# Nutrition and Gastrointestinal Disease

Edited by

Mark H. DeLegge,

MD, FACG, AGAF, FASGE

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# Nutrition and Gastrointestinal Disease

# CLINICAL GASTROENTEROLOGY

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Cover Illustrations: Degraded percutaneous endoscopic gastrostomy tube; percutaneous endoscopic gastrojejunostomy tube; forceps intubating a percutaneous endoscopic gastrostomy tube in preparation for jejunal tube placement.



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To my GI colleague Steve, who has trumpeted the education of gastroenterologists in nutrition, to my dietitian colleagues Carol and Pat, who have worked to make nutrition understandable for clinicians, and to my family, Becky, Taylor, Madison and Garrett, who have graciously and enthusiastically supported me through my career.

# Preface

Nutritional support of the hospitalized patient is important in improving patient outcome. The past 40 years have shown tremendous improvement in medicine's ability to deliver nutrition to at-risk patients. The use of parenteral nutrition (PN) was introduced in the 1960s and has continued to be an important tool for the nutrition support of patients with gastrointestinal (GI) impairment. Advances in enteral access techniques and in the development of specialized enteral nutrition (EN) feeding formulas have created interest in the development of disease-specific nutrition management.

Gastroenterologists, by the nature of their expertise in gut physiology and disease, should be the experts in nutrition, knowledgeable about the effects of nutrition on disease management. Many of the diseases a gastroenterologist encounters, such as short bowel syndrome, inflammatory bowel disease, celiac disease and obesity, require expert nutrition knowledge and management to improve outcomes.

To date, many gastroenterology training programs in the United States remain deficient in their nutrition curriculum. This book serves as a hands-on, practical reference in nutrition support for the clinical gastroenterologist and for other clinicians with similar interests.

***Mark H. DeLegge, MD***

# Contents

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# 1 Nutritional Assessment

*Mark H. DeLegge, MD, FACG, AGAF, FASGE and Luke M. Drake, MD*

***Contents***



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*Summary*

Protein calorie malnutrition leads to poor clinical outcomes. In order to effectively treat patients with protein calorie malnutrition, a process must be in place to identify patients at nutrition risk. A nutrition assessment tool must be incorporated into clinical practice to identify malnourished patients. Nutrition assessment tools include those focusing on physical examination, laboratory testing, physiologic function testing, clinical scoring systems and measurements of body energy and protein expenditure.

**Key Words:** Nutrition assessment, Malnutrition, Anthropometrics, Usual body weight, Body weight, Calorimetry, Bioelectric impedence, Nutrition screening tools, Plasma proteins, Muscle function

## 1. INTRODUCTION

Thirty years ago, hospital malnutrition was described as being very prevalent, yet poorly identified by medical teams [1]. Unfortunately, this situation has not changed. Protein calorie malnutrition (PCM) is still very common in hospitalized patients and remains poorly recognized by many clinicians [2]. In a recent study of Brazilian hospitalized patients, 48% of the patients were deemed to be malnourished. Despite this alarming number, the majority of physicians in this study did not assess their patient's nutritional status nor make nutritional therapy a major component of their patient's hospital medical plan [3].

PCM is important clinically when it is severe enough to impact patients' physiologic functions, inhibit their response to medical therapies and/or prolong the time to recovery. The physiologic devastation seen with PCM is secondary to loss of total body protein and muscle function [4].When more than 20% of a patient's usual body weight is lost, most physiologic body functions become significantly impaired [5]. Studies evaluating the relationship of loss of body weight to loss of body protein have shown a strong correlation [6].

End organ function is adversely affected by malnutrition Protein malnutrition can be divided into two generalized categories: marasamus and kwashiorkor. Patients with marasmus have a significant deficit of total body fat and body protein with a slight increase in extracellular water. Clinically, this presents as obvious body wasting (Fig. 1.1). The eyes may be sunken and the skull and cheekbones may be prominent [7]. The plasma albumin is often in the low normal range. Resting energy expenditure in these individuals is not increased

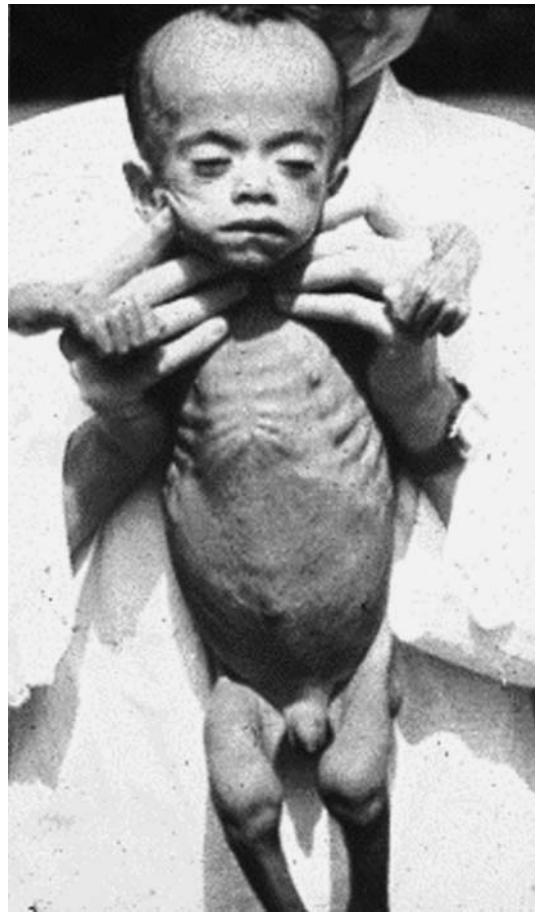


**Fig. 1.1.** Marasmus.

despite severe physiologic dysfunction. In contrast, while patients with kwashiorkor have similar deficits of body protein and fat, they also have markedly increased extracellular fluid and low plasma albumin levels (Fig. 1.2) [7]. To the casual observer, this increase in extracellular fluid may mask underlying weight loss. Patients with kwashiokor typically have an accelerated metabolic rate, and if measured, their physiologic function would also be significantly impaired.

With malnutrition muscle strength decreases over time. Respiratory function, including forced expiratory volume, vital capacity and peak expiratory flow, all decline. An association between impaired respiratory gas exchange and malnutrition in chronic obstructive respiratory disease patients has been described [8]. Malnutrition can also reduce

**Fig. 1.2.** Kwashiokor.

cardiac output, impair wound healing and depress immune function [9]. Nutritional repletion, however, can often reverse these degenerative processes and significantly improve patient outcomes. The difficulty lies not only in the treatment of such conditions, but also in identifying individuals at risk so that appropriate interventions can be made.

## 2. NUTRITION ASSESSMENT

Research in nutrition assessment continues to develop. Early research in assessing for the presence of malnutrition resulted in tools and markers being developed for surveying large populations over a short period of time. Many of these tools and markers were then brought to the hospitalized setting and used on individual patients. Jones et al. reported on 44 separate tools published in the past 25 years for determining nutritional status [10]. Most of the perceived traditional markers of protein-calorie malnutrition, such as serum albumin, have such poor sensitivity and large variance that their use on individual patients is of limited value.

A traditional nutrition assessment will often include a dietary, medical and body weight history. Measurements of current body weight and height are recorded. Serum proteins levels, body anthropometrics measurements, immune competence efficacy and functional measurements of muscle strength may be incorporated into the overall final assessment. Individually these measurements often have limited value in accurately determining a patient's nutrition risk. For example, dietary history as recalled by patients can be overestimated by an average of 22% [11]. Most physicians and nurses rely upon a patient's recall of their own weight, rather than a direct measurement, a very unreliable practice [12].

Studies have consistently revealed the inadequacy of any single assessment method or tool to assess a patient's nutritional state. As a result, combinations of diverse measurements have been developed into "scoring systems" designed to increase our sensitivity and specificity in determining nutritional status [13]. In general, global approaches to nutrition assessment of the hospitalized patient can provide a much more definitive picture of a patient's true nutrition risk.

## 3. WEIGHT HISTORY

Recent weight loss is a very sensitive marker of a patient's nutritional status [14]. Weight loss of more than 5% in 1 month or 10% in 6 months prior to hospitalization has been shown to be clinically significant [15]. When 20% of usual body weight has been lost in 6 months or less, severe physiologic dysfunction occurs. In one studied surgical population, weight loss of more than 5% in the month prior to hospital admission correlated with both an increased length of hospital stay and time of rehabilitation [16].

It is not always possible to diagnose malnutrition based on body habitus visualization alone. For example, patients who are obese, or those with edema, may be very difficult to nutritionally assess solely relying upon their body size or body weight.

Even though measured weights are an accurate, easily trackable and reliable assessment of nutritional status, recalled weights are much less accurate. Obtaining a patient's weight in the inpatient or outpatient setting should be a common and easily performed process. Patients may not be able to give a history of their usual body weight or their recent weight history due to a neurological impairment. Numerous studies have documented huge variances in reported weights when a patient's own weight recall is used as the sole determining factor, with sensitivities as low as 65%. A recent randomized study from Europe

noted that in 500 patient admissions, a weight was recorded only 67% of the time [17]. In a separate study of 4,000 patients, weights were only recorded 15% of the time even though a scale was available within 150 feet of the patient's bed in 75% of the cases [2].

## 4. ANTHROPOMETRICS

Anthropometrics is the scientific study of measurements of the human body. Estimates of body energy stores can be estimated by measurement of body compartments. Anthropometrics is used as a bedside method of estimating body fat and protein stores using two bedside instruments, a Lange$^{R}$ caliper and tape measure (Fig. 1.3). The measurements obtained from anthropometrics are compared to reference study "normals" and then followed in the same patient over time. A drawback of anthropometrics is its reliance on age-, sex- and race-matched reference values. Additionally, because muscle mass is somewhat dependent on exercise, bedridden patients can have decreased muscle mass without a corresponding reduction in body protein stores.

Inaccurate measurements of body protein and fat stores using anthropometric methods are common in certain patient populations. For example, critically ill patients, as well as patients with liver disease and/or renal disease, often present with total body water increase and significant edema. Furthermore, there is significant variance among clinicians measuring anthropometrics in the same patient, reported to range from 5 to 23 percent [2].

The measurement of the triceps skinfold with a Lange$^{R}$ caliper has been recognized as an indirect marker of body fat stores. Body fat stores can be tracked over time to provide an estimate of the chronicity of a weight loss process. The measurement of the circumference of the mid-point of the upper arm using a tape measure or midarm muscle circumference (MAMC) has also been recognized as an indirect marker of body protein stores [18]. The minimum MAMC known to be compatible with survival is between $900\,mm^2$ to $1,200\,mm^2$ [19]. Lastly, a widely accepted definition of malnutrition is a BMI less than $20\,kg/m^2$ and an MAMC less than the $15^{th}$ percentile.

## 5. PLASMA PROTEINS

Plasma proteins, such as albumin, prealbumin, transferrin, ferritin and retinol binding protein, have all been used as nutritional markers (Table 1.1). In the past 30 years, there have been over 20,000 citations

**Fig. 1.3.** Bedside anthropometric tools: Lange calipers and tape measure.

on albumin [20]. One-third of albumin is maintained in the intravascular compartment and two-thirds in the extravascular compartment. Serum albumin levels are a representation of both liver albumin synthesis and albumin degradation or losses. The serum concentrations of albumin

Table 1.1
Serum protein half lives

| | |
|---|---|
| Albumin | 18 days |
| Transferrin | 8 days |
| Prealbumin | 2–3 days |
| Retinol-binding protein | 2 days |
| Ferritin | 20 hours |

and other plasma proteins are affected by a patient's total body water status, liver function and renal losses. Although purported as reliable nutritional markers, serum proteins are best considered markers of a patient's overall health status rather than a true nutritional marker. Reinhardt and associates demonstrated a linear correlation between the degree of hypoalbuminemia and the 30-day mortality rate in hospitalized patients [21]. An increase in hospital mortality was also seen in geriatric patients with low serum albumins undergoing cardiovascular surgery [22]. Careful studies have shown serum albumin to be a less sensitive indicator of a patient's nutritional status as compared to clinical judgment based on a patient's medical history and physical examination [23].

## 6. DIRECT MEASUREMENTS OF BODY PHYSIOLOGIC FUNCTION

Direct measurements of body functions can be used as markers of the degree and significance of malnutrition. For example, skeletal muscle function can be rapidly affected by malnutrition regardless of other major disease processes such as sepsis, trauma or renal failure [24].

In critically ill patients who are not able to follow commands, bedside muscle function can still be tested. Stimulation of the ulnar nerve at the wrist with measurement of contraction of the abductor pollicus longus has been standardized [25]. Force-frequency curves have been recorded in controls and standardized.

In the patient who is able to follow commands, muscle mass can be determined from handgrip strength by the use of a bedside tool known as a handgrip dynamometer (Fig. 1.4). Hospitalized patients with poor grip strength have been shown to have an increase in hospital length of stay, reduced ability to return home and increased mortality [26].

**Fig. 1.4.** Handgrip dynammometer.

## 7. CLINICAL SCORING SYSTEMS

Because no one test or marker exists that accurately identifies patients who are malnourished or at nutritional risk, scoring systems have been developed that combine history, physical and laboratory information. Some of this information can be obtained from the patient, while other information is obtained by the clinician. More recently, these scoring systems have gained popularity and acceptance as reliable mechanisms for determining nutritional status.

### *7.1. Subjective Global Assessment*

The Subjective Global Assessment (SGA) is a tool used to recognize and document nutritional problems in patients. It includes a dietary

and medical history, a functional assessment and a physical examination (Table 1.2) [27]. Fiaccadori et al. validated the SGA system by both anthropometry and serum albumin measurements and predicted morbidity and mortality in patients with acute renal failure [28]. An SGA (A) level is designated as a minimal change in food intake, a minimal change in body function and a steady body weight. An SGA (B) level consists of clear evidence of decreased food intake with some physiologic functional changes, but no significant change in body weight. An SGA (C) level consists of a significant decrease in body weight and food intake along with a reduction in physiologic function. Hasse et al. demonstrated that the SGA scoring system was able to accurately detect the nutritional status in liver transplant patients [29]. There was a significant degree of intraobserver agreement with regards to the reported SGA scoring. Detsky et al. demonstrated that the SGA model could be easily taught to practitioners with good reproducibility from clinician to clinician [27].

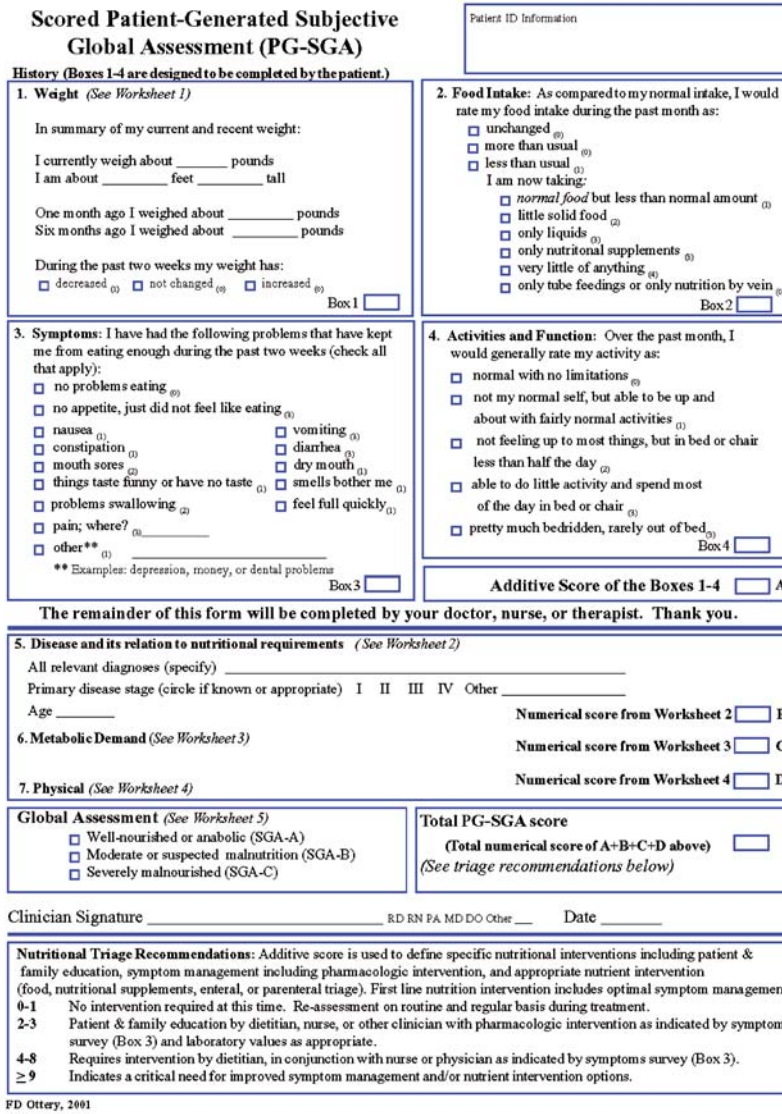
### *7.2. Mini-Nutritional Assessment*

The Mini Nutritional Assessment (MNA) is a rapid and reliable tool for evaluating the nutritional status of the elderly (Table 1.3). It is composed of 18 items and takes approximately 15 min to complete [30]. The assessment includes an evaluation of a patient's health, mobility, diet, anthropometrics and a subject self assessment. A developmental study demonstrated that the MNA was as accurate as a nutrition assessment by two expert nutrition physicians [30]. A second validation study determined that the MNA was as accurate as a physician-performed nutrition assessment combined with the addition of biochemical markers [31]. An MNA score of $> 24$ indicates no nutritional risk, while a score of 17–23 indicates a potential risk of malnutrition and a score $< 17$ indicates definitive malnutrition.

### *7.3. Nutrition Risk Score*

The Nutrition Risk Score (NRS) was developed in 1992 to assess a patient's nutritional risk at hospital admission [32]. The NRS contains variables of weight loss, BMI, food intake and physiologic stress (Table 1.4). The NRS is obtained on hospital admission and re-assessed weekly. In one validation study, the NRS correlated well with the 16-item nutrition risk index [33]. There was little variance in scores between dietitians or between dietitians and nurses when evaluating the same patient. The NRS has been adopted as the national nutrition assessment standard in the United Kingdom [34].

Table 1.2
Subjective global analysis



**Scored Patient-Generated Subjective Global Assessment (PG-SGA)**

Patient ID Information

**History (Boxes 1-4 are designed to be completed by the patient.)**

**1. Weight** *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____ pounds
I am about _____ feet _____ tall

One month ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds

During the past two weeks my weight has:
☐ decreased (0) ☐ not changed (0) ☐ increased (0)

Box 1

**2. Food Intake:** As compared to my normal intake, I would rate my food intake during the past month as:
☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (2)
I am now taking:
☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritonal supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0)

Box 2

**3. Symptoms:** I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):
☐ no problems eating (0)
☐ no appetite, just did not feel like eating (1)
☐ nausea (1)
☐ constipation (1)
☐ mouth sores (2)
☐ things taste funny or have no taste (1)
☐ problems swallowing (2)
☐ pain; where? (3)_____
☐ other** (1) _____
** Examples: depression, money, or dental problems
☐ vomiting (3)
☐ diarrhea (3)
☐ dry mouth (1)
☐ smells bother me (1)
☐ feel full quickly (1)

Box 3

**4. Activities and Function:** Over the past month, I would generally rate my activity as:
☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bedridden, rarely out of bed (3)

Box 4

**Additive Score of the Boxes 1-4** ☐ A

**The remainder of this form will be completed by your doctor, nurse, or therapist. Thank you.**

**5. Disease and its relation to nutritional requirements** *(See Worksheet 2)*

All relevant diagnoses (specify) _____
Primary disease stage (circle if known or appropriate) I II III IV Other _____
Age _____

**Numerical score from Worksheet 2** ☐ B

**6. Metabolic Demand** *(See Worksheet 3)*

**Numerical score from Worksheet 3** ☐ C

**7. Physical** *(See Worksheet 4)*

**Numerical score from Worksheet 4** ☐ D

**Global Assessment** *(See Worksheet 5)*
☐ Well-nourished or anabolic (SGA-A)
☐ Moderate or suspected malnutrition (SGA-B)
☐ Severely malnourished (SGA-C)

**Total PG-SGA score**
**(Total numerical score of A+B+C+D above)** ☐
*(See triage recommendations below)*

Clinician Signature _____ RD RN PA MD DO Other __ Date _____

**Nutritional Triage Recommendations:** Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

| | |
|---|---|
| **0-1** | No intervention required at this time. Re-assessment on routine and regular basis during treatment. |
| **2-3** | Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and laboratory values as appropriate. |
| **4-8** | Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms survey (Box 3). |
| **≥ 9** | Indicates a critical need for improved symptom management and/or nutrient intervention options. |

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## *7.4. Nutritional Risk Index*

The Nutrition Risk Index (NRI) was developed by the Veteran's Affairs Total Parenteral Nutrition group in 1991 for use in the evaluation of the efficacy of peri-operative total parenteral nutrition in patients

## Table 1.3
## Mini Nutritional Assessment (MNA)

NESTLÉ NUTRITION SERVICES

Nestlé

**Mini Nutritional Assessment**
**MNA®**

Last name: First name: Sex: Date:

Age: Weight, kg: Height, cm: I.D. Number:

*Complete the screen by filling in the boxes with the appropriate numbers.*
*Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.*

**Screening**

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe loss of appetite
1 = moderate loss of appetite
2 = no loss of appetite ☐

B Weight loss during last months
0 = weight loss greater than 3 kg (6.6 lbs)
1 = does not know
2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chair bound
1 = able to get out of bed/chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F Body Mass Index (BMI) (weight in kg) / (height in m²)
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

**Screening score** (subtotal max. 14 points) ☐☐

12 points or greater Normal – not at risk – no need to complete assessment

11 points or below Possible malnutrition – continue assessment

**Assessment**

G Lives independently (not in a nursing home or hospital)
0 = no 1 = yes ☐

H Takes more than 3 prescription drugs per day
0 = yes 1 = no ☐

I Pressure sores or skin ulcers
0 = yes 1 = no ☐

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals ☐

K Selected consumption markers for protein intake
• At least one serving of dairy products (milk, cheese, yogurt) per day? yes ☐ no ☐
• Two or more serving of legumes or eggs per week? yes ☐ no ☐
• Meat, fish or poultry every day yes ☐ no ☐
0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes ☐☐

L Consumes two or more servings of fruits or vegetables per day?
0 = no 1 = yes ☐

M How much fluid (water, juice, coffee, tea, milk…) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups ☐☐

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem ☐

O Self view of nutritional status
0 = view self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem ☐

P In comparison with other people of the same age, how do they consider their health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better ☐☐

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC 22 or greater ☐☐

R Calf circumference (CC) in cm
0 = CC less than 31 1 = CC 31 or greater ☐

**Assessment** (max. 16 points) ☐☐☐
**Screening score** ☐☐
**Total Assessment** (max. 30 points) ☐☐☐

**Malnutrition Indicator Score**

17 to 23.5 points at risk of malnutrition ☐
Less than 17 points malnourished ☐

Ref.: Guigoz Y, Vellas B and Garry P.J. 1994. Mini Nutritional Assessment: A practical assessment tool for grading the nutritional state of elderly patients*Facts and Research in Gerontology*Supplement #2:15-59.
Rubenstein L.Z, Harker J, Guigoz Y and Vellas B. Comprehensive Geriatric Assessment (CGA) and the MNA: An Overview of CGA, Nutritional Assessment, and Development of a Shortened Version of the MNA. In: "Mini Nutritional Assessment (MNA): Research and Practice in the Elderly". Vellas B, Garry P.J and Guigoz Y., editors. Nestlé Nutrition Workshop Series. Clinical & Performance Programme, vol. 1. Karger, Bâle, in press.



08.98 US A

undergoing thoracic or abdominal surgery [35]. The NRI relies on serum albumin measurements and differences in a patient's current and previous body weight (Table 1.5). It has been used in clinical studies with reasonable reliability [36]. In a mixed group of Irish medical and

Table 1.4
Nutrition risk score

| | | | | |
|---|---|---|---|---|
| Patient's Name: | | | Ward: | |
| Date of Birth: | | | Date: | |
| Weight: | | Height/Length: | | |
| Please circle relevant score. Only select **one** score from each section. | | | | |
| **1.** | **PEDIATRICS (0–17 years) PRESENT WEIGHT** | **SCORE** | **ADULTS (≥18 years) WEIGHT LOSS IN LAST 3 MONTHS (Unintentional)** | **SCORE** |
| | Expected weight for length | 0 | No weight loss | 0 |
| | 90–99% of expected weight for length | 2 | 0–3 kg weight loss | 1 |
| | 80–89% of expected weight for length | 4 | >3–6 kg weight loss | 2 |
| | ≤79% of expected weight for length | 6 | 6 kg or more | 3 |
| | | | **BMI (Body Mass Index)** | |
| | | | 20 or more | 0 |
| **2.** | Omit Question 2 | | 18 or 19 | 1 |
| | For Pediatrics | | 15–17 | 2 |
| | | | Less than 15 | 3 |
| **3.** | **APPETITE** | | | |
| | • Good appetite, manages most of 3 meals/day (or equivalent) | | | 0 |
| | • Poor appetite, poor intake – leaving > half of meals provided (or equivalent) | | | 2 |
| | • Appetite nil or virtually nil, unable to eat, NBM (for > 4 meals) | | | 3 |

*(Continued)*

Table 1.4
*(Continued)*

| | | | |
|---|---|---|---|
| 4. | **ABILITY TO EAT/RETAIN FOOD** | | |
| | • No difficulties eating, able to eat independently. | | 0 |
| | • No diarrhea or vomiting. | | |
| | • Problems handling food, e.g., needs special cutlery. | | 1 |
| | Vomiting/frequent regurgitation, or diarrhea). | | |
| | • Difficulty swallowing, requiring modified consistency. | | 2 |
| | Problems with dentures, affecting food intake. Problems with chewing, affecting food intake. | | |
| | Slow to feed. Moderate vomiting and/or diarrhea (1-2/day for children). | | |
| | Needs help with feeding (e.g., physical handicap). | | |
| | • Unable to take food orally. Unable to swallow (complete dysphagia). | | 3 |
| | Severe vomiting and/or diarrhea (> 2/days for children). Malabsorption. | | |
| 5. | **STRESS FACTOR** | | |
| | • **No Stress Factor**: | (Includes admission for investigation only). | 0 |
| | • **Mild** | Minor surgery. Minor infection. | 1 |
| | • **Moderate** | Chronic disease. Major Surgery. Infections. | 2 |
| | | Fractures. Pressure sores/ulcers. CVA. | |
| | | Inflammatory bowel disease. Other gastrointestinal disease. | |
| | • **Severe** | Multiple injuries. Multiple fractures/burns. | 3 |
| | | Multiple deep pressure sores/ulcers. Severe sepsis. | |
| | | Carcinoma/malignant disease. | |
| | | | **TOTAL____** |

**Table 1.5**
**Nutritional Risk Index**

| |
|---|
| NRI = 1.519 × serum albumin (g/l) + 0.417× (current weight/usual weight) ×100 |
| No nutrition risk: NRI > 100 |
| Borderline nutrition risk: NRI > 97.5 |
| Mild nutrition risk: NRI 83.5–97.5 |
| Severe nutritional risk: NRI < 83.5 |

surgical patients, the NRI identified patients with a prolonged length of stay in the hospital, or a reduced ability to return home, and higher patient mortality [16].

### *7.5. Malnutrition Universal Screening Tool*

The malnutrition universal screening tool (MUST) is designed to detect protein-energy malnutrition as well as those individuals at risk of developing malnutrition by using three independent criteria: current weight status, unintentional weight loss and acute disease effect [37]. The patient's current body weight is determined by calculating the body mass index (BMI) ($kg/m^2$). Weight loss (over the past 3–6 months) is determined by looking at the individual's medical record. An acute disease factor is then included if the patient is currently affected by a pathophysiological condition and there has been no nutritional intake for more than 5 days. A total score is calculated placing the patients in a low-, medium- or high-risk category for malnutrition (Table 1.6). A major advantage of this screening tool is its applicability to adults of all ages across all health care settings. Additionally, this method provides the user with management guidelines once an overall risk score has been determined. Studies have shown that MUST is quick and easy to use, and has good concurrent validity with most other nutrition assessment tools tested [37].

### *7.6. Geriatric Nutritional Risk Index*

The Geriatric Nutrition Risk Index (GNRI) is an adaptation to the Nutritional Risk Index (NRI). The GNRI is specifically designed to predict the risk of morbidity and mortality in hospitalized elderly patients (Table 1.7) [38]. Because the normal weight of the elderly patients is often difficult to determine, this tool substitutes "ideal weight" in place of "usual weight" used by the NRI. The GNRI is calculated using a special formula incorporating both serum albumin

Table 1.6
Malnutrition Universal Screening Tool (MUST)

| BMI Score Effect | Weight Loss Score (unemplanned weight loss in 3-6 months) | Acute Disease |
|---|---|---|
| BMI >20.0 ( >30 obese) = 0 | Wt loss <5% = 0 | Add a score of 2 if there |
| BMI 18.5-20.0 = 1 | Wt loss 5-10% = 1 | has been or is likely to |
| BMI <18.5 = 2 | Wt loss >10% = 2 | be no nutritional intake for > 5 days |
| | ↓ | |
| | Add all scores | |
| | ↓ | |
| | Overall risk of malnutrition and management guidelines | |
| 0 | 1 | ≥2 |
| Low Risk | Medium Risk | High Risk |
| Routine Clinical Care | Observe | Treat |
| Repeat screening to dietitian, | Document dietary intake | Refer to dietitian |
| Hospital: weekly | for 3d if subject in hospital | nutrition support |
| Care homes: Monthly | or care home | team or implement |
| Community:annually for | if improved adequate intake, | orlocal policy |
| special groups ( >75 years old ) | little clinical concern; if no | Improve and |
| | Improvement,clinical conern: | Increase overall |
| | Follow local policy | nutritional intake |
| | Repeat screeing | Monitor and |
| | Care home:at least monthly | Hospital:weekly |
| | Community:at least every 2-3 | Care home: monthly |
| | Months | Community:month |

and weight loss. Ideal body weight is calculated using the Lorentz formula based on the patient's height and sex [38]. After determining the GNRI score, patients are categorized into four grades of nutrition-related risk: major, moderate, low and no risk. Finally, the GNRI scores are correlated with a severity score that takes into account nutritional-status-related complications.

The GNRI is not an index of malnutrition, but rather a "nutrition-related" risk index. Two independent predictors of mortality in the

**Table 1.7**
**Geriatric Nutrition Risk Index**

| $GNRI = [1.489 \times \text{albumin (g/l)}] + [41.7 \times (\text{weight}/\text{WLo})]$ |
|---|

The GNRI results from replacement of ideal weight in the NRI formula by usual weight as calculated from the Lorentz formula (WLo). Four grades of nutrition-related risk: major risk (GNRI $< 82$), moderate risk (GNRI 82–91), low risk (GNRI 92 to $\leq 98$), no risk (GNRI $> 98$)

**Table 1.8**
**Instant Nutritional Assessment parameters**

| *Parameter* | *Abnormal if:* |
|---|---|
| Serum albumin ----------→ | Less than 3.5 g % |
| Total lymphocyte count ----------→ | Less than $1,500/mm^3$ |

elderly, weight loss and serum albumin, are used to calculate the GNRI. Interestingly, studies have shown that by measuring these two variables, the GNRI is a more reliable prognostic indicator of morbidity and mortality in hospitalized elderly patients than are other techniques using albumin or BMI alone [39].

### *7.7. Instant Nutritional Assessment*

The most rapid and simplest measure of nutritional status is the Instant Nutritional Assessment (INA) (Table 1.8). A serum albumin and the total lymphocyte count form the basis of this evaluation [40]. Significant correlations among depressed levels of these parameters and morbidity and mortality have been previously noted. Not surprisingly, abnormalities of these same parameters are even more significant in critically ill patients [41]. Although not designed to replace more extensive assessment measures, this technique allows for quick identification and early intervention in those individuals in greatest danger of developing complications of malnutrition.

## 8. OTHER BEDSIDE TECHNOLOGIES

Bioelectric impedance (BIA) is a non-invasive method to determine body composition. It is based on the resistance of a fat-free mass to administration of a high frequency, alternating, low amplitude

(50 kHz) electrical current. It is inexpensive, easy to perform and reproducible [42]. Bioelectrical impedance has been validated against both underwater weighing and isotope dilution, two bench research gold standards used for determining body composition [43]. One drawback of BIA is its assumption of a normal body water status being approximately 72%–74%. Therefore, in clinical cases of body edema or body dehydration, BIA may be inaccurate [44]. A study in patients with renal failure found BIA to be inaccurate secondary to an abnormal volume status [45]. In contrast, BIA was found to be accurate in determining muscle mass in a group of patients with cystic fibrosis when compared to isotope dilution methods [46].

## 9. RESEARCH LABORATORY METHODS OF NUTRITIONAL ASSESSMENT

Research tools found in the laboratory are available to determine body composition such as fat and muscle mass. These tools serve as gold standards against which bedside clinical body composition tests are compared [47]. Bedside nutritional assessment tools, however, are generally more practical and cost effective to perform.

### *9.1. Dual Energy Absorptiometry*

Dual energy absorptiometry (DEXA) was originally designed for the determination of bone density and mass. It was subsequently found to be effective for quantifying fat and muscle mass of the human body. A typical scan takes approximately 30 min and exposes the patient to 1 mrad of radiation [48].

### *9.2. Whole Body Counting/Nuclear Activation*

Shielded whole body counters can measure the X-ray decay of various, naturally occurring minerals and substances such as $^{40}K$ [48]. The $^{40}K$ count can be used to determine total body potassium. Total body potassium can then be used to calculate body cell mass and fat-free mass. Whole body counting/nuclear activation is considered a gold standard for determining body composition.

### *9.3. Computerized Axial Tomography and Magnetic Resonance Imaging*

Computerized axial tomography (CT) and magnetic resonance imaging (MRI) are imaging modalities capable of measuring body composition

including muscle mass and visceral tissue [48]. Computerized axial tomography measures X-ray scatter of tissue based on density, while magnetic resonance imaging measures nuclear relaxation times from the nuclei of atoms within a magnetic field.

### *9.4. Hydrodensitometry*

For years, hydrodensitometry or underwater weighing has been regarded as a gold standard for body composition analysis. This laboratory technique is based on Archimedes' principle, which states that the volume of an object submerged in water is equal to the volume of water the object displaces. Additionally, it assumes that the density and specific gravity of lean tissue (muscle and bone) are greater than those of fat tissue. Therefore, lean tissue will sink and fat tissue will float.

In order to perform hydrodensitometry the subject is first placed in a temperature-regulated tank or pool and submerged. After complete exhalation the subject is weighed underwater on a suspended chair or frame for approximately 10–15 s. Archimedes' principle is applied by comparing the mass of the subject in air to the mass of the subject in water. Of note, corrections for the density of water corresponding to the water temperature are made. Because body density is simply a ratio of body mass to body volume it can easily be calculated from the above measurements. Once body density is known, percent body fat can be easily estimated by one of two different equations [49]. Because the density of fat-free mass is known to differ with age, gender, ethnicity, level of body fitness and activity level, population-specific formulas for the conversion of body density to %BF have been developed [50]. Overall test-retest reliability for hydrodensitometry has been reported to be good ($r = 0.99$) [51].

### *9.5. Near-Infrared Interactance*

Near-infrared interactance (NIR), although originally designed by the agriculture industry to asses the composition of grains and seeds, is used today by nutritionists and exercise scientists alike to provide estimates of %BF in patients and/or athletes [52]. This field technique operates on the principles of light absorption and reflection. By comparing the light absorption of two different wavelengths in combination with anthropometric data (weight and height), and the use of appropriate regression equations, %BF is estimated.

Some of the main advantages of this device are its speed, ease of use, high degree of portability and low cost. The test is performed in a

matter of minutes (approximately 3 min) by placing an infrared probe over the biceps muscle and measuring optical densities of the underlying tissue. To standardize testing, two specific wavelengths based on the absorption of fat and water are used, and the instrument is calibrated by measuring a signal from a reference block made of Teflon [53]. Additionally, specific equations catered to individual patient populations can be used to help reduce variance [54].

Despite the appeal of this method, controversy exists regarding its validity. While some studies have claimed good reliability and validity in young athletes, others have shown poor correlation in specific patient populations, such as the obese [49]. The reviewed research consistently shows that NIR underestimates %BF, and this error is accentuated with increasing body fatness [55].

## 10. CALORIMETRY IN NUTRITION

The roots of nutrition science are based on the principles of calorimetry, or heat measurement. Although direct calorimetry, or the measure of total heat loss from the body, was first studied and served as the gold standard for studying human metabolism, it is indirect calorimetry (IC), or the measure of total energy production by the body, that is utilized more extensively today.

### *10.1. Indirect Calorimetry*

Indirect calorimetry is able to quantify energy expenditure based on the physiologic relationship between oxygen intake and carbon dioxide release and heat and energy production. More simply, IC measures $O_2$ consumption and $CO_2$ production [56]. Calculation of the resting energy expenditure (REE) is the end result of IC and is estimated to be approximately 10% greater than the basal energy expenditure (BEE), which can only be measured in deep sleep [57, 58]. REE is thought to account for 75%–90% of total energy expenditure (TEE). The remainder of TEE is made up of thermogenesis resulting from nutritional intake (diet-induced thermogenesis), environment (shivering/non-shivering thermogenesis) and physical activity [59]. It should, however, be noted that IC is unable to differentiate non-protein calories from total calories. Although protein requirements are not measured by IC, they can be easily determined by several different methods (see below).

In addition to determining the 24-h caloric requirements as reflected by the REE, IC also provides the investigator with a measure

of substrate utilization by calculation of the respiratory quotient (RQ) [59]. Defined by the ratio $VC0_2/VO_2$, the RQ is purported to be a measurement of substrate utilization in vivo. An $RQ > 1.0$ is generally considered to be consistent with overfeeding and an $RQ < 0.80$ is considered to be consistent with underfeeding. Notably, there is an associated physiologic range for the RQ (0.67–1.3), and values outside this range can only be generated by error. Therefore, in practice this value is used as a determinant of test validity [59–61].

The necessary duration of IC testing to provide accurate and valid results is not known. At present, most procedures continue for predetermined intervals or until a "steady state" is reached [62]. Prior to testing, patients should be maintained on bed rest for 30 min and kept in a thermoneutral environment [63]. Patients on oral diets should fast overnight, while patients on total parenteral nutrition (TPN) or enteral tube feeds (ETF) should be placed on a continuous infusion rate up until the point of testing. Analgesics and anxiolytics should be administered appropriately if clinically required [62].

The two instruments currently available for conducting IC include the "classic" metabolic cart and hand-held instruments [64]. The "classic" metabolic cart measures both oxygen consumption and carbon dioxide production and automatically calculates EE and the RQ (Fig. 1.5). The majority of the predictive calorie equations in use today were derived from the use of this device. Unfortunately, "classic" carts are expensive, difficult to mobilize and calibrate, and require additional staffing (i.e., respiratory therapists) to perform the testing.

Recently, small hand-held IC devices have been developed (Fig. 1.6). These devices calculate REE by measuring only oxygen consumption, and therefore no RQ is determined [64]. So far, these devices have only been validated in healthy individuals. Conversely, these hand-held devices are highly portable, self calibrating, require minimal operator training and cost considerably less than "classic" carts. Nutrition enthusiasts are optimistic that the reduced cost and ease of operation of these new devices will make IC more commonplace in the monitoring of energy metabolism in the hospital and outpatient setting.

### *10.2. Whole-Room Calorimetry*

The most precise measurements of energy expenditure are obtained through the practice of whole-room indirect calorimetry (WRC). This technique provides extremely accurate measurements (>98%) of oxygen consumption and carbon dioxide production over long periods of time in individuals moving freely about a room [65]. Whole

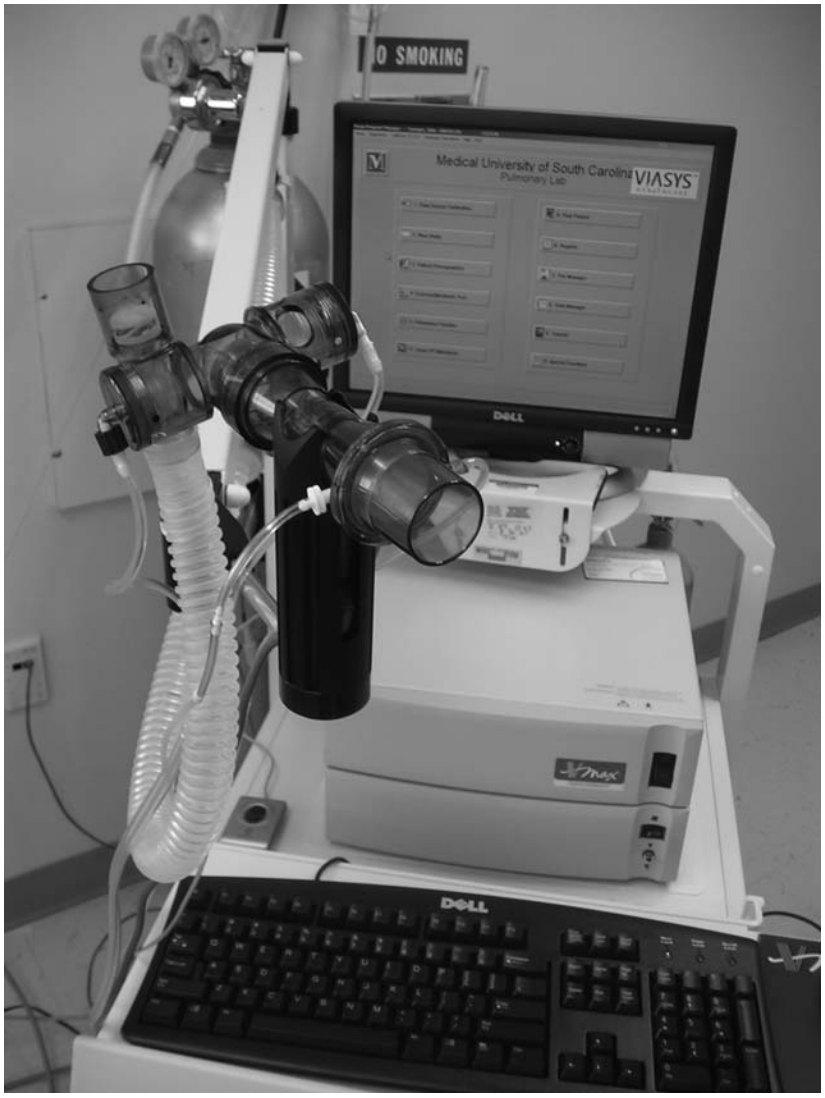


**Fig. 1.5.** Metabolic cart.

room calorimetry uses the same principles and equations as IC and helps bridge the gap between laboratory research and the free living environment. Whereas IC uses the metabolic cart to measure EE, WRC measures changes in oxygen and carbon dioxide inside an airtight room to obtain the same result. WRC is not only able to measure the subject's EE, but also his or her usage of energy fuels including fats, protein and


**Fig. 1.6.** MEDGEM$^{R}$ hand-held oximeter for basal energy assessment.

carbohydrate. The individual being studied is held in a closed room and gas exchange is measured through analyzers attached to the unit. Subjects are instructed to follow strict study protocols dividing their time among reading, sleeping, sitting and exercising over a period of 24–72 h. Although precise, this technique of measuring energy expenditure is not practical considering few individuals are willing to submit themselves to such a lengthy test.

## 11. NUTRITIONAL INTERVENTION

After determination of an individual's nutritional status and/or degree of malnutrition, then appropriate intervention can be initiated. Nutritional intervention can include dietary advice, enteral supplementation, appetite stimulation, enteral tube feeding and parenteral nutrition. Specialized nutritional intervention may include the use of anabolic agents, immune-stimulating enteral formulations, medium-chain triglycerides, probiotics or other novel approaches. In order to begin intervention, clinicians must first attempt to determine the patient's caloric, protein and water requirements.

## 12. CALORIE NEEDS

There are multiple formulations used to determine a patient's caloric needs. The most commonly used formula is the Harris-Benedict

equation [66]. This equation estimates a patient's basal energy expenditure (BEE) using the following formulas:

$$\text{Men}: \; 66 + \{13.7 \times \text{weight (kg)}) + (5.0 \times \text{height (cm)}\} - \{(6.8 \times \text{age})\} = \text{kcal/day}$$

$$\text{Women}: \; 655 + \{(9.6 \times \text{weight (kg)}) + (1.8 \times \text{height (cm)}\} - \{4.7 \times \text{age}\} = \text{kcal/day}$$

### *12.1. What Weight Should I Use in this Calculation?*

If a patient is $<80\%$ or $>120\%$ of their ideal body weight, an adjusted body weight should be calculated. If their body weight is between 80%–120% of their ideal body weight, their actual body weight is their dosing weight.

*Ideal body weight* = Men (130 lb for first 5 feet and 3 lb for each additional inch)
Women (120 lb for first 5 feet of height and 3 lb for each additional inch)

*Adjusted body weight* (if needed) = {(Current body weight-ideal body weight) × 25%} + ideal body weight

Using the patient's actual body weight or adjusted weight, the patient's BEE is calculated using the Harris Benedict equation. The patient's BEE is multiplied by a physiologic stress factor to arrive at their actual daily calorie needs as shown below.

*Physiologic Stress Factor Multiplier*

Maintenance–mild stress 1–1.2
Moderate stress 1.3–1.4
Severe stress 1.5
BEE × stress factor = daily caloric needs

## 13. PROTEIN/NITROGEN NEEDS

A patient's daily nitrogen balance is a measure of their daily intake of nitrogen minus their excretion of nitrogen. The intake is nutritional intake and the excretion is measured by urinary losses plus 2–4 g of

nitrogen losses through skin and stool. Daily nitrogen balance can be calculated as below:

## 14. TWENTY-FOUR-HOUR NITROGEN CALCULATION

Collect 24-h urine for urea nitrogen and obtain total grams of nitrogen. Add 4 g of nitrogen for insensible losses (stool and skin) 24-h UUN + 4 g = daily nitrogen needs to maintain a stable nitrogen balance.

### *14.1. Nitrogen Balance*

A positive nitrogen balance is known as anabolism and is important for wound healing, recovery from illness and growth. A positive nitrogen balance consists of a greater daily nitrogen intake as compared to nitrogen excretion. On the contrary, a negative nitrogen balance is known as catabolism. This is commonly seen in critically ill patients and is the result of a greater daily nitrogen excretion as compared to nitrogen intake.

### *14.2. Converting Nitrogen to Protein*

Daily nitrogen needs can be converted to daily protein needs by using the following formula:

Total grams in nitrogen $\underline{\times}$ 6.25 = Total grams of protein required/day

## 15. QUICKIE FORMULAS FOR PROTEIN AND CALORIE NEEDS

There are more rapid methods available to determine a patient's daily calorie and protein needs. These "quickie" formulas have been shown to be reliable in most patients.

| | *Protein Needs* | *Calorie Needs* |
|---|---|---|
| Minimal severity of illness | 0.8 g/kg/day | 20–25 kcal/kg/day |
| Moderate severity of illness | 1.0 g/kg/day | 25–30 kcal/kg/day |
| Severe severity of illness | 1.5–2.5 g/kg/day | 30–35 kcal/kg/day |

## 16. DAILY WATER NEEDS

Daily water needs for patients are based on maintenance needs plus losses through urine, stool, emesis and wound output. However, there

are "quickie" methods for determining water needs that are reliable for most patients as noted below:

30 cc $H_20$/kg body weight/day
or
1 ml $H_20$/kcal delivered of tube feeding
*** Add 300 cc for every average degree of centigrade temperature elevation in 24 h
*** Patients with significant stool, emesis, wound or urine output may require more volume
*** Patients on fluid restriction may require less volume

## 17. CONCLUSION

Nutrition assessment is a very important component of a patient's medical therapy. Good clinical studies have shown that no single body measurement, laboratory measurement or body functional assessment is capable of adequately predicting nutritional risk. A global assessment, relying heavily on a patient's weight history, diet history and clinical examination, is better able to predict a patient's nutritional status and nutritional risk. Physicians should become familiar with determining nutritional risk, especially in the preoperative setting, in order to determine who requires nutritional intervention to improve clinical outcomes. Familiarity with basic formulas or estimations of a patient's calorie, protein and water needs is imperative in order to provide safe, efficacious nutritional intervention.

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# 2 Malnutrition and Disease Outcomes

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***Contents***



*Summary*

Malnutrition is a significant global problem in health care. There are strong associations between malnutrition and increased morbidity and mortality and elevated health care costs. This chapter discusses malnutrition and outcomes in geriatrics, renal disease, respiratory disease, transplantation, and in the perioperative setting. Although there is substantial evidence documenting the benefits of medical nutrition therapy, more studies are needed to better quantify these benefits in not only hospitalized patients but in all who have a chronic disease.

**Key Words:** Malnutrition, Chronic Disease, Outcomes

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## 1. INTRODUCTION

Malnutrition is a global health burden and serves as a major risk factor for illness and death. A strong association with increased morbidity and mortality remains. This chapter will focus on illness-associated malnutrition in the United States and its effects on chronic disease outcomes.

Malnutrition can arise from primary or secondary causes, with the former resulting from inadequate or poor-quality food intake and the latter from diseases that alter food intake or nutrient requirements, metabolism, or absorption. Primary malnutrition, which occurs mainly in developing countries and is unusual in the United States, will not be discussed. Secondary malnutrition, the main form encountered in developed countries, was largely unrecognized until the late 1960s or early 1970s. It was not well appreciated that persons with adequate food supplies can become malnourished as a result of acute or chronic diseases that alter nutrient intake or metabolism.

## 2. PROTEIN ENERGY MALNUTRITION

The two classic types of protein-energy malnutrition (PEM) often seen in developing countries are marasmus and kwashiorkor. Marasmus and kwashiorkor can occur separately or in combination as marasmic kwashiorkor. Marasmus is characterized by a state of chronic deprivation of energy intake to maintain body weight. This is a gradual process that passes through stages of underweight then mild, moderate and severe cachexia. Severe marasmus occurs with extreme weight loss and cachexia, when virtually all available body fat stores have been exhausted due to starvation. In developed countries, chronic illnesses such as cancer, chronic pulmonary disease, and anorexia nervosa are conditions most likely to cause marasmus. The diagnosis is based on severe fat and muscle wastage resulting from prolonged calorie deficiency. These conditions are compared in Table 2.1, and criteria used by the authors for diagnosing them are listed in Table 2.2.

In contrast to marasmus, kwashiorkor is a condition that has been assumed to occur when carbohydrates are the main source of energy and protein is relatively absent from the diet for a long period of time. However, in developed countries the manifestations of acute and chronic illnesses and of kwashiorkor (e.g., hypoalbuminemia) have led to debate over whether true kwashiorkor exists [1]. Kwashiorkor is thought to occur mainly in connection with acute, life-threatening illnesses such as trauma and sepsis, and chronic illnesses

**Table 2.1**
**Comparison of Marasmus and Kwashiorkor**

| | *Marasmus* | *Kwashiorkor* |
|---|---|---|
| Clinical setting | ↓ Energy intake | ↓ Protein intake during stress state |
| Time course to develop | Months or years | Weeks |
| Clinical features | Starved appearance<br>Weight $< 80\%$ standard for height<br>Triceps skinfold $< 3$ mm<br>Midarm muscle circumference $< 15$ cm | Well-nourished appearance<br>Easy hair pluckability<br>Edema |
| Laboratory findings | Creatinine-height index $< 60\%$ standard | Serum albumin $< 2.8$ g/dl<br>Total iron binding capacity $< 200\,\mu$g/dl<br>Lymphocytes $< 1,500/\text{mm}^3$<br>Anergy |
| Clinical course | Reasonably preserved responsiveness to short-term stress | Infections<br>Poor wound healing, decubitus ulcers, skin breakdown |
| Mortality | Low unless related to underlying disease | High |

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that involve an acute-phase inflammatory response. The physiologic stress produced by these illnesses is thought to increase the protein and energy requirements at a time when intake is often limited. Although the etiologic mechanisms are not clear, the fact that the adaptive response of protein sparing normally seen in starvation is blocked by the stress state and by carbohydrate infusion may be important factors. It has been argued that this stress state of malnutrition differs enough from kwashiorkor seen in developing countries and that it should be given a different label such as "stressed-induced hypoalbuminemia" [2]. However, these two conditions are substantially similar in physiology, clinical findings, and prognosis. When clinical findings such as poor skin integrity, poor wound healing, edema unexplained by other conditions, and easy hair pluckability are noted in addition to hypoalbuminemia, it is difficult not to label the conditions as kwashiorkor. Furthermore, the long-term stress-induced condition does

Table 2.2
Minimum Criteria for the Diagnosis of Marasmus and Kwashiorkor

| *Marasmus* | *Kwashiorkor** |
|---|---|
| Triceps skinfold $< 3$ mm<br>Mid-arm muscle circumference $< 15$ cm | Serum albumin $< 2.8$ g/dl<br>At least one of the following:<br>• Poor wound healing, decubitus ulcers, or skin breakdown<br>• Easy hair pluckability†<br>• Edema |

* The findings used to diagnose kwashiorkor must be unexplained by other causes
† Tested by *firmly* pulling a lock of hair from the top (not the sides or back), grasping with the thumb and forefinger. An average of three or more hairs removed easily and painlessly is considered abnormal hair pluckability
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not reflect a state of malnutrition, but rather the body's physiologic response to injury and infection.

The prognosis of adult patients with full-blown kwashiorkor is not good, even with aggressive nutritional support. Surgical wounds often dehisce, pressure sores develop, gastroparesis and diarrhea can occur with enteral feeding, the risk of gastrointestinal bleeding from stress ulcers is increased, host defenses are compromised, and death from overwhelming infection may occur despite antibiotic therapy. Unlike treatment in marasmus, aggressive nutritional support is indicated to restore better metabolic balance rapidly. Marasmic kwashiorkor, the combined form of PEM, develops when the cachectic or marasmic patient is subjected to an acute stress such as surgery, trauma, or sepsis, superimposing kwashiorkor onto chronic starvation. An extremely serious, life-threatening situation can occur because of the high risk of infection and other complications.

## 3. PREVALENCE OF MALNUTRITION

Since Butterworth's call to recognize the "skeleton in the hospital closet" [3], focusing on iatrogenic (physician-induced) malnutrition in the United States in 1974, malnutrition has been a frequent finding in hospitalized patients. Various studies have shown that protein-energy malnutrition affects 20% to 60% of patients on general medical and

surgical wards not only in the United States [4–9], but also in other industrialized countries (see Table 2.3) [10–12]. In addition, PEM has been documented in the institutionalized elderly [13] and patients in the community [14–15]. Some authors consider this figure to underestimate the true prevalence as some patients cannot participate in prevalence studies due to illness or extreme age [16]. Not only are a significant number of patients malnourished on admission, a considerable number deteriorates over their hospital course [5–6, 17–18]. Thus, the question arises whether there is an iatrogenic cause to the worsening documented malnutrition, or is it simply the interrelatedness of malnutrition and disease progression? The etiology of malnutrition is complex. At-risk patients are among the most ill, and their poor nutritional status is due in part to prolonged stress responses to underlying chronic disease or hospitalization, to inadequate dietary intake, especially in elderly patients [19], or to a combination of these factors.

Although there is little debate that the incidence of malnutrition is high among hospitalized patients, some authors have cast doubt on whether surrogate nutritional markers, specifically hepatic proteins, truly reflect nutritional status. Seres concluded that these indicators are poorly reproducible, insensitive, and unreliable. He noted there are many different definitions of malnutrition, and its prevalence depends on how malnutrition is measured [20]. In a review of 99 studies evaluating 12 nutritional parameters for concordance with outcomes, Koretz reported a high degree of discordance between the comparisons [21]. Although there may be associations between decreases in these surrogate nutritional markers and adverse outcomes, Koretz concluded that nutritional markers do not predict clinical outcomes. In addition, Klein and others in a national consensus statement concurred that there is no "gold standard" for determining nutritional status and noted the difficulty of isolating the effects of malnutrition from the influence of chronic disease and the lack of reliability of nutrition parameters [22]. Herein lies the difficulty of documenting true relationships between malnutrition and chronic disease outcomes.

## 4. OUTCOMES OF MALNUTRITION

Many retrospective and prospective studies provide evidence that malnourished patients have longer hospital stays [23–31] and significantly increased health care costs [10, 23, 32–33]. Studies comparing specific outcomes with malnutrition are summarized in Table 2.4. In a prospective analysis, Robinson and coworkers found that hospital charges were doubled in malnourished patients when compared with

Table 2.3
Malnutrition Prevalence in Populations

| *Author* | *n* | *Prevalence (%)* | *Age (mean)* | *Patient group* | *Assessment tool* | *Comment* |
|---|---|---|---|---|---|---|
| Chima (1997) [24] | 173 | 32 (at risk) | 58′ | Medical, hospitalized | Height, weight, IBW, serum albumin | • At risk ≥ 1: height for weight <75% IBW, albumin <30g/l, > 10% weight loss 1 month prior to admission |
| Chailleux (2003) [97] | 4, 088 | 23 (♂), 30 (♀) | 69 | COPD on long-term oxygen therapy | BMI | • Malnutrition = BMI <20<br>• BMI independent effect on all cause and respiratory mortality in patients with $FEV_1$ <55% |
| Edington (1996) [15] | 441 | 9 | 68 | Non-hospitalized cancer and chronic disease | BMI, TST, MAMC | • Mild: BMI < 20, TST/MAMC <15%ile<br>• Mod: BMI <18, TST/MAMC <5%ile<br>• Severe: BMI <16, TST/MAMC <5%ile |
| Kagansky (2005) [27] | 414 | 49 | 85 | Geriatric, hospitalized | MNA* and MNA subscore | • MNA groups <17, 17–23, >23<br>• Serum albumin is independent risk factor for death |
| McWhirter & Pennington (1994) [6] | 500 | 40 | 16–64 | Surgery and medicine, hospitalized | BMI, TSF, MAMC | • Greatest weight loss in patients who were already depleted on admission<br>• Subgroup prevalence (%): 27 (surgery), 46 (medicine), 43 (geriatrics) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Reilly (1988) [32] | 771 | 55 | 59 | Medical and surgical, hospitalized | Serum albumin, height and weight, total lymphocyte count | • "Likelihood of malnutrition" (LOM) based on laboratory data and subjective information of weight loss and physical appearance |
| Naber (1997) [8] | 155 | 45 (SGA)<br>57 (NRI)<br>62 (MI) | 57 | Medical and gastrointestinal, hospitalized | SGA, NRI†, MI†† | • Malnourished on admission = more complications |
| Suominen (2005) [51] | 2424 | 29 | 82 | Geriatric, nursing home | MNA | • MNA $< 17$ = malnutrition<br>• Mean BMI = 23 |
| Thomas (2002) [30] | 837 | 29 | 76 | Subacute care | Anthropometrics, MNA, biochemical markers | • 53% hypoalbuminemia<br>• 63% at risk of malnutrition |
| Weinsier (1979) [23] | 134 | 48 | 52 | General med, hospitalized | LOM | • LOM uses anthropometrics, serum albumin, lymphocyte count, hematocrit, folate, and vitamin C<br>• 33% remained hospitalized $> 2$ weeks |

BMI (body mass index); MAMC (midarm muscle circumference); TSF (triceps skinfold), TST (triceps skinfold thickness); SGA (subjective global assessment)

MNA (Mini Nutritional Assessment)–questionnaire, incorporates four subscores: MNA-1 (anthropometrics), MNA-2 (global evaluation), MNA-3 (assessment of dietary habits), MNA-4(subject assessment of nutrition status)

NRI (Nutritional Risk Index) = [(1.5*albumin) + (41.7*present/usual weight)]

MI (Maastricht Index) = [20.68 − (0.24*albumin) − (19.21*transthyretin) − (1.86*lymphocytes) − (0.04*ideal weight)]

Table 2.4
Malnutrition and Outcome in Chronic Disease Populations

| *Author* | *N* | *Patient* | ↑ *LOS* | ↑ *Mortality* | *Outcomes* | *Nutrition index* | *Comment* |
|---|---|---|---|---|---|---|---|
| Chima (1997) [24] | 173 | General medicine | + | | ↓ Discharge home<br>↑ Medical costs | Height-weight ratio, serum albumin | • 56% at risk, had higher prevalence of liver disease (?)confounder<br>• 1-month follow-up |
| Edington (1999) [36] | 10,128 | Cancer and CVD patients (UK database) | | + | ↑ Consultation<br>↑ Prescriptions | BMI | • In <65-year-old group BMI is "U" shaped in its association with mortality |
| Kagansky (2005) [27] | 414 | Geriatric, hospitalized | + | + | ↑ Infection | MNA and MNA-3 subscores | • Significant ↓ survival in low MNA over 2.7 years<br>• MNA-3 strong predictor of mortality |
| Martyn (1998) [14] | 11,357 | Chronic diseases (neuro, GI, pulm) | | + | ↑ Consultation<br>↑ Prescriptions | BMI | • Community-based patients<br>• Mortality 2× greater in patients with BMI <20 |
| Mühlethaler (1995) [26] | 219 | Geriatric | + | + | ↓ Length of overall and at home survival | Anthropometrics, serum biochemical markers | • Prealbumin with hazard ratio = 1.9<br>• 4.5-year follow-up |
| Pirlich (2003) [12] | 502 | General medicine | + | | | SGA, NRI, BMI, body composition | • Malnourished patients were older<br>• LOS independent of medical disease |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Potter (1995) [29] | 69 | Geriatric | + | | ↑ Infection | BMI | • Episodes of sepsis in 73% malnourished |
| Reilly (1988) [32] | 771 | Medical and surgical | + | + | ↑ Medical costs<br>↑ Complications | LOM | • Likelihood of malnutrition uses albumin, total lymphocyte, height/weight < 80% and clinical assessment |
| Robinson (1987) [31] | 100 | General medicine | + | | ↑ Medical costs | Visceral proteins, nutrition assessment | • Hospital charges and LOS 2× in malnourished patients |
| Sullivan (1999) [43] | 497 | Geriatric, medical and surgical | | + | ↑ Weight loss | Nutrient intake | • Low nutrient group higher in-hospital and 90-day mortality |
| Thomas (2002) [30] | 837 | Geriatric, subacute care | + | | ↑ Admissions<br>↑ Depression | MNA, biomarkers anthropometrics | • >91% malnourished or at risk on admission<br>• 25% readmission after 14-month follow-up |
| Tucker (1996) [64] | 2,485 | Medical and surgical | + | | ↑ Medical costs | Weight, height, <75% IBW, serum alb, weight loss > 10% last month before admission | • Early nutritional intervention =↓ LOS, 75% variance of LOS account for by Dx, days of intervention and expected LOS |

*(Continued)*

Table 2.4
*(Continued)*

| *Author* | *N* | *Patient* | ↑ *LOS* | ↑ *Mortality* | *Outcomes* | *Nutrition index* | *Comment* |
|---|---|---|---|---|---|---|---|
| Veterans Affairs TPN Cooperative Study Group (1991) [114] | 2,448 | Perioperative surgical | − | | Equal complication rates in TPN vs. no TPN<br>↑ mortality in TPN | SGA, NRI | • Effect of TPN on operative outcome depended on baseline nutrition status<br>• No significant reduction in morbidity in heterogeneous group of surgical patients |
| Weinsier (1979) [23] | 134 | General medicine | + | + | | LOM | • Nutrition status (LOM) worsened with hospitalization in 69% patients.<br>• LOM uses anthropometrics, vitamin C, folate and lymphocytes, albumin, and hematocrit |

BMI (body mass index); MAMC (midarm muscle circumference); TSF (triceps skinfold), TST (triceps skinfold thickness); SGA (subjective global assessment); LOM (likeliness of malnutrition)
MNA (Mini Nutritional Assessment)–questionnaire, incorporates four subscores: MNA-1 (anthropometrics), MNA-2 (global evaluation), MNA-3 (assessment of dietary habits), MNA-4 (subject assessment of nutrition status)
NRI (Nutritional Risk Index) = [(1.5*albumin) + (41.7*present/usual weight)]

well-nourished patients [31]. In a retrospective cohort in Brazil, Correia et al. reported the mean daily hospital costs of malnourished patients were 60% to 300% higher than in well-nourished patients [34]. And although hospital charges are not accurate measures of each specific group's perspective, they illustrate the magnitude of the problem. Higher costs are directly attributable to increased length of stay and increased use of resources for further treatment of complications. Furthermore, the fact that hospital length of stay (LOS) has declined over the last decade secondary to pressures of third party payers compounds the problem.

