOGICAL AND NEUROLOGICAL MANIFESTATIONS.

- the most common neurocutaneous disorders are:
  1. NEUROFIBROMATOSIS
  2. TUBEROUS SCLEROSIS
  3. STURGE-WEBER DISEASE
  4. VON HIPPEL-LINDAU DISEASE
  5. ATAXIA-TELANGIECTASIA
- Arise from a defect in differentiation of the primitive ectoderm except:. *von Hippel-Lindau disease* and *Sturge-Weber disease* (mesenchymal origin)
- von *Hippel-Lindau disease* has no characteristic cutaneous lesions.
- PHAKOMATOSIS : "mother spots" or "birthmarks" and refers to tuberous sclerosis and NF

## NEUROFIBROMATOSIS

### VON RECKLING-HAUSEN DISEASE



- **NF-1 (**1 in 3000**)** diagnosed when 2/7 signs are present:
  1. Six or more **café-au-lait macules** over 5mm in greatest diameter in prepubertal and over 15mm in greatest diameter in postpubertal. present 100% of patients. On trunk and extremities, sparing of the face.
  2. **Axillary or inguinal freckling** : multiple hyperpigmented areas 2-3mm in diameter.
  3. Two or more iris Lisch nodules. hamartomas located within the iris , identified by a slit-lamp examination . >74% with NF-1. prevalence increases with age 90% of adults / 25% of children
  4. Two or more neurofibromas or one plexiform neurofibroma.
     - A. Neurofibromas : involve the skin, or along peripheral nerves and blood vessels and viscera. Appear characteristically during adolescence or pregnancy. small, rubbery lesions with a slight purplish discoloration of the overlying skin.
     - B. Plexiform neurofibromas :evident at birth and result from diffuse thickening of nerve trunks that are frequently located in the orbital or temporal region of the face. The skin overlying is hyperpigmented to a greater degree than a café-au-lait spot. *Plexiform neurofibromas produce overgrowth of an extremity and a deformity of the corresponding bone*.
  5. A distinctive osseous lesion such as sphenoid dysplasia (which may cause pulsating exophthalmos) or cortical thinning of long bones with or without pseudoarthrosis.
  6. Optic gliomas ≈15% of patients with NF-1. Most are asymptomatic with normal or near-normal vision, but ≈20% have visual disturbances or precocious sexual development secondary to tumor invasion of the hypothalamus.
  7. first-degree relative with NF-1
- Patients with NF-1 are at risk for hypertension, which may result from renal vascular stenosis or a pheochromocytoma.

NOTE:
Scoliosis is the most common orthopedic manifestation of NF-1, although it is not specific enough to be included as a diagnostic criterion.

- **segmental neurofibromatosis:** Somatic mosaicism, in which an abnormality in one copy of the *NF1* gene is present in some cells but not others, indicates a postzygotic mutation.

- **NF-2** accounts for 10% of all cases of NF
  - ✓ incidence of 1/50,000*( NF2* gene mutation)
  - ✓ diagnosed when one of the following two features :
    1. *bilateral eighth nerve masses* consistent with acoustic neuromas as demonstrated by CT scanning or MRI.
    2. *A parent, sibling, or child with NF-2* and either unilateral eighth nerve masses or any two of the following:
       - ♦ neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacities≈50%.
  - ✓ **Bilateral acoustic neuromas** are the most distinctive feature of NF-2.
  - ✓ Symptoms of hearing loss, facial weakness, headache, or unsteadiness may appear during childhood
  - ✓ café-au-lait spots and skin neurofibromas are classic findings in NF-1, they are much less common in NF-2.
- As with NF-1, CNS tumors, including Schwann cell and glial tumors, and meningiomas are common in patients with NF-2.
- The average life span is less than 40 years.
- COMPLICATIONS :
  2. learning disability
  3. scoliosis
  4. macrocephaly
  5. headache
  6. peripheral nerve malignancy
  7. pheochromocytoma
  8. re-novascular hypertension
  9. epilepsy
  10. Malignancy is the most common cause of death.

## STURGE-WEBER SYNDROME

- Sturge-Weber syndrome is sporadic and not genetic.
- *characterized by angiomas of the leptomeninges overlying the cerebral cortex in + ipsilateral facial port-wine nevus that at the least, covers part of the forehead and upper eyelid.*
- **The nevus** may more extensive and with bilateral distribution. ( ectasia of superficial venules, not a hemangioma, because it has no endothelial proliferation).
- **Ocular defects** of Sturge-Weber syndrome include:
  1. glaucoma: 30% to 50%, progressive.
  2. hemangiomas of the choroid, conjunctiva, and episclera.
- ***seizures****The most common associated neurologic abnormality. Due to brain ischemic injury by the meningeal angiomas.*
  - ✓ most patients in the 1st year of life
  - ✓ They are focal tonic-clonic and contralateral to the side of the facial nevus.

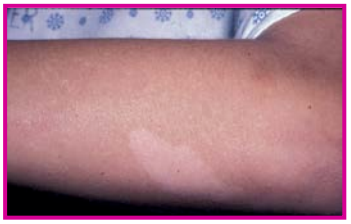
- **mental retardation** is commonin ,at least 50% in later childhood.
- Angiomas, most commonly located in the posterior parietal, posterior temporal, and anterior occipital lobes, within the pia mater.
  - ✓ hemiparesis, hemianopia, intractable focal seizures, and dementia.
- **"tram track" or "railroad track" calcifications** is seen in about 60% of cases.

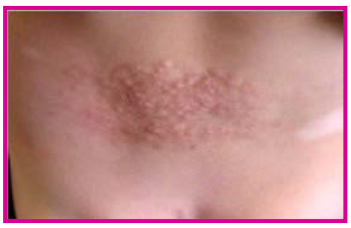
## TUBEROUS SCLEROSIS

- autosomal dominant disorder
- characterized by hamartomas in many organs, especially the brain, eye, skin, kidneys, and heart.
- incidence is 1 in 10,000 births
- 2/3 sporadic ,Germline mosaicism is uncommon ( explains normal parents with affected children).

### CLINICAL MANIFESTATIONS

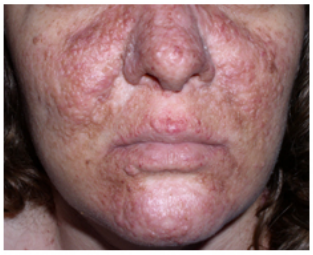
- extremely heterogeneous disease with a wide clinical spectrum varying from severe mental retardation and seizures → normal intelligence and no seizures.
- The classic clinical features are:
  1. facial angiofibromas (**adenoma sebaceum**)
  2. mental retardation
  3. Severe epilepsy.
- < 50% of patients exhibit all three features.
- major signs are:
  1. **ungual fibromas**
  2. **retinal hamartomas**
  3. **hypopigmented macules**
  4. **shagreen patches** :plaques of skin specially lumbar and gluteal regions, develop in late childhood or early adolescence.
  5. **Sebaceous adenomas** develop between 4 and 6yr of age; they appear as tiny red nodules over the nose and cheeks
  6. **Renal angiomyolipoma***: may undergo malignant transformation , most common cause of death in adults with tuberous sclerosis.*
  7. **cardiac rhabdomyoma** 50% :largest in prenatal life & infancy, rarely symptomatic.
  8. **brain tubers:** The characteristic brain lesion is a cortical tuber.
  9. **brain subependymal nodules**
  10. **astrocytomas**.
  11. **ash-leaf spots** 90%:hypomelanotic macules, called, are present in infancy and best detected with a Wood lamp under UV light.



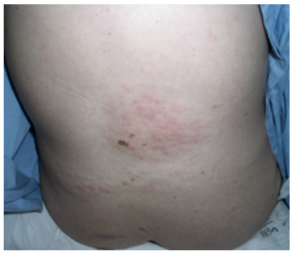


- Tuberous sclerosis is one of the most common causes of infantile spasms= intractable epilepsy, mental retardation; autism, hyperactivity.
- directly by MRI and indirectly by CT, shows periventricular calcifications within the nodule, especially around the foramen of Monro.

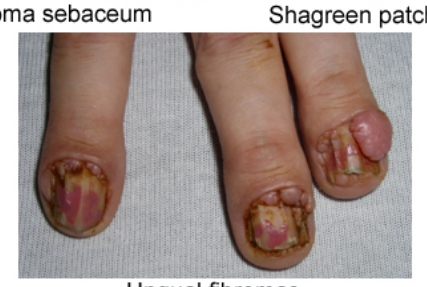
Tuberous sclerosis



Adenoma sebaceum



Shagreen patch



Ungual fibromas

# FEBRILE SEIZURES

- Benign convulsions by any viral illness except: CNS disease, infection or metabolic disorders. Seizures not caused by fever or viral toxin.
- The most common seizure disorder during childhood.
- the incidence approaches 3–4% of young children.
- The peak age of onset is 14–18 mo of age. rare < 9 mo and > 5 yr of age.
- Each child with a seizure + fever → carefully examined and investigated for the cause of the fever.
- Have an excellent prognosis but may also signify a serious underlying acute infectious disease such as sepsis or bacterial meningitis.
- A strong family history of febrile convulsions → genetic predisposition.
  - ✓ AD inheritance pattern is demonstrated in some families.
- D/D :
  1. Febrile convulsion
  2. epilepsy caused by fever
  3. CNS infection

## CLINICAL MANIFESTATIONS.

- Associated with rapidly raising temperature when core temperature = ≥39°C.

| | SIMPLE | COMPLEX |
|---|---|---|
| *Pattern* | *Generalized* | *Partial/focal* |
| *Duration* | *Brief<15 min* | *Prolonged >15 min* |
| *Occurrence in 24 hours* | *Once* | *> 1 attack* |
| *Neurological statue* | *Normal* | *compromised* |
| *History of febrile convulsion* | *Negative* | *positive* |

- 30–50% of children have recurrent seizures with later episodes of fever. RISKS:
  1. age <12mo
  2. lower temperature before seizure onset
  3. positive family history of febrile seizures
  4. complex seizure.
- Children with simple febrile seizures are at no greater risk of later epilepsy than the general population, some factors are associated with increased risk.
  1. presence of complex seizure or atypical postictal period / multiple SFC.
  2. positive family history of epilepsy
  3. initial febrile seizure before 12mo of age
  4. delayed developmental milestones
  5. Pre-existing neurologic disorder.
- The incidence of epilepsy is 9% when several risk factors are present, compared with an incidence of 1% in children who have febrile convulsions and no risk factors.
- During the acute evaluation, a physician's most important responsibility is to determine the cause of the fever and to rule out meningitis and encephalitis (examine meningial signs).
- Convulsive status epilepticus (one seizure lasting 30min or multiple seizures during 30min without regaining consciousness) → CNS infection (viral or bacterial meningitis).
- If there is possibility of meningitis, a lumbar puncture

**NOTE:**
- ✓ <12 months at 1st attack → 50% 2nd attack
- ✓ >12 months at 1st attack → 30% 2nd attack
- ✓ Those with 2nd attack → 50% at least one another attack.

with examination of the cerebrospinal fluid (CSF) is indicated (CSF is normal in early meningitis).

- A lumbar puncture should be strongly considered in children <12mo of age and considered in those 12-18mo of age.
- Seizure-induced CSF abnormalities are rare in children and all patients with abnormal CSF after a seizure should be thoroughly evaluated for other causes.
- viral meningoencephalitis should also be kept in mind, especially herpes simplex.
- Viral infections of the upper respiratory tract, roseola, and acute otitis media are most frequently the causes of febrile convulsions.
- glucose determination, serum electrolytes and toxicology screening should be ordered based on individual clinical circumstances .
- EEG is not warranted after a simple febrile seizure but → complex seizure or with other risk factors for later epilepsy.
- neuroimaging → considered with atypical features, including focal neurologic signs or pre-existing neurologic deficits.
- No evidence that SFC cause structural damage to the brain or induce cognitive disorders.

### TREATMENT (No treatment = risk / benefit = negative balance)

- Routine treatment of a normal infant with simple febrile convulsions includes
  1. careful search for the cause of the fever,
  2. Active measures to control the fever, antipyretics ( not effective for FC).
  3. Reassurance of the parents.

  4. Prolonged anticonvulsant prophylaxis for preventing recurrent febrile convulsions is controversial and no longer recommended.
  - ✓ Antiepileptics such as phenytoin and carbamazepine have not effective.
  - ✓ Phenobarbital effective in preventing recurrent febrile seizures /side effect:decrease cognitive function in treated children.
  - ✓ Sodium valproate is effective in ,but:
    - A. Risk / benefit is negative balance for disease with excellent prognosos w/out tt.
    - B. The incidence of fatal valproate-induced hepatotoxicity is highest in children younger than 2 yr of age.
    - C. Other side effects: thrombocytopenia, weight gain and drop of hair.
  - ✓ Oral diazepam (assival) is an effective and safe method of reducing the risk of recurrence of febrile seizures by 44%.
    - A. At the onset of febrile illness, oral diazepam, 0.3mg/kg q8h (1mg/kg/24hr), is administered for the duration of the illness (usually 2–3 days).
    - B. The side effects are usually minor, but symptoms of lethargy, irritability, and ataxia = cover encephalitis symptoms and golden days of its diagnosis.
    - C. Seizure could occur before fever = no benefit at this state.
    - D. Useful when parental anxiety associated with febrile seizures is severe.

## ENCEPHALOPATHIES

- Encephalopathy is a generalized disorder of cerebral function that may be acute or chronic, progressive or static.
- The etiology of the encephalopathies in children includes :
  1. infectious
  2. toxic (e.g., carbon monoxide, drugs, lead),
  3. metabolic
  4. Ischemic causes

**NOTE:**
- ✓ Paraplegia: only lower limbs.

### CEREBRAL PALSY

- Group of motor syndromes resulting from disorders of early brain development.
- Static? Encephalopathy defined as non-progressive disorder of posture & movement, associated with epilepsy, abnormalities in speech, vision & intellect resulting from lesion or defect in the developing brain dating to events in the prenatal or perinatal periods.
- Most common cause is idiopathic 80%.
- CP is caused by a broad group of etiologies:
  1. developmental
  2. genetic

3. metabolic
4. ischemic
5. infectious

- NEUROLOGICAL FEATURES OF CP CHANGE OR PROGRESS OVER TIME= NOT STATIC ENCEPHALOPATHY
- CP is associated with motor systems disorders, epilepsy and abnormalities of speech, vision, and intellect.
- Its seizures are epileptical : because it is caused by chronic brain pathology.

## EPIDEMIOLOGY AND ETIOLOGY.

- CP is the most common and costly form of chronic motor disability in childhood.
- Prevalence of 2/1000.
- Most children with CP had been born at term with uncomplicated labors and deliveries.
- Features pointing to antenatal factors causing abnormal brain development ( in 80%) .
- Many CP children had congenital anomalies external to the CNS.
- ↓10% of children with CP had evidence of intrapartum asphyxia.
- Intrauterine exposure to maternal infection is associated with a significant increase in the risk of CP in normal birthweight infants:
  1. chorioamnionitis
  2. umbilical cord inflammation
  3. foul-smelling amniotic fluid
  4. maternal sepsis
  5. temperature greater than 38°C during labor
  6. urinary tract infection
- The prevalence of CP is increased among low birthweight infants, particularly < 1,000g at birth→ intracerebral hemorrhage and periventricular leukomalacia (PVL).

## CLINICAL MANIFESTATIONS.

- CP is divided into several major motor syndromes that differ ( neurologic involvement, neuropathology, and etiology).
- The physiologic classification: major motor abnormality/ the topographic taxonomy: the involved extremities.
- CP is associated with: mental retardation, epilepsy, and visual, hearing, speech, cognitive, and behavioral abnormalities.

### SPASTIC HEMIPLEGIA:

- ✓ decreased spontaneous movements on the affected side and show hand preference at a very early age.
- ✓ The arm is often more involved than the leg and difficulty in hand manipulation is obvious by 1 yr of age.
- ✓ Walking is usually delayed until 18–24 mo, and a circumductive gait is apparent.
- ✓ growth arrest, particularly in the hand and thumbnail, especially if the contralateral parietal lobe is abnormal, because extremity growth is influenced by this area of the brain.
- ✓ Spasticity is apparent in the affected extremities, particularly the ankle, causing an equinovarus deformity of the foot.
- ✓ An affected child often walks on tiptoes because of the increased tone, and the affected upper extremity assumes a dystonic posture when the child runs.
- ✓ Ankle clonus and a Babinski sign may be present, the deep tendon reflexes are increased, and weakness of the hand and foot dorsiflexors is evident.
- ✓ 1/3 have a seizure disorder that usually develops during the first year
- ✓ 25% have cognitive abnormalities including mental retardation.
- ✓ CT scan or MRI (more sensitive) study may show an atrophic cerebral hemisphere with a dilated lateral ventricle contralateral to the side of the affected extremities.
- ✓ important cause of hemiplegic CP: Focal cerebral infarction (utro or neonatal stroke) → intrauterine or perinatal thromboembolism ( thrombophilic disorders, especially anticardiolipin antibodies), Infection Genetic/developmental ,Periventricular hemorrhagic infarction.

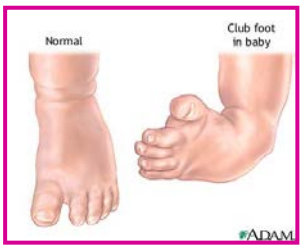
### SPASTIC DIPLEGIA

- ✓ Bilateral spasticity of the legs greater than in the arms.

- ✓ The first noted when an affected infant begins to crawl→The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind (commando crawl)
- ✓ If the spasticity is severe, application of a diaper is difficult because of the excessive adduction of the hips.
- ✓ Examination of the child reveals
  1. spasticity in the legs
  2. brisk reflexes & ankle clonus,
  3. bilateral Babinski sign.
  4. scissoring posture of the lower extremities is maintained when left from axilla.
  5. Walking is significantly delayed and the child walks on tiptoes.
  6. the feet are held in a position of equinovarus
  7. Severe cases: disuse atrophy and impaired growth of the lower extremities with normal development of the upper torso → disproportionate growth.

- ***Intellectual development is excellent for these patients, and seizures is minimal.***
- The most common neuropathologic finding is periventricular leukomalacia, (in the area where fibers innervating the legs course through the internal capsule). *Causes:* Prematurity, Ischemia, Infection & Endocrine/metabolic (e.g., thyroid)

## SPASTIC QUADRIPLEGIA:




- The most severe form of CP because of marked motor impairment of all extremities and the high association with mental retardation and seizures.
- Swallowing difficulties are common as a result of bulbar palsies, often leading to aspiration pneumonia.
- The most common lesions seen on pathologic examination or on MRI scanning are severe PVL and multicystic cortical encephalomalacia.
- Neurologic examination shows:
  1. increased tone and spasticity in all extremities,
  2. brisk reflexes,
  3. Flexion contractures of the knees and elbows are often present by late childhood.
  4. Speech and visual abnormalities are prevalent in this group of children.
  5. Spastic quadriparesis often have athetosis and classified as mixed CP.

**NOTE:**
**D/D:** progressive encephalopathy, spinal cord injury, peripheral neuropathy, neuromascular disease, myopathies, begin congenital hypotonia.

## ATHETOID CP

- called choreoathetoid or extrapyramidal CP
- Less common than spastic cerebral palsy.
- Pathology: putamen, globus pallidus, thalamus, basal ganglia
- infants are characteristically hypotonic with poor head control and marked head lag
- Develop increased variable tone with rigidity and dystonia over several years.
- Feeding may be difficult, and tongue thrust and drooling may be prominent.
- Speech is typically affected because the oropharyngeal muscles are involved.
- *upper motor neuron signs are not present*, seizures are uncommon, and intellect is preserved in many patients.
- most likely to be associated with birth asphyxia.
- CAUSES:

1. acute intrapartum near-total asphyxia
2. kernicterus secondary to high levels of bilirubin, MRI → bilateral globus pallidus lesions.
3. Metabolic genetic disorders such as mitochondrial disorders and glutaric aciduria.

## TREATMENT

- A team of physicians from various specialties, as well as occupational and physical therapists, speech pathologists, social workers, and developmental psychologists.
- Personal autonomy (economical, physiological and physical) – golden years for that is when mother can carry her baby.
- Parents should be taught how to handle their child in daily activities in ways that limit the effects of abnormal muscle tone.
- Series of exercises designed to prevent the development of contractures, especially a tight Achilles tendon.

# SEIZURES (PAROXYSMAL DISORDERS):

- **PAROXYSMAL DISORDERS**: Sudden reversible changes in the mental status or somtosensory function, have repetitive nature. Variable duration (seconds-minutes), end abruptly, and followed by gradual return to baseline, their may be aura before or altered state of awareness afterward "postictal state" .
- D/D( transient paroxysmal disorders in childhood):
  1. seizures
  2. migraine
  3. transient ischemic attack
  4. syncope
  5. vertigo
  6. hypoglycemia
  7. breath-holding spells
  8. tics
  9. conversion reactions
- EEG is the most useful neurodiagnostic test in distinguishing seizures from non-epileptical paroxysmal disorders.
  - ✓ Must interrupt with the history: normal child may have abnormal EEG and child with seizures may have normal EEG between attacks.
  - ✓ If diagnosis still not clear, do prolongs simultaneous video and EEG monitoring.
- DEFINITIONS;
  1. **ATTACK**: violent act starting on with vigor. Ex attacks of laughing, breath holding attack of spell (begnin1-5years), epileptic attack, non-epileptic attackm attack of FC.
  2. **CONVULSION**: abnormal movements, involuntary contractions, or series of contraction of voluntary muscles. Ex epileptic or non-epileptic motor, shaking, startling 'must their be displasment of place" . clonic convulsions, but not tonic convulsion, tonic clonic convulsion, myclonic convulsion but not absence
  3. **SEIZURE** : takes hold of suddenly and with force, not all seizures are convulsions, but all convulsions are seizures ex epileptic and non-epileptic, grand male seizures, petit male.
  4. **FIT**: sudden short attack exclusively epileptic.
     - Seizure phases: preictall, ictal (intraictal), postictal (immediate or late postictal)
- EPILEPSY: recurrent unprovoked seizures.
  - ✓ Epileptic seizures are generally separated on the basis of the mechanism of the electrical phenomena
  - ✓ TYPES:
  1. seizures that arise from one region of the cortex (focal, partial, or localization related): 40% to 60%, most partial seizures in children are due to genetic influences (rolandic seizures) or Focal brain lesions (tumors, infarct, dysgenesis),
  2. seizures that arise from both hemispheres simultaneously (generalized).
- Most children with exclusively primary generalized tonic-clonic seizures have genetic epilepsy
- The presence of an aura indicates a focal origin of the attack.
- absence seizures :
  - ✓ Typical generalized (petit mal epilepsy).
  - ✓ 6% to 20% of epileptic children have it.
  - ✓ There is a 75% concordance rate in monozygotic twins→ genetic etiology.
  - ✓ 40% to 50% of children with absence seizures have generalized seizures (60% before and 40% after the onset of absence seizures).
- Myoclonic, tonic, atonic, and atypical absence seizures compose 10% to 15% of childhood epilepsies.
  - ✓ frequently associated with underlying structural brain disease

NOTE:

| Metabolic Causes |
|---|
| Hypoglycemia* |
| Hypocalcemia |
| Hypomagnesemia |
| Hyponatremia |
| Hypernatremia |
| Storage diseases |
| Reye syndrome |
| Degenerative disorders |
| Porphyria |
| Pyridoxine dependency and deficiency |

- ✓ difficult to treat and classify.
- ✓ occur in combination with each other and with generalized tonic-clonic seizures.
- ✓ The peak age of occurrence of myoclonic absence seizures is in the first year (37%)
- ✓ status epilepticus is the first ictal manifestation in 77% of patients.

## CLINICAL MANIFESTATIONS:

### PARTIAL SEIZURES

- arise from a specific anatomic focus
- motor, sensory, psychic, or autonomic abnormalities, but consciousness is preserved.
- Complex partial seizures vs. simple partial seizures →consciousness is impaired.
- **jacksonian seizures** : partial seizures spread to involve the whole brain and produce a generalized tonic-clonic seizure→ secondary generalization.
- **Uncinate seizures**: arising from the medial temporal lobe manifest with an olfactory hallucination of an extremely unpleasant odor (burning rubber).
- **Gelastic seizures:** spells of uncontrolled laughter, originating from hypothalamic tumors.
- **Lip-smacking seizures** arise from the anterior temporal lobe.
- **macropsia, micropsia, altered depth perception, and vertigo**: posterior temporal lobe.
- **dreamlike states** (déjà vu and bizarre psychic abnormalities):Limbic temporal lobe
- **Episodic autonomic phenomena**, such as fever, tachycardia, shivering, and increased gastrointestinal motility, rarely seizures of temporal lobe origin.

### GENERALIZED SEIZURES

- **Generalized Tonic, Clonic, and Tonic-Clonic Seizures (Generalized Major Motor Seizures)**
  - ✓ Typically the attack begins abruptly, but may preceded by a series of myoclonic jerks.
  - ✓ DURING A TONIC-CLONIC SEIZURE: consciousness and control of posture are lost → tonic stiffening and upward deviation of the eyes, Pooling of secretions, pupillary dilation, diaphoresis, hypertension, and piloerection → Clonic jerks → child is briefly tonic again → flaccid and urinary incontinence →child awakens→ irritability and headache.
  - ✓ During an attack, the EEG shows repetitive synchronous bursts of spike activity followed by periodic paroxysmal discharges.
  - ✓ Brief seizures of any type are not believed to produce brain damage directly.
  - ✓ Generalized tonic-clonic activity lasting longer than 20 minutes is defined as **status epilepticus** and may lead to irreversible brain injury.
  - ✓ CLONIC TYPE: paroxysm (intense or not)involuntary repetitive series of contractions and relaxation of voluntary muscles, jerky movement, generalized or partial , symmetrical or asymmetrical, high frequency or low, in digressive manner, up to sudden total abortion.
  - ❖ May or not associated with cynosis, apnea, frothy secretions, urination, stool passage or loss of consciousness.
  - ❖ If all 4 limbs = generalized (upper>lower), stimulation of both agonist and antagonist: upper flex> extension, lower extension > felx, head flex=extension.
  - ✓ TONIC TYPE : paroxysm of variable intensity and duration of increase tonus of voluntary muscles, generalized or partial, symmetrical or asymmetrical.
  - ❖ generalized tonic pattern :axial + four limbs are hypertonic, fixed uprolling eyes, apnea, erythrosis and cyanosis, duration few seconds, fast return to precedent activity by inspiration and cry, usually one or repeated accesses.
  - ❖ Partial tonic pattern :lateral deviation of the head and eye toward the lesion.
  - ❖ in the same time both agonist and antagonist are functioning causing vibration around organ axis
  - ❖ D/D feverish chills
  - ✓ TONIC CLONIC TYPE: consist of 2 phases:
  1. hypertonia for seconds then muscular relaxation with or without apnea, cyanosis, erythrosis.
  2. Involuntary shaking or series of voluntary muscle contractions
  - ❖ Others tonic-clonic-tonic, clonic-tonic-clonic
  - ✓ risk of recurrence for children whose first seizure is generalized tonic-clonic is 50%.