The failure of accurate identification of malnutrition on hospital admission can lead to further nutritional deterioration, lengthened hospitalizations, and an overall increase in costs. Despite JCAHO's mandate to screen patients for malnutrition, many hospital systems have not implemented efficient ways to collect and study the data. This can partly be explained by both past and present literature that fails to define and properly measure malnutrition. This same trend is consistent outside the United States [35]. A separate Polish study demonstrated a strong correlation between BMI and hospital LOS; only 10% of admissions had a measured BMI.

Although the relationship between malnutrition and length of stay and health care costs remains strong, the causality of these connections is not clear. Appropriate medical nutrition therapy leads to decreased LOS, reductions in hospital costs, and overall improvement in clinical outcomes. Yet, nutritional support is often not provided. The fact that 45% of the malnourished patients exceeded their estimated DRG length of stay suggests that early recognition and treatment of malnourished patients may decrease the length of stay and hospital costs [5, 31].

While specific malnourished patient subpopulations have documented benefits from nutritional support, e.g., perioperative, gastrointestinal, cancer, COPD, chronic dialysis, critical care and elderly, the benefits remain largely debatable. Hospital malnutrition rates are not homogenously distributed among specialty services [36]. This chapter will discuss five patient subgroups not covered elsewhere in this volume, in which malnutrition has affected clinical outcomes.

## 5. GERIATRICS

As the elderly population continues to grow, the number of elderly with chronic illnesses will expand as well. Studies show that up to 60% of hospitalized elderly have clinically significant PEM [37]. The best

indicator of mortality in community-based, hospitalized, and institutionalized elderly is weight loss. Kagansky and colleagues reported PEM in 15% of the elderly community, over 60% of the hospitalized, and up to 85% of nursing home residents [27]. Sullivan and colleagues investigated nursing home residents for 6 months and concluded that weight loss can have an ominous implication for mortality. However, when weight loss is reversed, survival is improved [38].

Although PEM among the elderly has been well established, it remains largely ignored [39–42]. One study found that more than 50% of severe nutritional deficiency cases in the elderly are undiagnosed or undetected [41]. Even when geriatric nutritional problems were properly addressed, adequate nutritional support was rarely provided. Sullivan and colleagues concluded that insufficient nutrient intakes in elderly patients may contribute to increased risk of mortality [43]. The authors reported that the poor nutritional status in elderly populations likely occurs before hospitalization and continues to have a strong association with mortality after discharge [9]. Some literature states that because of strong correlations of serum albumin and low BMI with mortality even years after discharge, emphasis needs to be placed on nutritional support after discharge [44]. Prospective studies have shown strong associations between nutritional parameters, e.g., low serum albumin levels, and both short- and long-term mortality (see Table 2.5). So strong were the associations for more than 9 years that Phillips et al. compared it with that for cigarette smoking [45].

**Table 2.5**
**Variables that Correlate with 1- and 6-year Mortality**

| *Variable* | *Significant at 1 year* | *Significant at 1 and 6 years* |
|---|---|---|
| Age | + | |
| Diagnosis | + | |
| Serum albumin | | + |
| BMI | | + |
| Weight loss > 5% over prior 6 months | | + |
| Number of chronic diseases[†] | | + |

[†] Number of diagnoses (0–7) of the following diseases: congestive heart failure, type 2 diabetes mellitus, cerebral vascular accident, dementia (Alzheimer's or MID), Parkinson's, COPD, and ESRD.
Adapted from Sullivan and Walls [44]

Despite stabilization of the acute illness, the elderly have less recuperative powers after discharge [46] and have more frequent hospital readmissions, placing them at increased risk of death within 1 to 4 years after discharge [26, 47, 48]. In a comparison study with younger men with equal health status, elderly men were found to have poorer eating habits and took longer to recover. After 1 year, they had greater weight loss and more health problems [49], suggesting the aging process might play a role in recovery.

PEM has a variety of deleterious effects in the elderly, including infections [50, 51], pressure ulcers (though its causality is yet to be determined) [52], hip fractures [53–55], and cognitive abnormalities. Malnutrition impairs immune function, especially cell-mediated immunity [56, 57]. Most if not all of these effects can be reversed with adequate nutrition. Though a recent meta-analysis of mostly randomized clinical trials of oral supplementation confirmed short-term outcome benefits and improvement of nutritional status [58], other studies did not result in significant improvement in patients' caloric intakes [59], BMI or body weight [60]. Lauque et al. showed improvement in weight after 60 days' supplementation with 400 kcal/day [61]. Appetite stimulants (orexigenics) can also contribute to weight gain. Megesterol acetate was found to produce weight gain in elderly nursing home patients [62], and dronabinol has shown weight gain in the elderly, but has mostly been used for palliative care [63].

Nutritional support is used in elderly persons who are unable to sustain their weight and increase their oral food intake. Enteral nutrition is the recommended route and can reverse weight loss and produce weight gain. Tucker and Miguel suggested that hospital length of stay is shortened by nutritional support reducing complications [64]. However, reduced survival has been documented in elderly persons with cognitive impairments [65, 66]. Some authors suggest that aging must influence the refeeding process as nutritional intervention cannot maintain weight despite adequate caloric intake [67, 68]. Although malnutrition is not an inevitable process in aging, many changes occur in the elderly that promote malnutrition outside of the hospital. Most important is anorexia, which causes decreased energy intake through several different disturbances, e.g., deterioration of taste and smell sensations and changes in gastrointestinal function, leading to early satiety. In addition, poor appetite, poor dentition, impaired physical activity, poor cognition, depression, and poor social functioning can further potentiate declines in energy intake.

The causal connections between malnutrition and poor prognosis are complex. It cannot automatically be inferred that nutritional support

will improve the clinical course of elderly patients. Little evidence exists that confirms that long-term outcomes will be improved with parenteral nutrition (PN) in the elderly population; therefore, exclusive parenteral nutrition is generally not recommended. There are obvious indications for PN, especially in patients with intestinal failure, high output enterocutaneous fistulas, short bowel syndrome and some perioperative situations in patients with cancer.

## 6. RENAL DISEASE

Malnutrition has been reported to occur in up to 50% of patients with acute and chronic renal failure [69, 70]. It is implicated as the main cause of mortality in chronic dialysis patients [54, 71–77]. In this population where the annual mortality rate is 20% to 25%, atherosclerotic heart disease is thought to be the major cause of morbidity and mortality [76]. Because there is a strong association between hypoalbuminemia and cardiovascular disease, both malnutrition and inflammation have been implicated as the main factors in the high mortality of these patients [78]. The presence of PEM and inflammation are common and usually concurrent in dialysis patients to the extent where some investigators have termed the relationship the malnutrition-inflammation complex syndrome (MICS) [79]. There is overlap between patients with malnutrition and patients with inflammation. Both show evidence of depressed negative acute phase reactants such as serum albumin and transferrin, and increased inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6). These serum marker abnormalities are common in dialysis patients; CRP and IL-6 in particular have shown superior outcome predictabilities when compared with serum albumin [80]. Although chronic hemodialysis patients already have elevated levels of CRP in comparison to healthy adults, Ikizler et al. showed that CRP levels and reactance values of BIA were independent predictors of hospitalization in this population. In this small prospective study, serum albumin and other visceral proteins were not predictive of hospitalization and were thought to be mainly influenced by inflammation [76]. This has led some investigators to ask whether malnutrition alone is a risk factor for morbidity and mortality or only in its association with inflammation. In fact, low serum protein levels may primarily indicate inflammation and not malnutrition.

Over time, malnutrition and inflammation lead to weight loss in the dialysis patient, which can be explained by three main factors, low nutrient intake, the underlying disease, and the dialysis procedure.

A progressive decrease in dietary intake is frequently observed in patients with progression of kidney failure. Gastroparesis, taste disturbances, and diet restrictions in the "renal diet" are likely contributors. Anorexia plays a major role in PEM and is independently associated with mortality [81]. As these patients are unable to meet their energy requirements, loss of weight and muscle mass ensue. Kopple found poor intake and muscle mass to be independently associated with increased 1-year mortality [82]. In addition, protein and nutrient losses occur daily with patients on different forms of dialysis. Ikizler et al. describe a progressive decline in dietary protein intake in patients with a decreasing GFR [83].

Though nutritional status at the onset of dialysis is a good predictor of short- and long-term survival [84], the most effective method of managing malnutrition in these patients is still unclear. Improving nutritional status remains difficult in ESRD patients because of the associated anorexia. Nutritional support methods like oral supplementation, enteral feeding, and appetite stimulants can improve nutrient intake; however, there needs to be close follow-up with the patient. Enteral and parenteral nutrition are suggested after failure of oral supplementation. The addition of specialized amino acids like α-ketoglutarate and ornithine, glutamine, and arginine to hemodialysis has been shown to improve protein balance. Although recombinant human growth hormone (rhGH) administration produces short-term benefits in nitrogen balance, lean body mass and serum albumin levels in hemodialysis patients, it remains unclear whether GH administration reduces morbidity and mortality [85]. Furthermore, despite low serum and muscle levels of insulin-like growth factors (e.g., IGF-1), there is no evidence to suggest any outcome benefits of its administration in ESRD patients [84, 86]. Although evidence shows that nutritional support in various forms can improve nutritional indices in dialysis patients, it does not improve outcomes [54]. In reality, the clinical trials designed to answer these questions have not been adequately designed. The few studies on intradialytic parenteral nutrition (IDPN), i.e., intravenous supplementation of mixtures of glucose, amino acids, and/or lipids during the hemodialysis session, have been inconsistent in improving survival [69, 87–89].

## 7. PULMONARY DISEASE

The prevalence of malnutrition varies between 30% and 60% in different patient groups with chronic obstructive pulmonary disease (COPD); it is highest in patients with emphysema [90, 91]. Since

Vandenbergh first reported a shorter 5-year survival rate in COPD patients with weight loss 30 years ago [92], it has been well documented that low body weight is an independent predictor of morbidity and mortality in COPD patients [93–96]. Even after adjusting for age, gender, smoking status, and especially $FEV_1$ and home oxygen use, Gray-Donald and colleagues showed that a low BMI has an independent effect on all-cause mortality [93]. A large cohort of over 4,000 severe COPD patients treated with long-term oxygen therapy confirmed an ongoing premise that survival rates improve with increasing BMI and are best in the obese population [94]. In this study, patients with low BMIs ($< 20 kg/m^2$) had the worst 5-year survival rate (24%). The BMI was the most powerful predictor of rate of hospitalization and length of stay [97].

Malnutrition in patients with COPD is associated with an imbalance between energy expenditure and dietary intake [98]. COPD patients have higher energy needs, despite their seemingly low level of physical activity, which can be explained by the inefficiency of the peripheral skeletal muscles and thus overcompensation of the respiratory muscles. The increased work of breathing and the greater respiratory muscle activity account for the increased resting energy expenditure (REE). The functional consequences of nutritional depletion not only relate to muscle wasting (e.g., loss of lean body mass), but also to alterations in muscle morphology and metabolism. Malnutrition is known to affect types of diaphragm muscle fibers, potentially influencing contractility and fatigue [99]. Clinically, malnourished COPD patients are predisposed to pulmonary infections and failure to wean from mechanical ventilation from adverse effects on muscle strength [100], ventilatory drive [101], and immune defense mechanisms [102]. Hyperinflation-induced early satiety and poor appetite are the major factors contributing to insufficient energy intake in COPD patients. Medication use, chronic systemic inflammatory response, and negative nitrogen balance also contribute to the nutritional depletion of COPD patients [103].

The association of malnutrition and weight loss with advanced lung disease has been termed pulmonary cachexia syndrome. General nutritional goals for these patients include preservation of lean body mass by providing adequate energy and protein to produce a positive nitrogen balance. The importance of medical nutrition therapy for COPD patients is widely accepted and successful in improving weight and muscle strength, but nutritional support trials have shown little in improved outcomes and provided mixed results. Most of the randomized controlled trials with oral supplementation, particularly in

short-term studies, note positive effects on respiratory function and respiratory muscle strength, but offer no comment on mortality [104]. However, poor treatment responses might be attributed to limitations such as non-compliance, individual variation, and the observation that patients take the supplements instead of their regular meals. In a Cochrane review of randomized controlled trials of nutritional interventions lasting at least 2 weeks, Ferreira and colleagues concluded that prolonged nutritional supplementation had no benefit on lung function, anthropometric measurements, or exercise capacity in stable COPD patients [105]. This result was homogeneous across all studies. Other studies evaluating the effects of adjuvant treatments with anabolic steroids and growth hormone in COPD patients showed improvements in body weight and lean body mass, but not in functional capacities [106–108]. Hypercarbic COPD patients fed a high-fat, low-carbohydrate diet have shown weight gain [109] and improvements in respiratory function [110, 111] and exercise capacity [112]. Overall, most nutritional supplementation studies show improvements in predictors of survival in COPD patients, but evidence confirming survival benefits is lacking.

## 8. PERIOPERATIVE NUTRITIONAL SUPPORT

Malnutrition is associated with increased postoperative complications in surgical patients [113]. Numerous studies have evaluated preoperative and postoperative nutritional support with controversial results. RCTs [114–116] and a meta-analysis [117] indicate clear preoperative total parenteral nutrition (TPN) benefits in a selected group of the most severely malnourished patients. In addition, Klein and others in a consensus statement concluded that malnourished patients receiving 7 to 10 days of TPN before surgery had a 10% absolute reduction in postoperative complications [22].

The largest and most cited study on perioperative nutritional support is the VA TPN Cooperative Study [114]. In this study, the most severely malnourished male patients had fewer non-infectious and overall complications, but no change in the length of stay. Furthermore, the mildly malnourished subgroups who received TPN had increased infectious complications. Heyland et al. concluded that the study showed no effect on mortality [117].

Selection bias is likely responsible for much of the inconclusiveness regarding the benefits of nutritional support in the perioperative setting [118, 119]. In addition, evidence is lacking that nutritional support affects outcomes favorably, partly because of difficulty finding

accurate measures of nutritional outcome. Thus, some authors argue that a lack of clear-cut benefits exists in groups other than selected groups [120]. This has prompted investigators to carefully select the most beneficial candidates, including patients with major trauma, severely malnourished patients undergoing elective surgery, and well-nourished minimally stressed patients unable to eat for 7 to 10 days postoperatively. Most comparative studies show enteral nutrition to be equal to parenteral nutrition. In a prospective study of well-nourished patients with a gastrointestinal malignancy undergoing elective surgery, Gianotti showed a decreased length of stay with 7 days of preoperative oral supplementation consisting of omega-3 fatty acids, arginine, and nucleotides [121].

## 9. TRANSPLANTATION

Organ transplant patients are sometimes at the extreme end of the nutritional status spectrum. Not only have they endured years of suffering from chronic disease, but they are subjected to a surgical procedure and great risks of complications from immunosuppressive drugs. Malnutrition is often present in end-stage disease patients; it is associated with an increased post-transplantation risk of infection, and it may reduce survival.

Malnutrition is common in patients awaiting liver transplantation and may contribute to operative and postoperative mortality, although this is controversial. Pikul and colleagues found that 60% of liver transplant patients were moderately to severely malnourished and had longer intensive care and hospital stays than better nourished patients [122]. Using triceps skinfold and midarm muscle circumference, Harrison et al. reported that malnourished subjects had more cases of bacterial infections and had a reduced 6-month survival [123]. In describing her earlier work with more than 1,200 liver transplant patients, Hasse reported that although there was less frequent transplant rejection in the severely malnourished patients, there was no effect of malnutrition on post-transplant infection rates. One- and three-year graft and patient survival rates were lower in severely malnourished patients than in well-nourished patients [124].

Much as in patients with chronic pulmonary or chronic kidney diseases, low BMI [125] and hypoalbuminemia [126] are associated with increased morbidity and decreased survival in lung transplant and kidney-pancreas transplant recipients. Malnutrition is seen in up to 60% of patients seeking lung transplantation [127]. Post-transplant

weight gain may improve survival in this population [128], while transplantation may reverse malnutrition [129].

In transplantation patients, nutritional assessment and education are beneficial in both the pre- and post-transplantation periods [124]. Nutritional support can prevent continued symptoms of end-stage organ failure by, for example, implementing dietary sodium restriction and fluid retention in ESRD patients or branched-chain amino acids supplementation in patients with severe cirrhosis. A small intervention study using oral supplementation in liver transplant candidates reported that the benefit in reducing the frequency of hospitalizations before transplantation could be partly due to increased energy consumption [130]. The post-transplant nutritional goal is to provide adequate nutrition to promote wound healing and anabolism, to prevent infection, and to minimize side effects of medications. Nutritional intervention is documented to be able to provide adequate nutrition and to treat underlying malnutrition, but it is also important to prevent excessive weight gain, as both malnutrition and obesity significantly affect morbidity and length of hospital stay after transplantation [131].

## 10. CONCLUSIONS

Malnutrition is a significant global problem in health care. There are strong associations between markers of malnutrition and increased morbidity and mortality and elevated health care costs. Although there is substantial evidence documenting the nutritional benefits of medical nutrition therapy and the ability to improve some health care outcomes, nutritional interventions have often failed to produce clear disease-outcome benefits such as shortened lengths of hospital stay and mortality. In addition, malnutrition remains underappreciated in general medical care. Given today's emphasis on reducing health care costs, more malnutrition outcomes studies are needed to better quantify nutrition benefits in hospitalized patients and in all who have chronic diseases.

The execution of nutritional support studies in chronically ill patients is challenged by several methodological problems, including no generally accepted definition of PEM, difficulties distinguishing malnutrition from the effects of inflammatory and stress responses, uncertain patient compliance with supplementation, and a wide range of outcome variables. Few studies have combined clinical observations with biomarkers and questionnaires in assessing and monitoring malnutrition.

We suggest it would be easier to identify those patients with a greater likelihood of malnutrition [23, 32] and base this definition of the likelihood of malnutrition on several clinical findings mixed with serology and anthropometric data. This would establish a consistency of markers, methods, and evaluations from which further studies could benefit.

## RECOMMENDATIONS AND CONCLUSIONS

- Malnutrition continues to affect one-third to one-half of hospitalized patients, especially the elderly population, and has been shown to be an independent predictor of mortality.
- Nutritional parameters are unreliable in isolating the effects of malnutrition from the influence of chronic disease.
- Weight loss is the best predictor of mortality in institutionalized, hospitalized, and community-based elderly.
- The short-term outcome benefit of oral supplementation in the elderly is still unclear.
- There is difficulty in distinguishing the independent affects of malnutrition versus stress responses on mortality of chronic kidney disease patients.
- Low body weight is an independent predictor of morbidity and mortality in COPD patients.
- Prolonged nutritional support ($> 2$ weeks) did not improve lung function in COPD patients; its effect on mortality is unclear.
- Perioperative nutritional support benefits the most severely malnourished patients, so these patients should receive nutritional support for 7 to 10 days preoperatively to reduce postoperative complications.
- Malnutrition and obesity significantly affect length of hospital stay and morbidity in organ transplant patients. Nutritional support while patients wait for organ transplantation may improve survival.
- The optimal timing of commencement of nutritional support in hospitalized patients with poor intake is unclear.

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# 3 Nutrition in Inflammatory Bowel Disease

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***Contents***



*Summary*

Discussed in this chapter are ways in which inflammatory bowel disease (IBD) and nutrition are intimately related. Both Crohns disease and ulcerative colitis can have a profound effect on the nutritional status of those afflicted with these diseases. This can occur as a result of decreased food intake, digestion and absorption, increased requirements, altered metabolism of nutrients, increased losses and drug-nutrient interactions. There have also been implications of diet in the etiology of IBD. Finally, nutrition in the treatment of IBD is outlined. If it is found that nutrients are potential immunomodulators in these diseases, some intriguing dietary treatments may come to the forefront in the future.

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**Key Words:** Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Malabsorption, Malnutrition

## 1. INTRODUCTION

Inflammatory bowel disease comprises several diagnoses with bowel inflammation, the most common of which are Crohn's disease and ulcerative colitis. These diseases are associated with malnutrition, including protein-calorie malnutrition, vitamin deficiency and mineral deficiencies. Various dietary practices have been implicated as attempts have been made to determine the etiologies of these diseases. Nutritional support of patients with inflammatory bowel disease has been directed toward serving as a primary therapy, correcting nutritional deficiencies and correction of growth failure.

There have been numerous reviews of inflammatory bowel disease and nutrition over the years. These, for the most part, vary regarding concepts of nutritional management of Crohn's disease, depending on whether the reviews have originated in the United States or Europe. This chapter will concentrate primarily on the literature from the past decade, as well as some of the older, but classical references on the topic.

In inflammatory bowel disease (IBD) as in many gastrointestinal diseases, the disease itself may have a profound effect on an individual's nutritional status. In some intestinal diseases there may be a role for dietary practices in the pathogenesis of the disease. Additionally, nutrition and manipulation of food intake may alter the course of the disease. This review will concentrate initially on the nutritional consequences of Crohn's disease and chronic ulcerative colitis. The possible effects of diet and lifestyle in the etiology of IBD will be addressed. Finally, the use of nutrition support and special diets in the treatment of IBD will be discussed.

## 2. IBD DEFINED

For the purpose of this review, Crohn's disease involving any part of the intestine and chronic ulcerative colitis will be the topics discussed. While these diagnoses are only part of the group of disease states included under the heading of IBD, they do include the largest proportion of inflammatory diseases of the small intestine and colon.

Crohn's disease can affect any part of the gastrointestinal tract from the mouth to the anus. It is a transmural disease that involves the terminal ileum and colon in 35–45% of cases, the terminal ileum only

in 25–35%, the colon only in 15–25% and the proximal small bowel or diffuse distribution throughout the small bowel in the remaining 5–10%. Skip lesions with interspersed normal mucosa are the typical form of Crohn's disease. Treatment prior to the past decade was primarily based on corticosteroids and surgical resection, though the more recent therapies using immunomodulating drugs have focused on sparing intestine lost to resection as well as decreasing complications of steroid therapy. The incidence of Crohn's disease is increasing worldwide [1].

Ulcerative colitis, by contrast, involves only the colon, sometimes with associated "backwash ileitis" affecting the most distal several centimeters of the terminal ileum. It is characterized by continuous inflammatory changes of the colon from the rectum to its proximal extent of disease. It typically involves only the mucosal and submucosal layers of the intestine. There is pancolitis in about 20% of cases. The implications for nutritional status in IBD, not surprisingly, vary based on the anatomic and pathophysiological differences between Crohn's disease and ulcerative colitis.

## 3. MECHANISMS OF MALNUTRITION

In virtually all disease states, the mechanisms of malnutrition fall under seven general categories (Table 3.1). These include decreased food intake, maldigestion, malabsorption, alterations in metabolism of nutrients, increased nutrient requirements, increased nutrient losses and drug-nutrient interactions. The effect of inflammatory bowel disease will be addressed with each of these causes individually (Table 3.2).

Decreased food intake is commonly encountered in IBD, especially in Crohn's disease. This frequently occurs because of anorexia and association of food intake with nausea, vomiting, diarrhea or pain, as well as the imposition of various restrictive diets by a variety of individuals and for a variety of reasons.

**Table 3.1**
**Mechanisms of Malnutrition in Disease**

| |
|---|
| Decreased food intake |
| Maldigestion |
| Malabsorption |
| Altered intermediary metabolism of nutrients |
| Increased nutrient losses |
| Increased nutrient requirements |
| Drug: nutrient interactions |

**Table 3.2**
**Causes of Malnutrition in IBD**

| *Factor* | *Cause* | *Consequence* |
|---|---|---|
| Anorexia | TNF-α; other pro-inflammatory cytokines | ↓ dietary intake |
| Nausea, vomiting | Stricture, abscess | ↓ dietary intake |
| Abdominal pain, diarrhea | Inflammation; obstruction | ↓ variety & amount of food |
| Restrictive diets | Recommendations from family, friend, physicians | ↓ dietary intake |
| Maldigestion | Sclerosing cholangitis, intestinal bacterial overgrowth | ↓ fat & fat soluble vitamin absorption |
| Malabsorption | ↓ absorptive surface area | Vitamin & mineral deficiencies |
| | Absence of terminal ileum | (Vitamin B12 not absorbed) |
| Increased requirements | Inflammation, fever | Weight loss |
| Losses from the gut | Inflammation | Protein & mineral losses |
| | Bleeding | Iron deficiency anemia |
| Altered intermediary metabolism | TNFα, IL-1β and IL-6 | ↓ albumin and other protein synthesis |
| Drug nutrient interactions | Steroids | ↓ calcium absorption, ↑magnesuria, ↑muscle wasting |
| | Sulfasalazine | ↓ folate absorption & reduction to tetrahydrofolate |

Adapted from Jeejeebhoy KN: Management of nutritional problems of patients with Crohn's disease. CMAJ 2002;163:913–918. With permission.

Recent research efforts have investigated the possibility that pro-inflammatory cytokines may have a role in anorexia of IBD. An increased 5-hydroxytryptamine (5-HT) release from the hypothalamic paraventricular nucleus has been observed in a rat model of colitis by Ballinger et al. In these animals, dietary intake was decreased compared to healthy controls, and food intake was subsequently normalized when brain 5-HT was depleted with p-chlorophenylalanine injection into the hypothalamus [2].

Injection of interleukin-1β (IL-1β) had been shown more than a decade ago to increase hypothalamic release of 5-HT [3]. Leptins have also been identified to be elevated in inflammation and to be associated with suppression of food intake [4]. It is also well known that the pro-inflammatory cytokines, tumor necrosis factor alpha (TNF-α), IL-1β and interleukin 6 (IL-6) are increased in active Crohn's disease [5] and that they play a role in the pathogenesis of IBD [6]. These findings suggest a possible interrelationship of the pro-inflammatory cytokines and anorexia of IBD. Recent observations by Bannerman and coworkers [7] of subjective appetite parameters in a small number of patients with active and inactive Crohn's disease support the animal studies, in that hunger was significantly lower in those with active Crohn's compared with healthy subjects. Serum leptins were significantly associated with percentage of body fat and, when data were corrected for body composition, leptins showed a tendency to be higher in patients with active Crohn's disease.

In addition, food intake may be curtailed by symptoms that the patient associates with eating, such as nausea, pain, diarrhea and embarrassing incontinence. Furthermore, it is not unusual for the clinician to find that patients have restricted their food intake based on diets provided by not only the medical profession, but also a variety of sources such as well-meaning acquaintances, relatives or, more recently, the Internet. When a patient has had multiple suggestions of limiting a variety of foods, it is common to learn that entire food groups have been eliminated from the diet. Additionally, dietary beliefs of patients with IBD can significantly alter food patterns, and in particular have been shown to decrease the intake of calcium and folic acid [8]. These special dietary recommendations and beliefs can cause the food that is ingested to be deficient in various nutrients.

In Crohn's disease involving the small intestine, the diseased mucosa may cause maldigestion of nutrients. This can occur in proximal disease where mucosal disaccharidases are destroyed by mucosal injury, causing undigested carbohydrates to provide osmotic loads with resulting diarrhea and flatulence from metabolism by colonic flora. Additionally, ileal disease may result in decreased bile acid absorption, thus decreasing the bile acid pool. The result is that lipids are prevented from being solubilized, and thus they are poorly digested within the lumen of the proximal small bowel as a result of inadequate mixing of triglycerides with pancreatic enzymes. Furthermore, primary sclerosing cholangitis, a biliary complication of IBD, especially ulcerative colitis, may also result in decreased bile secretion and decreased digestion and absorption of fats and fat-soluble vitamins. Small intestinal bacterial

overgrowth may also cause fat maldigestion as a result of deconjugation of bile salts by bacteria. The effect of increased and altered flora in the small intestine is progressive damage to the mucosa with depletion of disaccharidases.

Malabsorption occurs as a result of inflammation of the intestinal mucosa, as well as intestinal resection causing decreased mucosal surface area available for absorption, especially Crohn's disease. Distal ileal resection affects absorption of bile acids, mentioned previously, and vitamin $B_{12}$. Bacterial overgrowth also causes malabsorption of vitamin $B_{12}$ as a result of the utilization of the vitamin $B_{12}$ preferentially by the bacteria and depletion of the $B_{12}$ supply available to the distal ileum. Malabsorption is less of an issue in ulcerative colitis.

Altered intermediary metabolism of nutrients by cytokines has become the topic of recent studies of Crohn's disease [1]. Inflammatory cytokines, including TNFα, IL-1β and IL-6, are produced by activated monocytes/macrophages and lymphocytes in response to various stimuli and cause alteration of metabolism of protein, carbohydrate and lipid. In Crohn's disease these inflammatory cytokines are produced in excessive amounts in blood and intestinal mucosa [9, 10, 11, 12]. Reimund and colleagues found that univariate analysis of various anthropometric and biochemical measures of nutritional status in patients with Crohn's disease were significantly linked with inflammatory cytokine levels [13]. Specifically, mean arm circumference (MAC), triceps skinfold thickness (TSF), albumin and transthyretin were negatively correlated with TNFα levels, while IL-1β was negatively correlated with body weight, body mass index, MAC and albumin. Furthermore, there was a negative correlation between the nutritional parameters, albumin and transthyretin, and inflammatory proteins, including erythrocyte sedimentation rate, C-reactive protein, fibrinogen and orosomucoid. Insulin-like growth factor (IGF-I) was positively associated with albumin, transthyretin, retinol-binding protein and vitamin A levels. These data, as well as knowledge of the role of TNF-α in switching amino acids toward acute-phase reactant synthesis and away from albumin synthesis [14], led to the suggestion that reduction of inflammation with associated correction of nutritional protein synthesis should be a goal of therapy in Crohn's disease [13].

Increased requirement of calories may result from fevers and sepsis in IBD. Increased basal metabolic rate in active IBD has been suggested to cause malnutrition [15], though in quiescent disease this probably does not occur [16]. Indeed in those with active disease, the increased basal energy requirements are likely offset by decreased requirements for activity, since those who are more ill are usually less

active [15]. Al-Jaouni and coworkers identified that patients with active Crohn's disease had increased resting energy expenditures, enhanced lipid oxidation and decreased diet-induced thermogenesis compared to controls [17]. The effect of lipid peroxidation was directly related to disease activity. Yet, increased lipid oxidation was even seen in patients with inactive Crohn's disease [18]. Accelerated mucosal cell turnover may also increase nutrient requirements in IBD.

Increased nutrient losses occur in either Crohn's disease or ulcerative colitis as a result of inflammation and transudation of protein and fluid from the affected mucosa. Furthermore, mucosal hemorrhage causes loss of iron in both diseases. Fistulae, which most commonly occur in Crohn's disease, cause a loss of zinc, fluids and electrolytes. Unabsorbed fats, found primarily in Crohn's disease, bind calcium and magnesium within the intestinal lumen, causing wastage of both minerals.

Drug:nutrient interactions are an additional potential source of malnutrition in IBD. Sulfasalazine decreases absorption of folic acid and also decreases dihydrofolate reductase, so folic acid is not metabolized to its active form, tetrahydrofolate. Corticosteroids inhibit calcium absorption, cause magnesuria (thus magnesium wasting) and alter protein metabolism, causing muscle wasting. Antibiotics can decrease the vitamin K available from colonic bacterial metabolism. Cholestyramine binds bile acids, making them unavailable for adequate digestion of fat and fat soluble vitamins.

## 4. DIET IN THE PATHOGENESIS OF IBD

The etiology of Crohn's disease and ulcerative colitis has been elusive, and questions regarding the pathogenesis of the disease have led to many proposals, including some related to diet. Over the years there have been theories that a cow's milk allergy was an underlying factor in these diseases. Other related proposals have implicated lack of breast feeding. High sugar consumption and lack of dietary fiber have been suggested to be associated with the occurrence of IBD [19].

It has been proposed that in genetically susceptible individuals exposure to various environmental factors may cause an upregulation of immunological response that could result in IBD [20]. Gassull and Cabré suggest that changes in lifestyle, including dietary changes that have resulted from economic well being in the western world may be responsible for the increasing incidence of IBD [20]. They propose that exposure of the intestinal lumen to specific nutrients may act as an

antigenic agent or possibly as a moderator of regulatory mechanisms of the mucosal cells, potentially leading to IBD.

Short chain fatty acids have long been recognized to be the preferred fuel for colonocytes. Butyrate, a four-carbon saturated fatty acid, is the most abundant of the short chain fatty acids in the intestinal lumen, as it is the main product of bacterial fermentation of unabsorbed carbohydrate, primarily dietary fiber. Segain et al. found that butyrate has an anti-inflammatory effect, decreasing the TNFα production, cytokine messenger RNA expression and production of nuclear factor κB in tissue cultures derived from colonic biopsies of patients with Crohn's colitis [21]. The final mediator was proposed to be nuclear factor κB, the regulator of transcription of cytokine genes, including that of TNFα. This raises the question of whether a decreased intake of dietary fiber could have a role in the etiology of IBD, particularly in colonic disease.

Dietary fat as a putative etiologic agent has been implicated in part based on the observed lower incidence of inflammatory diseases in the Eskimos of Greenland [22]. This population group has a very high intake of fish, thus of omega-3 fatty acids [23], which have anti-inflammatory effects [24, 25]. Geerling and coworkers published case-control studies that found an association between high intakes of monounsaturated fats, omega-6 fatty acids and vitamin $B_6$and increased incidence of developing ulcerative colitis [26].

## 5. MALNUTRITION IN IBD

The occurrence of malnutrition in both ulcerative colitis and Crohn's disease is common (Table 3.3). Weight loss in regional ileitis (Crohn's disease) was described in the early observations of Crohn [27]. Indeed, death as a result of malnutrition in those with Crohn's disease was not unusual in the first half of the last century. Protein-calorie malnutrition is still seen in up to 80% of those with Crohn's disease and in as many as 50–60% of those with ulcerative colitis. Hypoalbuminemia is present in 25–80% of those with Crohn's disease and in 25–50% of patients with ulcerative colitis, but it has been identified that this primarily reflects disease activity rather than nutritional deficiency per se [28].

Growth failure in children and adolescents with Crohn's disease is a classical presentation. In addition to inadequate caloric intake, this may result from a growth-inhibiting effect of pro-inflammatory cytokines [29]. This topic will be addressed later in this chapter.

Anemia is present in a high percentage of individuals with IBD. This usually is the result of iron, vitamin $B_{12}$ or folate deficiency. Iron

**Table 3.3**
**Prevalence of Malnutrition in Inflammatory Bowel Disease**

| *colitis* | *Crohn's disease* | *Ulcerative* |
|---|---|---|
| Weight Loss | 65–76% | 18–62% |
| Growth retardation | 40% | – |
| Hypoalbuminemia | 25–80% | 25–50% |
| Anemia | 29% | – |
| Iron | 39% | 81% |
| Folate | 54% | 36% |
| Vitamin $B_{12}$ | 48% | 5% |
| Calcium | 13% | – |
| Magnesium | 14–88% | – |
| Potassium | 6–20% | – |
| Zinc | 40–50% | – |

Kelly DG, Fleming CR. Nutritional considerations in inflammatory bowel diseases. Gastroenterology Clinics of North America 1995,24:597–611. With permission from the publisher.

deficiency anemia is found in over 80% of patients with ulcerative colitis, primarily resulting from blood loss. It is seen in nearly 40% of anemic patients with Crohn's disease, especially in disease involving the colon. By contrast, vitamin $B_{12}$ deficiency is found predominantly in patients who have distal ileal Crohn's disease or a history of ileal resection with only a small prevalence occurring in ulcerative colitis. Folate deficiency is found in one-third to one-half of those with IBD with a somewhat higher prevalence in Crohn's disease. Three studies have measured the status of multiple vitamins in patients with IBD [30, 31, 32]. Blood levels less than the 15th percentile of normal controls for biotin, folate, thiamine, vitamin A, E, C and β-carotene were present in 40–90% of patients with IBD. These were identified in patients who had no clinical signs [31] and who did not have apparently decreased intakes [32], making clinical suspicion of importance in monitoring patients at risk for impending deficiency states. Fat soluble vitamin deficiencies are found particularly in patients with decreased bile salt pools, in those with cholestasis, as occurs in sclerosing cholangitis, and in those with bacterial overgrowth syndrome (30% of those with Crohn's disease). Vitamin A deficiency has been of concern, in part because of its relationship to immune function. In pediatric patients with both Crohn's disease and ulcerative colitis an increased

prevalence of vitamin A deficiency has been reported that is correlated with the severity of disease [33].

Selenium deficiencies are of particular concern in patients with IBD, as it along with vitamins E, A and C is an antioxidant. Oxidative stress is likely involved in the IBD process. In an evaluation of 26 patients with Crohn's disease, serum selenium and glutathione peroxidase levels in red blood cells were decreased, leading Reimund and colleagues to suggest that selenium deficiency may facilitate inflammatory and immune activation in the disease [34].

Magnesium deficiency is particularly common in Crohn's disease, especially following distal small bowel resection and colectomy. Additionally, zinc is frequently deficient in those with Crohn's disease with associated fistulae.

Metabolic bone disease is commonly observed in those with inflammatory bowel disease. Clearly malnutrition contributes to this phenomenon. Hypocalcemia is seen in more than 10% of those with inflammatory bowel disease. This is often associated with decreased levels of vitamin D and in those patients on corticosteroid therapy. Osteopenia has been reported in more than half of patients with deficient 25-OH vitamin D levels (less than 25 nmol/l). However, a recent study of 242 patients with Crohn's disease low bone mineral density (BMD) was not more frequent in those with the low 25-OH vitamin D levels, although parathyroid hormone and alkaline phosphatase were significantly higher in this group [35]. Decreased sunlight exposure, compromised nutritional status (as indicated by low levels of red blood cell folate and serum iron) and smoking were associated with lower levels of 25-OH vitamin D in this geographically localized population of northwestern Canadian patients with Crohn's disease. Vitamin D levels measured in winter were four-fold lower than those measured in the spring and summer. Another large study examined the frequency of clinical consequences of bone disease, specifically vertebral fractures, in patients with Crohn's disease [35]. Of the 293 consecutive patients evaluated, 156 (53%) had lumbar osteopenia or osteoporosis, and of these, 34 (22%) patients had 63 osteoporotic vertebral fractures with one-third of them occurring in patients under 30 years of age. Other studies have attempted to document risk factors for metabolic bone disease in IBD. Habtezion et al. identified age, body mass index and serum magnesium levels to be correlated with BMD, while lifetime steroid use was a poor predictor [37]. In fact, 40 patients in this study had never used steroids, and of them 48% had osteopenia of the femur and 30% of the spine. In contrast, Deer and colleagues found that patients

with Crohn's disease who had a low lifetime corticosteroid use as a result of steroid sparing approaches to treatment, including diet, had BMD levels similar to normal controls, while those patients receiving steroids had a significantly lower BMD [38]. An investigation by de Jong and coworkers identified 48% of patients with osteopenia and 30% with osteoporosis [39]. In this study steroid use, long duration of Crohn's disease, body mass index and history of intestinal resection were indicators determined by univariate analysis, but with multiple regression analysis, only body mass index and history of intestinal resection were independent predictors of decreased BMD. Clinicians must be aware of the potential for osteoporosis in patients with IBD, monitor BMD and treat with calcium and vitamin D replacement as needed, as well as give consideration to bisphophonates in those affected.

Geerling et al. identified that there is already a risk of nutritional compromise in patients at the beginning of the IBD course [40]. A cohort of Dutch patients that was within 6 months of the initial diagnosis of IBD (23 Crohn's disease and 46 ulcerative colitis) demonstrated that those with Crohn's disease were taller than controls selected randomly from a patient database, yet the body mineral content, measured by absorptiometry, was lower in the patients with Crohn's. Those with ulcerative colitis had a significantly higher body mass index than controls. Fat free mass was higher in those with Crohn's disease and lower in patients with ulcerative colitis than in the respective control groups. Experienced dietitians assessed the daily nutrient intake by doing food intake interviews and analyzing frequency reports. From this analysis it was found that patients with Crohn's disease had a lower intake of polyunsaturated fatty acids, but a high intake of mono- and disaccharides than the control group. Those with ulcerative colitis took in a lower percentage of calories as protein, as well as lower amounts of phosphorus, calcium, riboflavin and vitamin C than controls. Both patient groups also consumed less alcohol than either control group. Biochemical markers identified significantly lower albumin and vitamin $B_{12}$ levels among those with Crohn's disease and lower albumin, β-carotene, magnesium and zinc levels in patients with ulcerative colitis. A high percentage of these patients were judged to be in clinical remission (83% of those with Crohn's disease and 92% of patients with ulcerative colitis) based on the Crohn's disease activity index (CDAI) and Truelove and Witt's criteria, respectively.

## 6. NUTRITION IN THE TREATMENT OF IBD

Nutrition in inflammatory bowel disease can be considered to be either "supportive" or primary treatment. It is well accepted that when intended to be supportive (i.e., addressing specific nutritional deficits), alteration of diet and provision of appropriate supplements are corrective. The use of nutrition as primary therapy has been more controversial.

## 7. CORRECTING DEFICIENCIES

Unless the physician has particular expertise in nutrition and time to adequately address these issues, the assistance of a dietitian can be useful in identifying nutrient deficits, indicating which dietary practices may contribute and correcting them, motivating patients to comply with recommendations and monitoring the patient. Inadequate caloric and protein intakes require an understanding of the limitations in specific patients in order to develop effective and sometimes creative approaches to correction with the diet itself, as well as the use of caloric supplements and specific therapies. Availability of a chewable multivitamin containing water soluble forms of the fat soluble vitamins will frequently help in those with specific deficits of vitamins A, D, E and K. However, achieving 25-OH vitamin D levels deemed necessary to treat osteoporosis usually requires very high doses (50,000 international units several times weekly) of ergocalciferol. When such high doses are used, it must be kept in mind that monitoring of blood levels of the vitamin are necessary to be reassured that hypervitaminosis does not occur.

In many patients with low levels of vitamin $B_{12}$, it is now known that oral dosing with very high doses of cyanocobalamin (1,000 mcg daily) will effectively replace the vitamin as a result of passive absorption of up to 10% of the dose [41]. However, it is important to monitor blood levels to be assured that oral replacement is adequate in a specific patient. Increased levels of homocysteine have been associated with decreased folate in patients with Crohn's disease [42]. This suggests that attention be given to replacement of the vitamin for purposes of decreasing deep venous thrombosis and coronary artery disease [43, 44]. Data from Lashner et al. suggest that folate supplementation may decrease the development of dysplasia in the intestinal mucosa of patients with IBD [45].

Mineral replacement, especially including zinc, may be achieved with available oral zinc supplements. In the case of magnesium replacement, the challenge is providing a magnesium salt that does

not cause catharsis. Effective magnesium replacement can be achieved with organic salts of magnesium, such as magnesium gluconate, available as a tablet or as an elixir (magnesium heptagluconate in Canada—personal communication, Kursheed Jeejeebhoy, MD). These organic salts dissociate slowly in solution, limiting the osmotic load and improving therapeutic effectiveness.

Gassull suggests that sub-clinical deficiencies may play a role in the perpetuation of Crohn's disease [46]. This may occur as a result of defects in mechanisms of tissue repair causing decreased defense against damage resulting from oxygen free radicals, thus favoring lipid peroxidation [47, 48]. It is intriguing that anti-oxidant nutrient levels may be stressed in IBD. Certainly, this suggests that clinicians must be attentive to diet and patients' nutritional status and that there may possibly be a role for primary nutritional therapy maintenance of remission.

## 8. GOALS OF PRIMARY THERAPY FOR IBD

Gassull [46] succinctly states that the therapeutic goal in IBD "is to down-regulate the immune response in order to heal bowel lesions and hence improve symptoms and quality of life, with minimal side effects." The pharmacologic therapies that are currently in use in IBD,

**Table 3.4**
**Factors Contributing to Treatment Failure of Crohn's Disease with Enteral Nutrition**

| |
|---|
| Formula |
| Palatability |
| High osmolality |
| Transient side effects: headache, nausea, dizziness, diarrhea |
| Patient |
| Poor motivation |
| Inability to cope with length of time without solid food |
| Stricturing disease or bulky inflammatory mass requiring surgery |
| Clinical support |
| Limited availability of dietitians |
| Lack of supportive staff |
| Lack of robust protocols |
| Physician skepticism |

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as well as those that have been used historically, are associated with serious side effects. This raises the possibility that dietary manipulation may offer a safe alternative or possibly an adjuvant approach to decrease dependence on various immunomodulatory drugs. This should be considered, especially in those who have a potential to require steroids over the long term, those who are refractory to, intolerant of or dependent on steroids and other drugs, those at particular risk for osteoporosis and those who request alternate treatment. However, before starting a dietary regimen, assessment should be done to determine whether the patient is likely to comply either because of inconvenience or poor acceptance of the treatment (Table 3.4).

## 9. NUTRITION AS PRIMARY THERAPY IN IBD

With the advent of total parenteral nutrition (TPN) came a surge of enthusiasm for placing patients with IBD on bowel rest and intravenous nutrition as primary treatment. This was particularly popular in the 1970s. Then in 1983 Muller recognized that while many patients could be put into remission of their Crohn's disease with exclusive use of TPN (aka bowel rest), the relapse rates were very high when oral intake was resumed [49]. TPN is certainly not without serious side effects and is very expensive. One of the classical studies was published in the late 1980s in a randomized, multi-center trial by Greenberg and colleagues [50]. They demonstrated that patients with refractory Crohn's disease (resistant even to steroid treatment) were not benefited by bowel rest and that there was no difference between the treatment with bowel rest, exclusive use of defined formula (tube feeding) and oral diet plus parenteral support. There was no benefit of either exclusive parenteral or enteral nutrition in patients with ulcerative colitis.

Enteral nutrition in Crohn's disease received the attention of clinicians initially as a result of the availability of elemental formulas (those containing amino acids rather than intact protein). Voink and colleagues observed, somewhat fortuitously, that patients being prepared for surgical resection of refractory Crohn's disease had remission of their disease when an exclusive elemental diet was given [51]. They raised the question of whether elemental formulas might be a potential primary therapy for Crohn's disease. O'Morain and colleagues [52] were proponents of the concept that the exclusive use of these pre-digested liquid diets avoided the antigenic effect of intact proteins on the inflamed intestine with Crohn's disease involvement. The use of an elemental diet has continued in pediatric patients in Great

Britain [53], although it has not been popular in North America [54]. Verma and coworkers utilized an elemental formula taken orally as a supplement to solid food intake in an attempt to maintain remission of Crohn's disease in a group of patients who had had an exacerbation within the past year and who were in documented remission [55]. Of the 17 of 21 subjects who tolerated the formula, 10 remained in remission for 12 months, compared to 4 of 18 in a control group who did not use the elemental supplement (statistically significant on an intention-to-treat basis). A later study by the same authors, however, has not supported a benefit of elemental diets, in that polymeric formulas (those containing intact protein) were equally effective in inducing clinical remission of Crohn's disease in patients who were steroid dependent [56]. Twenty-seven percent failed to tolerate the formulas (equally divided between elemental and polymeric). Of those who were successfully withdrawn from steroids (14/27), all remained in remission at 1 year and six at 2 years. Elemental formulas have been particularly challenging because of high cost and very poor compliance with treatment, as demonstrated by high drop-out rates in a variety of studies. This is at least in part due to the poor flavor of the elemental products.

Three meta-analyses found that tube enteral nutrition was not as effective as corticosteroids in inducing remission of Crohn's disease in adults [57, 58, 59]. Additionally, two Cochrane database systematic reviews [60, 61] presented a similar conclusion from available studies. However, the randomized controlled trials included in the meta-analyses were not strictly comparable, as they included very different enteral formulations and in some cases, heterogeneous disease involving small bowel only, colon only and ileo-colonic Crohn's disease. The issue of elemental vs. polymeric formulas is addressed in the meta-analyses [57, 58] and finds an odds ratio of 0.87 in favor of polymeric regimens. This speaks against the importance of avoidance of antigen exposure as being a factor in the efficacy of elemental feedings. Furthermore, the remission rates of 60% for enteral nutrition were much better than with placebo in these studies and equivalent to some treatment modalities used in lieu of prednisolone, while avoiding the complications of corticosteroids [20, 62]. Nevertheless, these meta-analyses undoubtedly damped the attitudes about a potential role for enteral nutrition in Crohn's disease, particularly in North America.

The pediatric literature does include a meta-analysis that indicates that exclusive enteral feedings are as effective as steroids in children with Crohn's disease [63]. In a small, multi-center trial comparing remission rates and weight gain in pediatric patients with active Crohn's

disease, Ludvigsson et al. reported equivalent clinical response rates with elemental and polymeric feedings, but greater weight gain with the polymeric formula [64]. They attributed this to the greater intake of formula with the polymeric formula, hypothesizing that since part of their patients drank the formula, the flavor of the feeding was more acceptable to that group. However, even after adjustments for caloric intake, the difference in weight gain persisted. Knight and colleagues recently published a retrospective study of 44 pediatric patients who were newly diagnosed with Crohn's disease and elected to use enteral nutrition in lieu of steroids and other medications [65]. In these patients median time to remission was 6 weeks, 25 of 40 relapsed with a mean duration of remission of 54.4 weeks and time to first steroid use of 68 weeks for the 23 who eventually required steroids. The avoidance of steroids in children is particularly important with respect to growth and bone health. It has been pointed out by Afzal et al. that colonic Crohn's disease in children is less likely to respond to enteral nutrition when the ileum is not involved [66]. It is of note, however, that the remission rate in those with colonic disease alone was 50%, comparable to stated adult remission rates with enteral diets, but less than their remission rates of 82% for ileo-colonic disease and 92% in the ileal Crohn's group. Several European centers have found improvement of quality of life reported by children who used enteral feedings exclusively for treatment of active Crohn's disease although mucosal healing did not correlate with quality of life [67]. This raised the concern that sole use of the patient's sense of well-being may mislead clinicians into thinking that a patient has had remission of disease.

The reason for complete exclusion of enteral diets from recent reviews outlining treatments in IBD was the topic of speculation among several gastroenterologist/nutritionists in a discussion at a recent workshop [68]. Proposals to answer this query include the relative knowledge of nutrition between adult and pediatric practitioners, with the latter being much better informed than the former and the previous lack of a scientific explanation for demonstrated effectiveness of nutrition therapy. Discussants also felt that as pediatric patients with IBD age, they might educate adult clinicians that enteral diets can actually effectively control their disease.

Recent attention, primarily in Europe, has again turned to the use of enteral diets and supplements in Crohn's disease with special attention now to the effect of such diets on their immune benefits. A major variable with respect to enteral formulas is the lipid composition, and this was not taken into account in the meta-analyses. Indeed, there is a growing body of literature that suggests that lipids alter inflammation and that this may be of importance in the pathogenesis and treatment

of IBD. Metabolites of arachidonic acid have been shown to trigger inflammation [69]. Furthermore, prostaglandins (derived from fish oil-enriched diets) were protective to the mucosa, while saturated and polyunsaturated fatty acid-enriched diets were injurious in an experimental rat model of colitis [70]. A subsequent study of hamsters given a shark fin-enriched diet found that the marine lipids partially protected against histological changes of colitis and prevented the associated permeability changes in an acetic acid model of ulcerative colitis [71]. These results in experimental animals suggest that lipids might have a causative and a curative role, depending on the specific types of triglycerides consumed.

González-Huix and coworkers had shown in a randomized, double-blind study that a polymeric enteral formula containing 41% of lipids as monounsaturated fatty acids (28% saturated, 18% polyunsaturated, 13% medium-chain triglycerides) was as effective as steroids in induced remission of active Crohn's disease [72]. As a result of these studies, the same investigators [73] comparing two polymeric enteral formulas of identical macronutrient caloric distribution, but with different lipid components (79% oleate and 6.5% linoleate vs. 28% oleate and 45% linoleate) multicenter double-blind, randomized European trial in Crohn's disease. Compared to a prednisolone-treated group with a 79% remission rate, the group with the high linoleate formula had 63% remission, and the group with high oleate intake had only 27% remission. Other confounding factors could not be identified, indicating that the type of lipid was of major importance. The authors concluded that the monounsaturated fatty acid formula was less beneficial than the formula with predominant ω-6 (n-6) polyunsaturated fatty acid, although this was an unanticipated outcome. It was believed that ω-6 fatty acids are precursors of the synthesis of eicosanoids that have pro-inflammatory activity (prostaglandin $E_2$, thromboxane $A_2$ and leukotriene $B_4$), and these may possibly be detrimental in IBD [74].

Reimund et al. subsequently studied in vitro production of cytokines and cell viability of peripheral blood mononuclear cells from healthy volunteers incubated with three different lipid emulsions containing different ratios of long chain and medium chain triglycerides [75]. The lipid formula containing the highest ratio of ω-6 to ω-3 fatty acids as well as the highest amount of the monounsaturated fatty acid—oleic acid—had the least inhibition of TNFα and IL-1β (i.e., had less anti-inflammatory effect) than the lipids with much lower amounts of oleic acid and lower ω-6 to ω-3 fatty acids ratios. The authors cautioned that inferences to the in vivo situation should be made cautiously, but

these findings in the context of currently available clinical studies add important information to support the concept that anti-inflammatory enteral feeding formulae may have a role in immunomodulation in the treatment of IBD.

Bamba and colleagues prospectively treated patients with active Crohn's disease using equicaloric, equinitrogenous elemental formulas supplemented with long chain triglyceride to provide 3.06, 16.56 and 30.06 g of fat daily (52% linoleic acid; 24% oleic acid) [76]. Their results showed an inverse relationship between the dietary long chain triglyceride content and 4-week rate of remission judged by C-reactive protein, erythrocyte sedimentation rates and International Organization of Inflammatory Bowel Disease symptom scores. The remission rates ranged from 80% for the low fat diet to 25% for the high fat diet. Subsequently, Yamamoto and coworkers reported the effects of a very low fat elemental formula ($< 2\%$ of calories as fat) on mucosal cytokine production and disease activity in active Crohn's disease [77]. They found that 71% of their patients had symptomatic remission, with endoscopic and histologic improvement in $\sim 77\%$ and resolution in $\sim 40\%$. Pro-inflammatory cytokine levels in biopsy tissue were significantly decreased, and anti-inflammatory cytokines were increased.

The ω-3 fatty acids—α-linolenic acid, eicosapentanoic acid and docosahexanoic acid—are important for their immunomodulatory and anti-inflammatory effects [78]. Thus, there have been suggestions that fish oil, which is rich in ω-3 fatty acids, could have a therapeutic benefit in Crohn's disease [79]. Indeed, increased consumption of ω-6 fatty acids and animal protein and the decreased level of ω-3 fatty acids have been implicated in the increased incidence of Crohn's disease in Japan [80]. Middleton reported that supplementation of the diet of patients who had active Crohn's disease with a liquid formula containing ω-3 fatty acids and antioxidants improved serum antioxidant status, decreased the pro-inflammatory arachidonic acid, increased the anti-inflammatory eicosapentanoic acid and docosahexanoic acid in plasmaphospholipid and adipose tissue [81]. Geerling and colleagues described similar effects of ω-3 fatty acids and antioxidants in quiescent Crohn's disease [82]. Belluzzi et al. found that supplementation of diet with 2.7 g ω-3 fatty acids was effective in maintaining remission of Crohn's disease compared to placebo [83]. However, the results of a randomized, controlled, multicenter trial reported by Lorenz-Meyer and colleagues failed to demonstrate such effectiveness when ω-3 fatty acids (6 g of ethyl ester fish oil concentrate containing 55% eicosapentanoic acid and 30% docosahexanoic acid) were used in conjunction with a low carbohydrate diet in patients with Crohn's disease [84]. Of note, 23% of individuals

in the supplement group and 36% of the placebo were judged to be non-compliant with the study protocol.

A double-blind, placebo-controlled, crossover study of fish oil (4.2 g daily: 2.7 g eicosapentanoic acid; 1.8 g docosahexanoic acid) given to patients with mild to moderate ulcerative colitis reported improvements histologically and by a disease activity index, but the pro-inflammatory cytokine, leukotriene B4, levels were not decreased contrary to expectations [85]. Eight of the patients could either stop or reduce anti-inflammatory drugs. However, 6 of the original 17 patients in this study withdrew, and analyses were done on only the remaining 11. A recent randomized, placebo-controlled trial of a lipid supplement providing a lower daily dose of ω-3 fatty acids (1.6 g gamma linolenic acid, 270 mg eicosapentanoic acid and 455 mg docosahexanoic acid) to patients with ulcerative colitis showed no benefit in maintaining remission of disease [86].