- **Absence Seizures**
  - ✓ The clinical hallmark of absence seizures is a brief loss of environmental awareness accompanied by eye fluttering or simple automatisms, such as head bobbing and lip smacking.
  - ✓ 4 and 6 years of age.
  - ✓ Duration 5-10 seconds
  - ✓ Girls> boys
  - ✓ No motor effect, no post-ictal,
  - ✓ Types:
    1. simple absence: petit male, no additional manifestations.
    2. complex absence; with other manifestations: myoclonic absence, enuretic absence
  - ✓ Neurologic examination and brain imaging are normal.
  - ✓ *The characteristic EEG patterns consist of synchronous **3-Hz spike-and-wave activity** with frontal accentuation. 3 cycles/sec.*
  - ✓ provoked by hyperventilation or strobe light stimulation
  - ✓ Treatment: valproate, ethosuxmide.
  - ✓ Staring spells can be either primary generalized absence (petit mal) or complex partial seizures (temporal lobe epilepsy).

| | ABSENCE SEIZURE | COMPLEX PARTIAL SEIZURE |
|---|---|---|
| CLINICALLY | stoppage of activity, staring, and alteration of consciousness | stoppage of activity, staring, and alteration of consciousness |
| AUTOMATISMS | Less complicated | more complicated and may involve repetitive swallowing, picking of the hands, or walking in nonpurposeful circles. |
| POSTICTAL CONFUSION. | yes | No |
| PROVOCATION | by hyperventilation | spontaneously |
| DURATION | Few seconds | Several minutes |
| NUMBER/DAY | dozens of absence seizures per day. They rarely have. | Rarely more than one or two partial complex seizures in a day |

- **Myoclonic, Tonic, Atonic, and Atypical Absence Seizures**
  - ✓ Atypical absence seizures manifest as episodes of impaired consciousness with automatisms, autonomic phenomena, and motor manifestations, such as eye opening, eye deviation, and body stiffening.
    - ♥ The EEG shows slow spike-and-wave activity at 2 to 3 Hz.
  - ✓ Myoclonus is a lightning-like jerk of part of the body.
    - ♥ The phenomenon is epileptic if the EEG shows epileptiform discharges during the jerk and nonepileptic if it does not.
    - ♥ muscle clony, 2-3 clusters over 1-2 seconds
    - ♥ one muscle, group of muscles, segment of limb, whole limb.
    - ♥ Usually shoulder may also face( lips, upper lids)
    - ♥ Types
      1. physiological myoclony 1st phase of sleep and at awaking or whole mark during sleep (anti epileptics according to Agravacation)
      2. audiogenic myclony by noise as in Tay-Sacks disease, krabbe disease
      3. cerebello-epso-myoclonic syndrome pt is awake, ataxia, opsoclony(rapid eye movement)
    - ♥ Nonepileptic myoclonus originate in the basal ganglia, brainstem, or spinal cord. It may be benign, as in sleep myoclonus, or indicate serious pathology.
    - ♥ Myoclonic epilepsy usually is associated with multiple seizure types.
    - ♥ The underlying illness producing myoclonic epilepsy :
      1. developmental and static
      2. progressive with neurologic deterioration (neuronal ceroid lipofuscinosis, Lafora body, and Univerricht-Lundborg disease).

- ♥ Myoclonic absence: body jerks + absence seizures and atypical absence seizures.
- ♥ Bilateral massive epileptic myoclonus is symmetric and varies in intensity.

✓ **ATONIC TYPE**: sudden and synchronous total loss of contact and tonus, sometimes with apnea, no associated movements clonic or tonic.

- ♥ in children most attacks occurs while watching TV due to intermittent illumination / flashing lights.
- ♥ No absence attack
- ♥ D/D: faintness/syncope gradual loss of muscle imbalance proceeded by predrome.

## EPILEPTIC SEIZURES

- Epilepsy: hyper-synchronous electrical discharge of a population of neurons, chronic state, characterized by recurrence of non-occasional fits.
- Acute illnesses affecting brain to the 1st time:
  1. pyretic
  2. infections
  3. traumatic
  4. metabolic (hypoglycemia,↓ Ca, ↓O2)
  5. toxic (antipsychotic, cocain)
  6. vascular (CVA)
- Non occasional, chronic, repetitive.
- First single attack cant considered an epileptic attacks
- Neurocutanous disease cause epileptic seizures due to their chronic damage to the brain.
- ETIOLOGY:
  1. idiopathic (primary): no origin in physical examination.
  2. chronic(secondary): tumor, IEOM, neurocutanous syndrome, cerebral malformation " seen by actual methods of exploration": origin on neurological examination.
  3. chronic, neurological exam abnormal but no evident of obscure or doubtful origin by actual methods "cryptogenic epilepsy"
- BY PATTERN OF EXTENSION:

- clinical presentation
- EEG record.
  1. generalized epilepsy: clinically and by EEG = generalized form eg. Absence attacks, generalized tonic clonic.
  2. partial epilepsy ( motor, sensory, psychiatric, autonomic):if EEG or clinical exam is not generalized from the beginning ., aura = focal.
  3. Secondary generalized epilepsy: start as partial → generalized "grand mal epilepsy" may come with aura.

## EPILEPTIC SYNDROMES

### BENIGN FOCAL EPILEPSY (ROLANDIC EPILEPSY)

- 5 and 10 years
- Comprising 16% of all afebrile seizures in children younger than age 15 years (most common childhood epilepsy syndrome)
- usually focal motor seizures involving the face and arm
- tend to occur only during sleep or on awakening in ↑50%
- Symptoms: abnormal movement or sensation around the face and mouth with drooling and a rhythmic guttural sound.
- Speech and swallowing are impaired
- Family history of similar seizures is found in 13% of patients.
- The disorder is called benign because seizures usually respond promptly to anticonvulsant therapy; intellectual outcome and brain imaging are normal,
- *Epilepsy resolves after puberty.*

### BENIGN NEONATAL CONVULSIONS

- autosomal dominant genetic disorder localized to chromosome 20.

- Generalized clonic seizures occur toward the end of the first week of life ("3-day fits" or familial 5th day fits).
- Response to treatment varies, but the outlook generally is favorable.

## JUVENILE MYOCLONIC EPILEPSY ("OF JANZ")

- occurs in adolescence
- autosomal dominant disorder localized on chromosome 6 with variable penetrance.
- The patient may have absence, generalized tonic or clonic, and myoclonic seizures.
- *The hallmark is morning myoclonus occurring predominantly within 90 minutes of awakening.*
- Seizures usually resolve promptly with therapy with valproic acid
- therapy must be maintained for life.

## INFANTILE SPASMS (WEST SYNDROME)

- Brief contractions of the neck, trunk, and arm muscles, followed by a phase of sustained muscle contraction lasting 2 to 10 seconds.
- Description:
  - contraction of the whole body (0.5-2 seconds)
  - repeated clusters/cluster= few number of spasms
  - between clusters= muscle relaxation of 5-20 seconds
  - each group of cluster is attack
  - may cry between attacks
  - no loss of consciousness
  - Types
  1. inflexion 75% salam spasm, like moror reflex.
  2. inextension 25%
  - in both contraction of flexor and extensor with predominance of once.
  - No difference in prognosis
  - any asymmetry (head and eyes) → cerebral lesion
- The initial phase consists of flexion and extension in various combinations such that the head may be thrown either backward or forward. The arms and legs may be either flexed or extended.
- Spasms occur most frequently when the child is awakening from or going to sleep.
- Each jerk is followed by a brief period of relaxation, then repeated multiple times in clusters of unpredictable and variable duration.
- Many clusters occur each day.
- The EEG:
  1. waking state, **hypsarrhythmia**, is dramatically abnormal, consisting of high-voltage slow waves, spikes, and polyspikes accompanied by background disorganization.
  2. during sleep: Burst suppression patterns are seen
- The peak age of onset is 3 to 8 months,
- 86% of infants experience the onset of seizures before age 1 year.
- D/D: awaking manifestations, generalized contractions due to abdominal pain, moro reflex beyond 4 months.
- The etiology is not determined in 40% of children.
- This idiopathic or "cryptogenic" group (normal development before seizures; no etiology) has a better response to therapy than the group with a clear etiology, and 40% have a good intellectual outcome.
- Etiology is determined in 60%.***Tuberous sclerosis*** *is the most common cause.*
- Infantile spasms have a poor prognosis.
- Treatment of infantile spasms includes ACTH IM most effective, 4-8 weeks,Valporic acid , clonzepem and oral corticosteroids.
- Irritability, swelling, hypertension, glycosuria, and severe infections are complications to be anticipated with steroid therapy.
- FDA not yet approved vigabatrin, promising drug, because it cause visual field deficits.

## LENNOX-GASTAUT SYNDROME

- variable age of onset. Most before age 5 years.

- Multiple seizure types-including atonic-astatic, partial, atypical absence, and generalized tonic, clonic, or tonic-clonic varieties-characterize the disorder.
- *Many children have underlying brain injury or malformations*.
- These seizures usually respond poorly to treatment, but some patients have a good response to valproic acid.

### ASTATIC-AKINETIC OR ATONIC SEIZURES

- onset between 1 and 3 years of age.
- The seizures last 1 to 4 seconds
- characterized by a loss of body tone, with falling to the ground, dropping of the head, or pitching forward or backward.
- A tonic component usually is associated.
- The seizures frequently result in repetitive head injury if the child is not protected with a hockey or football helmet.
- They are most frequent on awakening and on falling asleep
- 50 or more daily seizures are usual.
- Children with astatic-akinetic seizures usually have mental retardation and underlying brain abnormalities.
- **Tuberous sclerosis** is a frequent cause.

### ACQUIRED EPILEPTIC APHASIA (LANDAU-KLEFFNER SYNDROME) is

- Characterized by the abrupt loss of previously acquired language in young children.
- Some patients develop partial and generalized epilepsy.
- The EEG is highly epileptiform in sleep.
- The peak area of abnormality often in the dominant perisylvian region (language areas).
- The cause is unkown if caused by frequent temporal lobe seizures or inflammatory temporal lobe pathology.

### RASMUSSEN ENCEPHALITIS

- chronic, progressive focal inflammation of the brain of unknown origin.
- An autoimmune origin and focal viral encephalitis have been postulated.
- The usual age of onset is 6 to 10 years.
- The disease begins with focal, persistent motor seizure activity, including epilepsia partialis continua.
- Over months, the child develops hemiplegia and cognitive deterioration.
- EEG shows focal spikes and slow wave activity.
- Brain imaging studies are initially normal, then show atrophy in the involved area.
- Hemispherectomy only successful therapy as measured by seizure eradication and prevention of cognitive deterioration, but permanent hemiparesis is an inevitable consequence.

## STATUS EPILEPTICUS

- ongoing seizure activity for greater than 20 minutes or repetitive seizures without return of consciousness for greater than 30 minutes.
- Other definition: two or more sequential seizures without full recovery of consciousness between seizures or more than 30 minutes of continuous seizure activity.
- Any convulsive seizure associated with reductions in oxygen saturations and cortical perfusion produces a risk for irreversible brain injury.
- ***50%, there is no etiology***, but in 50% of this group, status is associated with fever.
- 25% of children presenting with status epilepticus have an acute brain injury, such as meningitis, encephalitis, electrolyte disorder, or acute anoxia.
- 20-% have history of brain injury or congenital malformation.
- Sudden cessation of anticonvulsant medication is another frequent cause.
- Overall the mortality rate of status epilepticus is less than 10% and related to the etiology of the seizure pattern.

## IMMEDIATE MANGEMENT

- ensure an adequate airway and to assess the cardiovascular status
- child's oropharynx should be cleared and suctioned, and the airway should be secured.
- Oxygen is administered.
- If there is doubt concerning the adequacy of the airway→ intubates
- IV infusion should be started, and laboratory evaluation should be undertaken.
- Hypoglycemia and electrolyte abnormalities must be addressed.
- Initial management is usually with a benzodiazepine.
  1. Lorazepam (0.05 to 0.1 mg/kg)
  2. diazepam (0.1 to 0. mg/kg)
  3. midazolam (0.2 mg/kg)
- Diazepam distributes rapidly to the brain, but has a short duration of action.
- Alternatively, or even simultaneously, administration of either phenytoin (10 to 15 mg/kg) or fosphenytoin (10 to 20 mg/kg) at a rate of 1 mg/kg/min is effective.
- Phenytoin &fosphenytoin distribute more slowly, have a much longer duration of action.
- If the seizures do not stop with these measures, a continuous IV infusion of diazepam, loading dose of 10 to 20 mg/kg of phenobarbital, or IV valproic acid at a dose of 20 mg/kg
- If this approach is ineffective, preparations for general anesthesia are undertaken.

## LABORATORY AND DIAGNOSTIC EVALUATION OF SEIZURES

- ✓ complete blood count
- ✓ blood chemistries, including glucose, calcium, sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, magnesium, and phosphorus;
- ✓ blood or urine toxicology screening
- ✓ analysis of CSF
- ✓ EEG
- ✓ Brain imaging (MRI).

- Neonates :testing of blood ammonia for inborn errors of metabolism, CSF glycine, lactate and herpes simplex polymerase chain reaction, urine and stool culture of viruses (especially cytomegalovirus and enterovirus), and a clinical trial of pyridoxine.
- Analysis of CSF is not necessary if the patient is afebrile and has no other neurologic signs or if the history does not suggest a meningeal infection or subarachnoid hemorrhage.
- Children with **simple febrile seizures** who have recovered completely may require little or no laboratory evaluation other than to evaluate the source of the fever.
- **MRI** is superior to CT in showing brain pathology, but in the emergency department setting, CT may be desirable because it can be performed rapidly and shows acute intracranial hemorrhage more clearly than MRI.

# WEAKNESS AND HYPOTONIA

## SPINAL MUSCULAR ATROPHY

- Progressive degeneration of anterior horn cells

### ETIOLOGY

- genetic illness that may begin in intrauterine life or anytime and may progress at a rapid or slow pace.
- The earlier in life the process starts, the more rapid the progression.
- **Werdnig-Hoffmann disease**:early fulminant form of the illness, Infants affected at birth or within the first several months of life, weakness progress to flaccid quadriplegia with bulbar palsy, respiratory failure, and death within the first year of life.
- **Kugelberg-Welander syndrome**:mild form of the illness, begins in late childhood or adolescence with proximal weakness of the legs and progresses slowly over decades.
- SMA is one of the most frequent autosomal recessive diseases
- All types of SMA are caused by mutations in the survival motor neuron gene (*SMN1*).
- Only homozygous absence of *SMN1* is responsible for SMA

### CLINICAL MANIFESTATIONS:

- begin between 6 months -6 years of age
- Progress rapidly or slowly or may progress rapidly initially, then seemingly plateau.
- The clinical manifestations include:

1. Progressive proximal weakness
2. decreased spontaneous movement
3. floppiness
4. Atrophy
5. Head control is lost
6. legs stop moving altogether
7. children play only with toys placed in their hands
8. The range of facial expression diminishes
9. drooling and gurgling increase
10. The eyes remain bright, open, mobile, and engaging.
11. early loss of reflexes
12. **Fasciculations** sometimes can be seen in the tongue and are best identified when the child is asleep
13. normal mental, social, and language skills and sensation
14. Breathing becomes rapid, shallow, and predominantly abdominal.
15. Extremely weak child, respiratory infections lead to atelectasis, pulmonary infection, and death.

## Laboratory and Diagnostic Studies

- creatine phosphokinase mildly elevated.
- The EMG : fasciculations, fibrillations, positive sharp waves, and high-amplitude, long-duration motor units.
- Muscle biopsy specimens show grouped atrophy.
- *The diagnosis is established by DNA probe for SMA*.

## Treatment

- No treatment for SMA exists.
- Respiratory infections are managed early and aggressively with pulmonary toilet, chest physical therapy, oxygen, and antibiotics.

## Poliomyelitis

- **asymmetric flaccid weakness** as groups of anterior horn cells become infected
- acute enteroviral illness with prodromal vomiting and diarrhea associated with an aseptic meningitis picture

## Guillain-Barré Syndrome

- postinfectious autoimmune peripheral neuropathy that often occurs after a respiratory or gastrointestinal infection.
- Infection with *Campylobacter jejuni* is associated with a severe form of the illness.

## Clinical manifestations:

- The characteristic symptoms are :
  5. areflexia
  6. flaccidity
  7. symmetric weakness beginning in legs and ascending to the arms, trunk, throat, &face.
- Progression can occur rapidly, in hours or days, or more indolently, over weeks.
- Typically the child complains of numbness or paresthesia in the hands and feet, then experiences a "heavy," weak feeling in the legs→inability to climb stairs or walk.
- Objective signs of sensory loss are minor compared with the dramatic weakness
- Progression to bulbar and respiratory insufficiency may occur rapidly.
- **Dysfunction of autonomic**:
  1. hypertension, hypotension, orthostatic hypotension
  2. tachycardia & other arrhythmias
  3. urinary retention or incontinence
  4. stool retention
  5. episodes of abnormal sweating
  6. flushing
  7. peripheral vasoconstriction.
- This polyneuropathy can be difficult to distinguish from an acute spinal cord syndrome.
- Preservation of bowel and bladder function, loss of arm reflexes, absence of a sensory level, and lack of spinal tenderness → Guillain-Barré syndrome.

- **Miller Fisher variant** : cranial nerve variant of Guillain-Barré syndrome manifests with *ataxia, partial ophthalmoplegia, and areflexia*.

- D/D:
  1. Porphyria
  2. tick paralysis
  3. vasculitis
  4. nutritional deficiency (vitamins $B_1$, $B_{12}$, and E)
  5. endocrine disorders
  6. infections (diphtheria, Lyme disease)
  7. toxins (organo-phosphate, lead).
- may resolve spontaneously
- 75% of patients recover normal function within 1 to 12 months.
- 20% of patients are left with mild to moderate residual weakness in the feet and lower legs.
- The mortality rate is 5%, and death is caused by:
  3. autonomic dysfunction (hyper-hypotension, tachy-bradycardia, and sudden death)
  4. respiratory failure
  5. complications of mechanical ventilation
  6. cardiovascular collapse
  7. pulmonary embolism.

## Laboratory and Diagnostic Studies

- The CSF in Guillain-Barré syndrome is often normal in the first days of the illness→elevated protein levels without significant pleocytosis.
- NCV and EMG also may be normal early in the disease→ delay in motor NCV and decreased amplitude and temporal dispersion of the evoked compound motor action potential

## Treatment

- Moderate or severe weakness or rapidly progressive weakness → pediatric ICU.
- Endotracheal intubation in patients who exhibit early signs of hypoventilation, accumulation of bronchial secretions, or obtunded pharyngeal or laryngeal reflexes.
- Plasma exchange and IV immunoglobulin are beneficial in rapidly progressive disease.
- Most patients are treated initially with IV immunoglobulin (total dose 1 to 2 g/kg/day given for 4 to 5 days).

## Hereditary Motor Sensory Neuropathy (Charcot-Marie-Tooth Disease)

- chronic, genetic polyneuropathy characterized by weakness and wasting of distal limb muscles.
- The most common form (Charcot-Marie-Tooth type 1A)
- HMSN type II : neuronal form with mildly decreased NCV and no hypertrophic changes.
- Type I HMSN and type II HMSN are inherited as autosomal dominant traits with variable expressivity.

## Clinical manifestations:

- complaints begin in the preschool years with **pes cavus deformity of feet** and weakness of the ankles with frequent tripping
- Early Examination:
  1. high-arched feet
  2. bilateral weakness of foot dorsiflexors
  3. Normal sensation despite occasional complaints of paresthesia.
- Progression of HMSN is slow, extending over years and decades
- patients develop weakness and atrophy of the entire lower legs and hands and mild to moderate sensory loss in the hands and feet.
- Some patients never have more than a mild deformity of the feet & loss of ankle reflexes.

## Lab studies:

- HMSN type I is a demyelinating illness with severely decreased NCV and hypertrophic changes on nerve biopsy.

## Treatment

- No specific treatment.

## Myasthenia Gravis

- autoimmune condition in which antibodies to the acetylcholine receptors at the neuromuscular junction block.
- complement-mediated pathways, damage the neuromuscular junction.

### Clinical Manifestations

- begin in the teenage years with the onset of ptosis, diplopia, ophthalmoplegia, and weakness of extremities, neck, face, and jaw.
- Fluctuating and generally minimal symptoms are present on awakening in the morning and gradually worsen as the day progresses or with exercise.
- **ocular myasthenia**: the disease never advances beyond ophthalmoplegia and ptosis.
- **systemic myasthenia**: progressive and potentially life-threatening illness that involves all musculature, including that of respiration and swallowing.

### Diagnostic Studies

- Diagnosis is *confirmed with IV edrophonium chloride (Tensilon)*, which transiently improves strength and decreases fatigability.
- Antiacetylcholine receptor antibodies often can be detected in the serum.
- Repetitive nerve stimulation shows a decremental response at 1 to 3 Hz.

### Treatment:

- acetylcholine esterase inhibitors (pyridostigmine), thymectomy, prednisone, plasmapheresis, and immunosuppressive agents.
- When respiration is compromised→immediate intubation and admission to an ICU

## Neonatal Transitory Myasthenia Gravis

- 10% to 20% of neonates born to mothers with myasthenia gravis.
- Symptoms persist for 1 to 10 weeks (mean 3 weeks).
- Almost all infants born to mothers with myasthenia have antiacetylcholine receptor antibody
- antibody titer or extent of disease in mother doesn't predicts which neonates have clinical disease.
- Symptoms and signs include ptosis, ophthalmoplegia, weak facial movements, poor sucking and feeding, hypotonia, and variable extremity weakness.
- The diagnosis: clinical improvement lasting approximately 45 minutes after IM administration of neostigmine methyl-sulfate, 0.04 mg/kg.
- Treatment with oral pyridostigmine or neostigmine 30 minutes before feeding is continued until spontaneous resolution occurs.

## Congenital Myasthenic Syndrome

- variety of rare disorders of the neuromuscular junction have been reported that are not autoimmune mediated.
- The conditions manifest as hypotonic infants with feeding disorders and variable degrees of weakness.
- Some of the identified variants include abnormities of:
  1. presynaptic region (familial infantile myasthenia)
  2. synaptic defects (congenital end plate acetylcholinesterase deficiency)
  3. postsynaptic disorders (slow channel myasthenic syndrome).

## Duchenne Dystrophy

- sex-linked recessive Muscular dystrophy
- 1/3 cases represent new mutations.
- Appearing in 20 to 30 per 100,000 boys.
- The disease results from absence of a large protein called **dystrophin** that is associated with the muscle fiber plasma membrane.
- **Becker muscular dystrophy**:

- ✓ rises from an abnormality in the same gene locus that results in the presence of dystrophin that is abnormal in either amount or molecular structure.
- ✓ It has the same clinical symptoms as Duchenne dystrophy
- ✓ Later onset and slower progression.

## CLINICAL MANIFESTATIONS:

- At 2 to 3 years of age, boys develop an awkward gait and an inability to run properly.
- Some have an antecedent history of mild slowness in attaining motor milestones, such as walking and climbing stairs.
- Examination:
  1. firm calf hypertrophy
  2. mild to moderate proximal leg weakness exhibited by a hyperlordotic
  3. waddling gait
  4. Inability to arise from the ground easily.
  5. **Gower sign**: child typically arises from a lying position on the floor by using his arms to "climb up" his legs and body.
- Arm weakness is evident by 6 years of age.
- Most boys are confined to a wheelchair by 12 years of age.
- By age 16, little mobility of arms remains, and respiratory difficulties increase.
- Death is caused by pneumonia or congestive heart failure from myocardial involvement.

## DIAGNOSTIC STUDIES:

- Serum creatine phosphokinase levels are always markedly elevated.
- Muscle biopsy specimen shows muscle fiber degeneration and regeneration accompanied by increased intrafascicular connective tissue.
- Diagnosis is by DNA probe for Duchenne muscular dystrophy.
- Prenatal diagnosis of both diseases is possible by genetic testing.

## TREATMENT

- Supportive care includes physical therapy, bracing, proper wheelchairs, and prevention of scoliosis.

## LIMB-GIRDLE DYSTROPHY

- autosomal recessive disease
- presenting with proximal leg and arm weakness.
- The genetic defect lies within one of the many muscle proteins that compose the muscle fiber plasma membrane cytoskeleton complex.
- The clinical manifestations are similar to the manifestations of Duchenne dystrophy, but:
  1. seen in an older child or teenager
  2. progress slowly over years.
  3. By midadulthood, most patients are wheelchair bound.

## FACIOSCAPULOHUMERAL DYSTROPHY

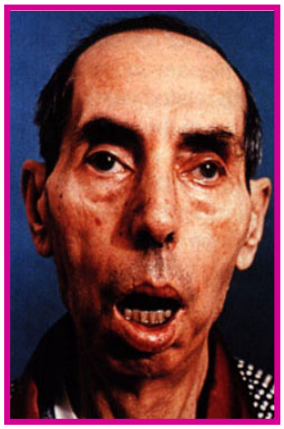
- autosomal dominant disease
- presenting in teenagers with facial and proximal arm weakness.
- Genetic diagnosis is possible by finding a characteristic 4q35 deletion.
- The child has:
  1. mild ptosis
  2. decrease in facial expression
  3. inability to pucker the lips or whistle
  4. neck weakness
  5. difficulty in fully elevating the arms
  6. scapular winging
  7. thinness of upper arm musculature.
- Progression is slow
- Most patients retain excellent functional capabilities for decades.

## MYOTONIC DYSTROPHY

- autosomal dominant genetic disease
- Myotonia is a disorder of muscle relaxation
- caused by progressive expansion of a triplet repeat, GCT, on chromosome 19 in a gene designated myotonin protein kinase (*MP-PK*).

## CLINICAL MANIFESTATIONS:

- Patients grasp onto an object and have difficulty releasing their grasp, "peeling" their fingers away slowly.
- Myotonic dystrophy presents either:
  1. birth, with severe generalized hypotonia and weakness
  2. adolescence, with slowly progressive facial and distal extremity weakness and myotonia.
- The adolescent type is the classic illness and is associated with:
  1. cardiac arrhythmias
  2. cataracts
  3. male pattern baldness
  4. infertility in males (hypogonadism).



- The facial appearance is characteristic" hatchet face "
  1. hollowing of muscles around temples, jaw, and neck
  2. ptosis
  3. facial weakness
  4. drooping of the lower lip.
- The voice is nasal and mildly dysarthric.
- Some myotonic dystrophy mothers give birth to infants with the disease who :
  1. mobile and hypotonic
  2. expressionless faces
  3. tented upper lips
  4. ptosis
  5. absence of sucking and Moro reflexes
  6. poor swallowing and respiration
  7. weakness and atony of uterine smooth muscle during labor lead to associated hypoxic-ischemic encephalopathy and its sequelae.
  8. presence of clubfoot or a history of poor fetal movements indicates intrauterine neuromuscular disease.

## METABOLIC MYOPATHIES:

- **Glycogen storage disease type II** (Pompe disease) and muscle carnitine deficiency
- **Mitochondrial myopathies** are characterized by muscle biopsy specimens that display ragged red fibers(collections of abnormal mitochondria) Typical symptoms are:
  1. hypotonia
  2. ophthalmoplegia
  3. progressive weakness
- **Endocrine myopathies**, including hyperthyroidism, hypothyroidism, hyperparathyroidism&Cushing syndrome, are associated with proximal muscle weakness.
- Hypokalemia and hyperkalemia produce fluctuating weakness (periodic paralysis) and loss of tendon jerks.

## DISEASES OF SPINAL CORD:

- Acute spinal cord lesions, such as infarction or compression, may produce a **flaccid, areflexic paralysis** that mimics lower motor neuron disease.
- A child who exhibits an acute or subacute flaccid paraparesis is most likely to have either an acute cord syndrome or Guillain-Barré syndrome.
- The acute cord syndrome :
  1. transverse myelitis
  2. cord tumor
  3. infarction
  4. demyelination
  5. trauma.
- The hallmarks of spinal cord disease are:
  1. sensory level
  2. motor level
  3. disturbance of bowel and bladder function
  4. local spinal pain or tenderness.