## 10. SPECIALIZED ROLES FOR NUTRITION SUPPORT IN IBD

There are currently limited indications for the use of parenteral nutrition (PN) in IBD. The most common of these is short bowel syndrome, resulting from extensive intestinal resection. This topic is discussed in detail in another chapter in this book. Complications of Crohn's disease, and to a lesser extent ulcerative colitis, can also be responsible for the need for PN. Fistulae arising from diseased areas of the intestine or leaks with or without fistulae resulting from surgical complications may be treated with PN either to treat the fistulae primarily or to temporize the patient until reparative operation can be undertaken. On occasion short-term TPN and bowel rest are also used in extensive stenosing Crohn's disease to limit the extent of resection or to provide nutritional support until drug therapy effectively controls disease. Evans et al. reported experience with 15 patients dismissed from the hospital on home TPN in an attempt to circumvent or delay early surgery for complicated IBD and found that the therapy was deemed successful in 80%, although 8 of those patients ultimately required surgical intervention [87]. All patients preferred receiving the therapy at home and felt that they had either good or excellent quality of life, yet seven of these patients continued to require nursing visits until the TPN was discontinued, and only six were considered to be independent with TPN care after 2 weeks of treatment.

Growth failure in children and adolescents is seen in 50% of those with Crohn's disease, and weight loss is present in up to 90% at

presentation [88]. By contrast, in ulcerative colitis, growth failure occurs in only about 5% of affected children [89]. Growth retardation frequently antedates the diagnosis of the disease, often by years. The causes include poor nutritional status, especially from the point of view of protein-calorie malnutrition. However, with more understanding of systemic effects of inflammation, the role in growth failure is beginning to be elucidated. Insulin-like growth factor-I (IGF-I), which is a stimulus for linear growth [90], has been shown to be low in children with Crohn's disease [91]. Suppression of growth velocity in Crohn's disease was demonstrated by Murch and colleagues to be directly correlated with TNF-α levels [92]. Animal studies have shown that proinflammatory cytokines can suppress IGF-I concentrations [93, 94]. Ballinger, using an experimental rat model of human Crohn's disease, found that, as expected, animals with disease had linear growth that was less than controls, but that pair fed healthy animals had greater growth than the diseased animals [95]. This indicates that another factor, likely inflammation, is responsible for growth failure over and above that due to compromised nutrition.

Fell and coworkers treated 29 pediatric patients with Crohn's disease (18 newly diagnosed) using a casein-based enteral formula that contains transforming growth factor $\beta_2$ [96]. Clinical remission occurred in 79% of patients after an 8-week course of therapy. With histological healing there was associated down-regulation of mucosal pro-inflammatory cytokine mRNA. Banarjee et al. found that children with moderate to severe active Crohn's disease who were alimented exclusively with enteral feedings had improvement in inflammatory markers, clinical score and growth factor (IGF-I) before nutritional parameters showed improvement [97]. These studies suggest that inflammation is a major factor in growth failure in children with Crohn's disease and that enteral nutrition may play a role in the primary treatment of Crohn's disease and growth failure.

The role of nutrition support in IBD continues to be important. Future therapies are likely to evolve, including diet as an immunomodulator of Crohn's disease and ulcerative colitis.

## 11. CONCLUSIONS

- IBD is associated with malnutrition in a high percentage of patients.
- The causes of malnutrition in IBD are multifactorial: decreased food intake, maldigestion, malabsorption, altered metabolism, increased requirements, increased losses and drug:nutrient interactions.

- Malnutrition in IBD includes protein-calorie malnutrition as well as deficiencies of vitamins and minerals
- Nutrition in IBD includes supportive therapies intended to correct deficiencies, diet as primary therapy and specialized roles for nutrition support (i.e., short bowel syndrome, fistulae and growth failure).

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# 4 Nutrition Aspects of Liver Failure

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***Contents***



*Summary*

Because the liver performs hundreds of metabolic functions, nutritional status and nutrient metabolism are altered in individuals with liver disease. This chapter reviews relationships between nutritional status and liver disease, describes effects of malnutrition and nutrition support on outcomes, and defines nutrition therapies for patients with liver disease.

Objective nutrition assessment parameters are often confounded by symptoms of liver disease; therefore, subject global assessment criteria are often applied. The degree of malnutrition is influenced by the type and severity of liver disease. The cause of malnutrition

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is multifactorial including diet inadequacy, malabsorption, gastrointestinal symptoms and altered nutrient metabolism.

Nutrition supplementation (through oral, tube feeding or parenteral routes) can be used to supply macro- and micronutrients to patients at nutritional risk. Protein should not be restricted for patients with liver disease. Calories, electrolytes, fluid, vitamins and minerals should be individualized for each patient taking into consideration his/her nutritional status, type and stage of liver disease, and medical treatments. There is not strong evidence to support the use of herbal supplements in individuals with liver failure.

**Key Words:** Liver disease, Cirrhosis, Nutrition, Nutritional status, Nutritional support, Nutrition assessment, Nutrition therapy

## 1. INTRODUCTION

Liver disease is prevalent, affecting 5.5 million Americans; it is the 12th leading cause of death in the US [1]. A majority (60–70%) of adults in industrialized countries drink alcohol which is one of the leading causes of liver disease [2]. Because the liver is intimately involved with hundreds of metabolic processes, there is a strong association between liver disease and nutrition abnormalities. The purpose of this chapter is to review the relationships between nutritional status and liver disease, effects of malnutrition and nutrition support on outcomes, and finally, to describe recommended nutrition therapies for individuals with liver disease.

## 2. THE LIVER AND NUTRIENT METABOLISM

The liver performs over 500 metabolic functions. In fact, the metabolic activity of the liver accounts for 20–30% of the oxygen consumption and energy expenditure of the body [3]. When liver dysfunction occurs, a catabolic state is induced, and increased serum levels of insulin (often with insulin resistance), glucagon, epinephrine and cortisol are present. Because the liver is involved in the metabolism of all nutrients (Table 4.1), an alteration of liver function causes a concomitant alteration in nutrient metabolism and storage.

## 3. NUTRITION ASSESSMENT IN THE PRESENCE OF LIVER DISEASE

In early stages of liver disease, whether caused by alcohol, autoimmune processes, viral hepatitis, nonalcoholic fatty liver disease (NAFLD), metabolic disorders or other causes, typical objective nutrition

**Table 4.1**
**Role of the Liver in Nutrient Metabolism**

Protein metabolism

- Synthesizes serum proteins
- Synthesizes blood-clotting factors
- Forms urea from ammonia
- Deaminates/transaminates amino acids
- Forms creatine
- Oxidizes the amino acids arginine, histidine, lysine, methionine, alanine, tryptophan and tyrosine

Carbohydrate metabolism

- Glycogenesis
- Gluconeogenesis
- Glycogenolysis

Fat metabolism

- Hydrolyzes triglycerides, cholesterol and phospholipids to fatty acids and glycerol
- Stores fat
- Synthesizes cholesterol
- Performs ketogenesis
- Forms lipoproteins
- Produces bile necessary for fat absorption

Vitamin metabolism

- Site of enzymatic steps in vitamin activation
  - Thiamine (thiamine pyrophosphate)
  - Pyridoxine (pyridoxal phosphate)
  - Folic acid (tetrahydrofolic acid)
  - Vitamin D (25-hydroxycholecalciferol)
- Synthesizes carrier proteins for vitamins such as A and $B_{12}$
- Synthesizes lipoproteins to transports vitamin E
- Stores vitamins A, D, E, K, $B_{12}$

Mineral metabolism

- Stores copper, iron and zinc

Reprinted from Hasse JM. Nutritional aspects of adult liver transplantation. In: Busuttil RW, Klintmalm GB, eds. Transplantation of the liver, 2nd edn. Philadelphia: W.B. Saunders. 2005, with permission from Elsevier.

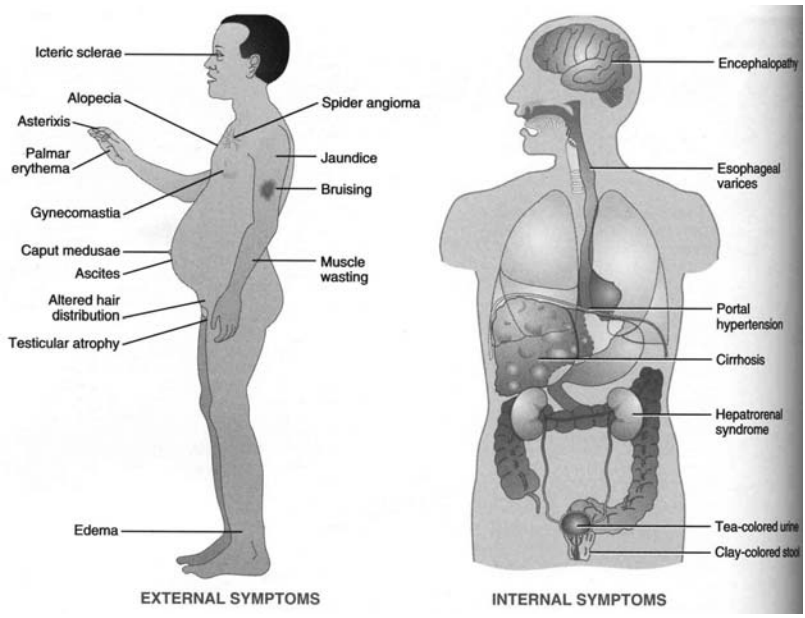


**Fig. 4.1.** Clinical manifestations of cirrhosis. Reprinted from Hasse JM, Matarese LE. Medical nutrition therapy for liver biliary system, and exocrine pancreas disorders. In: Mahan LK, Escott-Stump S (eds) Krause's food, nutrition, and diet therapy, 11th edn. Philadelphia: W.B. Saunders. 2004, with permission from Elsevier.

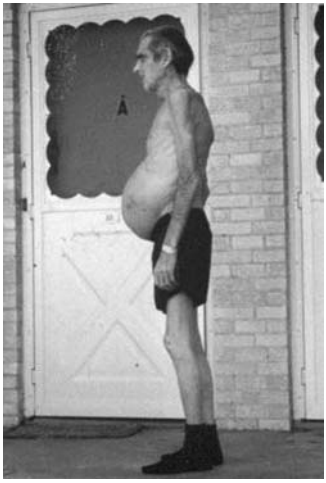

**Fig. 4.2.** Severe malnutrition and ascites in a man with end-stage liver disease. Reprinted from Hasse JM, Matarese LE. Medical nutrition therapy for liver biliary system, and exocrine pancreas disorders. In: Mahan LK, Escott-Stump S (eds) Krause's food, nutrition, and diet therapy, 11th edn. Philadelphia: W.B. Saunders. 2004, with permission from Elsevier.

assessment parameters can be used to determine nutrition status. However, when signs of end-stage liver disease (ESLD) develop (Figs. 4.1 and 4.2), objective parameters are not always valid. See Table 4.2 for a summary of the benefits and drawbacks of specific assessment techniques in the presence of liver disease.

**Table 4.2**
**Benefits and Drawbacks of Nutritional Assessment Parameters when Assessing Individuals with End-Stage Liver Disease**

| *Parameter* | *Benefits* | *Drawbacks* |
|---|---|---|
| Body weight | • Simple to perform<br>• Reproducible<br>• Low cost<br>• Universal measurement | • Affected by body fluid changes |
| Anthropometric measurements (triceps skinfold, arm muscle circumference) | • Low cost<br>• Portable | • Low interrater reliability<br>• Influenced by a patient's fluid status<br>• Low specificity and sensitivity |
| Hand-grip strength | • Low cost<br>• Portable | • Low specificity and sensitivity<br>• Influenced by patient's mood and neurologic status |
| Serum protein values | • Reproducible<br>• Easily available<br>• Relatively low cost | • Affected by many non-nutritional factors (e.g., fluid status, liver function, vitamin status) |
| Urinary tests (e.g., nitrogen balance, creatinine-height index) | • Relatively low cost | • Influenced by many non-nutritional factors (e.g., renal and liver function, fluid status) |
| Immunocompetence tests [e.g., skin test antigens, total lymphocyte count (TLC)] | • Reproducible<br>• Relatively low cost<br>• TLC easily available | • Influenced by immunosuppressive states and drugs |

*(Continued)*

Table 4.2
*(Continued)*

| *Parameter* | *Benefits* | *Drawbacks* |
|---|---|---|
| Other tests such as bioelectrical impedance (BIA), dual energy X-ray absorptiometry (DXA) | • DXA considered highly accurate | • BIA affected by fluid status; BIA equation must be valid for population being evaluated<br>• Increased cost<br>• Unavailability or lack of daily clinical application |

Adapted from: Hasse JM, Matarese LE. Solid organ transplantation. In: Gottschlich MM (Ed) The A.S.P.E.N. Nutrition Supportcore curriculum: A case-based Approach-The adult Patient. Silver Spring, MD: The American Society for Parenteral and Enteral Nutrition. 2007:599–618, with permission from the American Society for Parenteral and Enteral Nutritio (A.S.P.E.N). A.S.P.E.N does not endorse the use of this material in any from other than its entinety.

## 4. MALNUTRITION AND LIVER DISEASE

The prevalence and cause of malnutrition associated with liver disease depend on the method used to assess the nutritional status, type of liver disease, degree of liver decompensation, presence or absence of malabsorption, level of hypermetabolism and hypercatabolism, severity of early satiety and anorexia, and occurrence of psychosocial factors influencing nutrient intake

### *4.1. Prevalence of Malnutrition*

#### 4.1.1. By Nutrition Assessment Parameters

Malnutrition prevalence depends in part on the parameters that were chosen to determine nutritional status. For example, when 50 patients with cirrhosis were assessed according to subjective global assessment (SGA), prognostic nutritional index (PNI) and handgrip strength (HG), malnutrition was diagnosed in 28% based on SGA, 18.7% by PNI and 64% by HG. HG was superior in predicting poor clinical outcome when compared with SGA and PNI [4]. In another study, Figueiredo et al. [5] measured body cell mass (BCM) by isotope dilution in 69 patients awaiting liver transplantation. Patients were also evaluated based on SGA, anthropometry, HG dynamometry, laboratory tests and dual-energy X-ray absorptiometry (DXA). Only one-half of the patients in

the lowest quartile of BCM were diagnosed as malnourished by SGA. BCM was correlated (although not strongly) with arm-muscle circumference ($r = 0.55$) and midarm muscle circumference ($r = 0.48$). None of the serum laboratory values (bilirubin, prothrombin time, albumin, total lymphocyte count, micronutrient levels, lipid concentrations, amino acid concentrations) were correlated with BCM. Parameters in which the lowest quartile correlated with low BCM included serum blood levels of urea nitrogen ($p = 0.002$) and creatinine ($p = 0.01$), HG ($p < 0.001$), bone mineral density ($p < 0.001$) and lean body mass by DXA ($p < 0.001$). When multiple logistic regression was applied to all of the assessment variables, arm-muscle circumference and HG had the greatest influence on BCM. The authors concluded that HG and arm-muscle circumference were the most sensitive markers in diagnosing BCM loss in the liver disease patient.

### 4.1.2. By Type of Liver Disease

The prevalence of malnutrition also depends on the type of liver disease (see Table 4.3). Over 15 years ago, DiCecco et al. [6] evaluated the rate of malnutrition in patients undergoing liver transplantation based on diagnosis (chronic active hepatitis, primary sclerosing hepatitis, primary biliary cirrhosis and acute/subacute hepatitis) and assessment parameters (diet history, anthropometrics and biochemical measurements). They found that modest decreases in all nutrition parameters occurred in patients with chronic hepatitis. Patients with sclerosing cholangitis had the lowest mean levels of midarm muscle circumference as well as vitamin and mineral levels; however, they maintained their fat stores. Patients with primary biliary cirrhosis experienced the greatest fat and muscle loss, but maintained hepatic synthetic function.

**Table 4.3**
**Pattern of Malnutrition in Liver Disease**

| | *Muscle wasting* | *Loss of fat stores* | *Reduced synthetic function* |
|---|---|---|---|
| Alcohol | +++ | + | ++ |
| Viral | ++ | ++ | |
| Primary biliary cirrhosis | +++ | +++ | + |
| Primary sclerosing cholangitis | ++ | + | + |

+, mild abnormalities; ++, moderate abnormalities; +++, severe abnormalities Reprinted from McCullough AJ. Malnutrition in liver disease. Liver Transplant 2000;6(4 Suppl 1):S85–S96.

Finally, patients with acute hepatitis had acute, rapid loss of nutrient stores. Similar findings were found more recently by Zaina et al. [7]: 219 liver transplant candidates were classified as having cholestatic disease ($n = 21$) or noncholestatic disease ($n = 198$). Those with cholestatic disease tended to have calorie malnutrition and those with noncholestatic disease were more affected by malnutrition associated with protein depletion.

#### 4.1.3. By Stage of Liver Disease

The degree of malnutrition in patients with liver disease also varies depending on the stage of liver disease. In a study by Figueiredo et al. [8], nutritional status was evaluated according to Child's score (a measure of the severity of liver disease). Those with Child's A classification (lowest severity) exhibited mainly fat loss. Patients classified with Child's B disease tended to have losses in at least one of two body compartments. Finally, those classified with Child's C disease (highest severity) tended to have depletion of both fat and muscle compartments. This conflicted with an earlier study by the same author in which there was no relationship between Child's score and BCM [5], as well as a study by Müller et al. [9] in which there were no significant differences in BCM and body fat based on Child's score. The findings that malnutrition was related to severity of liver disease were, however, confirmed in other studies by Rongpisuthiopong [10], Campillo [11] and Alberino [12].

### *4.2. Cause of Malnutrition in Liver Disease*

The cause of malnutrition among those with liver disease is multifactorial. Nutritional status is influenced by inadequacy of diet (including iatrogenic restrictions), malabsorption (biliary and sometimes pancreatic), anorexia, nausea and vomiting, dysguesia, gastroparesis, alcohol toxicity and altered nutrient metabolism [13].

It is theorized that energy expenditure may be elevated in patients with liver failure, thus contributing to a malnourished state. However, in one study comparing energy expenditure in 74 patients with cirrhosis and 9 healthy controls, the energy expenditures were not different between the groups except when the patients were stratified based on the level of malnutrition. Those patients with cirrhosis who were considered malnourished had a lower basal energy expenditure than did the controls [14]. Even then, if the energy expenditures were evaluated according to BCM, there were no differences. Refer to the section on calorie needs for a full review on energy expenditure and liver disease.

Ascites also influences the degree of malnutrition. The physical presence of ascites can restrict stomach volume and induce early

satiety [15]; thus, satiety is often relieved by paracentesis. On the other hand, drainage of ascitic fluid also results in losses of protein and further malnutrition. Campillo et al. [11] showed that anthropometric measurements and dietary intake paralleled the degree of ascites. Midarm muscle circumference <5th percentile was present in 49% of patients with no ascites, 49.1% of patients with mild ascites and 65.5% of patients with severe ascites ($p < 0.05$). Likewise, tricep skinfold measurements <5th percentile occurred in 30.4% of patients without ascites, 40.5% of those with mild ascites and 48.3% of those with tense ascites ($p = 0.02$). Reduced calorie and protein intakes were also correlated with tense ascites. Moreover, Santolaria et al. [16] showed that patients with ascites were more significantly malnourished (based on anthropometric measurements) than patients without ascites.

When ascites is relieved, nutritional status can improve. A small study showed that patients ($n = 10$) who underwent a trans-intrahepatic portal shunt (TIPS) procedure for ascites management experienced an increase in dry weight, total body nitrogen and resting energy expenditure (REE) 3 and 12 months after the procedure [15]. There was also a significant increase in total body fat 12 months post-TIPS. There was, however, no change in total body potassium, muscle force or Child-Pugh score underscoring the difficulty in reaccumulating lean body mass in the presence of liver dysfunction. Similar findings were reported in a study in which 21 patients were evaluated before and 6 and 12 months after a TIPS procedure [17]. Body cell mass (BCM) based on total body potassium counting, bioelectrical impedance and anthropometry improved 6 and 12 months after TIPS.

Psychosocial factors also influence nutritional status. Santolaria et al. [16] studied 181 hospitalized alcoholic men. Malnutrition was related to intensity of alcohol intake, development of social or family problems, irregularity of eating habits and presence of cirrhosis and ascites. The "skid row" alcoholic was found to be the most nutritionally impaired in the group with 73% of those patients having a body mass index (BMI) $< 20\,kg/m^2$, 55% having a tricep skinfold measurement <50th percentile and 75% of the group displaying a midarm muscle area measurement <50th percentile.

## 5. OBESITY

At the opposite spectrum of malnutrition and wasting is obesity. As the prevalence of obesity increases in the general population, it is also increasing in the liver disease population. Specifically, there is a rise in the incidence of obesity and NAFLD. NAFLD is a

syndrome ranging from steatosis to cirrhosis; it affects 10–25% of people in the U.S. [18–20]. Nonalcoholic steatohepatitis (NASH) is the most severe form of NAFLD; it is characterized by fatty liver, inflammation, necrosis and fibrosis and occurs in 50% of the obese population, but in only 3% of lean individuals [20]. Like many other chronic diseases, NASH is associated with metabolic syndrome [21, 22]. Obesity, dyslipidemia, hypertension, diabetes mellitus, hyperinsulinemia and insulin resistance are common problems linked with the metabolic syndrome and NASH. Treatment of NAFLD includes diet changes, weight loss and insulin-sensitizing drugs [23].

## 6. EFFECT OF MALNUTRITION ON PATIENT OUTCOME

Malnutrition in cirrhotic patients has been identified as a risk factor for complications of cirrhosis such as ascites [24]. The effect of cirrhosis on mortality is mixed with one study showing malnutrition as an independent risk factor for mortality [12] and another study showing that malnutrition is not an independent risk factor [25].

## 7. EFFECT OF NUTRITION SUPPLEMENTATION ON PATIENT OUTCOME

Because malnutrition increases complications, one would theorize that providing nutrition support would improve nutritional status and therefore clinical outcomes. However, there are factors that interfere with improvement of nutritional status. First, achieving adequate nutrient intake can be difficult because the symptoms of liver failure (e.g., ascites, encephalopathy) impair a patient's appetite and food tolerance. In addition, there are potential impairments in nutrient absorption and metabolism induced by liver disease or associated complications such as infection. Nutrition supplementation, whether by the oral, tube feeding or parenteral route, may be necessary for individuals with serious liver disease to achieve adequate nutrient intake.

### *7.1. Oral Nutrition Supplementation*

If a patient's nutrient intake is inadequate, he/she should be counseled to eat small, frequent meals of nutrient-dense foods. If oral intake is still inadequate, oral nutrition supplements should be considered. Several studies evaluated the effect of oral nutrition supplementation on liver disease outcomes [26–28]. Cunha et al. attempted to improve nutrition status in 29 patients with alcoholic cirrhosis [27].

Diet and a 500-calorie oral supplement were provided to patients; 62% of the subjects completed the 3-month trial. The intake of non-alcoholic calories increased by 48% by the end of study, and alcohol calories decreased by 77%. Subjective nutrition status improvement was associated with a concomitant improvement in the Child-Pugh score and tricep skinfold measurements. This study had promising results, but the drop-out rate was more than one-third of the population.

Positive improvements were not attributed to oral supplements in a study by Le Cornu et al. [28]; 42 liver transplant candidates with a midarm muscle circumference <25th percentile were given oral supplements and compared with a similar group of 43 patients who received dietary counseling, but no supplementation. Nutrient intake improved in both groups, but there was no additional benefit of oral supplementation.

In another study of patients awaiting liver transplantation [29], supplementation with a branched-chain supplement ($n = 24$) or casein-based supplement ($n = 26$) improved calorie and protein intake to an average of 85–90% of the goal compared with an unsupplemented control group ($n = 12$) who achieved only 75% of calorie and 72% of protein goals. In addition, those receiving the branched-chain amino acid supplement experienced fewer hospitalizations while awaiting transplantation than did the other groups.

A final study used an immuno-enhanced supplement (Impact, Novartis, Minneapolis, MN) for patients awaiting liver transplantation [29]. Patients near the top of the waiting list for transplant were given 600 kcal/day of Impact. After transplantation, a combination of tube-fed and orally fed Impact was provided to the study group. The control group included 17 control patients, 11 of whom were prescribed 720 kcal/day of Ensure Plus (Ross, Columbus, OH) and 6 of whom did not received preoperative supplementation. All of the control patients received standard TF formula after transplantation. During the preoperative phase (median 55 days), body weight, body fat and total body protein increased in the study patients; body protein increased significantly more in the study vs. control group. The 1-year graft and patient survivals were 100% in both groups. This study was not a randomized trial in which the controls received matched diet and that must be taken into consideration when considering the results of this study.

### *7.2. Tube Feeding*

Tube feeding (TF) should be considered for patients with liver disease when nutrient intake is inadequate and oral supplementation fails. There are some circumstances that warrant consideration when providing TF to patients with liver failure. The type of tube to be

used is determined by the expected duration of feeding as well as the presence or absence of ascites. Typically, a small-bore nasoenteral tube is selected for this group because it is more comfortable than a larger-bore nasoenteral tube. Ascites usually precludes the use of gastrostomy or jejuonostomy tubes because of leakage of ascites and the potential for peritonitis. Active gastrointestinal bleeding and recent variceal banding may delay the insertion of a feeding tube, but varices themselves are not always deterrents for placing a feeding tube. Thrombocytopenia may need to be corrected before placing a tube. Once a tube is placed, one must be aware that a patient with encephalopathy may pull the tube unless restrained and that diarrhea induced by lactulose may worsen when nutrient intake is given in the form of a liquid formula.

A study by De Leninghen et al. [30] highlights difficulties associated with providing TF to patients with severe liver disease. This report compared a group of 12 cirrhotic patients receiving 1,665 calories/day via a nasogastric tube with 10 cirrhotic patients who remained NPO for 4 days after a gastrointestinal bleed. Although the patients who received TF had a significant improvement in nitrogen balance compared with the control group, they also had a higher rate of rebleeding.

Several other studies have shown benefits of providing TF to patients with liver disease. A summary of study design and results are listed in Table 4.4.

**Table 4.4**
**Tube Feeding Studies in Adult Patients with Liver Disease**

| *Authors* | *Study design* | *Results summary* |
|---|---|---|
| Cabre et al. [50] 1990 | 35 patients with cirrhosis were randomized to a low-sodium diet vs. TF. | Caloric intake, serum albumin level, Child's score and survival rate were improved in the TF vs. control group |
| Kearns et al. [51] 1992 | 31 patients with alcoholic liver disease were randomized to receive either a general diet alone or a diet supplemented with casein-based TF. | Compared with the control group, the mean nutrient intake, hepatic encephalopathy measurements and serum bilirubin levels were improved in the study group. |
| Soberon et al. [52] 1987 | 35 kcal/kg provided as TF or diet for 6 days in a crossover design to 14 patients. | Nitrogen balance improved 5-fold at 2 weeks. |

| | | |
|---|---|---|
| Cabre et al. [53] 2000 | A randomized, controlled study was performed whereby 71 patients were randomized to receive TF via a nasogastric tube (2,000 calories, 72 g protein) or a diet (1 g/kg protein) plus 40 mg prednisone. | There was an equal improvement in the groups with regards to serum albumin level, Child's score, Maddrey score and infection rate. |
| Campillo et al. [11] 2003 | Authors reported the outcomes of 24 patients with ESLD who received TF during hospitalization. | When compared with patients who did not receive TF, those who were tube-fed were older, had a higher Child-Pugh score and a higher mortality rate. However, TF was initiated late in the patients' course and survival reflects the severity of the liver disease and not the presence of TF. |
| Hu et al. [54] 2003 | 135 patients with Child's B or C cirrhosis undergoing surgery were randomized to receive TF ($n = 65$), parenteral nutrition (PN, $n = 40$) or nothing (control, $n = 30$). | Those receiving TF reached positive nitrogen balance first and had the lowest body weight loss. TF also showed a benefit in gut barrier integrity as measured by urinary excretion of lactulose and mannitol. This was not true of the PN or control groups. |
| Zhang et al. [55] 2005 | TF with Vivonex TEN (Novartis, Minneapolis, MN) was given via nasojejunal tube at a maximum dose of 2,100 ml, by postoperative day 4 and compared with PN (40–50% of calories as medium-chain/long-chain triglyceride blend). The 40 patients in this study had portal hypertension and were undergoing pericardial devascularization. | Nutritional status improved in both groups. However, there were fewer complications in the TF vs. PN group. In addition, TF increased blood velocity of the portal vein, stimulated gut motion, prevented bowel bacterial translocation, shortened hospital stay and reduced costs. |

### 7.3. Parenteral Nutrition

Because of the hepatotoxic potential of parenteral nutrition (PN), it should be reserved for use only during ileus or active gastrointestinal bleeding. As with other types of patients, one should transition from PN to TF or an oral diet as soon as possible. More information on hepatic complications of PN is included in Chap. 10.

## 8. NUTRIENT NEEDS

Nutrient requirements of individuals with liver failure are specific and individualized depending on the type and degree of liver failure, presence and degree of malnutrition and symptoms of liver disease. Table 4.5 summarizes basic nutrient recommendations based on symptoms of ESLD.

### 8.1. Calories

Energy requirements are highly variable among patients with liver disease [9] depending on body composition (fat vs. muscle), current

Table 4.5
Dietary Considerations for Adult Patients with End-Stage Liver Disease

| *Symptom* | *Nutrition recommendations* |
|---|---|
| Cachexia | • Provide at least 120% of estimated energy expenditure<br>• Provide increased calories if malabsorption or malnutrition is present<br>• Offer small, frequent meals of calorie-dense foods |
| Encephalopathy | • Maximize medical therapy (e.g., lactulose, neomycin)<br>• Identify and treat cause(s) of acute bouts encephalopathy (e.g., variceal bleed, infection, electrolyte imbalance, sedatives, constipation, etc.)<br>• Supplement with zinc if deficiency is suspected<br>• Provide adequate calories to prevent catabolism of endogenous protein stores |
| Ascites and edema | • Limit sodium (restriction below 2 g/day may result in inadequate calorie and protein intake)<br>• Supplement protein if patient is undergoing frequent paracenteses |
| Hyponatremia | • If hyponatremia is due to excess fluid, restrict fluid to 1,000–1,500 ml/day<br>• If hyponatremia is due to sodium deficiency, supplement sodium cautiously |

| | |
|---|---|
| Hyperglycemia | • Institute carbohydrate-controlled meal plan<br>• Treat with insulin or oral hypoglycemic agent as needed |
| Hypoglycemia | • Provide frequent meals or snacks containing carbohydrate and protein<br>• Infuse intravenous dextrose if needed |
| Steatorrhea | • Restrict dietary fat; if diarrhea does not resolve or if restriction causes poor dietary intake, discontinue fat restriction<br>• Try medium-chain triglyceride supplementation<br>• Consider pancreatic insufficiency as a potential cause of steatorrhea<br>• Check fat-soluble vitamin levels and supplement if needed |
| Osteopenia | • Maintain an appropriate weight<br>• Encourage intake of a well-balanced diet with a wide variety of food choices<br>• Provide enough protein to maintain muscle mass<br>• Provide 1,500 mg of calcium per day via diet and/or supplements<br>• Provide enough vitamin D via diet and/or supplementation (may need water-miscible form)<br>• Monitor for the development of steatorrhea and adjust the diet as needed to minimize nutrient losses<br>• Avoid alcohol<br>• Consider need for bone-rebuilding medications |

Adapted with permission from Hasse J, Weseman B, Fuhrman MP, et al. Nutrition therapy for end-stage liver disease: a practical approach. Support Line 1997;19:8–15.

medical state, presence or absence of ascites and activity level. Measured energy expenditure of patients with cirrhosis has been shown in some studies to be similar to expenditure of controls [14, 31]. At least one study suggested that only a percentage (about one third) of patients with cirrhosis is hypermetabolic; others are normometabolic [32]. Other studies also reported no significant increase in REE, but found inverse relationships between energy expenditure and liver disease severity [33, 34]. Greco et al. [35], however, reported increased 24-h energy expenditure in ten male patients with Child B cirrhosis. Two studies reported that REE increased at 3 or 6 and 12 months after placement of a TIPS [15, 18]. The increase could have been due to an increase in lean body mass. Because of the variability of these findings, indirect calorimetry is recommended to determine caloric needs in patients in whom accurate caloric delivery is necessary [36]. In the absence of that technology, clinicians generally recommend 25

to 40 kcal/kg estimated dry weight depending on the current medical condition as well as the degree of liver and nutrition decompensation [13].

Fat is a preferred fuel in liver failure [14, 33, 37]. The preference for alternate fuels is due, in part, to alterations in insulin, glucagon, cortisol and epinephrine levels. Despite the preference toward fat as fuel, there is an impairment of triglyceride oxidation, and fat can deposit in the liver. Insulin resistance occurs frequently in patients with liver failure due to alcohol ingestion [2] and viral hepatitis. Insulin resistance impairs glucose uptake in the muscle cells; glycogen production is reduced resulting in reduced energy stores [2]. With severe liver impairment, storage of glycogen can be limited.

On the other hand, as many as two-thirds of individuals with cirrhosis have hyperglycemia. This can be caused by hyperinsulinism and insulin resistance in peripheral tissues [37]. Increased insulin production and reduced hepatic clearance or portosystemic shunting of insulin released from the liver can also contribute to insulin resistance [39]. An earlier section discussed insulin resistance as it relates to metabolic syndrome and NAFLD.

### *8.2. Protein*

Protein requirements are affected by alcohol intake as well as the degree of malnutrition and liver disease. Alcohol ingestion impairs hepatic amino acid uptake and protein synthesis, reduces protein secretion from the liver and increases catabolism in the gut [2]. Patients with Child's A cirrhosis have been found to have normal protein catabolism with increased protein synthesis when a high-protein diet was fed [38]. A follow-up study was done to evaluate protein synthesis in patients with more severe liver disease. Six patients with Child's B or C cirrhosis were analyzed with a $^{15}$N-glycine kinetic study and were also found to have higher protein catabolism while fasting than did controls [39]. In the patients with cirrhosis, a high-calorie (46 kcal/kg), high-protein (1.6 g/kg) diet reduced protein catabolism slightly (although not significantly) compared with fasting.

Protein is necessary to help the liver regenerate and recover from hepatitis. A moderate protein intake (0.8–1 g/kg) is probably adequate for uncomplicated hepatitis or cirrhosis. However, protein needs are increased to about 1.2–1.3 g/kg to promote nitrogen balance [40]. If alcoholic hepatitis, decompensated liver disease and/or malnutrition is present, protein needs may be as high as 1.5 g/kg [13].

For many years, the idea that protein should be restricted in the presence of hepatic encephalopathy was promoted. The basis for this

recommendation was that protein intake increased serum ammonia levels, which in turn increased encephalopathy. This theory has never been proven in a controlled study. Moreover, a study published in 2004 showed that there was no benefit of a low-protein diet on serum ammonia levels or encephalopathy [41]. In this landmark study, 30 encephalopathic patients admitted to an emergency department were randomized to receive either a normal protein diet (1.2 g/kg) or a low-protein diet with a slow progression to a normal diet. Encephalopathy was not different between the two groups. Although protein synthesis was equal between the two groups, the low-protein group had increased protein breakdown.

Branched-chain amino acid (BCAA)-enriched formulas have been touted as beneficial for patients with hepatic encephalopathy. The literature is equivocal in regards to their true benefit. In a large study, Marchesini et al. [42] randomized 174 patients with liver disease to receive either a BCAA, lactoalbumin or maltodextrin supplement for a year. Those who received the BCAA formula had reduced event outcomes (death and deterioration to exclusion criteria) compared to the lactoalbumin group ($p = 0.039$). In addition, the average hospital admission rate was lower in the BCAA group vs. the lactoalbumin group ($p = 0.006$) and the maltodextrin group ($p = 0.003$). Those who received BCAA had stable or improved nutritional parameters, liver function tests, anorexia and heath-related quality of life scores. In addition, those patients also had a reduction in their mean Child-Pugh score.

On the other hand, a Cochrane review evaluating the effectiveness of BCAA in liver failure published in the same year found no significant improvements associated with BCAA when high methodological quality studies were evaluated [43]. The BCAA studies are difficult to evaluate as a whole because they vary in study design, study and control groups, composition of formulas, type of disease, level of encephalopathy and duration of therapy.

### *8.3. Electrolytes*

Sodium restriction is key in the treatment of ascites and edema. Generally, a restriction of 1,500–2,000 mg sodium/day is adequate. Because diuretic use (and subsequent nutrient alterations) in these patients is prevalent, the nutrition clinician should remain aware of electrolyte levels. For example, loop diuretics can result in low serum levels of sodium, potassium, magnesium and calcium. On the other hand, spironolactone (often used to treat ascites) is potassium sparing.

### *8.4. Fluid*

Hyponatremia can occur when there is a decreased ability of the kidneys to excrete water. Hyponatremia can also be caused from persistent release of antidiuretic hormone, sodium losses via paracentesis, excessive diuretic use or overly aggressive sodium restriction [44]. If hyponatremia is caused by excessive fluid, fluid intake must be restricted; typical free water restrictions are from 1,000–1,500 ml per day. If hyponatremia is due to an excessive loss of sodium, sodium must be supplemented cautiously.

### *8.5. Vitamins and Minerals*

Because the liver is involved in the transport, storage and metabolism of micronutrients, it is reasonable to assume that liver disease could result in abnormal micronutrient activity and levels. Plasma and erythrocyte trace elements were measured in 50 patients with nonalcoholic liver disease [45]. Compared with controls, patients with cirrhosis had reduced serum levels of iron, zinc and selenium; erythrocyte levels of glutathione and selenium were also low. Trace element decrease was not related to the degree of liver function impairment; however, glutathione levels were related to the degree of failure.

Micronutrient losses and needs are often dictated by the type of liver disease and specific conditions associated with liver failure. For example, alcoholic liver disease can create deficiencies of B vitamins. Deficiency of folate or $B_{12}$ can cause macrocytic anemia; $B_1$, $B_6$ and $B_{12}$ deficiencies can cause neuropathy. In addition, Wernicke's encephalopathy is linked to thiamine deficiency. Since copper and manganese are excreted via the bile, the levels of these elements may be elevated when cholestasis is present. Iron levels may be high such as in hemochromatosis or hemosiderosis, but can be low following gastrointestinal bleeding.

Supplementation can be in the form of general over-the-counter multivitamin-mineral preparations. However, when significant micronutrient alterations are suspected, supplementation should be tailored to meet needs based on measured levels.

## 9. OTHER SUPPLEMENTS

Alternative therapies are popular among individuals with liver failure. The safety and efficacy of some of these products are just now being evaluated. Probiotics are being investigated as potential therapy for hepatic encephalopathy. They may improve encephalopathy via several

mechanisms including reduction of ammonia in portal blood, inflammation and oxidative stress in the hepatocyte, and uptake of other toxins [46].

Many herbal products are promoted to people with liver dysfunction, but there is a lack of safety and efficacy data. Some products that have been identified as being hepatotoxic include borage, chaparral, coltsfoot, comfrey, DHEA, germander, jin bu huan, kava kava, liferoot, pennyroyal, periwinkle, poke root, American skullcap and shark cartilage. Other herbal or alternative medicine supplements may have adverse interactions with medications prescribed to those with liver failure, so caution must be taken in recommending any product.

The two most popular herbal supplements for liver disease are milk thistle and S-adenosyl-methionine (SAMe). Milk thistle contains silymarin, which supposedly reduces free radical production and lipid peroxidation associated with hepatotoxicity; it is also promoted to be an antifibrotic agent [47]. SAMe is a methyl donor for methylation reactions and a participant in glutathione (an anti-oxidant) synthesis [48]. Meta-analysis [49] and Cochrane reviews [49, 50] did not show any beneficial effects of either of these products for patients with liver disease. Until more is known about alternative medicine products, most patients should be cautioned about using any of these products.

## 10. SUMMARY

The liver is intimately involved in nutrient metabolism and storage. Therefore, malnutrition is likely to occur in the presence of liver failure. The degree of malnutrition depends on the type and degree of liver disease, presence of malabsorption, metabolic rate and psychosocial factors. Nutrition prescriptions should be individualized for patients with liver dysfunction. Common dietary restrictions for individuals with ESLD include sodium and fluid restrictions. Protein should not be restricted. Nutrition supplementation may improve nutritional status and outcomes. If TF is considered, nasoenteral tubes are usually the safest, lowest-risk access. Research currently does not support the use of herbal/alternative medicine supplements such as milk thistle or SAMe.

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# 5 Nutrition and Acute Pancreatitis

*Stephen J. D. O'Keefe*

***CONTENTS***



*Summary*

Acute pancreatitis is a disease of variable severity and outcome: mild disease may be treated at home, while severe disease often leads to several weeks in the ICU with mortality rates approaching 50%. Cell and molecular biological studies have increased our knowledge of the pathophysiology of the disease dramatically over the past decade, but have not, as yet, led to a specific treatment. All of the improvement in outcome can be attributed to supportive measures, such as nutrition. Clinical investigations have shown that acute pancreatitis is a highly catabolic illness, and protein deficiency could occur before the 2nd week of illness if no feeding is given. Parenteral nutrition (PN) is effective in preventing protein catabolism, and also

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'rests' the pancreas, but increases the already high risk of septic and metabolic side-effects, and worsens outcome in mild illness. Enteral feeding is superior to PN in the management of acute pancreatitis, even if it is polymeric or infused directly into the stomach. Unfortunately, however, enteral feeding stimulates pancreatic trypsin production and may exacerbate the disease process unless delivered well down the jejunum. The most likely reason for the superiority of enteral over parenteral feeding is its capacity to maintain intestinal function and suppress the cytokine-mediated systemic inflammatory response and consequent multiple organ failure.

**Key Words:** Acute pancreatitis, Enteral feeding

## 1. INTRODUCTION

Acute pancreatitis is a common cause for hospital admission. In 2000, there were 224,000 admissions to non-federal hospitals in the USA, with an average length of stay of 6 days (US Census Bureau, Washington, DC). In 75%, the disease is self limited, and most patients leave the hospital by day 5, but in the remainder the initial illness progresses into the 'severe' form, lasting weeks, with mortality rates between 15–30% [37]. In 2001 there were 3,075 deaths reported. The majority of deaths were in people of Caucasian origin, although the disease itself is more common in African Americans (Fig. 5.1).

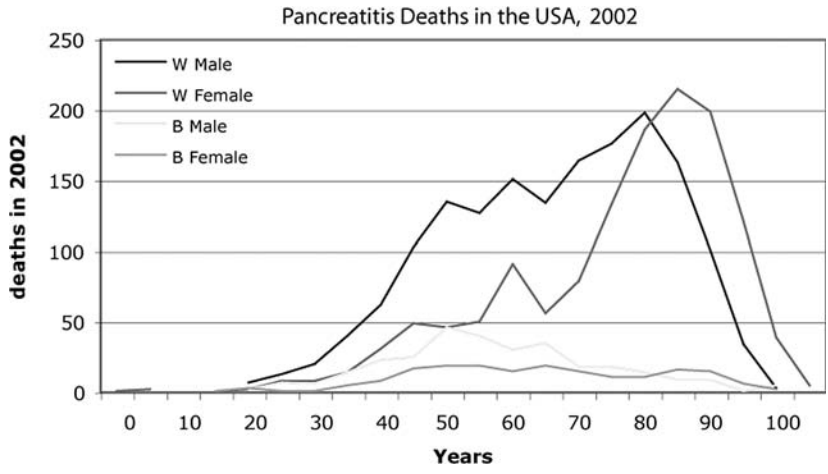


**Fig. 5.1.** Pancreatitis deaths in the USA, 2002, divided by race and sex.

## 2. THE PATHOPHYSIOLOGY

It is essential to understand the pathophysiological response to acute pancreatitis to understand how nutritional support may help patients. The excess mortality of severe acute pancreatitis is associated with the consequences of pancreatic injury rather than the pancreatic damage itself. In contrast to patients with mild disease, those with severe pancreatitis develop a systemic inflammatory response characterized by a flood of pro-inflammatory cytokines [1], which impairs respiratory, renal and intestinal function resulting in multiple organ failure [2]. This process has been extensively studied in animal models. The initiating factor in the inflammatory cascade is accepted to be an increase in intracellular calcium flux with premature activation of trypsinogen within the pancreas, leading to intracellular proteolysis or 'autophagia' [3, 4].

Figure 5.2 helps illustrate some of what is known to happen in the evolution of multiple organ failure and emphasizes the key role of the intestine in its genesis. Intracellular injury results in the generation of a cascade of pro-inflammatory cytokines such as IL-1β, TNF alpha, IL- 17, IL- 18 via activation of periacinar myofibrocytic NF

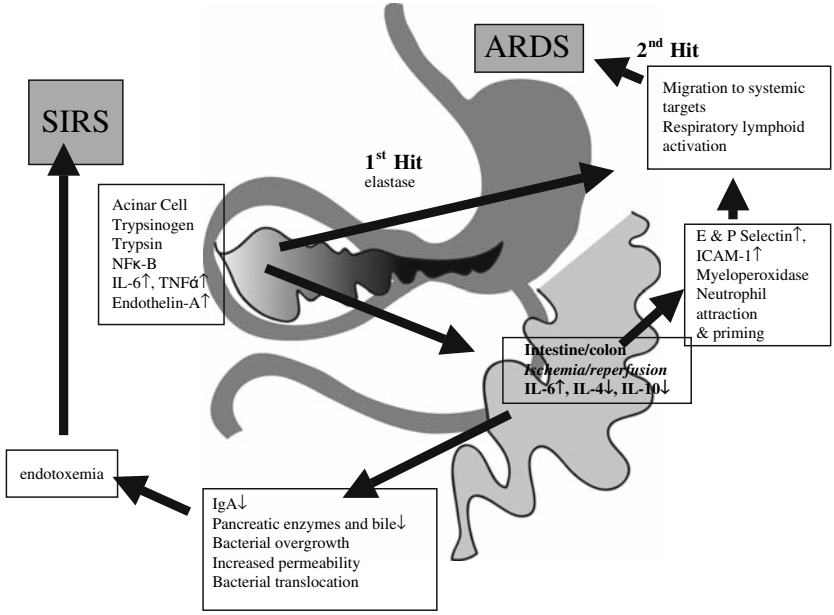


**Fig. 5.2.** Generation of the systemic inflammatory response (SIRS) and acute respiratory distress syndrome (ARDS) by acute pancreatitis.

kappa B and MAP kinase [5–7]. This in turn stimulates the release of IL- 6 and the cytoattraction of neutrophils, which in turn leads to further cytokine generation. The intense inflammatory response with endothelin-A activation results in the arterial constriction with resultant apoptosis and necrosis affecting not only the pancreas, but also the intestine [8, 9]. Splanchnic and whole body protein catabolism is accelerated [10]. If the inflammation is contained within the pancreatic bed, the disease process would be far less serious. Unfortunately, the cytokines are released into the circulation, and a secondary response commences approximately 48 h later, which leads to the generation of PG-2, thromboxane, LTB-4 and oxygen-derived free radicals within the bronchial and intestinal mucosa leading to cytotoxic injury [11]. The situation is compounded further by the release of proteolytic enzymes such as trypsin, elastase, phospholipase and caspase l into the circulation, which leads to amplification of cell injury within the lung ('2nd hit') and GI tract leading to ARDS, intestinal ischemia, bacterial translocation and the well-recognized systemic inflammatory response syndrome (SIRS) (Fig. 5.2) [12–16]. It is these complications that account for the high mortality rates, which can approach 30–50%, in severe necrotizing pancreatitis.

Despite the accumulating knowledge of the mechanisms involved, there have unfortunately been no major breakthroughs in treatment. The use of antiprotease therapy has been disappointing, and the initial excitement that specific anti-cytokine therapy might prevent the cytokine activation cascade has not been realized on formal testing in the clinical arena [17]. Most of the improvement in mortality can be attributed to better supportive management in the ICU. Knowledge of this pathophysiological response is crucial to our understanding of why feeding patients with acute pancreatitis is so incredibly difficult. The pros and cons of the various nutritional approaches advocated, namely, fasting, PN and enteral feeding, can be summarized as follows:

1. The pro-inflammatory cytokine 'storm' activates proteolysis, resulting in protein catabolism, increasing the demand for protein for tissue repair either from body stores or the diet.
2. Starvation produces 'pancreatic rest' and prevents further trypsinogen activation within the inflammatory mass, but deprives the intestine of luminal nutrition, thus exacerbating the mucosal damage initiated by the acute pancreatitis cytokine response. Furthermore, it results in severe negative nitrogen balance and protein deficiency due to unopposed protein catabolism, thus impairing tissue repair.

3. PN also 'rests the pancreas,' but aggravates the intestinal injury in the same way described for starvation above. It does, however, stem the loss of body protein.
4. Enteral feeding, as currently practiced, aggravates the pancreatic injury by stimulating trypsinogen production, but counteracts the intestinal injury by providing luminal nutrition.

## 3. THE PROBLEM WITH TPN AND BOWEL REST

The cornerstone of management of acute pancreatitis has been pancreatic rest, as the presence of food in the proximal gut is the most potent stimulus for trypsin synthesis and secretion, and continued trypsin synthesis can be expected to perpetuate the inflammatory response. Further studies have shown that acute pancreatitis is one of the most catabolic of illnesses [18, 19]. Consequently, the maintenance of pancreatic rest through starvation is a less than ideal option as an adequate supply of amino acids is essential for the repair process. The development of PN was heralded as a potential major breakthrough as, for the first time, feeding could be maintained without stimulating the pancreas. We, and others, have shown in human studies that PN is efficacious in meeting nutritional requirements without stimulating the pancreas [20]. Unfortunately, its use was also associated with an alarming increase in metabolic (namely, hyperglycemia) and septic complications. Indeed, one study showed that PN use worsened outcome when compared to no feeding at all [21]. The explanation is complex. First, PN and bowel rest probably exacerbate the intestinal and distant organ dysfunction that characterizes acute pancreatitis. Kudsk's studies in rats showed that PN and bowel rest result in atrophy of the mucosa and the gut immune system, with suppression of Th-2 responses and activation of adhesion molecules, which leads to neutrophil priming and migration to distant targets, such as the lung, producing a 'first hit' phenomenon [22]. This is remarkably similar to what is found in the acute pancreatitis-associated gut injury shown in Fig. 5.2. Other studies have shown that IL-6 is the mediator of gut barrier dysfunction [23], and both acute pancreatitis and PN induce intestinal IL-6 production [22, 24]. The use of PN (i.e., failure to feed patients enterally) further reduces motility and blood flow, increases the risk of small bowel bacterial overgrowth with antegrade colonization with colonic organisms and increases mucosal permeability as discussed above, thus exacerbating the pathophysiological response to acute pancreatitis [25, 26]. This may be of critical importance, as the organisms most commonly responsible

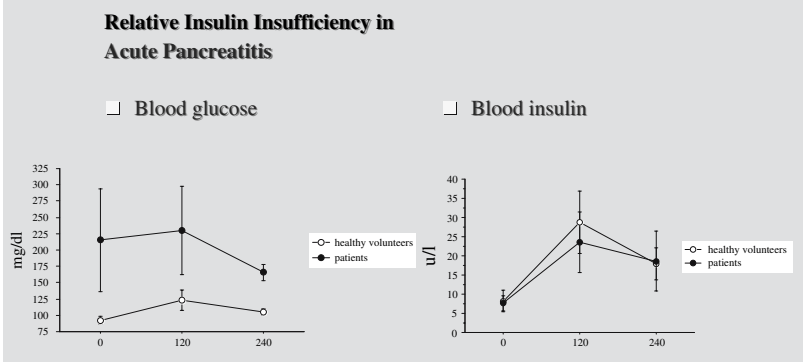


**Fig. 5.3.** Blood glucose and insulin responses to enteral feeding in patients with severe acute pancreatitis compared to healthy volunteers demonstrating relative insulin insufficiency.

for pancreatic infections are of colonic origin [27], and endotoxemia commonly accompanies severe disease [28]. Second, the presence of a central vein catheter in PN-fed patients provides an open conduit for nosocomial infection. Third, intravenous feeding invariably results in hyperglycemia in patients with severe acute pancreatitis because (1) the glycemic effect of glucose administered parenterally is greater than if it is given enterally [29], (2) acute pancreatitis impairs pancreatic endocrine function resulting in a relative insulin deficiency [30] and (3) the acute inflammatory response and secretion of counter-regulatory hormones increases endogenous glucose production and creates insulin resistance [31] (Fig. 5.3).

Recent studies have clearly demonstrated that hyperglycemia worsens outcome in any form of critical illness [32]. In hyperglycemia, leukocyte function is impaired and intestinal motility reduced, leading to increased infection risk from enteric pathogens [33]. Consequently, it is likely that the potential benefits of PN on 'resting' the pancreas are overshadowed by its detrimental effects on intestinal function and mucosal integrity, and by its septic and metabolic complications.

## 4. WHY ENTERAL FEEDING IS SUPERIOR TO TPN AND BOWEL REST

The complications associated with PN have led us and others to explore the use of specialized forms of enteral feeding (EN). In the five major randomized comparative studies published thus far, enteral feeding has been shown consistently to be superior to PN with regard to cost, complications and outcome [34–38]. A recent metanalysis concluded

that enteral nutrition should be the preferred route of nutritional support in acute pancreatitis [39]. While most of us have used jejunal feeding with semi-elemental formulae to minimize pancreatic stimulation, one study just reported from Glasgow, Scotland, found that patients could simply be fed by nasogastric tube without obvious exacerbation of the pancreatitis [38]. How can we explain the better results seen utilizing these forms of EN compared to TPN considering the pathophysiology of acute pancreatitis? It is not because any of the specialized forms of feeding used in these studies avoided pancreatic stimulation, as studies of ours in healthy volunteers have shown that even the avoidance of the cephalic and gastric phases of pancreatic stimulation by post-pyloric infusion failed to reduce food-induced pancreatic secretion [29] (Fig. 5.4). Furthermore, even the use of an intestinal elemental formula diet only reduced the stimulatory effect by 50%, a rate considerably higher than that measured during fasting or IV feeding [29]. Another suggestion, based on experimental studies, was that the pancreas becomes unresponsive in acute pancreatitis. Investigating this possibility, we indeed found that the duodenal secretory response to feeding was reduced roughly 90% [30]. However, when we measured the de novo rate of synthesis of secreted trypsin by isotope-labeling techniques, we found that even in patients with necrotizing disease affecting over 50% of the gland trypsin continued to be synthesized and that a good proportion of the reduction in luminal secretion could be attributed to leakage of enzymes into the inflammatory mass and the bloodstream [30]. Further studies showed that the low rate of

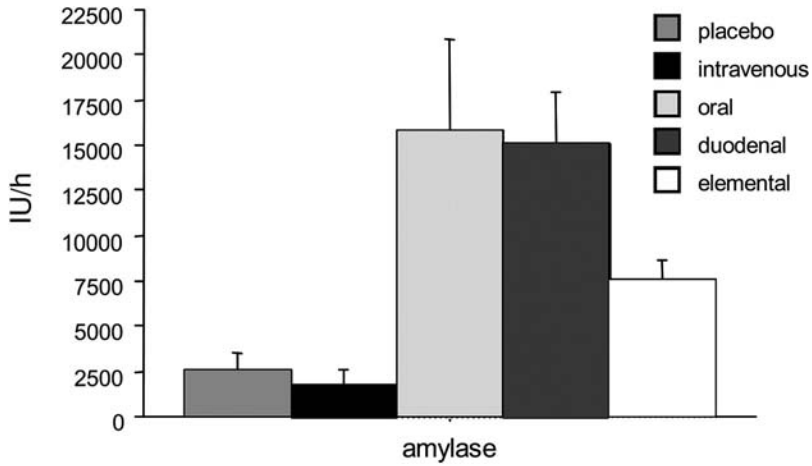


**Fig. 5.4.** The relative effects of enteral and parenteral feeding on pancreatic amylase secretion in healthy volunteers [29].

secretion in acute pancreatitis could be increased by conversion from PN to enteral feeding [40, 41]. These findings led us to the conclusion that the superiority of proximal enteral feeding over PN could not be accounted for by its beneficial effects on the pancreas, but by the greater efficiency of enteral feeding in preserving intestinal function and splanchnic metabolism, and by the avoidance of PN-associated complications. Support for this conclusion was gained by our further observation that in acute pancreatitis, splanchnic amino acid flux and mucosal turnover were increased three-fold and that compartmentation between the splanchnic and systemic amino acid circulations was increased, thus preventing thorough mixing of IV and splanchnic amino acids [42]. Consequently, enteral feeding would be better positioned than PN to target the region of increased metabolic demand for tissue repair. Furthermore, if we refer back to our illustration in Fig. 5.2, one of the chief effects of acute pancreatitis is to provoke intestinal ischemia, which in turn leads to mucosal leakage and the risk of bacterial organism and endotoxin translocation. For example, Rahman et al. demonstrated in patients with severe acute pancreatitis that the urinary excretion of intestinal fatty acid-binding protein, an accepted measure of intestinal ischemia, positively correlated with severity of disease, mucosal permeability (urinary PEG 400:3,500), CRP and with endotoxin levels [43]. Enteral nutrition undoubtedly plays a key role in preventing this cycle of events as it is the most potent stimulator of blood flow, through its stimulation of intestinal growth factors [44, 45] because of its content of arginine, which is the natural precursor for nitric oxide [45]. Experimental studies in the rat acute pancreatitis model have shown that nitric oxide antagonizes endothelin-A and that endothelin-A receptor blockade abolished the acute pancreatitis-associated capilliary constriction and attenuated the inflammation-associated leukocytic response and pancreatic injury [47].

## 5. IS PROXIMAL ENTERAL FEEDING DANGEROUS?

While several studies [53, 54] and expert advisory groups [55, 56] have shown that early enteral feeding is beneficial in the management of critically ill patients, no study has addressed the question of whether the avoidance of pancreatic stimulation during feeding early in the course of acute pancreatitis hastens the resolution of the acute inflammatory response and the duration of disease. The observation by the Glasgow group [38] that outcome was no different whether patients were fed by stomach or 'jejunum' [(it is likely that most patients received duodenal feeding] does not address this concern, as our

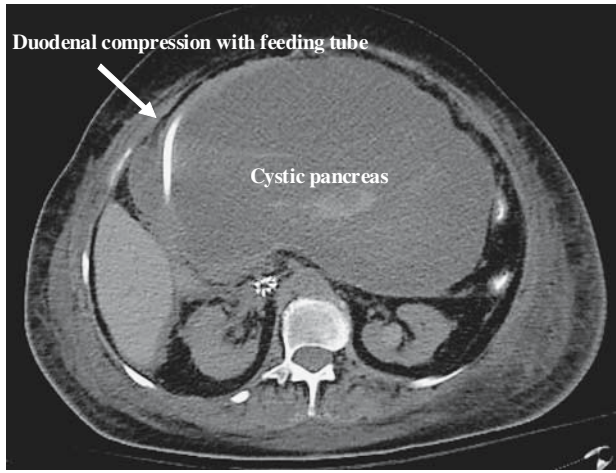


**Fig. 5.5.** CT scan illustrating extrinsic compression of the stomach and duodenum by cystic transformation of pancreatic necrosis.

investigations have shown that the stimulatory effect of feeding is no different whether the diet is taken as a drink or infused directly into the duodenum [29], and studies of Vu et al. showed that feeding in the proximal jejunum still stimulates secretion [59]. Consequently, both forms of feeding were stimulatory, and it remains possible that neither were better than no feeding, particularly in view of the observed high mortality rates of 20–30%. Although clinical deterioration has not been commonly recognized in the enteral vs. parenteral feeding trials, we published compelling evidence of exacerbation in a patient with necrotizing disease during advancement of enteral feeding, based on the combination of clinical signs (abdominal pain), blood tests (increased WBC) and CT scanning (extension of necrosis) [41]. Furthermore, objective evidence that the injured pancreas can still respond to enteral stimulation was obtained from our measurements of secretion in patients with severe necrotizing disease fed by enteral and parenteral nutrition [42]. We are not alone in observing exacerbation of disease during enteral feeding [34]. Following from this, we are concerned that conventional enteral feeding may be providing a mixed bag of benefits and risks in patients with acute pancreatitis.

Finally, it must be remembered that enteral feeding, like TPN, has its own difficulties and complications. We are surprised that the Glasgow group did not encounter problems when trying to feed patients with necrotizing disease by NG tube, as it is our experience that most have gastric outlet obstruction due to compression of the distal stomach and duodenum by the inflammatory mass (Fig. 5.5). Unless a second

decompression tube is used, which would also be counter-productive as it would prevent effective feeding, the risk of aspiration and pulmonary complications in ICU patients would be greatly increased [40, 57].

## 6. ENTERAL FEEDING WITHOUT PANCREATIC STIMULATION: DISTAL JEJUNAL FEEDING

A recent publication of our findings [58] has supported the results of an earlier study from Holland [59] that it is possible to use enteral feeding without stimulating the pancreas, if the infusion is delivered 40–60 cm down the jejunum. This makes physiological sense, as there has to be a null point in between the duodenum, where feeding stimulates through cholinergic reflexes and CCK release [60, 61] and the ileum where feeding inhibits via the ileal brake mechanism [62]. We have shown that this distance is easy to achieve in clinical practice with tube systems that are commercially available [58] (Fig. 5.6). There is extensive literature that the presence of nutrients (in particular long chain fatty acids [63, 64], carbohydrate [63] and amino acids [65]) in the ileum suppresses pancreatic secretion in humans, principally through release of GLP-I and PYY from ileal L-cells and neurotensin

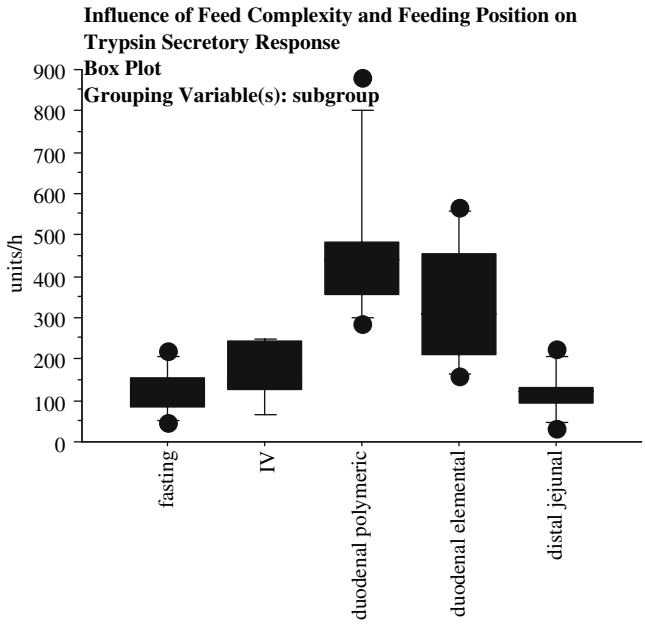


**Fig. 5.6.** Influence of feed complexity and feeding position on the pancreatic secretory response to feeding in healthy volunteers [58].

from N-cells [66]. Activation of the ileal brake in this way may have the additional benefit of inhibiting gastric acid secretion [62] and the need for NG decompression. Finally, it must be remembered that although the glycemic response to enteral feeding is lower than that to PN [29], hyperglycemia can still occur due to islet cell damage, and that the more effective the mode of enteral feeding, the greater the risk of hyperglycemia. Consequently, all forms of feeding must be closely monitored, with judicious use of insulin to control hyperglycemia.

## 7. SHOULD ENTERAL FEEDING BE COMPARED TO NO FEEDING?

Bearing in mind these practical issues, an easy alternative to non-stimulatory enteral feeding would be no feeding until body stores become depleted. Indeed, no study has yet tested whether enteral feeding is better than no feeding in clinical practice, although a small underpowered study suggested that the cytokine response was no different [67]. If pancreatic rest is useful, then this is the surest way of imposing it. The problem is that we have no easy way of knowing when body stores run out. From studies in starved healthy volunteers, it has been estimated that protein stores last about 14 days [68], but with protein catabolism, patients will become depleted earlier. A further concern is that starvation, like TPN and bowel rest, will result in disuse atrophy of the mucosa, stasis, bacterial overgrowth and increased permeability, and increased risk of infection from enteric organisms, thus exacerbating the pathological changes associated with acute pancreatitis. With these considerations in mind, it would be prudent to start nutritional support before the 2nd week of illness.

## 8. CAN FEEDING INFLUENCE OUTCOME?

A recent prospective study designed specifically to evaluate the therapeutic use of Lexipafant, a platelet-activating antagonist, again from the Scottish group, examined the relationship between SIRS and mortality in the subgroup of Scottish patients with severe disease ($n = 121$) and found that the incidence of SIRS on admission, at 24 h and 48 h, as well as the persistence of SIRS, was correlated with survival as shown in Table 5.1 and Fig. 5.7 [69]. The authors also examined the relationship between multiple organ failure (MOF) and death risk, and showed that transient MOF, i.e., MOF that resolved with the 1st week, was associated with no mortality, but 'permanent" or progressive MOF was associated with a mortality rate of 55%. More recently,

**Table 5.1**
**Association Between Systemic Inflammatory Response Syndrome and Overall Survival in Patients with Severe Acute Pancreatitis**

| | *SIRS present* | | *SIRS absent* | | |
|---|---|---|---|---|---|
| | *n* | *Survivors* | *n* | *Survivors* | *P** |
| Admission | 87 | 74 (85) | 34 | 34 (100) | 0·019 |
| 24 h | 45 | 35 (78) | 76 | 73 (96) | 0·002 |
| 48 h | 32 | 21 (66) | 89 | 87 (98) | <0·001 |
| Persistent | 27 | 17 (63) | 94 | 91 (97) | <0·001 |

Values in parentheses are percentages. SIRS, systemic inflammatory response syndrome. *$\chi^2$ test [69].

a full evaluation of all the patients with severe disease enrolled in the UK Lexipafant study ($n = 290$) was reported, confirming the predictive value of permanent MOF on mortality [70]. In addition, they examined the relationship between MOF and local complications, such as pancreatic necrosis and infection. They found that there was a significant association, such that 52% of patients with permanent MOF developed local complications, as opposed to none with no organ failure and 26% with transient MOF ($p < 0.001$). These studies suggest that there is a 'window of opportunity' in the 1st week of hospitalization to reduce mortality if we can apply measures to suppress the development of SIRS, and thus MOF. The reverse is also true, that exacerbation of SIRS may prevent the reversal of early MOF, and therefore lead to an increase in mortality. From what we have discussed above, it is likely that enteral feeding will reduce the risk of MOF as it reverses ileus, and jejunal feeding bypasses the obstructed upper GI

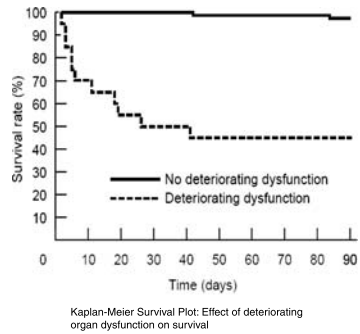


**Fig. 5.7.** Kaplan-Meier survival plot illustrating that all the mortality associated with acute pancreatitis is associated with progressive multiple organ failure [70].

tract, thus preventing intestinal failure. Secondly, the maintenance of mucosal health and prevention of bacterial overgrowth will suppress the systemic cytokine-generated inflammatory response, also reducing the risk of MOF and mortality. On the other hand, proximal feeding may exacerbate the pancreatic injury and increase the risk of aspiration pneumonia, thereby increasing the risk of MOF and mortality.

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# 6 Celiac Disease

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***Contents***



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*Summary*

Celiac disease, also known as celiac sprue or gluten-sensitive enteropathy, is a chronic disorder that is readily recognized when it presents in its classical form with diarrhea, bloating, flatulence, weight loss and evidence of malabsorption. However, non-gastrointestinal GI and non-specific GI manifestations are currently the more common presentations of this disease. Withdrawal of gluten from the diet results in a rapid clinical improvement and a slower but corresponding return of normal small bowel histology. Inappropriate T-cell responses to ingested gluten in genetically predisposed individuals result in the intestinal injury that characterizes celiac disease. The discovery that tissue transglutaminase (tTG) is a target of the immune response in celiac sprue has led to the development of new diagnostic tests. With the increasing numbers of celiacs being identified in the USA and elsewhere, it is important that physicians and other health care providers continue to be educated about this disorder including recent developments in the field.

**Key Words:** Malabsorption, Diarrhea, Autoimmunity, Food allergy, Iron deficiency, Osteopenic bone disease, Intestinal biopsy, Serological tests, Gluten-free diet

## 1. INTRODUCTION

Celiac disease, also referred to as celiac sprue or gluten-sensitive enteropathy, is a chronic disorder that is readily recognized when it presents in its classical form with diarrhea, bloating, flatulence, weight loss and evidence of malabsorption. Withdrawal of immunogenic grains including wheat, rye and barley from the diet of affected patients results in a rapid clinical improvement and a slower return of small bowel histology to normal. Over the past two decades it has become increasingly evident that celiac disease can present in many other ways including non-specific gastrointestinal complaints, anemia, recurrent miscarriages, neuropsychiatric disorders and osteopenic bone disease [1]. In addition, celiac disease may complicate other disorders, particularly autoimmune endocrine and connective tissue diseases. Celiac disease is a unique disorder representing both a form of food allergy and an autoimmune disease. Until relatively recently, celiac disease was thought to be rare and primarily a disease of childhood, even a disease that one could grow out of. As will be discussed it is now recognized the celiac disease is common, affecting both adults and children, and is a lifelong condition that is treated almost exclusively by dietary measures.

## 2. EPIDEMIOLOGY

Until the advent of widespread serological testing the highest reported prevalence of celiac disease in the world was in western Ireland where 1 in 300 individuals had celiac disease with prevalence as low as 1:2,000 in other parts of Europe. It was estimated that 1 in 2,000 Canadians had celiac disease, while one study conducted in Olmstead County, Minnesota, reported a prevalence of 21.8 per 100,000 [2]. It is still not clear why the reported frequency of celiac disease was so much less in the USA than in other parts of the world inhabited by individuals of similar ethnic origin. The use of serological methods to screen for celiac disease indicates that celiac disease is much more common than previously thought, with prevalence as high as 1:50 to 1:300 in the western world. A recent prevalence study conducted in the United States by Fasano and colleagues indicated a prevalence of 1:133 in asymptomatic subjects, but higher in symptomatic subjects or those with disorders associated with celiac disease (1:56) or first-degree relatives of celiac patients (1:22) [3]. The range of the reported prevalence is wide, reflecting varying populations and modalities of detection. Recognizing these issues it is thought that the prevalence of celiac disease in the western world including the United States is approximately 1:100 (1%). The true prevalence of celiac disease remains to be established by large multicenter studies in which serology in conjunction with small bowel histology is consistently evaluated.

**Table 6.1**
**Prevalence of Celiac Disease in Various Settings**

| |
|---|
| 1st degree relatives of patients with celiac disease (10–15%) |
| 2nd degree relatives of patients with celiac disease (2.6–5.5%) |
| Type I DM (2–5% adults, 3–8% children) |
| Autoimmune thyroid disease (3%) |
| Symptomatic iron deficiency anemia (10–15%) |
| Asymptomatic iron deficiency anemia (2–9%) |
| Microscopic colitis (15–27%) |
| IBS (3.4%) |
| Osteoporosis (1–3%) |
| Elevated transaminases (1.5–9%) |
| Autoimmune hepatitis (3–6%) |
| Primary biliary cirrhosis (0–6%) |
| Down's syndrome (3–12%) |
| Chronic fatigue syndrome (2%) |
| Unexplained infertility (2–4%) |

Celiac disease occurs with increased frequency in various settings as summarized in Table 6.1. These include relatives of celiac patients and those with various autoimmune disorders including type I diabetes and autoimmune thyroid disorders. These individuals possess the HLA genes (reviewed below) that can predispose them to celiac disease. Other groups in which celiac disease is more commonly found are those with conditions that may result from celiac disease including iron deficiency and osteopenic bone disease. In other conditions such as Down's syndrome the mechanism of the association is less clear.

## 3. SPECTRUM OF CLINICAL PRESENTATIONS AND ASSOCIATED CONDITIONS

The classical presentation of celiac disease includes diarrhea, failure to thrive or weight loss, abdominal distention, flatulence and fatigue. However, during the past two decades there has been an increasing awareness that there are many less dramatic or classical presentations of celiac disease including iron-deficiency anemia, folate deficiency, osteopenic bone disease, as well as relatively non-specific gastrointestinal (GI) symptoms (Table 6.2). These so-called "atypical" forms of celiac disease are now more common than classical celiac

**Table 6.2**
**Presentations of Celiac Disease**

| |
|---|
| Classical celiac disease of childhood |
| Later onset GI symptoms |
| Often mistaken for IBS |
| Can be non-specific |
| Extraintestinal presentations |
| Dermatitis herpetiformis |
| Iron deficiency |
| Folate deficiency |
| Osteopenic bone disease |
| Chronic fatigue |
| Neuropsychiatric manifestations |
| Short stature |
| Infertility |
| Obstetrical complications |
| Asymptomatic celiac disease |
| Often in relatives |
| Latent celiac disease |

disease [4]. Studies as well as anecdotal experience indicate that many of these patients remain undiagnosed for years in spite of unexplained symptoms or abnormal blood tests. Other terms of questionable clinical significance are "silent" or "latent" celiac disease, which are used respectively when subjects are asymptomatic, but have serological and histological evidence of celiac disease or when serology is positive without symptoms or histological changes of celiac disease.

## 4. NON-SPECIFIC GASTROINTESTINAL SYMPTOMS AND OTHER NON-MALABSORPTIVE PRESENTATIONS

Patients with celiac disease can present with altered bowel habits, bloating, dyspepsia and abdominal discomfort [5].

Some studies suggest a subset of patients diagnosed as having irritable bowel syndrome (IBS) may have celiac disease [6, 7]. The mean prevalence of celiac disease was 3.4% in published series of IBS patients, and celiac disease is seven times more common in IBS patients than in age-matched controls.

A recent decision analysis study suggests that there is an acceptable cost of testing for celiac disease in diarrhea predominant IBS patients when the prevalence of celiac disease is greater than 1% [8], and another study suggests celiac screening is more worthwhile than searching for infections, malignancies and inflammatory bowel disease in IBS subjects with diarrhea [9].

### *4.1. Dermatitis Herpetiformis*

Dermatitis herpetiformis (DH) is a condition characterized by pruritic papulovesicular skin lesions in which granular or linear IgA deposits are found at the dermal-epidermal junction [10]. The majority of patients with DH have the characteristic findings of celiac disease in small bowel biopsy specimens, although relatively few have GI symptoms. DH patients have similar HLA profiles to celiac patients and develop similar antibody elevations to gliadin and tissue transglutaminase (tTG). They are also at increased risk of malignancies as discussed later. Institution of a gluten-free diet will reverse both the skin and intestinal lesions, while standard therapies for DH such as dapsone improve only skin disease. It is not clear why only a small subset of celiacs has DH, while virtually all DH patients have the intestinal pathology of celiac disease.

### *4.2. Celiac Disease and Autoimmune Disorders*

Celiac disease is increased in frequency in various autoimmune conditions [11] (Table 6.3) including insulin-dependent diabetes mellitus [12], autoimmune thyroid disease and Addison's disease. Other associations with celiac disease including systemic lupus erythematosis, rheumatoid arthritis, psoriasis, Sjogren's syndrome and inflammatory bowel diseases are less strong. Microscopic colitis and lymphocytic gastritis can be found in untreated celiac disease patients reflecting immunologic stimulation outside the small intestine [13–15].

**Table 6.3**
**Conditions Associated with Celiac Disease**

| |
|---|
| Autoimmune endocrine disorders |
| Insulin-dependent diabetes mellitus |
| Autoimmune thyroid disease |
| Autoimmune adrenal disease |
| Autoimmune connective tissue disorders |
| Sjogren's syndrome |
| Rheumatoid arthritis |
| Systemic lupus erythematosis |
| Hepatobiliary conditions |
| Primary sclerosing cholangitis |
| Primary biliary cirrhosis |
| Autoimmune cholangitis |
| Elevated transaminases |
| Other gastrointestinal disorders |
| Lymphocytic gastritis |
| Microscopic colitis |
| Irritable bowel syndrome |
| Miscellaneous conditions |
| IgA deficiency |
| IgA nephropathy |
| Down's syndrome |
| Turner's syndrome |
| Aphthous stomatitis |
| Dental enamel defects |
| Neurological disorders |
| Peripheral neuropathy |
| Ataxia |
| Epilepsy ± occipital calcification |

Often these findings resolve on a gluten-free diet. It is estimated that between 15 and 17% of patients with microscopic colitis have celiac disease. In addition to the recognized autoimmune hepatobiliary diseases associated with celiac disease (autoimmune hepatitis, primary biliary sclerosis and, to a lesser extent, primary sclerosing cholangitis), cryptogenic cirrhosis and otherwise unexplained elevations of serum transaminases are associated with celiac disease [16–18] (Table 6.1). While the mechanisms contributing to abnormal transaminases in celiac disease are unknown, the biochemical abnormalities typically respond to a gluten-free diet.

A significant number of studies have examined the increased prevalence of celiac disease in populations of patients with type I diabetes mellitus, yet relatively few patients were diagnosed prior to conducting screening tests for celiac disease [12]. It remains controversial as to how often celiac-diabetics present with symptoms that suggest the diagnosis of celiac disease, but many do not report gastrointestinal complaints. Similarly, whether there are benefits of treatment with a gluten-free diet is not established [19–20]. There are some reports to suggest weight gain and improved growth on a gluten-free diet. However, better blood sugar control has not been consistently demonstrated. It has been suggested that all type I diabetics, particularly pediatric patients, should be screened for the presence of celiac disease. While this has not become standard practice in the United States, it can be recommended that symptomatic type I diabetics are screened and that any type I diabetics undergoing upper GI endoscopy have duodenal biopsies. Both disorders share the same HLA DQ susceptibility genes rendering HLA screening less helpful in this at-risk population.

### *4.3. Other Manifestations*

A variety of gynecologic and obstetrical presentations are associated with celiac disease including delayed menarche, infertility, miscarriages, intrauterine growth retardation and low birth weight [21–24]. The risk of celiac disease is high enough in unexplained recurrent miscarriages to consider evaluating such women for the presence of celiac disease. Neuropsychiatric disorders that have been associated with celiac disease range from peripheral neuropathy, ataxia, epilepsy and schizophrenia to cognitive deficits, depression and hyperactivity-attention deficit disorder [25–27]. A large number of other conditions are associated with celiac disease including Turner's syndrome, Down's syndrome, IgA deficiency and IgA nephropathy [28–29] (Table 6.3). The mechanisms by which these conditions are linked with celiac disease are not clear, although presumably chromosomal

factors and perhaps HLA linkages are involved. The higher prevalence of IgA deficiency in celiac disease has an effect on diagnostic tests, several of which are IgA-based serologic tests (see below).

## 5. PATHOGENESIS

Inappropriate T-cell responses to ingested gluten in genetically predisposed individuals results in the intestinal injury that characterizes celiac disease [30–31]. The discovery that tissue tTG is a target of the immune response in celiac disease has enhanced the understanding of the pathogenesis of the disease and led to the development of new diagnostic tests [32]. Prolamins (gliadin in wheat, secalin in rye and hordein in barley, collectively referred to as gluten) have been identified as the component of those grains capable of inducing damage in celiacs [33–34]. Over 50 peptides have been shown to stimulate T cells in celiac subjects, although a given patient may react to only a few of these peptides. Most recent studies suggest that avenin in oats does not induce immunoreactivity [35], although there are reports to suggest that some T cells may react to oat-derived peptides [36]. There is also some evidence that in celiac subjects regulation of the intestinal tight junctions is altered such that levels of zonulin are increased [37] and permitting enhanced uptake of gluten via the tight junctions [38, 39].

Genetic factors are suggested by the 70% concordance rate in identical twins and a prevalence of 10–15% in first-degree relatives. HLA studies indicate that most celiacs possess the extended haplotype, DR3-DQ2, or, less often, DR5/7-DQ2. The DQ2 $\alpha/\beta$ heterodimer is encoded by the alleles DQA1$^{*}$0501 and DQB1$^{*}$0201. Some celiac patients have DR4-DQ8 encoded by the DQA1$^{*}$0301 and DQB1$^{*}$0302 alleles. Since approximately one third of the US population has these haplotypes, this suggests that additional susceptibility gene(s) not yet identified are required for the development of celiac disease. Antigen-presenting cells bearing these HLA haplotypes present gliadin peptides to intestinal mucosal T cells [40], which mediate the immune response resulting in intestinal damage through cytokines such as IL-15 and interferon gamma (IFN-$\gamma$). The deamidating activity of tTG modifies gliadin to become the dominant alpha-gliadin T-cell epitope [41, 42].

Celiac disease is characterized by a two- to six-fold increase in the number of intestinal plasma cells and increased levels of antibodies to mesenchymal proteins including tTG. The number of intraepithelial lymphocytes (IEL) is increased in celiac disease including the CD45RO$^{+}$ subset that can act as antigen-primed memory cells

and $CD8^-$ IEL bearing the γ/δ T cell receptor (TCR). Increased IL-15 enhances receptor-ligand interaction between IEL and enterocytes leading to enterocyte killing [43]. Experimental studies show that mitogen-activated T cells in fetal small bowel explants develop an injury similar in appearance to that of celiac disease, including crypt hypertrophy that is mediated by IFN-γ [44].

## 6. DIAGNOSIS OF CELIAC DISEASE

### *6.1. Serological Tests*

There is a significant role for serological tests in the diagnosis and management of celiac disease. Antigliadin antibodies (AGA) measured by enzyme-linked immunosorbent assays are a sensitive although nonspecific test for the presence of celiac disease. False-positive gliadin antibodies have been reported in other conditions including small bowel bacterial overgrowth as well as in healthy individuals. This is particularly true for IgG AGA, which has a high false-positive rate. IgA AGA is more specific, but its sensitivity (∼80%) is less, in part due to the fact that IgA deficiency is increased in celiacs. The use of antigliadin antibodies in the detection of celiac disease has been recently questioned because of their lower specificity. However, they can play a role in assessing young children in whom tTG assays are less sensitive [45] and in following some celiacs on a gluten-free diet when the tTG levels are slow to decline. Serum antireticulin antibodies (ARA) should no longer be used due to lower sensitivity and specificity.

Endomysial IgA antibody (EMA) reacts with the endomysium or loose connective tissue around smooth muscle bundles and is assayed by immunofluorescence using monkey esophagus or human umbilical cord as the substrate. It is now known that tissue transglutaminase (tTG) is the antigen to which EMA reacts, and ELISAs have been developed that use guinea pig or human recombinant tTG as the antigen. Human sources of tTG are superior to guinea pig as the assay substrate. The sensitivities of EMA and IgA tTG are similar and can approach 98%, although lower levels of sensitivity are reported for EMA testing. Both have lower sensitivity in the presence of lesser degrees of villous atrophy. The EMA is virtually 100% specific, while the tTG IgA specificity is about 95% with false-positive tests reported in autoimmune diseases, liver disease, inflammatory bowel disease and heart failure. The IgG tTG may have value in diagnosing celiac disease in the presence of IgA deficiency, although the literature suggests the sensitivity of this test overall is only 40% on average. However,

Table 6.4
Summary of Serological Tests and their Usefulness in Adults

| *Test* | *Sensitivity* | *Specificity* |
|---|---|---|
| IgA AGA | <80% in 50% of studies | >80% in most studies |
| IgG AGA | Variable | Non-specific |
| IgA EMA | 96–97% ME 90% HUV | 100% ME 100% HUV |
| IgA tTG | 90% GP 98% HR | 95% GP 98% HR |
| IgG tTG | 40% | 98% |

Source: Adapted from Rostom et al. [48].
*AGA* antigliadin antibody; *EMA* endomysial antibody; *tTG* tissue transglutaminase; *ME* monkey esophagus; *HUV* human umbilical vein; *GP* guinea pig; *HR* human recombinant

some studies suggest a higher sensitivity of the IgG tTG assay in IgA deficiency. Options to exclude IgA deficiency as a cause for a false-negative serological IgA test include obtaining a total IgA level or assessing the concentration of tTG IgA [46]. Table 6.4 summarizes numerical data regarding the sensitivity and specificity of these serological tests [47, 48].

Antibody tests should not replace intestinal morphology for making a diagnosis of celiac disease, but in those unable or unwilling to undergo endoscopy, the presence of a positive EMA or high titer IgA tTG is most suggestive of the diagnosis of celiac disease. These antibody assays are useful in monitoring compliance since levels will decrease on a gluten-free diet and increase after the ingestion of gluten. tTG or EMA can also play a role in the timing of endoscopy and biopsy during a gluten challenge (Table 6.5) used in diagnosing patients who had been on a gluten-free diet without an initial proven diagnosis of celiac disease. Another potential role for the antibody tests is in screening higher risk individuals including relatives of celiac patients and those with autoimmune conditions including type I diabetics. The optimal antibody or panel of antibodies to use for screening has not been determined and will depend on the prevalence in the population being screened [48]. Intestinal biopsy specimens should be obtained in all individuals with elevated EMA or tTG antibodies wherever possible.

## *6.2. Histopathology*

The diagnosis of celiac disease still requires a characteristic appearance on histological examination of mucosal biopsy specimens obtained from the small intestine. These findings include varying degrees of

**Table 6.5**
**Strategy to Diagnose Patients on a Gluten-free Diet without a Confirmed Diagnosis of Celiac Disease**

| |
|---|
| Who to challenge: |
| Patients started on gluten-free diet (GFD) without confirmatory histology |
| Patients with an equivocal diagnosis or equivocal response to GFD |
| Those who are HLA DQ2 and/or DQ8 positive and may have celiac disease |
| What to challenge with: |
| Diet containing gradually increasing amounts of gluten |
| Final amount will vary according to patient sensitivity |
| Minimum of 10 g gluten/day (four slices of bread–one slice has ~2.25 g) |
| Maximum of as much gluten as tolerated |
| Standard is four slices whole wheat bread a day |
| How long to challenge: |
| Varying opinions on this issue! |
| Depends on duration of GFD, amount of gluten in challenge |
| Use serology and symptoms as a guide to timing the EGD with biopsy |
| Even if patient remains asymptomatic and seronegative, EGD with biopsy recommended after two to six months |
| Other considerations: |
| Avoid challenges in patients reporting severe reactions to gluten/wheat |
| After long-term GFD expect a prolonged time to develop a response to gluten |
| Elderly and very young patients are not ideal candidates |
| Many patients do not want to undergo challenge |
| There are reports of relapses after a year on the diet |

villous atrophy, a change in the normal columnar appearance of the absorptive epithelium with crypt hyperplasia and increased numbers of IEL and lamina propria mononuclear cells. More minor degrees of histopathology may be missed on routine examination since the earliest changes are an increase in IEL. These features are not specific for celiac disease in that some or all of the histological findings can be found in tropical sprue, small intestinal bacterial overgrowth, viral gastroenteritis, intestinal lymphoma and severe acid-induced injury associated with a gastrinoma. Duodenal biopsies obtained at endoscopy are usually sufficient to make the diagnosis, but occasionally additional samples from the more distal jejunum are needed. It is recommended that multiple biopsies be obtained throughout the segments of the duodenum as the disease can be patchy. Newer

endoscopic technologies including higher resolution imaging can be helpful in differentiating abnormal mucosa with fissuring, notching or scalloping and loss of villi from areas of more normal appearing mucosa [49].

With the availability of improved serologic testing, a second set of biopsies to confirm histological improvement or complete healing on a gluten-free diet is not necessary in most instances. A second endoscopy with biopsies should be reserved for patients failing to improve clinically or serologically in spite of adequate dietary treatment. The clinical improvement is rapid, while months to years are usually needed before complete histological resolution is seen [50].

### *6.3. Genetic Testing*

As discussed HLA studies indicate that most celiacs possess the extended haplotype, DR3-DQ2, or, less often, DR5/7-DQ2. Some celiac patients have DR4-DQ8. Virtually all celiacs bear one of these three haplotypes, which has led to the development of new assays for diagnosis and screening. PCR assays to detect a restricted set of HLA antigens (HLA DQ2 and DQ8) are available and can be helpful in defining those at risk of developing celiac disease. Although the prevalence of these HLA haplotypes is approximately 35% of the North American population, essentially celiac disease occurs only in the subset bearing at least one of these two genes. Thus, such testing can be useful in determining who should undergo a gluten challenge and also for screening family members.

### *6.4. Other Diagnostic Tests*

While individuals presenting with severe and classical celiac disease may have steatorrhea and evidence of malabsorption including decreased serum levels of cholesterol, carotene, calcium, magnesium, phosphorus, potassium and albumin, increased levels of alkaline phosphatase and a prolonged prothrombin time, many patients with celiac disease do not have overt malabsorption. More common laboratory manifestations are parameters of iron deficiency and sometimes folate deficiency. Vitamin B12 deficiency can occur in celiac disease, but is relatively rare. The D-xylose test and barium studies have little role in the current assessment of patients with celiac disease. Endoscopic findings include scalloping or the absence of duodenal folds, but these are both insensitive and not entirely specific markers for celiac disease [51]. Videocapsule imaging and enteroscopy

can play a role in addition to standard esophagogastroduodenoscopy in some cases of celiac disease [49].

## 7. STRATEGIES FOR CONFIRMING A DIAGNOSIS

Increasing numbers of patients are labeled as having celiac disease based on serological testing or even clinical presentation alone. A beneficial response to a gluten-free diet does not indicate celiac disease as it is not unusual for patients with irritable bowel syndrome and other conditions to benefit from such a diet. Individuals who have been diagnosed as having celiac disease without initial biopsy specimens obtained while on a gluten-containing diet should undergo additional testing including HLA testing and gluten challenge to confirm the diagnosis (Table 6.5). The optimum length of the gluten challenge has not been defined, but the recent literature suggests that serological and histological changes can be found as early as after one to two weeks of a diet containing at least 10 g of gluten per day (equivalent to four slices of bread). Sensitivity varies, however, and some patients quickly become ill on smaller amounts of gluten, while others, particularly those who have been gluten free for a longer time, will require a longer challenge. Typically, biopsies are obtained once the patient develops positive serologic studies, but a clinical response such as diarrhea may also be the basis for scheduling endoscopy. Most experts would recommend that small bowel biopsies are obtained even if there are no clinical or serological responses to the gluten change after a defined period of time, usually by six months.

## 8. COMPLICATIONS OF CELIAC DISEASE

Malignancy is the most feared complication of celiac disease, but more concerning than the risk of malignancy are other, more common complications of celiac disease that can develop when celiac disease is not recognized and/or treated. These include osteopenic bone disease, growth retardation in children, iron deficiency and other nutritional deficiencies. There are also issues related to fertility including increased rates of infertility, spontaneous abortions and intrauterine growth retardation that are associated with untreated celiac disease [21–24]. There is some suggestion that untreated celiac disease may be complicated by developing other autoimmune diseases at a higher rate than expected, but this may only be true in children, and even then, not all studies support this observation. Complications of the malabsorption associated with celiac disease include metabolic bone

disease, anemia and other manifestations of nutritional deficiencies. Celiac patients may also develop hyposplenism with splenic atrophy, Howell Jolly bodies, thrombocytosis and deformed erythrocytes. In general, these malabsorptive complications respond to the institution of a gluten-free diet and correction of nutritional deficits [52].

## 9. MORTALITY ASSOCIATED WITH CELIAC DISEASE

Various studies suggest that there is a small increase in mortality in subjects with celiac disease compared to the general population, which returns to baseline within a few years. In two recent studies the standardized mortality ratio was 2.0 [53, 54]. In another recent study the hazard ratio for all mortality was 1.31, and this fell to 1.17 the 1st year after treatment [55]. In an earlier study, five-year survival was the same for celiac patients as for the general population [56]. Corrao et al. performed a large study of Italian celiacs, which showed that there was a small increase in death rate returns to baseline in the first few years after diagnosis [53]. In this study increased mortality was observed in subjects with malabsorptive presentations if the diagnosis was delayed and in those poorly compliant with diet. The main cause of excess death in this study, as in others, was lymphoma

## 10. NON-RESPONSIVE AND REFRACTORY CELIAC DISEASE

Although continued ingestion of gluten is the most frequent cause of non-responsive celiac disease, other considerations include associated or complicating conditions (small bowel bacterial overgrowth, carbohydrate malabsorption, microscopic colitis) or an incorrect initial diagnosis. Failure to respond to a gluten-free diet or recurrence of symptoms on a gluten-free diet, particularly in an older patient, should also prompt a search for lymphoma provided that ingestion of gluten has been excluded as the cause of the symptoms. Refractory sprue is a presentation of celiac disease characterized as being unresponsive to dietary therapy, usually requiring immune modulating therapy and associated with a poor prognosis [57]. A subset of these patients with a band of subepithelial collagen present in small intestinal histological specimens is referred to as having collagenous disease. Other variants include structuring or ulcerative forms. It is thought that chronic stimulation of T cells leads to clonal expansion of IEL characterized by T cell TCR-$\gamma$ gene rearrangements [58]. Chromosomal abnormalities have been demonstrated in refractory sprue and in enteropathy associated

T cell lymphoma (EATCL) including partial trisomy of the 1q region in refractory sprue and gain of chromosome 1q and loss of heterozygosity at chromosome 9p21 in EATCL [59]. Uncontrolled studies show corticosteroids including budesonide, immunosuppressive agents and infliximab to be of benefit in refractory celiac disease [60, 61]. Elemental enteral or parenteral nutrition may be required to manage these patients. These patients should be evaluated for the development of EATCL as described below.

## 11. RISK OF MALIGNANCY IN CELIAC DISEASE

Patients with celiac disease have an increased risk of certain malignancies including intestinal T cell lymphoma, non-Hodgkin lymphoma of both T and B cell type occurring both in the intestinal and at extraintestinal sites, oropharyngeal and esophageal squamous cell cancers and intestinal adenocarcinoma [62]. Recent studies suggest the risk of lymphoma is much lower than earlier estimates and returns to baseline with dietary therapy [53, 63]. A recent large Swedish study of 12,000 patients with celiac disease or dermatitis herpetiformis (DH) in which cancer risk was assessed by standardized incidence ratios (SIR) demonstrated that SIR was increased for lymphomas, small bowel adenocarcinoma (~10-fold), oropharyngeal (SIR 2.3) and esophageal (SIR 4.2) squamous cell cancer and colon (SIR 1.5) [64]. Pancreatic and hepatobiliary cancer was also increased in celiacs. Increased lymphoma and leukemia rates were observed in DH. The increased rates of colon cancer noted in this study have not been found in other studies. Several studies, including that of Askling et al., have noted a decreased rate of breast cancer in celiac patients [55, 64, 65].

### *11.1. Enteropathy-Associated T Cell Lymphoma (EATCL)*

Earlier studies had shown increased relative risks of lymphoma in celiac disease and DH ranging from 50–100. However, recent studies indicate the risks are much lower, ranging from two to ten in both celiac disease and DH [62]. Celiac disease is associated with various subtypes of lymphoma, but the highest association is with T cell lymphoma. This has been referred to as enteropathy-associated T cell lymphoma (EATCL) as originally reported by Cellier and colleagues [66]. Celiac disease is responsible for 25% of T cell lymphoma, but the attributable risk for celiac disease for lymphoma overall is very small [67]. It is worth noting that when evaluating a patient with lymphoma for celiac disease there is an increased false-positive rate with tTG antibody

testing compared to endomysial antibody (EMA) in NHL. A recent study of the association of lymphomas with autoimmune and chronic inflammatory conditions indicates that there is a statistically significantly increased odds ratio (OR) for rheumatoid arthritis (1.5), primary Sjogren's syndrome (6.1), SLE (4.6) and celiac disease (2.1) [67]. For celiac disease and T cell lymphoma, the OR was 17 (95% CI, 6.3–46).

EATCL may develop in the setting of refractory celiac disease including ulcerative and collagenous forms. Symptoms suggesting the development of EATCL include malaise, anorexia, weight loss, diarrhea, abdominal pain and fevers [57, 68]. Physical findings can include fever, lymphadenopathy, skin rash, hepatomegaly or an abdominal mass. The tumor can occur at nodal or extranodal sites, and it may be multifocal. Often the lesions are ulcerative, and the tumor can frequently manifest as a perforation at the time of presentation or with chemotherapy. Survival from celiac-associated lymphomas is poor. Evaluation for possible EATCL should include an ENT evaluation, CT of the chest and a CT enteroclysis. Barium X-rays may also be performed. Capsule endoscopy and/or conventional or double-balloon enteroscopy are helpful in evaluating refractory celiac disease and can be used to diagnose EATCL. Endoscopically acquired mucosal or laparoscopic full thickness biopsies of the intestine are needed for diagnosis. Tissues should be sent for immunohistochemistry, T cell flow cytometry and PCR for TCR-γ gene rearrangements.

### *11.2. Small Bowel Adenocarcinoma*

Small bowel (SB) cancers also occur with increased frequency in patients with celiac disease. The true risk of SB adenocarcinoma is unknown, but the older literature suggested relative risks ranging to over 82. A more recently published study with a strong study design suggests that the risk of SB adenocarcinoma is increased approximately ten-fold in celiac disease [64]. Other recent studies report the risk of small bowel adenocarcinoma ranging from no increased risk [65] to a standardized mortality rate of 34 [69]. It is generally thought that there is no evidence for a polyp-cancer sequence in celiac disease-associated small bowel adenocarcinoma, but one report of seven cases of SB neoplasia showed three adenomas and four adenocarcinomas, with one being adjacent to a jejunal tubulovillous adenoma [70].

### *11.3. Prevention of and Screening for Malignancy*

Although there are no prospective randomized trials that address the hypothesis that a gluten-free diet protects against the development of

malignancy, the available literature does support this hypothesis. As reviewed in recent articles by Loftus and Loftus [71] and by Catassi et al. [62], studies published over several decades and from various countries indicate the risk of malignancies is reduced or decreases to baseline after being on a gluten-free diet. There are inherent methodological flaws with many of the studies including reliance on self-reporting of whether subjects were gluten free and to what degree they were able to comply with the diet over time. In spite of the limitations of the studies, the findings that a gluten free-diet reduces cancer risks are consistent with the observation that chronic inflammation is generally associated with an increased risk of malignancy and thus a reduction in immune stimulation on a gluten-free diet should be of benefit.

As in any condition where a disease is associated with a complication that might be detected earlier or even prevented by screening, celiac disease is one condition in which such screening may be considered. However, given the prevalence of the malignancies in the general population and the relatively small increased risks conferred by celiac disease, screening is not advocated. The incidence of non-Hodgkin lymphoma in western populations is 0.5–1 per million per year, and for small bowel adenocarcinoma it is estimated at 0.6–0.7 per 100,000 per year [62]. This situation is in contrast with ulcerative colitis where the risks of colon cancer are high in the general population, the relative risk is significant, and there is also a stage that precedes the development of cancer that screening may detect. In general, searches for malignancy in celiac disease are based on clinical presentations concerning the development of cancer. Although it would no longer be considered screening, the development of refractory celiac disease or other symptoms concerning malignancy would justify a search for EATCL as discussed above, as well as for intestinal adenocarcinoma.

## 12. MANAGEMENT ISSUES IN CELIAC DISEASE

### *12.1. The Gluten-Free Diet*

The management of confirmed celiac disease is a life-long diet that is devoid of gluten. While this seems like a simple treatment it is often difficult for patients to comply with this dietary restriction. Factors that contribute to non-compliance include the lack of readily available gluten-free foods, particularly when eating out of the home, the less acceptable taste of gluten-free products and the difficulties associated with preparing dishes with gluten-free ingredients [72].

Inadvertent ingestion of gluten may occur as a result of trace amounts of gluten in a wide variety of food stuffs and medications, contamination of gluten-free products with gluten during processing and misinformation about food contents on the part of manufacturers, restaurant staff and even well-meaning friends and relatives. The diet poses particular difficulties for children, teenagers and their parents. Newly diagnosed celiacs should be encouraged to join local chapters of the various national celiac organizations. Information supplied by certain of these organizations can be superior to that provided by physicians or even dieticians since these health care workers may not have sufficient opportunity to become familiar with the dietary care of celiac patients.

There is some controversy as to what constitutes a gluten-free diet. One standard defines a product as gluten-free when the total nitrogen content of the gluten containing cereal grains used in the product does not exceed 0.05 g per 100 g of these grains on a dry matter basis. Recent studies suggest that 10 mg of gluten or less per day can be considered safe, and the new FDA labeling will take this into account. Oats have been an area of controversy since in older studies avenin (oat prolamine) was shown to activate an immune response in intestinal biopsy specimens, yet a significant number of recent studies showed that oats were well tolerated in adult and pediatric celiac patients and that avenin does not induce Th1 responses in celiac tissues [35, 73–75]. There are reports, as noted above, that challenge whether this is always the case [36]. These suggest that a very small subset of celiacs may react to oat peptides. It is generally recommended that oats be omitted from the diet of newly diagnosed celiacs largely since there are issues of cross-contamination with most commercially available sources of oats, but oats are generally well tolerated in celiac patients in remission, and there is no strong evidence that oats should be excluded from the diet of those who tolerate them [76].

## *12.2. Other Nutritional Considerations*

Newly diagnosed patients with malabsorptive symptoms should adhere to a lactose-free diet for the first few weeks on a gluten-free diet. This time period will allow for healing of the intestinal epithelium and regeneration of intestinal lactase unless the patient has constitutive lactose intolerance in which case the patient should be maintained on a lactose-free diet. Adequate calcium intake must be insured, especially in this latter group of patients, since celiac patients are at risk of osteopenic bone disease [77]. Until their nutritional status is restored,

celiac patients may require supplemental nutrients including iron, folate and other vitamins and minerals.

### *12.3. Benefit of a Gluten-Free Diet*

Although general clinical experience and the literature suggest that most adult celiacs are not highly compliant with a gluten-free diet, most patients are symptom free in spite of continued gluten ingestion. As discussed above there is some evidence that the incidence of malignancy is reduced in celiac patients and those with DH who adhere to a gluten-free diet. Other benefits of a gluten-free diet include improvement of body size and composition, iron deficiency [52] and osteopenia. There is also the suggestion from some studies that a gluten-free diet may delay or prevent the development of other autoimmune disorders, although this is not supported by other reports [78]. The question of how much gluten is safe remains unanswered. In the absence of data to support specific recommendations, patients should be encouraged to stay free of dietary gluten wherever possible in order to induce and maintain remission and potentially prevent complications of the disease.

## 13. SCREENING FOR CELIAC DISEASE

Because of concerns relating to the complications of not recognizing celiac disease and leaving it untreated, screening for celiac disease has been advocated. The disease itself does meet established criteria for screening, but there are issues related to resources and also ethical considerations that weigh against widespread screening programs for detecting celiac disease. Screening has been advocated in some settings including relatives of those with celiac disease and in type I diabetics, but none of the recommendations for screening is without controversy [79–*91*].

## 14. PREVENTION OF CELIAC DISEASE

Given the growing rise in prevalence of celiac disease, there is interest in trying to prevent the development of celiac disease. There are studies that suggest breast-feeding and delayed introduction of gluten into the diet may reduce the risk of developing celiac disease [82, 83]. However, while these observations make sense, there are other reports that suggest early introduction of gluten in a defined period of time in infancy may also reduce the risk [84, 85]. There is also interest

in whether dietary changes such as increased consumption of strains of wheat that contain greater amounts of potentially immunogenic peptides could play a role in the apparent increase in celiac disease [86]. Further studies are needed to answer these questions.

## 15. CONCLUSION

Substantial advances have been made in our understanding of celiac disease, including the development of non-invasive techniques that can aid in the diagnosis and management of this disorder. Areas for further investigation include the pathogenesis and immunogenetics of celiac disease, and its relationship to other autoimmune diseases. Observations of an increased incidence of celiac disease have been attributed to increased amounts and the timing of the introduction of gluten in the diet of infants, and these warrant further examination. There is also a need for optimizing screening and diagnostic strategies and improving management, including the possible development of wheat strains deficient in gliadin [86]. New therapies are being developed and tested, including methods to digest gluten to non-immunogenic substances [87, 88], an inhibitor of zonulin and immunomodulatory therapies.

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# 7 Nutrition in Gastrointestinal Cancer

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***CONTENTS***



*Summary*

Gastrointestinal cancers can significantly impact nutrition status. Data indicate that the presence of malnutrition in cancer patients negatively impacts response to treatment, quality of life and survival. The nutritional support of patients with gastrointestinal cancer should be individualized and may be dependent upon anticancer treatment modality. Interventions with parenteral nutrition, enteral nutrition and immunonutrition are indicated in certain situations. Nutritional modifications may also be important in the prevention of cancer. This chapter will review some of the nutritional issues related to gastrointestinal cancer patients.

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## 1. INTRODUCTION

Cancers of the gastrointestinal system account for approximately 20 percent of all cancers and cancer deaths in the United States annually [1] (Table 7.1). Colorectal cancer alone is the fourth most common cancer and the third leading cause of cancer death in the United States [1]. Gastrointestinal cancers may be devastating and have lasting effects on weight, body composition and quality of life. Adequate nutrition care prior to, during and after treatment is vital. This chapter explores the role of diet in carcinogenesis, cancer treatment and cancer prevention.

## 2. DIET AND GASTROINTESTINAL CARCINOGENESIS

In 1981, Doll and Peto estimated that 35% of all cancer deaths may be attributable to diet and lifestyle factors (including exercise) [2]. More recently, Willett arrived at a similar estimate with narrower upper and

**Table 7.1**
**Estimated New Cases of Gastrointestinal Cancers and Cancer Deaths in the US in 2005 [1]**

| *Cancer* | *New cases* | *Cancer deaths* |
|---|---|---|
| Esophagus | 14,520 | 13,570 |
| Stomach | 21,860 | 11,550 |
| Small intestine | 5,420 | 1,070 |
| Colon | 104,950 | 56, 290* |
| Rectum | 40,340 | * |
| Anal | 3,990 | 620 |
| Pancreas | 32,180 | 31,800 |
| Liver and intrahepatic Duct | 17,550 | 15,420 |
| Gallbladder and biliary | 7,480 | 3,340 |
| Other | 5,210 | 2,400 |
| Total | 253,500 | 136,060 |

* Colon and rectal deaths combined

Adapted from: American Cancer Society. Cancer Facts and Figures 2005. Atlanta; American Cancer Society:2005.

lower boundaries (20–42%) [3]. It is important to consider the mechanisms by which dietary factors may influence GI cancer risk. First, the process of cancer development usually occurs over decades and may occur in response to the synergistic effects of multiple factors. This makes it difficult to identify specific dietary causes of cancer, and also obscures the relevant mechanisms. Furthermore, it is rarely possible to determine a dietary cause for an individual cancer. Tables 7.2 and 7.3 summarize some of the dietary components implicated in GI carcinogenesis. Both in-vitro and in-vivo studies have been helpful in elucidating the mechanisms of dietary carcinogenesis.

In-vitro investigations are very important for understanding the biochemical and molecular interactions between diet and carcinogenesis. Mutations in oncogenes are crucial for the development of cancer, and in-vitro studies have shown how dietary components may play a role in the generation of such mutations; food-based substances may also protect against such alterations [4]. Animal models help to generate hypotheses concerning biological effects of foods and food-based substances on GI carcinogenesis. Furthermore, animal models may be used to test mechanisms of carcinogenesis and of cancer prevention. Animal systems allow the design of experiments that require strictly defined dietary interventions under tightly controlled circumstances. Species differences, however, make it impossible to directly extrapolate these data to humans.

Epidemiologic studies are the primary source of information regarding the effects of foods and dietary substances on cancer risk [5]. However, these studies cannot control for all confounding factors. Exposures to exogenous and endogenous carcinogens including radiation, physical agents, bacteria and viruses impact carcinogenesis and may further complicate analysis of epidemiologically derived data [6]. Although case-control and human dietary intervention studies provide more specific information, these studies are expensive and difficult to carry out. Interventional dietary trials require years to test narrow sets of nutritional hypotheses. It is also unknown if the effectiveness of individual nutrients relies on a critical exposure period or are tumor specific [7]. Because of methodological difficulties with all of the methods for assessing the impact of diet on cancer risk, results need to be approached with caution [5].

Observations regarding diet types are more reliable than those regarding specific foods or nutrients. This is highlighted by several unsuccessful intervention studies. Individual nutrients (i.e., beta-carotene, vitamin E and vitamin A) previously identified as protective through epidemiologic studies have been found to be ineffective or

Table 7.2
Dietary Components Implicated in the Development of Gastrointestinal Cancer

| *Component* | *Relationship* | *Proposed mechanism* |
|---|---|---|
| Alcohol | Low "doses" (equivalent of 1–2 ounces of hard liquor): protective [12, 22]<br>Higher doses: increased risk [12] | Solvent for tobacco carcinogens; acetaldehyde (principal metabolite of alcohol) is likely carcinogenic [25, 135]; related micronutrient deficiencies [14]; direct hepatocyte toxicity [136]; reaction with MTHFR and subsequent antagonization of DNA methylation pathways [41] |
| Carbohydrate | Overall: decreased [28];<br>Simple carbohydrates: increase risk [12, 19, 137, 138] | Overall: association with lower fat intake [28];<br>Simple: leads to increases in IGF-1; association with high overall caloric intake [26]; associated with excess energy intake and decreased fruit and vegetable intake [12]; conversion of nitrate to nitrite [18, 19]; high glycemic load [32] |
| Red meat | Increased risk [12, 20, 41, 137, 138] | Formation of carcinogenic heterocyclic amines and nitrosamines [20, 139]; excess salt used in cooking damages the gastric mucosa and causes gastritis [27, 28] |
| Dietary fat | Conflicting [12, 28, 48, 140] | Formation of carcinogenic heterocyclic amines [21] and oxidative stress; high dietary fat intake associated with high meat intake [12]; alteration of cell membranes and enzymes [41] |
| Fruits and vegetables | Decreased risk [12–14, 27, 29, 137, 141] | Antioxidant, antiproliferative and anti-inflammatory constituents [12, 13, 142, 143]; bind bile acids; reduction of intestinal transit; increase in stool bulk [141] |

| | | |
|---|---|---|
| Micronutrients | Antioxidants: decreased [12] | Antioxidants: modulation of endogenous antioxidant systems [8]; decreases the ability of H-pylori to cause inflammatory damage [23, 24]; |
| | Zinc: decreased [12, 16] | Zinc: COX 2 overexpression [16]; |
| | Calcium: decreased [36–39] | Calcium: binds secondary bile acids and ionized fatty acids [36–38]; decreased colon epithelial hyperproliferation induced by bile and fatty acids [41]; |
| | Folate: conflicted [40, 142] | Folate: modulation of DNA methylation [142]; |
| | Lycopene: decreased [144] | Lycopene: inhibition of gap junction communication; activation of phase II enzymes; suppression of COX-2 synthesis; repression of IGF-1 GF activation [144]; |
| | Selenium: decreased [41] | Selenium: inhibition of prostaglandin E2 levels; enhancement of the peroxidation-inhibiting enzyme glutathione peroxidase; induction of apoptosis |
| Green tea | Decreased [12, 15, 34] | Intracellular antioxidant; inhibition of procarcinogen formation; suppression of angiogenesis and cancer cell proliferation [15, 30] |

even harmful when supplemented in human dietary trials [5, 8]. This may be due to the isolation of the nutrients from the whole food source, specific population characteristics or many other variables. Many healthful compounds are found in vegetables and fruits, and it is likely that these compounds work synergistically to exert a beneficial effect. There may be important, but unidentified components of whole foods that are not included in individual supplements. There is little

Table 7.3
Nutrients Implicated in Carcinogenesis by Site

| *Site* | *Protective* | *Carcinogenic* |
|---|---|---|
| Esophagus | Fruits and vegetables [12–14] | Alcohol [12, 14, 25, 135]<br>Red meat [12, 20]<br>Dietary fat [21] |
| Gastric | Fruits and vegetables [12, 14, 27, 29]<br>Green tea [15, 30] | Alcohol [12, 22, 25]<br>Red meat [27, 28] |
| Pancreatic | Fruits and vegetables [12, 142, 143] | Red meat [139] |
| Colorectal | Fruits and vegetables [137, 141]<br>Calcium [36–39]<br>Folate [40]<br>Green tea [15] | Alcohol [41] |
| Hepatic | Unknown | Alcohol [136] |

evidence that dietary supplements can reproduce the benefits of a well-conceived, nutrient-rich diet.

### *2.1. Dietary Components Implicated in Carcinogenesis*

Procarcinogenic factors in the diet include sedentary lifestyle, excess energy intake and specific dietary substances. Energy intake is positively correlated with cancer risk and mortality [9]. Interestingly, elevated BMI, an indicator of obesity and therefore a surrogate for excess energy intake, does not seem to influence cancer risk, whereas actual energy expenditure and energy intake significantly influence risk [10]. Epidemiologic studies indicate that cancers of the gastrointestinal tract are amongst the most susceptible to modification by dietary factors [11]. The mechanisms of dietary carcinogenesis fall into several categories: direct DNA damage (e.g., nitrites), cytochrome activation or inhibition (e.g., alcohol), carcinogen activation (e.g., pickled/salted foods), direct cytotoxicity (e.g., mycotoxins), oxidative damage (e.g., saturated fats), alterations in physiology (e.g., rice, dietary fiber) and hormonal effects (e.g., phytoestrogens).

### *2.2. Esophageal Cancer*

Several dietary compounds, including fruits and vegetables [12–14], green tea [12, 15], vitamin C [12] and zinc [12, 16], have been suggested as protective for esophageal cancer. Fruit and vegetables are postulated to decrease the production of nitrosamines and modulate the endogenous antioxidant systems [12–14]. Suboptimal fruit and vegetable consumption is associated with a lower intake of dietary fiber

and phytochemicals. These foods may provide site-specific benefits. For example, phytochemicals may be beneficial in gastric cancer prevention, whereas fiber is important in the sequestration and removal of procarcinogens in the colon and rectum [12].

The chief component of green tea, EGCG (epigallocatechin gallate) appears to have several mechanisms of action, including intracellular antioxidant, inhibition of procarcinogen formation and suppression of angiogenesis and cancer cell proliferation [15]. Green tea consumption may afford protection against the development of a number of GI cancers, including esophageal cancer [15]. Dietary substances that have been linked with an increased risk of esophageal cancer include alcohol, red meat, simple carbohydrates and dietary fat.

Smoked, broiled and charred foods and those rich in nitrites contain procarcinogens and carcinogens. Dietary intake of polycyclic aromatic hydrocarbons (PAHs), a family of toxicants found in cigarette smoke and contaminated foodstuffs, constitutes a major source of exposure in humans. PAHs have been found to be highly carcinogenic in laboratory animals with implications in breast, lung and colon cancers in humans [17]. Simple carbohydrate [18, 19] and red meat consumption [20] has been linked with production of nitrosamines, a possible procarcinogen. Similarly dietary fat [21] and red meat consumption [12, 20] is associated with increased intake of heterocyclic amines, another possible procarcinogen.

### *2.3. Gastric Cancer*

A definite relationship exists between h-pylori colonization and distal gastric cancer risk. Many of the dietary components implicated as chemoprotective to the stomach exert their effect via the control of the H-pylori infection. For example, the acidic nature of wine [22] and the antioxidant capacity of vitamin C [23, 24] appear to impede H-pylori growth. Alcohol [12, 22, 25], simple carbohydrates [26] and red meat [27, 28] appear to increase the risk of gastric cancer. Pickled and other salty foods also increase cancer risk by acting as co-carcinogens in the stomach, increasing oxidative stress and thereby inducing lipid peroxidation and cellular proliferation [27, 28]. Fruit, vegetable [12, 14, 27, 29] and green tea [15, 30] intake is associated with a decreased risk.

### *2.4. Pancreatic Cancer*

Dietary components that are implicated in pancreatic cancer exert their influence as factors for pancreatitis and diabetes mellitus. For example, excessive alcohol intake is associated with pancreatitis, which is a risk

factor for pancreatic cancer [31]. Similarly, excessive intake of simple carbohydrates exacerbates hyperglycemia in susceptible individuals, and diabetes is a risk factor for pancreatic cancer [32, 33].

### *2.5. Liver Cancer*

Other than alcohol-related cirrhosis, carcinogenesis in the liver appears to be influenced only minimally by dietary constituents [34]. Factors such as cirrhosis, HBV and aflatoxin contamination seem to exert more of an influence over carcinogenesis [35].

### *2.6. Colorectal Cancer*

Multiple micronutrients including calcium [36–39], vitamin D [39], folate [40] and selenium [41] appear to have colorectal chemopreventive properties. Calcium decreases colon epithelial hyperproliferation induced by bile and fatty acids [41], while vitamin D seems to modulate the effects of calcium. Folate is involved in the donation of methyl groups and the proper functioning of methyltetrahydrofolate reductase. Interestingly, it appears that folate supplementation in those individuals without cancer confers a protective effect; however, in those with neoplastic tissue, it may increase risk of cancer [39]. Selenium enhances the peroxidation-inhibiting enzyme glutathione peroxidase and promotes coloncyte apoptosis, which may afford protection against colon carcinogenesis [41].

It has been suggested that high dietary fat intake may increase colon cancer risk. The proposed mechanism involves dietary fat-enhanced secretion of primary bile acids, which are converted to more cytotoxic secondary and tertiary bile acids by colonic bacteria [42]. The correlation of dietary fat intake with cancer incidence is somewhat controversial [42]. Although initial studies indicated a link between high dietary fat intake and cancer, more recently several epidemiologic studies have indicated a weak or no association [3, 43].

## 3. WEIGHT LOSS IN GASTROINTESTINAL CANCER

### *3.1. Epidemiology*

The prevalence of weight loss and malnutrition in patients with gastrointestinal malignancies ranges from 40% to 87% [44, 45], depending upon tumor site and stage (Table 7.4). The presence of pre-treatment weight loss in patients with GI malignancies is a poor prognostic indicator [46].

Table 7.4
Incidence of Weight Loss in Gastrointestinal Cancer Patients

| *Site* | *Percentage* |
|---|---|
| Esophageal | 79% [45] |
| Gastric | 83–87% [44] |
| Pancreatic | 83% [44] |
| Colon | 54% [44] |

Subjects with advanced GI malignancies often experience large decreases (>50%) in muscle mass and protein content, as well as a 30%–40% loss in body fat [47]. Patients with solid tumors can lose as much as 1.34 kg of fat-free mass in 4 weeks [48]. Changes in body composition seem to affect symptom control and complication rates. Cancer patients with GI malignancies who experience losses of lean body mass have elevated complication rates associated with surgical interventions [49].

### *3.2. Mechanisms*

Multiple factors contribute to the weight loss observed in cancer patients [50, 51]. Weight loss can be attributed to the physiologic abnormalities associated with the tumor, such as malabsorption, obstruction, diarrhea and vomiting; these mechanisms are especially significant in patients with GI cancers. Host responses to the presence of a tumor, particularly through the generation of cytokines, can cause anorexia and altered metabolism. Side effects of anti-cancer treatments also contribute to anorexia and GI symptoms [50, 51]. For example, patients receiving radiation to the abdomen or pelvis can develop acute or chronic radiation enteritis, with resultant diarrhea and/or obstructive symptoms. Oral and gastrointestinal symptoms can cause changes in weight early in the course of cancer [52, 53]. Fatigue, depression, anxiety and pain may result in weight loss as well [50].

### *3.3. Cancer Cachexia*

Clinical features of cancer cachexia include host tissue wasting, anorexia, skeletal muscle atrophy, anergy, fatigue, anemia and hypoalbuminemia unresponsive to aggressive nutrition intervention [54, 55]. The cancer cachexia syndrome (CCS) involves a heterogeneous medley of physiological and metabolic derangements resulting in potentially life-threatening malnutrition [56, 57]. Cytokines, especially

tumor necrosis factor (TNF), interferon-γ (IFN-γ) and interleukins 1 and 6 (IL-1 and IL-6), are implicated in the development of specific symptoms associated with cachexia, such as anorexia and early satiety, as well as derangements in protein, carbohydrate and fat metabolism [55].

Although often seen in patients with advanced malignancies, CCS may be present in the early stages of tumor growth and may even be the iatrotropic stimulus [58]. The importance of CCS is highlighted by the prognostic significance of weight loss. For any given tumor type, survival is shorter in patients who experience pretreatment weight loss [44]. Early recognition and intervention to prevent worsening of CCS may afford the best opportunity to prevent its debilitating consequences [52, 59]. As discussed in Chap. 1, nutrition screening and assessment are vital to this early recognition of malnutrition and CCS.

Weight loss and malnutrition are problematic causes of symptom distress in cancer patients. Anorexia, weight loss and the associated fatigue as well as changes in body image can contribute to depression and decreased social interactions [59, 60]. It is especially relevant in relation to cancer patients to keep in mind that poor intake is rarely the most important cause of cancer-induced weight loss. Patients fed intravenously generally still lose weight, despite intake of adequate or even supraphysiologic calories. CCS is a metabolic syndrome that affects intermediary metabolism and substrate utilization, not just appetite. Therefore, particularly in patients with primary GI tract malignancies, it is rarely appropriate to undertake specialized nutrition support for anorexia or even GI obstruction unless there is a plan in place to treat the obstruction and the underlying cancer.