Note:

- Carbamazepine( tegretol): anemia, neutropenia, liver dysfunction, drowsiness & diplopia.
- Valporic acid(depalept):hepatotoxicity, tremor, sedation, weight gain, nausea & vomiting.
- Clonazepam (rivotril): excessive sweating, irritability, drowsiness.
- Phenobarbital: hyperactivity, altered sleep pattern, irritability, short attention span.
- Phenytoin: gum hypertrophy, hirsutism, steven Johnson syndrome, nystagmus, ataxia, nausea & vomiting.

- **Transverse myelitis**, an acute postinfectious demyelinating disorder of the spinal cord, is treated with high-dose steroids.
- Trauma and tumors necessitate immediate neurosurgical management to preserve vital function

# Nephrology & urology

# INTRODUCTION

- Glomerular filtration begins during the third month of gestation.
- Fetal urine production contributes to amniotic fluid volume.
- History of hypoxiaischemia increases the risk of compromise from renal vein thrombosis (especially in neonates) or acute tubular necrosis.
- history of seizures (hypertension, alteration of sodium or calcium levels) = in case of renal disease
- **Common Manifestations of Renal Disease**

| | **Neonate** |
|---|---|
| Flank mass | Dysplasia, polycystic disease, hydronephrosis, tumor |
| Hematuria | Asphyxia, malformation, trauma, renal vein thrombosis |
| Anuria and oliguria | Agenesis, obstruction, asphyxia, vascular thrombosis |
| | **Child and Adolescent** |
| Cola-red colored urine | Hemoglobinuria (hemolysis); myoglobinuria (rhabdomyolysis); pigmenturia (porphyria, urate, beets, drugs); hematuria (glomerulonephritis, Henoch-Schönlein purpura, hypercalciuria) |
| Gross hematuria | Glomerulonephritis, benign hematuria, trauma, cystitis, tumor, nephrolithiasis |
| Edema | Nephrotic syndrome, nephritis, acute or chronic renal failure, cardiac or liver disease |
| Hypertension | Acute glomerulonephritis, acute or chronic renal failure, dysplasia, coarctation of the aorta, renal artery stenosis |
| Polyuria | Diabetes mellitus, central and nephrogenic diabetes insipidus, hypokalemia, hypercalcemia, psychogenic polydipsia, sickle cell anemia, polyuric renal failure, diuretic abuse |
| Oliguria | Dehydration, acute tubular necrosis, interstitial nephritis, acute glomerulonephritis, hemolytic uremic syndrome |
| Urgency | Urinary tract infection, vaginitis, foreign body, hypercalciuria |

- Preauricular tags and deformities of the external ear sometimes are present in children with congenital renal defects.
- **Oliguria:** Urine output <300 mL/$m^2$ /24 hr, or <1 mL/kg/hr in infants & <0.5 mL/kg/hr in children .
- **GFR** is measured most accurately by the infusion of a substance that is freely filtered by the glomerulus but is not metabolized, reabsorbed, or secreted in or by the tubules.

$$\text{GFR (mL/min/1.73 m}^2) = k \times \text{L (cm)}/P_{Cr}\text{ (mg/dL)}$$

K: 0.33 preterm , 0.45 full-term, 0.55 children & adolescent girls, 0.7 in adolescent boys.

- increases rapidly during the first 2 years of life and achieves adult values (110 to 125 mL/min/1.73 $m^2$) by this age.
- GFR and body size increase proportionately, and GFR/1.73 $m^2$ remains stable.
- **Serum creatinine** reflects muscle mass and increases with age. excreted by the kidneys and is used as a marker of GFR.
- **BUN** estimate renal function(affected by states of hydration and nutrition).
- The **leukocyte esterase test** detects the presence of white blood cells.
- **nitrate test** may detect bacteriuria if the bacterium reduces nitrate to nitrite. This reduction requires a relatively long contact time.
  - A. False-negative : frequent voiding & low bacterial count
  - B. false-positive test:.Gross hematuria or prolonged contact (uncircumcised boys)
- ratio of urine protein to creatine concentrations ( spot urine): (mg/mg) :
  1. <0.5 in <2 years old & <0.2 in older children = normal.
  2. >2 suggest nephrotic range proteinuria.

NOTE:
dipstick with results of negative, trace, 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), and 4+ (>2000 mg/dl)..

# ACUTE RENAL FAILURE

- ARF is defined as an abrupt and significant decrease in GFR or in tubular function.
- Urine output may be low, normal, or high.
- ARF often is subdivided into two forms:
  3. **oliguric renal failure** (<1 mL/kg/hr in neonates and infants, <0.5 mL/kg/hr in others)
  4. **nonoliguric renal failure**: urine output is maintained in the nonoliguric variant, complicated by fluid and electrolyte disturbances & azotemia. Urinary osmolality is typically similar to serum osmolality in such patients.
- Causes:
  1. **prerenal** causes, characterized by renal underperfusion.
  2. **intrinsic renal** causes: vascular, immunologic, ischemic, or toxic injury to the kidney
  3. **postrenal** causes, which typically relate to urinary tract obstruction.
- If a patient has an acutely elevated serum creatinine +no period of oliguria= not prerenal .
- If a child has renal underperfusion (prerenal) or obstruction (postrenal) for an extended period, there is a high probability of intrinsic renal disease being present.
- Sepsis is a major morbid complication of ARF.

| Prerenal, Hypovolemic, Hypotension | Postrenal (Obstruction) | Intrinsic |
|---|---|---|
| Dehydration | Urethral obstruction | Acute tubular necrosis |
| Septic shock | Stricture | Nephrotoxins (drugs) |
| Heart failure | Posterior urethral valves | Acute cortical necrosis |
| Hemorrhage | Diverticulum | Glomerulonephritis |
| Burns | Ureteral obstruction | Interstitial nephritis |
| Peritonitis, ascites, cirrhosis | Calculi/crystals | Vascular |
| | Clot | Renal vein thrombosis |
| | Ureterocele | Arterial thromboemboli (umbilical artery catheter) |
| | Extrinsic tumor compressing bladder outlet | Disseminated intravascular coagulation |
| | Extrinsic urinary tract tumors | Immune-mediated (scleroderma) |
| | Neurogenic bladder | Pigmenturia |
| | Tumor lysis syndrome | Hemoglobinuria |
| | | Myoglobinuria |

- **Acute tubular necrosis** is the most common cause of ARF in children and is usually the consequence of renal underperfusion.
  - poor perfusion → hypotensive ischemia (or hypoxia) resulting → early vasoconstriction → tubular injury.
  - Toxic injury secondary to drugs, exogenous toxins (ethylene glycol, methanol), or endogenous toxins (myoglobin, hemoglobin) cause ATN .
  - Severe vascular compromise may lead to arterial or venous thrombosis with **acute cortical necrosis**.
  - Acute tubular necrosis is commonly reversible, but acute cortical necrosis represents tissue death(permanent loss of renal function).

## CLINICAL MANIFESTATIONS

- Precipitating illness associated with vomiting and diarrhea and an inadequate oral intake → hypotension and oliguria → prerenal causes.
- Obstructive causes; Flank masses or a distended & absent of dehydration .
  - with 2 functioning kidneys, obstruction must be bilateral to result in ARF.
- Intrinsic renal failure associated with hypertension, cardiac enlargement, or a gallop rhythm, which would suggest volume overload.
  - Urine output characteristically is decreased.
  - Signs of systemic involvement (systemic lupus erythematosus, Henoch-Schönlein purpura, HUS).
  - Urinalysis : RBC and granular casts, with mild to moderate proteinuria.

## Laboratory Studies and Imaging

- **anemia** (dilutional or hemolytic, as in SLE, renal vein thrombosis, HUS)
- **leukopenia** (SLE)
- **thrombocytopenia** (SLE, renal vein thrombosis, HUS)
- **hyponatremia** (dilutional)
- serum C3 level may be depressed (postinfectious glomerulonephritis, SLE, or membranoproliferative glomerulonephritis)
- **antibodies :**
  1. streptococcal (poststreptococcal glomerulonephritis)
  2. nuclear (SLE),
  3. neutrophil cytoplasmic (Wegener granulomatosis, microscopic polyarteritis),
  4. glomerular basement membrane (Goodpasture disease) antigens.
- The **fractional excretion of sodium** ($FE_{Na}$) : is the percent of sodium filtered by the glomeruli that is reabsorbed by the tubules. calculated as follows:
  $[U/P\ Na \div U/P\ creatinine] \times 100$
  A. Values less than 1% : prerenal azotemia.
  B. Values that exceed 3% : tubular and intrinsic renal dysfunction.
- ratio of serum **BUN** and **creatinine**
- **Urinalysis**:
  1. hematuria, proteinuria, or casts suggests intrinsic ARF.
  2. WBC and WBC casts + low-grade hematuria & proteinuria→ tubulointerstitial disease.
- **Hyperkalemia** :in ARF as a result of increased catabolism & absence of K excretion.
- **Acidosis** is due to catabolism and the impaired secretion of hydrogen ions.
- **Hypocalcemia** & **hyperphosphatemia** in ARF.
- Ultrasound imaging: increased echogenicity in children with ATN, loss of cortico-medullary differentiation when cortical necrosis, Enlarged kidneys when nephritis.
- Radiologic studies (ultrasound, VCUG, CT, nuclear imaging) are often helpful to determine the cause of obstruction if it is the suspected cause of renal failure.
- **Renal biopsy**, performed percutaneously, may be indicated if:
  1. the presentation is atypical
  2. assess the severity of systemic disease involvement (systemic lupus erythematosus)
  3. guide therapy
  4. establish a prognosis

| | PRERENAL ARF | INTRINSIC ARF |
|---|---|---|
| SPECIFIC GRAVITY | elevated (>1.020) | High(<1.010) |
| URINE OSMOLALITY | Elevated(>500 mOsm/kg) | Low(<350 mOsm/kg) |
| URINE SODIUM | Low(<20 mEq/L) | High(>40 mEq/L) |
| AND FRACTIONAL EXCRETION OF SODIUM | 1% (<2.5% in neonates) | > 2% (>10% in neonates) |

| | HYPOVOLEMIA | ACUTE TUBULAR NECROSIS | ACUTE INTERSTITIAL NEPHRITIS | GN | OBSTRUCTION |
|---|---|---|---|---|---|
| SEDIMENT | Bland | Broad, brownish granular casts | WBC, eosinophils, cellular casts | RBC, red blood cell casts | Bland or bloody |
| PROTEIN | None or low | None or low | Minimal / increased with NSAIDs | Increased, >100 mg/dL | Low |
| URINE SODIUM, MEQ/L* | <20 | >30 | >30 | <20 | <20 (acute)<br>>40 (few days) |
| URINE OSMOLALITY, MOSM/KG | >400 | <350 | <350 | >400 | <350 |
| $FE_{Na}$ %† | <1 | >1 | Varies | <1 | <1 (acute)<br>>1 (few days) |

## TREATMENT

- Fluid balance:
  - weight (at least every 12 hours in severely ill children)
  - If hypovolemia : IV administration of physiologic saline (0.9% sodium chloride) 20mL/kg over 30 to 60 minutes.
  - If hypervolemia, 2 mg/kg of furosemide, or an equal dose of other loop diuretics.
  - Severe fluid overload +marked oliguria or anuria = one indication for **dialysis**.
  - Urine output and serum and urine electrolytes levels should be determined frequently during the acute phase.
- Potassium:
  - The major risk of hyperkalemia is arrhythmia.
  - earliest electrocardiographic change seen in patients with developing hyperkalemia is the appearance of peaked T waves.
  - followed by widening of the QRS intervals, ST segment depression, ventricular arrhythmias, and cardiac arrest.
  - Procedures to deplete body potassium stores ():
    1. Exogenous sources of potassium (dietary, intravenous fluids, total parenteral nutrition) should be eliminated.
    2. Kayexalate, 1 g/kg, PO or by retention enema. exchanges sodium for potassium, several hours to take effect. single dose ↓ K by 1 mEq/LM ,repeated q 2 hr.
  - severe elevations in serum potassium (>7 mEq/L) require emergency measures in addition to Kayexalate. agents should be administered:

1. Calcium gluconate 10% solution, 1.0 mL/kg IV, over 3-5 min - counteracts the K-induced increase in myocardial irritability but does not lower K level.
2. Na bicarbonate, 1-2 mEq/kg IV, over 5-10 min - shift K extracellular - intracellular
3. Regular insulin, 0.1 U/kg, with glucose 50% solution, 1 mL/kg, over 1 hr - shift K extracellular – intracellular.

- Acidosis:
  - common in ARF because of retention of hydrogen ions, phosphate, and sulfate
  - requires treatment If acidosis is severe (arterial pH <7.15; serum bicarbonate <8 mEq/L) or contributes to hyperkalemia.
  - sodium Bicarbonate counteracts, but ↑risk of fluid overload, hypernatremia, tetany and hypertension.
- hypocalcemia and hyperphosphatemia:
  - primarily involves efforts to lower the serum phosphorus level.
  - Dietary phosphorus restriction & administration of phosphate binders, calcium acetate, and calcium carbonate are the first therapeutic steps.
  - Symptomatic hypocalcemia → parenteral calcium/ given cautiously because it may precipitate in the body with circulating phosphorus.
- **dialysis** :
  - Indications for dialysis in ARF include the following:
    1. Volume overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy
    2. Persistent hyperkalemia
    3. Severe metabolic acidosis unresponsive to medical management
    4. Neurologic symptoms (altered mental status, seizures)
    5. Blood urea nitrogen greater than 100-150 mg/dL (or lower if rapidly rising)
    6. Calcium/phosphorus imbalance, with hypocalcemic tetany
- Potential renal replacement therapies in children for ARF include peritoneal dialysis, hemodialysis, and the variations of continuous renal replacement therapy, such as continuous hemofiltration and hemodialysis or continuous venovenous hemodiafiltration.

# CHRONIC KIDNEY DISEASE

- defined as either renal injury (proteinuria) and/or a glomerular filtration rate <60 mL/min/1.73 $m^2$ for >3 mo.
- **Standardized Terminology for Stages of Chronic Kidney Disease**

| STAGE | DESCRIPTION | GFR (ML/MIN/1.73 M²) |
|---|---|---|
| STAGE 1 | Kidney damage with normal or increased GFR | >90 |
| STAGE 2 | Kidney damage with mild decrease in GFR | 60-89 |
| STAGE 3 | Moderate decrease in GFR | 30-59 |
| STAGE 4 | Severe decrease in GFR | 5-29 |
| STAGE 5 | Kidney failure | <15 or on dialysis |

- (ESRD) defining all patients treated with dialysis or kidney transplantation. subset of the patients with Stage 5 CKD.
- The etiologies of chronic renal disease in childhood relate to the age of the child at the time the kidney disease occurs.
  - ♥ younger than 5 yr is most commonly a result of :
    1. congenital abnormalities such as renal hypoplasia, dysplasia
    2. obstructive uropathy
    3. congenital nephrotic syndrome
    4. prune belly syndrome
    5. cortical necrosis
    6. focal segmental glomerulosclerosis
    7. polycystic kidney disease
    8. renal vein thrombosis
    9. hemolytic uremic syndrome.
  - ♥ After age 10, acquired diseases, such as :
    1. acquired diseases (various forms of glomerulonephritis including lupus nephritis)
    2. inherited disorders (familial juvenile nephronophthisis, polycystic kidney disease & Alport syndrome)
    3. metabolic disorders (cystinosis, hyperoxaluria)
- Children often present during late puberty as pubertal growth spurt increases demand on the damaged kidneys.

## CLINICAL MANIFESTATIONS:

- **Growth failure** is prominent. The factors include :
  1. undernutrition
  2. osteodystrophy
  3. hormonal abnormalities
  4. medications (steroids)
  5. acidosis.
- Increased calorie intake leads to a slight increase in growth in some children.
- progressive anemia :
  1. failure of the kidney to produce adequate **erythropoietin** in response to anemia
  2. impaired response to erythropoietin because of the uremia
- **Renal osteodystrophy** is common, associated with:
  1. hyperphosphatemia
  2. high serum alkaline phosphatase levels
  3. secondary hyperparathyroidism
  4. low levels of 1,25-dihydroxyvitamin D

## GROWTH

- Children with CKD have an apparent growth hormone (GH)-resistant state with elevated GH levels but decreased insulin-like growth factor 1 levels and major abnormalities of insulin-like growth factor-binding proteins.
- Children with CKD who remain less than -2 SD for height despite optimal medical support (adequate caloric intake and effective treatment of renal osteodystrophy, anemia, and metabolic acidosis) may benefit from treatment with pharmacologic doses of recombinant human GH (rHuGH).

- rHuGH continues until the patient
1. reaches the 50th percentile for midparental height
2. achieves a final adult height
3. Undergoes renal transplantation.

## RENAL OSTEODYSTROPHY

- spectrum of bone disorders seen in patients with CKD.
- The most common condition seen in children is high-turnover bone disease caused by secondary hyperparathyroidism→ pathologic finding: osteitis fibrosa cystica.
- GFR declines 50% of normal→ decline in renal 1α-hydroxylase activity+ decreased production of activated vitamin D (1,25-dihydroxycholecalciferol→ decreased intestinal calcium absorption→ hypocalcemia→ increased parathyroid hormone (PTH) → increase in bone resorption.
- Later,when the GFR declines to 20-25% of normal, compensatory mechanisms to enhance phosphate excretion become inadequate→ hyperphosphatemia, → further hypocalcemia → increased PTH secretion.
- **Clinical manifestations:**
  1. muscle weakness, bone pain, and fractures with minor trauma.
  2. rachitic changes, varus and valgus deformities of the long bones, and slipped capital femoral epiphyses
- **lab** : Hypocalcemia & hyper-phosphatemia, ↑alkaline phosphatase, and a normal PTH
- Radiographs of the hands, wrists, and knees show subperiosteal resorption of bone with widening of the metaphyses.
- **Treatment**:
  1. low phosphorus diet, and infants should be provided with a low-phosphorus formula such as Similac PM 60/40.
  2. phosphate binders: calcium carbonate and calcium acetate, non-calcium-based binders.
  3. aluminum may be absorbed from the gastrointestinal tract and can lead to aluminum toxicity, aluminum-based binders should be avoided.
  4. The cornerstone of therapy for renal osteodystrophy is vitamin D administration. indicated in patients with
     A. 25-hydroxy-vitamin D levels below the established goal range for his or her particular stage of CKD →treated with ergocalciferol.
     B. PTH levels above the established goal range for CKD stage→ calcitriol

## LAB RESULTS:

- hyperkalemia & hyponatremia (if volume overloaded)
- Acidosis
- Hypocalcemia & hyper-phosphatemia
- elevation in uric acid
- heavy proteinuria→hypoalbuminemia
- normochromic, normocytic anemia
- Serum cholesterol and triglyceride levels are elevated
- CKD from congenital lesions such as renal dysplasia, the urinalysis usually has a low specific gravity and minimal abnormalities.

## TREATMENT

- Recombinant-produced growth hormone is useful in children with chronic renal failure on or off dialysis.
- The initial therapy for **renal osteodystrophy** is to restrict phosphate in the diet.
- When the serum phosphorus is under control, therapy with either 1-hydroxylated vitamin D or its analogues is indicated.
- HTN with volume overload → salt-restricted diet (2-3 g/24 hr) and +Thiazide diuretics as initial diuretic class of choice for mild renal dysfunction (CKD stages 1-3)/GFR falls into stage 4 CKD loop diuretics (furosemide )become the diuretic class of choice.
- **Angiotensin-converting enzyme (ACE) inhibitors** (enalapril, lisinopril) and angiotensin II blockers (losar-tan) are the antihypertensive medications of choice in all children with

proteinuric renal disease because of their potential ability to slow the progression to ESRD.

- Recombinant-produced erythropoietin has resolved much of the anemia formerly seen in chronic renal failure.
- The optimal treatment of ESRD is **renal transplantation**.
- 93% of transplants of any type (living or deceased donor) are functioning 1 year post-transplant; 50% are still functioning 19 years later.

# NEPHROTIC SYNDROME AND PROTEINURIA

## ETIOLOGY AND EPIDEMIOLOGY

- Proteins and albumin are filtered by the glomerulus.
- The high concentration of albumin in blood results in albumin in the ultrafiltrate.
- Most albumin is reabsorbed and catalyzed in the proximal tubule.
- A small amount of protein is found in the urine of healthy children (<4 mg/m$^2$/hr).
- **Nephrotic proteinuria** in children is defined as protein > 40 mg/m$^2$/hr .
- Proteinuria between these two levels is abnormal, but not consistent with nephrotic syndrome

4 MG/M²/HR (150 MG/24 HR) ---------- 40 MG/M²/HR

NORMAL ABNORMAL NEPHROTIC PROTEINURIA

- **Glomerular proteinuria** is classified by its degree.
  1. **Intermittent (mild) proteinuria** (<0.5 g/m$^2$/day) : pyelonephritis, renal cystic diseases, obstructive uropathies, mild glomerulonephritis.
  2. **Moderate proteinuria** (0.5 to 1 g/m$^2$/day) : acute post-streptococcal glomerulonephritis, mild Henoch-Schönlein nephritis, severe pyelonephritis, chronic glomerulonephritis, and hemolytic uremic syndrome (HUS).
  3. **Severe proteinuria** (>1 g/m$^2$/day) characteristically with nephrotic syndrome.
- Several mechanisms result in proteinuria:
  1. Impaired reabsorption of proteins by proximal tubule,ex: **Fanconi syndrome**
  2. Drug or heavy metal exposure
  3. Factors that increase glomerular permeability
  4. physical damage
  5. abnormal hemodynamics
  6. hormone-mediated changes

NOTE:
Membranoprolifrative GN:
A. TYPE I: Low C1, C4, C3-C9
B. TYPE II: Normal C1, C4, low C3-C9.

## NEPHROTIC SYNDROME

- characterized by:
  - heavy **proteinuria** (mainly albuminuria) (>1 g/m$^2$/24 hr),
  - **hypoproteinemia** (serum albumin <2.5 g/dL),
  - **hypercholesterolemia** (>250 mg/dL),
  - **edema**.
- Genatics role: Certain HLA types (HLA-DR7, HLA-B8, and HLA-B12) ↑incidence of nephrotic S.
- The primary disorder is an increase in glomerular permeability to proteins.
- Massive proteinuria →↓ serum proteins( albumin) →↓ Plasma oncotic pressure → shift of fluid from the vascular to the interstitial compartment → contraction in plasma volume→ activation of the renin-angiotensin-aldosterone system→ increase in tubular NaCl reabsorption→more Edema.
- Renal blood flow and GFR are not ↓
- Hypoproteinemia→ stimulates hepatic lipoprotein synthesis / diminished lipid metabolism→ ↑serum lipids (cholesterol and triglycerides) + lipoprotein
- The majority of affected children will have steroid-sensitive minimal change disease.
- nephrotic syndrome forms:
  1. **idiopathic nephrotic syndrome (90%)** Causes of include:
     a. minimal change disease (85%)
     b. focal segmental glomerulosclerosis (10%)
     c. mesangial proliferation (5%)

2. **secondary nephrotic syndrome(10%)** such as membranous nephropathy or membranoproliferative glomerulonephritis
3. **genetic disorder:** congenital nephrotic syndrome, Denys-Drash syndrome**,** FSGS**,** Charcot-Marie-Tooth disease**,** Alport syndrome**,** Sickle cell disease**.**

## IDIOPATHIC NEPHRITIC SYNDROME:

- C3 and C4 levels are normal.

### MINIMAL CHANGE NEPHROTIC SYNDROME (MCNS)

- 85% of total cases of nephrotic syndrome in children
- Males 2 : 1 ratio.
- Most children < 7 years old with nephrotic syndrome have MCNS.
- 7 to 16 years old with nephrotic syndrome → 50% chance of having MCNS.
- the glomeruli appear normal or show a minimal increase in mesangial cells and matrix.
- immunofluorescence microscopy is typically negative
- electron microscopy: effacement of the epithelial cell foot processes.
- A diagnosis other than MCNS should be considered if:
  1. presence of age <1 yr
  2. family history
  3. extrarenal findings (arthritis, rash, anemia)
  4. hypertension or pulmonary edema
  5. acute or chronic renal insufficiency
  6. hematuria.
- More than 95% respond to corticosteroid therapy.

### FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

- 10% of total cases.
- glomeruli show mesangial proliferation and segmental scarring on light microscopy
- Immunofluorescence microscopy:IgM and C3 staining in areas of segmental sclerosis.
- Electron microscopy : segmental scarring of the glomerular tuft with obliteration of the glomerular capillary lumen.
- A similar lesion may be seen with HIV infection, vesicoureteral reflux, and intravenous heroin abuse.
- FSGS may progress from MCNS or present as a separate entity.
- Only 20% of patients with FSGS respond to prednisone.
- The disease is frequently progressive→end-stage renal disease in most patients.
- May cause hematuria.

### MESANGIAL PROLIFERATION

- (5% of total cases)
- characterized by a diffuse increase in mesangial cells and matrix on light microscopy.
- Immunofluorescence microscopy : trace mesangial IgM and/or IgA staining.
- Electron microscopy :↑ mesangial cells & matrix + effacement of epithelial foot processes.
- 50% respond to corticosteroid therapy.

## SECONDARY NEPHROTIC SYNDROME

- Secondary nephrotic syndrome should be suspected in patients:
  1. age >8 yr
  2. hypertension
  3. hematuria
  4. renal dysfunction
  5. extrarenal symptomatology (rash, arthralgias, fever)
  6. depressed serum complement levels.
- Causes:
  1. Membranous nephropathy
  2. membranoproliferative glomerulonephritis
  3. postinfectious glomerulonephritis
  4. lupus nephritis
  5. Henoch-Schönlein purpura nephritis

6. infectious agents : .malaria and schistosomiasis, hepatitis B + C virus, leprosy, HIV

- Hodgkin lymphoma, the renal pathology most often resembles MCNS.
- carcinomas of the lung and gastrointestinal tract, the renal pathology resembles membranous glomerulopathy.
- glomerulopathy (penicillamine, captopril, gold, NSAID, mercury compounds)

## MEMBRANOUS NEPHROPATHY

- is infrequent in childhood. 1% of children with nephrotic syndrome .
- It is seen most commonly in adolescents and children with systemic infections, such as hepatitis B, syphilis, malaria, and toxoplasmosis, or receiving drug therapy (gold salts, penicillamine)
- Hematuria is common.

## CONGENITAL NEPHROTIC SYNDROME

- nephrotic syndrome within the first 3 mo of life
- **Finnish-type congenital nephrotic syndrome** The most common cause of syndrome.
  - autosomal recessive disorder
  - most common in populations of Scandinavian descent
  - The major pathologic features are dilatation of the proximal tubules, mesangial hypercellularity, and glomerular sclerosis.
  - antenatal diagnosis :elevated amniotic fluid α-fetoprotein level → diagnosis confirmed by DNA analysis.
  - Infants present with massive proteinuria (detectable in utero by increased α-fetoprotein), a large placenta, and marked edema.
  - prematurity, respiratory distress, and separation of the cranial sutures.
  - The natural history of the disease is one of persistent edema, recurrent infections, and progressive renal failure with death by the age of 5 yr.
  - Corticosteroids and immunosuppressive agents are of no value.
- congenital nephrotic syndrome include congenital infections such as syphilis, toxoplasmosis, rubella, and cytomegalovirus also HIV and hepatitis B.
- **Diffuse mesangial sclerosis** :
  - rare glomerular disease
  - The characteristic pathologic finding is progressive sclerosis of the glomerular mesangium→ end-stage renal disease developing within months to years.
  - Diffuse mesangial sclerosis occours:
    1. isolated disease
    2. part of **Denys-Drash syndrome,** a condition characterized by Wilms tumor and male pseudohermaphroditism, caused by a mutation in the Wilms tumor gene *(WT1)* on chromosome 11.