## 4. SPECIALIZED NUTRITION SUPPORT IN GASTROINTESTINAL CANCER PATIENTS

### *4.1. Dietary Interventions*

There are no controlled trials that suggest that any specific diet interventions assist curing cancer [5]. Many diets such as the macrobiotic diet, Gerson therapy and the Gonzalez protocol claim to cure cancer; there is no evidence that substantiates these dubious claims. Dietary interventions that may be of help should be directed at maintaining appropriate calorie and protein intake to prevent malnutrition in cancer patients [61]. Nutrition status can affect a cancer patient's surgical outcomes, QOL, complication rates and tolerance of therapy [5].

### *4.2. Specialized Nutrition Support*

In 2002, the American Society for Parenteral and Enteral Nutrition (ASPEN) published guidelines for the use of specialized nutrition support (SNS) in oncology patients. The guidelines provide evidence-based direction regarding the use of enteral nutrition (EN) and parenteral nutrition (PN) support.

Enteral nutrition (EN) has been associated with improvements in nitrogen balance and sometimes associated with weight gain in cancer patients [46]. PN has also been associated with improvements in nitrogen balance, and PN appears to more consistently cause weight gain [46]. However, this weight gain is primarily body fat [62] and produces little benefit above improving patient comfort and sense of well-being [46, 63]. Neither EN nor PN in cancer patients has beneficial effects on serum proteins, such as albumin when administered for 7–49 days. SNS appears to have less of a beneficial impact on cancer patients than non-cancer patients, likely because of the overriding importance of the underlying metabolic abnormalities induced by CCS [64].

Enthusiasm for the use of SNS in cancer patients has historically been tempered by concern that provision of nutrients may stimulate tumor growth and metastasis. Investigators have found that PN provision in excess of energy requirements more than doubles the rate of tumor growth in murine models [65–67]. Limited data are available in humans. An increase in tumor cell proliferation and protein synthesis has been observed in head and neck and colorectal cancer patients receiving PN, but it is unlikely that this is of clinical significance [68–70].

The American Gastroenterological Association (2001) and ASPEN (2002) hold similar positions on the use of PN in oncology patients [64, 71]. The use of SNS in cancer patients should generally be reserved for those circumstances where a patient is moderately or severely malnourished as a result of their cancer or cancer therapy or is likely to be unable to meet their nutritional requirements orally for more than 7–10 days, AND in whom future active therapy is planned to treat the underlying malignancy [64]. Table 7.5 presents the general contraindications to SNS. PN should not routinely be given to patients undergoing cancer chemotherapy or radiation therapy. ASPEN guidelines further state that PN is appropriate only in malnourished patients who are anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time, defined as greater than 7 to 10 days [64]. PN should be avoided in most cases if a patient's life expectancy is less than 40–60 days [64]. If intravenous therapy is felt

Table 7.5
**Contraindications to Specialized Nutrition Support in Cancer Patients [64]**

| *Enteral nutrition* | *Parenteral nutrition* |
|---|---|
| Malabsorption | Functional gastrointestinal tract |
| GI obstruction | Need for nutrition support <5 days |
| GI bleeding | Prognosis not consistent with aggressive nutrition support |
| Severe diarrhea | Inadequate vascular access |
| Intractable vomiting | Patient/caregiver request |
| Hemodynamic instability | Hemodynamic instability |
| Prognosis and/or social circumstances not consistent with aggressive specialized nutrition support | Profound metabolic and/or electrolyte disturbances |

From: Huhmann MB, Cunningham RS. Importance of nutritional screening in treatment of cancer-related weight loss. *Lancet Oncology*. 2005;6: 334–43.

appropriate in an individual with a life expectancy of less than 40 days, hydration therapy with intravenous fluids only is recommended [64].

### *4.3. Perioperative Nutrition Support*

In the 1980s and 1990s, numerous studies examined the relative benefits of enteral nutrition (EN) versus parenteral nutrition (PN) on outcome in cancer patients undergoing elective surgical resections with curative intent.

Early studies indicated reduced morbidity and mortality with perioperative PN supplementation in cancer patients, especially those with gastrointestinal malignancies [72]. However, these studies have been criticized because of the inclusion of heterogeneous populations, variable and likely suboptimal macronutrient provision, and inadequate sample sizes [5]. More recent studies of perioperative PN, primarily in GI cancer patients, indicate increased incidence of infection in patients receiving parenteral nutrition, with no improvement in survival [73–75]. The limited data in significantly malnourished GI cancer patients also indicate no benefit of perioperative PN over EN, but does indicate a benefit over standard isotonic fluids [73–75]. Risks associated with postoperative PN include increased infection rate, increased complication rate and increased cost [74, 76–78].

The many trials attempting to assess the efficacy of enteral nutrition in perioperative care are difficult to compare because of differing definitions of malnutrition and study designs. Enteral administration of nutrients postoperatively is generally acknowledged as the first choice [79] because it is theoretically more physiologic, may be

associated with fewer complications and is less expensive [80]. Arguments against EN include increased risk of gastrointestinal side-effects including diarrhea and vomiting. Enteral nutrition is generally well tolerated postoperatively, and complications can usually be corrected with temporary decreases in the enteral formula infusion rate.

Studies indicate EN has advantages over PN. An early meta-analysis indicated cost benefits of EN over PN [81]. Subsequent meta-analyses confirmed this economic advantage and also indicated a decreased risk of infection associated with EN in comparison to PN [64, 82]. Studies also indicate decreased intestinal permeability and lower incidence of hyperglycemia in comparison to the PN [83]. American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend that perioperative EN is indicated in patients anticipated to be unable to meet nutritional needs orally for a period of 7 to 10 days whose GI tract is functional [64].

Tolerance of SNS is often an issue in oncology care. Studies indicate that the incidence of diarrhea, distention, vomiting, and other side effects is decreased [74, 77] with the use of PN when compared to EN postoperatively; however, there are some reports that contradict this [76, 78, 84].

### *4.4. Perioperative Feeding Considerations*

Historically, oral and enteral feeding have been discouraged following GI surgical procedures, with "bowel rest" recommended to promote anastomotic healing and prevent nausea and vomiting [85]. More recently, it has become clear that GI function returns rapidly postoperatively in most patients, and intraluminal nutrients promote bowel hypertrophy and anastomotic healing [85]. Even in the absence of peristalsis, the small intestine regains the ability to absorb nutrients quickly after surgery. Early enteral nutrition in malnourished surgical patients is associated with improved wound healing, maintenance of gut function and improved gut immune function. It is also associated with decreased length of stay in intensive care [80, 85, 86]. Furthermore, early resumption of oral/enteral feeding is only occasionally associated with unwanted side effects such as nausea, vomiting, colic and anorexia.

Maintenance of nutrition status perioperatively can be facilitated by careful preoperative planning and creation of a postoperative nutrition care plan [82]. Failure to consider nutrition and diet issues perioperatively can result in lost opportunities to maintain nutrition status and to avoid nutrition related complications. The postoperative nutrition

care plan should be determined and discussed with the patient prior to surgery.

It has become commonplace to establish enteral feeding access during major gastrointestinal procedures [87, 88]. Facilitation of early enteral feeding in patients with moderate or severe preoperative malnutrition can improve surgical outcomes [5, 64, 89]. In patients with established preoperative malnutrition, the benefits of enteral access outweigh the risks of enteral access related complications [90]. Intraoperative placement of a gastrostomy or jejunostomy tube for enteral access should be strongly considered in patients who are malnourished preoperatively or in whom a prolonged period of poor oral intake is anticipated (7–14 days).

In addition to planning for access for nutrition support preoperatively, it is also important to discuss transition back to an oral diet. Upper gastrointestinal surgical resection may be associated with significant postoperative morbidity, including dumping syndrome, delayed gastric emptying, prolonged ileus, obstruction, gastroesophageal reflux and post-gastrectomy syndrome (dumping, fat maldigestion, gastric stasis and lactose intolerance) [91, 92]. Manifestation of these complications can lead to weight loss, malnutrition and increased mortality [93]. Preoperative education to inform patients of normal and abnormal postoperative events can assist them to play an active role in their recovery.

Nutrition education by a registered dietitian has become common place in many settings, including diabetes clinics and even some doctor's offices. For example, the high incidence of malnutrition in bariatric surgery patients [94] has prompted many insurance companies to require nutrition education by a registered dietitian preoperatively [95, 96]. Unfortunately, there are few data on the role of nutrition education in patients undergoing gastrointestinal cancer surgery. Several studies indicate that patients who receive preoperative education regarding expectations and pain management [97] experience less anxiety [98, 99] and pain [100, 101], have improved outcomes [102, 103] and increased satisfaction [104, 105].

### *4.5. Nutrition Support during Chemotherapy*

The routine use of PN during chemotherapy in GI cancer patients does not seem to improve patient outcomes [106, 107]. Bone marrow suppression, tumor response and patient survival are not improved in patients receiving adjuvant PN during chemotherapy [108, 109]. PN and EN do have a role in the primary treatment of malnutrition that may be seen as a side effect of chemotherapy, but should be reserved

for those patients for whom active treatment options remain and who are clearly malnourished and at risk for worsening malnutrition. It is important to mention that oncology patients appear to prefer PN to EN. The perceived comfort of IV feeding over tube feeding seems to strongly influence patients' choices in this matter [110].

### *4.6. Immunonutrition*

Multiple studies have investigated the impact of "immunonutrition" (EN supplemented with micro- or macronutrients) intended to preserve or improve immune function and thereby improve outcomes in GI cancer patients. Immune enhancing nutrients that have been explored in gastrointestinal cancer patients include omega-3 fatty acids (*n*3), glutamine (GLN), arginine (ARG), nucleic acids and combinations of these nutrients (Table 7.6). Meta-analyses have demonstrated improved outcomes (reductions in morbidity and mortality) with the use of immunonutrition perioperatively in patients undergoing major GI cancer resections [111, 112].

Glutamine (GLN), the most abundant amino acid in the human body, is an important substrate for rapidly proliferating cells such as lymphocytes, macro-phages, enterocytes, fibroblasts and renal epithelium [113]. There are limited data on the effectiveness of enteral GLN alone because it is commonly supplemented with other immunonutrients. One prospective, randomized study of perioperative parenteral GLN in colorectal cancer patients indicated improved nitrogen balance with glutamine supplementation [114].

The *n*-3 fatty acids, essential in the diet, favor production of prostaglandins in the 3-series ($PGE_3$) and leukotrienes in the 5-series, which are associated with improved immunocompetence and reduced inflammatory responses. Studies of enteral *n*-3 fatty acid administration performed in pancreatic cancer patients indicate that *n*-3 fatty acid supplementation in the range of 2–3 g per day help stabilize weight [115–117]. Parenteral n-3 fatty acid supplementation in colorectal cancer patients increases leukotriene 5 levels and decreases TNF levels [118].

Studies of ARG in combination with other immunonutrients indicate improved immune parameters and a decreased incidence of infection in patients undergoing elective upper and lower gastrointestinal surgery for cancer [119–121]. Patients with colorectal cancer receiving perioperative parenteral ARG experienced enhanced immune responsiveness when compared to controls [122].

Nucleotides, administered in the form of nucleic acids, seem to stimulate nonspecific parameters of immune function; the mechanism

Table 7.6
Studies of the use of Immunonutrients in Gastrointestinal Cancer

| *First author* | *Year* | *Study design* | *n* | *Results* | *Comments* |
|---|---|---|---|---|---|
| Arginine, RNA and omega-3 fatty acids | | | | | |
| Daly [66] | 1992 | EN vs. isEN | 85 | Improved nutrition and immune parameters, clinical outcomes in isEN group | Criticized because of post hoc grouping of endpoints |
| Senkal [145]<br>Kemen [145] | 1995 | EN vs. isEN; upper GI cancer | 42 | Improved nutrition and immune parameters in isEN group | No clinical endpoints |
| Daly [66] | 1995 | EN vs. isEN; upper GI cancer | 60 | Improved immune parameters, clinical outcomes in isEN group | |
| Braga [146] | 1996 | Pre-op, oral EN vs. isEN; colorectal and stomach cancer | 40 | Improved nutrition and gut function parameters in isEN group | No clinical endpoints |
| Heslin [147] | 1997 | Intravenous crystalloid vs. isEN; upper GI cancer surgery | 195 | Trend toward increased morbidity, mortality in isEN group | isEN outcomes not attributable to jejunostomy-related complications. Mean volume of isEN 300 ml/day |
| Braga [148] | 1998 | PN vs. EN vs. isEN; gastric and pancreatic cancer | 166 | Increased incidence of cardio-pulmonary complications in PN group. Lower severity of post-op infections and shorter LOS in malnourished isEN group compared to PN group. Earlier return of bowel function in EN groups | 78% of subjects classified as malnourished pre-op |

| | | | | | |
|---|---|---|---|---|---|
| Di Carlo [77] | 1999 | PN vs. EN vs. isEN; pancreatic cancer | 100 | Decreased morbidity, infections, LOS in the isEN group. Earlier return of bowel function in EN groups | EN not tolerated in 16% of patients |
| Senkal [121] | 1999 | Pre-op and post-op Oral isEN + SOD vs. pre-op and post-op oral EN + SOD; upper gastrointestinal cancer | 154 | Decreased infections; lower cost of complications | No information on pre-operative nutrition status |
| Gianotti [119] | 2002 | Pre-op isEN + SOD vs. pre- and post-op isEN + SOD vs. SOD alone; cancer of the gastrointestinal tract | 305 | Decreased post-operative infections and shorter LOS in isEN groups | Malnourished patients excluded |
| Braga [119] | 2002 | Pre-op oral isEN = SOD vs. pre-op and post-op isEN + SOD vs. pre-op oral EN + SOD vs. SOD; colorectal cancer | 200 | Improved immune response, gut oxygenation and microprofusion in both isEN groups | Primarily well-nourished patients |
| Farreras [120] | 2005 | Early post-op EN vs. early post-op isEN; gastric cancer | 66 | Lower episodes of surgical wound complications; improved parameters of wound healing | |

*(Continued)*

Table 7.6
*(Continued)*

| *First author* | *Year* | *Study design* | *n* | *Results* | *Comments* |
|---|---|---|---|---|---|
| Arginine, glutamine, and n-3 fatty acids | | | | | |
| Wu [38] | 2001 | Post-op EN vs. post-op supplemented EN; gastrointestinal cancers | 48 | Improved immune parameters, decreased pro-inflammatory cytokines in immune-supplemented EN group | |
| Omega-3 fatty acids | | | | | |
| Fearon [116] | 2001 | SOD + standard oral supplement vs. SOD + n-3 FA enriched liquid supplement; pancreatic cancer | 200 | Gain of weight and LBM in n-3 fatty acid group | |
| Jatoi [115] | 2004 | n-3 FA enriched oral supplement vs. megestrol acetate vs. n-3 FA enriched oral supplement + megestrol acetate; incurable malignancies | 421 | Weight stabilization and improved appetite in both groups; no effect on mortality or QOL | |
| Moses [117] | 2004 | SOD + standard oral supplement vs. SOD + n-3 FA enriched oral supplement; pancreatic cancer | 24 | Increased physical activity and total energy expenditure in n-3 fatty acid group. | Patients with BMI > 30 excluded |
| Klek [149] | 2005 | PN vs. PN + GLN vs. PN + n-3 FA; gastric cancer | 105 | Improved prealbumin and TLC in GLN and n-3 FA group; shorter hospital stay | |

SOD, standard oral diet; isEN, immunonutrients supplemented enteral nutrition

of action is not understood [70]. There was no effect on survival with nucleotide supplementation in colorectal cancer patients in one study [123].

## 5. NUTRITION AND GASTROINTESTINAL CANCER PREVENTION

### *5.1. Chemoprevention*

Chemoprevention refers to the prevention of cancer or cancer recurrence through the use of drugs, vitamins or other agents [124]. Some of the mechanisms by which dietary components may cause chemoprotective effects include: cytochrome activation or inhibition (e.g., alcohol), carcinogen detoxication (e.g., yellow-green vegetables), antioxidant activity (e.g., vitamins A, C, and E), immune stimulation (e.g., arginine), alterations in physiology (e.g., fiber) and hormonal effects (e.g., phytoestrogens). The following is a brief description of the chemopreventive mechanisms of some specific dietary behaviors and substances.

### *5.2. Dietary Approaches*

Obesity is a risk factor for all of the gastrointestinal cancers [125–128]. Several overall diet approaches have been recommended to prevent gastrointestinal cancer. The American Cancer Society and the American Institute for Cancer Research provide evidence-based recommendations to maintain a healthy weight [129]. These dietary modifications include a plant-based diet, low in fat, with adequate exercise and physical activity [129]. In practice these general recommendations alone do not provide enough detail for individuals to make specific changes to the diet, but they do provide suggestions.

### *5.3. Calcium*

As mentioned previously calcium and vitamin D appear to have chemopreventive effects in the colon and rectum. Calcium appears to decrease colon epithelial hyperproliferation [41], while vitamin D seems to modulate the effects of calcium. Calcium binds secondary bile acids and ionized fatty acids [36–38] that stimulate epithelial cell proliferation of the colorectal mucosa [130]. Initial studies of the impact of calcium on colorectal cancer risk were conflicting [131]. The synergistic effect of vitamin D and calcium was elucidated in the Calcium Polyp Prevention Study where the benefits of calcium supplementation were observed only in individuals with high serum 25-hydroxy

vitamin D levels [132]. It appears that both nutrients are necessary for efficacy in polyp prevention.

### *5.4. Fiber*

The mechanisms through which fiber appears to prevent cancer are site dependent. For example, in the colon, fiber appears to sequester potential carcinogens and bile acids, decrease transit time and promote the production of short chain fatty acids [133]. On the other hand, in the esophagus and stomach fiber's nutrient scavenging properties appear to be important [134].

### *5.5. Green Tea*

Green tea's protective effects span the gastrointestinal tract. The chief active components identified as chemoprotective in green tea are catechins, especially EGCG (epigallocatechin gallate). Other components of green tea include flavonols, caffeine, phenolic acid, thearubins and flavor compounds [15]. A review of the literature would suggest that green tea may be a panacea for all ills with proposed effects including anti-oxidative, anti-inflammatory, anti-mutagenic, anti-carcinogenic, antiangiogenic, apoptotic anti-obesity, hypocholesterolemic, anti-arteriosclerotic, anti-diabetic, anti-bacterial, anti-viral and anti-aging [15]. The anticancer mechanisms proposed for the chemoprotective effect in the GI tract include inhibition of H-pylori, prevention of chronic gastritis, reduction of nitrosomine compounds, decreased conversion of carcinogens and modification of intestinal microflora [15]. Studies have indicated there may be a benefit in the prevention of esophageal [12], gastric [30], hepatic [34] and colorectal [15] cancers.

## 6. CONCLUSION

- Multiple factors play a role in gastrointestinal carcinogenesis including age, genetic factors and possibly food substances.
- Mechanisms of dietary carcinogenesis fall into several categories: direct DNA damage, cytochrome activation or inhibition, carcinogen activation, direct cytotoxicity, oxidative damage, alterations in physiology and hormonal effects.
- Weight loss, prevalent in gastrointestinal cancer patients, results from multiple etiologies including physiologic abnormalities associated with the tumor, host response and side effects of anti-cancer treatment. This weight loss can cause symptom distress and decreased quality of life.

- The use of SNS in cancer patients should generally be reserved for those circumstances where a patient is moderately or severely malnourished as a result of their cancer or cancer therapy or is likely to be unable to meet their nutritional requirements orally for more than 7–10 days, and in whom future active therapy is planned to treat the underlying malignancy.
- Preoperative planning for postoperative nutrition care, feeding method and access is imperative for the maintenance of optimal nutrition status and therefore improved wound healing and maintenance of gut function.
- Immune-enhancing diets that contain omega-3 fatty acids (*n*3), glutamine (GLN), arginine (ARG) and nucleic acids in combination may be beneficial perioperatively in patients undergoing major GI cancer resections.
- Chemoprevention studies are now underway to prevent the development of gastrointestinal cancers. Dietary components may cause chemoprotective effects through a variety of mechanisms including: cytochrome activation or inhibition, carcinogen detoxication, antioxidant activity, immune stimulation, alterations in physiology and hormonal effects.

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# 8 Management of the Short Bowel Syndrome

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***CONTENTS***



*Summary*

Short bowel syndrome (SBS) results from extensive intestinal resection. It is associated with significant morbidity and mortality, a reduced quality of life and a high rate of health care resource utilization. The management of patients with SBS requires a multidisciplinary approach that includes dietary, fluid and pharmacological management, co-morbid disease management and, occasionally, surgery. An understanding of the physiological alterations that occur in SBS patients is useful to understand the therapeutic strategies employed. In the pages that follow, these physiological alterations are discussed as are the roles of diet and fluids, specialized nutrition support, medications including trophic factors and surgery in the care of these complex patients.

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Short bowel syndrome (SBS) is a malabsorption syndrome resulting from extensive intestinal resection [1, 2]. In infants, necrotizing enterocolitis and congenital intestinal anomalies are frequently responsible. In older children and adults, multiple resections for Crohn's disease and massive resections due to catastrophic mesenteric vascular events, radiation enteritis, adhesive obstruction and trauma represent the more common causes of SBS [3]. These patients frequently experience chronic diarrhea, dehydration, and macro- and micronutrient deficiencies often requiring enteral or parenteral nutrition support at home. It has been demonstrated, using nutrient absorption studies, that patients who absorb $<1.4$ kg/day of wet weight or $<84\%$ of their calculated energy needs will likely require parenteral fluid and/or nutrition support [4]. This typically translates into a patient with $<50$–$70$ cm of small bowel when the colon is intact, or $<100$–$150$ cm of small bowel when the colon is absent [5]. For practical purposes, in adults, SBS can be defined as the presence of $<200$ cm of the remaining small intestine. In infants, the diagnosis of SBS relies less on an anatomical definition and more on a functional definition. The amount of resection required to produce malabsorption in infants varies with factors such as age, the presence or absence of an ileocecal valve and length of residual colon [6].

**Key Words:** Short Bowel Syndrome, Multidisciplinary Treatment, Parenteral Nutrition, Intestinal Transplantation

The prevalence of SBS is unclear. A 1997 European survey indicated a point prevalence of home parenteral nutrition (HPN) use of about 4 per million, of whom approximately 35% had SBS [7]. In the United States, the annual prevalence of HPN use was estimated at about 120 per million, of whom approximately 25% had SBS [8]. These numbers likely underestimate the prevalence of SBS as they do not reflect patients with SBS who never required HPN or were able to be successfully weaned from parenteral nutrition (PN). The difference in HPN use between the US and Europe may reflect differences in both the calculation of the prevalence of HPN patients and in the ease of accessibility of HPN in the US. Importantly, there is no single reliable database available to precisely capture the number of SBS patients on HPN in either the US or Europe.

While SBS is clearly uncommon, it remains an important clinical problem due to its effect on these patients' quality and duration of life, the high rate of associated complications and the subsequent high costs involved in the their care [8]. Quality of life has been shown to be worse in HPN patients, many of whom had SBS, compared to SBS patients not requiring PN [9]. Table 8.1 lists complications occurring

**Table 8.1**
**Complications in Short Bowel Syndrome Patients**

| |
|---|
| Central venous catheter-related |
| Infection |
| Occlusion |
| Breakage |
| Central vein thrombosis |
| Parenteral nutrition-related |
| Hepatic |
| Biliary |
| Bowel anatomy-related |
| Malabsorptive diarrhea |
| Malnutrition |
| Fluid and electrolyte disturbances |
| Micronutrient deficiency |
| Essential fatty acid deficiency |
| Small bowel bacterial overgrowth |
| D-lactic acidosis |
| Oxalate nephropathy |
| Renal dysfunction |
| Metabolic bone disease |
| Acid peptic disease |
| Anastomotic ulceration/stricture |

in SBS patients that can be related to either the altered bowel anatomy or its treatment [1, 5, 10]. With respect to survival, studies from France and the US have demonstrated 2-year and 5-year survival rates for SBS at over 80% and 70%, respectively [11, 12]. Furthermore, the study from France reported PN-dependency at 2 years of 49% and 45% at 5 years [12]. Survival rates were lowest in the end-jejunostomy and ultra-short small bowel groups. Other factors affecting survival include the patient's age, primary disease process, co-morbid diseases, presence of chronic intestinal obstruction and the experience of the team managing the patient [13].

## 1. ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The proximal 100 to 200 cm of the jejunum is the primary site of carbohydrate, protein and water-soluble vitamin absorption [14]. Fat absorption occurs over a larger length of small bowel, a length

that increases as the amount of fat ingested increases. The junctions between jejunal epithelial cells are relatively large compared to other areas of the bowel, allowing rapid flux of fluids and nutrients so that the jejunal contents can become iso-osmolar. As a result, the concentration of sodium in jejunostomy fluid is about 100 mEq/l (range, 90–140). Sodium absorption in the jejunum can only occur against a concentration gradient, is dependent upon water fluxes and is coupled to the absorption of glucose [15].

In contrast to the jejunum, the ileum has tighter intercellular junctions [15]. This leads to less movement of water and sodium. The active transport of sodium chloride allows for significant fluid reabsorption and the ability to concentrate its contents. The ileum is also the primary site of carrier-mediated bile salt and B12 absorption and is the site of production of many gastrointestinal (GI) hormones such as glucagon-like peptides 1 and 2 and peptide YY. These GI hormones are important for control of bowel motility and growth [16]. Although it is commonly believed that the ileocecal valve is beneficial in slowing transit and preventing reflux of colonic contents into the small bowel, studies in patients who have previously undergone ileocecal valve excision have not confirmed these benefits [17, 18]. Reports suggesting a benefit due to the presence of the ileocecal valve may in fact reflect the retention of a significant length of terminal ileum.

Knowledge of the remaining small bowel length can be useful to predict the clinical outcome in SBS patients. Nevertheless, establishing an accurate estimation of bowel length is often difficult. While information from operative reports is preferred, such notes frequently record the amount of bowel removed rather than the amount remaining. A barium contrast small bowel series may provide an estimate of bowel length and is useful to delineate other structural features such as the presence of bowel dilatation [23]. The normal small bowel length depends upon the measurement method used, but typically ranges from about 300 to 800 cm in adults and between 200 and 250 cm in full-term infants at birth [24]. The large range of small bowel length in humans underscores the importance of being aware of the small bowel length remaining following a resection rather than the length of small bowel removed. Importantly, when considering small bowel length, measurements begin at the duodeno-jejunal flexure.

Anatomical factors that affect the outcome of the SBS patient include not only the length, but also the region of the remaining small intestine and the presence of the colon. The ileum is capable of both structural and functional adaptation, while the jejunum mainly adapts

functionally (see Intestinal Adaptation) [25, 26]. As a result, a jejunal resection is generally better tolerated [13]. Unfortunately, in most patients with SBS, the ileum has been resected, leaving only a portion of jejunum, often in combination with a portion of the colon. There is evidence to support functional small bowel adaptation in those with a jejuno-colic anastomosis, but not an end-jejunostomy [26, 27]. The presence of the colon has clearly been shown to be beneficial in SBS patients given its ability to absorb water, electrolytes and fatty acids, slow intestinal transit and stimulate intestinal adaptation. It has been suggested that, in terms of need for PN, the presence of at least half of the colon is equivalent to about 50 cm of small bowel [27]. It has also been suggested that those adult SBS patients with a jejuno-colic anastomosis who have at least 100 cm of jejunum may not require long-term PN, while most adult SBS patients who have <50 cm of jejunum attached to colon will require long-term PN [13, 27]. Similarly, those without a colon and <100 cm of jejunum are likely to require permanent PN. In comparison to adults, infants with less than 30 cm of small bowel are unlikely to be weaned from parenteral nutrition.

The colon plays a vital role in fluid and electrolyte reabsorption with a capacity to absorb up to 6 l daily [19]. Complete loss of the colon often leads to problems with dehydration and electrolyte abnormalities for SBS patients. Enteroglucagon, neurotensin and peptide YY are produced in the proximal colon (and ileum) and are responsible for the jejunal, ileal and colonic brake phenomena that slow small intestinal transit in response to fat intake [16, 20, 21]. In addition to the resorptive capabilities of the colon, bacterial fermentation of malabsorbed carbohydrates to short-chain fatty acids with subsequent absorption in the colon provides an additional energy source which can be substantial, up to 1,000 kcal daily [22].

In general, a SBS patient will have one of the following bowel anatomies: jejuno-colic anastomosis, end-jejunostomy or jejuno-ileocolonic anastomosis. Patients with a jejuno-colic anastomosis rarely have an ileocecal valve. Patients with a jejuno-ileal anastomosis have the best prognosis; however, this anatomy is the least common. Patients with an end-jejunostomy are the most difficult to manage and are most likely to require permanent parenteral support [13].

## 2. INTESTINAL ADAPTATION

Following massive intestinal resection, three distinct clinical stages have been described [28]. The first stage is characterized by large fluid and electrolyte losses and generally occurs over the first few

weeks following resection. In the second stage, a shift of emphasis to nutritional support is the primary concern. This stage may last for up to 2 years, and it is during this time that most adaptation and most PN weaning occur. Stage three is considered a homeostatic phase where no further adaptive changes occur.

Intestinal adaptation refers to a process following intestinal resection in which the remaining bowel undergoes a variety of macroscopic and microscopic changes in response to a variety of stimuli (Table 8.2), in order to increase its ability to absorb fluid and nutrients [29, 30]. Both morphological (i.e., structural) and functional intestinal adaptive changes can occur depending upon the extent and site of the intestine removed and the nutrient components of the diet. Changes described in structural adaptation include an increase in villus height, crypt cell depth and enterocyte number, while functional adaptive changes include modifications of the brush border membrane fluidity and permeability, up- or down-regulation of carrier-mediated transport and a slowing in the rate of transit allowing increased time for absorption to occur [31].

It is important to recognize that most investigations on intestinal adaptation following bowel resection have utilized animal models, and, importantly, few studies have confirmed these adaptive responses in humans. In addition, most studies investigating the process of adaptation have utilized animal models with a jejuno-ileal anastomosis; therefore, the physiological and structural changes that occur are of unclear clinical relevance to humans with SBS who uncommonly have this bowel anatomy. Furthermore, while animal intestinal

**Table 8.2**
**Factors Affecting Intestinal Adaptation**

| |
|---|
| Hyperphagia |
| Remaining bowel anatomy |
| Colon present |
| Ileum present |
| Luminal factors |
| Nutrients |
| Pancreaticobiliary secretions |
| Hormones/growth factors |
| Trophic |
| Antimotility |

adaptation is characterized by epithelial hyperplasia, human intestinal adaptation appears to be primarily associated with an increase in the absorptive function of the enterocyte irrespective of morphological changes [32–34].

## 3. TREATMENT

The care of patients with SBS requires a comprehensive approach and attention to detail. Although a multidisciplinary approach [35] is preferred, it is important for a physician experienced in the care of patients with intestinal failure to oversee and guide the evaluation and management of these highly complex patients.

## 4. ROLE OF DIET AND FLUIDS

For reasons previously discussed, SBS patients would be expected to differ in their response to dietary manipulation depending upon their bowel anatomy, specifically, the presence or absence of a colon [36, 37]. Norgaard and colleagues compared the effect of a high carbohydrate (60%), low fat (20%) diet with a high fat (60%), low carbohydrate (20%) diet in a small number of SBS patients with a colon in continuity [37]. They found that the high carbohydrate, low fat diet reduced fecal calorie loss and increased overall energy absorption (69% vs. 49%). In addition, the high carbohydrate, low fat diet seemed to result in improved wet weight absorption. In contrast, when they compared the same diets in SBS patients without a colon, they found that the high carbohydrate, low fat diet resulted in no improvement in energy or wet weight absorption [37]. Both McIntyre et al. and Woolf et al. have also demonstrated that end-jejunostomy patients do not benefit from dietary modifications [36, 38]. Indeed, a constant proportion of dietary fat is absorbed in the end-jejunostomy patient; therefore, more is absorbed when more is consumed. Because nitrogen absorption is least affected by the decreased absorptive surface in SBS patients, no change in dietary protein is generally necessary and, specifically, the use of peptide-based diets in these patients is unnecessary.

Because of the limited experimental evidence relevant to humans regarding the importance of luminal nutrients in the management of SBS, there is limited consensus on the importance of the oral diet in the management of SBS. Nevertheless, clinical experience confirms the important role that diet plays in the successful management of these patients and further suggests that with appropriate follow-up and compliance, this can result in the long-term reduction of PN

needs while maintaining nutrition and hydration status in some SBS patients. The long-term success of an optimized diet requires extensive education and monitoring to maintain compliance and needs to be translated into foods and meal patterns that meet the individual's preferences, lifestyle and, in children, developmental age [39]. The establishment of daily calorie and fluid intake goals for the patient followed by careful follow-up and adjustments based on tolerance as determined by the development of symptoms, stool output, micronutrient levels, weight and hydration status is critical. Individual calorie goals can generally be estimated using the calculated resting energy expenditure (e.g., Harris-Benedict estimation) multiplied by activity and malabsorption factors. In general, most stable adult SBS patients absorb only about one-half to two-thirds as much energy as normal; thus, dietary intake must be increased by at least 50% (i.e., hyperphagic diet). The increased quantity of food tends to best tolerated when consumed throughout the day in five to six meals periods. Supplemental tube feeding may be useful in selected patients of any age to meet their calorie needs, particulary when trying to wean PN [40]. Clinical experience suggests that nocturnal gastric tube feeding of a semi-elemental or polymeric formula administered continuously via an infusion pump in small quantities may be better tolerated than bolus tube feeding due to greater absorption of nutrients and a reduced occurrence of osmotic diarrhea. In infants and children, small oral feedings should be used in conjunction with tube feeding as they are necessary at developmentally appropriate times to prevent eating disorders, such as oral food aversion, that may arise later.

The optimal fluid components of the diet also depend upon the remaining bowel anatomy (Table 8.3). Because of the regional differences in water and sodium handling described previously, those SBS patients without a colon generally require the use of a glucose-electrolyte oral rehydration solution (ORS) to enhance absorption and reduce secretion, whereas most of those patients with a colon can maintain adequate hydration without excessive fluid loss with hypotonic fluids. Nevertheless, ORS may still be of value in the SBS with a colon and, as long as sufficient sodium is present in the diet, the amount of sodium in the ORS may not need to be as great. The ingestion of an ORS with a sodium concentration from 90 to 120 mEq/l has been shown to provide optimal jejunal absorption [41, 42]. Examples of such solutions include Oral Rehydration Salts (Jianas Brothers Packaging Co., Kansas City, MO; jianasp@aol.com) and Cera-Lyte (CeraProducts, LLC, Jessup, MD; www.ceralyte.com). One to three liters of such fluid daily, sipped throughout the day, may

**Table 8.3**
**Diet and Fluid Recommendations in Short Bowel Syndrome**

| | *Colon present* | *Colon absent* |
|---|---|---|
| Carbohydrate | 50–60% of caloric intake<br>Complex carbohydrates | 40–50% of caloric intake<br>Complex carbohydrates |
| Fat | 20–30% of caloric intake<br>Ensure adequate essential fats<br>MCT/LCT | 30–40% of caloric intake<br>Ensure adequate essential fats<br>LCT |
| Protein | 20–30% of caloric intake | 20–30% of caloric intake |
| Fiber | Net secretors<br>Soluble | Net secretors<br>Soluble |
| Oxalate | Restrict | No restriction needed |
| Fluids | ORS and/or hypotonic<br>Avoid hyperosmolar | ORS<br>Avoid hyperosmolar |

MCT = medium-chain triglycerides
LCT = long-chain triglycerides
ORS = oral rehydration solution

be needed to maintain adequate hydration. While fluid composition is less important in those with a colon, adequate dietary sodium should be provided [43]. Regardless of bowel anatomy, hyperosmolar fluids such as regular soda and fruit juices should be avoided, as they will aggravate stool losses. While lacking evidence to support this practice, clinical experience suggests that those patients who tend to experience bowel movements shortly after eating (i.e., dumping) may benefit from avoiding drinking fluids during meals [38]. Parenteral fluids will be necessary if the ostomy output continues to exceed fluid intake ("net secretors").

The provision of complex macronutrients in the diet of SBS patients is preferred (Table 8.3). Complex carbohydrates reduce the osmotic load and potentially exert a positive effect on the adaptation process. Because the proximal jejunum is rarely resected in SBS patients, lactose is generally well tolerated [44] and should not be restricted unless the patient is clearly intolerant, as milk-based products provide an important source of calories and calcium. Concentrated sugars, fruit juices in particular, should be avoided as they generate a high osmotic load and potentiate stool output. With respect to protein, those with high biological value such as those found in beef, pork, poultry and fish are preferred. For reasons described previously, the restriction of fat to 20%–30% of the daily calories is recommended in only those adult

SBS patients with a colon. This results in a reduction in steatorrhea, magnesium and calcium loss and a reduction in oxalate absorption. Normally, dietary oxalate binds to calcium and is excreted in the stool; however, in the setting of fat malabsorption, calcium binds to fatty acids leaving oxalate free to pass into the colon to be absorbed and then filtered by the kidney. In the kidney, oxalate binds to calcium, resulting in oxalate nephropathy. Therefore, oxalate restriction is important in those SBS patients with a colon in order to decrease the risk of oxalate nephropathy that may occur in up to 25% [27]. Examples of foods and beverages high in oxalates are listed in Table 8.4 [1].

Medium-chain triglycerides (MCT) are an alternative energy source and are absorbed from both the small and large intestine. In a randomized, controlled, crossover study, 19 SBS patients (10 with colon and 9 without colon) were assigned to a long-chain triglyceride (LCT) or a MCT + LCT group [45]. The diet enriched with MCT resulted in improved overall energy and fat absorption in the patients with a colon only. The improvement in fat absorption in the group without a colon was offset by malabsorption of the other macronutrients. MCTs do not require digestion by pancreatic enzymes for their absorption and may be useful in the presence of bile acid or pancreatic insufficiency [45]. However, clinical experience suggests MCTs are not well tolerated long term. Furthermore, MCT have a slightly lower caloric density than LCT (8.3 vs. 9 kcal/g), do not contain essential fatty acids, exert a greater osmotic load in the small bowel and have less stimulatory effect on adaptation compared to LCT. The provision of essential fatty acids (e.g., safflower oil and soybean oil) is important

**Table 8.4**
**Examples of Oxalate-Containing Foods and Beverages**

| |
|---|
| Beverages |
| Colas, tea, instant coffee, draft beer, ovaltine, cocoa |
| Nuts |
| Almonds, peanuts, cashews, pecans, nut butters |
| Fruits |
| Apricots, cherries, figs, concord grapes, orange, pear, rhubarb, strawberries, prunes, lemons |
| Vegetables |
| Artichoke, baked and green beans, beets, red cabbage, okra, green peppers, parsley spinach, tomatoes |
| Other |
| Grits, bran cereal, tofu, black olives, chocolate, French fries, whole wheat bread |

as deficiencies are common, particularly in the setting of low fat diets and fat malabsorption [46]. Finally, soluble fiber supplementation may be useful given its potential effect on enhancing adaptation and slowing gastric emptying; although it may result in increased gas and bloating for the patient [1]. The energy derived from bacterial fermentation of soluble fiber, yielding short chain fatty acids that are absorbed in the colon, may be substantial [47]. While anecdotal reports of dietary supplementation with soluble fiber suggest improvement in nitrogen absorption [48], others have described an adverse effect of soluble fiber on fat and glucose absorption [49, 50].

## 5. ROLE OF PHARMACOLOGICAL MANAGEMENT

The long-term use of antimotility and antisecretory agents is frequently necessary to control stool losses in SBS. Massive enterectomy is associated with a transient gastric hypergastrinemia and hypersecretion [51]. $H_2$ receptor antagonists and proton pump inhibitors may be beneficial, particularly during the first year following resection, in reducing the volume of gastric secretions and, thus, stool losses. The acidity can also lead to peptic complications and/or impairment in the function of digestive enzymes [52]. As gastric acid has a role in suppressing overgrowth of upper intestinal bacteria, acid-suppressing agents should be used sparingly in conditions of bacterial overgrowth [53]. Uncommonly, certain patients, particularly the net secretors such as those with high-output jejunostomies, may benefit from treatment with the somatostatin analogue, octreotide. Octreotide reduces production of a variety of gastrointestinal secretions and slows jejunal transit [54, 55]. Open-label studies suggest clinical benefit of both short-acting (e.g., 100 μg given subcutaneously three times daily 30 min before meals) and long-acting forms [56, 57]. However, this beneficial effect is often short lasting, and, furthermore, the use of octreotide has not been shown to improve absorption or lead to the elimination of the need for PN. Due to an increased risk for cholelithiasis, expense and studies in animal models suggesting that octreotide may inhibit bowel adaptation, the use of this agent should be reserved for patients with large volume stool losses in whom fluid and electrolyte management is problematic and should be avoided in the immediate period soon after intestinal resection [58, 59].

Antidiarrheals work mainly to reduce intestinal motility, but also cause a slight reduction in intestinal secretion. Commonly used agents include loperamide, diphenoxylate, codeine and tincture of opium (Table 8.5). The use of codeine and tincture of opium tends to be

Table 8.5
Antidiarrheal use in Short Bowel Syndrome

| *Agent* | *Dosage* |
|---|---|
| Loperamide | 2–8 mg before meals and at bedtime as needed |
| Diphenoxylate | 2.5–10 mg before meals and at bedtime as needed |
| Codeine | 15–60 mg before meals and at bedtime as needed |
| Tincture of opium | 0.25–2 ml three times daily (note: 0.25 ml = 2.5 mg morphine) |

limited by their sedating effect, potential for addiction when used long term and cost. In adults, loperamide, 4 mg four times daily, has been shown to be more effective than codeine, 60 mg four times daily; however, there may be a synergistic effect when these agents are used together [60]. The use of diphenoxylate has been largely replaced by loperamide due to a decreased incidence of central nervous system side effects with the latter agent. It should be remembered that loperamide enters the enterohepatic circulation, which is disrupted in SBS patients without an ileum; therefore, high doses are frequently needed. In the setting of SBS, these agents seem to be most effective when administered before meals and at bedtime. Clonidine, which can be administered transdermally, may also be useful to treat high output stool losses via its effects on intestinal motility and secretion [61, 62]. Finally, it should be noted that while antimotility agents may be effective in reducing intestinal transit, in cases where bowel dilatation has occurred, antimotility agents might actually worsen diarrhea by allowing bacterial proliferation.

With the loss of significant portions of the ileum (i.e., $>100$ cm in adults), bile acid malabsorption may exceed maximal hepatic synthesis, leading to a decrease in the bile acid pool and resulting in impairment of luminal fat digestion. In an attempt to improve the bile salt pool without aggravating stool losses, several uncontrolled case studies using ox bile supplements and the synthetic conjugated bile acid, cholylsarcosine, have demonstrated improvements in fat absorption [63, 64]. While the initial reports are encouraging, these agents are not readily available at present. The use of bile acid sequestrants, such as cholestyramine, may worsen steatorrhea and fat-soluble vitamin losses in those with $>100$ cm of distal ileum resected and should generally be avoided in the SBS patient [65].

Pancreatic function is reduced in patients on PN when no concomitant enteral diet is given [66]. Nevertheless, there has been no

consistent evidence demonstrating a reduction in pancreatic secretions in patients with SBS who are given an oral diet. There is currently no evidence supporting the usefulness of pancreatic enzyme supplementation in humans with SBS.

The development of small intestinal bacterial overgrowth (SIBO) appears to be common in SBS patients and may affect their ability to successfully wean PN because of symptoms that impede oral intake and an exacerbation of malabsorption [67]. The anatomical and physiological changes that occur in SBS together with medications commonly used in these patients facilitate the development of SIBO. Excess bacteria in the small bowel can induce inflammatory changes in the gut impairing nutrient absorption, causing a number of gas-related symptoms and aggravating stool losses [68, 69]. While the identification of an excessive number of bacteria in small bowel fluid is considered the gold standard in the diagnosis of SIBO, it has several limitations that have led some to questions its utility [70]. Nevertheless, the use of the primary noninvasive test to diagnose SIBO, the hydrogen breath test, has greater limitations due to rapid transit in the shortened bowel making it difficult to differentiate small bowel versus colonic hydrogen production. Therefore, collection of small bowel fluid for quantitative culture is recommended to diagnose SIBO in the setting of SBS [67]. Once pathologic SIBO has been identified, oral antimicrobial treatment incorporating a broad spectrum of coverage is generally prescribed. A variety of antibiotics can be used with success being judged by an improvement in symptoms, reduction in stool output and/or weight gain. The continuous use of low-dose antibiotics in SBS may be necessary. To reduce the risk of antibiotic resistance, periodic rotation of the antibiotic used is advised. Although without evidence from controlled studies to support their utility, other strategies for controlling SIBO in SBS include limiting the use of antisecretory and antimotility agents, use of nonabsorbable antibiotics, intermittent bowel flushing with polyethylene glycol, use of probiotic agents and bowel tapering operations [67].

## 6. ROLE OF TROPHIC FACTORS

Many SBS patients are unable to be weaned completely from PN even after implementation of an optimized diet and medical care as described. Despite advances in the provision of PN, this mode of nutritional support carries with it significant risks to the patient such as catheter sepsis, venous thrombosis and liver disease. This expensive, invasive therapy has also been shown to impair a patient's quality

of life. As a consequence, there has been intense investigation to identify treatments that maximize intestinal absorption/adaptation with the goal of eliminating or at least minimizing the need for PN. Recent investigations in humans have focused on the use of trophic substances such as growth factors [e.g., growth hormone (GH) and glucagon-like peptide-2 (GLP-2)] and nutrients (e.g., glutamine).

A number of pharmacological agents including GH, glutamine and GLP-2 have been demonstrated to induce trophic properties on the intestinal epithelium in animal models of SBS. These encouraging reports have been followed by conflicting reports of efficacy in humans regarding the enhancement of intestinal absorption, adaptation and PN weaning. Several only uncontrolled trials with PN weaning as the primary endpoint using a combination of GH, glutamine and an optimized diet have been published [71–73]. Byrne et al. treated 47 patients, most of whom had a colon in continuity, with a combination of GH, oral glutamine and an optimized diet for 3 weeks followed by continued use of the diet and glutamine. With follow-up for as long as 5 years, they showed that 40% of patients could be weaned completely from PN, while another 40% could make significant reductions in their PN use. In a more recent uncontrolled, prospective case series, Zhu et al. used a similar treatment program and demonstrated very similar, long-lasting results [74]. Nevertheless, due to conflicting findings on nutrient absorption reported in three prospective, randomized, controlled trials [34, 75, 76], the role of this combination of trophic factors and diet remains controversial [77, 78].

Byrne and colleagues have recently completed a randomized, controlled, prospective study of this combination treatment approach in 41 PN-dependent SBS patients (most with colon in continuity) in which PN reduction was the primary endpoint [79]. The control group was treated with an optimized diet supplemented with glutamine. They demonstrated a significant reduction in PN requirements in all groups studied; however, the extent of reduction was greatest in the group in which GH was administered in addition to the diet and glutamine. The effect of this treatment on nutrient absorption and bowel morphology was not studied in this trial. On the basis of this evidence and the safety of the treatment program, the United States Food and Drug Administration recently approved the use of recombinant-human growth hormone [Zorbtive™, somatropin [rDNA origin] for injection; Serono Inc., Rockland, MA] in patients with SBS on PN as an aid for PN weaning. While encouraging, further controlled studies investigating the optimal dose, duration and timing of administration in relation

to the onset of SBS are needed before this therapy can be routinely advocated for SBS patients [80].

Glucagon-like peptide-2, secreted from distal small intestine and colonic mucosal L-cells after eating, appears to be a promising hormone that plays a role in adaptation [81]. GLP-2 administration induces epithelial proliferation in the stomach, small bowel and colon by stimulating crypt cell proliferation and inhibiting enterocyte apoptosis [82, 83]. Additional effects of GLP-2 include its abilities to increase absorptive capacity [84] and inhibit gut motility and secretion [85, 86]. In a small, open-label trial investigating the effects of GLP-2 in humans with SBS, eight patients including four without a colon and receiving PN and four without a colon who did not require PN, received 400 μg GLP-2 twice daily for 35 days [87]. An increase in overall energy absorption, decrease in fecal wet weight, slowing of gastric emptying and nonsignificant trend toward increased jejunal villus height and crypt depth were demonstrated. More recently, a longer acting GLP-2 analogue, teduglutide (NPS Pharmaceuticals, Salt Lake City, UT), was shown to be safe, well-tolerated, intestinotrophic and significantly increase intestinal wet weight, but not energy absorption in 16 SBS patients with an end-jejunostomy or a colon in continuity [88]. Although there are currently no data on teduglutide's utility in PN weaning, a large, multinational, randomized, controlled trial to study this issue is currently in progress.

Peptide YY levels, also produced by L-cells in the distal small bowel and colon, are markedly elevated in patients with short-bowel syndrome [89]. Since this hormone inhibits gastrointestinal motility, peptide YY might play a role in functional adaptation. Although a peptide YY analogue is available, it has yet to be studied in humans with SBS [90].

Glutamine is a "conditionally essential" amino acid that is a primary energy source for the enterocyte and has been shown to prevent mucosal atrophy and deterioration of gut permeability in patients receiving PN [91]. In a study in which glutamine was added to an ORS provided to SBS patients with an end-jejunostomy, no benefit was seen in terms of fluid or sodium absorption [92]. In a recent randomized, controlled, crossover study, the role of oral glutamine was evaluated in eight patients with SBS. No difference in small bowel morphology, transit time, D-xylose absorption or stool output was seen [93]. Despite these negative studies, there is evidence that glutamine may have a synergistic effect with GH with regards to intestinal adaptation and PN weaning [79, 94, 95].

## 7. ROLE OF SURGICAL MANAGEMENT

The majority of patients with short bowel syndrome will require additional surgery at some point [96]. It is crucial that in subsequent operations as much bowel as possible be preserved, and the focus should be on maximizing the function of the remaining bowel. Examples of such operations include surgeries that restore continuity, relieve obstruction, repair a fistula and eliminate diseased bowel. In addition, non-transplant surgical therapeutic procedures have been devised with the goal of maximizing the function of the SBS patient's existing intestine [97]. These procedures are sometimes referred to as surgical intestinal rehabilitation or autologous gastrointestinal reconstruction. The choice of surgery is influenced by the existing bowel length, function and caliber and can be divided into procedures that optimize function (e.g., lengthen, taper) or slow transit (e.g., reversed segment). These procedures should only be considered after the initial adaptive period and with specific goals in mind. Additionally, operations such as these should only be considered when the patient is stable and medical and dietary management has been maximized. While there are encouraging results from case series, evidence of long-term success has not yet been documented, and only a small proportion of SBS patients are candidates for these procedures [98].

Intestinal transplantation may be considered in SBS patients with a life-long need for PN when complications of PN such as liver disease, loss of venous access sites or recurrent episodes of life-threatening catheter sepsis occur [1, 99]. Small bowel transplantation (SBT) can be performed in isolation, in combination with liver transplantation or in combination with transplantation of multiple organs. The outcome following intestinal transplantation has improved considerably with the development of more potent immunosuppressants and improvements in surgical techniques and other aspects of care following transplantation [99]. The SBT patient survival rates are beginning to approach those of liver transplant patients, particularly in those patients who are well enough to wait at home for their transplant [100]. Nevertheless, graft survival rates remain significantly lower than patient survival rates and a considerable percentage of patients with a functioning graft may still require PN [100, 101]. Therefore, while transplantation remains a very promising and exciting therapeutic option, before it can be recommended to more SBS patients, improved patient and graft survival and an increased likelihood of graft function in order to ensure the discontinuation of PN are necessary.

## 8. WEANING OF PARENTERAL NUTRITION

The relatively recent concept of intestinal rehabilitation emphasizes strategies to reduce or eliminate the need for PN and intestinal transplantation and can be applied both to adult and pediatric populations [102] (Fig. 8.1). A major component of intestinal rehabilitation consists of medication, dietary and fluid manipulation. Major lifestyle changes and increased out-of-pocket expenses are required on the part of the patient. In addition, the 'trade-off' to the patient for not being on PN is the need to take several medications orally and increase the amount of food and fluid ingested daily. Patient education relative to the underlying disease process and the treatments being prescribed is important to enhance compliance with the care plan.

Table 8.6 lists a number of clinical factors considered useful in predicting the success of eliminating the use of PN in SBS patients [5]. Regardless of the bowel anatomy, an aggressive attempt to wean PN should be undertaken in all SBS patients. Recently, Crenn and colleagues evaluated plasma citrulline, a non-protein amino acid

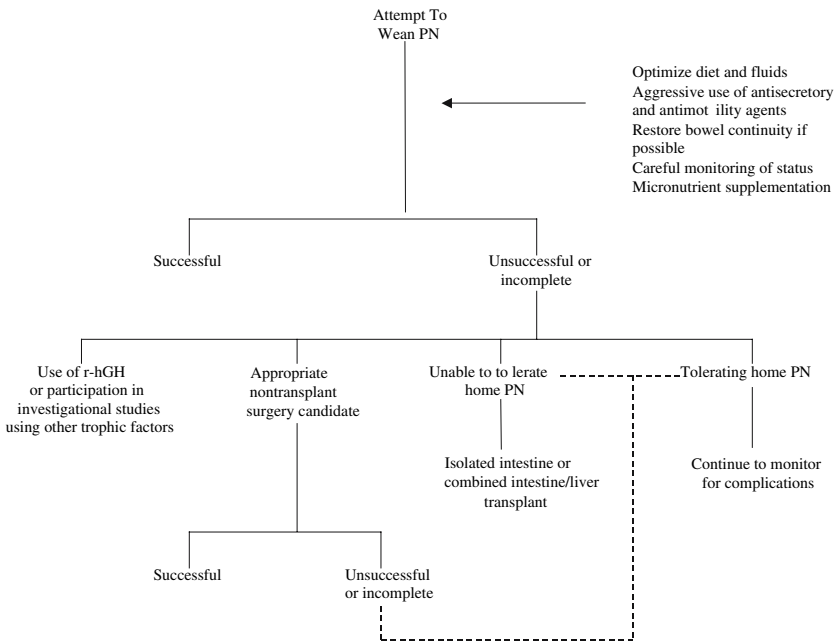


**Fig. 8.1.** Suggested approach to wean parenteral nutrition. Modified from [102] with permission from Blackwell Publishing. *PN* parenteral nutrition; *r-hGH* recombinant human growth hormone.

Table 8.6
Clinical factors predictive of successful weaning from parenteral nutrition

| |
|---|
| Length of the remaining bowel |
| Presence of a colon |
| Presence of an ileum/ileocecal valve |
| Absence of residual mucosal disease in the bowel |
| Degree to which intestinal adaptation has occurred |
| Patient age |
| Duration of time on parenteral nutrition |
| Nutritional status prior to attempted weaning parenteral nutrition |
| Fasting plasma citrulline level (?) |
| Use of recombinant human growth hormone (?) |

produced by the intestinal mucosa, as a potential biological marker of either permanent or transient intestinal failure. A level $<20\,\mu mol/l$ classified SBS patients with permanent intestinal failure with high positive and negative predictive values, and was a more reliable indicator than anatomic variables to distinguish transient from permanent intestinal failure [103]. Nevertheless, successful elimination of PN long-term has been demonstrated in several patients with fasting plasma citrulline levels $<20\,\mu mol/l$ using techniques discussed in this review [104].

A critical component of PN weaning is to have goals in mind when deciding the frequency and amount of PN to wean [105]. Importantly, diet, fluid intake and medications should be optimized before PN weaning begins. It should be established from the outset whether the realistic goal is to reduce PN requirements or to completely eliminate PN based on factors discussed previously. In addition, certain criteria should be met before reducing PN. In general, meeting the daily calorie and fluid intake goals established for the patient with careful and frequent follow-up and subsequent reductions in PN based on tolerance as determined by the development of symptoms, stool and urine output, electrolyte and micronutrient levels, weight and hydration status is sufficient. With regards to monitoring hydration status, one approach that may be useful is to maintain the urinary sodium concentration $>20\,mEq/l$ and daily urinary volume $>1\,l$. Although an optimal interval for making PN reduction decisions has not been defined, once/week would seem appropriate while acknowledging that this needs to be individualized. PN reductions can be made by either decreasing the days that PN is infused/week or by decreasing the daily PN infusion volume equally throughout the week.

Micronutrient supplementation becomes necessary as PN is weaned and levels require periodic monitoring. The frequency of monitoring will depend upon the stage of PN weaning and the presence of existing or prior deficiencies [105]. Table 8.7 provides examples of vitamin and mineral supplementation for SBS patients. Because water-soluble vitamins are absorbed in the proximal small bowel, deficiencies in SBS patients are uncommon. In contrast, fat-soluble vitamin and essential fatty acid deficiencies are more commonly encountered. Supplemental zinc, and occasionally selenium, may be required in the presence excessive stool losses. Iron supplementation is infrequently needed as it is absorbed in the upper gastrointestinal tract, an uncommon site of resection in SBS patients. Lifetime administration of supplemental vitamin B12, usually administered subcutaneously on a monthly basis, is needed in those with more than 50 to 60 cm of terminal ileum removed [106].

Hypomagnesemia occurs commonly as a result of secondary hyperaldosteronism, which generally results from the loss of magnesium-absorbing gut, the binding of magnesium by unabsorbed fatty acids and sodium/water depletion that increases urinary magnesium losses. This can become a difficult problem to correct non-parenterally [1]. Because magnesium deficiency can be seen despite a normal serum level, measurement of 24-h urine magnesium has been suggested [107]. Hypomagnesemia may lead to hypocalcemia as a result of impaired

**Table 8.7**
**Non-Intravenous Micronutrient Supplementation in Short Bowel Syndrome**

| | |
|---|---|
| Vitamin A | Oral: 5,000–30,000 IU daily; IM administration also available |
| Vitamin B12 | SQ/IM: 300–1, 000 μg monthly; intranasal administration also available |
| Vitamin C | Oral: 250–500 mg daily |
| Vitamin D | Oral: 800–1,600 IU daily (or calcitriol 0.25–2 μg daily); IM administration also available |
| Vitamin E | Oral: 400 U up to three times daily |
| Folate | Oral: 1 mg daily |
| Iron | Oral: 325 mg up to three times daily; IM administration also available |
| Zinc | Oral: 50 mg elemental zinc (220 mg tablet) once or twice daily |
| Selenium | Oral: 100 μg daily |
| Calcium | Oral: 1,500–2,000 mg daily |
| Potassium | Oral: 20–80 mEq daily |
| Magnesium | See text |
| Multivitamin | Oral: 2 capsules daily |

parathyroid hormone release [108]. The correction of sodium depletion is an important factor in treating hypomagnesemia. Measurement of urinary sodium may assist in the assessment of sodium balance in some patients; a random urinary sodium concentration of $<10$ mEq/l is generally a good indicator of sodium depletion. Oral magnesium oxide can be administered in doses of 12 to 24 mEq/day and does not appear to increase stomal output, particularly when taken at night when intestinal transit is at its slowest. Finally, the oral administration of 1$\alpha$-hydroxycholecalciferol can be given as it can increase both intestinal absorption and renal absorption of magnesium [109]. If moderate to severe hypomagnesemia ($<1$ mg/dl) persists, parenteral magnesium may be necessary.

## 9. CONCLUSION

The management of the SBS patient is complex, requiring a comprehensive, multidisciplinary approach. Specific dietary intervention combined with careful medical management and, sometimes, surgical strategies offer the potential of PN reduction and overall improved clinical outcome. While still controversial, the administration of trophic factors alone or combined with diet modification may allow for enhanced adaptation and PN reduction. Intestinal transplantation remains a promising treatment for the appropriate candidate.

## KEY POINTS/HIGHLIGHTS

- The management of short bowel syndrome is complex and frequently requires PN support to ensure the sufficient administration of nutrients and fluids. Despite advances in the provision of PN, this mode of nutritional support carries with it significant risks to the patient, impairs the quality of life and is costly.
- An understanding of the physiological abnormalities that occur in SBS is important to better understand the rationale for the therapeutic strategies employed in the care of these patients.
- Dietary and fluid recommendations are dependent upon the remaining bowel anatomy. Those SBS patients with colon remaining may benefit from a high carbohydrate, low fat, oxalate-restricted diet while those without a colon will benefit from the use of an oral rehydration solution.
- The aggressive use of antimotility and antisecretory medications is frequently necessary to control stool losses in SBS.
- Small intestinal bacterial overgrowth may be an important complication in some SBS patients and should be investigated in suspected patients and treated aggressively if present.