## CLINICAL MANIFESTATIONS

- the most common presentation: sudden onset of dependent pitting edema with weight gain or ascites.
- Abdominal pain and malaise, especially with significant ascites.
- Blood pressure is usually normal
- Diarrhea (intestinal edema)
- respiratory distress (pulmonary edema or pleural effusion)

## DIAGNOSTIC STUDIES

- Proteinuria of 1+ or greater on two to three random urine specimens suggests a degree of proteinuria
- urine protein-to-creatinine ratio>0.5 ( normal ratio < 0.2) measured on the first morning specimen.
- Most serum lipids (including cholesterol and triglycerides) + levels of lipoprotein =↑
- low level C3 is the most sensitive and specific test → lesion not minimal change disease.
- Microscopic hematuria (20% of cases), but does not predict response to steroids.

## DIFFERENTIAL DIAGNOSIS

- **Transient proteinuria** : mild proteinuria after vigorous **exercise** , **febrile** or **dehydrated** children. **(protein-to-creatinine ratio <1)** and does not indicate renal disease.
- **Postural (orthostatic) proteinuria** : benign condition defined by moderate proteinuria when upright. normal protein excretion while recumbent.
- If proteinuria is persistent, renal disease should be considered.

## TREATMENT

- more than 80% of children 1 to 7 years old with typical MCNS respond to corticosteroids
- Specific therapy for MCNS is prednisone, 2 mg/kg/day divided into 2-4 doses per day.
- 92% of children who respond to steroids do so within 4 weeks.
- The optimal duration of steroid therapy for responders is 12 weeks.
- If not respond to daily prednisone therapy→ renal biopsy is indicated because steroid resistance greatly increases the chance for something other than MCNS.
- Frequent relapses or steroid resistance in MCNS → immuno-suppressive therapy.
- More than 80% of patients with FSGS do not respond to corticosteroid therapy.
- aggressive medical therapy of familial congenital nephrotic syndrome, with early nephrectomy, dialysis, and subsequent transplantation, is the only effective approach to this syndrome.
- Edema is treated with restriction of salt intake & use of diuretic therapy.
- if ineffective in alleviating severe edema:
    1. 25% albumin (0.5 g/kg intravenously over 1 to 2 hours)
    2. IV loop diuretic (furosemide) during or after albumin results in diuresis.
- Acute hypertension is treated with β-blockers or calcium channel blockers.
- Persistent hypertension is often responsive to angiotensin-converting enzyme inhibitors.

## COMPLICATIONS

- Infection is a major complication in children with the nephrotic syndrome of any type.
- **Bacteremia** and **peritonitis** , particularly *Streptococcus pneumoniae* or *Escherichia coli*.
- Hypovolemia result of diarrhea or use of diuretics.
- The loss of proteins → hypercoagulable state with a risk of thromboembolism. (Warfarin & low-dose aspirin minimize the risk of clots)

## PROGNOSIS

- Most children with nephrotic syndrome eventually go into remission.
- **80%** of MCNS experience a relapse of the proteinuria at some point (as heavy proteinuria that persists for 3 to 5 days).
- Transient (1 to 2 days) proteinuria in children with MCNS with an intercurrent infection, not a relapse.
- Steroid therapy is rapidly effective for a true relapse.
- Patients with FSGS may be initially responsive to steroids, but become late nonresponders.
- **Many** children with FSGS progress to end-stage kidney failure.
- Recurrence of FSGS occurs in **30%** of children who undergo renal transplantation.

# HEMOLYTIC UREMIC SYNDROME

## ETIOLOGY AND EPIDEMIOLOGY

- HUS is characterized by :
    1. **microangiopathic hemolytic anemia**
    2. **renal cortical injury**
    3. **thrombocytopenia**.
- Occurs between 6 months and 4 years.
- 80%: Shiga-like toxin from *E. coli* O157:H7 implicated as a major etiology, which causes the classic prodrome of hemorrhagic enterocolitis
- After ingestion of undercooked hamburger at fast food restaurants.
- HUS presenting without a prodrome of diarrhea

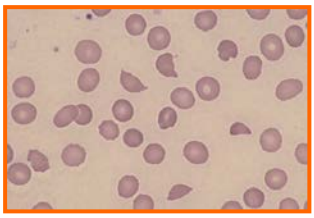
- May have a genetic component (often autosomal recessive).

## CLINICAL MANIFESTATIONS

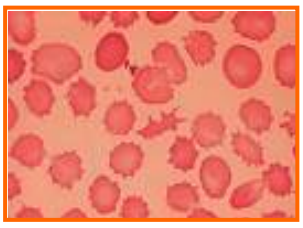
- Sudden onset of pallor, irritability, weakness, lethargy, and oliguria usually occurs 5-10 days after the initial gastrointestinal or respiratory illness.
- Preceded by a gastroenteritis characterized by fever, vomiting, abdominal pain, and diarrhea that is initially watery but then becomes bloody.
- Less commonly, patients may present after an upper respiratory tract infection.
- Physical examination reveals:
  1. irritability
  2. pallor
  3. petechiae
  4. edema
  5. hepatosplenomegaly
  6. varies hydration state (n↑↓)
  7. Hypertension
- microangiopathic hemolytic anemia, thrombocytopenia, and ARF.
- Seizures ( CNS involvement) in 20% of cases.
- **D/D: thrombotic thrombocytopenic purpura**( Seizures, hemolytic anemia, thrombocytopenia ) -*young adult women as a relapsing illness with fever.*

## LABORATORY STUDIES

- thrombocytopenia :90%
- Peripheral blood smear reveals **signs of intravascular hemolysis**: schistocytes, helmet burr cells, and fragmented erythrocytes cells
- The hemoglobin value is commonly in the 5-9 g/dL range.
- disseminated intravascular coagulation( DIC) is rarely present.
- The reticulocyte count ↓
- plasma haptoglobin levels ↓.
- Coombs test is negative.
- Leukocytosis
- urinalysis : microscopic hematuria, proteinuria, and casts.
- Stool specimens can be cultured, and strains can be serotyped.



FRAGMENTED ERYTHROCYTES



BURR CELLS

## TREATMENT AND PROGNOSIS

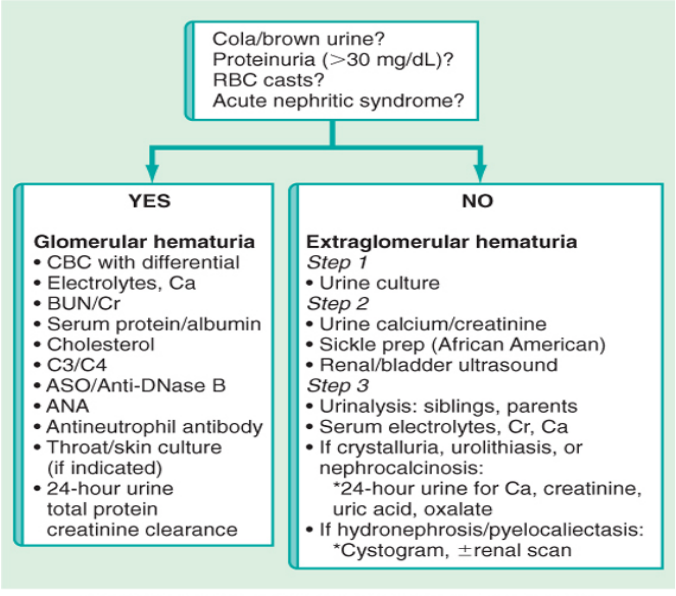
- Therapy is supportive with:
  1. dialysis control of hypertension
  2. transfusion of blood products
- Antibiotics for the prodromal diarrhea state → increased risk of HUS.
- Antidiarrheal agents prolong exposure → avoid.
- 90% survive the acute phase
- > 50% recover normal renal function.
- Familial cases, HUS without diarrhea, and sporadic HUS have poorer outcomes than Toxin-induced disease.

# GLOMERULONEPHRITIS AND HEMATURIA

- Hematuria : the presence of at least 5 red blood cells (RBCs) per microliter of urine
- **Gross hematuria:** Bright red blood, clots in urine, or tea-colored urine.
- Dipstick test for hematuria:
  1. False-negative : presence of formalin (urine preservative) or high urinary concentrations of ascorbic acid.
  2. False-positive : child with fever or after exercise , in the presence of menstrual blood , alkaline urine with a pH >9 or contamination with oxidizing agents .
- Red urine **without** RBCs **:**
  1. **Hemoglobinuria** : acute intravascular hemolysis, DIC, or any cause of hemolysis .
  2. **Myoglobinuria** : rhabdomyolysis secondary to crush injury, burns, myositis, asphyxia, , severe electrolyte abnormalities (hypernatremia, hypophosphatemia), hypotension, DIC, toxins (drugs, venom), and prolonged seizures..
     - Myoglobin reacts with the "blood-determining" portion of the dipstick and causes a positive result.
- **level of hematuria (upper vs lower urinary tract):**

| | UPPER URINARY TRACT | LOWER URINARY TRACT |
|---|---|---|
| SOURCE | Nephron = glomerulus+ tubules+interstitium | pelvocalyceal system+ ureter+ bladder+ urethra |
| URINE GROSSLY | brown, cola-colored urine | brown, cola-colored urine, terminal hematuria (onset of gross hematuria at the end of the urine stream), blood clots |
| PROTEINURIA | >100 mg/dL on dipstick | <100 mg/dL on dipstick |
| URINARY MICROSCOPIC | RBC casts | leukocyte or renal tubular epithelial cell casts |
| URINARY RBCS | deformed (acanthocytes). | normal urinary RBC morphology |

- Glomerular injury may be the result of:
  1. **immunologic injury** [PSAGN],
  2. **inherited disease** (Alport syndrome)
  3. **vascular injury** (acute tubular or cortical necrosis).
- **nephritic syndrome**=Tea or cola-colored urine+facial/body edema+ HTN +oliguria
  1. postinfectious glomerulonephritis
  2. IgA nephropathy
  3. membranoproliferative glomerulonephritis
  4. Henoch-Schönlein purpura (HSP) nephritis
  5. systemic lupus erythematosus (SLE)
  6. Wegener granulomatosis
  7. microscopic polyarteritis nodosa
  8. Goodpasture syndrome,
  9. hemolytic-uremic syndrome
- A history of:
  1. Recent URT, skin or GI infection →acute GN, HUS or HSP nephritis.
  2. Rash + joint complaints → HSP or SLE.
  3. Frequency dysuria& unexplained fever→UTI
  4. Renal colic →nephrolithiasis.
  5. Flank mass→ hydronephrosis, cystic disease, renal vein thrombosis, or tumor.
  6. Headache, visual changes, epistaxis, or heart failure → significant hypertension.
- Blood without casts is also seen with the hematuria associated with:
  1. **sickle cell trait** or **disease**
  2. after strenuous **exercise** (in some children)
  3. renal **trauma**.



- Anemia in this setting may be caused by
  1. intravascular dilution secondary to hypervolemia associated with acute renal failure
  2. decreased RBC production in chronic renal failure
  3. hemolysis from hemolytic-uremic syndrome or SLE
  4. blood loss from pulmonary hemorrhage as seen in Goodpasture syndrome or melena in patients with Henoch-Schönlein purpura or hemolytic-uremic syndrome.
- peripheral blood smear → microan-giopathic process consistent with:
  1. HUS
  2. renal vein thrombosis
  3. vasculitis
  4. SLE.
- Thrombocytopenia :
  1. decreased platelet production (malignancies)
  2. increased platelet consumption (SLE, ITP, HUS, renal vein thrombosis).
- the most common imaging modalities used in the evaluation of hematuria:
  1. **Ultrasound, CT**
  2. **IV pyelography**
- Asymptomatic patients with isolated microscopic hematuria should not undergo diagnostic evaluation until at least 2 additional urine specimens collected over a 1- to 2-wk period demonstrate an abnormal number of RBCs.

## CAUSES OF GROSS HEMATURIA:

1. PSAGN:
   - classic example of the **acute nephritic syndrome** characterized by the sudden onset of gross hematuria, edema, hypertension, and renal insufficiency.
   - Manifestations develop 5 to 21 days (10 days on average) after "nephritogenic" strains of group A β-hemolytic streptococci infection (pharyngitis or impetigo).
   - bacteria → immunologic reaction → activation of complement→ proliferative glomerulonephritis.
   - the most common form of proliferative glomerulonephritis ( Immune-mediated inflammation) .
   - in children 5 - 12 years old. uncommon before the age of 3 yr.
   - Boys >girls.
   - epidemic outbreaks: Crowded conditions, poor hygiene, malnutrition, and intestinal parasites .
   - associated with :
   1. edema (75% of cases)
   2. hematuria (gross in 65% of cases)/ occasionally microscopic.
   3. Hypertension (50% of cases).
   - The most common clinical presentations: Edema & cola-colored urine.
   - **nephrotic syndrome may develop in 10-20% of cases**
   - Laboratory studies in **PSAGN**:
     1. hematuria,
     2. mild to moderate proteinuria
     3. concentrated urine
     4. casts, particularly granular and RBC casts.
     5. The BUN and serum creatinine may be transiently elevated .
     6. ↑ASO titers (70%):titers of antistreptococcal antibodies in the serum.
     7. Positive streptozyme (95%)
     8. ↓C3-C9; normal C1, C4, (returns to normal by 6 to 8 weeks,If persisting beyond 8 weeks → membra-noproliferative glomerulonephritis)
     9. Serum IgG and IgM are usually elevated
   - Acute renal failure →oliguria & hypertension → encephalopathy(10%) & heart failure.
   - Treating the streptococcal infection does not prevent PSAGN.
   - Specific therapy for PSAGN involves :
     1. dietary sodium restriction
     2. diuretics
     3. antihypertensive agents

NOTE:
**Most common glomerular cause of gross hematuria in children:**
1ST: IgA nephropathy
2ND: PSAGN

4. 10-day systemic antibiotic therapy with penicillin is recommended to limit the spread of the nephritogenic organisms/ does not affect the natural history of GN.

- Proteinuria and edema characteristically decline rapidly (in 5 to 10 days) along with the gross hematuria and renal insufficiency.
- benign disease > 95% of children recover completely→ The acute phase resolves within 6-8 wk/ hypertension usually normalize by 4-6 wk after onset, /persistent microscopic hematuria may persist for 1-2 yr after the initial presentation.
- Few children progress to ESRD.

2. UTI : most common identifiable diagnosis in a child with gross hematuria.
3. **Coagulopathies**
4. **Hypercalciuria**
   - important cause of isolated hematuria in children
   - 25% to 30% of children with isolated hematuria have elevated urinary calcium excretion.
5. UROLITHIASIS
   - cause of painful hematuria.
   - rare in children→ often secondary to metabolic predisposition or areas of urine stasis
6. STRUCTURAL ABNORMALITIES
7. MALIGNANT TUMORS: Wilms tumor, rhabdomyosarcoma in the bladder or prostate
8. SLE NEPHRITIS
9. HENOCH-SCHÖNLEIN PURPURA NEPHRITIS
10. OBSTRUCTION
11. CYSTIC DISEASE
12. TRAUMA

## CAUSES OF MICROSCOPIC HEMATURIA:

1. IGA NEPHROPATHY((BERGER DISEASE))
   - the most common chronic glomerular disease worldwide.
   - It is characterized by a predominance of IgA within mesangial deposits of the glomerulus in the absence of systemic diseases as SLE & HSP.
   - after an URTI (1 to 2 days)→ microscopic hematuria (50%), recurrent gross hematuria , proteinuria , nephritic syndrome, nephrotic syndrome (rare), nephritic-nephrotic syndrome.
   - associated with recurrent bouts of hematuria after or during respiratory infections.
   - boys > girls
   - age: teens and 20s.
   - IgA nephropathy is associated with:
     1. normal complement levels/not like PSAGN.
     2. IgA levels↑ in < 20%( no diagnostic value).
     3. Urinalysis : microscopic hematuria or proteinuria or both.
     4. Macroscopic hematuria is seen most often with concurrent infections.
   - prognosis is good in children
   - Progressive disease &ESRD = 20-30% 15-20 yr after disease onset
   - poor prognostic factor in children and adults:
     1. Persistent or heavy proteinuria.
     2. Persistent hypertension,
     3. severe glomerular lesions on biopsy specimens
     4. reduced GFR at presentation (in adults)
   - Therapy for children with IgA nephropathy is uncertain.
   - Adults have been treated with angiotensin-converting enzyme inhibitors & high-dose IV methyl-prednisolone (delay the development of renal failure).
   - Recurrence of IgA deposits in transplanted kidneys is often observed, but does not alter graft survival significantly
2. BENIGN FAMILIAL HEMATURIA
   - common, nonprogressive
   - usually autosomal dominant disorder.
   - accompanied by thinning of the glomerular basement membrane on electron microscopy.
   - Other family members also have hematuria.

- Need long-term follow-up to exclude the progressive forms of familial hematuria.

3. ALPORT SYNDROME
   - Hereditary nephritis. is a genetically heterogeneous disease caused by mutations in the genes coding for type IV collagen, a major component of basement membranes.
   - Approximately 85% of patients have X-linked disease
   - *All patients with AS* → asymptomatic microscopic hematuria( intermittent in girls and younger boys).
   - 50% of pts→ Single or recurrent episodes of gross hematuria after 1-2 days URTI
   - Proteinuria is seen in males but may be absent, mild, or intermittent in females.
   - Progressive proteinuria, often exceeding 1 g/24 hr, is common by the 2nd decade of life and can be severe enough to cause nephrotic syndrome.
   - **Extrarenal manifestations of AS :**
     A. **Bilateral sensorineural hearing loss**:
     1. 90% of hemizygous males with X-linked AS
     2. 10% of heterozygous females with X-linked AS
     3. 67% of individuals with autosomal recessive AS.

     B. **Ocular abnormalities,** in 30-40% with X-linked AS:
     1. anterior lenticonus *is pathognomonic* (extrusion of the central portion of the lens into the anterior chamber)
     2. macular flecks
     3. Corneal erosions.

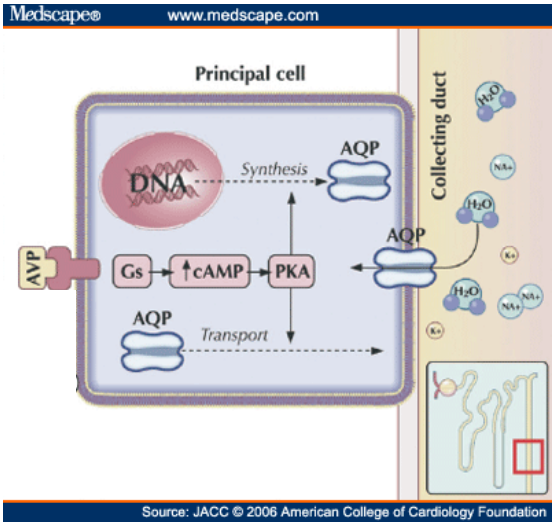
     C. **Leiomyomatosis** ( esophagus, tracheobronchial tree, and female genitals) & **platelet abnormalities** – rare.
   - ESRD : before age 30 yr in approximately 75% of hemizygotes with X-linked AS.
   - The risk of ESRD in X-linked heterozygotes is 12% by age 40 and 30% by age 60.
   - Risk factors for progression are :
     1. gross hematuria during childhood
     2. nephrotic syndrome
     3. prominent GBM thickening.
4. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)
   - clinical syndrome of rapidly progressing disease+ deterioration of kidney function.
   - Signs and symptoms of RPGN include:
     1. edema
     2. gross hematuria
     3. hypertension
     4. renal failure
   - **Renal biopsy :** epithelial proliferation typically with **crescent** formation.
   - more common in late childhood and adolescence.
   - **10-20% develop nephritic syndrome.**
   - idiopathic or seen in various conditions, including:
     1. membranoproliferative glomerulonephritis
     2. PSAGN
     3. IgA nephropathy
     4. ANCA-induced vasculitis
     5. Henoch-Schönlein purpura.
   - TTT depends on the underlying disease ( usually involves high-dose corticosteroids)
5. **Acute postinfectious glomerulonephritis** : follows other bacterial and viral infections.

# NEPHROGENIC DIABETES INSIPIDUS

- Rare disorder of water metabolism characterized by an inability to concentrate urine even in the presence of antidiuretic hormone (ADH).
- The most common pattern of inheritance is as an X-linked recessive disorder.
- Secondary (acquired)forms of NDI:
  1. obstructive uropathies
  2. acute or chronic renal failure
  3. renal cystic diseases
  4. interstitial nephritis
  5. nephrocalcinosis
  6. toxic nephropathy: hypokalemia, hypercalcemia, lithium, or amphotericin B.

## PATHOPHYSIOLOGY:

- The ability to concentrate urine (and thus absorb water) requires:
  1. intact concentrating gradient in the renal medulla
  2. Ability to modulate water permeability in the collecting tubule (by ADH (arginine vasopressin) synthesized in the hypothalamus & stored in the posterior pituitary).
- Under basal situations, the collecting tubule is impermeable to water.
- increased serum osmolarity and/or severe volume depletion → detected by osmoreceptors in the hypothalamus→ ADH released → binds to its receptor, vasopressin V2 (AVPR2) → activates cAMP-dependent cascade → movement of preformed water channels (aquaporin 2 [AQP2]) to the membrane → collecting duct became permeable to water.




- Defects in the *AVPR2* gene cause the more common X-linked form of NDI.
- Mutations in the *AQP2* gene have been identified in patients with the rarer autosomal recessive form.
- Secondary ADH resistance :
  1. owing to defective aquaporin expression (lithium intoxication).
  2. loss of the hypertonic medullary gradient due to solute diuresis or tubular damage→inability to absorb sodium or urea.

## CLINICAL MANIFESTATIONS

- **congenital NDI**:
  1. Typically present in the newborn period with massive polyuria, volume depletion, hypernatremia, and hyperthermia.
  2. Irritability and crying
  3. Constipation and poor weight gain
  4. developmental delay and mental retardation (After multiple episodes of hypernatremic dehydration)
  5. Enuresis(caused by large urine volumes).

6. poor food intake (Because of the need to consume large volumes of water every day)
7. growth abnormalities
8. behavioral problems(hyperactivity & short-term memory problems)

- **secondary form** :
  1. generally present later in life
  2. Typically with hypernatremia and polyuria
  3. developmental delay
  4. behavioral abnormalities.

  } **Less common**

## DIAGNOSIS

- Male infant + polyuria + hypernatremia+ dilute urine= DI.
- If the serum osmolality value is 290 mOsm/kg or higher with a urine osmolality value of less than 290 mOsm/kg→ water deprivation test
- administration of vasopressin (10-20 µg intranasally) followed by serial urine and serum osmolality measurements hourly for 4 hr→ D/D: **central diabetes insipidus,**
- Criteria for premature termination of a water deprivation test include a decrease in body weight of more than 3%.
- patients with congenital NDI have nonobstructive hydronephrosis of varying severity.

## TREATMENT

1. maintenance of adequate fluid intake and access to free water
2. minimizing urine output by limiting solute load with a low-osmolar-low-sodium diet
   - infants, human milk or a low solute formula, such as Similac PM 60/40, is preferred.
   - Most infants with congenital NDI require gastrostomy or naso-gastric feedings to ensure adequate fluid administration throughout the day and night.
   - Sodium intake in older patients <0.7 mEq/kg/24 hr.
3. Administering medications directed at decreasing urine output.
   - **Thiazide diuretics** (2-3 mg/kg/24 hr of hydrochlorothiazide) effectively induce sodium loss and stimulate proximal tubule reabsorption of water.
   - Potassium-sparing diuretics, amiloride (0.3 mg/kg/24 hr in 3 divided doses)
   - **indomethacin** (2 mg/kg/24 hr), For Patients who have an inadequate response to diuretics alone , has an additive effect in reducing water excretion. may cause deterioration in renal function over time.

# RENAL TUBULAR ACIDOSIS

- Disease state characterized by a normal anion gap metabolic acidosis resulting from either impaired bicarbonate reabsorption or impaired urinary acid (hydrogen ion) excretion.
- Both inherited and acquired forms exist.
- There are 3 main forms of RTA:
  1. distal (type I) RTA
  2. proximal (type II) RTA
  3. hyperkalemic (type IV) RTA.
  - type III RTA Mixed lesions (type I and II RTA), which occur in patients with inherited carbonic anhydrase deficiency.
- The RTA syndromes : characterized by a normal GFR do not progress to renal failure.

NOTE:
**Blood anion gap** = $[Na^+]$ - $[Cl^-+HCO_3^-]$
- ✓ <12 : the absence of an anion gap.
- ✓ >20 : highly suggestive of anion gap.

## DISTAL (TYPE I) RENAL TUBULAR ACIDOSIS

- Is the result of impaired distal urinary acidification (hydrogen ion secretion)
- Hereditary or secondary to a systemic disorder (e.g., obstructive uropathy, sickle cell nephropathy, toxins).
- **features**:
  1. urine pH cannot be reduced below 5.5
  2. severe non-anion gap metabolic acidosis
  3. hyperchloremia
  4. hypokalemia

5. **Hypercalciuria → nephrocalcinosis or nephrolithiasis**〓distinguishing features
6. **Hypocitraturia** (cause chronic metabolic acidosis)→ risk of Ca deposition in tubules.
7. growth failure.
8. absent of phosphate & massive bicarbonate wasting (characteristic of proximal RTA )

- Treatment is easily achieved with 1–3 mEq/kg/day $NaHCO_3$ ,a characteristic which distinguishes it from type II RTA.
- **Medullary sponge kidney**: characterized by cystic dilatation of the terminal portions of the collecting ducts.
  - ♥ US: medullary nephrocalcinosis .
  - ♥ Typically maintain normal renal function through adulthood
  - ♥ complications include hyposthenuria (inability to concentrate urine) and distal RTA.
  - ♥ Associations of medullary sponge kidney with Beckwith-Wiedemann syndrome.

## PROXIMAL (TYPE II) RENAL TUBULAR ACIDOSIS

- Impaired proximal tubule bicarbonate reabsorption.
- hereditary (Fanconi syndrome) or a secondary (tubular immaturity in premature infants).
- **Fanconi syndrome**: global proximal tubular dysfunction (low molecular weight proteinuria+ glycosuria+ phosphaturia+ aminoaciduria+ proximal RTA).
- **Lowe syndrome** *(oculocerebrorenal syndrome of Lowe)* is a rare X-linked disorder characterized by congenital cataracts, mental retardation, and Fanconi syndrome.
- **Features:**
  1. Growth failure in the 1st year of life.
  2. polyuria
  3. dehydration (due to sodium losses)
  4. anorexia, vomiting, constipation
  5. hypotonia
  6. if with primary Fanconi syndrome→ rickets.
  7. non-anion gap metabolic acidosis
  8. **The urine pH is acidic (<5.5)** because distal acidification mechanisms are intact.
  9. Fanconi syndrome demonstrates: phosphaturia, aminoaciduria, glycosuria, uricosuria, and ↑urinary sodium or potassium.