- Intestinal adaptation plays a key role in the successful management of patients with SBS. Recent investigations have focused on the use of trophic substances to increase the absorptive function of the remaining gut. Glucagon-like peptide 2 appears to be a promising trophic factor. Ongoing studies will determine its efficacy on the weaning of parenteral nutrition.
- In a recent randomized, controlled trial of somatropin (i.e., recombinant-human growth hormone), glutamine and a specialized oral diet in patients with PN-dependent short bowel syndrome, there was a significant reduction in PN requirements amongst the treatment group as compared to the control group. The United States Food and Drug Administration recently approved the use of somatropin in patients with SBS on parenteral nutrition as an aid in weaning. Further study is needed regarding the optimal dosage and length of administration of somatropin as well as its safety, long-term benefit and use in the pediatric and geriatric populations.
- Non-transplant surgical procedures have been devised with the goal of maximizing the function of the SBS patient's existing intestine. The choice of surgery can be divided into procedures that optimize function (e.g., lengthen, taper) or slow transit (e.g., reversed segment). These procedures should only be considered after the initial adaptive period and after medical and dietary management has been maximized.
- Intestinal transplantation may be considered in SBS patients when complications of parenteral nutrition such as liver disease, loss of venous access sites or recurrent episodes of life-threatening catheter sepsis occur. While substantial improvements in outcome after intestinal transplantation have been seen in recent years, before it can be recommended to more SBS patients, improved patient and graft survival and an increased likelihood of graft function must be seen.
- A critical component of PN weaning is to have goals in mind when deciding the frequency and amount of PN to wean. Micronutrient supplementation becomes necessary as PN is weaned and levels require periodic monitoring. The frequency of monitoring will depend upon the stage of PN weaning and the presence of existing or prior deficiencies.

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# 9 Management of the Obese Patient

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***Contents***



*Summary*

Overweight and obesity are the most common medical problems seen in primary care practice, affecting over two-thirds of adults and almost one-fifth of adolescents. Physicians must address and counsel patients to halt this escalating disease. The primary goal of lifestyle treatment is to improve obesity-related co-morbid conditions by relying on safe and effective diet and lifestyle modifications that produce a caloric deficit of 500 to 1000 kcal/day.

Patients with a body mass index (BMI) $\geq$30 kg/m$^2$ or with a BMI $\geq$27 kg/m$^2$ with concomitant obesity-related diseases should be considered for adjuvant pharmacologic therapy. The two medications

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approved by the FDA for long-term weight loss are sibutramine and orlistat. Surgical intervention is an option for patients with clinically severe obesity (BMI $\geq$40 kg/m$^2$ or $\geq$35 kg/m$^2$ with co-morbid conditions) judged by experienced clinicians to have a low probability of success with non-surgical measures, as demonstrated by failure in established weight control programs.

**Key Words:** Obesity, Lifestyle changes, Pharmacotherapy, Bariatric surgery

## 1. INTRODUCTION

Overweight and obesity are the most common medical problems seen in primary care practice, affecting over 60% of adults and 15.5% of adolescents [1, 2]. The rising prevalence of obesity among adults, paralleled by an increasing prevalence of obesity in children and adolescents, is one of the most significant threats to our nation's health as we enter the twenty-first century. According to the Surgeon General's Call to Action [3], obesity is a major cause of preventable death, which now accounts for approximately 365,000 deaths per year resulting from an unhealthy diet and physical inactivity [4]. Obesity affects nine organ systems and is linked to the most prevalent and costly medical problems seen in daily practice. This chapter will review obesity and the nutritional, pharmacologic and surgical treatment strategies.

## 2. EXAMINATION OF THE OBESE PATIENT

According to the NHLBI guidelines [5], assessment of risk status due to overweight or obesity is based on the patient's body mass index (BMI), waist circumference and the overall risk status. BMI is calculated as weight (kg)/height (m)$^2$, or as weight (pounds)/height (inches)$^2 \times 703$. A BMI table is more conveniently used for simple reference (see Table 9.1). Classifying obesity by BMI units replaces previous weight-height terminology such as percent ideal or desirable body weight. These previous terms were often difficult to interpret and difficult for patients to understand. BMI is recommended since it provides an estimate of body fat, is related to risk of disease and has been established as an independent risk factor for premature mortality [6]. A desirable or healthy BMI is 18.5 to 24.9 kg/m$^2$, overweight is 25 to 29.9 kg/m$^2$, and obesity is $\geq$30 kg/m$^2$. Obesity is further sub-defined into class I (30.0–34.9 kg/m$^2$), class II (35.0–39.9 kg/m$^2$) and class III ($\geq$40 kg/m$^2$) (Table 9.2). Lower BMI cut-offs for overweight

## Table 9.1
## Body Mass Index (BMI) [5]

| Body Mass Index Table | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Normal | | | | | | | Overweight | | | | | | Obese | | | | | | | | | | | | Extreme Obesity | | | | | | | | | | | | | |
| BMI | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 |
| Height (inches) | Body Weight (pounds) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 58 | 91 | 96 | 100 | 105 | 110 | 115 | 119 | 124 | 129 | 134 | 138 | 143 | 148 | 153 | 158 | 162 | 167 | 172 | 177 | 181 | 186 | 191 | 196 | 201 | 205 | 210 | 215 | 220 | 224 | 229 | 234 | 239 | 244 | 248 | 253 | 258 |
| 59 | 94 | 99 | 104 | 109 | 114 | 119 | 124 | 128 | 133 | 138 | 143 | 148 | 153 | 158 | 163 | 168 | 173 | 178 | 183 | 188 | 193 | 198 | 203 | 208 | 212 | 217 | 222 | 227 | 232 | 237 | 242 | 247 | 252 | 257 | 262 | 267 |
| 60 | 97 | 102 | 107 | 112 | 118 | 123 | 123 | 133 | 138 | 143 | 148 | 153 | 158 | 163 | 168 | 174 | 179 | 184 | 189 | 194 | 199 | 204 | 209 | 215 | 220 | 225 | 230 | 235 | 240 | 245 | 250 | 255 | 261 | 266 | 271 | 276 |
| 61 | 100 | 106 | 111 | 116 | 122 | 127 | 132 | 137 | 143 | 148 | 153 | 158 | 164 | 169 | 174 | 180 | 185 | 190 | 195 | 201 | 206 | 211 | 217 | 222 | 227 | 232 | 238 | 243 | 248 | 254 | 259 | 264 | 269 | 275 | 280 | 285 |
| 62 | 104 | 109 | 115 | 120 | 126 | 131 | 136 | 142 | 147 | 153 | 158 | 164 | 169 | 175 | 180 | 186 | 191 | 196 | 202 | 207 | 213 | 218 | 224 | 229 | 235 | 240 | 246 | 251 | 256 | 262 | 267 | 273 | 278 | 284 | 289 | 295 |
| 63 | 107 | 113 | 118 | 124 | 130 | 135 | 141 | 146 | 152 | 158 | 163 | 169 | 175 | 180 | 186 | 191 | 197 | 203 | 208 | 214 | 220 | 225 | 231 | 237 | 242 | 248 | 254 | 259 | 265 | 270 | 278 | 282 | 287 | 293 | 299 | 304 |
| 64 | 110 | 116 | 122 | 128 | 134 | 140 | 145 | 151 | 157 | 163 | 169 | 174 | 180 | 186 | 192 | 197 | 204 | 209 | 215 | 221 | 227 | 232 | 238 | 244 | 250 | 256 | 262 | 267 | 273 | 279 | 285 | 291 | 296 | 302 | 308 | 314 |
| 65 | 114 | 120 | 126 | 132 | 138 | 144 | 150 | 156 | 162 | 168 | 174 | 180 | 186 | 192 | 198 | 204 | 210 | 216 | 222 | 228 | 234 | 240 | 246 | 252 | 258 | 264 | 270 | 276 | 282 | 288 | 294 | 300 | 306 | 312 | 318 | 324 |
| 66 | 118 | 124 | 130 | 136 | 142 | 148 | 155 | 161 | 167 | 173 | 179 | 186 | 192 | 198 | 204 | 210 | 216 | 223 | 229 | 235 | 241 | 247 | 253 | 260 | 266 | 272 | 278 | 284 | 291 | 297 | 303 | 309 | 315 | 322 | 328 | 334 |
| 67 | 121 | 127 | 134 | 140 | 146 | 153 | 159 | 166 | 172 | 178 | 185 | 191 | 198 | 204 | 211 | 217 | 223 | 230 | 236 | 242 | 249 | 255 | 261 | 268 | 274 | 280 | 287 | 293 | 299 | 306 | 312 | 319 | 325 | 331 | 338 | 344 |
| 68 | 125 | 131 | 138 | 144 | 151 | 158 | 164 | 171 | 177 | 184 | 190 | 197 | 203 | 210 | 216 | 223 | 230 | 236 | 243 | 249 | 256 | 262 | 269 | 276 | 282 | 289 | 295 | 302 | 308 | 315 | 322 | 328 | 335 | 341 | 348 | 354 |
| 69 | 128 | 135 | 142 | 149 | 155 | 162 | 169 | 176 | 182 | 189 | 196 | 203 | 209 | 216 | 223 | 230 | 236 | 243 | 250 | 257 | 263 | 270 | 277 | 284 | 291 | 297 | 304 | 311 | 318 | 324 | 331 | 338 | 345 | 351 | 358 | 365 |
| 70 | 132 | 139 | 146 | 153 | 160 | 167 | 174 | 181 | 188 | 195 | 202 | 209 | 216 | 222 | 229 | 236 | 243 | 250 | 257 | 264 | 271 | 278 | 285 | 292 | 299 | 306 | 313 | 320 | 327 | 334 | 341 | 348 | 355 | 362 | 369 | 376 |
| 71 | 136 | 143 | 150 | 157 | 165 | 172 | 179 | 186 | 193 | 200 | 208 | 215 | 222 | 229 | 236 | 243 | 250 | 257 | 265 | 272 | 279 | 286 | 293 | 301 | 308 | 315 | 322 | 329 | 338 | 343 | 351 | 358 | 365 | 372 | 379 | 386 |
| 72 | 140 | 147 | 154 | 162 | 169 | 177 | 184 | 191 | 199 | 206 | 213 | 221 | 228 | 235 | 242 | 250 | 258 | 265 | 272 | 279 | 287 | 294 | 302 | 309 | 316 | 324 | 331 | 338 | 346 | 353 | 361 | 368 | 375 | 383 | 390 | 397 |
| 73 | 144 | 151 | 159 | 166 | 174 | 182 | 189 | 197 | 204 | 212 | 219 | 227 | 235 | 242 | 250 | 257 | 265 | 272 | 280 | 288 | 295 | 302 | 310 | 318 | 325 | 333 | 340 | 348 | 355 | 363 | 371 | 378 | 386 | 393 | 401 | 408 |
| 74 | 148 | 155 | 163 | 171 | 179 | 186 | 194 | 202 | 210 | 218 | 225 | 233 | 241 | 249 | 256 | 264 | 272 | 280 | 287 | 295 | 303 | 311 | 319 | 326 | 334 | 342 | 350 | 358 | 365 | 373 | 381 | 389 | 396 | 404 | 412 | 420 |
| 75 | 152 | 160 | 168 | 176 | 184 | 192 | 200 | 208 | 216 | 224 | 232 | 240 | 248 | 256 | 264 | 272 | 279 | 287 | 295 | 303 | 311 | 319 | 327 | 335 | 343 | 351 | 359 | 367 | 375 | 383 | 391 | 399 | 407 | 415 | 423 | 431 |
| 76 | 156 | 164 | 172 | 180 | 189 | 197 | 205 | 213 | 221 | 230 | 238 | 246 | 254 | 263 | 271 | 279 | 287 | 295 | 304 | 312 | 320 | 328 | 336 | 344 | 353 | 361 | 369 | 377 | 385 | 394 | 402 | 410 | 418 | 426 | 435 | 443 |

Source: Adapted from *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults:* The Evidence Report.

Table 9.2
Classification of Weight Status and Risk of Disease

[If a patient is 18 years or older, use the body mass index (BMI) and waist circumference to estimate weight status and relative risk for diabetes, high blood pressure or heart disease]

| | | Risk of disease (relative to having a healthy weight and waist size) | |
|---|---|---|---|
| | | Waist circumference:* 35″ or less (women) 40″ or less (men) | Waist circumference:* More than 35″ (women) More than 40″ (men) |
| Underweight | BMI below 18.5 | | |
| Healthy weight | BMI 18.5–24.9 | | |
| Overweight | BMI 25.0–29.9 | Increased | High |
| Obesity class I | BMI 30.0–34.9 | High | Very high |
| Obesity class II | BMI 35.0–39.9 | Very high | Very high |
| Obesity class III (extreme obesity) | BMI 40 or more | Extremely high | Extremely high |

* Measure waist circumference at the level of the iliac crest. An increased waist circumference may indicate increased disease risk even at a normal weight.
Source (adapted from): National Institutes of Health, National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. U.S. Department of Health and Human Services, Public Health Service; 1998 [5]

and obesity for the Asian-Pacific region have been proposed. After obtaining the patient's measured height and weight, the BMI and Classification Tables should be used to categorize overweight and obesity and to document this information in the medical record.

Although BMI is the accepted methodology to categorize obesity, it does not distinguish the composition of fat versus lean tissue. An older adult with a normal BMI may be obese due to having an unusually low lean body mass, while a body builder may have an elevated BMI due to having increased muscularity, but may not actually be obese. Skinfold anthropometry and bioelectrical impedance analysis (BIA), two bedside tests, can be routinely recommended for office use in evaluating an obese patient's lean body mass and body fat mass.

An increased waist circumference is independently associated with impaired health and increased cardiovascular risk compared to those with normal waist circumferences [7, 8]. Abdominal fat is clinically defined as a waist circumference $\geq$102 cm ($\geq$40 inches) in men and $\geq$88 cm ($\geq$35 inches) in women. According to the Practical Guide, "to

measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration." Any person with a BMI <35 and a waist circumferences exceeding these limits should be urged more strongly to pursue weight reduction as their increased waist circumference increases disease risk for each BMI class (see Table 9.2).

Determination of fitness level is another factor in assessing risk associated with BMI. Longitudinal studies from The Cooper Institute in Dallas, Texas, have shown that cardiorespiratory fitness (as measured by a maximal treadmill exercise test) is an important predictor of all-cause mortality independent of BMI and body composition. The authors observed that fit obese men had a lower risk of all-cause and CVD mortality than did unfit, lean men [9]. Similar results have been demonstrated among women [10].

The exact contribution of genetics or biology to obesity is a topic currently under debate, the main question being how large of a role do biology, psychology and the environment actually play? James O. Hill, M.D., states that, "Despite obesity having strong genetic determinants, the genetic composition of the population does not change rapidly. Therefore, the large increase in obesity must reflect major changes in non-genetic factors." In the upcoming decade, research into potential hormones related to obesity may uncover further aspects to this discussion [11].

## 3. TREATMENT

The primary goal of obesity treatment is to improve obesity-related co-morbid conditions and reduce the risk of developing future co-morbidities. The decision of how aggressively to treat the patient and which modalities to use is determined by the patient's risk status, their expectations and by what resources are available. Therapy for obesity always begins with lifestyle management as the backbone of treatment and may include pharmacotherapy or surgery (see Fig. 9.1). Not all the medications listed in Fig. 9.1 are FDA approved for weight loss therapy.

## 4. LIFESTYLE CHANGES

Successful weight loss involves dietary change, behavior modification and increased physical activity. A common belief is that an energy deficit of 500–1,000 calories per day leads to weight loss of 1 to 2

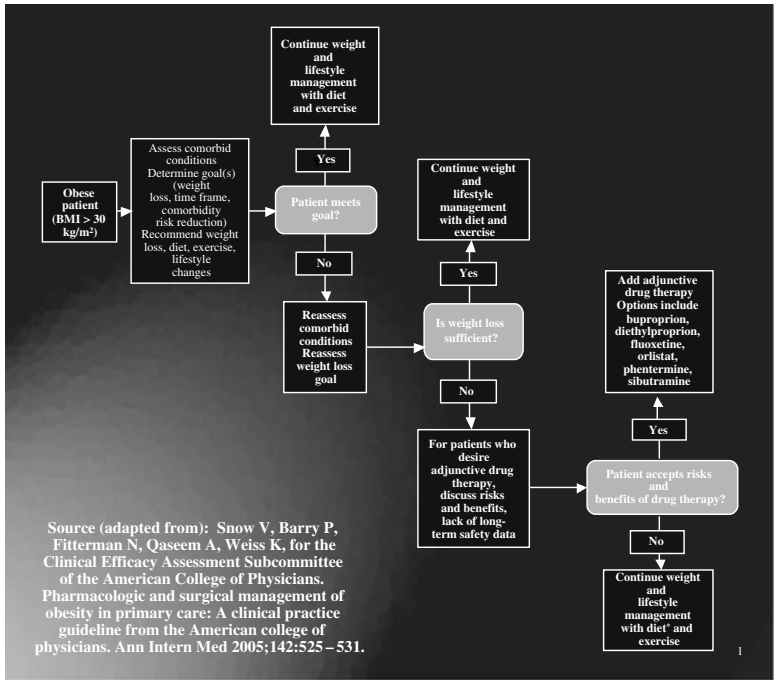


**Fig. 9.1.** Obesity treatment algorithm.

pounds per week. This reduction typically results in a 1,000–1,200 calorie/day diet for most women and a 1,200–1,600 calorie/day diet for most men [12]. As obesity rates continue to escalate, low carbohydrate diets have become attractive as they allow for rapid weight loss and unlimited quantities of high protein foods and in some cases, unlimited dietary fat. These diets include, but are not limited to, Dr. Atkins' Diet Revolution [13], the Zone [14] and the South Beach Diet [15]. As research and public opinion continue to change regarding the safety and efficacy of these low carbohydrate diets, other diet approaches have gained popularity such as Weight Watchers, the New Glucose Revolution, Volumetrics and Slim Fast.

Americans are bombarded with changing professional and popular approaches to altering dietary intake. This next section will review the approach, safety and efficacy of some popular diets with particular emphasis on low-carbohydrate diets. It will also offer recommendations from the United States Department of Agriculture (USDA) and the National Institutes of Medicine (IOM) regarding dietary modification. Table 9.3 compares the key aspects of each of these popular approaches.

**Table 9.3**
**Comparison of Popular Diet Approaches**

| | Atkins Diet | The Zone Diet | The South Beach Diet | The Glucose Revolution | Volumetrics | Weight Watchers | Slim-Fast |
|---|---|---|---|---|---|---|---|
| Source | Dr. Robert Atkins MD: *Dr. Atkins' New Diet Revolution* | Dr. Barry Sears, MD: *Enter the Zone* | Dr. Aurther Agaston, MD: The South Beach Diet | Jennie Brand-Miller and Thomas Wolever: The New Glucose Revolution | Dr. Barbara Rolls: The Volumetrics Weight-Control Plan | Weight Watchers Corporation: www.weight-watchers.com | The Slim Fast Plan: www.slimfast.com |
| Rationale | carbohydrates trigger insulin release which leads to excessive hunger and fat storage; restricting carbohydrates (CHO) will prevent this effect | Excess CHO and portions lead to increased ecosanoid production which causes inflammation and fat promotion. The right combination of foods (40% CHO, 30% protein, 30% fat) will allow for a *weight loss zone.* | Chosing the right CHO and the right fats will help lose belly fat first and decrease cravings | Chosing foods with a low glycemic index (GI) will help regulate blood sugars, hunger, improve exercise endurance and manage diabetes and heart disease | Eating high volume, low-energy-dense foods allows for increased satisfaction which helps dieters stick with low-calorie diet | Portion control is key to permanent weight loss. All foods are monitored on daily *points* system vs. lists of *allowed* or *avoid* foods | Calorie reduction using meal replacement shakes and bars for 1–2 meals/day. |

*(Continued)*

Table 9.3
*(Continued)*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| The Plan | 4 phases: *induction, weight loss, pre-maintence and maintenance.* Goal of induction phase to induce ketosis by consuming 20 gm CHO daily. The weight loss and pre-maintence phase allow for incremental additions of carbs until final CHO level is 25–90 gm/day for maintenance. | Splits macronutrients into "blocks" that can be measured for CHO, fat and protein content allowing the dieter to calculate 40-30-30 breakdown at each meal and snack. A typical meal for a woman might include 27 gm CHO, 21 gm protein and 9 gm fat. | 3-phase plan that introduces varying amounts and types of CHO depending on the stage. Phase I eliminates all fruit and whole grains for 2 weeks. Phase 2 and 3 promote the addition of limited amounts of *allowed* fruits, nuts and whole grains. | Glycemic index (GI) provides a ranking of individual CHO and their effects on blood glucose after a meal. Low GI considered <55, medium =56–69, High > 70. Generally, high fiber, less refined foods have a lower GI than more refined CHO. The GI of various foods are listed in the book as well as on-line at www.glycemicindex.com | Calorie restriction is bottom line for weight loss. Compliance of low-calorie diet can be enhanced with increased satiety. High volume, low-energy dense foods help increase satiety and allow for reduction in eating. Overall, high fiber, low-fat diet. | 2 variations: Flex and Core. Flex assigns a point level to each food depending on calories, fat and fiber content. Each member receives daily point level for tracking. The Core plan encourages food selection from a healthy "core list" that does not require tracking points. | Replace 1 to 2 meals/day with Slim-Fast meal replacement products which are approximately 65% CHO, 20% protein and 15% fat and allow for long-term calorie restriction. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Final Points | Diet is low in calories ranging 1200–1500 calories/day and does not appear to be more effective at one year vs.other low-calorie diets | Low-calorie diet plan providing roughly 1200 calories/day. After one year, Zone dieters are no more effective than other approaches [16] | Positively emphasizes healthier choices of proteins, fats and whole grains but un-necessarily restricts healthy CHO. Also low-calorie and there is no long-term data to support its safety or efficacy. | Low GI foods do translate to better post-prandial glucose levels in controlled metabolic studies that are not reproducable under normal conditions [17]. Diet may not be low calorie since no emphasis on portion size. | Diet recommends healthy, high fiber, high volume foods which do positively impact total calories and weight loss in the short term. Long term studies in over-weight and obese are needed. | Appears to be most successful of popular diet programs in terms of client's results and attrition rates. Widely considered a healthy eating program[16]. | Long-term data on meal replacements endorse their safety and efficacy for weight loss and maintance up to 10 years. Not feasible or palatable to all clients. |

## 5. LOW CARBOHYDRATE DIETS: WHAT DOES THE SCIENCE SAY?

Several randomized trials have examined the efficacy of low carbohydrate diets in terms of weight loss and improvement of metabolic parameters compared with conventional, low fat, low calorie diets. Multiple randomized controlled trials demonstrate low carbohydrate dieters lose significantly more weight at 6 months versus conventional dieters [18–20]. At 6 months, low carbohydrate dieters also experience greater decreases in triglyceride levels, serum fasting glucose and body fat than low fat dieters [19, 20]. At 12 months, however, there is no significant difference in weight loss between the two groups as low-carbohydrate dieters regain some weight while conventional dieters maintain a consistent weight level [18].

## 6. LOW CARBOHYDRATE DIETS: ARE THEY SAFE?

Health care professionals continue to be concerned with the potential negative side effects of high dietary protein intake associated with low carbohydrate diets. Concerns include dehydration, fatigue, increased calcium excretion, colon cancer and increased renal burden [21]. Additionally, high saturated fat intake and increased risk of heart disease are associated with low carbohydrate, high protein diets [22]. Diabetics are one population in whom the use of low carbohydrate diets needs to be carefully monitored given the high incidence of renal disease [23]. Some research has demonstrated a decrease in microalbuminuria with improvement in glycemic control [24] with no increase in serum creatinine concentrations [19]; however, few studies have directly addressed more sensitive markers of renal function such as the glomular filtration rate (GFR). Although the data suggests that at 6 months there is an improvement of co-morbid conditions among low-carbohydrate dieters, the potential for associated side effects needs to be further investigated.

## 7. USDA AND IOM RECOMMENDATIONS

The USDA and the IOM each have evidence-based approaches for addressing diet and lifestyle modification: *Dietary Guidelines for Americans 2005*, released by the USDA and the US Department of Health and Human Services (DHHS) on 12 January 2005 [25] and the Institute of Medicine's IOM's *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino*

**Table 9.4**
**IOM Report and USDA Guidelines**

| IOM REPORT |
|---|
| Adults should consume 45% to 65% of their total calories from carbohydrates; |
| Adults should consume 20–35% of their total calories from fat (infants and younger children need 25% to 40%); |
| Adults should consume 10% to 35% of their total calories from protein; |
| Adults and children should engage in activities equivalent to a total of 60 min of moderately intense physical activity each day |
| **USDA GUIDELINES** |
| Consume a variety of foods within and among basic food groups while staying within energy needs; |
| Control calorie intake to manage body weight; |
| Be physically active every day; |
| Increase daily intake of fruits, vegetables, whole grains, and non-fat or low-fat milk and milk products |
| Choose fats wisely for good health; |
| Choose carbohydrates wisely for good health; |
| Choose and prepare foods with little salt; |
| If you drink alcohol, do so in moderation; |
| Keep food safe to eat |

*Acids*, released on 5 September 2002 [26]. These reports include evidence-based guidelines for diet and exercise aimed at reducing chronic disease. In response to public and professional interest in low carbohydrate diets, the IOM recommends a minimum of 130 g of total carbohydrates daily (45%–65% of total calories), a value above the range of many low carbohydrate diets. The USDA guidelines translate these macronutrient guidelines into specific foods to include as part of a healthy diet. The key findings of the IOM report and the USDA guidelines are included in Table 9.4. A sample 1,500-calorie diet is also included in Table 9.5, illustrating the recommendations of both reports.

## 8. NATIONAL WEIGHT CONTROL REGISTRY

Started in 1993 by Drs. Rena Wing and James Hill, the National Weight Control Registry (NWCR) is an on-going surveillance project to learn more about the healthy behaviors of those individuals who have successfully lost weight (>30 pounds) and maintained that loss

Table 9.5
IOM and USDA Sample Menus

**IOM DIET SAMPLE MENU:**
**BREAKFAST**
1 cup complete bran flakes
1 mini box of raisins (.5 oz)
1 cup of skim milk

**SNACK**
1 medium tart apple
2 oz (28 halves) walnuts

**LUNCH**
McDonald's grilled chicken caesar salad
One packet of low fat balsamic vinagrette dressing
1 Orange
Bottle Water

**SNACK**
6 oz of low-fat fruited yogurt
1/2 cup blueberries

**DINNER**
3 oz lean, Grilled Flank Steak
1 cup steamed asparagus tips
1 small ear of corn
1 tsp of low-fat tub margarine
1 wedges of watermelon (approximately 1/16 of melon)
*Nutrient Information:*
*Calories: 1500*
*Fat: 49 gm fat (30%), 7% saturated, 11% polyunsaturated, 6% monounsaturated*
*Carbohydrates: 201 gm (47%)*
*Fiber: 28 gm*
*Protein: 82 gm (22%)*

**USDA DIET SAMPLE MENU:**
**BREAKFAST**
1 cup bran flakes
1 cup fat-free milk
1 small banana

**SNACK**
1 orange
1 oz part-skim mozzarella cheese

**LUNCH**
Open-face tuna fish sandwich
1 slice rye bread
3 oz tuna (water packed, drained)
2 tsp mayonnaise
1 tbsp diced celery
1 cup shredded romaine lettuce
2 slices tomato
1 medium pear

**SNACK**
1/4 cup dried apricots
1 cup low-fat fruited yogurt

**DINNER**
3 oz boneless, skinless chicken breast
1 small (2′ diameter, 5″ long) baked sweet potato
1/2 cup peas and onions
1 cup leafy greens salad
3 tsp sunflower oil and vinegar dressing
1/2 cup red grapes
*Nutrient Information:*
*Calories: 1500*
*Fat: 46 gm fat (29%), 6% saturated, 12% polyunsaturated, 7% monounsaturated*
*Carbohydrates: 217 gm (52%)*
*Fiber: 29 gm*
*Protein: 68 gm (19%)*

Final recommendations

- Measure patient's height, weight and waist circumference
- Calculate patient's BMI
- Assess patient's risk factors (diabetes mellitus, hypertension, coronary artery disease, hypercholesterolemia)
- Lifestyle changes
  - Aim for 5–10% weight loss over 6 months
  - Consume a variety of foods within and among the basic food groups while staying within energy needs
  - Caloric deficit: 500 to 1,000 calorie deficit/day
  - Increase physical activity: 30 min on most, preferably all, days of the week
- Consider pharmacotherapy if patient's BMI $\geq$30 kg/m2 or $\geq$27 kg/m2 with comorbidities
  - Unsuccessful weight loss or weight maintenance with lifestyle changes
- If pharmacotherapy used, monitor side effects
  - Daily multivitamin with orlistat
  - Blood pressure and heart rate with sibutramine
- Consider surgical therapy if patient's BMI $\geq$40 kg/m2 or $\geq$35 kg/m2 with comorbidities
  - Patient with low probability of success with non-surgical measures, as demonstrated by failure in established weight control programs
  - Informed, well-motivated patient with acceptable operative risks

for at least 1 year [27]. All of the data collected are self-reported by registry members who volunteer information.

There was no single, common approach that members reported for weight loss; however, the majority of members reported calorie reduced diets as well as regular exercise. Members reported several common themes for weight maintenance such as eating a low calorie, low fat diet, consuming breakfast daily, engaging in self-monitoring techniques such as food logs or self-weighing or both and regular physical exercise for approximately 1 h daily (www.nwcr.ws). In a recent paper by Wyatt et al. [27], the key lessons of the NWCR were reported and are listed as follows:

- There is an important difference between weight loss and weight maintenance.
- Individuals who have successfully maintained weight loss have similarities in how they keep weight off.
- Many people wishing to lose weight experience an important "trigger" event in their lives that becomes self-motivating.
- Maintenance of weight loss becomes easier over time.
- Weight loss is reported to improve the overall quality of a person's life.
- Maintaining weight loss does not increase eating disorders.
- Successful weight loss maintenance is achievable.

While the lessons of the NWCR may not be applicable to all individuals seeking weight loss, they do clarify healthful diet and lifestyle approaches that reach beyond popular diets and speak to comprehensive lifestyle change. The behaviors of the NWCR members also mirror the recommendations of the IOM and the USDA with regard to energy intake, lifestyle change and regular physical activity.

## 9. PHARMACOLOGIC OPTIONS

Patients with a BMI $\geq 30\,kg/m^2$ or with a BMI $\geq 27\,kg/m^2$ with concomitant obesity-related diseases should be considered for adjuvant pharmacologic therapy. Pharmacotherapy is appropriate in individuals who have not responded to previous weight loss attempts (diet, exercise and behavioral changes) or have been unsuccessful with sustaining previous weight loss attempts. The two medications approved by the FDA for long-term weight loss are sibutramine (Abbott laboratories, Abbott Park, IL; a norepinephrine and serotonin reuptake inhibitor that enhances satiety) and orlistat (Roche Pharmaceuticals, Nutley, NJ; a lipase inhibitor that reduces fat absorption). Both agents are approved for long-term use, have proven effective in large-scale multicenter trials and have side effects that may be easily monitored by the clinician.

Sibutramine produces a dose-dependent weight loss (available doses are 5, 10 and 15 mg capsules), with an average loss of about 8–10% of initial body weight at 6 months [28]. A greater proportion of participants achieve 5% and 10% weight loss on sibutramine than placebo in studies lasting 44 to 54 weeks [29–42]. Wadden et al. [32] demonstrated significantly greater weight reduction in patients combining pharmacotherapy with lifestyle modifications. Studies have demonstrated improvement in glycemic control in patients with type 2 diabetes [30, 33–35] and in cardiovascular risk factors [36–38]. Sibutramine can cause small increases in both blood pressure and pulse; however, studies have shown sibutramine

to be safe in the treatment of obese patients with well-controlled hypertension [39, 40]. The most commonly reported side effects of sibutramine include headache, dry mouth, constipation and insomnia, all of which are generally mild and well tolerated. It is advisable to monitor blood pressure and heart rate monthly when starting patients on sibutramine. Contraindications to sibutramine use include uncontrolled hypertension, congestive heart failure, symptomatic coronary heart disease, arrhythmias or history of stroke.

Orlistat is a synthetic hydrogenated derivative of a naturally occurring lipase inhibitor, lipostatin, produced by the mold *Streptomyces toxytricini*. Taken at a therapeutic dose of 120 mg tid, orlistat blocks the digestion and absorption of about 30% of dietary fat. Recently, the XENDOS trial randomized 3,305 obese subjects to lifestyle changes, plus either 120 mg of orlistat or placebo [41]. After 4 years, orlistat plus lifestyle changes led to a 37.3% ($P = 0.0032$) risk reduction in the development of diabetes and improved weight loss compared with placebo plus lifestyle changes. Multiple randomized, 1- to 2-year double-blind, placebo-controlled studies have shown that after 1 year, orlistat produces a weight loss of about 9–10% compared with a 4–6% weight loss in the placebo-treated groups [42, 43]. Orlistat has been demonstrated to reduce the incidence of type 2 diabetes [41, 44], improve diabetic control and insulin sensitivity [45–47], and reduce cardiovascular risk factors [48, 49]. A pilot study by Beck-da-Silva et al. [50] demonstrated that orlistat can promote significant weight loss and symptoms of relief in obese patients with heart failure, as measured by 6-min walk test and functional capacity. The lipid profile in these patients also improved. Since orlistat is minimally (<1%) absorbed from the gastrointestinal tract, it has no systemic side effects. Tolerability to the drug is related to the malabsorption of dietary fat and subsequent passage of fat in the feces. Gastrointestinal tract side effects reported to occur in at least 10% of orlistat-treated patients include: oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation and increased defecation. The events are generally experienced early, diminish as patients control their dietary fat intake and infrequently cause patients to withdraw from clinical trials. Cavaliere et al. [51] demonstrated that psyllium mucilloid is helpful in controlling the orlistat-induced GI side effects when taken concomitantly with the medication. Due to potential deficiency of fat-soluble vitamins, a daily multivitamin is recommended.

Rimonabant (Sanofi-Aventis, Paris, France), an endocannabinoid receptor antagonist in clinical development, offers a unique approach

to appetite control and weight reduction. Two randomized studies have demonstrated a reduction in body weight and waist circumference and an improvement in cardiovascular risk factors with rimonabant combined with a hypocaloric diet over 1 year [52, 53].

## 10. SURGICAL OPTIONS

Surgical intervention is an option for patients with clinically severe obesity (BMI $\geq 40\,kg/m^2$ or $\geq 35\,kg/m^2$ with comorbid conditions) judged by experienced clinicians to have a low probability of success with non-surgical measures, as demonstrated by failure in established weight control programs. There are currently no defined criteria for a specified length of time or description of what constitutes such treatment, although many consider formal participation in a medically supervised diet and exercise program for at least 6 months or longer. The surgery should be considered only for well-informed and motivated patients with acceptable operative risks. The patient should be able to participate in long-term follow-up. Patients should be evaluated by a multidisciplinary team comprised of professionals with medical, surgical, psychiatric and nutritional expertise.

Surgical procedures for weight loss range from restrictive, to restrictive with malabsorption to primarily malabsorptive. The Roux-en-Y gastric bypass (RYBG) (see Fig. 9.2) is the most commonly performed procedure in the U.S. It provides a small gastric pouch for oral restriction in combination with some degree of small bowel malabsorption. It has a maximum weight loss of approximately 68% of the excess body weight. This plateau is reached between 12 and 18 months, postoperatively.

Weight loss with a malabsorptive procedure, such as ileal bypass (see Fig. 9.3) is reported to be greater than with a restrictive procedure, but with a greater incidence of metabolic complications. These complications include vitamin deficiency, mineral deficiency, electrolyte deficiency, dehydration and liver failure.

Multiple studies have demonstrated complete resolution or improvement of obesity-related comorbid conditions following obesity surgery including type 2 diabetes, hypertension, obstructive sleep apnea and hyperlipidemia [54]. The Swedish Obese Subjects (SOS) Study [55] compared obese subjects who underwent gastric surgery and contemporaneously matched, conventionally treated obese control subjects. The study followed the participants for 2 to 10 years to determine if short-term benefits seen with gastric surgery persist over

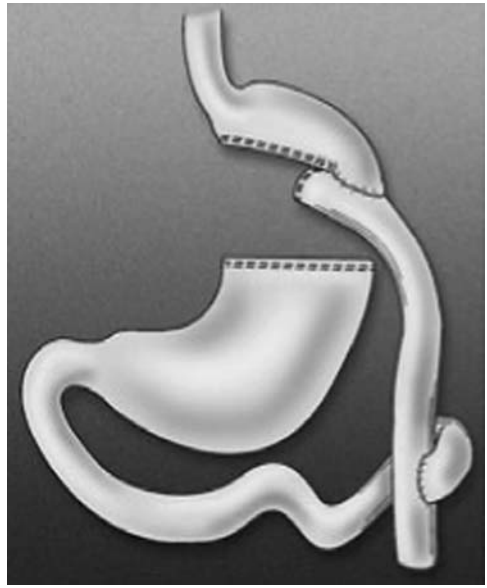

**Fig. 9.2.** Roux-en-Y Gastric Bypass Surgery.

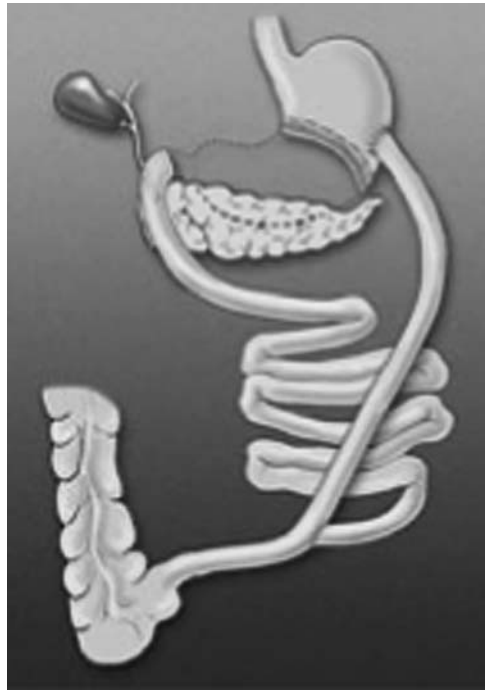

**Fig. 9.3.** Ileal Bypass Surgery.

time. It did not demonstrate a difference in the incidence of hyperlipidemia and hypertension when compared to conventional therapy at 2 or 10 years. Quoted mortality rates range from 0.1 to 0.2% (adjusted in-hospital mortality) [56] to 2.0%, 2.8% and 4.6% for 30-day, 90-day and 1-year mortality, respectively [57].

## 11. CONCLUSION

The increasing incidence of overweight and obesity in adults and children is a significant threat to our nation's health. Physicians must address and counsel patients to halt this escalating disease. The primary goal is to reduce caloric intake by 500 to 1,000 kcal/day and establish long-term healthy eating and physical activity habits. The strategies and counseling methods used will vary depending on the patient's needs and abilities. Overall, the best diet is one that can be followed for a lifetime. Pharmacotherapy and surgical options should be considered in appropriate patients.

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# 10 Enteral Access and Enteral Nutrition

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***CONTENTS***



*Summary*

Enteral nutrition is the route of choice in patients with a functioning gastrointestinal tract. Early enteral nutrition has been shown to improve outcomes in a variety of critically ill patient populations. Enteral nutritional support is indicated for patients with poor volitional intake, neurological impairment, oropharyngeal dysfunction, short gut syndrome, and major trauma or burns. A number of enteral access options are available to patients in need of nutritional support. Consideration of the appropriate device, position in the gastrointestinal tract, and insertion method are critical to ensure optimal outcomes. Percutaneous enteral feeding tubes are indicated in patients requiring long-term (>4–6 weeks) enteral access. Enteral access tubes may be placed by endoscopic, fluoroscopic, or surgical methods. The exact method utilized often depends on local expertise and availability. In addition, appropriate aftercare and monitoring with early recognition and treatment of any complications are crucial to the success of enteral nutrition access.

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**Key Words:** Enteral nutrition, Enteral feeding tubes, Enteral access, Percutaneous feeding tubes

## 1. INTRODUCTION

In a variety of patient populations, ranging from critical illness on mechanical ventilation and acute pancreatitis to trauma and burns, provision of early enteral feeding has been shown to improve outcome compared to the provision of parenteral therapy or standard therapy (in which no specialized nutritional support is provided) [1, 2]. Compared to parenteral nutrition (PN), early enteral nutrition (EN) has been shown to maintain gut integrity and prevent gut permeability [3–5]. This reduces bacterial challenge to the immune system and results in a lower incidence of systemic endotoxemia [6]. Feeding through the gut helps set the tone for systemic immunity through stimulation of Th-2 pathways of $CD_4$ helper lymphocyte proliferation (a process that opposes proliferation of Th-1 proinflammatory cellular pathways) [7–9]. Maintaining gut integrity and preventing increased permeability help attenuate oxidative stress and, in some cases, actually reduce disease severity such as seen in acute pancreatitis [10]. The effect of these physiologic changes is a dramatic favorable impact on patient outcome.

The most consistent outcome improved with use of EN is reduced infectious morbidity (specifically, pneumonia, abdominal abscess, and bacteremia), compared to use of PN [1]. Better gut integrity also correlates to reduced incidence of multiple organ failure syndrome [4, 5, 11]. In patients with head injury, early enteral feeding speeds recovery and return of cognitive function compared to PN [12]. In acute pancreatitis, enteral feeding compared to PN reduces the need for surgical intervention for associated complications of pancreatitis (such as bleeding or pancreatic gland infection) [13].

These positive outcomes associated with EN cannot be attributed to a deleterious effect of PN, as now improved outcome is seen with use of enteral feeding compared to standard therapy in which no nutritional support is provided [2]. In a large metanalyses, Lewis showed that early EN provided postoperatively in surgical critical care reduced infections, length of hospital stay, and anastomotic dehiscence compared to standard therapy [2]. The innate benefits of early EN may be further enhanced by the addition of immune modulatory agents [14]. Adding arginine and nucleotides to an enteral formula, both of which are direct immune stimulants, may enhance proliferation of Th-2 lymphocyte cell populations. Substitution of omega-3 fatty

acids from fish oil for the more routinely used omega-6 fatty acids helps modify the leukotrienes, thromboxanes, and prostaglandins produced by immune active cells and helps generate an anti-inflammatory effect. Agents such as glutamine, vitamin C, and selenium act as antioxidants, reducing the overall level of oxidative stress. A recent meta-analysis by Montejo of 26 studies in which immune active formulas were compared to standard enteral formulas showed that infections were reduced by 46–74%, organ failure was reduced by 79%, and length of stay in the ICU and hospital were reduced between 1.6 and 3.4 days with the use of immune-enhanced formulas (compared to standard formulas) [14] (Table 10.1).

These aforementioned studies highlight the role that the gut plays in critical illness and emphasizes the need for provision of early enteral feeding. At a time when the patient is at the height of critical illness with ileus, hypotension, and an active systemic inflammatory response syndrome, placement of an enteral feeding tube and initiation of EN are most important. Having the skills to place the feeding tube and the capability to monitor for complications and tolerance of EN are of utmost importance in optimizing patient outcome.

Enteral nutritional support is indicated for patients with poor volitional intake, neurological impairment, oropharyngeal dysfunction, short gut syndrome, and major trauma or burns [15]. Generally, the nutritional needs of patients who meet one or more of these criteria for less than 4 weeks are addressed with nasally or orally placed tubes; these include nasogastric tubes (NGT) or nasoenteric tubes (NET) [16]. These can be placed at the bedside, endoscopically, or fluoroscopically [17]. Percutaneous tube enterostomies are placed into the stomach and/or small bowel when longer-term placement (>4 weeks) is needed.

Enteral access tube location (i.e., stomach versus small bowel) is determined by patient characteristics. Gastric feeding is preferred for most patients with normal gastric emptying and a low risk of gastric aspiration. However, in the certain clinical situations small bowel feedings may be preferred. Gastrojejunal tubes allow for simultaneous gastric decompression and small bowel feedings and are indicated when gastric outlet obstruction, gastroesophageal reflux/aspiration, and gastroparesis are present [18, 19]. Direct jejunal feeding may also be useful for patients with pancreatitis, previous gastric resection, after major abdominal surgery or an increased risk of gastric reflux and/or aspiration. Enteral access tubes may be placed by endoscopic, fluoroscopic, or surgical methods. The exact method utilized often depends on local expertise and available [20–26].

**Table 10.1**
**Immune-enhancing Enteral Formulations**

| *Product* | *Type of formula* | *Arginine per 1,000 calories* | *Omega-3 fish oil/canola oil per liter* | *Borage oil* | *Manufacturer* |
|---|---|---|---|---|---|
| Impact 1.5 | Immune-enhancing | 12.5 g | 2.6 g combined | | Novartis Medical Nutrition (St. Louis Park, MN) |
| Crucial | Immune-enhancing | 10 g | 4.3 g combined | | Nestle Nutrition (Glendale, CA) |
| Pivot 1.5 | Immune-enhancing | 8.6 g | 3.9 g combined | 2.86 gm/ 1000 cal | Ross Division, Abbott Labs (Columbus, Ohio) |
| Optimental | Immune-enhancing | ≈ 5 g | Unspecified amount | | Ross Division, Abbott Labs (Columbus, Ohio) |
| Perative | Immune-enhancing | ≈ 6 g | Unspecified amount | | Ross Division, Abbott Labs (Columbus, Ohio) |
| Oxepa | Anti-inflamatory | 1.4 g | Unspecified amount | | Ross Division, Abbott Labs (Columbus, Ohio) |
| Peptamen AF | Anti-inflamatory | 0.0 g | 9.3 g fish oil | | Nestle Nutrition (Glendale, CA) |

## 2. NASAL TUBES

Nasogastric and nasoenteric feeding tubes are used for short-term access, and they allow for assessment of tolerance of enteral nutrition in cases where permanent access may be needed. Nasogastric tubes are placed at the bedside by clinicians at all levels of training. Nasogastric and nasoenteric feeding tubes are contraindicated in patients with obstructing head, neck, or esophageal pathology or injury, which may preclude safe insertion. Correct placement should be confirmed prior to use. Although there are some data using pH step-up or capnography to confirm proper tube placement, radiography remains the gold standard [27, 28]. With experienced clinicians and radiographic confirmation, success rates of 95–100% are attainable [29, 30].

### *2.1. Techniques for Placement*

Nasoenteric tubes are placed anywhere distal to the pylorus, while nasojejunal tubes specifically are placed distal to the ligament of Treitz. Both may be placed at the bedside, endoscopically, or fluoroscopically, but typically nasojejunal tubes require endoscopic or fluoroscopic placement. Bedside placement requires an experienced clinician most commonly using the technique described by Zaloga [31]. In this method, the patient lies in the right lateral decubitus position, and the feeding tube with the distal tip angulated is advanced slowly using air insufflation, tube rotation, and auscultation as guidance. Erythromycin and metoclopramide are often used as prokinetic pharmacologic agents for advancement of feeding tubes from the stomach to the small intestine. Their use has been met with variable success [32].

Endoscopic and fluoroscopic placement may be performed at the bedside, thus eliminating the need for transport to the endoscopy or radiology suite, but depends on local availability. Multiple endoscopic methods have been described including: drag and pull, over the wire, and through the scope [33]. These methods require sedation and/or oronasal transfer of the initially orally placed tube. More recently, an over the wire technique using an ultrathin transnasal endoscope has been described that does not require sedation or oronasal transfer [34, 35]. The success rates for all these endoscopic techniques range from 84–95% [36]. Fluoroscopic placement is similar to that of bedside nasal tube placement, but the location of the tube is monitored fluoroscopically as the tube and/or guidewire is advanced into position. This method generally requires no sedation, but it may require patient travel to the radiology suite and exposure to radiation. Success rates are high and similar to endoscopic placement. Overall success rates

for nasogastric and nasoenteric feeding tube placement, regardless of placement method, exceed 90%, with decreasing success with more distal placement (84–90% success in the distal duodenum and as low as 25–50% distal to the ligament of Treitz) [36].

## *2.2. Complications*

Complications of nasal feeding tubes can be divided into those that occur during the procedure and those that occur post-procedurally (Table 10.2).

### 2.2.1. Procedural Complications

Procedural complications occur in approximately 10% of nasal tube placements, and include aspiration, epistaxis, or cardiopulmonary compromise related to sedation [19, 37]. Initial misplacement of the nasal tube into the tracheopulmonary tree is the most serious procedural complication, occurring in 2–4% of placements. However, it is clinically unsuspected in 80% of incidences, and as many as half of those cases results in pneumothorax [16, 19, 37–39]. Radiography should be performed prior to tube use to confirm location of those tubes placed without endoscopic or fluoroscopic visualization. Protocols requiring radiographic confirmation have been shown to decrease inadvertent use of malpositioned feeding tubes [16].

### 2.2.2. Post-Procedural Complications

Post-procedural complications include inadvertent tube dislodgement, malfunction or occlusion of the tube, aspiration of tube feeds, sinusitis, and rarely intestinal ischemia. Dislodgement occurs in up to 41% of cases and often requires removal and replacement [40–42]. Preventative measures include taping or stapling the tube to the nose and/or

**Table 10.2**
**Complications of Nasogastric and Nasoenteric Feeding Tubes**

| *Procedural* | *Post-procedural* |
|---|---|
| -Aspiration | -Tube dislodgement |
| -Epistaxis | -Aspiration of feeds |
| -Intrapulmonary placement | -Occlusion of tube |
| | -Sinusitis |
| -Pneumothorax | -Intestinal ischemia |

cheek and the use of a nasal bridle. Nasal bridle use has been shown to decrease dislodgement, but the risk of nasal septal and tissue trauma and its invasive nature have prevented its widespread acceptance [43] (Fig. 10.1).

Nasal tube occlusion complicates 9–20% of cases and often requires tube replacement [42, 44, 45]. Increasing tube length, decreasing tube caliber, inadequate flushing, frequent medication administration, and the use of the tube to measure residual volumes are all associated with an increased incidence of occlusion [46]. A cytology brush, an ERCP catheter, or a commercial corkscrew device may be used in attempts at clearing occlusion [47]; pancreatic enzyme (Viokase, Axcan, Birmingham, AL) mixed with bicarbonate has been shown more effective than traditional measures at resolving tube occlusion [48]. Tube malfunction, including cracking, breaking, or kinking, occurs in 11–20% of nasal tubes; these issues typically result in removal and replacement of the tube [44, 45]. Average in situ functional tube duration is ~ 10–11 days in most studies [34, 35].

Aspiration of tube feeding occurs more frequently in patients with previous aspiration events, decreased level of consciousness, significant

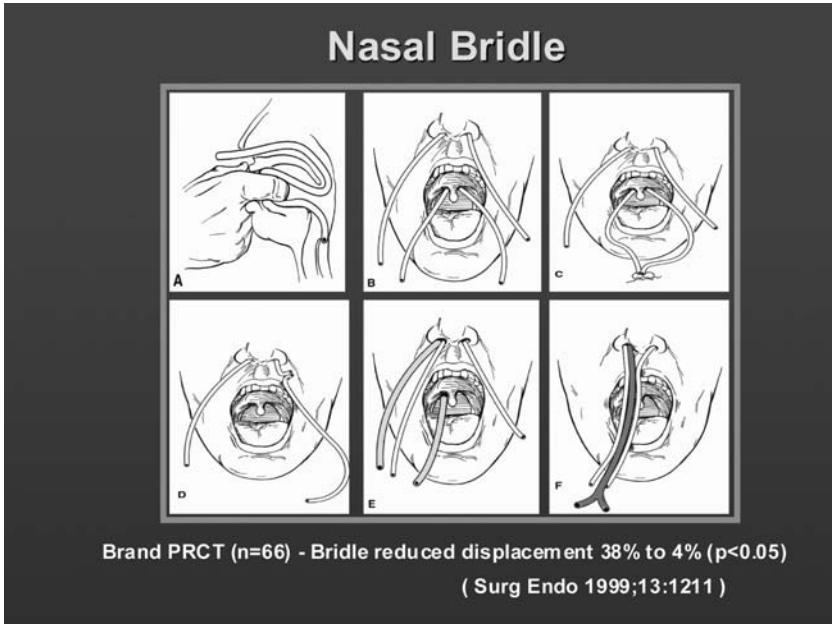


**Fig. 10.1.** Bridle technique.

neuromuscular disease, contaminated oropharyngeal environment, structural abnormalities of the aerodigestive tract, supine position, and elevated residual gastric volumes [49]. The risk of aspiration may be reduced by changing the level of feeding infusion from the stomach to the small bowel, elevation of the head of the bed to >45 degrees, implementing continuous rather than bolus feeding, using chlorohexidene mouthwashes, and administering a prokinetic drug [50].

Microbiologically confirmed sinusitis occurs in approximately 10% of cases of nasal feeding tubes and is thought to be secondary to obstruction of anatomic sinus drainage [51]. In rare cases, enteral nutrition has been linked to intestinal ischemia. The typical situation is one in which a critically ill, hypotensive patient on pressors exhibits decreasing tolerance (ileus, abdominal bloating, abdominal pain) of the tube feedings. In this clinical setting, tube feeding should be suspended pending further evaluation [52, 53].

## *2.3. Initiating Enteral Feeding*

### 2.3.1. Selecting the Formula Type

The most important question upon initiation of enteral feeding is whether the disease process warrants the use of an immune-modulating formula. A recent US Summit on Immunonutrition helped identify those patients who were candidates for an immune-modulating formula [54]. Candidates were designated based on literature showing that use of an immune formula in that particular disease process would favorably impact outcome (compared to use of a standard enteral formula alone). Such candidates would include patients undergoing elective major GI surgery such as esophagectomy, gastrectomy, or pancreatotomy. Trauma with injury severity scores >18 or abdominal trauma index scores >20 (especially if severe head injury is involved) would be candidates for an immune formula. Patients with burns over a total body surface area of >30% would be candidates, as would patients with head and neck cancer. Critically ill patients on mechanical ventilation would also be considered a candidate for an immune-modulating formula, with the exception of those with ongoing sepsis. In any of these patients, an immune arginine-containing formula should be utilized and should be provided for at least 10–14 days before switching back to a standard formula [54].

Caution is indicated in those patients who are critically ill who have ongoing sepsis, with the concern related to the possibility that arginine would stimulate inducible nitric oxide synthetase leading to production of nitric oxide and worsening hypotension. Such concern

is based primarily on two studies in the literature by Bower [55] and Bertilini [56] and a third unpublished study by Ross/Abbott Laboratories [57]. In two of the studies, the Bower study and the unpublished study by Ross, mortality was 2–2½ times greater in patients receiving the immune-enhanced formula compared to controls receiving standard formula [55, 57]. In the third study by Bertilini mortality was higher in the group receiving an immune-enhanced enteral formula compared to controls receiving PN [56]. In all three of these studies, less than 25–30% of patients had sepsis, and only in the Bower study was a truly high arginine-containing formula utilized [55–57]. In contrast, in a different study by Galban in which 100% of the patients were septic, use of a high-arginine formula improved mortality compared to controls receiving a standard formula [58]. Not surprisingly, in animal models with sepsis, supplementation with arginine in most studies improved survival [59].

Until more studies are available, the consensus opinion indicates that there is probably no evidence of a deleterious effect of arginine-containing immune formulas in a systemic inflammatory response syndrome alone. Use of arginine-containing immune formulas should be initiated if patients are not septic and meet the criteria for candidacy for use of an immune formula. Once started, such formulas may be continued if the patient becomes septic. However, if the patient is septic at initiation of enteral feeding, use of a non-arginine immune formula or standard formula is probably indicated.

If patients are not candidates for an immune formula, a standard enteral formula (at 1 cal/cc) should be utilized (Table 10.3). The only other decision upon initiating enteral feeding with regard to formula selection pertains to whether or not there is possible malassimilation (either maldigestion from pancreatic insufficiency or malabsorption because of abnormalities in small bowel physiology). In these situations, use of a small peptide formula fortified with medium-chain triglyceride oil or a fiber-containing formula may improve assimilation. Specialty formulas designed for chronic liver disease, respiratory failure, diabetes, stress, or renal failure are rarely indicated (because of increased cost and the fact that no data exist to show an impact from their use on patient outcome).

### 2.3.2. Monitoring Tube Feeding

Once feeding has been initiated, monitoring for tolerance is important. The clinician should evaluate segmental contractility. Evidence that the stomach is functioning is indicated by a nasogastric output $<1,200$ml/day (in light of the fact that over 5,000ml/day are produced

**Table 10.3**
**Categorization of Enteral Formulas**

- Oral supplements

  Rationale – Carbohydrate added to facilitate taste
  Examples – Carnation Instant Breakfast, Boost, Ensure, Resource

- Enteral formulas (primarily for tube only; exceptions* are palatable and may be used orally)

  Standard – 1 kcal/ml, standard protein (35–45 g/l)
  Examples – Osmolite, Isocal, Nutren*, Isosource
  High protein – Higher protein content (45–65 g/l), 1.5 kcal/ml
  Examples – Osmolite HN, Isocal HN, Replete*, Promote
  High caloric density – 2 kcal/ml
  Examples – 2 Cal HN*, Nutrin 2.0, Resource 2.0
  Fiber containing – Fiber added to reduce diarrhea
  Examples – Fibersource, Jevity, Ultracal, Probalance
  Elemental – Protein as individual amino acids, nearly fat free
  Examples – Vivonex TEN, Free Amino Acid (FAA), Vital HN
  Semi-elemental – Protein as small chain peptides, fat mostly as MCT oil
  Examples – Peptamen*, Subdue*, Peptinex, Perative, Alitraq

- Specialty formulas

  Pulmonary – Higher fat:carbohydrate ratio to reduce $CO_2$ production
  Examples – Pulmocare, Nutren Pulmonary
  Hepatic – Higher branch chain:aromatic AA ratio to ↓ encephalopathy
  Examples – Nutrihep, Hepaticaid
  Renal – Higher essential AA to ↑ nitrogen cycling, better electrolyte profile
  Examples (PreDialysis) – Renal Cal, Suplena
  (Dialysis) – Nepro, Novasource Renal
  Diabetic – Lower nonprotein calorie:nitrogen ratio, alternate carb sources
  Examples – Glucerna, Resource Diabetic, Glytrol
  Inflammatory bowel - Transforming Growth Factor Beta added to ↓ inflammation
  Example – Modulin
  Immune modulating – Arginine to ↑ immunity, omega-3 fish oil to ↓ inflammation
  Examples – Crucial, Impact, Resource Arginaid

through salivary and gastric secretion). Small bowel contractility may be evaluated by abdominal distention, presence of bowel sounds, and air-fluid levels on abdominal radiograph. Contractility in the colon may be indicated by passage of flatus and stool. Use of gastric residual volume is a very poor, inaccurate measure of gastric emptying and overall tolerance of enteral feeding. Identification and correction of electrolyte abnormalities and reassessment of the need for sedation and analgesia may help improve tolerance and minimize ileus. Naloxone (Narcan; Endo Pharmaceuticals, Inc., Chadds Ford, PA) may be given through the feeding tube into the small bowel to remove the effects of opioid narcotics at the level of the bowel without disturbing central nervous system analgesia. Minimizing the period that the patients are NPO helps improve tolerance. Clinicians should be encouraged to "feed an ileus" as long as there is no evidence of septic hypotension or need for pressor agents.

## 3. ENTEROSTOMY TUBES

Percutaneous enterostomy tubes are indicated when long-term enteral access of 4 weeks is necessary; these may be placed by endoscopic, fluoroscopic, or surgical techniques. The administration of a single dose of a broad-spectrum antibiotic pre-procedurally has been shown to reduce the risk of wound infection [60–68] and be cost-effective for percutaneous endoscopic gastrostomy. It is also recommended for other enterostomy placements as well [35] (Table 10.4).

### *3.1. Gastrostomy Tubes*

#### 3.1.1. Techniques for Placement

**3.1.1.1. Endoscopically.** The most common means of obtaining long-term gastric access is percutaneous endoscopic gastrostomy (PEG), the second most common indication for endoscopy of the upper gastrointestinal tract [69]. Typically performed under conscious sedation, it may also be performed at the bedside of critically ill patients [70]. Absolute contraindications to PEG placement are the same as those of upper gastrointestinal endoscopy as well as an inability to transilluminate the abdominal wall and appose the anterior gastric wall. Relative contraindications to PEG placement include coagulopathy, gastric varices, morbid obesity, prior gastrointestinal surgery, ascites, chronic ambulatory peritoneal dialysis, and neoplastic, infiltrative, or inflammatory disease of the abdominal wall [71].