## HYPERKALEMIC (TYPE IV) RENAL TUBULAR NECROSIS

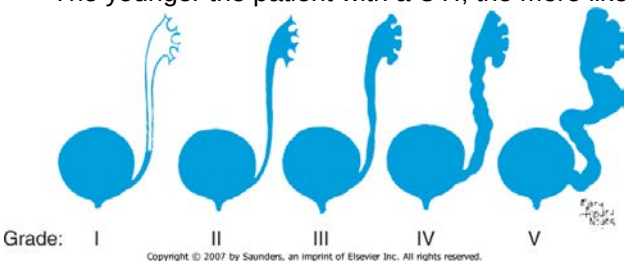
- Impaired aldosterone production (hypoaldosteronism) or impaired renal responsiveness to aldosterone ("pseudo" hypoaldosteronism).
- mineralocorticoid deficiency (e.g., adrenal failure, congenital adrenal hyperplasia [CAH], diabetes mellitus, pseudohypoaldosteronism, interstitial nephritis).
- **Features**:
  1. growth failure in the first few years of life like those with type I and II RTA.
  2. Polyuria and dehydration (from salt wasting)
  3. Life-threatening hyperkalemia rarely,(especially those with pseudo hypoaldosteronism type 1)
  4. hyperkalemic non-anion gap metabolic acidosis
  5. Urine alkaline or acidic.
  6. Elevated urine Na levels + low urine K levels→ no aldosterone effect.

## NOTES:

- D/D: diarrheal dehydration - Metabolic acidosis : acidosis improve with correction of volume depletion.
- normal or low potassium suggests type I or II.
- A urine pH <5.5 in the presence of acidosis suggests proximal RTA, whereas patients with distal RTA typically have a urine pH >6.0.
- **urine anion gap** ([urine $Na^+$+urine $K^+$] - urine $Cl^-$) is calculated to confirm the diagnosis of distal RTA( positive gap). IF negative gap = proximal tubule bicarbonate wasting.
- The mainstay of therapy in all forms of RTA is bicarbonate replacement.

# VESICOURETERAL REFLUX

- Retrograde flow of urine from the bladder to the ureter and renal pelvis
- Reflux usually is congenital, occurs in families, and affects 1% of children.
- *low-pressure* or *passive* reflux :Reflux occurring during bladder filling. less likely to show spontaneous reflux resolution .
- *high-pressure* or *active* reflux: reflux during voiding.
- result from:
  1. **congenital** incompetence of the ureterovesical junction.
  2. **familial** (30% of siblings of a child with reflux have reflux)
  3. **distal bladder obstruction**(in 50% of boys with posterior urethral valves).
  4. **neurogenic bladder** associated with myelomeningocele (25%)
  5. **Duplications of the ureters** with ureteroceles → obstruct upper collecting system.
- Reflux expose of the kidney to increased hydrodynamic pressure during voiding.
- Incomplete emptying of the ureter and bladder predisposes the patient:
  1. **UTIs** .Without complete emptying it is difficult to prevent bacterial colonization.
  2. **Reflux nephropathy** : development and progression of gross and histologic renal scarring if reflux is associated with infection or obstruction .
  3. **megacystis-megaureter syndrome:** In most severe cases→ massive reflux into the upper tracts that the bladder overdistends, primarily in males, unilateral or bilateral
- VUR characteristically is discovered during radiologic evaluation after a UTI
- The younger the patient with a UTI, the more likely reflux is present.





- Grading of vesicoureteral reflux:
  1. Grade I: reflux into a nondilated ureter.
  2. Grade II: reflux into the upper collecting system without dilatation.
  3. Grade III: reflux into dilated ureter and/or blunting of calyceal fornices.
  4. Grade IV: reflux into a grossly dilated ureter.
  5. Grade V: massive reflux, with significant ureteral dilatation and tortuosity and loss of the papillary impression.

## DIAGNOSTIC STUDIES AND IMAGING

- A **VCUG** : performed in all infants and all children < 8 years old with first UTI
- The VCUG should be performed after the infection has been treated
- renal scarring in low grade VUR is low (15%) → increases with higher grades of reflux (grade IV or V) - 65%.
- Grade I or II VUR resolve without surgical intervention
- grade IV or V < 50% resolve without surgical intervention
- **Nuclear renal scanning best identifies renal scars.**

## TREATMENT

- VUR is generally an indication for long-term prophylactic antibiotic therapy (trimetho-prim-sulfamethoxazole, sulfisoxazole, or nitrofurantoin).
- **Complications** of reflux nephropathy are hypertension and ESRD.
- **Treatment Recommendations for Vesicoureteral Reflux Diagnosed Following a Urinary Tract Infection**

| GRADE | INITIAL TREATMENT | FOLLOW-UP |
|---|---|---|
| I-II | Antibiotic prophylaxis | No consensus |
| III-IV | Antibiotic prophylaxis, except if 6-10 years old bilateral →surgery | Surgery |
| V | <5 years→ Antibiotic prophylaxis<br>1-5years With scarring or bilateral /<br>6-10 years→ surgery | Surgery |

# Congenital and Developmental Abnormalities of the Urinary Tract

## Polycystic kidney diseases

- group of genetic diseases affecting both kidneys and other tissues.
- The two major forms are autosomal recessive and autosomal dominant in transmission.
- appear in infancy or in older children.
- Renal cysts are observed in other inherited disorders, ex: von Hippel-Lindau syndrome and tuberous sclerosis.

### Autosomal recessive polycystic kidney disease

- 1 in 10,000 to 40,000 children.
- Characterized by marked enlargement of both kidneys.
- Small cysts in the cortex and medulla, which are dilated collecting ducts.
- Interstitial fibrosis and tubular atrophy may present at birth→ kidney failure.
- **Hepatic fibrosis** → portal hypertension.
- Bile duct ectasia and biliary dysgenesis.
- The diagnosis made by in utero ultrasound.
- In some, Massive renal enlargement → lethal pulmonary hypoplasia.
- Most have clinical manifestations:
  1. flank masses
  2. hepatomegaly
  3. pneumothorax
  4. proteinuria
  5. hematuria.

### Autosomal dominant polycystic kidney disease

- 1 in 1000 births
- most common inherited kidney disease.
- characteristically presents in the 30s or 40s(may in infancy or childhood).
- Infants have a clinical picture similar to that in autosomal recessive polycystic kidney disease
- older children → pattern similar to adults(large isolated cysts developing and enlarging)
- Renal pathology : glomerular and tubular cysts.
- Hepatic cysts, Pancreatic, splenic, and ovarian cysts .
- **Cerebral aneurysms** : risk of hemorrhage depends on size, blood pressure, and family history of intracranial hemorrhage.
- Therapy for polycystic renal disease is limited to:
  1. conservative measures,
  2. renal replacement therapy,
  3. kidney transplantation.

## Bilateral renal agenesis,

- result of failure of development or degeneration of the ureteric bud.
- Renal agenesis is a component of **Potter syndrome** (flat facies, clubfoot, and pulmonary hypoplasia resulting from oligohy-dramnios).
- The pulmonary hypoplasia is fatal.

## Unilateral renal agenesis :

- More common in infants of diabetic mothers and in African Americans.
- Accompanied by normal or minimally reduced renal function.
- found with VUR and other anomalies ( genital tract, ear, skeletal system, CVS)
- Unilateral renal agenesis can be a component of:
  1. **VACTERL** (vertebral abnormalities, anal atresia, cardiac abnormalities, TEF or esophageal atresia, renal agenesis and dysplasia, and limb defects)
  2. **Turner syndrome,**
  3. **Poland syndrome.**

# HYPERCALCIURIA

- Causes:
  1. distal renal tubular acidosis
  2. vitamin D intoxication
  3. hyperparathyroidism
  4. steroids
  5. immobilization
  6. excessive calcium intake
  7. loop diuretics
  8. idiopathic (associated with hematuria and renal calculi).
- Diagnosis is as follows:
  1. 24-hour urine: Calcium >4 mg/kg/24 hr.
  2. Spot urine: Determine Ca>Cr ratio.
  3. 24-hr urine calcium determination (if abnormally elevated spot urine Ca>Cr ratio )

# The endocrine system

Dr. Abd-Alsalam Abu-Libdeh

Nelson Last Minute

# PHYSIOLOGY OF PUBERTY

- In prepubertal stage the hypothalamic-pituitary-gonadal axis is suppressed as reflected by undetectable serum concentrations of luteinizing hormone (LH**),** and sex hormones (estradiol in girls, testosterone in boys).
- **GnRH** is the primary, if not the only hormone responsible for the onset & progression of puberty.
- *1-3y before the onset of clinically evident puberty*, low serum levels of LH *during sleep* become demonstrable, in *a pulsatile fashion*, reflecting endogenous episodic discharge of hypothalamic GnRH.
- Nocturnal pulses of LH continue to increase in amplitude and in frequency as clinical puberty approaches.
- This pulsatile secretion of gonadotropin is responsible for enlargement and maturation of the gonads and the secretion of sex hormones.
- *By mid-puberty LH pulses* become evident even during the daytime and occur at about 90-120min interval.
- A second critical event occurs in *middle or late adolescence* in girls in whom *cyclicity and ovulation* occur. A positive feedback mechanism develops where by increasing levels of estrogen in mid-cycle cause a distinct increase of LH.
- Factors normally activate or restrain the hypothalamic neurons responsible of GnRH secretion (a neurosecretory unit known as the *GnRH pulse generator*) are unknown.

## INTERPRETATION OF HORMONAL CHANGES DURING PUBERTY

- complex due to**:**
  1. Pituitary gonadotropins are heterozygous and circulate in multiple isoforms.
  2. LH immunoreactivity is variable in different immunoassays.
  3. Pulsatile secretion of gonadotropins.
  4. Important sex differences exist in the maturation of the hypothalamus and pituitary gland and serum LH concentrations increase earlier in the course of the pubertal process in boys than in girls.
- The effects of gonadal steroids on bone growth and osseous maturation are critical.
- **Estrogens**, rather than androgens are responsible of the process of **bone maturation** that ultimately leads to **epiphyseal fusion** and cessation of growth.
- *Estrogens also mediate the increased production of growth hormone*, which along with a direct effect of sex steroids on bone growth is responsible for the *pubertal growth spurt*.
- The age of onset of puberty varies and more closely correlated with osseous maturation than with chronological age.
- In females, **the breast bud is the first sign of puberty (10-11y),** followed by the appearance of **pubic hair 6-12m later**. The interval to **menarche is 2-2.5y** .*Peak height* velocity occurs early, at **breast stage II-III** (11-12y) in girls and *always precedes menarche.*
  1. Breast bud
  2. Pubic hair
  3. Peak height
  4. Menarche
- In males, **growth of the testis** (>3ml in volume or 2.5cm in longest diameter) and **thinning of the scrotum** are the first signs of puberty. These are followed by **pigmentation of the scrotum** and **growth of the penis, pubic hair then appears**. Appearance of **axillary hair** usually occurs in mid-puberty.
- In males, acceleration of growth begins at **genital stage IV-V** (13-14y).
  1. Testes
  2. Thinning of scrotum
  3. Pigmentation of scrotum
  4. Penis
  5. Pubic hair
  6. Axillary hair
- The growth spurt occurs approximately **2y later in males than in females** and growth may continue beyond 18y of age.
- Genetic and environmental factors affect the onset of puberty.
- Adrenocortical androgens also have a role in sexual maturation.

- Serum levels of dehydroepiandrosterone DHEA and its sulphate DHEAS begin to increase at approximately 6-8y of age before any increase in LH or sex hormones and before the earliest physical changes of puberty are apparent.
- **DHEAS** is the **most abundant** adrenal C-19 steroid in the blood, and its serum concentrations remains fairly stable over 24hrs.

# DISORDERS OF THE THYROID GLAND

## THYROID DEVELOPMENT AND PHYSIOLOGY

- Fetal development:-
  - Hypothalamic neurons synthesize Thyrotropin-Releasing Hormones (TRH) by (6-8) wk, the pituitary portal vessel system begins development by 8-10 weeks, and thyroid stimulating hormones (TSH) secretion is evident by 12 weeks of gestation.
  - Maturation of the hypothalamic pituitary-thyroid axis occurs over the second half of gestation but normal feed back relationships are not mature until approximately 3 months of postnatal life.

## THYROID PHYSIOLOGY:

- The main function of the thyroid gland is to synthesize T4 and T3.
- The recommended dietary allowance of iodine is 30 mcg/kg/d for infants. 90-120 mcg/24h for children, and 150 mcg/24 h for adolescents and adults.
- Whatever the chemical form ingested, iodine eventually reaches the thyroid gland as **iodide**.
- Iodination of tyrosine forms monoiodotyrosine and diiodotyrosine ; 2 molecules of diiodotyrsine then couple to form 1 molecule of T4 , or 1 molecule of diiodotyrosine and 1 of monoiodotyrosine to form T3.
- Once formed, hormones are stored **as thyroglobulin** in the lumen of the follicle (colloid).
- The metabolic **potency of T3 is 3-4 times that of T4**.
- Only 20 % of circulating T3 is secreted by the thyroid, the remainder is produced by deiodination of T4 in the liver, Kidney and other peripheral tissues by type I 5‘ – deiodinase.
- In the pituitary and brain, approximately 80% of required T3 is produced locally from T4 by a different enzyme, type 2 5’– deiodinase.
- The level of T3 in blood is 1/50$^{th}$ that of T4 but T3 is the physiologically active thyroid hormone.
- Thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation and affect carbohydrate, lipid and vitamin metabolism.
  - About **70%** of circulating T4 is firmly **bound** to thyroxine-binding globulin (TBG)
  - Only 0.03% of T4 in serum is not bound and comprises free T4.
  - 0.3% of T3 is unbound or free T3.

## THYROID REGULATION:-

- The thyroid is regulated by TSH, a glycoprotein produced and secreted by the anterior pituitary.
- TSH synthesis and release are stimulated by TSH – releasing hormone (TRH).

## THYROID HORMONE STUDIES:

- T4, free T4, T3, and free T3, reverse T3.
- Thyroglobulin
- TSH levels in serum are an extremely sensitive and indicator of primary hypothyroidism.
- After the neonatal period, normal levels of TSH are less than 6mu/ml.

## FETAL AND NEWBORN THYROID

- Approximately 1/3 of maternal T4 crosses the placenta to the fetus.
- Maternal T4 may play a role in fetal development, especially of the brain, before the synthesis of fetal thyroid hormone begins.
- At birth, there is an acute release of TSH; peak serum concentrations reach 60mu/L in 30min in full term infants.
- A rapid decline occurs in the ensuing 24hrs and a more gradual decline within the next 5 days to less than 10mU/L.

# HYPOTHYROIDISM

- Hypothyroidism results from deficient production of thyroid hormone or a defect in thyroid hormone receptor activity.
- The disorder may be manifested from birth or acquired.

## CONGENITAL HYPOTHYROIDISM:

- Most cases of congenital hypothyroidism are not hereditary and result from thyroid dysgenesis.

### EPIDEMIOLOGY:

- The prevalence of congenital hypothyroidism is 1:4000, twice as many girls as boys are affected.

### ETIOLOGY:

- Thyroid dysgenesis is the most common cause of congenital hypothyroidism accounting for 85% of cases; 10% are caused by inborn error of thyroxine synthesis and 5% are the result of transplacental maternal thyrotropin receptor blocking antibody (TRBAb).
- In about 1/3 of cases of dysgenesis, even sensitive radionuclide scans can find no remnants of thyroid tissue (aplasia)
- In the other 2/3 of infants, rudiments of thyroid tissue are found in an ectopic location, anywhere from the base of the tongue (lingual thyroid) to the normal position in the neck (hypoplasia).
- The **most common form of thyroid dysgenesis is an ectopic gland**.

1. Defective synthesis of thyroxine (dyshormogenesis)
2. Defect of Iodide transport
3. Thyroid peroxidase defects of organification and coupling
4. Defects in deiodination
5. Defects in thyroid hormone transport
6. Thyrotropin receptor blocking antibody
7. Radioiodine administration
8. Thyrotropin deficiency
9. Thyrotropin hormone unresponsiveness
10. Thyrotropin releasing hormone receptor abnormality
11. Thyroid hormone unresponsiveness
12. Iodine exposure
13. Iodine deficiency endemic goiter

### CLINICAL MANIFESTATIONS

- Most infants with congenital hypothyroidism are asymptomatic at birth, even if there is complete agenesis of the thyroid gland.
- Birth weight and length are normal, but head size may be slightly increased because of myxedema of the brain.
- Prolongation of physiologic jaundice.
- Feeding difficulties, lack of interest, somnolence and choking spells during nursing are often present during first month of life and respiratory difficulties.
- Affected infants cry little, sleep much, have poor appetites and are generally sluggish.
- Constipation, abdomen is large, umbilical hernia.
- The temperature is subnormal; skin may be cold and mottled.
- Edema of the genital and extremities may be present.
- The pulse is slow, heart murmurs, cardiomegaly and asymptomatic pericardial effusion.
- Macrocytic anemia is often present.
- 10% of infants with congenital hypothyroidism have associated congenital anomalies.
- Without treatment retardation of physical and mental development becomes greater by 3-6m of age.The child growth will be stunted, the extremities are short, and the head size is normal or even increased.
- The anterior and posterior fontanels are open widely.
- The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow and the eyelids swollen.
- The mouth is kept open, and the thick broad tongue protrudes. Dentition will be delayed.
- The neck is short and thick. The hands are broad and the fingers short.
- The skin is dry and scaly.

- The scalp is thickened and the hair is coarse, brittle and scanty. The hairline reaches far down the forehead.
- Development is delayed
- The muscles are usually hypotonic.

### Laboratory findings:

- Newborn screening that measure levels of T4: identifies infants with primary hypothyroidism, some with hypothalamic or pituitary hypothyroidism and infants with delayed increase in TSH levels.
- Screening that measures levels of TSH detects infants with subclinical hypothyroidism (normal T4, elevated TSH) but it misses infants with delayed TSH elevation and with hypothalamic or pituitary hypothyroidism.
- Serum levels of T4 or free T4 are low. TSH is high.
- T3 may be normal and are not helpful in the diagnosis.
- Serum levels of prolactine are elevated.
- Retardation of osseous development can be shown radiographically at birth in about 60%. The distal femoral epiphysis, normally present at birth is often absent.
- Roentograms of the skull show large fontanel and wide sutures.
- Demonstration of ectopic thyroid tissue is diagnostic of thyroid dysgenesis and establishes the need for lifelong treatment with T4.

### Treatment:

- Levothyroxine is the treatment of choice.
- In neonates the recommended initial starting dose is 10-15mcg/kg.
- Thyroxine should not be mixed with soy protein formulas or iron, because these can bind T4 and inhibit its absorption.
- In older children, after catch-up growth is complete the growth rates provide a good index of the adequacy of therapy.

### Prognosis:

- 20% of children have a neurosensory hearing deficit.
- Thyroid hormone is critical for normal cerebral development in the early postnatal moths; biochemical diagnosis must be made soon after birth and effective treatment must be initiated promptly to prevent irreversible brain damage.

## Acquired hypothyroidism:

### Epidemiology:

- Hypothyroidism occurs in 0.3% of school age children.

### Etiology:

- The most common cause of acquired hypothyroidism is **chronic lymphocytic thyroiditis**.
- Protracted ingestion of medications containing iodides can cause hypothyroidism e.g amiodarone.
- Other causes: subtotal thyroidectomy, irradiation, nephropathic cystinosis and hemangiomas.

### Clinical manifestations:

- **Deceleration of growth** is usually the first clinical manifestation.
- Goiter which may be a presenting feature typically is non-tender and firm, with a rubbery consistency.
- myxedematous changes of the skin, constipation, cold intolerance, decreased energy and increased need for sleep develop insidiously.
- Osseous maturation is delayed.
- Adolescents typically have delayed puberty, whereas younger children may present with galactorrhea or pseudoprecocious puberty.
- Some children have headaches and visual problems.

### TREATMENT

- All these changes return to normal with adequate replacement of T4, but in children with long standing hypothyroidism catch-up growth may be incomplete.
- During the first 18m of treatment, skeletal maturation often exceeds expected linear growth, resulting in a loss about 7cm of predicted adult height.

# Congenital Adrenal Hyperplasia

- Congenital adrenal hyperplasia (CAH) is a family of autosomal disorders of cortisol biosynthesis.
- Cortisol deficiency increases secretion of corticotropin (ACTH) which in turn leads to adrenocortical hyperplasia and over production of intermediate metabolites.
- Depending on the enzymatic step that is deficient, there may be signs, symptoms & laboratory findings of mineralocorticoid deficiency or excess;
  - Incomplete virilization or premature puberty in affected **males**
  - Virilization or sexual infantilism in affected **females**.

## CAH due to 21-hydroxylase deficiency:

- More than 90% of CAH cases are caused by 21-hydroxylase deficiency.
- This P450 enzyme hydroxylates progesterone and 17-hydroxyprogesterone to yield 11-deoxycorticosterone, DOC & 11-deoxycortisol respectively.
- These conversions are required for synthesis Aldosterone & Cortisol respectively.
- Both hormones are deficient in the most severe “Salt wasting” form of the disease.
- Slightly less severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin, termed simple virilizing disease.
- These two forms are collectively termed Classical 21-hydroxylase deficiency.
- Patients with nonclassical disease have relatively mildly elevated levels of androgens & may have signs of androgen excess after birth.

### Pathogenesis & Clinical Manifestations:

- Both Cortisol & Aldosterone are deficient in the most severe “Salt wasting” form of the disease. constitutes 70% of cases of classical 21-Hyroxylase deficiency.
- *Progressive weight loss, anorexia, vomiting, dehydration, weakness, **hypotension**, hypoglycemia, hyponatremia & hyperkalemia.*
- These problems typically first develop in affected infants **at 2 weeks of age**.

### Prenatal Androgen excess:

- Begins in affected fetuses by 8-10 weeks of gestation and leads to abnormal genital development in females.
- Affected females who are exposed inutero to high levels of androgens of adrenal origin have masculinized external genitalia.
- This is manifested by enlargement of the clitoris and by partial or complete labial fusion.
- The vagina usually has a common opening with the urethra (urogenital sinus).
- The internal genital organs are normal.
- Male infants appear normal at birth.

### Postnatal Androgen excess:

- Untreated or inadequately treated children of both sexes develop additional signs of androgen excess after birth.
- Boys with the simple virilization form of 21-hydroxylase deficiency often have delayed diagnosis because they appear normal and rarely develop adrenal insufficiency.
- Similar but unusually milder signs of androgen excess may occur in nonclassic 21-hydroxylase deficiency. In this attenuated form, Cortisol & Aldosterone levels are normal and affected females have normal genitals at birth. Males and females may present with precocious pubarche and early development of pubic and axillary hair.

### Laboratory findings:

- Patients with salt-losing disease have typical lab findings associated with Cortisol & Aldosterone deficiency. These include *hyponatremia, hyperkalemia, metabolic acidosis*, and often *hypoglycemia*, but these abnormalities can take 1-2 weeks or longer to develop after birth.
- Good levels of 17-OHP are markedly elevated. However, levels of these hormones are high during the first 2-3 days of life even in unaffected infants and especially if they are sick or premature. Blood levels of Cortisol are usually low in patients with the Salt-losing type of the disease.
- Androstenedione and testosterone are elevated in the affected female.
- Levels of urinary 17-ketosteroid and pregnanetriol are elevated.
- ACTH levels are elevated

- Plasma renin levels are elevated.
- Serum Aldosterone is inappropriately low for the renin level.
- Most reliable test to diagnose 21-hydroxylase deficiency is by measuring 17-OHP before and 30 or 60 minutes after IV ACTH.

### Newborn Screening:

- Because 21-hydroxylase deficiency is often undiagnosed is affected males until they have severe adrenal insufficiency, newborn screening for 17-OHP in dried blood obtained by heel stick and absorbed on filter paper cards.
- Screening programs are effective in preventing many cases of adrenal crisis in affected males. The non-classical form of the disease is not reliably detected by newborn screening.

### Treatment:

**Glucocorticoid replacement:**

- Cortisol deficiency is treated with glucocorticoids.
- Treatment also suppresses excessive production of androgens by the adrenal cortex and thus minimizes problems such as excessive growth and skeletal maturation and virilization.
- Typically 15-20mg/m2/24hrs of **hydrocortisone** daily administered orally in 3 divided doses.
- Double or triple doses are indicated during periods of stress, such as infection or surgery.
- Glucocorticoid treatment must be continued indefinitely in all patients with classical 21-hydroxylase deficiency.
- It is desirable to maintain linear growth along percentile lines; crossing to higher height percentiles may suggest under treatment, whereas loss of height percentiles often indicated over treatment with glucocorticoids.

**Mineralocorticoid replacement:**

- Patients with salt wasting disease ( aldosterone deficiency ) require mineralocorticoid replacement with **fludrocortisone** 0.1mg/day.

## Short stature

- A child who is 2SD or more below the mean chronological height is considered to have short stature.
- A single measurement of height is much less important in assessing growth than is the pattern of growth over a period of time.
- The key finding is slowed growth that progressively deviates from a previously defined growth channel.
- Height measurements must be made with an appropriate apparatus
- These measurements should be plotted accurately on the appropriate growth chart.
- Because growth is one of the most important parameters in monitoring the health of children, a child's height and weight should be measured at each child visit.

### Phases of growth

- ***Infantile:*** growth during this period is about 30-35cm. Infants often cross percentile lines in the first 24 months as they grow toward their genetic potential and get further away from the excesses or constraints of the intrauterine environment.
- ***Childhood:*** Characterized by growth at a relatively constant velocity of 4.8-6 cm/y.
- ***Pubertal:*** Growth spurt of 8-14cm/y due to synergistic effects of increasing gonadal steroid and growth hormone secretion.

### Prediction of height potential

- An estimate of a child's adult height potential can be obtained by calculation of the midparental height, adjusted for the sex of the child.
- For girls, 13cm is subtracted from the father's height and averaged with the mother's height.
- For boys, 13cm is added to the mother's height and averaged with the father's.
- In general , the rule of "fives" for length or height should suffice to estimate normal growth.

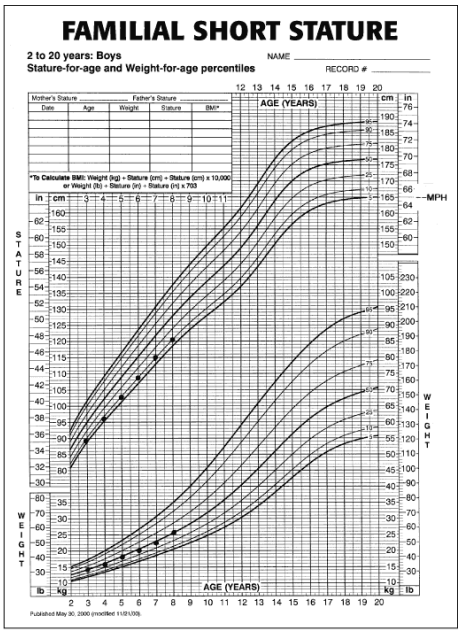
| | BIRTH | | 1Y | | 4Y | | 8Y | | 12Y |
|---|---|---|---|---|---|---|---|---|---|
| LENGTH OR HEIGHT | **50** | | **75** | | **100** | | **125** | | **150** |
| GROWTH VELOCITY | | **25** | | **10** | | **5** | | **5** | |

## EVALUATION

- Does the child have dysmorphic features or disproportionate short stature ?
- Does the child have growth failure ?
- Although the child is short, is his growth velocity normal or impaired ?

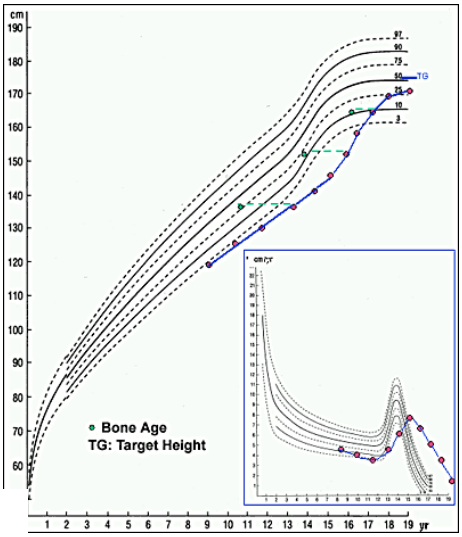
## CLASSIFICATION OF SHORT STATURE

- NON-ENDOCRINE CAUSES
  1. Familial, Genetic Short Stature
  2. Short Stature of Chronic Disease
  3. Skeletal Dysplasia
  4. Psychosocial Growth Failure
  5. Genetic Syndromes – Turner, Russell-Silver, Prader Willi.
  6. Idiopathic Short Stature
- ENDOCRINE CAUSES
  1. Hypothyroidism
     - Congenital
     - Acquired
  2. Cushing's Syndrome, usually iatrogenic
     - Pituitary derived > age 9 yrs
     - Primary Adrenal Tumor < age 9 yrs
  3. Growth Hormone Deficiency




## FAMILIAL SHORT STATURE

- Child's projected height is within 2 SD of MPH
- Normal Height Velocity
- Parents height centiles are comparable
- **CA ~ BA**
- Onset of puberty is normal
- Adult height: short
- Is there a familial growth problem that has retarded parents' growth?




## CONSTITUTIONAL DELAY OF GROWTH

- THE MOST COMMON
- Position on growth chart is lower than MPH.
- Parents or first deg. relative have similar hx.
- **Delayed puberty.**
- Laboratory evaluation is normal.
- **Bone age is delayed**
- Recovery to normal height is (not always) complete.

**Differential features of familial short stature and constitutional delay of growth and adolescence**

| Feature | Familial short stature | Constitutional Delay |
|---|---|---|
| Parents' stature | Small (one or both) | Average |
| Parents' puberty | Usual timing | Delayed |
| Birth length | Normal | Normal |
| Growth (0 to 2 years) | Normal | Normal to slow |
| Growth (puberty) | Normal | Slow |
| Bone age | Normal | Delayed |
| Timing of puberty | Normal | Delayed |
| Puberty growth rate | Lower range of normal | Diminished |
| Adult height | Short | Normal |

## Chronic Disease

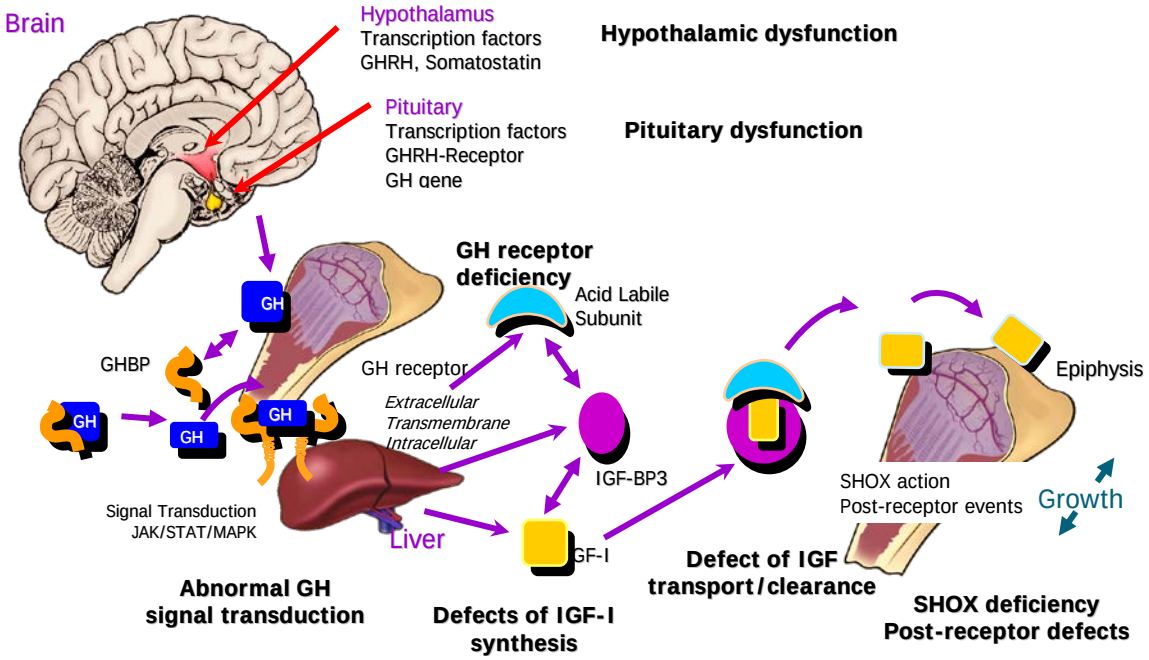
1. Hematalogic diseases: i.e. Sickle cell, other anemias
2. Pulmonary : asthma, cystic fibrosis
3. Cardiac causes: L to R shunts more growth-impairing
4. Protein and calorie malnutrition
5. GI causes: Crohn's Disease (IBD), Celiac
6. Renal causes: RTA, dysplasia, phosphate-losing tubular defects (Inherited, drugs)
7. Malignancy: location of tumor (hypothalamus) vs effect of inflammatory cytokines
8. Vitamin D deficiency or resistance

- Usually Weight decline is first
- Height declines later
- Recovery of growth is usually complete if underlying illness is addressed successfully and before puberty

## Growth Hormone Deficiency

- Rarely Genetic; Occurs in 1:5000 children
- 30% Structural< 5 yrs (SOD most common) and >5 yrs due to tumor (cranio, glioma etc.)
- 70% Mostly idiopathic
- Can be associated with autoimmune conditions: rheumatoid arthritis, diabetes or can be due to meningitis or CNS trauma
- IGF-1
  - Synthesized primarily in the liver
  - Circulating levels of IGF-1 are related to the blood levels of GH and to the nutritional status
  - The mitogenic actions of GH are mediated through increase in the synthesis of insulin-like growth factor.

## Hypothalamic-Pituitary-IGF Axis: Possible Sites of Defects




## Idiopathic Short Stature (ISS)

- Defined as the presence of significant growth failure in childhood without definable etiology.
- Multifactorial disorder with many potential causes.
- Diagnosis of exclusion -i.e. no evidence of systemic disease, malnutrition, hypothyroidism or GHD
- ***Ht. is -2 SDS or below 3rd % <u>and</u>***
- ***There is persistently low growth rate for age.***
- Final height is >> - 2 SD below MPH ( abnormal).
- *Respond to growth hormone, quite well.*
- *Growth hormone stimulation tests*, GH can be stimulated using:
  - Arginine
  - Clonidine
  - Glucagon
  - Insulin
  - Levodopa

## Indications for Growth Hormone Rx

1. GHD (Growth Hormone Deficiency)
2. TS (Turner's Syndrome)
3. CRI (Chronic Renal Insufficiency)
4. SGA (Small for Gestational Age)
5. PWS (Prader-Willi Syndrome)

## Evaluating a Child with Short Stature

- History and Physical examination.
- Accurate measurement of height and weight
- Mid-parental Height
- Laboratory: Thyroid function test , CBC, ESR, celiac Serology, Karyotype, Comprehensive Metabolic Profile, IGF-1, IGF- BP3, urinalysis
- X-ray: Bone Age, MRI of hypothal-pituitary, each case is individualized.

## Causes of Short Stature

| |
|---|
| **Variations of Normal** |
| Constitutional (delayed bone age) |
| Genetic (short familial heights) |
| **Endocrine Disorders** |
| GH deficiency |
| Congenital |
| Isolated GH deficiency |
| With other pituitary hormone deficiencies |
| With midline defects |
| Pituitary agenesis |
| With gene deficiency |
| Acquired |
| Hypothalamic/pituitary tumors |
| Histiocytosis X (Langerhans cell histiocytosis) |
| CNS infections and granulomas |
| Head trauma (birth and later) |
| Hypothalamic/pituitary radiation |
| CNS vascular accidents |
| Hydrocephalus |
| Autoimmune |
| Psychosocial dwarfism (functional GH deficiency) |
| Amphetamine treatment for hyperactivity* |
| Laron dwarfism (increased GH and decreased IGF1) |
| Pygmies (normal GH and IGF2 but decreased IGF1) |
| Hypothyroidism |
| Glucocorticoid excess |
| Endogenous |
| Exogenous |
| Diabetes mellitus under poor control |
| Diabetes insipidus (untreated) |
| Hypophosphatemic vitamin D-resistant rickets |
| Virilizing congenital adrenal hyperplasia (tall child, short adult) |
| P-450$_{c21}$, P-450$_{c11}$ deficiencies |
| **Skeletal Dysplasias** |
| Osteogenesis imperfecta |
| Osteochondroplasias |
| **Lysosomal Storage Diseases** |
| Mucopolysaccharidoses |
| Mucolipidoses |
| **Syndromes of Short Stature** |
| Turner syndrome (syndrome of gonadal dysgenesis) |
| Noonan syndrome (pseudo-Turner syndrome) |
| Autosomal trisomy 13, 18, 21 |
| Prader-Willi syndrome |
| Laurence-Moon-Bardet-Biedl syndrome |
| Autosomal abnormalities |
| Dysmorphic syndromes (e.g., Russell-Silver, Cornelia de Lange) |
| Pseudohypoparathyroidism |
| **Chronic Disease** |
| Cardiac disorders |
| Left-to-right shunt |
| Congestive heart failure |

| |
|---|
| Pulmonary disorders |
| Cystic fibrosis |
| Asthma |
| Gastrointestinal disorders |
| Malabsorption (e.g., celiac disease) |
| Disorders of swallowing |
| Inflammatory bowel disease |
| Hepatic disorders |
| Hematologic disorders |
| Sickle cell anemia |
| Thalassemia |
| Renal disorders |
| Renal tubular acidosis |
| Chronic uremia |
| Immunologic disorders |
| Connective tissue disease |
| Juvenile rheumatoid arthritis |
| Chronic infection |
| AIDS |
| Hereditary fructose intolerance |
| **Malnutrition** |
| Kwashiorkor, marasmus |
| Iron deficiency |
| Zinc deficiency |
| Anorexia caused by chemotherapy for neoplasms |

# HYPOGLYCEMIA

- occurs most frequently in the **early neonatal period**, often as a result of inadequate energy stores to meet the large metabolic needs of premature or SGA newborns.
- Hypoglycemia in the first few days of life in an otherwise normal newborn is less frequent and warrants concern.
- After 2 to 3 days of life, hypoglycemia is less common and is more frequently the result of endocrine or metabolic disorders.
- **Serum glucose concentrations < 45 mg/dL** (abnormal and necessitate treatment).
- Serum glucose < 55 mg/dL can occur in normal individuals, especially with prolonged fasting→ suspect, if + symptoms of hypoglycemia.
- The **diagnosis** of hypoglycemia should be made on the basis of:
  1. low serum glucose concentration
  2. symptoms compatible with hypoglycemia
  3. resolution of the symptoms after administration of glucose.

## CLINICAL MANIFESTATIONS

- The symptoms and signs of hypoglycemia result from direct depression of the CNS owing to lack of energy substrate and the counterregulatory response to low glucose via catecholamine secretion.

### SYMPTOMS AND SIGNS OF HYPOGLYCEMIA

| FEATURES ASSOCIATED WITH EPINEPHRINE RELEASE* | FEATURES ASSOCIATED WITH CEREBRAL GLYCOPENIA |
|---|---|
| Perspiration | Headache, Hunger |
| Palpitation (tachycardia) | Mental confusion |
| Pallor | Inability to concentrate, Somnolence |
| Paresthesia | Dysarthria |
| Trembling | Personality changes |
| Anxiety | Staring, Diplopia |
| Weakness | Convulsions ,Ataxia |
| Nausea | Stroke |
| Vomiting | Coma |

- The manifestations in infants differ compared with the manifestations in older children.
- Symptoms and signs of hypoglycemia in infants are nonspecific and include:
  1. jitteriness
  2. feeding difficulties
  3. pallor
  4. hypotonia
  5. hypothermia
  6. episodes of apnea and bradycardia
  7. depressed levels of consciousness
  8. seizures
- In older children, symptoms and signs include:
  1. confusion & irritability
  2. headaches
  3. visual changes
  4. tremors
  5. pallor
  6. sweating
  7. tachycardia
  8. weakness& seizures
  9. coma
- Failure to recognize and treat severe prolonged hypoglycemia can result in serious long-term morbidity, including mental retardation and nonhypoglycemic seizures.

## Classification of Hypoglycemia in Infants and Children

| Abnormalities in the Hormonal Signal Indicating Hypoglycemia |
|---|
| **Counterregulatory Hormone Deficiency** |
| Panhypopituitarism |
| Isolated growth hormone deficiency |
| ACTH deficiency |
| Addison disease |
| Glucagon deficiency |
| Epinephrine deficiency |
| **Hyperinsulinism** |
| Infant of a diabetic mother |
| Infant with erythroblastosis fetalis |
| Persistent hyperinsulinemic hypoglycemias of infancy |
| Beta cell adenoma (insulinoma) |
| Beckwith-Wiedemann syndrome |
| Anti-insulin receptor antibodies |
| **Inadequate Substrate** |
| Prematurity/small for gestational age infant |
| Ketotic hypoglycemia |
| Maple syrup urine disease |
| **Disorders of Metabolic Response Pathways** |
| **Glycogenolysis** |
| Glucose-6-phosphatase deficiency |
| Amylo-1,6-glucosidase deficiency |
| Liver phosphorylase deficiency |
| Glycogen synthase deficiency |
| **Gluconeogenesis** |
| Fructose-1,6-diphosphatase deficiency |
| Pyruvate carboxylase deficiency |
| Phosphenolpyruvate carboxykinase deficiency |
| **Fatty Acid Oxidation** |
| Long, medium, or short chain fatty acid acyl-CoA dehydrogenase deficiency |
| Carnitine deficiency (primary or secondary) |
| Carnitine palmitoyltransferase deficiency |
| **Other** |
| *Enzymatic defects* |
| Galactosemia |
| Hereditary fructose intolerance |
| Propionicacidemia |
| Methylmalonic acidemia |
| Tyrosinosis |
| Glutaric aciduria |
| *Global hepatic dysfunction* |
| *Reye syndrome* |
| *Hepatitis* |
| *Heart failure* |
| *Sepsis, shock* |
| *Carcinoma/sarcoma (IGF-2 secretion)* |
| *Malnutrition-starvation* |
| *Hyperviscosity syndrome* |
| **Drugs/Intoxications** |
| Oral hypoglycemic agents, Propranolol, Pentamidine, Quinine , Trimethoprim-sulfamethoxazole (with renal failure), Insulin,Alcohol, Salicylates, Valproic acid, Ackee fruit (unripe) |

## HORMONAL SIGNAL

- In a normal individual, a decrease in serum glucose concentrations leads to:
  1. ↓ insulin secretion
  2. ↑ counterregulatory hormones (GH, cortisol, glucagon, and epinephrine).
- This hormonal signal promotes:
  1. the release of amino acids (particularly alanine) from muscle to fuel gluconeogenesis
  2. the release of triglyceride from adipose tissue stores to provide FFAs for hepatic ketogenesis.
  3. This hormonal signal stimulates the breakdown of hepatic glycogen and promotes gluconeogenesis.
- Failure of any of the components of this hormonal signal can lead to hypoglycemia.

### HYPERINSULINEMIA

- Failure of suppression of insulin secretion in response to low serum glucose concentrations can occur in infants, but is uncommon beyond the neonatal period.
- In neonates, this situation arises most frequently in infants of diabetic mothers
- exposed to high maternal glucose in utero→ fetal islet cell hyperplasia→ hyperinsulinemic state ( transient, lasting hours to days).
- Hyperinsulinism that persists beyond a few days of age can result from a condition previously referred to as nesidioblastosis= **persistent hyperinsulinemic hypoglycemia of the newborn**.
  - hyperplasia of the pancreatic islet cells in the absence of excess stimulation by maternal diabetes.
- **Beckwith-Wiedemann syndrome**, a condition characterized by:
  1. Hyperinsulinism
  2. neonatal somatic gigantism: macrosomia, macroglossia, omphalocele, visceromegaly, and earlobe creases.
- In children, hyperinsulinemia is rare and usually results from an **islet cell adenoma**.
  - characteristically have a voracious appetite, obesity, and accelerated linear growth.
  - As in infants, *diagnosis* = insulin concentrations > 5 μU/mL during an episode of hypoglycemia.
  - CT or MRI of the pancreas : visualization of an adenoma is usually difficult.
  - Surgical removal of the adenoma is curative.
- Regardless of the cause, neonates with hyperinsulinism are characteristically large for gestational age .
- Hypoglycemia is severe and frequently occurs within 1 to 3 hours of a feeding.
- Glucose requirements are increased, often two to three times the normal basal glucose requirement of 4 to 8 mg/kg/min.
- The *diagnosis* of hyperinsulinism is confirmed by the detection of serum **insulin concentrations > 5 μU/mL** during an episode of hypoglycemia.
- **The absence of serum and urine ketones** at the time of hypoglycemia is an important diagnostic feature, distinguishing hyperinsulinism from defects in counterregulatory hormone secretion.
- *Treatment*:
  1. initially involves the infusion of IV glucose at high rates + diazoxide to suppress insulin secretion.
  2. If this therapy is unsuccessful, long-acting somatostatin analogues can be tried.
  3. if medical therapy for persistent hyperinsulinemic hypoglycemia of the newborn is unsuccessful→ subtotal (90%) pancreatectomy to prevent long-term neurologic sequelae of hypoglycemia.

### FACTITIOUS HYPERINSULINEMIA

- insulin or a hypoglycemic medication is administered by a parent or caregiver to a child as a form of child abuse=**Munchausen syndrome by proxy**.
- This *diagnosis* should be suspected if extremely high insulin concentrations are detected (>100 μU/mL).
- **C-peptide concentrations** are low or undetectable,confirms that the insulin is exogenous

## Defects in Counterregulatory Hormones

- Abnormalities in the secretion of counterregulatory hormones that produce hypoglycemia usually involve GH, cortisol, or both.
- Deficiencies in glucagon and epinephrine secretion are rare.
- GH and cortisol deficiency occur as a result of :
  1. deficiency of hypothalamic releasing factors (more common).
  2. hypopituitarism from congenital hypoplasia or aplasia of the pituitary
  3. Deficient cortisol secretion also can occur in primary adrenal insufficiency
     - **infants**, often results from (CAH), most frequently - **21-hydroxylase deficiency**
     - **older children**, most frequently in **Addison disease(**hyperpigmentation, hyponatremia, and hyperkalemia**)**, also **adrenoleukodystrophy**
- Clues to diagnosis in infants include the presence of hypoglycemia in association with:
- **midline facial or neurologic defects** (e.g., cleft lip and palate or absence of the corpus callosum)
- **pendular nystagmus** (indicating visual impairment from possible abnormalities in the development of the optic nerves, which can occur in septo-optic dysplasia)
- **the presence of microphallus and cryptorchidism in boys** (indicating abnormalities in gonadotropin secretion).
- Jaundice and hepatomegaly can occur, simulating neonatal hepatitis.
- in GH deficiency, infants are usually of normal size at birth.
- Older children with hypopituitarism have short stature & a subnormal growth velocity.
- Confirmation of GH or cortisol deficiency as the cause of hypoglycemia requires the detection of low serum GH and cortisol concentrations during an episode of hypoglycemia or after other stimulatory testing.
- In contrast to hyperinsulinism:
  1. **serum and urine ketones are positive at the time of hypoglycemia**
  2. **FFAs are elevated**
- Treatment involves supplementation of the deficient hormones in physiologic doses.

# ENERGY STORES

- Sufficient energy stores in the form of glycogen, adipose tissue, and muscle are necessary to respond appropriately to hypoglycemia.
- Deficiencies in these stores are a common cause of hypoglycemia in neonates who are small for gestational age or premature .
- Beyond the early neonatal period, energy stores are usually sufficient to meet the metabolic requirements except in malnourished children.
- Release of substrate from energy stores is abnormal in one common form of childhood hypoglycemia, ketotic hypoglycemia.

## Ketotic Hypoglycemia

- Ketotic hypoglycemia is seen in children between 18 months and 5 years of age.
- the most common cause of new-onset hypoglycemia in children > 2 years of age.
- The disorder usually resolves spontaneously by 7 to 8 years of age.
- Patients have symptoms of hypoglycemia after a period of prolonged fasting, often in the setting of an intercurrent illness with decreased feeding.
- Children with this disorder are often thin and small and may have a history of being small for gestational age.
- Defective mobilization of alanine from muscle to fuel gluconeogenesis is the cause.
- ketotic hypoglycemia is a *diagnosis of exclusion* (no specific diagnostic tests).
- *Treatment* : avoidance of fasting and frequent feedings of a high-protein, high-carbohydrate diet.

# METABOLIC RESPONSE PATHWAYS

- Maintenance of normal serum glucose concentrations in the fasting state requires:
- glucose production via glycogenolysis and gluconeogenesis
- production of alternative energy sources (FFAs and ketones) via lipolysis and fatty acid oxidation.

## GLYCOGENOLYSIS

- Glycogen storage diseases occur in a variety of subtypes that differ in severity
- the most severe form is glucose-6-phosphatase deficiency. characterized by severe hypoglycemia, massive hepatomegaly, growth retardation, and lactic acidosis.
- deficiencies in the glycogen phosphorylase enzymes may cause isolated hepatomegaly with or without hypoglycemia.
- The *diagnosis* of glycogen storage disease is suggested by a finding of:
  1. hepatomegaly without splenomegaly.
  2. Ketosis occurs with hypoglycemic episodes.
  3. Confirmation: specific biochemical studies of leukocytes or liver biopsy specimens.
- *Treatment* involves frequent high-carbohydrate feedings during the day and continuous feedings at night via nasogastric tube.
  - uncooked cornstarch during bedtime is sufficient to maintain serum glucose concentrations in some patients.

## GLUCONEOGENESIS

- Defects in gluconeogenesis are uncommon and include fructose-1,6-diphosphatase deficiency and phosphoenolpyruvate carboxykinase deficiency.
- Affected patients exhibit:
- fasting hypoglycemia
- Ketosis
- lactic acidosis
- hepatomegaly (fatty infiltration)
- hyperuricemia
- FFA and alanine are high.
- *Treatment* involves frequent high-carbohydrate, low-protein feedings .

## FATTY ACID OXIDATION

- Fatty acid oxidation disorders of ketogenesis include:
  1. the fatty acid acyl-coenzyme A (CoA) dehydrogenase deficiencies: long chain, medium chain, and short chain
  2. Hereditary carnitine deficiency
- **medium chain acyl-CoA dehydrogenase deficiency** is the most common.
- patients are well in infancy and have the first episode of hypoglycemia ≥2 years of age .
- Episodes occur with prolonged fasting or during episodes of intercurrent illness.
  1. Mild hepatomegaly
  2. mild elevations in hepatic transaminases.
  3. mild hyperammonemia
  4. hyperuricemia
  5. **Ketone are low or undetected.**
- The *diagnosis* is confirmed by the finding of ↑**dicarboxylic acids** in the urine.
- *Treatment* involves avoidance of fasting.

## Other Metabolic Disorders

- metabolic disorders → hypoglycemia: galactosemia, hereditary fructose intolerance, and disorders of organic acid metabolism.
- Hypoglycemia in these disorders is a reflection of global hepatic dysfunction secondary to the buildup of hepatotoxic intermediates.
- Many of these disorders present with low concentrations of ketone bodies because ketogenesis also is affected.
- The finding of non-glucose-reducing substances in the urine suggests a diagnosis of galactosemia or hereditary fructose intolerance.
- Occurrence of symptoms after ingestion of fructose or sucrose **suggests hereditary fructose intolerance**.
- *Treatment* requires dietary restriction of the specific offending substances.

## EMERGENCY MANAGEMENT

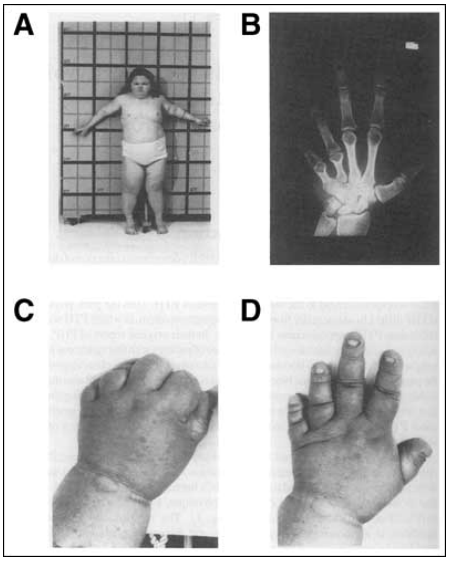
- Acute care consists of rapid administration of IV glucose (2 mL/kg 10% dextrose water).
- After the, an infusion of IV glucose to provide 1.5 times the normal hepatic glucose production rate (8 to 12 mg/kg/min in infants, 6 to 8 mg/kg/min in children).
- Higher infusion rates may be needed for hyperinsulinemic states.
- if adrenal insufficiency is suspected, stress doses of glucocorticoids should be administered.

## HYPOCALCEMIA

- hypocalcemia :ionized calcium <4.5 mg/dL; total calcium <8.5 mg/dL if serum protein is normal.
- The **clinical manifestations** of hypocalcemia result from increased neuromuscular irritability and include:
  1. muscle cramps
  2. carpopedal spasm (tetany)
  3. weakness
  4. paresthesia
  5. laryngospasm
  6. seizure-like activity (patient is often awake and aware during these episodes, in contrast to many episodes of epilepsy).
  7. Latent tetany is detected by:
     - A. the *Chvostek sign* (facial spasms are produced by lightly tapping over the facial nerve just in front of the ear)
     - B. the *Trousseau sign* (carpal spasms when arterial blood flow to the hand is occluded for 3 - 5 minutes with a blood pressure cuff inflated to 15 mm Hg above systolic blood pressure.
- Total serum calcium concentration is usually measured
- serum ionized calcium = half the total calcium in normal circumstances. the biologically active form, It is best to measure if hypocalcemia or hypercalcemia is suspected.
- Albumin is the major reservoir of protein-bound calcium.
- Disorders that alter plasma pH or serum albumin concentration must be considered when circulating calcium concentrations are being evaluated.
  - The fraction of ionized calcium is inversely related to plasma pH; **alkalosis** can precipitate hypocalcemia by ↓**ionized calcium** without changing total serum calcium.
  - Alkalosis may result from hyperpnea caused by anxiety or from hyperventilation related to physical exertion.
  - **Hypoproteinemia** → false suggestion of hypocalcemia →↓ **serum total calcium** even though the ionized $Ca^{2+}$ remains normal.
- **Primary hypoparathyroidism** causes hypocalcemia, but does not cause rickets. The etiology of primary hypoparathyroidism includes the following:
  1. Congenital malformation (**DiGeorge syndrome**)
     - resulting from developmental abnormalities of the third and fourth branchial arches
     - leading to:
       1. hypoparathyroidism
       2. mandibular hypoplasia
       3. hypertelorism
       4. short philtrum
       5. low-set and malformed ears
       6. malformations of the heart and great vessels: ventricular and atrial septal defects, right aortic arch, interrupted aortic arch, and truncus arteriosus .
  2. **Surgical procedures**, such as thyroidectomy or parathyroidectomy.
  3. **Autoimmunity**, which destroy the parathyroid gland
- **Pseudohypoparathyroidism** may occur in one of three forms, all with hypocalcemia and hyperphosphatemia, as follows:

  1. *Type Ia*-an abnormality of the $G_{s\alpha}$ protein linking the PTH receptor to adenylate cyclase; biologically active PTH is secreted in great quantities, but exerts no effect because there is no way for PTH to stimulate its receptor

2. *Type Ib*-normal $G_{s\alpha}$ with other abnormalities in the production of adenylate cyclase
3. *Type II*-normal production of adenylate cyclase, but a distal defect eliminates the effects of PTH




- Pseudohypoparathyroidism is an autosomal dominant condition that may present at birth or later.
- Other *clinical manifestations* of pseudohypoparathyroidism associated with **Albright hereditary osteodystrophy** include:

1. short stature
2. stocky body habitus
3. round facies
4. short fourth and fifth metacarpals
5. calcification of the basal ganglia
6. subcutaneous calcification
7. developmental delay
8. disproportionate shortening of the limbs
9. generalized obesity
10. Fist with the characteristic 'dimples' over the 3rd, 4th, and 5th digits replacing the knuckles formed by the distal head of normally sized metacarpal bones (**Archibald sign**).
11. very short, wide thumbnail (**potter's thumb**).