Table 10.4
**Randomized Controlled Trials Evaluating Efficacy of Antibiotic Prophylaxis in Percutaneous Endoscopic Gastrostomy**

| | I——Treatment group——I | | | I——Control group——I | | | |
|---|---|---|---|---|---|---|---|
| *Reference* | *Treatment* | *N* | *Wound infections* | *Control* | *N* | *Wound Infections* | *P-value* |
| [60] | Cefoxitin 1 g IV | 17 | 5 | Placebo | 16 | 5 | N.S. |
| [61] | Cefazolin 1 g IV | 27 | 2 | Placebo | 28 | 9 | <0.025 |
| [62] | Am 3 g/Clav 1.2 g IV | 36 | 5 | No treatment | 60 | 21 | 0.05 |
| [63] | Cefazolin 1 g IV | 30 | 4 | Placebo | 31 | 6 | N.S. |
| [64] | Cefotaxime 2 g IV or Pip 4 g/Tazo 0.5 g IV | 201 | 1 | No treatment | 106 | 8 | <0.01 |
| | Am 1 g/Clav 1.2 g IV | 41 | 6 | Placebo | 43 | 19 | 0.004 |
| [65] | Ceftriaxone 1 g IV | 69 | 4 | No treatment | 72 | 17 | <0.05 |
| [66] | Cefuroxime 750 mg IV | 33 | 1 | Placebo | 33 | 6 | 0.03 |
| [67] | Am 1 g/Clav 1.2 g IV or Cefotaxime 2 g IV | 45 | 5 | Placebo | 38 | 18 | 0.001 |
| [68] | | | | | | | |

IV = intravenous; N.S. = not significant; Am = amoxicillin; Clav = clavulanic acid; Pip = piperacillin; Tazo = tazobactam

Percutaneous endoscopic gastrostomy tubes are most commonly placed using the Ponsky ("pull") technique, first described in 1981 [20]. After advancement of the endoscope, the stomach is insufflated with air, and an optimal site for PEG placement is determined by simultaneously transilluminating the gastric/abdominal wall and indenting the abdominal wall with a finger while visualizing that indention endoscopically. After a small incision is made, a needle/trocar is inserted through the abdominal wall and into the stomach. A guidewire is passed through this needle/trocar and grasped endoscopically. The guide wire is then withdrawn through the mouth, and a gastrostomy tube is affixed to it. Finally, the guidewire is pulled back through the esophagus, stomach, and abdominal wall and held into place by an internal retention device and an external bumper.

Advantages of PEG for obtaining gastric enteral access are the avoidance of general anesthesia, travel to the radiology suite, and radiation exposure that are required by other techniques.

**3.1.1.2. Fluoroscopically.** First described in 1981 [72], fluoroscopically guided gastrostomy is performed in the radiology suite and may be performed with only local anesthetic. After insufflation of the stomach with a nasogastric tube, a puncture is created using a needle; the location of the needle is confirmed by injection of contrast medium or aspiration of air bubbles. Usually T-fasteners are inserted around the puncture site to maintain apposition of the stomach and anterior abdominal wall. The gastrostomy tract is created in the center of the T-fasteners with serial dilation. The gastrostomy tube is placed through a peelaway sheath and the nasogastric tube removed [73].

Fluoroscopic gastrostomy is an attractive alternative in that typically only local anesthesia or light sedation is required. It also remains an option for those patients with obstructive pharyngeal or esophageal pathology that renders upper GI endoscopy difficult or impossible.

**3.1.1.3. Surgically.** First performed in 1876, surgical gastrostomy was the only means of ensuring long-term enteral nutrition until the late 1970s. A gastrostomy tube placed using the open or laparoscopic methods is typically performed in the operating room under general anesthesia; however, local anesthesia combined with conscious sedation may also be used. The most commonly used method, the Stamm technique, requires a small laparotomy in the medial upper abdomen. A small incision is made into the stomach, and the feeding tube is inserted and secured with purse-string sutures. The stomach is then affixed to the anterior abdominal wall, and the tube is often kept

in place with an inflated balloon or by attachment to the abdominal wall [18, 74].

Laparoscopic gastrostomy placement likewise occurs in the operating room under general anesthesia or conscious sedation. A gastrostomy tube is placed over a guidewire into the stomach under direct visualization from outside the stomach. T-fasteners are used to affix the stomach to the anterior abdominal wall. The procedure then takes place similarly to fluoroscopic placement except monitoring occurs intraperitoneally [75–78].

Benefits of surgical gastrostomy over endoscopic and fluoroscopic methods are limited. Gastrostomy tubes may be placed during other operative procedures, thus eliminating the need for additional sedation/anesthesia for a second procedure. Surgical gastrostomy also remains an option in patients with obstructive pharyngeal or esophageal pathology that renders endoscopy or nasogastric tube passage impossible.

Endoscopic and fluoroscopic methods are associated with less morbidity and cost than surgical methods, but the overall success rates are similar [16, 79–87], with published success rates typically greater than 90%. Factors that can lead to unsuccessful gastrostomy placement include unexpected obstruction of the pharynx or esophagus, deterioration of the clinical status of the patient intraprocedurally, incidental finding of gastric cancer, development of a hematoma at the gastrostomy site, and prior surgery that has altered esophageal, abdominal, or gastric anatomy [88].

### 3.1.2. Complications

As with nasal feeding tubes, complications of gastrostomy tubes can be divided into procedural and post-procedure complications (Table 10.5).

**Table 10.5**
**Complications of Percutaneous Endoscopic Gastrostomy (PEG) Tubes**

| *Procedural* | *Post-procedural* |
|---|---|
| -Aspiration | -Peristomal infection |
| -Hemorrhage | -Stomal leakage |
| -Perforation of abdominal viscera | -Buried bumper syndrome |
| -Prolonged ileus | -Fistulous tracts |
| -Peritonitis | -Inadvertent removal |
| -Cardiopulmonary complications related to sedation | -Gastric ulcer |
| | -Tumor implantation |

**3.1.2.1. Procedural Complications.** The procedural and long-term mortality rate directly related to gastrostomy placement is very low; however, the overall mortality of patients receiving gastrostomy tubes is up to 50% [89]. This high rate reflects the significant co-morbidities present in this population receiving PEGs rather than the procedure itself. Serious complications related to the procedure itself are comparable among methods of placement and range from 0.1–4% of cases. These include intraprocedural aspiration, hemorrhage, perforation of abdominal viscera, and prolonged ileus [84, 90, 91]. Risk factors for intraprocedural aspiration include supine position, advanced age, excessive sedation, and neurological impairment. The clinician can minimize the risk of intraprocedural aspiration by avoiding oversedation, minimizing air insufflation of the stomach, and thoroughly emptying the gastric contents prior to the procedure [71].

Acute hemorrhage during gastrostomy placement is uncommon, but is likely increased in the setting of a coagulopathy, iatrogenic or otherwise. Checking coagulation studies prior to the procedure is recommended [81]. On the other hand, pneumoperitoneum as a result of percutaneous approaches is common and of no clinical consequence in the absence of signs of peritoneal irritation [92].

**3.1.2.2. Post-Procedural Complications.** The overall post-procedural complication rate of gastrostomy tubes ranges from 4.8–10.8% regardless of the method of placement [84, 93]. Peristomal infection is the most common complication of gastrostomy placement, but the vast majority of infections are mild and easily treated with oral antibiotics [64, 94]. To minimize morbidity and even mortality of peristomal infections, the administration of prophylactic antibiotics prior to placement, early recognition of wound infections, treatment with antibiotics, and local wound care are fundamental to the successful management of peristomal infections [61, 62, 64].

Leakage around the gastrostomy site is a common problem [95]. Peristomal infection, excessive cleansing with irritating solutions (e.g., full strength hydrogen peroxide and betadine), and excessive tension and side torsion on the external portion of the feeding tube all increase risk of leakage. Management of excessive leakage consists of treating infection if present, providing quality ostomy skin care, loosening the outer bumper to minimize tension, and stabilizing the external gastrostomy tube to prevent side torsion [47].

Buried bumper syndrome results from the partial or complete growth of gastric mucosa over the internal bumper of the gastrostomy tube and can result in migration of the bumper externally where it may

lodge anywhere along the gastrostomy tract. Risk factors include excessive tension between the internal and external bumpers, poor wound healing, and significant weight gain [36]. Clinically, buried bumper syndrome leads to peristomal leakage or infection, abdominal pain, an immobile catheter, or resistance with infusion of formula. The buried bumper can be confirmed endoscopically when possible, or by gastrografin study with the patient in the prone position. Treatment consists of salvaging the stoma tract while returning the internal bumper back into the lumen of the stomach [96, 97].

Fistulous tracts connecting the stomach, colon, and skin are uncommon, but potentially life-threatening complications of gastrostomy tubes. If the colon is inadvertently punctured during endoscopic or fluoroscopic gastrostomy placement, or less commonly, if the tube erodes into the adjacent colon, patients may present acutely ill with colonic perforation. If the colon is traversed inadvertently during initial placement the patient may be asymptomatic until gastrostomy tube replacement when the replacement tube is inserted only as far as the colon. Then patients will present with leakage of stool around the gastrostomy site and diarrhea resembling feeding formula. Diagnosis can be made by infusion of gastrografin into the gastrostomy tube and observing the filling of the colon radiographically. Elevation of the head of the bed to displace the colon inferiorly and use of the safe track technique may minimize the risk of inadvertent puncture of the colon (Fig. 10.2) [98]. Treatment usually consists of gastrostomy tube removal, but surgical repair is indicated if peritoneal signs are present.

Inadvertent gastrostomy tube removal should be managed urgently. Gastrostomy tract maturation usually occurs within the first 7–10 days, but in the presence of malnutrition or poor wound healing it may be delayed as long as 4–6 weeks [90]. A gastrostomy tube that is inadvertently removed during this time period should be promptly replaced endoscopically or fluoroscopically as the tract may be immature and the stomach and anterior abdominal wall can separate, resulting in free perforation. If recognition is delayed, management includes nasogastric decompression, broad-spectrum antibiotics, and repeat gastrostomy after 7–10 days. Surgical exploration is indicated in patients with clinical evidence of peritonitis. Once maturation of the tract has occurred, a replacement tube may be placed at the bedside without endoscopic or fluoroscopic guidance if done without delay. Patients prone to pulling at tubes may receive benefit from an abdominal binder or placement of a low profile device (button) [90].

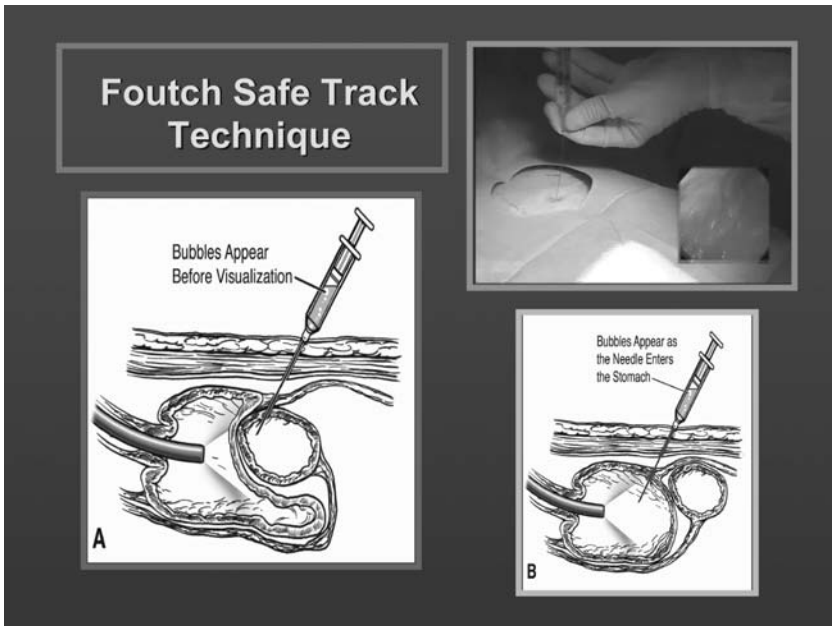


**Fig. 10.2.** Safe tract technique.

## *3.2. Jejunal Tubes*

### 3.2.1. Gastrojejunal Tubes

In the setting of impaired gastric motility, pancreatitis, risk for reflux and/or aspiration, gastric outlet obstruction or any time enteral feeding into the small bowel with simultaneous gastric decompression is desired, a gastrojejunal tube should be placed [22, 99].

**3.2.1.1. Techniques for Placement.** ***Endoscopically*** The jejunal arm of a percutaneous endoscopic gastrojejunostomy (PEG-J) tube is placed using an initially placed PEG tube. Most commonly, a guidewire is placed through an existing gastrostomy, and it is grasped endoscopically and carried into the jejunum. The guidewire is left in the jejunum and the endoscope withdrawn. The jejunal extension tube is then threaded over the guidewire into the small bowel [33, 100]. Advantages of PEG-J are similar to those of PEG; additionally, if a patient already has a PEG tube in place, conversion to PEG-J does not require an additional skin puncture. Success rates over 90% have been reported for PEG-J [101–104].

***Fluoroscopically and Surgically*** Gastrojejunal tubes may be placed fluoroscopically or during laparotomy or laparoscopy. Fluroscopic technique is similar to endoscopic PEG-J. Using an existing gastrostomy, a guidewire is advanced through the stomach past the ligament of Treitz, and the jejunal extension tube is advanced over the wire into the jejunum under fluoroscopic guidance. Gastrojejunal tubes can be placed during laparotomy or laparoscopy methods using any of the above methods. Using manual and/or endoscopic methods the jejunal tube is positioned into the small bowel. The gastric component of the tube is left in the stomach. These modalities have success rates that are comparable to those of PEG-J [105].

### 3.2.2. Direct Jejunal Tubes

In patients without a need for gastric decompression, it may be desirable to place a enterostomy tube directly into the jejunum. Jejunostomy tubes are placed primarily endoscopically or surgically. Advantages and disadvantages of endoscopic vs. surgical methods are similar to those of gastrostomy placement.

**3.2.2.1. Techniques for Placement.** ***Endoscopically*** Direct percutaneous endoscopic jejunostomy (D-PEJ) is performed in a manner similar to that of the PEG 'pull' technique. A pediatric colonoscopy or enteroscope is advanced to the small bowel, and transillumination and finger indentation are performed over the jejunum rather than the stomach. A needle/trocar is inserted through the abdominal wall into the jejunum, and an insertion wire is passed through the trocar and grasped endoscopically. The remainder of the procedure is as described for the PEG 'pull' technique [106, 107]. In comparison studies, D-PEJ has been demonstrated to have greater longevity and decreased need for re-intervention compared PEG-J [101, 108, 109]. Therefore, in some cases it may be advantageous to place separate direct gastrostomy and jejunostomy tubes rather than a single combined gastrojejunal tube.

***Surgically*** There are three basic types of surgical jejunostomy techniques in use: the Witzel technique, Roux-en-Y jejunostomy, and needle catheter jejunostomy. In the Witzel technique, the surgeon creates a submucosal tunnel in the small bowel through which the jejunostomy tube is threaded. In doing so, leakage of small bowel contents is minimized [19]. Needle catheter jejunostomy may be placed by laparotomy or laparoscopy; in this case a needle is threaded into the small bowel, and a guidewire is passed into the jejunum. A small jejunostomy catheter is passed over the guidewire into the jejunum. However, the smaller size of this catheter may lead to more frequent occlusion.

Jejunostomies may also be placed laparoscopically. After ports are placed in the left upper quadrant and medial lower abdomen, the jejunum is approximated to the anterior abdominal wall using T-fasteners. A guidewire is then passed into the jejunum, and a jejunostomy tube is advanced into the small bowel [76, 110]. Direct percutaneous endoscopic jejunostomy placement is successful in 68–100% of attempts [101, 106, 111, 112], while success rates approach 100% with surgical jejunostomy [76].

#### 3.2.3. Complications

Complications of jejunal tubes are similar to those of gastrostomy tubes described above. It deserves mention that gastrojejunal feeding tubes have a higher incidence of malfunction (up to 70%), migration, and/or occlusion of the distal, smaller jejunal extension tube [103, 113]. Additional complications of direct jejunostomy tubes include jejunal volvulus and small bowel perforation [112]. Despite expert opinion, the data are controversial as to whether more distal feeding with jejunal tubes decreases a patient's aspiration risk significantly [50, 114].

## 4. CARE OF THE FEEDING TUBE

### *4.1. Skin Care*

The skin around tube enterostomies should be cleaned with mild soap and water, then rinsed and dried thoroughly. Use of irritant cleansers or full strength hydrogen peroxide should be avoided as they may lead to poor wound healing and leakage around the tube. Likewise, routine use of antibiotic ointments is not advised, and dressings at the tube insertion site are not necessary unless there is drainage at the site.

Skin care of the nasal area is important in patients with nasal tubes as the tubes can be irritating, and there is often prolonged exposure to adhesive products. Additionally, regular repositioning of the nasal tube reduces the risk of pressure necrosis.

Regardless of the method of placement, oral hygiene is appropriate for patients with feeding tubes. This is especially important in patients with a decreased level of consciousness or those on mechanical ventilation.

### *4.2. Prevention of Clogging*

Tubes with smaller lumens are more prone to clogging, but maintenance of all sizes of tube is important to minimize clogging. Flushing with water regularly is paramount. Other causes of clogging include

accumulation of pill fragments, frequent checking of residuals, and formulas containing high protein concentrations [115, 116]. Use of medications in liquid form is recommended, as is flushing after each medication administration [117].

### *4.3. Replacement Enterostomies*

The external portion of gastrostomy and gastrojejunostomy tubes may be several centimeters long, requiring that caution be used to avoid traction or side torsion, which may promote tube leakage. In patients at high risk of pulling at the tube, or in patients desiring a more cosmetically acceptable option, a low-profile port ("button") may be used. The internal retention bolster of percutaneous tubes is constructed of either solid material (silicone or polyurethane) or a silicone balloon. Solid internal bolsters may last a year or longer and are most commonly used in initial endoscopic enterostomy tube placement. Balloon-type internal bolsters have a lifespan of 3–6 months and are more commonly used in radiological tube placements as well as replacement tubes due to the ease of placement [118].

## 5. CONCLUSIONS

Enteral nutrition is the route of choice in patients with a functioning gastrointestinal tract. A number of enteral access options are available to patients in need of nutritional support. Consideration of the appropriate device, level in the gastrointestinal tract, and insertion method are critical to ensure optimal outcomes. In addition, appropriate aftercare and monitoring with early recognition and treatment of any complications are crucial to the success of enteral nutrition access.

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# 11 Parenteral Nutrition

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***Contents***



*Summary*

Parenteral nutrition becomes necessary when the gastrointestinal tract has insufficient function as to afford sufficient fluid, electrolyte and nutrient absorption. Indications for this therapy include prolonged postoperative ileus, prolonged intestinal obstruction, short bowel syndrome, various malabsorptive disorders, proximal enteric fistulas for which an enteral feeding tube cannot be placed distal to, severe acute pancreatitis and severe mucositis/esophagitis. Parenteral nutrition, although typically delivered through a large central vein, can also be infused peripherally with special techniques. Rarely, intradialytic parenteral nutrition is required. Parenteral nutrition

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includes macronutrients (protein in the form of a balanced, free amino acid solution, carbohydrate in the form of a dextrose monohydrate and fat in the form of a lipid emulsion), fluid, electrolytes (sodium, potassium, magnesium and acetate/chloride to adjust pH), minerals (calcium, phosphorous, iron in some individuals), trace minerals (zinc, copper, selenium) and vitamins (water and fat-soluble). Numerous complications may develop as a result of parenteral nutrition including mechanical issues related to the catheter for solution delivery or its insertion, that include infection, occlusion (venous thrombosis or non-thrombotic occlusion), electrolyte disturbances and hyperglycemia, as well as hepatic, renal, pulmonary, and bone complications. Therapy should be appropriately prescribed and rigorously monitored for efficacy and safety.

**Key Words:** Parenteral nutrition, Malnutrition

## 1. INTRODUCTION

Parenteral nutrition (PN) is necessary when enteral feedings are either contraindicated or cannot be provided in sufficient quantities to meet necessary nutritional requirements to maintain life and overcome malnutrition in certain patients. It the late 1960s the question was asked if total parenteral nutrition (TPN) could be another means of supplying nutrition other than enteral nutrition (EN) or peripheral parenteral nutrition (PPN). The use of enteral nutrition had already been an established means of delivering nutrition since ancient times, where rectal feedings were used to deliver nutrition [1, 2]. PPN was initially developed in 1955 and was used until 1965 until serious side effects of Lipomul™ led to its discontinuation from the United States market in the early 1960s [3]. The absence of a lipid emulsion posed a major problem in the delivery of glucose, because large hypertonic volumes were being infused peripheral veins. Later in the decade, TPN was shown to be an effective method of administering nutrition after Stanley Dudrick and Johnathan Rhoads initially inserted catheters into the superior vena cava of beagle dogs to provide their sole source of nutrition from 72 to 256 days [4]. Later they showed that the administration of TPN could improve the growth and clinical status of malnourished infants [5]. Since that time, TPN has become and is still considered to be lifesaving therapy in certain clinical scenarios. Currently, PN is often recommended if

enteral intake (oral or tube feeding) has been or is anticipated to be inadequate for a 5- to 10-day period [6]. However, carefully performed, prospective, randomized controlled trials to support the efficacy of this approach are few in number. Due to the lack of controlled data, the use of PN requires an integration of information from heterogeneous sources, including: pertinent clinical trials, clinical expertise in the illness or injury being treated, reasonable estimates of inadequate enteral intake and clinical expertise in nutritional therapy.

## 2. INDICATIONS FOR PARENTERAL NUTRITION

The purpose of TPN is to provide the critically ill and non-critically ill patients with all of the basic nutrient requirements, which include: fluids, proteins, carbohydrates, fats, minerals, trace elements and vitamins. The intent is to help the patient recover from preexisting nutritional deprivation and/or significant multiorgan system failure and to prevent malnutrition from dictating the patient clinical course [7]. Malnutrition can potentially cause a number of deleterious outcomes such as: increased susceptibility to infection, poor wound healing, increased frequency of decubitus ulcers, overgrowth of bacteria in the gastrointestinal tract and abnormal nutrient losses through the stool [8–12]. These alterations result in increased morbidity and mortality among malnourished, hospitalized patients [13–17].

PN is indicated to prevent adverse effects of malnutrition in patients who are unable to consume adequate nutrition via oral or enteral routes. In general, PN is indicated if the small intestine and/or colon is anticipated to be dysfunctional, obstructed or inaccessible for longer than 5 to 10 days [6, 18]. Short bowel syndrome (SBS), radiation enteritis, proximal fistulas that nasoenteric feeding tubes cannot be placed distal to, mucosal disease of the small bowel causing malabsorption, distal high output gastrointestinal fistulas, non-operative mechanical obstructions, persistent postoperative ileus, intestinal pseudoobstruction unresponsive to enteral feedings, intractable vomiting, severe diarrhea (>500ml/day), severe mucositis/esophagitis, severe acute pancreatitis and small bowel or colonic obstructions (including strictures) are examples of disease states that are indications for PN (Table 11.1).

Table 11.1
Indications for Total Parenteral Nutrition

1. Malabsorption
   a. Short bowel syndrome (SBS) (<150 cm small bowel in the absence of colon in continuity or <100 cm small bowel with colon in continuity)
   b. Radiation enteritis
   c. Other (refractory sprue, microvillus inclusion disease and others)
2. Ileus/pseudoobstruction
3. Small bowel or colonic obstruction
4. High output gastrointestinal fistulas for which feeding distal to the fistula is impossible or would result in inadequate absorptive surface for adequate absorption
5. Severe mucositis/esophagitis
6. Intractable vomiting

## 3. TYPES OF PARENTERAL NUTRITION

### *3.1. TPN (also referred to as central parenteral nutrition or CPN)*

TPN can be accomplished via percutaneous infraclavicular subclavian vein catheterization with advancement of the catheter tip to the junction of the superior vena cava and right atrium. Cannulation of a large-bore, high-flow central vein such as the superior vena cava permits infusion of hyperosmolar (usually $>1,600$ mOsm/l) nutrient solutions that cannot be not tolerated by smaller, low-flow peripheral veins. Central catheterization of the subclavian vein is preferred because lower rates of bacterial colonization have been observed when compared to other routes of central catherization [19]. There have been many other approaches that have been successfully performed when the subclavian vein is not accessible such as: internal jugular, basilic, saphenous and femoral vein catheterization. Thoracotomy with direct insertion into the right azygos vein [20] or right atrial appendage has also been performed when more accessible access is unavailable. A peripheral approach to access the central veins can be accomplished using a peripherally inserted catheter (PICC) to provide TPN. Though this technique is associated with a dramatically lower risk of associated pneumothorax,

there is a higher risk of thrombosis compared to percutaneous insertion if the catheter tip is placed proximal to the superior vena cava [21, 22].

### *3.2. Peripheral Parenteral Nutrition (PPN)*

PPN should be provided to patients who require only short-term therapy, which is defined as less than 5 to 10 days. These patients should also be able to meet some, but not all of their nutritional requirements via enteral means. Essential to the development of PPN was the development of a non-toxic fat emulsion and recognition that fat emulsions administered with dextrose represented an optimal provision of energy [23]. The use of the peripheral vein to provide nutritional support avoids many of the potential mechanical and infectious complications of TPN [24, 25], but is associated with a high risk of developing thrombophlebitis, due to the hypertonic nature of the solution as well as the osmolality rate (product of osmolality and infusion rate) [26–28]. There are several factors in the pathogenesis of thrombophlebitis in patients receiving PPN: (1) osmolality, pH and lipid content of the PPN solution and the presence of particulate matter; (2) diameter length and composition of the catheter; (3) duration, rate and volume of the infusion; (4) diameter and anatomic position of the vein; (5) insertion technique [29, 30]. Early studies of PPN using crystalline amino acid- and glucose-based solutions found phlebitis rates of almost 100 percent when the osmolarity was increased above 600 mosmol/l [31, 32]. A correlation between hyperosmolarity and phlebitis is not apparent when lipid-based solutions are utilized. Kane et al. randomized 36 patients to receive feeds of osmolarity of 1,200 or 1,700 mosmol/l. They found no difference in the incidence of thrombophlebitis [33]. Similarly, Williams et al. demonstrated no significant difference in the incidence of thrombophelibitis between patients receiving lipid-based feeds with an osmolality of 650 mosmol/kg and the those receiving an osmolality of 860 mosmol/kg (13 and 18 percent, respectively) [34]. There are ways to reduce the risk of the development of thrombophlebitis: (1) administration of 10 mg of hydrocortisone and 1,000 units of heparin per liter of PN solution, (2) avoidance of medications in the PN solution that are known to cause thrombophlebitis (acyclovir, aminoglycosides, amphotericin, erythromycin, high-dose penicillin, phenytoin, potassium and vancomycin), (3) dextrose solutions of greater than 10% concentration or 900 mOsm should not be used and (4) at least 50% of the total energy should be provided as lipid emulsion. Adherence to these principles can decrease the risk of the development of thrombophlebitis [23, 35].

### *3.3. Intradialytic Parenteral Nutrition (IDPN)*

Malnutrition is an important problem in patients treated with chronic hemodialysis or peritoneal dialysis. It occurs in 40 to 70 percent of patients (depending upon the method used to measure nutritional status), with an increasing length of time on dialysis correlating with an increasing decline in nutritional parameters [36, 37]. Prior to initiating IDPN, the presence of certain pathologic processes such as: underdialysis [38, 39], drug toxicity, gastroparesis [40, 41] and singultus [42] need to be ruled out. Similar to the aforementioned forms of parenteral nutrition, IDPN is indicated only in patients who cannot tolerate enteral supplementation and who do not have available central venous access.

There are certain limitations to IDPN. It is the most costly and least efficient nutritional supplement. IDPN often costs twice as much as dialysis itself, and only 70 percent of the nutrients are actually delivered to the patient because of loss into the dialysate [43]. Malnutrition may persist, since IDPN is administered only 3 days per week for approximately 4 h [44]. It may be associated with a lower than expected delivered dose of dialysis, possibly due to increased urea generation [45]. Nevertheless, IDPN is convenient (because it is delivered during dialysis) and is likely to be beneficial in some patients [46]. However, although a number of studies suggest that IDPN provides substantial benefit, most were case reports, retrospective or poorly designed [47]. In one study, a 9-month treatment period was associated with a 12 percent rise in the plasma albumin concentration and an apparent improvement in survival (64 versus 52 percent in patients not receiving IDPN) [48]. However, the applicability of these findings is uncertain since the study was retrospective, IDPN was compared to no therapy rather than other nutritional interventions and the two groups were not strictly comparable at baseline [49].

The optimal indications for IDPN have not been established. The use of this modality should be provided to malnourished dialysis patient who cannot tolerate oral supplements, but who can consume at least 50 percent of the prescribed caloric intake. If this degree of oral intake cannot be reached, either a nasoenteral feeding tube with nighttime enteral nutrition or, if oral intake is not tolerated, the institution of TPN should be considered [49]. Total parenteral nutrition is often required in the rare patient with severe malabsorption, severe malnutrition, or severe intolerance of oral supplements. Although generally well tolerated, TPN solutions typically contain added potassium, phosphorus and magnesium. Thus, patients with end-stage renal disease receiving TPN are at risk for the development of hyperkalemia, hyperphosphatemia and hypermagnesemia. Elimination

of the added electrolytes can prevent these problems, but carries the reverse risk of electrolyte deficiencies with prolonged therapy. The patient should then be carefully monitored, and electrolytes should be added if the plasma levels fall below the normal range. There is a theoretical risk of developing hypoglycemia with abrupt discontinuation of IDPN secondary to the longer half-life of insulin as compared to dextrose. This has been studied, including a randomized trial that showed that progressive versus abrupt discontinuation of TPN did not reveal a significant change in counter-regulatory hormones or increased hypoglycemia [50–52]. Nevertheless, close monitoring of blood glucose values should still occur. The rate should not be greater than 150 ml/h to avoid profound hyperglycemia. Blood glucose monitoring should be frequent during the infusion and at 30 and 60 min after the infusion to detect reactive hypoglycemia. The rate is then gradually increased so that the full liter can be infused during a 4-h dialysis session [18].

## 4. COMPONENTS OF TOTAL PARENTERAL NUTRITION

The specific formulation prescribed for a patient depends on the patient's estimated nutrient requirements and ability to tolerate specific nutrients without adverse effects. The patient's protein, energy and fluid requirements are the most important considerations in designing an appropriate parenteral formulation. For example, basal energy expenditure (BEE) of a relatively unstressed middle-aged patient with restricted activity, who has no fever or other hypermetabolic condition, should be maintained in an acceptable range of approximately 20–25 kcal (7.2 kJ)/kg/body weight/day. The BEE is the amount of energy required to perform metabolic functions at rest and is influenced by both body size and illness. BEE classically is estimated by the Harris-Benedict equation [53–55]. The use of this measurement in the critically ill has traditionally involved multiplication by a stress factor of 0.5 to 2.5 [54, 56]. However, the use of the stress factor may result in overfeeding and may predispose the patient to liver steatosis, hyperglycemia, electrolyte imbalances, respiratory embarrassment due to increased CO2 production and macrophage dysfunction. There is evidence to suggest that the total energy expenditure is maximal during the 2nd week of critical illness and may reach 50 to 60 Kcal/kg per day [57]. However, there are no data supporting the delivery of nutritional support at this caloric level.

### 4.1. Glucose/Carbohydrates

One of the primary sources of energy is glucose. Dextrose is usually the predominant energy source in TPN formulations and is the required fuel for erythrocytes, white blood cells, bone marrow and the renal medulla because they lack the enzymatic machinery to oxidize fatty acids, whereas the brain prefers to use glucose as fuel, but can use other sources. Dextrose given parenterally is in the form of a monohydrate providing 3.4 kcal/g. It is readily available in various concentrations in liquid form. Using dextrose as a primary means to meet large energy needs within a reasonable fluid volume requires an extremely hypertonic solution (Table 11.2). Providing calories as dextrose stimulates insulin secretion and decreases hepatic glucose output, thereby reducing the need for skeletal muscle protein to provide amino acid precursors for gluconeogenesis. In addition, direct oxidation of dextrose spares the oxidation of amino acids.

### 4.2. Lipid Emulsion

Another major source of energy is lipid. Lipid emulsions consist of tiny droplets ($<0.5\,\mu m$) with hydrophobic triglycerides as the core and cholesterol derived from egg yolk phospholipids, soybean oil or a combination of soybean and safflower oil triglycerides surrounded by a solubilizing and stabilizing surface layer of the emulsifying phospholipids. Lipid emulsions should not be used in patients who have an allergy to eggs. Glycerol is added during the manufacturing process rendering lipid emulsions isotonic to plasma. Once in the bloodstream, lipid emulsion particles rapidly acquire apolipoproteins from contact with circulating high density lipoprotein particles and are metabolized in a similar fashion to chylomicrons. Once sufficient

**Table 11.2**
**Osmolalities and energy values of intravenous dextrose solutions**

| | | |
|---|---|---|
| 5 | 278 | 170 |
| 10 | 523 | 320 |
| 15 | 896 | 510 |
| 20 | 1,250 | 680 |
| 25 | 1,410 | 850 |
| 30 | 1,569 | 1,020 |
| 70 | 3660 | 2,330 |

Dextrose conc. (in grams) Osmolality (mOsm/kg $H_20$) kcal/l

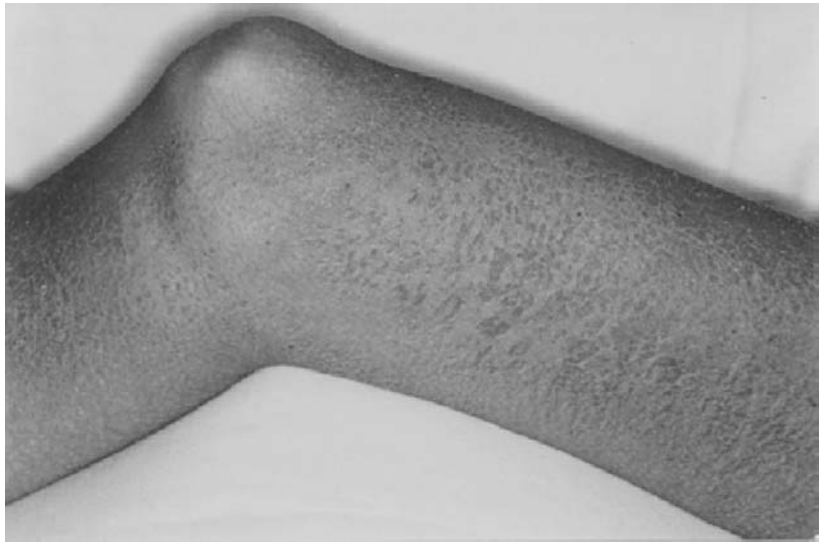


**Fig. 11.1.** Cutaneous rash associated with fatty acid deficiency.

amounts of dextrose have been provided to meet the requirements of glucose-dependent tissues and the brain, lipid calories are effective as glucose calories in conserving body nitrogen and supporting protein metabolism [58, 59]. When used as a caloric source, typically 20% to 30% of total calories are provided; 2% to 4% of the total calories should be given as linoleic acid as a minimum to prevent fatty acid deficiency [60]. Administering a TPN solution devoid of lipid can cause biochemical evidence of essential fatty acid deficiency within 2 weeks [61] (Figs. 11.1 and 11.2).

Providing a portion of infused calories as lipid reduces plasma insulin concentration, sodium and water retention and hepatic fat accumulation [62]. Lipid emulsions may be used in the setting of pancreatitis, not associated with hypertriglyceridemia as long as the triglyceride concentration is monitored as with any other patient who is receiving intravenous lipids [63].

Uncommon side effects of lipid infusions include fever, headache, back pain, dyspnea, chills, nausea, chest pain and oily taste. Lipid emulsion can cause pulmonary dysfunction [64], hepatic phospholipidosis [65], impaired immune system function [66], pancreatitis [67], decreased platelet aggregation [68], fat overload syndrome [69] and hypersensitivity reactions [70].

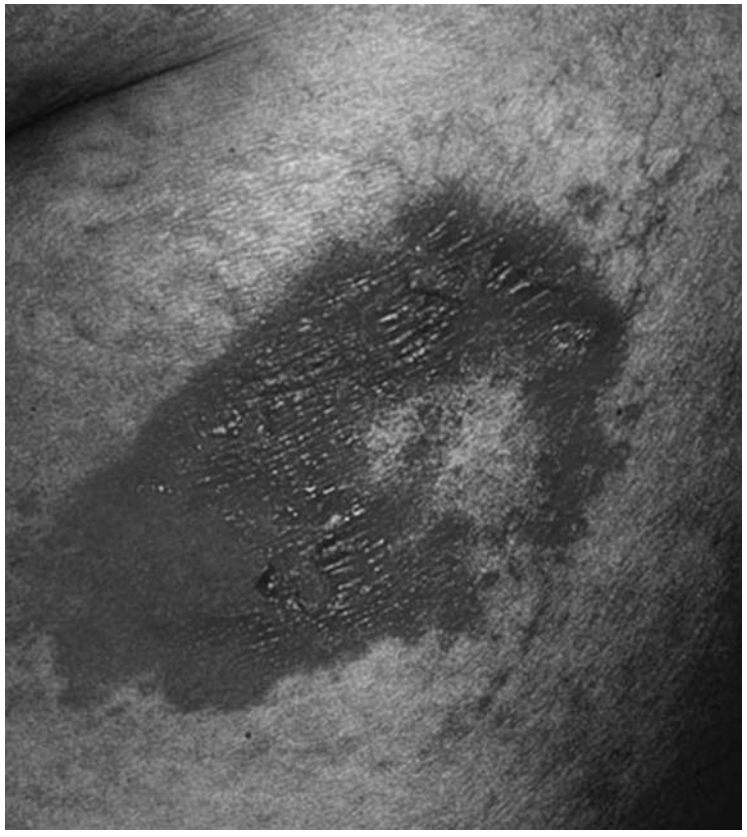


**Fig. 11.2.** Biochemical evidence of essential fatty acid deficiency.

### *4.3. Use of Medium-Chain Triglycerides to Decrease the Risk of Immunosuppression in Lipid Emulsions*

Lipid emulsions (LE) for parenteral use are complex emulsions containing fatty acids, glycerol, phospholipids and tocopherol in variable amounts and concentrations. Fatty acids may have different impacts on phagocytic cells according to their structure. Experimental and clinical studies have consistently shown that LE modifies monocyte/macrophage and polymorphonuclear phagocytosis causing an inhibitory effect on the functional activity of the phagocytic system. Though this is still clinically controversial, current formulations of lipid emulsions may have a harmful impact because TPN with lipids is recommended in hypercatabolic conditions where inflammation and infection are present. Over the past 2 decades, the clinical use of lipid emulsion for the nutritional support of hospitalized patients has relied

exclusively on long-chain triglycerides, or LCTs, providing both a safe, calorically dense alternative to dextrose and a source of essential fatty acids needed for biological membranes and maintenance of immune function. LE based on long-chain triglycerides (LCTs) are the main parenteral fat source and may have adverse effects on the immune system, especially when given in high doses over a short period of time. Recent studies have demonstrated that LE containing medium chain triglycerides (MCT) may have some advantages because of their positive effects on polymorphonuclear cells, macrophages and cytokine production, particularly in critically ill or immunocompromised patients [71]. In a study where patients underwent abdominal surgery in which TPN was considered to be necessary, Koller et al. randomized patients to a conventional prescription in which lipid was composed of (LCTs) or to an isocaloric mixture of LCTs and MCTs. There was a statistically significant increase in the relatively non-inflammatory leukotriene, LT-B5, in those patients receiving the MCT product [72]. A double-blind study performed by Grau et al. showed that there were fewer intraabdominal abscesses in the group receiving a lipid emulsion containing a MCT mixture as compared to a mixture containing LCTs. Lower mortality was observed in the group receiving MCTs, but this did reach statistical significance [73]. Montero et al. observed that septic patients who received a mixture of MCT and LCT had a significant increase in certain nutritional parameters (retinol-binding protein and nitrogen balance), when compared to those receiving LCT only. There was no difference in mortality or hospital stay [74].

### *4.4. Protein (Amino Acids)*

The purpose of providing amino acids is to maintain the nitrogen balance and replete lean tissue in cachetic patients. The amount of protein needed to achieve these goals is affected by the amount of non-protein calories provided and the patient's clinical condition. Insufficient non-protein calories, catabolic illness, protein losing enteropathy, nephropathy, hemodialysis and peritoneal dialysis increased protein requirements. In general, most hospitalized patients need 0.8 to 1.5 g of protein per kilogram (kg) body weight per day.

Formulations of crystalline L-amino acids have been developed for specific clinical problems, with varying claims for superiority in certain clinical situations such as renal and hepatic failure, trauma and growth in infants. The eight amino acids essential for physiologically normal adults are present in all formulas, as are histidine and arginine, which are needed for young children. Glycine, alanine and proline are

present in moderately high concentrations in general adult formulations as sources of nonessential amino nitrogen. The ratio by weight of essential to total amino acids in the pediatric and adult solutions varies between 0.41 and 0.54; higher ratios are present in formulas intended for patients with renal or hepatic failure. Some amino acid formulas contain sodium bisulfate as a preservative, and thus patients with hypersensitivity to sulfa should not receive these formulas. Even though the energy cost of amino acids is high, amino acids delivered to patients should be included in the estimate of energy provided by the PN. There is a small contribution from amino acids involved in the daily synthesis and accumulation of stored glucose (as glycogen derived from gluconeogenesis from amino acids is limited).

Crystalline amino acids are available in concentrations of 8.5% to 15%. The amino acid solution is then diluted with an appropriate amount of dextrose to achieve a desired concentration, usually between 3.5% to 5.0%. In patients with non-oliguric renal failure in patients who are dialysis dependent, protein intake should not be restricted due to increased losses via the dialysate. This amounts to 6 to 8 g in hemodialysis, 12 to 16 g during peritoneal dialysis and continuous hemofiltration. In hepatic failure the concentration should be less than 3.5% [18, 75]. In patients who are fluid restricted or undergoing fluid restriction, a concentration of greater than 4.25% should be used.

Solutions containing only essential amino acids have been developed for patients with acute renal failure. It was initially thought that by only providing essential amino acids an overall lower amino acid load would be created that would result in a lesser deterioration of renal function and would help to synthesize non-essential amino acids. Unfortunately, when compared to mixed formulations of essential and non-essential amino acids, there was no improvement in renal function [76]. Amino acids metabolism is more effective when a formulation of mixed essential/non-essential amino acids is used [77]. Nevertheless, there may be benefit from the addition of histidine to the renal formulas. Between 67% to 100% of the total amino acids in these formulas are composed of the eight amino acids and histidine. Histidine is considered to be an essential amino acid in patients with renal failure. In a small study, Druml et al. showed that histidine clearance is elevated when compared to controls in acute renal failure, chronic renal failure and hemodialysis patients [78]. Recently, Yatzidis et al. showed that oral supplementation with histidine along with glycine, aspartic acid, glutamic acid, glutamine and arginine increased urine volumes within a 24-h period and decreased 24-h albuminuria [79]. Further studies need

to be performed to show the effectiveness of supplemental histidine combined with parenteral formulations in renal dysfunction.

### *4.5. The Role of Branched Chain Amino Acids (BCAA)*

Modified amino acid solutions have been developed for specific disease states and physiologic conditions. Solutions containing high concentrations of BCAA have been advocated for the use in patients with hepatic encephalopathy. These solutions contain 35% to 40% of branched chain amino acids, whereas standard formulas only contain 20%. The clinical efficacy of parenteral BCAA-enriched TPN solutions in patients with acute hepatic encephalopathy were evaluated in nine prospective randomized controlled trials through 1989. Five of the trials were reviewed using meta-analytical methodology to pool data across studies [80]. Patients who received BCAA-enriched solutions demonstrated a statistically significant improvement in mental recovery from high-grade encephalopathy during short-term (7–14 days) nutritional therapy. There was enough heterogeneity in mortality rates among the studies to preclude a meaningful aggregation of accrued mortality data. Although a pooled analysis of all of the trials suggested a beneficial effect of BCAA-enriched formulas as a primary therapy in patients with acute hepatic encephalopathy, the studies had several shortcomings that limit their use in current clinical practice. For example, the control groups usually received suboptimal, and possibly harmful, nutritional support consisting of high-dextrose solutions without amino acids. Another study only compared BCAA-enriched TPN with a standard amino acid TPN solution. None of the studies reported on the complications associated with nutritional therapy or whether short-term benefits of nutritional therapy led to a long-term reduction in complications. More recent reviews that included additional data concluded there was no affect on mortality from BCAA use and that the current evidence-based literature did not support the routine use of BCAAs [81–83]. Data from a subsequent 1-year double-blind randomized multicenter trial of 174 patients found that treatment with oral BCAA supplementation significantly reduced the length of hospital stay, mortality, anorexia and improved Child-Pugh score, although the compliance was poor [84]. A Cochrane-based review of the use of BCAA in patients with chronic hepatic encephalopathy identified 11 randomized trials that included a total of 556 patients [85]. A significant improvement was seen in BCAA use on the severity of hepatic encephalopathy, but mortality was unaffected. Although this positive outcome was observed, the studies that elucidated this were those of poor methodological quality. The concept that

increasing the plasma BCAA:AAA (aromatic amino acids) ratio leads to decreased encephalopathy has been questioned by some investigators as brain uptake of BCAA in some cirrhotics may be similar to that of healthy controls [86] and may be a better correlate of hepatic function than the degree of encephalopathy in others [87].

### *4.6. Fluid Volume*

The fluid component must meet individual requirements as determined by evaluation of the clinical and laboratory data. In addition to clinical factors that could cause excessive retention or loss, consideration must be given to insensible fluid losses, fluid intake with medications and infusions designed to keep veins patent. Meticulous recording of fluid intake and output is necessary. Assessment of volume status by hemodynamic monitoring may be necessary in critically ill patients. PN mixtures can be administered to patients with varying fluid needs. Similar to the acute care setting, the extra fluid requirements can be added to the PN mixture in the home setting. In a fluid-restricted patient, both dextrose and amino acid concentrations can be increased and the opposite can be performed in volume overloaded patients. For patients receiving continuous ambulatory peritoneal dialysis (CAPD), the amount of glucose absorption from the dialysate should be estimated and included in the calculation of delivered calories. Fluid that is incorporated in the PN composition should not be used as a replacement fluid for additional losses beyond maintenance needs in this patient population [18].

### *4.7. Electrolytes*

Prior to adding electrolytes to PN, electrolyte imbalances should be corrected prior to initiating parenteral nutrition. Parenteral nutrition should not be used as replacement fluid for additional losses of electrolytes beyond maintenance. Parenteral electrolyte content should be adjusted to the patient's serum electrolyte concentration.

Sodium bicarbonate interferes with calcium phosphate compatibility and should not be used in parenteral nutrition solutions. Sodium bicarbonate also should not be injected in the vein that is being used for PN.

### *4.8. Vitamins and Minerals*

The original vitamin concentrations for intravenous formulations were based on the recommendations proposed by the Nutrition Advisory Group of the AMA in 1975 [88]. Ten years later, an FDA/AMA

sponsored workshop proposed several changes for parenteral formulations of vitamins and in 2000 vitamin K was added. Long-term vitamin A should be avoided in renal failure due to the potential of possibility of toxic accumulation as this vitamin cannot be removed during dialysis.

### *4.9. Trace Elements*

There is acceptable evidence that indicates that iron, copper and selenium are essential human nutrients. Though considered an essential nutrient, iodine deficiency may not occur in patients receiving TPN secondary to the use of betadine® (Iodophor) [89]. Chromium ($Cr_1$) supplementation is unnecessary due to its intrinsic concentration in TPN components [90, 91]. Manganese ($Mn_2$) is essential for several non-human species, but clear evidence for $Mn_2$ deficiency in humans is lacking. A single case of molybendum deficiency has been documented in a patient receiving long-term PN [92]. Clinical signs and symptoms of zinc, selenium and copper deficiency are listed in Table 11.3.

### *4.10. Additives to TPN*

(1) Insulin: If a patient's blood sugar concentration is sufficiently elevated as to require a continuous insulin drip, PN should not be initiated until the blood glucose is controlled. The patient's blood glucose should be 150–180mg/dl before PN is started. This will avoid glucosuria

**Table 11.3**
**Risk Factors and Etiologies of Refeeding syndrome**

1. Prolonged starvation
2. Anorexia nervosa
3. Prolonged vomiting and diarrhea
4. Nasogastric suction
5. Homelessness
6. Metastatic cancer
7. Prolonged intravenous hydration
8. Uncontrolled diabetes mellitus
9. Abdominal surgery
10. Alcoholism
11. Depression in the elderly

with subsequent fluid and electrolyte loss, impairment of neutrophil chemotaxis and natural killer cell activity [93]. When insulin is necessary, usually one unit of regular insulin per 10 g dextrose (i.e., 10 units with D10, 25 units with D25) will often be sufficient. This should be added directly to the parenteral nutrition after solution compounding just prior to use as insulin adheres to glass and intravenous tubing. The suggested maximum dose of insulin should be 2 units of regular insulin per gram of dextrose (i.e., 50 units/l of D25). If there are episodes of hyperglycemia, a sliding scale of insulin should be ordered to cover the hyperglycemic episodes. The use of the sliding scale dosage of insulin should be incorporated in the TPN formulation. This is accomplished by adding 2/3 of the previous day's sliding scale dosage into the following day's PN. The total insulin dose needs to be divided by the total number of liters of daily PN. If hyperglycemia continues, the dextrose concentration should be reduced and the source of the hyperglycemia should be investigated. Increasing the insulin dosage not only can cause hypoglycemia, but it activates the Na/K/ATPase pump, which shifts potassium intracelluarly and decreases the serum potassium concentration, which can cause hypokalemia [18, 94]. A recent retrospective analysis determined that increased blood glucose levels in patients receiving PN were associated with an increased risk of cardiac complications, infection, systemic sepsis, acute renal failure and death. These effects were independent of age, sex or prior diabetes status [1].

(2) Heparin and corticosteroids: It appears that heparin and corticosteroids have a synergistic effect in reducing thrombophlebitis in those patients receiving PPN. This finding has been demonstrated on patients receiving crystalloid infusions of parenteral nutrition [95–97]. One thousand units of heparin and 5 to 10 mg of hydrocortisone may be added to each liter of PPN to reduce the risk of phlebitis [95–97].

(3) Albumin: The use of albumin in parenteral nutritional support is controversial. Exogenous albumin infusions will not directly improve a patient's nutritional status. There is evidence that it can improve oncotic pressure and can improve edema in the setting of hypoalbuinemia [98]. Albumin provides up to 75% of the normal oncotic pressure in the intravascular space when the serum concentration is $<3.0$g/dl [99]. There is little increase in the plasma oncotic pressure as the serum albumin increases above 3.0g/dl [100]. It is still unclear if the provision of exogenous albumin leads to improved enteral formula tolerance in hypoalbuminemic patients. One study showed an improvement in enteral feeding tolerance when serum albumin was increased from 3.0 g/dl to 3.4 g/dl [101]. Another study found that when patients with a serum albumin of $<2.5$g/dl receiving TPN were given exogenous albumin there was no improvement in morbidity or

mortality as compared to placebo [102]. Other studies have found that enteral feeding tolerance was unaffected by serum albumin concentration and 97% of the patients studied with an albumin less than <2.5g/dl tolerated enteral feeding [103–104]. If the use of albumin is being contemplated, a slow infusion should be used rather than a rapid bolus injection as the half-life is prolonged in the former. An increased serum albumin concentration may persist for up to a week [105]. The total albumin deficit should be calculated and used as an endpoint in the use of supplemental albumin using this formula:

$$\text{Deficit (g)} = \text{weight (kg)} \times 3\text{dl/kg} \times 3.5\text{-initial serum albumin g/dl}$$

The 3 dl/kg reflects the average percent of exchangeable albumin in the plasma compartment [105].

(4) Acid suppression: H2 antagonists may be added to parenteral nutrition solutions to control excessive gastric secetion in new onset short bowel syndrome, stress ulcer prophylaxis or the treatment of peptic ulcer disease. It is more cost effective to add H2 antagonists to the formulation than to infuse them separately. Proton pump inhibitors are not stable in TPN solutions and therefore should not be added. If necessary, they should be infused separately.

## 5. PRESCRIBING TPN

### *5.1. Overview*

Prior to initiating TPN, a patient's fluid and nutrient requirements need to be assessed. The assessment requires a careful medical examination, including a history, physical examination and laboratory studies to evaluate for specific nutrient deficiencies and to determine nutritional needs of the patient. In particular, a complete biochemical evaluation should be performed before starting nutritional support. Energy requirements can be roughly estimated using the Harris-Benedict equation, although this formula has not been validated in critically ill patients.

$$\text{Men: BEE} = 66 + (13.7 \times \text{weight}) + (5 \times \text{height}) - (6.8 \times \text{age})$$

$$\text{Women: BEE} = 655.1 + (9.6 \times \text{weight}) + (1.8 \times \text{height}) - (4.7 \times \text{age})$$

Weight is expressed in kg.
Height is expressed in cm.
Age is expressed in years.
BEE= basal energy expenditure

It should be noted that the thermodynamic effect of food (typically 15–25% of the energy content of food) used to metabolize that food is added to the BEE to obtain the resting energy expenditure (REE). Careful monitoring is needed to ensure safety and adequate therapy. Vital signs, body weight, fluid intake and fluid output need to be evaluated daily. Serum electrolytes, phosphorus and glucose should be measured every 2 days until stable and then rechecked weekly while the patient is hospitalized. Patients receiving TPN should be monitored daily for refeeding edema [106], hypophosphatemia [106] (Table 11.3) and hypokalemia [107]. Glucose concentration should be checked three times per day to achieve euglycemia. The ideal blood glucose concentration should be between 100–160mg/dl in order to reduce the incidence of infectious complications [108]. New onset glucose intolerance in patients receiving TPN may represent an early sign of sepsis [109]. In patients who have abnormal glucose homeostasis, finger-stick evaluations for glucose should be performed regularly. Regular insulin can be added to the nutrient solution to maintain blood glucose concentrations between 100 and 160 mg/dl, which may reduce the risk of infection [93, 94]. The direct addition of insulin to the parenteral nutrient solution reduces the risk of hypoglycemia, which can occur when insulin is given subcutaneously and infusion of the TPN solution has been inadvertently or purposely stopped [18]. TPN infusion is typically started at a rate of 25 to 50ml/h. This rate is then increased by 25 ml/h until the predetermined rate is achieved [105].

If lipid emulsions are being given, serum triglyceride concentration should be evaluated early in the course of TPN to document adequate clearance. Triglyceride concentrations of greater than 400 mg/dl require either reduction of the rate of infusion or complete discontinuation of lipid supplementation, although patients with triglyceride concentrations $>1,000\,\mathrm{mg/dl}$ are at risk for developing acute pancreatitis [110, 111]. Retrospective studies in infants suggested an inverse relationship between the rate of lipid infusion and infectious morbidity [112]. However, in an extensive clinical trial in patients undergoing bone marrow transplantation while receiving TPN there was no evidence that moderate doses of lipid emulsions containing long-chain triglycerides (LCT) were associated with increased incidence of bacterial or fungal infections [113].

### *5.2. Protein Requirements*

Protein requirements depend upon the degree of catabolic stress to which the patient is exposed. Unstressed, well-nourished individuals

require between 0.8 and 1.0 g of protein per kilogram of ideal body weight per day [18]. Postoperative patients generally require between 1.2 and 1.5 g of protein per kilogram of ideal body weight per day [18]. Highly catabolic patients (i.e., patients with burns or sepsis) require at least 2 g of protein per kilogram of ideal body weight per day [18]. Renal or hepatic failure patients should receive 0.6g protein/kg/day as a minimum requirement. Six to 9 g of additional protein/kg/day should be given to patients undergoing hemodialysis or chronic venovenous dialysis [114–115]. Twelve to 16 g protein/kg/day should be given to patients undergoing peritoneal dialysis [114–115]. This will result in 1.2 to 1.4 g/kg/day of protein delivered. In patients receiving IDPN, a typical infusion is a single liter and includes approximately 7 kcal/kg from dextrose, 1.6 g/kg of lipid emulsion and 0.22 g/kg of amino acids.

### *5.3. Writing TPN Orders*

Please refer to Table 11.4 for more information.

## 6. MONITORING THE EFFECTIVENESS OF NUTRITIONAL THERAPY

The best method of assessing the effectiveness of supplemental nutritional therapy is calculating a nitrogen balance in hospitalized patients. Nitrogen balance, which is the difference between the intake and output of nitrogen, is determined by measuring protein intake over 12 or 24 h and urinary excretion of total urine urea nitrogen over the same time interval. One way to determine nitrogen intake:

$$\text{N (g)} = \text{gproteinperday}/6.25$$

The average protein is 15% nitrogen, hence 6.25 is used as the denominator.

In order to calculate nitrogen output either the total urine nitrogen (TUN) or urine urea nitrogen (UUN) should be calculated, though the TUN is preferable. The UUN represents on average only 80% to 90% of the TUN. In order to calculate a UUN an accurate 24-h urine measurement is needed. In order to calculate nitrogen balance the intake must be subtracted from the output [115]

$$\text{Nitrogen balance} = \text{Nitrogen intake} - \text{Nitrogen output}$$

OR

$$\text{Nitrogen balance} = \text{Nitrogen intake} - (\text{UUN} + 4) \text{ OR } (\text{TUN} + 2)$$

Table 11.4
Steps in Writing TPN Orders

1. Determine ideal body weight (IBW)
2. Calculate the non-protein caloric requirement.
   IBW = 70 kg
   $70\,\text{kg} \times 25\,\text{kcal} \cdot \text{kg} - 1 \cdot \text{day} - 1 = 1,750\,\text{kcal/day}$
3. Calculate the protein requirement
   IBW = 70 kg
   $70\,\text{kg} \times 1.4\,\text{g protein} \cdot \text{kg} - 1 \cdot \text{day} - 1 = 98\,\text{g protein/day}$
4. Determine the optimal concentration of amino acid and carbohydrate solutions while taking volume into account. Consider an example of a 5% amino acid solution (contains 50 g of protein/l) and a 25% dextrose solution (contains 250 g of dextrose/l)
   a. Protein requirement
      98 g protein/day/50 g protein/l = 1.96 l/day OR 1,960 ml/day OR 82 ml/h
   b. Non-protein calorie requirement
      $1,960\,\text{ml/day} \times (250\,\text{g dextrose}/1,000\,\text{ml}) \times 3.4\,\text{kcal/gdextrose} =$ 1,666 kcal/day
5. Determine the extra calories needed
   a. 1,750 kcal- 1,666 kcal = 84 kcal
   b. The extra calories that are needed can be delivered via lipid emulsion. Lipids are available in 10% and 20% concentrations in units of 50 ml; 50 ml of 10% lipid contains 50 kcal. Therefore, the patient can receive 84 ml of the 10% lipid emulsion in the TPN to make up the difference in caloric needs. A minimal amount of lipids needs to be given in order to prevent the development of essential fatty acid deficiency. The minimal accepted amount is 4% of the total provided calories in the form of linoleic acid.

A positive or negative protein balance is used to determine the adequacy of protein and energy intake of the patient [116]. In the initial stages of critical illness, the goal of nutritional therapy is to maintain a nitrogen balance of zero. A negative balance of 0 to 5g would represent moderate stress, and greater than 5g would represent severe stress. Once the anabolic or recovery phase is entered, the goal is to maintain a positive nitrogen balance to allow for repletion of protein stores [117]. Achievement of a positive nitrogen balance not only requires sufficient protein and amino acids, but adequate calories as well [118].

## 7. COMPLICATIONS IN THE HOSPITALIZED PATIENT RECEIVING PARENTERAL NUTRITION

### *7.1. Overview of Complications*

There are multiple complications associated with the use of PN. These can be divided into mechanical, vascular, infectious, metabolic and gastrointestinal. The incidence of most complications is reduced with careful management and supervision by an experienced nutritional support team.