- During the first 3 days after birth, serum calcium concentrations normally decline in response to withdrawal of the maternal calcium supply via the placenta.
- **transient hypoparathyroidism**: Hypocalcemia caused by suppresses fetal PTH release in the neonatal period in infants of mothers with hyperparathyroidism and hypercalcemia.
- **Hypomagnesemia** may cause a secondary hypoparathyroidism, which responds poorly to therapies other than magnesium replacement.
- **Neonatal tetany** from excessive phosphate intake classically in a 1week-old to 1month-old infant who is fed cow's milk. Hyperphosphatemia→↓ calcium →symptomatic hypocalcemia. Cow's milk: ↑calcium& phosphorus than human milk.
- phosphate retention, as occurs in renal failure, produces hypocalcemia.

## THE ETIOLOGY OF HYPOCALCEMIA

1. clinical presentation
2. serum ionized calcium
3. phosphate
4. alkaline phosphatase
5. PTH (preferably at a time when the calcium is low)
6. magnesium
7. albumin
8. X-rays of the long bones and hands and knees are important if the problem occurs after the neonatal period.

- If the PTH concentration is not elevated appropriately relevant to a low serum calcium, hypoparathyroidism (transient, primary, or caused by hypomagnesemia) is present.
- Vitamin D stores can be estimated by measuring serum 25-hydroxyvitamin D.

## TREATMENT

- severe tetany or seizures from hypocalcemia : **IV calcium gluconate** (1 - 2 mL/kg of 10% solution) slowly over 10 minutes+ cardiac ECG monitor for bradycardia, may be fatal.
- Long-term treatment of hypoparathyroidism :
  1. **vitamin D**, 1,25-dihydroxyvitamin D.
  2. **calcium**.
- keep the serum calcium in the lower half of the normal range to avoid hypercalcemia ( **nephro-calcinosis** and **pancreatitis)**.

# SEXUAL PRECOCITY

## CLASSIFICATION

- Sexual precocity (precocious puberty) is classically defined as secondary sexual development occurring before the age of 9 years in boys or 8 years in girls.
- The lower limit of normal puberty may be 7 years in white girls and 6 years in African American girls.
- the mean age at which girls exhibit Tanner II breast development (the-larche) is 10 years for white girls and 9 years for African American girls (normal range 8- 13 years).
- The mean age at which girls exhibit Tanner II pubic hair development is 9 years for white girls and 10.5 years for African American girls.
- Menarche usually occurs at 12.2 and 12.9 years (range 10-15 years).
- The normal developmental sequence is **thelarche** followed closely by **pubarche** and finally **menarche** 2 to 3 years later.
- In boys, the first normal event is enlargement of testes followed by appearance of pubic hair (long diameter of the testis >2.5 cm, volume >4 mL).
- The first distinction regarding puberty is that of central versus peripheral.
  - **central precocious puberty** if it emanates from premature activation of the hypothalamic-pituitary-gonadal axis (GnRH-dependent)
  - **peripheral precocious puberty** when the hypothalamic-pituitary-gonadal axis is not involved in the process (GnRH-independent).
- The second distinction :
  - **isosexual** recocity is virilization in a boy and feminization in a girl
  - **heterosexual** (or contrasexual) puberty is virilization in a girl and feminization in a boy.
- incomplete isosexual precocious puberty(GnRH independent):
  - A boy : autonomous production of testosterone or other androgens from the testes or adrenal glands or as a result of a tumor that produces HCG, stimulating the testes.
  - A girl :autonomous production of estrogens from the ovaries or heterosexual puberty from androgens from the adrenal glands.

## CENTRAL PRECOCIOUS PUBERTY (CONSTITUTIONAL OR FAMILIAL PRECOCIOUS PUBERTY)

- In **central precocious puberty** every endocrine and physical aspect of pubertal development is normal but too early includes:
  1. tall stature
  2. advanced bone age
  3. increased sex steroid
  4. increased pulsatile gonadotropin secretion
  5. increased response of LH to GnRH
- **constitutional** or **familial precocious puberty**: Individuals who begin puberty only a few months early may have, in which members of some families enter puberty before the lower age limits of normal.
- if much earlier → other forms of central precocious puberty.
- The clinical course of central precocious puberty may wax and wane.
- If no cause can be determined= idiopathic precocious puberty; girls >boys.
- Obese girls have earlier menarche than normal weight girls.
- Boys with precocious puberty have a higher incidence of CNS disorders, such as tumors and hamartomas, precipitating the precocious puberty.
- Affected boys always must be investigated for the possibility of harboring a tumor.
- Almost any condition that affects the CNS → central precocious puberty, including:
  1. hydrocephalus
  2. meningitis
  3. encephalitis
  4. suprasellar cysts
  5. head trauma
  6. irradiation
  7. epilepsy
  8. mental retardation

- A CNS tumor or disease must be considered in all children with precocious puberty before the condition is diagnosed as idiopathic.
  - **Hamartomas** of the tuber cinereum have a characteristic appearance on CT or MRI; biopsy is rarely required. are not true neoplasms because they do not grow. medical therapy with GnRH agonists, and surgery is rarely indicated.
  - Other masses that cause precocious puberty are not benign:
  1. **Optic** or **hypothalamic gliomas** (with or without neurofibromatosis)
  2. astrocytomas
  3. ependymomas
     - disrupting the negative restraint of the areas of the CNS that normally inhibit pubertal development throughout childhood.
     - These tumors may require radiotherapy, which contributes to a significant risk for hypopituitarism.

## Gonadotropin-Releasing Hormone-Independent Precocious Puberty

- **McCune-Albright syndrome**, The most common cause of GnRH-independent precocious puberty, more frequent in girls than boys, includes:
  1. precocious gonadarche :results from ovarian hyper-function and sometimes cyst formation
  2. a bone disorder with polyostotic fibrous dysplasia
  3. hyper-pigmented cutaneous macules (café au lait spots).
  4. hyperthyroidism, hyperadrenalism, or acromegaly.
- **Adrenal carcinomas** usually secrete adrenal androgens, such as DHEA
- **adrenal adenomas** may virilize a child as a result of the production of androgen or may feminize a child as a result of the production of estrogen.
- **familial GnRH-independent sexual precocity with premature Leydig cell maturation**,
  - Boys precocious gonadarche on the basis of a rare entity
  - germ cell maturation caused by an X-limited dominant defect producing constitutive activation of the LH receptor→ continuous production and secretion of testosterone without requiring the presence of LH or HCG.
- secreting tumors stimulate LH receptors and increase testosterone secretion, including
  1. the pineal gland (**dysgerminomas**, which are radiosensitive)
  2. the liver (**hepatoblastoma**, death in just a few months after diagnosis).

## Evaluation of Sexual Precocity

- The first step in evaluating sexual precocity is to determine by physical examination which characteristic of normal puberty is apparent and whether estrogen effects or androgen effects or both are present.
- In girls,
  - androgen effect manifests as adult odor, pubic and axillary hair, and facial skin oiliness and acne.
  - estrogen effect manifests as breast development, uterine increase, and eventually menarche.
- In boys,
  - androgen effect manifests as adult odor, pubic and axillary hair, and facial skin oiliness and acne;if testes are enlarged more than 2.5 cm in length→ gonardarche.
  - If the testes are not enlarged, but virilization is progressing, the source of the androgens may be the adrenal glands or exogenous sources.
  - If the testes are slightly enlarged but not consistent with the stage of pubertal development: ectopic production of HCG or familial Leydig and germ cell maturation .
  - Most of the enlargement of testes during puberty is the result of seminiferous tubule maturation.
  - If only Leydig cells are enlarged as in these conditions, the testes make considerable testosterone, but show only minimal enlargement.
- **Laboratory examinations** include:
  1. determination of sex steroid (testosterone, estradiol, or DHEA)
  2. baseline gonadotropin concentrations.

- low secretory rates throughout childhood and pulsatile secretion in adolescents and adults.
- If baseline gonadotropin values are elevated into the normal pubertal range, central precocious puberty is likely.
- If baseline gonadotropins are low→ assess 3

3. Assessment of gonadotropin responsiveness to GnRH stimulation.
   - A prepubertal GnRH response is FSH predominant
   - pubertal response is more LH predominant.
4. Thyroid hormone determination: because severe primary hypothyroidism can cause incomplete precocious puberty.
5. CT or MRI: If there is a suggestion of a CNS anomaly or a tumor (CNS, hepatic, adrenal, ovarian, or testicular).

## TREATMENT

- Long-acting, superactive analogues of GnRH are the treatment of choice for central precocious puberty , they suppress gonadotropin secretion by down-regulating GnRH receptors in the pituitary gonadotropes .
  - After a brief (2 to 3 days) ↑gonadotropin and, rarely, some withdrawal bleeding in girls, values decrease, and the pubertal process reverts to the prepubertal state.
- Boys with GnRH-independent premature Leydig cell and germ cell maturation do not respond to GnRH analogues, but require treatment with:
  1. an inhibitor of testosterone synthesis (e.g., ketoconazole)
  2. an antiandrogen (e.g., spironolactone)
  3. an aromatase inhibitor (e.g., testolactone).
- Patients with precocious puberty from a hormone-secreting tumor require surgical removal, if possible.
- McCune-Albright syndrome is GnRH independent and unresponsive to therapy with GnRH analogue: testolactone and antiandrogens or antiestrogen, such as tamoxifen.
- After successful therapy, central precocious puberty may develop secondarily; GnRH agonist administration is effective therapy

### PHARMACOLOGIC THERAPY OF SEXUAL PRECOCITY

| Disorder | Treatment | Action and Rationale |
|---|---|---|
| **GnRH-dependent true or central precocious puberty** | GnRH agonists | Desensitization of gonadotropes; blocks action of endogenous GnRH |
| **GnRH-independent incomplete sexual precocity** | | |
| **Girls** | | |
| 1. Autonomous ovarian cysts | Medroxyprogesterone acetate | Inhibition of ovarian steroidogenesis; regression of cyst (inhibition of FSH release) |
| 2. McCune-Albright syndrome | Medroxyprogesterone acetate* | Inhibition of ovarian steroidogenesis; regression of cyst (inhibition of FSH release) |
| | Testolactone* or fadrozole | Inhibition of P-450 aromatase; blocks estrogen synthesis |
| **Boys** | | |
| Familial testotoxicosis | Ketoconazole* | Inhibition of P-450$_{c17}$ (mainly 17,20-lyase activity) |
| | Spironolactone* or flutamide *and* testolactone or fadrozole | Antiandrogen |
| | | Inhibition of aromatase; blocks estrogen synthesis |
| | Medroxyprogesterone acetate* | Inhibition of testicular steroidogenesis |

## Differential Diagnosis of Sexual Precocity

| | Serum Gonadotropin Concentration* | LH Response to GnRH | Serum Sex Steroid Concentrations | Gonadal Size | Miscellaneous |
|---|---|---|---|---|---|
| **True precocious puberty** | Pubertal values | Pubertal | Pubertal values of testosterone or estradiol | Normal pubertal testicular enlargement or ovarian and uterine enlargement (by sonography) | MRI scan of brain to rule out CNS tumor or other abnormality; bone scan for McCune-Albright syndrome |
| **Incomplete sexual precocity (pituitary gonadotropin-independent)** | | | | | |
| *Males* | | | | | |
| Chorionic gonadotropin-secreting tumor in males | High HCG (low LH) | Prepubertal (suppressed) | Pubertal values of testosterone | Slight to moderate uniform enlargement of testes | Hepatomegaly suggests hepatoblastoma; MRI scan of brain if chorionic gonadotropin-secreting CNS tumor suspected |
| Leydig cell tumor in males | Suppressed | Suppressed | Very high testosterone | Irregular asymmetric enlargement of testes | |
| Familial testotoxicosis | Suppressed | Suppressed | Pubertal values of testosterone | Testes symmetric and >2.5 cm but smaller than expected for pubertal development; spermatogenesis may occur | Familial; probably sex-limited, autosomal dominant trait |
| Premature adrenarche | Prepubertal | Prepubertal | Prepubertal testosterone; DHEAS values appropriate for pubic hair stage 2 | Testes prepubertal | Onset usually after 6 yr of age; more frequent in brain-injured children |
| *Females* | | | | | |
| Granulosa cell tumor (follicular cysts may present similarly) | Suppressed | Suppressed | Very high estradiol | Ovarian enlargement on physical examination, MRI, CT, or sonography | Tumor often palpable on abdominal examination |
| Follicular cyst | Suppressed | Suppressed | Prepubertal to very high estradiol values | Ovarian enlargement on physical examination, MRI, CT, or sonography | Single or repetitive episodes; exclude McCune-Albright syndrome (e.g., perform skeletal survey and inspect skin) |
| Feminizing adrenal tumor | Suppressed | Suppressed | High estradiol and DHEAS values | Ovaries prepubertal | Unilateral adrenal mass |
| Premature thelarche | Prepubertal | Prepubertal | Prepubertal or early pubertal estradiol | Ovaries prepubertal | Onset usually before 3 yr of age |
| Premature adrenarche | Prepubertal | Prepubertal | Prepubertal estradiol; DHEAS values appropriate for pubic hair stage 2 | Ovaries prepubertal | Onset usually after 6 yr of age; more frequent in brain-injured children |

# Metabolic Disorders

## ASSESSMENT

- inborn error of metabolism is in D/D of causes of::
  1. mental retardation
  2. seizures
  3. sudden infant death
  4. neurologic impairment
- They affect all age groups.
- Inborn errors of metabolism result from a genetic deficiency in a metabolic pathway
  - ♣ signs and symptoms result from the accumulation of metabolites related to the pathway.
  - ♣ These metabolites may be toxic or may destroy cells because of storage in organelles.
  - ♣ Deficiency of metabolites downstream of the block also plays a role in pathogenesis.
- All mechanisms of inheritance occur.

## SIGNS AND SYMPTOMS THAT SHOULD SUGGEST AN INBORN ERROR OF METABOLISM

- The **signs and symptoms of an inborn error are protean**. Because any organ or system can be involved.
- Presentation varies among different age groups.
- Inborn errors of metabolism usually do not present immediately after birth. There is an interval that may last a few weeks during which the infant appears well.
- In infants who survive the neonatal period without developing recognized symptoms, the history is often marked by intermittent illness separated by periods of being entirely well.
- Family history may be helpful if positive.
- A history of early infant deaths is particularly suggestive.
- A negative family history does not exclude an inborn error of metabolism because this may be the first affected child in the family.
- The presentations may include:
  1. toxicity
  2. specific organ involvement
  3. energy deficiency
  4. dysmorphic findings
  5. Appearance of organ storage

## TYPES OF CLINICAL PRESENTATION OF INBORN ERRORS

### TOXIC PRESENTATION

- The toxic presentation often presents as an **encephalopathy**.
- A **metabolic acidosis**, vomiting, lethargy, and other neurologic findings may be present.
- The patient may have periods of being well that are punctuated by an acute illness.
- Fever, infection, fasting, or other catabolic stress may precipitate the symptom complex.
- During the acute presentation, diagnostic testing is most effective when diagnostic metabolites are present in highest concentration in blood and urine during this time.
- Abnormal metabolism of amino acids, organic acids, ammonia, or carbohydrates may be at fault.
- Hyperammonemia is an important diagnostic possibility if an infant or child presents with features of toxic encephalopathy.
- Symptoms and signs depend on the underlying cause of the hyperammonemia, the age at which it develops, and its degree.
- The severity of hyperammonemia may provide a clue to the etiology.

### SEVERE NEONATAL HYPERAMMONEMIA

- ammonia 100 times normal (>1000 µmol/L) in the neonatal period, Infants with:
  1. genetic defects in urea synthesis
  2. transient neonatal hyperammonemia
  3. impaired synthesis of urea and glutamine secondary to genetic disorders of organic acid metabolism
- manifestations:
  1. Poor feeding
  2. vomiting
  3. hypothermia
  4. hypotonia

5. apnea
6. Rapidly give way to **coma** and occasionally to intractable seizures.
7. Death within days if untreated.

### Etiologies of Hyperammonemia in Infants

| Etiology of Hyperammonemia | Comments |
|---|---|
| Disorders of the urea cycle | Lethal hyperammonemia is common |
| Disorders of the propionate pathway | Severe hyperammonemia may precede acidosis |
| Disorders of fatty acid catabolism and of ketogenesis | Reye-like syndrome possible |
| Transient neonatal hyperammonemia | Idiopathic, self-limited |
| Portal-systemic shunting | Thrombosis of portal vein, cirrhosis, hepatitis |
| Idiopathic Reye syndrome | Uncommon |
| Drug intoxication: salicylate, valproic acid, acetaminophen | Obtain drug levels |
| Hyperinsulinism/hyperammonemia syndrome | Clinical hypoglycemia, subclinical hyperammonemia |

## Moderate Neonatal Hyperammonemia

- Moderate neonatal hyperammonemia (range 200- 400 µmol/L) is associated with:
  1. Depression of the CNS
  2. poor feeding
  3. vomiting
  4. Seizures are not characteristic.
- This type of hyperammonemia may be caused by partial blocks in urea synthesis and commonly is caused by disorders of organic acid metabolism that secondarily interfere with the elimination of nitrogen.

## Clinical Hyperammonemia in Later Infancy and Childhood

- Infants who are affected by defects in the urea cycle and who are not ill in the neonatal period may continue to do well while receiving the low-protein intake of breast milk, only to develop clinical hyperammonemia when dietary protein is increased or when catabolic stress occurs.
- The clinical presentation is dominated by **vomiting** and **lethargy**, which frequently progresses to **coma**.
- As protein intake is restricted by anorexia and vomiting or if IV glucose is given, the sensorium clears, and the infant recovers, but the infant may develop symptoms again when metabolically stressed or ingesting an increased protein intake.
- Seizures are not typical.
- During a crisis, the plasma ammonia level is usually 200 to 500 µmol/L, but when dietary protein is restricted, the ammonia level decreases and may become normal.
- If the CNS symptoms are not prominent, the condition may go unrecognized for years.
- When a crisis occurs during an epidemic of influenza, the child mistakenly may be thought to have **Reye syndrome**.
- Older children may have neuropsychiatric or behavioral abnormalities.

### Inborn Errors of Metabolism Presenting with Hepatomegaly or Hepatic Dysfunction in Infants

| Hepatomegaly | Hepatic Failure | Jaundice |
|---|---|---|
| GSD I | Galactosemia | Galactosemia |
| GSD III | Hereditary fructose intolerance | Hereditary fructose intolerance |
| Mucopolysaccharidosis I and II | Infantile tyrosinemia (fumarylacetoacetate hydrolase deficiency) | Infantile tyrosinemia (fumarylacetoacetate hydrolase deficiency) |
| Gaucher and Niemann-Pick diseases | | Crigler-Najjar disease |
| | GSD IV (slowly evolving) | Rotor, Dubin-Johnson syndromes |

### Energy Deficiency

- Disorders whose pathophysiology results in energy deficiency may manifest:
  1. myopathy
  2. CNS dysfunction including mental retardation and seizures
  3. cardiomyopathy

4. vomiting
5. renal tubular acidosis.

- Examples include:
  1. disorders of fatty acid oxidation
  2. disorders of mitochondrial function/oxidative phosphorylation
  3. disorders of carbohydrate metabolism

### Ketosis and Ketotic Hypoglycemia

- **Ketotic hypoglycemia** is a common condition.
  - ♣ Tolerance for fasting is impaired to the extent that symptomatic hypoglycemia with seizures or coma occurs when the child encounters a ketotic stress.
  - ♣ The stress may be significant (viral infection with vomiting) or minor (a prolongation by several hours of the normal overnight fast).
  - ♣ Ketotic hypoglycemia first appears in the second year of life and occurs in otherwise healthy children.
  - ♣ It is treated by frequent snacks and the provision of glucose during periods of stress.
  - ♣ In neonates, ketonuria indicates metabolic disease.
  - ♣ In older infants & children, ketonuria is a normal response to fasting but not to a normal overnight fast.
- **A high anion gap metabolic acidosis with or without ketosis suggests a metabolic disorder**.

## Disorders Associated with Dysmorphic Findings

- Conditions that cause congenital malformations include:
  1. carbohydrate-deficient glycoprotein syndrome
  2. disorders of cholesterol biosynthesis (Smith-Lemli-Opitz syndrome)
  3. disorders of copper transport (Menkes syndrome, occipital horn syndrome)
  4. maternal PKU syndrome
  5. glutaric aciduria II
  6. several storage diseases.

### Storage Disorders

- Storage disorders are caused by accumulation of incompletely metabolized large molecules.
- This storage often occurs in subcellular organelles, such as lyso-somes.
- The glycogen storage diseases and mucopoly-saccharide disorders are other examples of storage disorders.

## Different Age Groups and Differing Clinical Phenotypes

- A neonate no longer has the protective functions of the placenta to detoxify metabolites that accumulate because of an inborn error.
- Maternal metabolism no longer provides nutrition to the neonate who cannot metabolize substrates such as glycogen and fatty acids.
- Introduction of new foods in older infancy and frequency of metabolic stress with fasting and fever in that age group make the infant vulnerable.
- Increased protein intake associated with growth in older children and adolescents may stress deficient pathways that previously were compensated.
- Hormonal factors in adolescence influence intermediary metabolism in unpredictable ways.

### Examples include:

1. **Neonatal**
   - o Galactosemia: introduction of milk
   - o Fatty acid disorders: fasting/breastfeeding
   - o Loss of maternal detoxification: organic acid disorders: urea cycle
2. **Infancy**
   - o Hereditary fructose intolerance: introduction of fructose (sucrose)
   - o Disorders of fatty acid oxidation: fasting, infectious illness, fever
3. **Childhood**
   - o Disorders of ammonia detoxification, females with X-linked ornithine carbamoyltransferase (OTC) deficiency: increased protein intake
4. **Adolescence**
   - o Cobalamin C methylmalonic aciduria (cblCMMA) neurologic deterioration: unknown triggers, possible hormonal changes

## CLINICAL ASSESSMENT AND CLINICAL LABORATORY TESTING

- The combination of symptoms and abnormal clinical laboratory findings demands urgent metabolic evaluation.
- Features in the history that may reflect a metabolic emergency include:
  1. vomiting
  2. acidosis
  3. hypoglycemia
  4. ketosis (*or lack of appropriate ketosis*)
  5. intercurrent infection
  6. anorexia/failure to feed
  7. lethargy proceeding to coma
  8. Hyperventilation or hypoventilation.
- Clinical evaluation should focus particularly on:
  1. look for change in mental status
  2. seizures, abnormal tone, visual symptoms
  3. poor developmental progress, global developmental delay, loss of milestones,
  4. cardiomyopathy, cardiac failure
  5. Cystic renal malformation and renal tubular dysfunction.
- Plasma measurements of lactate and ammonia are particularly subject to spurious results if not handled correctly.
  - ♣ Significant ketosis in the neonate is unusual and suggests an **organic acid disorder**.
  - ♣ Ketosis out of proportion to fasting status in an older child occurs in **disorders of ketone usage**.
  - ♣ Lack of ketosis in an older child under conditions of metabolic stress is a feature of **fatty acid oxidation disorders**

### INITIAL DIAGNOSTIC EVALUATION FOR A SUSPECTED INBORN ERROR OF METABOLISM

| BLOOD AND PLASMA | URINE |
|---|---|
| Arterial blood gas | Glucose |
| Electrolytes-anion gap | pH |
| Glucose | Ketones |
| Ammonia | Reducing substances |
| Liver enzymes | Organic acids |
| CBC, differential,[T] and platelet count | Acylcarnitine |
| Lactate, pyruvate | Orotic acid |
| Organic acids | |
| Amino acids | |
| Carnitine | |

### DISORDERS IDENTIFIED BY NEONATAL SCREENING

- Most states screen for at least eight or nine disorders.
- In states where tandem mass spectrometry (MS/MS) is the method used, 30 metabolic disorders may be identifiable.
- The **disorders of amino acid metabolism**, PKU, homocystinuria, MSUD, and tyrosinemia all need to be treated early in infancy for treatment to be effective. In MSUD, severe ketoacidosis may supervene in the first 2 weeks of life.
- The disorders of **organic acid metabolism**, propionic acidemia, methylmalonic acidemia, and isovaleric acidemia may result in vomiting and ketoacidosis early in life; some forms of methyl-malonic acidemia present later, but CNS damage already may have occurred.
- **Galactosemia** is the disorder of carbohydrate metabolism screened for. Initial presentation of galactosemia not identified by screening includes jaundice, bleeding, cataract, and liver failure. Presymptomatic treatment affects outcome in all of these conditions; in some it is lifesaving.

# CARBOHYDRATE DISORDERS

## GLYCOGEN STORAGE DISEASES

- The glycogen storage diseases enter into the differential diagnoses of **hypoglycemia and hepatomegaly**.
- Glycogen is the storage form of glucose and is found most abundantly in the liver, where it modulates blood glucose and in muscles, where it facilitates anaerobic work.
- Glycogen is synthesized from uridine di-phospho-glucose through the concerted action of glycogen synthetase and brancher enzyme.

**Uridine diphosphoglucose** —(Glycogen synthetase)→ **glycogen**

  - ♣ The accumulation of glycogen is stimulated by insulin.
  - ♣ Glycogenolysis occurs through a cascade phenomenon that is initiated by epinephrine or glucagon

**glycogen** —(phosphorolysis)→ **glucose-1-phosphate**

- In the liver and kidneys, glucose-1-phosphate can produce glucose through the actions of phosphoglucomutase and glucose-6-phosphatase. The latter enzyme is not present in muscles.

- Glycogen storage diseases fall into the following four categories:
  1. Diseases predominantly affect **liver** and have a direct effect on blood glucose **(types I, VI, VIII)** = **1,6,8**
  2. Diseases predominantly involve **muscles** & affect the ability to do anaerobic work **(types V and VII)**=**5,7**
  3. Diseases affect the **liver & muscles** and directly influence blood glucose and muscle metabolism **(type III)**
  4. Diseases that affect various tissues but have no direct effect on blood glucose or on the ability to do anaerobic work **(types II and IV)**= **2,4**
- The **diagnosis** of glycogen storage disease:
  1. confirmed by :**DNA mutation testing** in blood cells.
  2. if not available, **enzyme measurements** in the tissue suspected to be affected (either liver or muscle) confirm the diagnosis.
  3. If the diagnosis cannot be established, metabolic challenge and exercise testing may be needed.
- **Treatment** of hepatic glycogen storage disease is aimed at maintaining satisfactory blood glucose levels or supplying alternative energy sources to muscle.
  - In glucose-6-phosphatase deficiency (type I), the treatment usually requires nocturnal intragastric feedings of glucose during the first 1 or 2 years of life.uncooked cornstarch may be satisfactory, but hepatic tumors (sometimes malignant) are a threat in adolescence and adult life.
  - No specific treatment exists for the diseases of muscle that impair skeletal muscle ischemic exercise.
  - Enzyme replacement is effective in Pompe disease (type II), which involves cardiac and skeletal muscle.