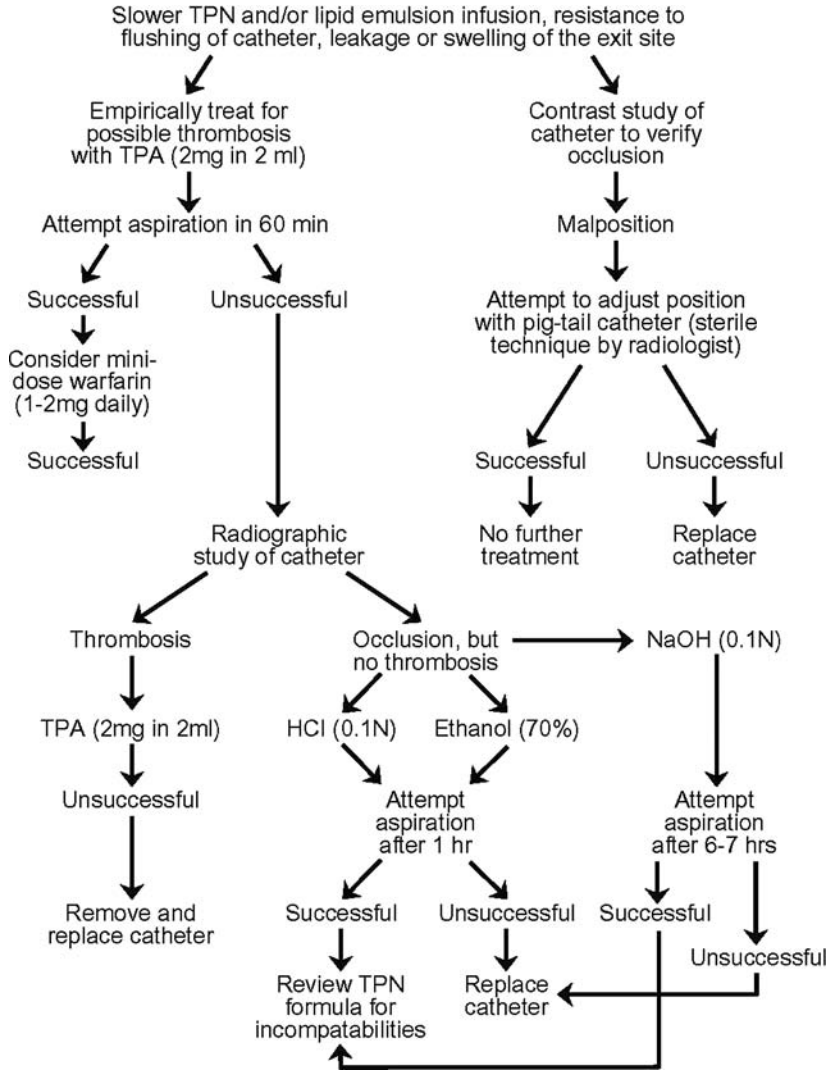
### *7.2. Mechanical Complications*

Central venous catheter insertion (CVC) can cause damage to local structures. A misguided approach can cause pneumothorax, hemothorax, thoracic duct injury, chylothorax, brachial plexus injury, subclavian and carotid artery puncture. Even when the subclavian vein is successfully cannulated, other mechanical complications can still occur. The catheter may be advanced upward into the internal jugular vein, or the tip of the catheter can be sheared off completely if it is withdrawn back through an introducer needle.

### *7.3. Vascular Complications*

Air embolism can occur during insertion or afterward if the connection between the catheter and intravenous tubing is not well secured. The catheter can become occluded because of thrombosis or precipitation of electrolyte salts. Subclavian vein thrombosis occurs commonly (in approximately 25% to 50% of patients) [119], but clinically significant manifestations such as upper extremity edema, superior vena cava syndrome or pulmonary embolism are rare during short-term TPN [120, 121]. Fatal microvascular pulmonary emboli caused by nonvisible calcium and phosphorus precipitate identified in the total nutrient admixtures have been reported [122, 123]. The iatrogenic mortality in these patients underscores the importance of maintaining strict pharmacy standards regarding physical-chemical compatibility. Furthermore, in-line filters should be used with all PN solutions despite careful inspection of solutions. These filters can be used to filter out particulate, precipitate or microbial contamination depending on the size of the pores in the filters. The smallest pulmonary capillaries are 5 μm in diameter, whereas the size limit for visually detecting microprecipitates is 50 to 100 μm [124].

(1) Complications secondary to catheter occlusion (Algorithm 11.1): The following findings may indicate catheter occlusion: (a) the inability




**Algorithm 11.1.** Identification and Treatment of Catheter Occlusion.

to infuse lipids even when dextrose and amino acid solution infuse, (b) difficulty flushing the central venous catheter (CVC), (c) inability to withdraw blood from the CVC or (d) blood back flow in the IV tubing. This may be secondary to thrombosis, malposition or by poor solubility of calcium, phosphorous or other divalent cations. In the absence of catheter malposition, there is an increased risk for the development of catheter thrombosis secondary to fibrin accumulation [125].

Administration of a small amount of a thrombolytic agent such as urokinase or tissue plasminogen activator (tPA) may clear the blockage located in the internal lumen of the catheter without causing a change in clotting times [126]. Please refer to Table 11.5 for a protocol for administration of tPA. Prior to the administration of thrombolytics, additional physical findings such as neck or face edema, edema of the limb proximal to the CVC or pain along the CVC infusion tract should be assessed to exclude the possibility of superior vena cava syndrome. A radio-opaque dye study, chest radiograph+ or ultrasound may be useful to determine the presence of venous thrombosis and/or catheter malposition. If the catheter occlusion is not resolved with TPA or urokinase, and there is no evidence for malposition, then non-

**Table 11.5**
**Protocol for tPA administration**

A. Preparation of enzyme:

1. Obtain tPA in a 50-mg vial.
2. Reconstitute enzyme according to instructions to provide 25 cc of enzyme at a concentration of 2 mg/ml.
3. Using sterile technique, divide the tPA into 1-cc aliquots (2 mg). Place in sterile vials suitable for freezing.
4. Store frozen at −70 °C.
5. When needed, remove vials from freezer and allow to thaw at room temperature.
6. Use immediately after thawing.

B. Technique for use:

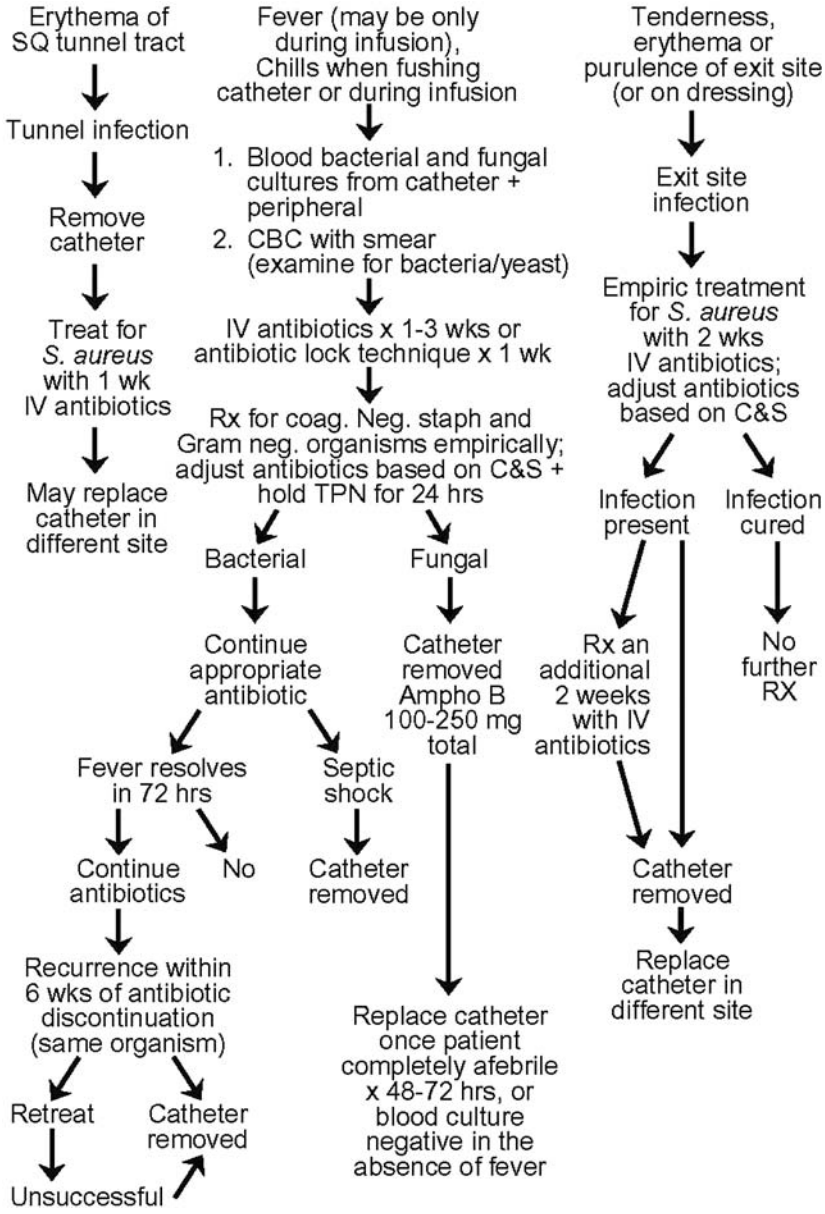
1. Attempt to aspirate the occluded catheter lumen to remove heparin.
2. Inject 2 mg (1 ml) of tPA into the occluded catheter lumen.
3. Make up the remainder of the catheter lumen fill volume with saline (e.g., for a 1.9 catheter lumen use 1 ml tPA and 0.9 ml saline).
4. Wait 15 min, then inject 0.3 ml of saline to again move the active enzyme towards the tip of the catheter.
5. After another 15 min, add another 0.3 ml to again move the active enzyme towards the tip of the catheter.
6. After a third 15-min period, try to aspirate the catheter.
7. If the catheter aspirates easily, forcefully flush several times with aspirated blood.
8. If the catheter cannot be aspirated easily, repeat the procedure.
9. If the second application of tPA is unsuccessful, refer the patient for catheter exchange.

thrombotic occlusion should be suspected; 0.1-N hydrochloric acid (HCl) or 0.1-N sodium hydroxide (NaOH) may be useful in clearing the mineral precipitate [127].(2) Prevention of recurrent catheter thrombosis: Patients susceptible to recurrent catheter thrombosis should receive prophylaxis with warfarin to achieve an INR equal to or greater than 1.6. Patients with severe malabsorption and short bowel syndrome may require higher doses of warfarin. Lipid emulsion and multivitamin formulations that contain vitamin K may also require increased doses of wafarin.

### *7.4. Infections (Algorithm 11.2)*

CVCs typically become infected at three sites: (1) the site of skin entry, (2) the catheter hub and (3) a fibrin sheath coating the outside of the catheter inside the vein. Catheter sepsis is the greatest concern in patients receiving PN because the indwelling catheter is a potential conduit for organism entry from skin contamination. A skin site is usually the source for infection for a period of 10 days following line insertion [128]. Afterwards the cathter hub should be implicated [18, 128–135]. A malnourished patient may be secondarily immunocompromised and thus become a good host for infection. Using aseptic techniques and following prescribed catheter care protocols are essential for minimizing infections.

A temperature greater than 38.5° C is considered to be a fever. If this occurs at any point during the administration of parenteral nutrition, close examination for a source should be undertaken. For example, in patients receiving cyclic TPN, a fever may only occur during an infusion. A small clot may be located at the catheter tip or the catheter may be colonized by bacteria or yeast; flushing the catheter may cause a transient bacteremia or fungemia. It is rare that a fever would develop secondary to an allergic reaction to nutrients or because of contaminated PN solutions. Blood cultures for bacteria and fungi should be obtained from the catheter and peripheral vein. A complete blood count, urinalysis and chest radiograph should be obtained as well to exclude other non-catheter sources of infection. Antibiotics to cover aerobic gram positive and gram negative organisms may be initiated prior to obtaining culture results if clinically suspected (i.e., rigors after flushing the catheter, persistent fevers spikes for more than 8 h or the patient progresses to septic shock). At this point, the PN solution should be held until the patient is afebrile. Vancomycin and an aminoglycoside or a third generation cephalosporin are usually started to cover the most common infecting organisms: *Staphylococcus epidermidis, Staphylococcus aureus* and *Klebsiella pneumoniae* [18]. Though




**Algorithm 11.2.** Identification and Treatment of Catheter-Related infections.

controversial, most long-term tunneled catheters can be salvaged with in vivo treatment, such as the antibiotic lock technique. This technique is a controversial method for sterilizing the catheter lumen and involves instilling high concentrations of antibiotics with or without heparin into the catheter lumen for extended periods of time. The efficacy of the antibiotic-lock technique for *S. epidermidis* infection in an attempt to maintain central venous access in patients with otherwise poor access has been called into question [136]. There are limited data using the antibiotic lock technique in cases of fungemia. Though there has been a successful case report in an adult, there have been multiple failures using the antibiotic lock technique. More studies will need to be performed to determine if this technique is useful. In general, the catheter should be removed in the presence of a fungal or mycobacterial infection, or in the presence of infectious of the subcutaneous tunnel in long-term catheters.

### *7.5. Metabolic Complications*

Many metabolic complications have been observed in patients receiving PN. Most complications are caused by inappropriate nutrient administration, resulting in nutrient excesses or deficiencies or both. Overzealous nutrient administration may provide excess delivery of water and sodium (fluid overload), glucose (hyperglycemia, nonketotic hyperosmolar coma), amino acids (hyperammonemia, azotemia), lipids (hypertriglyceridemia, pancreatitis) and calcium (hypercalcemia, pancreatitis, renal stones) [137]. Inadequate nutrient administration can cause deficiencies of glucose, electrolytes, vitamins, trace minerals and essential fatty acids [138].

## 8. CONCLUSION

Since the advent of peripheral nutrition in the late 1950s and the later development of total parenteral nutrition, parenteral nutrition has become an essential lifesaving measure in certain clinical scenarios by providing nutritional supplementation. Currently, there is increasing evidence that parenteral nutrition may not only have the ability to provide essential nutritional supplementation, but may be able to bolster the immune function of those patients who are immunosuppressed and may alter the course of hepatic encephalopathy. Nevertheless, there are potential multiple complications (mechanical, vascular, infectious and metabolic) that can be avoided in most instances if the proper care is given. Unfortunately, there are insufficient controlled prospective data available. The use of PN still requires

an integration of information from heterogeneous sources, including: pertinent clinical trials, clinical expertise in the illness or injury being treated, reasonable estimates of inadequate enteral intake and clinical expertise in nutritional therapy.

## BULLET POINTS

1. The best method for assessing the effectiveness of supplemental nutritional therapy is calculating a nitrogen balance in hospitalized patients.
2. There are multiple complications associated with the use of PN. These can be divided into mechanical, vascular, infectious, metabolic and gastrointestinal. The incidence of most complications is reduced with careful management and supervision by an experienced nutritional support team.
3. The concept that increasing the plasma aromatic amino acid ratio leads to decreased encephalopathy has been questioned by some investigators as brain uptake of BCAA in some cirrhotics may be similar to that of healthy controls and may be a better correlate of hepatic function than the degree of encephalopathy in others.
4. Recent studies have demonstrated that lipid emulsions containing medium chain triglycerides may have some advantages because of their positive effects on polymorphonuclear cells, macrophages and cytokine production, particularly in critically ill or immunocompromised patients.

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# 12 Vascular Access for Parenteral Nutrition

*Ezra Steiger, MD*

***CONTENTS***



*Summary*

Safe and effective vascular access is an important part of any program of parenteral nutrition. An appropriate vascular access device that is well placed and positioned will help to minimize complications associated with its use. The early recognition and treatment of device malfunction and complications associated with prolonged used will decrease any associated morbidity and mortality.

**Key Words:** Central parenteral nutrition, Peripheral parenteral nutrition, temporary vascular access, Permanent vascular access, Tunneled catheters, Subcutaneous ports, Peripherally inserted central catheters (PICC), Catheter occlusion, Catheter associated thrombosis, Catheter-related blood stream infection (CRBSI)

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## 1. INTRODUCTION

The ability to obtain and maintain prolonged safe venous access allows the infusion of hypertonic nutrient solutions into patients requiring parenteral nutrition (PN) and is an essential element for the success of intravenous feeding [1]. The history of developments in the area of vascular access spans several centuries. The use of central venous access for PN in the hospital setting was first reported in the late 1960s and at home in the early 1970s [2]. Clinicians caring for patients requiring PN in the hospital or at home must be familiar with the basic types of venous access devices, indications for their use and the prevention, diagnosis and management of associated complications.

## 2. VENOUS ACCESS DEVICES FOR PARENTERAL NUTRITION

Most PN solutions are hypertonic [1,500–2,000 milliosmoles (mOsm) per liter] because of their high concentration of dextrose. They must be given through a venous access device whose tip lies in a large bore central vein to rapidly dilute the irritant effects of the hypertonic dextrose on the vein wall. This type of PN is called central parenteral nutrition (CPN) and in the hospital setting is given through a jugular or subclavian central venous catheter or through a peripherally inserted central catheter (PICC). For prolonged PN in the home or outpatient setting tunneled cuffed silicone catheters or chest ports are used [3–5]. The optimum catheter tip position to minimize the incidence of central vein thrombophlebitis and catheter malfunction is at the junction of the superior vena cava and right atrium [6, 7]. Appropriate catheter tip position should be confirmed by a post-catheter-insertion chest X-ray prior to the infusion of CPN solutions.

PN solutions that provide a large percentage of their kilocalories (kCal) as isotonic fat emulsions and a smaller percent as dextrose are not as hypertonic (less than 900 mOsm/l) as the CPN solutions and are usually well tolerated by infusing through peripheral vein angiocatheters. See Table 12.1 for guidelines for estimating the osmolarity of PN solutions. This type of intravenous feeding is called peripheral parenteral nutrition (PPN). PPN solutions are usually used for short periods of time in hospitalized patients with reduced kCal requirements who are able to tolerate the relatively larger volumes of these dilute solutions needed to meet their caloric and amino acid needs.

Decisions concerning which venous access device and venous access route is appropriate for a particular patient are based primarily on

**Table 12.1**
**Estimating the Osmolarity of PN Solutions**

A. Total grams of amino acids per liter _____ ×10 = _____ mOsm
B. Total grams of dextrose per liter _____ ×10 = _____ mOsm
C. Total grams of 20% fat emulsion per liter _____ 1.3–1.5= _____ mOsm
D. Total mEq of chloride,
potassium and sodium per liter _____ ×1 = _____ mOsm
Add A, B, C and D to derive the total osmolarity= _____ mOsm
For peripheral vein tolerance, total osmolarity per liter should be 900 mOsm or less.
(Modified from Table II Errata JPEN 2006;30:177)

the anticipated duration of PN and if concentrated CPN solutions are needed to limit infused fluid volume while meeting caloric and amino acid needs (Tables 12.2 and 12.3). It would take 2,500 ml of fluid to deliver 2,000 kCal and 100 g of amino acids in a typical PPN solution, while the same nutrients could be provided in 2,000 ml of fluid using the more concentrated hypertonic CPN solution.

Other considerations are device and insertion costs and if the device can be placed at the bedside or needs to be placed in the interventional radiology or surgical suites [8] (Table 12.4).

Multilumen central venous catheters are most commonly used for hospitalized patients (Fig. 12.1). Although there is thought to be an increased incidence of infection associated with more than one lumen, this slightly increased risk is compensated for by the convenience of being able to infuse fluids, nutrients and medication through the same device [9]. When parenteral nutrition must be given to patients at home, a

**Table 12.2**
**Duration of Use Consideration in Choosing a Vascular Access Device**

| | *Anticipated duration of use* | | | |
|---|---|---|---|---|
| *Access device* | *Days* | *Weeks* | *Month(s)* | *Year(s)* |
| Peripheral IV | * | | | |
| Non-tunneled CVC | * | * | | |
| PICC | | * | * | |
| Tunneled CVC | | | * | * |
| Implanted port | | | * | * |

PICC=peripherally inserted central catheter; CVC=central venous catheter

**Table 12.3**
**Influence of Type of Parenteral Nutrient Fluid or Choice of Vascular Access Device**

| *Establishing intravenous access* | | |
|---|---|---|
| | *PPN* | *CPN* |
| Access device insertion site | Small hand or arm veins | Subclavian, PICC or jugular |
| Fluid restriction | No | Yes |
| Duration | <7 days | >7 days |
| Increased nutrient needs | No | Yes |

PPN=peripheral parenteral nutrition; CPN=central parenteral nutrition

**Table 12.4**
**Costs and Placement considerations for Venous Access Devices**

| *Type of device* | *Device cost ($)* | *Insertion cost ($)* | *Bedside placement* |
|---|---|---|---|
| Peripheral angiocatheters | 1–6 | 24–44 | Yes |
| PICC | 50–70 | 300–700 | Yes |
| CVC | 90 | 580 | Yes |
| Tunneled catheter | 50–225 | 2,800–3,200 | No |
| Implanted port | 350–600 | 1,000–3,500 | No |

(Modified from Ryder MA. Peripheral access options. Surg Oncol Clin N Am 1995;4:395–427.)

more durable device that the patient or caregiver can maintain in the home setting is used. PICC catheters, subcutaneous chest ports and tunneled cuffed catheters are indicated for long-term use in the home setting (Figs. 12.2, 12.3, 12.4). Each of these devices is positioned so that its tip is at the junction of the superior vena cava and right atrium. PICC lines are inserted via an antecubital vein at the bedside or in the interventional radiology suite under ultrasound guidance. Chest ports and tunneled cuffed catheters are placed surgically or in the interventional radiology suite by cutdown or percutaneously. Commonly used access veins for tunneled catheters and ports include the internal or external jugular veins or the subclavian vein. See Fig. 12.1 showing various venous access devices used for PN in the acute care and post-acute care settings. PICC lines are associated with an increased incidence of phlebitis and catheter

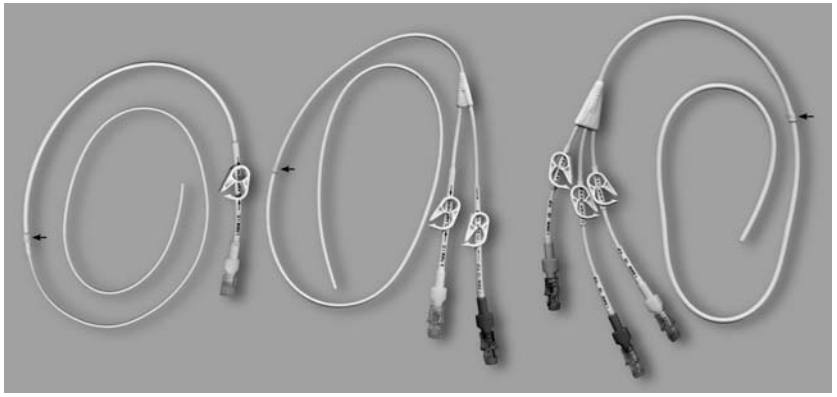

**Fig. 12.1.** Multilumen central venous catheters are most commonly used for hospitalized patients.

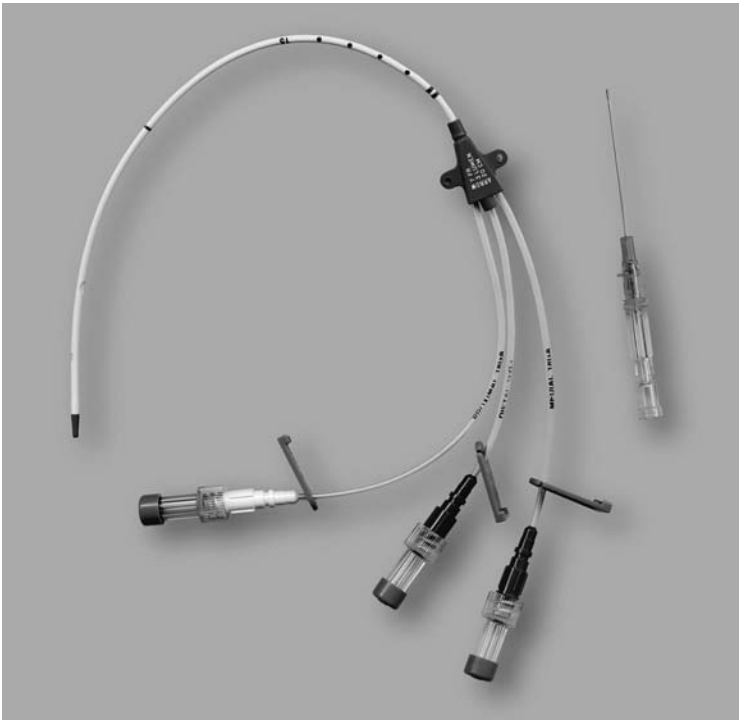

**Fig. 12.2.** PICC catheter.

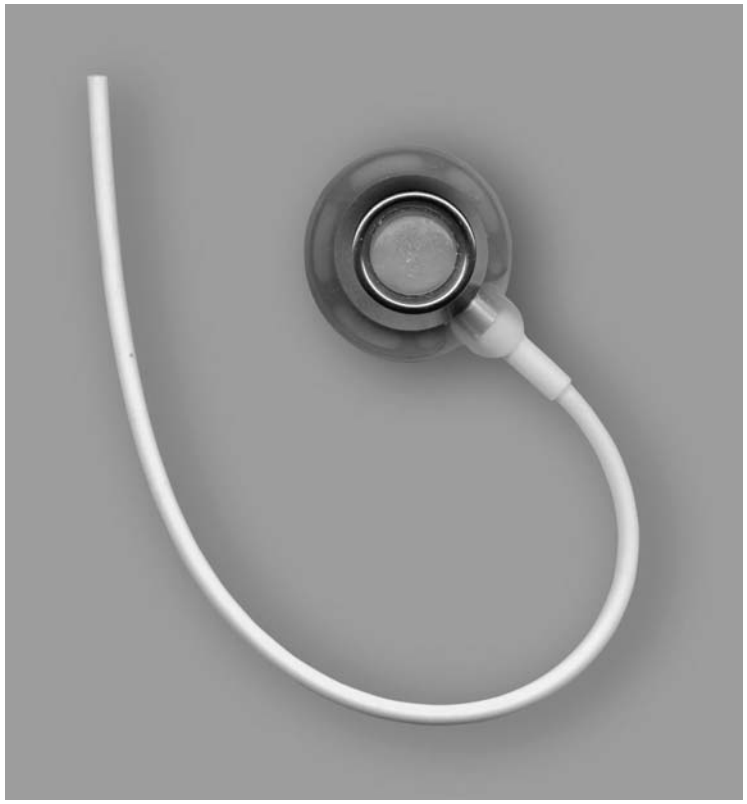

**Fig. 12.3.** Subcutaneous chest port.

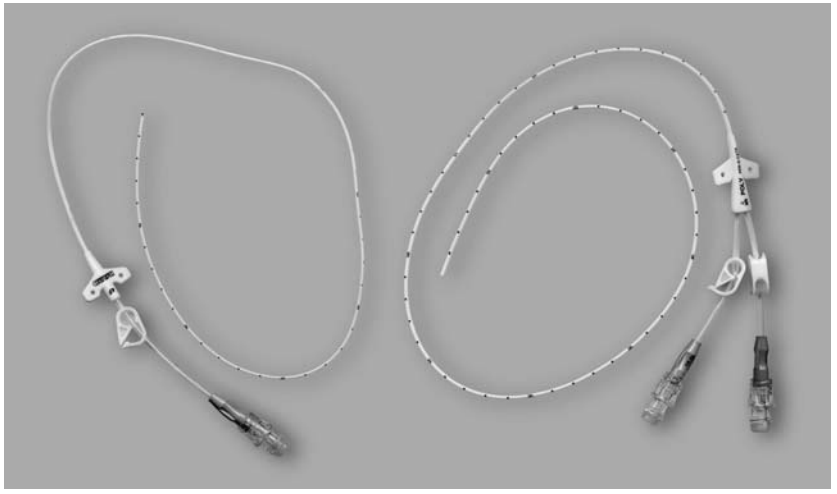

**Fig. 12.4.** Tunneled cuffed catheter.

dysfunction [10], and their use is usually limited to weeks or months. The decision regarding chest ports versus external cuffed catheters is mostly dependent on patient preferences. Ports require at least weekly cannulation, but do allow the patient periods of unencumbered activity, such as swimming or other social activities, when their ports are not cannulated. The advantages and disadvantages of ports versus tunneled catheters and the proposed location of the device are discussed with the patient prior to their placement in the home parenteral nutrition (HPN) patient. The catheter exit site or port site is marked on the patient's chest, and the surgeon or interventional radiologist is informed as to the number of lumens required.

## 3. VENOUS ACCESS IN PATIENTS WITH A MAJOR VEIN THROMBOSIS

Patients who have had central venous cannulation or previous thoracic surgery in the past may have developed occlusions of major upper torso venous branches. When both of the subclavian veins or the superior vena cava are occluded, vascular access for HPN is established by accessing the inferior vena cava. Tunneled cuffed catheters can be placed by cutdown or percutaneously via the saphenous or femoral vein in the operating room or interventional radiology suite. The catheter tip is advanced through the iliac veins and inferior vena cava and positioned at the junction of the inferior vena cava and right atrium. Patients who have had iliac vein thromboses will need direct access to the inferior vena cava established via the translumbar or transhepatic approach by an interventional radiologist [11].

## 4. COMPLICATIONS

### *4.1. Insertion Complications*

Potentially life-threatening complications of catheter insertion include pneumothorax, and arterial or venous damage with resultant significant blood loss or cardiac tamponade [12]. Insertion-associated complications are more likely to occur when multiple attempts at percutaneous cannulation are made, especially if the patient is cachectic or thin [13]. After successful or attempted central vein cannulation, a chest X-ray should be obtained not only to confirm catheter tip position, but also to rule out the occurrence of a pneumothorax.

### *4.2. Infections*

Catheter infections in vascular access devices used in the hospital or outpatient setting can occur at the exit site or systemically. Measures to prevent contamination of the external and internal lumen of the vascular access device have been recently summarized and include skin antisepsis, site dressing, hand hygiene, access-site disinfection and possibly the use of prophylactic flush solutions [14]. These measures along with previously published guidelines can help to reduce the incidence of catheter infections [15]. Every hospital, long-term care facility or home care provider should establish protocols for the care of vascular access devices to minimize the incidence of device-related infection. A comprehensive review of catheter-related infections has been recently published to guide the diagnosis and treatment of these serious complications [16].

### *4.3. Catheter Occlusion*

When fluid flow through the vascular access device suddenly stops, it is usually due to a mechanical complication such as clamped or kinked intravenous tubing or an acutely angulated catheter. A percutaneous subclavian catheter can be occluded at the junction of the clavicle and first rib and the occlusion temporarily relieved by having the patient shrug their shoulders. If these symptoms occur a chest X-ray will establish the diagnosis of catheter pinch-off [17], and the catheter must be replaced. A more gradual occlusion to flow and or difficulty in withdrawing blood may be due to a thrombus in the lumen or near the tip of the catheter. Patency and function are usually re-established by the instillation of a tissue plasminogen activator [18].

### *4.4. Catheter-Associated Venous Thromboses*

A recent review noted that fatal pulmonary emboli can occur associated with acute central venous thromboses in patients with central lines and must be treated aggressively with anticoagulation [6]. Diagnosis is established by a history of ipsilateral edema, discoloration, prominent chest wall venous distention, pain and tenderness over the involved vein. The diagnosis is confirmed by ultrasonography and/or venography. Preventative measures are controversial and may include oral low-dose coumadin, adding heparin to the PN solution and appropriate catheter tip positioning. Therapeutic anticoagulation should be considered for patients with a prior history of major venous thrombosis in whom prolonged central venous access is anticipated.

## 5. CONCLUSION

Obtaining safe vascular access for patients receiving PN in the hospital or home setting requires the skills and judgment of knowledgeable nurses and physicians. Choosing an appropriate access device for the patient in need of parenteral nutrition and its placement by experienced clinicians using established protocols is critical for the safe administration of PN.

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# 13 Nutrition-Based Home Care

*David S. Seres, MD, CNSP*

***CONTENTS***



*Summary*

Provision of artificial nutrition in the home is often necessary and has become a routine part of caring for patients with a variety of disorders. Indications for these therapies in the home do not differ from the hospital. The cost of these life-sustaining therapies, both economic and to quality of life, is substantial. Complications, while less often life-threatening, can be serious and include problems due both to the infusion or instillation of artificial nutrition, and to the techniques required to provide access. Lifespan is most often limited by the patient's underlying disease and not the nutrition support-related complications, but there are disease-specific considerations in applying these therapies. These issues are reviewed herein.

**Key Words:** Home parenteral nutrition, Enteral nutrition, Home care services, Economics of home parenteral nutrition, Economics of

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enteral nutrition, Quality of life, Adverse effects of enteral nutrition, Adverse effects of parenteral nutrition

## 1. INTRODUCTION

Outpatient parenteral nutrition (PN) has been available for more than 3 decades, while home tube feeding has been practiced for centuries [1]. These techniques for providing nutrients in the home setting have become a routine part of medical care for patients with chronic gastrointestinal dysfunction. With proper medical and social support, patients unable to meet nutritional needs due to problems of nutrient intake, nutrient absorption and nutrient excess losses may be managed with enteral nutrition (EN) or PN support at home for years [2, 3] with acceptable, albeit reduced, quality of life.

The incidence and prevalence of home parenteral and enteral nutrition (HPEN) support are not well documented. As with any technology, availability may lead to overuse. Complications of artificial nutrition support are not infrequent, but are usually manageable. The patients' primary and comorbid diseases are the usual determinant of longevity in patients receiving HPEN.

## 2. INDICATIONS

Indications for home enteral nutrition (HEN) and home parenteral nutrition (HPN) have been continually reexamined [1]. We have developed a better understanding of the limitations of artificial nutrition and are better able to quantify intestinal failure (IF) [4]. Enteral nutrition is always preferred over PN. Parenteral nutrition should only be used in patients with intestinal failure for the purpose of treating or preventing starvation. Parenteral nutrition for less than 2 weeks has no proven value [5]. Indications for HPEN are no different than those in the hospital. Some disease-specific indications and considerations are discussed below.

## 3. COST

The cost of a complex therapy such as HPEN is very difficult to quantify. In addition to the obvious costs of tubing, pumps and nursing, there are always intangible costs such as transportation, out-of-pocket expenses and loss of income. It is clear that HPN is far more expensive than HEN, due to both the cost of the technology and the ancillary and hospital services required. In the period 1991–1995, HPN was

**Table 13.1**
**Medicare Criteria for Coverage of Home TPN**

- Permanent condition of at least 3 months duration and
- Significant impairment of absorption or motility
  - Massive small bowel resection leaving ≤5 feet of small bowel beyond ligament of Treitz *and* surgery within 3 months *or*
  - Short bowel syndrome with enteral losses >50% of intake *and* intake ≥2.5–3 l/day *and* urine output <1 liter/day *or*
  - Bowel rest required for ≥3 months *and* patient receiving 20–35 kcal/kg/day IV *and* patient has one of the following
    - Symptomatic pancreatitis *or*
    - Severe exacerbation of regional enteritis *or*
    - High output enterocutaneous fistula and distal tube feeding not possible *or*
  - Complete mechanical bowel obstruction *and* surgery not an option *or*
  - 10% weight loss in ≤3 months *and* serum albumin ≤3.4 *and* fecal fat test demonstrates loss of >50% of oral/enteral intake on ≥50g fat/day diet *or*
  - 10% weight loss in ≤3 months *and* serum albumin ≤3.4 *and* patient is taking maximum doses of prokinetic agent *and* patient has daily nausea/vomiting *and* has diagnostic test documenting motility disturbance *and* radioisotope, barium, or pellets fail to reach the right colon by 6 h *and* patient is not acutely ill or on any medication that would decrease motility *or*
  - Documented failure of a tube feed trial *and* 10% weight loss in ≤3 months *and* serum albumin ≤3.4 *and* altering the composition of an enteral diet or administering medications to treat the etiology of the malabsorption will not maintain the patient's health status *and* patient has moderate abnormality such as:
    - 72-h fecal fat test shows >25% loss of ≥50 g fat/day diet *or*
    - Confirmation of malabsorption by other test (sudan stain, d-xylose, etc.) *or*
    - Gastroparesis unresponsive to prokinetic agent demonstrated on study with failure of isotope or barium or pellets to reach right colon in 3–6 h or by manometric motility study *or*
    - Small bowel dysmotility unresponsive to prokinetic agent demonstrated with gastric to right colon transit time between 3–6 h *or*

*(Continued)*

Table 13.1
*(Continued)*

- Small bowel resection that left > 5 feet of small bowel beyond the ligament of Treitz *or*
- Less severe short bowel syndrome *or*
- Mild to moderate exacerbation of regional enteritis or enterocutaneous fistula *or*
- Inoperable partial mechanical small bowel obstruction

Adapted from http://www.cignamedicare.com/dmerc/mr/pdfs/decisiontree.pdf accessed March 22, 2006.

estimated to cost $70,700 per patient per year, while HEN cost $18,000 per patient per year. This included clinic visits, medications, laboratory tests, nurse visits, hospitalizations, pump rental, intravenous or tube feeding solutions and other miscellaneous costs [6]. Adjusting for inflation, these costs likely now exceed $100,000 and $27,000 for HPN and HEN, respectively.

The cost of the HEN feeding product is frequently excluded from coverage by private health insurance companies. While standard feeding products may not cost more than normal groceries, specialized enteral formula products may place a significant financial burden on the patient. HPN is often covered by most insurers. The cost is rarely something a patient has the resources for if such coverage is lacking. Medicare has extremely stringent criteria for coverage of HPEN (Table 13.1).

## 4. QUALITY OF LIFE

It is difficult to assess prospectively the effect of HPEN on quality of life (QOL) as randomization of patients deemed to require nutrition support and to receive none raises ethical questions. Nevertheless, there are standardized and validated QOL assessment instruments that have been used to compare QOL of patients on HPEN to well subjects and those receiving other complex medical technologies [7].

There is no question that QOL of patients receiving HPEN is significantly reduced relative to normal. HPEN patients are more likely to have significant medical problems, for example, high-output stomas or neurological disease, which negatively impact on QOL. Complications and tube-related problems such as poor ostomy closure with spillage of

bowel contents onto clothing are not infrequently additional causes of decrements in QOL. In general, the QOL scores of patients on HPEN are comparable to those of patients on hemodialysis [6, 8]. While most HEN patients describe some improvement in QOL after initiation of nutrition support [9], half of all HEN patients in one series reported psychological intolerance to HEN [10].

HPEN patients are also at the mercy of a much less coordinated outpatient medical system once they are discharged from the hospital. Care of patients receiving HPEN at a dedicated HPEN expertise center may help ameliorate some of these problems. Additionally, a multidisciplinary team may be able to better anticipate problems with which the general gastroenterologist or other practitioner lacks familiarity [11, 12]. This team might consist of a pharmacist, a dietitian, a nurse and a social worker, often with physician oversight. Finally, improved nutrition support outcomes have been achieved when patients become affiliated with an organization such as the Oley Foundation, which provides ongoing educational and peer support for HPEN patients. HPN patients involved with the Oley Foundation have higher QOL scores, lower depression scores and a lower incidence of catheter-related infections [13]. Infection rates, depression rates and rehospitalizations for sepsis have also been reduced using interactive video educational programs [14].

Shifting nutritional care to the home setting also shifts to patients and their caregivers a huge technical and logistic burden [15]. Patients and caregivers must become their own nurses, providing care that requires skills completely foreign to them. Discharge planning should address not only training on and the delivery of equipment and products, but the attendant anxiety about new skills and potential complications. The physician should also be aware of and be prepared to address problems that occur in the home environment that are usually handled by the infrastructure of the hospital.

The difficulty of self-administration of HPEN is compounded by inconsistent quality of care delivery by home care companies, including delay of delivery, difficulty coordinating scheduling of deliveries and equipment and supplies missing from delivery (Table 13.2). These types of problems have been reported to occur in as much as 50% of the HPEN population [16]. Periodic evaluations by the practitioner should include questions about satisfaction with services provided by the home care and/or nursing companies.

Patients on HPEN are also at the mercy of the limitations in technology. Incidents such as power outages [17] and mass transit

Table 13.2
Special Problems Seen Transitioning Between Hospital and Home

| |
|---|
| Clearance and coverage by insurance |
| May delay discharge |
| Must be initiated ASAP prior to discharge |
| Need to insure proper documentation sent to prevent denials |
| Portions of therapy (e.g., enteral feeding product) often excluded from coverage |
| Delivery of supplies |
| Delay of arrival |
| Difficulty coordinating scheduling |
| Equipment and supplies missing from delivery |
| Training issues |
| Hospital and home care nurse must do training |
| Variable nurse knowledge and ability between hospital and home |
| Patient's ability to learn skills |
| Need for a willing designated caregiver (or several) to provide care |
| Emergencies |
| Variable availability of urgent nurse visit |
| Primary physician lack of familiarity with HPEN-related problems |
| Need designated physician and contact at home agency to answer calls related to HPEN |

strikes may be deadly to patients on HPEN who lack means of access to hydration or those without the ability to recharge electrical pumps. Practitioners should familiarize themselves with hospital and home-care agency contingency plans for such events and insure patients have available alternatives to prevent short-term complications such as dehydration. Alternatives that may serve to bridge the patient through such a crisis include providing a back-up supply of IV fluid that may be kept out of refrigeration and infused via a flow regulator, or a supply of enteral feeding bags that may be used for slow gravity EN bolus feeds in patients unable to tolerate bolus feeding.

## 5. INCIDENCE

As there is no reporting requirement or centralized data collection regarding the incidence of HPEN use, there is no accurate assessment of its use in the U.S. There have not been any recent attempts to create reliable estimates. Estimates from the early 1990s of total HPN patients in the United States were performed by extrapolation from Medicare

data bases. At that time, it was estimated that there were 40,000 HPN patients and 152,000 HEN patients, and the numbers were growing rapidly [18].

## 6. SURVIVAL

Life expectancy on HPEN is dependant mostly on surviving the underlying disease processes. While complications from HPEN techniques and technology are frequent, they are more commonly cause for hospitalization and morbidity rather than mortality. It is difficult to interpret comparisons in efficacy between HEN and HPN because the indications for each are often very different. There is a small, but nonsignificant increase in mortality on HEN vs. HPN when the therapies are compared prospectively [19].

### *6.1. Survival on HEN*

Survival in HEN patients is dependent on their underlying diseases. Survival in terminal cancer patients on HEN is 20% at 12 months, while survival in young patients with neuromuscular disease and malabsorption exceeds 80% for the same period of time [20] (Fig. 13.1). As would be expected, survival decreases with increasing age [21]. Survival is also better if patients on HEN can resume a normal diet [21]. However, this may be a reflection of generally better health in this cohort.

### *6.2. Survival on HPN*

Survival on HPN is also dependant on underlying disease. While HEN complications are less severe and are an unusual cause of significant

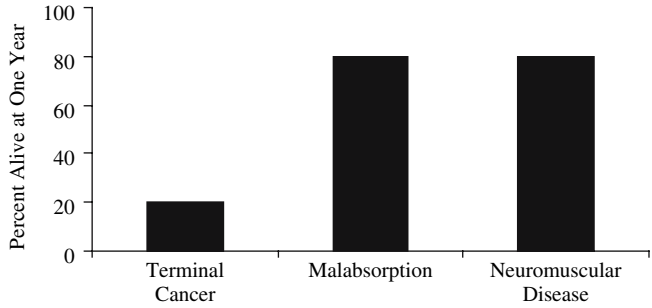


**Fig. 13.1.** Percent 1-year survival on HEN by selected disease states (data from [20]).

morbidity and even less often mortality, HPN complications are more frequent and may account for a significant proportion of the mortality (11% in one study). Survival at 1 year in non-cancer, non-HIV infected patients was 91% and 62% at 5 years [22]. In another series of 494 patients from nine European countries, the 6–12-month mortality rate was 4% in Crohn's disease, 13% in vascular diseases, 16% in others, 21% in radiation enteritis, 34% in AIDS and 74% in cancer for the year 1997 [23].

## 7. COMPLICATIONS OF HPEN

### *7.1. Complications of HEN*

Complications of HEN (Table 13.3) may include problems related to the tube, such as erosion or expansion of the stoma with leakage and excoriation of the skin, tube clogging and tube breakage, among others [24]. As discussed previously, these can be severely detrimental to QOL. Because feeding products are maximally 85% water by

**Table 13.3**
**Complications of HEN**

| |
|---|
| Metabolic |
| Fluid and electrolyte imbalance |
| Fatty acid and fat soluble vitamin deficiencies in malabsorption |
| Other vitamin/mineral deficiencies |
| B12 if no terminal ileum |
| Iron if no remaining or bypassed proximal small bowel |
| Mechanical |
| Pain at stoma |
| Erosion of stoma with leaking |
| Excoriation of skin around stoma |
| Cellulitis around stoma |
| Tube migration if no bolster |
| Tube degradation |
| Quality of life |
| Leakage or discharge from stoma |
| Poor end closure of tube/poor connection to infusion tubing with leakage |
| Prolonged feeding times |
| Nocturia |
| Depression/altered self-image |
| Other |
| Granulation at stoma with bleeding |
| Tube obstruction |

content and may have limited electrolyte content, patients often require additional water supplementation and may develop fluid and electrolyte imbalances. Patients with abnormal fluid and electrolyte physiology (e.g., renal insufficiency, CHF, diarrhea) should be monitored closely.

Patients with malabsorption and IF may develop reductions in essential fatty acid and fat soluble vitamin levels. Frank essential fatty acid deficiency is unusual, but reduction in serum levels is common in patients with malabsorption. Cholesterol, α-tochopherol and fatty acid levels decrease in proportion to the degree of malabsorption. Retinol deficiency is less common [25]. In the absence of malabsorption or losses due to fistulae or diarrhea, other deficiencies are uncommon as most tube feedings provide 100% of the RDA if a reasonable quantity is delivered daily to the patient (usually 1,000 kcal in adults).

### *7.2. Complications of HPN*

Patients receiving PN have alterations in physiology due to infusion of nutrients via an unnatural route. Despite the high frequency, complications from HPN are unlikely to cause mortality. Most patients who die do so as a result of their underlying illness [26]. Interestingly, HPN complications, especially infectious complications, are much less common in the home setting than the hospital [27]. This is unexplained, but may be due to factors such as the relative clinical stability of HPN patients. HPN complications accounted for 11% of deaths in a series of patients with IF and without malignancy in which the overall 5-year survival was 62% [22]. Catheter-related complications are far more common (2.4 fold) in patients with malignancy [28]. Complications (Table 13.4) may be mechanical, thrombotic, metabolic and infectious in nature [29].

Parenteral nutrition complications are far more likely to impact on hospitalization and survival than those related to HEN. In one series, HPN-related complications accounted for an average of $2,000 to $10,000 per year per patient, with one patient exceeding $150,000, while HEN patients in the series had no hospitalizations for EN-related complications in the same 5-year period. HPN patients suffered an average of 1 to 2 complications per year, 0.5–1.1 hospitalizations per year (depending on the year) and spent an average of 3–5 days per year hospitalized for HPN-related complications [6]. Survival rates vary from 20% at 1 year in cancer patients [30] to a range of 62% [22] to 70% [31] at 5–6 years in patients without malignancies.

Table 13.4
Complications of HPN

| |
|---|
| Metabolic |
| Fluid imbalance |
| Electrolyte imbalance |
| Hepatic dysfunction/failure |
| Vitamin deficiency or excess |
| Manganese toxicity |
| Aluminum toxicity |
| Metabolic bone disease |
| Progressive renal insufficiency |
| Mechanical/thrombotic |
| Complications of initial insertion |
| Bleeding |
| Pneumothorax |
| Venous thrombosis |
| Catheter occlusion |
| Pulmonary embolization due to particulate contamination or precipitation of incompatible components |
| Accidental removal of catheter |
| Infectious |
| Catheter sepsis |
| Tunnel infection |
| Entry-site infection |
| Other |
| Nocturia/insomnia |
| Depression/altered self-image |

### *7.3. Hepatic Dysfunction/Failure*

One of the more daunting complications of PN, particularly long-term PN, is that of hepatic dysfunction and failure. PN-related hepatic failure often progresses to end-stage liver disease (ESLD) and is a not uncommon reason for referral for hepatic transplant. Incidence of biochemically evident cholestasis approached 65% after a median duration of 6 months in one study. Prevalence rose to 72% after 6 years on HPN. Clinically significant hepatic dysfunction, fibrosis or cirrhosis was seen in 26% of patients after 2 years, 50% of patients after 6 years and accounted for 22% of deaths. It should be noted that this study reported a 30% death rate over 6 years. Unlike most other studies, PN-related complications (sepsis = 26%, ESLD = 22%) accounted for a far greater proportion of deaths than underlying disease (15%) [31].

Overfeeding, especially of carbohydrates, has been implicated in the development of cholestasis and PN-related hepatic dysfunction. Elevation of markers of inflammation has also been correlated to the development of HPN-related hepatic failure. Administration of omega-6 fatty acids, the sole source of parenteral fat available in the United States, has been implicated in increasing systemic inflammation. However, only total PN calories and total carbohydrate calories have correlated with the incidence of abnormalities in liver enzymes. Interestingly, inflammatory markers increase in a linear fashion proportionate to total and carbohydrate calories [32, 33]. Shorter lengths of small bowel in patients with short bowel syndrome (SBS) have also been found to predispose to liver enzyme abnormalities [34].

Specific nutrient deficiencies have been implicated in the development of PN-related liver dysfunction. In one study, supplementation of patients on HPN with choline reversed CT-scan appearance of hepatic steatosis and normalized alkaline phosphatase and other liver enzymes [35].

### *7.4. Infectious Complications*

Infections related to parenteral nutrition may occur at the point at which the catheter exits the skin (exit site infection), under the skin in tunneled catheters (tunnel infection) or in the bloodstream (catheter sepsis). The frequency of catheter-related sepsis is approximately 0.34 episodes per person per year [36] and comprises 80% of catheter-related infections [29]. Sixty percent are gram-positive organisms, mostly coagulase-negative staphylococci. However, 14% are fungal and 26% gram-negative organisms [29]. Infection rates may be inversely proportionate to the remaining small bowel in patients with SBS [37].

Infections may occur in clusters of patients [38]. These may not be readily noted without ongoing collection of quality improvement data. The origin may be difficult to identify, but may include such things as contamination of stock solutions or recurrent break in sterile technique by staff. These become all the more difficult to assess in patients dispersed in the home environment. Practitioners and home infusion companies must remain vigilant (Fig. 13.2).

Catheter choice may influence the frequency of catheter-related infections. A recent observational study compared the incidence of complications in patients on HPN through peripherally inserted central catheters (PICC) and other central access, either implantable ports or tunneled Hickman catheters. They found a nearly two-fold increase in catheter infections (0.458 episodes/100 days vs. 0.245/100 days, $p < 0.01$) in patients receiving HPN via PICC [39]. PICC catheters

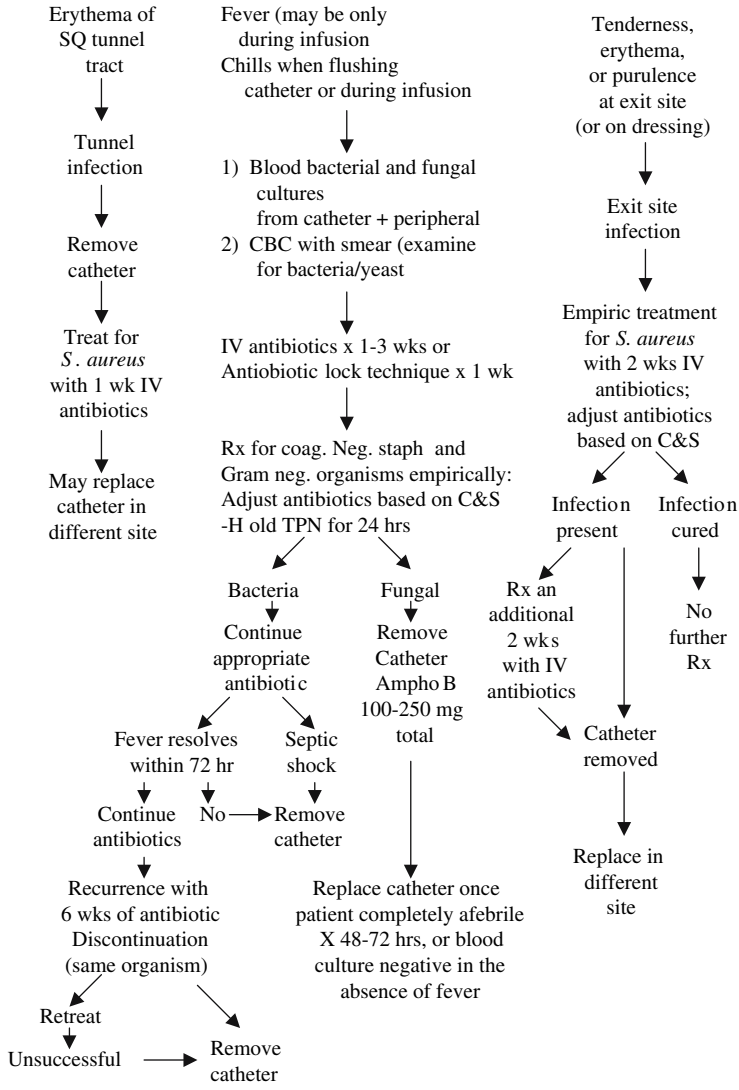


**Fig. 13.2.** Evaluation for catheter-related infections Reprinted with kind permission from Springer Science and Business Media from Buchman AL. Complications of long-term home total parenteral nutrition: their identification, prevention and treatment. Digestive Diseases & Sciences. 46(1):1–18, 2001, Figure 2.

may not be appropriate for HPN despite a reduction in complications related to insertion. Prospective, randomized, controlled studies are lacking to resolve this issue.

### *7.5. Non-Infectious Complications*

Non-infections complications include catheter occlusions (0.07 episodes per person year), central vein thrombosis (0.027 episodes per person year) and reduced renal function (5% per year) [36].

### *7.6. Deficiencies and Toxicities (Table 13.5)*

Any patient on HPN is at risk for nutrient deficiency due to omission from or under-prescription of nutrients in HPN solutions. Essential fatty acid deficiency is observed in patients with severe fat malabsorption or patients receiving HPN without lipids [25]. Selenium [40], arginine [41] and choline [42] deficiencies are among the many single-nutrient deficiencies reported.

**Table 13.5**
**Deficiencies and Toxicities Seen in HPN Patients**

| | *Nutrient* | *Signs/symptoms* | *Laboratory assessment* |
|---|---|---|---|
| Deficiency | EFA | Scaling skin, growth retardation, sparse hair, neuropathy | Triene:tetraene ratio > 0.4 |
| | Selenium | Cardiomyopathy | |
| | Argenine | Encephalopathy | Hyperammonemia |
| | Choline | | Liver enzyme abnormalities |
| | Iron | | Microcytic anemia |
| Toxicity | Aluminum | Apraxia, dementia, seizures, osteomalacia, microcytic anemia | Al level, deferoxamine stimulation test |
| | Manganese | Extrapyramidal symptoms | RBC Mn level, MRI of brain |

Patients entirely dependent on HPN are at risk for developing iron deficiency as iron is not administered as a component of parenteral nutrition. In one study, 55% of patients had evidence of iron deficiency anemia after $>6$ months of HPN [43]. Patients should be monitored for iron deficiency and may require parenteral iron, which may be administered in the home setting as a separate infusion.

Many, if not most, intravenous solutions are contaminated by aluminum. Long-term HPN patients may develop symptoms of aluminum toxicity that include encephalopathy and bone disease. Pediatric patients and those with cholestasis are at increased risk. Despite recent reformulations, aluminum exposures still remain significant [44]. Practitioners should be aware that aluminum exposure may be minimized by selecting additives carefully (e.g., sodium phosphate instead of potassium phosphate). Levels of contamination vary by manufacturer and batch and need to be continually monitored by the compounding pharmacy as variations may be in orders of magnitude. Consultation with the pharmacist at the home infusion company or home care agency responsible for the PN solution compounding may be necessary.

Manganese (Mn) toxicity may cause an extrapyramidal syndrome similar to Parkinson's disease and is associated with an alteration in MRI appearance. Unfortunately, there is no agreed-upon method for determining body stores of Mn. Red blood cell Mn concentrations have been proposed as most reliable and are more feasible than frequent MRI. Current recommended levels for intravenous supplementation of Mn may in fact be excessive. There is a fair amount of Mn contamination in standard HPN solutions. Therefore, delivery of Mn may be sufficient even if supplementation is withheld from HPN [45].

### *7.7. Metabolic Bone Disease*

Patients undergoing long-term HPN are at high risk for developing osteopenia and osteoporosis. Patients may become symptomatic with bone pain, spinal deformity and pathological fractures. In one study, the incidence of abnormal bone density (T-score $< -1$) was 84%, with 41% of patients having severe loss of bone density (T-score $< -2.5$). Thirty-five percent of patients had bone pain, and 10% suffered nontraumatic bone fractures [46]. Aluminum contamination of parenteral solutions with resultant aluminum toxicity has been implicated in this phenomenon, as have alterations in vitamin D metabolism and the presence of chronic inflammation.

## 8. INFUSION CONSIDERATIONS

HPN and HEN may be infused in many ways (Table 13.6). Infusion technique will depend on patient's lifestyle, support systems and tolerance. Most HPN is infused over 12 h and a minimum of 8 h has been recommended, but there is no prospective randomized data to support these recommendations. It is also common practice to provide a 1-h tapering up and down of the rate in the first and last hours of the HPN infusion to avoid hyper- and hypoglycemia. This practice also lacks strong evidence to support it and may be less necessary now that patients are not overfed. Fingerstick glucose monitoring may be performed 2 to 4 h after the infusion starts or stops if there is a concern. Nocturnal infusions are usual for HPN so that the patient is free of any connection during the day, but may cause intolerable nocturia. Portable pumps that may be loaded in a backpack may be used to allow patients intolerant of shorter or nocturnal infusions to be infused continuously, while allowing for mobility out of the house.

HEN may be infused in rapid boluses, slower boluses and continuously over several hours or around the clock. Nocturnal infusion may

**Table 13.6**
**Options for Infusion and Timing of HPEN**

| |
|---|
| HPN |
| Programmable electronic pump |
| Duration 8 to 24 h |
| Ramp up 1st hour |
| Ramp down last hour |
| Portable vs. fixed to pole |
| HEN |
| Electronic Pump |
| Duration 8 to 24 h |
| Useful if intolerant to bolus feeds |
| Portable pump with sealing bags available |
| Slow gravity bolus |
| 250-1,000 ml feed product in bag |
| Bag must be hung (pole or hook) |
| Rate adjusted by flow regulator |
| Reduced mobility during longer period |
| Rapid gravity bolus |
| Attach body of 60-ml catheter syringe to end of feeding tube |
| Patient holds syringe and pours aliquots of feeding product into syringe |
| Usually 250 to 500 ml feeding product per session |

also be used with HEN. Rapid boluses may be given by repeated injection. It is easier, in the author's experience, to remove the piston from a catheter syringe and then use the outer body of the syringe as a funnel on the end of the feeding tube. Most patients receiving HEN via gastrostomy will tolerate bolus feeds. However, some patients will require slower infusion due to gastroparesis and other gastric motility problems. Most jejunostomy tubes require continuous tube feeding delivered by a pump; however, slower bolus feeds via jejunostomy are possible. Portable pumps with sealing bags that may be loaded into a backpack are also available for HEN.

## 9. DISEASE-SPECIFIC CONSIDERATIONS

### *9.1. Crohn's Disease*

Even though therapy has become much more effective, Crohn's disease remains one of the more common causes of intestinal failure. Life expectancy has increased to 87% in one 20-year series, but in that same period the incidence of surgical interventions nears 80% in survivors. One bowel resection was performed on 30% of patients, and 22% underwent at least three resections. Despite this, only 3% required parenteral nutrition for an extended period (2–13) years [47].

### *9.2. Cancer*

The use of nutrition support for non-terminal cancer patients to provide support during curative therapy is appropriate and may improve outcome by enabling the patient to complete therapy. HPEN for terminal cancer patients remains controversial. There is a plethora of data showing no survival benefit, but the occasional study that shows improvements in selected quality of life indices makes for difficult ethical decision-making. Anyone caring for cancer patients knows that there are patients that occasionally defy statistics and medical prognostication by surviving for extended periods. Based on these outliers, some authors advocate for the judicious use of HPEN for these patients. There are no data, however, to help predict who these long-term survivors will be [30, 48]. Further, in the face of extremely high short-term mortality rates and with no controlled studies to prove actual benefit, wholesale use of PN in this group has long been questioned [28].

### *9.3. Dysphagea, Dementia, and Progressive Neurological Disease*

Tube feeding patients with dysphagia does not reduce the incidence of aspiration pneumonia as aspiration of saliva persists. Tube feeding in this patient group should be reserved for those who cannot maintain adequate nourishment. While there are no prospective data, there are two recent studies that fail to show any difference in longevity whether patients with advanced dementia are tube fed or not [49, 50]. PEG feeding has been shown to stabilize the nutritional state in patients with amyotrophic lateral sclerosis, but longevity from time of diagnosis was not effected [51]. Patients requiring HEN after cerebrovascular accidents should receive periodic assessment of swallowing as many may return to oral feeding (13% in one study) [52].

## 10. SUMMARY

HPEN is an effective means of preventing and treating starvation in patients with IF. HPN and HEN are not equivalent therapies and have distinct complications and administration considerations. Practitioners must become familiar with the added difficulties that HPEN patients face and help patients and their support systems deal with the transition to the home environment.

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