## GLYCOGEN STORAGE DISEASES

| Disease | Affected Enzyme | Organs Affected | Clinical Syndrome | Neonatal Manifestations | Prognosis |
|---|---|---|---|---|---|
| Type I: von Gierke | Glucose-6-phosphatase | Liver, kidney, **GI tract**, **platelets** | Hypoglycemia, lactic acidosis, ketosis, hepatomegaly, hypotonia, slow growth, diarrhea, bleeding disorder, **gout**, **hypertriglyceridemia**, xanthomas | **Hypoglycemia, lactic acidemia, liver may not be enlarged** | Early death from hypoglycemia, lactic acidosis; may do well with supportive management; hepatomas occur in late childhood |
| Type II: Pompe | Lysosomal α-glucosidase | All, notably striated muscle, nerve cells | Symmetric profound muscle weakness, cardiomegaly, heart failure, shortened P-R interval | **May have muscle weakness, cardiomegaly, or both** | Very poor; death in the first year of life is usual; variants exist; therapy with recombinant human α-glucosidase is promising |
| Type III: Forbes | Debranching enzyme | Liver, muscles | Early in course hypoglycemia, ketonuria, hepatomegaly that resolves with age; may show muscle fatigue | Usually none | Very good for hepatic disorder; if myopathy present, it tends to be like that of type V |
| Type IV: Andersen | Branching enzyme | Liver, other tissues | Hepatic cirrhosis beginning at several months of age; early liver failure | Usually none | Very poor; death from hepatic failure before age of 4 years |
| Type V: McArdle | Muscle phosphorylase | Muscle | Muscle fatigue beginning in adolescence | None | Good, with sedentary lifestyle |
| Type VI: Hers | Liver phosphorylase | Liver | Mild hypoglycemia with hepatomegaly, ketonuria | Usually none | Probably good |
| Type VII: Tarui | Muscle phosphofructo kinase | Muscle | Clinical findings similar to type V | None | Similar to that of type V |
| Type VIII | Phosphorylase kinase | Liver | Clinical findings similar to type III, without myopathy | None | Good |

Except for one form of hepatic phosphorylase kinase, which is X-linked, these disorders are autosomal recessive.

## GALACTOSEMIA

- Galactosemia is an autosomal recessive disease caused by deficiency of the enzyme **galactose-1-phosphate uridyltransferase**.
- Clinical manifestations are most striking in a neonate **who when fed milk** exhibits evidence of:
  1. **liver failure** (hyperbilirubinemia, disorders of coagulation, and hypoglycemia)
  2. **renal tubular function** (acidosis, glycosuria, and aminoaciduria),
  3. **Cataracts**.
- The neonatal screening test must have a rapid turnaround time because affected infants may die in the first week of life.
- Infants with galactosemia are at increased risk for severe neonatal ***Escherichia coli* sepsis**.
- Major effects on liver and kidney function and the development of cataracts are limited to the first few years of life, but older children have **learning disorders**.
- Girls may develop **premature ovarian failure**, which occurs despite treatment.
- **Laboratory manifestations** of galactosemia depend on dietary galactose intake.
  1. Levels of plasma galactose & erythrocyte galactose-1-phosphate ↑. When galactose is ingested (as lactose).
  2. **Hypoglycemia**
  3. **albuminuria**
  4. Galactose frequently is present in the urine and can be detected by:
     - ♣ positive reaction for reducing substances (**Clinitest tablets**)
     - ♣ No reaction with glucose oxidase on **urine strip tests**.
  5. **Blood gases**: Renal tubular dysfunction : normal anion gap **hyperchloremic metabolic acidosis**.
  6. extreme ↓ **erythrocyte galactose-1-phosphate uridyltransferase**.
  7. **DNA testing for the mutations** in galactose-1-phosphate uridyltransferase confirms the diagnosis
- **Treatment** by the elimination of dietary galactose results in rapid correction of abnormalities, but infants who are extremely ill before treatment may die before therapy is effective.
- The concentration of galactose-1-phosphate rarely returns to normal even after treatment is begun.

***Galactokinase deficiency***

- autosomal recessive disorder
- leads to the accumulation of galactose in body fluids, which results in the formation of galactitol (dulcitol) through the action of aldose reductase.
- ***The only clinical manifestations as*** Galactitol, acting as an osmotic agent***:***
  1. cataract formation
  2. rarely, increased intracranial pressure.
- Persons homozygous for galactokinase deficiency develop cataracts in the neonatal period, whereas heterozygous individuals may be at risk for cataracts as adults.
- ***Treatment*** consists of lifelong elimination of galactose from the diet.

***Hereditary fructose intolerance***

- many ways is analogous to galactosemia.
- When fructose is ingested, deficiency of fructose-1-phosphate aldolase leads to the intracellular accumulation of fructose-1-phosphate with resultant :
  1. emesis
  2. hypoglycemia
  3. severe liver and kidney disease
- Elimination of fructose and sucrose from the diet cures the clinical disease.
- Affected patients spontaneously avoid fructose-containing foods and have no dental caries.

# AMINO ACID DISORDERS

## DISORDERS OF AMINO ACID METABOLISM

- Disorders of amino acid metabolism : inability to catabolize specific amino acid derived from protein.
- Usually a single amino acid pathway is involved.
- This amino acid accumulates in excess and is toxic to various organs, such as the **brain, eye, skin, or liver**.
- Confirmatory testing includes quantitative specific plasma amino acid profiles along with specific mutation testing and sometimes enzymology.

## PHENYLKETONURIA

- autosomal recessive disease, primarily affects the brain.
- It occurs in 1:10,000 persons.
- the activity of **phenylalanine hydroxylase** in the liver is absent or greatly reduced→defect in the hydroxylation of phenylalanine to form tyrosine.
- Affected infants are normal at birth, but severe mental retardation (IQ 30) develops in the first year of life.
- The clinical syndrome classically described of :
  1. blond hair
  2. blue eyes
  3. eczema
  4. mousy odor of the urine
- A positive newborn screening test must be followed up by performing quantitative plasma amino acid analysis, measuring phenylalanine and tyrosine.
  - ♣ A plasma phenylalanine value > 360 μM (6 mg/dL) is consistent with the diagnosis of one of the hyperphenylalaninemias and demands prompt evaluation and treatment.
  - ♣ Untreated, classic PKU has blood phenylalanine concentrations > 600 μM.
  - ♣ Milder forms of hyperphenylalaninemia show values of plasma phenylalanine lower than this but > 360 μM.
- A significant percentage of premature infants and a few full-term infants have transient elevations in phenylalanine. Short-term follow-up usually identifies these infants promptly.
- Mutation testing of the *PAH* gene reveals more than 400 mutations.
  - ♣ R408W mutation, clinical correlation is almost always reliable; classic PKU is seen if pt has 2 copies of it.
  - ♣ Some mutations are associated with mild hyperphenylalaninemia.
- **Clinical care** is designed to maintain plasma phenylalanine values in the therapeutic range of 120- 360 μM, at least for the first 10 years of life.
- In classic PKU the outcome is excellent. Most infants who are treated using a diet specifically restricted in phenylalanine and begun within the first 10 days of life achieve normal intelligence.
- Learning problems and problems with executive function are reported; early and consistent dietary control provides the best chance for optimal outcome.
- In the disorders of biopterin biosynthesis, restriction of dietary phenylalanine reduces plasma phenylalanine, but does not ameliorate the clinical symptoms. This condition must be treated by replacement of the cofactor or by neuropharmacologic agents. Outcome is less predictable than in classic PKU.
- **Maternal hyperphenylalaninemia** is a major problem requiring rigorous management before conception and throughout pregnancy to prevent fetal **brain damage**, **congenital heart disease**, and **microcephaly** .

## TYROSINEMIAS

- Tyrosinemia is identified in neonatal screening programs using **MS/MS methods**.
  - ♣ Elevated tyrosine levels also can occur as a nonspecific consequence of severe liver disease.
  - ♣ transient tyrosinemia of the newborn, which responds to ascorbic acid treatment.
  - ♣ The inherited disorders of tyrosine metabolism, which are the target of neonatal screening.

### TYROSINEMIA I

- rare disease which is due to **fumaryl/aceto /acetate hydrolase** deficiency,produce :
  1. **severe liver disease** associated with bleeding disorder
  2. hypoglycemia
  3. hypoalbuminemia
  4. elevated transaminases
  5. defects in **renal tubular function**
  6. **Hepatocellular carcinoma** may occur eventually
- If positive neonatal screening test for hypertyrosinemia→ Quantitative measurement of plasma amino acid to look for excess tyrosine or the pattern of liver disease.
- The **diagnosis** of tyrosinemia I
  - ♣ confirmed by measuring **succinylacetone in urine**.
  - ♣ DNA testing is available for some mutations in tyrosinemia I.
- **Treatment** :
  - ♣ **NTBC** (an inhibitor of the oxidation of (para /hydroxy/phenyl/ pyruvic/acid) effectively eliminates the production of the toxic succinylacetone. ? if no risk of HCC with it.
  - ♣ A low-phenylalanine, low-tyrosine diet may also play a role.
  - ♣ These treatments decrease liver transplantation in many children identified by neonatal screening.

## TYROSINEMIA II AND III

- More benign forms of hereditary tyrosinemia.
- Blocked metabolism of tyrosine at earlier steps in the pathway is responsible, and **succinylacetone is not produced.**
- The clinical features include :
  1. hyperkeratosis of palms and soles
  2. keratitis, which can cause severe visual disturbance.
- **Treatment**: with a phenylalanine-restricted and tyrosine-restricted diet is effective.

## HOMOCYSTINURIA

- autosomal recessive disease (1:200,000 live births)
- Involving **connective tissue, the brain, and the vascular system.**
- caused by a deficiency of **cystathionine β-synthase**.
- Methionine → homocysteine → cystine
  - ♣ When cystathionine β-synthase is deficient, homocysteine accumulates in the blood and appears in the urine.
  - ♣ Another result is enhanced reconversion of homocysteine to Methionine resulting in an increase in the concentration of Methionine in the blood.
  - ♣ The neonatal screening test most commonly used measures Methionine in whole blood.
- excess of homocysteine produces a slowly evolving **clinical syndrome** that includes:
  1. **dislocated ocular lenses**
  2. long, slender extremities
  3. malar flushing
  4. livedo reticularis
  5. **skeletal features**: Arachnodactyly, scoliosis, pectus excavatum or carinatum, and genu valgum.
  6. **Mental retardation**, psychiatric illness, or both may be present.
  7. Major arterial or venous thromboses are a constant threat.
- Homocystinuria has no neonatal manifestations.
- **Diagnosis:**
  - ♣ **Confirmation of the diagnosis** requires demonstration of ↑total homocysteine in the blood.
  - ♣ A plasma amino acid profile reveals hypermethioninemia.
  - ♣ Measurement of cystathionine β-synthase can be performed, but is not clinically available.
  - ♣ Numerous mutations in the cystathionine β-synthase gene are known and can be tested.
- There are two clinical forms of homocystinuria:
  1. Activity of the deficient enzyme can be enhanced by large doses of **pyridoxine** (100 to 1000 mg/day); 50% of the cases, more likely form to be missed by neonatal screening because the methionine℞ concentrations are not always above the screening cutoff. folate supplementation is added .
  2. not responsive to pyridoxine therapy, the accumulation of homocysteine is controlled with a methionine-restricted diet and cystine and folate supplementation. The prognosis is good for infants whose plasma homocysteine concentration is controlled.

## MAPLE SYRUP URINE DISEASE

- autosomal recessive disease, more properly named **branched chain ketoaciduria**.
- caused by deficiency of the decarboxylase that initiates the degradation of the ketoacid analogues of the three branched chain amino acids-leucine, isoleucine, and valine.
- rare (1 : 250,000) in the general population but much more common in Pennsylvania Mennonites.
- Neonatal screening programs commonly include MSUD.
- have intermittent-onset and late-onset forms.
- **clinical manifestations** of the classic form typically begin within 1 to 4 weeks of birth
  1. Poor feeding
  2. vomiting
  3. tachypnea
  4. profound depression of the CNS: the hallmark of the disease
  5. alternating hypotonia and hypertonia (extensor spasms)
  6. opisthotonos
  7. seizures
  8. The urine has the odor of maple syrup.
- Laboratory manifestations of MSUD include:

1. hypoglycemia
2. variable presence of metabolic acidosis.

- The **definitive diagnosis** of MSUD is made by:
  A. showing large increases in plasma **leucine**, **isoleucine**, and **valine** concentrations
  B. The identification of **alloisoleucine** in the plasma in excess.
- The urinary organic acid profile also is usually abnormal and shows the ketoacid derivatives of the branched chain amino acids.
- **Treatment**
  - ♣ Consists of restricting the intake of branched chain amino acids (all three are essential amino acids) to the amounts required for growth in severely affected infants.
  - ♣ Hemodialysis, hemofiltration, or peritoneal dialysis can be lifesaving during acidotic crises.
  - ♣ Ordinary catabolic stresses, such as moderate infections or labor and delivery in a pregnant mother with MSUD, can precipitate clinical crises.
  - ♣ Treatment with special diets must be continued for life.
  - ♣ Liver transplantation effectively treats MSUD

## ORGANIC ACID DISORDERS

- Organic acid disorders result from a metabolic block in the pathways of catabolism of amino acid.
- Occurring at the end of the pathways of catabolism of amino acid after the amino moiety has been removed, they result in the accumulation of specific organic acids in the blood and urine.
- Outcome is influenced by frequency and severity of ketoacidotic crises and is optimal when diagnosis is made before the onset of the first episode.
- Liver transplantation has been employed in some patients and can be successful, but long-term outcome after liver transplantation has not been well studied.
- Confirmatory testing begins with a **urine organic acid profile and plasma amino acid profile**. When abnormal results confirm the specific organic acid disorder, **DNA testing** may identify the mutations involved. More specific testing if a mutation is not found requires **enzyme measurements in appropriate tissues**.

### PROPIONIC ACIDEMIA AND METHYLMALONIC ACIDEMIA

- Propionic acidemia and methylmalonic acidemia result from defects in a series of reactions called the *propionate pathway*.
- produce **ketosis** and **hyperglycinemia**.
- Propionic acidemia and methylmalonic acidemia are identified by neonatal screening when MS/MS methods.
- **clinical manifestations** in the neonatal period :
  1. tachypnea
  2. vomiting
  3. hypoglycemia
  4. intermittent ketoacidosis
  5. lethargy
  6. coma
  7. hyperglycinemia
  8. hyperammonemia
  9. thrombocytopenia
  10. neutropenia
- intermittent episodes of metabolic acidosis occur.
- Crises occur during periods of catabolic stress, such as fever, vomiting, and diarrhea; they also may occur without an apparent precipitating event.
- During periods of neutropenia, the risk of serious bacterial infection is increased.
- **Failure to thrive** and impaired development are common.
- **Propionic acidemia** results from deficiency in **propionyl CoA-carboxylase.** All forms of propionic acidemia are inherited in an autosomal recessive manner .
- **Methylmalonic acidemia** results from deficiency in **methylmalonyl mutase**.
- **Treatment** : massive doses of **hydroxycobalamin** (the active form of vitamin $B_{12}$) is helpful in some cases of methylmalonic acidemia.

## ISOVALERIC ACIDEMIA

- Isovaleric acidemia results from a **block in the catabolism of leucine**.
- Its clinical manifestations are similar to those of defects in the propionate pathway.
- Because isovaleric acid has a strong odor, infants have a **"sweaty feet" odor** when untreated.
- **diet restricted in the intake of leucine**,
- **glycine therapy** is beneficial through enhancement of the formation of iso-valerylglycine, a relatively harmless conjugate of iso-valeric acid which is excreted in the urine.

## GLUTARIC ACIDEMIA I

- Glutaric acidemia I results from a **deficiency at the end of the lysine catabolic pathway**.
- It is an autosomal recessive disease produced by deficiency of **glutaryl-CoA dehydrogenase** activity.
- **Clinical manifestations** include:
  1. **macrocephaly**, which may be present at birth,
  2. **dystonia**, characteristically develops after the first 18 months of life, after an episode of intercurrent illness associated with fever and metabolic distress.
  3. **"metabolic" strokelike episodes** associated with infarction of the basal ganglia.
- **Treatment** : protein-restricted diet accompanied by a medical food deficient in lysine.

## BIOTINIDASE DEFICIENCY

- Biotin is a ubiquitous vitamin that is covalently linked to many carboxylases, including propionyl CoA carboxylase, by holocarboxylase synthetase in a variety of tissues.
- Inherited biotinidase deficiency greatly increases the dietary requirement for biotin because biotin cannot be recycled from its attachment to the carboxylases.
- Affected individuals become biotin deficient while consuming normal diets. Clinical disease can appear in the neonatal period or be delayed until later infancy, depending on the degree of deficiency.
- The **clinical manifestations** of biotin deficiency vary greatly :
  1. seizures
  2. hypotonia
  3. alopecia
  4. skin rash
  5. metabolic acidosis
  6. immune deficits)
- Most patients with biotinidase deficiency excrete abnormal amounts of several organic acids, among which β-methylcrotonylglycine is prominent.
- **treatment** with large (10 to 40 mg/day) doses of biotin.
- Confirmatory testing is accomplished with quantitative measurement of bio-tinidase activity

# FAT METABOLIC DISORDERS

## DISORDERS OF FATTY ACID OXIDATION

- Fatty acids are derived from hydrolysis of triglycerides and catabolism of fat.
- The fatty acids important in human biology range in chain length from 18 carbons to 6 carbons.
- The catabolism of fatty acids proceeds through the serial, oxidative removal of two carbons at a time as acetyl groups (each as acetyl-CoA).
- medium chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common inborn error of β-oxidation.
  - Hypoketotic hypoglycemia is a common manifestation
  - as is **Reye syndrome-like** illness with hypoglycemia and elevated liver enzymes.
  - Fatty infiltration of the liver also occurs.
  - True hepatic failure is rare.
  - Reye syndrome-like illnesses may be recurrent in the patient or the family.
  - **Sudden infant death syndrome** may occur in infants with MCAD deficiency.
  - Most of the other rarer disorders of fatty acid oxidation involve skeletal and cardiac muscle more than does MCAD.
- In all of the disorders of β-oxidation, carnitine depletion can occur through excessive urinary excretion of carnitine esters of incompletely oxidized fatty acids.
- The **diagnosis** of disorders involving a deficiency of β-oxidation is suggested by the clinical picture and by **hypoketotic hypoglycemia**.

- The diagnosis is confirmed by analysis of urinary organic acid and acylglycine profiles, along with plasma acylcarnitine and free fatty acid profiles. Enzyme measurements and DNA testing complete the confirmatory testing.
- **Treatment** consists of a high-carbohydrate diet, carnitine supplements, avoidance of fasting, and aggressive administration of dextrose during intercurrent stresses.

## GLUTARIC ACIDURIA TYPE II

- Glutaric aciduria type II exhibits autosomal recessive inheritance.
- congenital anomalies are common, including renal cysts, facial abnormalities, rocker-bottom feet, and hypospadias.
- Severely affected infants have **hypoglycemia without ketosis**
- metabolic acidosis
- odor of sweaty feet soon after birth
- Less severely affected infants may have a more episodic, Reye syndrome-like illness.
- Skeletal and cardiac myopathy can be prominent in this complex, pansystemic disease.
- Onset in later childhood may be marked mainly by recurrent hypoglycemia and myopathy.
- **Treatment** has not been effective in infants with complete deficiency.
- Milder forms respond to avoidance of fasting and caloric support during metabolic stress.

## CARNITINE DEFICIENCY

- Carnitine is a crucial cofactor in the transport of long chain fatty acids across the mitochondrial inner membrane.
- It is synthesized from lysine by humans and is present in dietary red meat and dairy products.
- Carnitine deficiency:
  - ♣ primary (caused by failure of intake, synthesis, or transport to tissues of carnitine)
  - ♣ secondary (caused by the excretion of excessive amounts of carnitine as carnityl esters in patients with other inborn errors of metabolism or treatment with drugs that complex carnitine, such as valproic acid).
- **Primary systemic carnitine deficiency** is rare and results from inadequate renal reabsorption of carnitine secondary to a mutation in the sodium-dependent carnitine transporter. It responds well to carnitine supplementation.
- Clinical manifestations of carnitine deficiency include:
  1. failure to produce acetoacetic and β-hydroxybutyric acids ( **no keton bodies**)
  2. **hypoglycemia**
  3. lethargy, lassitude
  4. muscle weakness
  5. **cardiomyopathy**.

# LYSOSOMAL AND PEROXISOMAL DISORDERS

## PEROXISOMAL DISORDERS

- Peroxisomes are subcellular organelles that are involved in complex lipid metabolism, such as :
  1. metabolism and biosynthesis of bile acids
  2. membrane phospholipids
  3. some β-oxidation of long chain fatty acids
- Disorders include conditions caused by :
  1. abnormal peroxisomal enzyme function
  2. abnormal peroxisomal biogenesis
- **Clinical symptoms are protean** and nearly always include **:**
  1. **developmental delay**
  2. **mental retardation**
  3. **dysmorphic features** that can involve the skeleton and the head.
- examples of disorders of peroxisome biogenesis:
  1. Zellweger syndrome,
  2. neonatal adrenoleukodystrophy
  3. infantile Refsum disease

- examples of peroxisomal single enzyme disorders:
  1. Refsum disease
  2. neonatal adrenoleukodystrophy

malonic aciduria

- **Diagnostic testing** includes:
  - measurement of **very long chain fatty acids in plasma**
  - Measurement of **pipecolic acid in urine**.
  - Specific molecular testing, particularly for the disorders involving one in the series of *PEX* genes, is available for some disorders.
- **Treatment**:
  - Most of these conditions are untreatable;
  - bone marrow transplant can be helpful in X-linked adrenoleukodystrophy.

## ZELLWEGER SYNDROME

- called **cerebrohepatorenal syndrome**, death occurs within the first year.
- autosomal recessive disease (1:100,000 births)
- Peroxisomes are virtually absent, as are normal peroxisomal functions, which include the oxidation of very long chain fatty acids.
- Affected infants have :
  1. high foreheads
  2. flat orbital ridges
  3. widely open fontanels
  4. hepatomegaly
  5. hypotonia
  6. Failure to thrive
  7. nystagmus develop early
  8. seizures

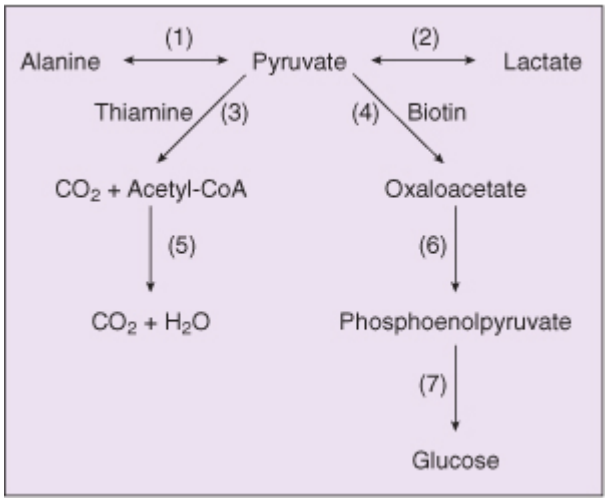
## LYSOSOMAL STORAGE DISORDERS

- Lysosomes are subcellular organelles that contain degradative enzymes for complex **glycosaminoglycans**, also called **mucopolysaccharides**.
- Most of these are inherited in an autosomal recessive fashion. Hunter syndrome is X-linked.
- Genetic disorders can result from:
  1. formation of the lysosome itself
  2. deficiency in specific hydrolytic enzymes
  3. mechanisms that protect intralysosomal enzymes from hydrolytic destruction
  4. transport of materials into the lysosome and of metabolites out of the lysosome
- These materials are stored in cells & ultimately result in their destruction, **especially in the nervous system.**
- Some disorders affect many tissues but spare the brain, whereas others are apparent only during adult life.
- Storage in solid organs results in **organomegaly**.
- common features include:
  1. **Developmental delay**
  2. **corneal clouding**
  3. **limitation of joint mobility**
- **Nonimmune hydrops fetalis** occurs in several lysosomal disorders.
- Diagnostic testing includes :
  1. measurement of glycosaminoglycans in urine
  2. enzyme assay in white blood cells.
- **Treatment** :
  - Available for some lysosomal disorders.
  - For some individuals, **bone marrow transplantation** can restore lysosomal function.
  - For others, **replacement of the missing hydrolytic enzyme** by systemic administration of the enzyme allows degradation of stored material.
  - The diseases that are treatable should be treated before clinical signs appear.

# MITOCHONDRIAL DISORDERS

## LACTIC ACIDOSIS

- Interference with mitochondrial oxidative metabolism results in the Accumulation of pyruvate.
- Because lactate dehydro-genase is ubiquitous, and because the equilibrium catalyzed by this enzyme greatly favors lactate over pyruvate, the accumulation of pyruvate results in lactic acidosis.
- **The most common cause of such lactic acidosis is oxygen Deficiency** caused by anoxia or poor perfusion, as seen in cardiac arrest, shock, severe cyanosis, and profound heart failure
- Poisons, such as **cyanide**, **sulfide**, and **carbon monoxide**, which, similar to anoxia, block the terminal reaction of the mitochondrialrespiratory chain, also produce lactic acidosis.
- Lactic acidosis also occurs when specific reactions of pyruvate are impaired.
- Pyruvate has three major fates:
  1. **In muscle**, it is transaminated to form alanine, which can be used for protein synthesis or transported to the liver and may appear in blood in the presence of intermittent lactic acidosis.
  2. **In the liver,** it undergoes carboxylation to form oxaloacetate using the enzyme pyruvate carboxylase; deficiency in this enzyme causes severe lactic acidosis.
  3. **In many tissues**, lactate is catabolized to form acetyl CoA. The reaction is catalyzed by the pyruvate dehydrogenase complex; pyruvate dehydrogenase deficiency cause lactic acidosis.




- **hypoglycemia** is a feature of these disorders.
- The clinical spectrum in this group of disorders ranges from **metabolic acidosis** and **mental retardation** to intractable, lethal acidosis in the first months of life or the CNS phenotype of **Leigh syndrome**.
- Defects of the mitochondrial respiratory chain itself also can produce lactic acidosis.
- Some defects show autosomal recessive inheritance; others show mitochondrial (maternal mtDNA) inheritance; some, particularly the mtDNA deletions, are sporadic.
- **Myopathy** is common, frequently showing ragged red fibers on muscle biopsy.
- **Alper disease** (cerebral degeneration and liver disease) and **Leigh disease** (subacute necrotizing encephalomyelopathy) show similar brain lesions, but in distinctly different areas of the brain.
- **Treatment** is limited for most mitochondrial defects. Vitamin cofactors for the respiratory chain and coenzyme Q are often employed.

### SOME DISORDERS OF THE RESPIRATORY CHAIN THAT CAUSE LACTIC ACIDOSIS

| Disease | Inheritance | Clinical Picture |
|---|---|---|
| Myoclonic epilepsy with ragged red fibers (**MERRF**) | Maternal mtDNA | Lactic acidosis may be severe; variable clinical picture |
| Myopathy, encephalopathy, lactic acidosis, strokelike episodes (**MELAS**) | Maternal mtDNA | Highly variable clinical picture, including **type 2 diabetes mellitus** |
| Pearson syndrome | Maternal mtDNA | Macrocytic anemia, sideroblasts, pancreatic insufficiency |
| Alpers syndrome | Unclear | Cerebral degeneration and liver disease |
| Leigh disease (CNS) | Autosomal recessive in some and maternal mtDNA in others | Degenerative disease of thalamus, basal ganglia, and spinal cord |

**Note:**
**Dr. Imad sheet about 'clinical approach to inborn errors of metabolism"**