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96

3rd Series

BACTERIAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Edited by:
KAREN L. ROOS
ALLAN R. TUNKEL

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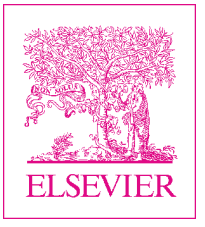

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Foreword

The recent development of new vaccines and antibiotics generated the hope that infectious diseases, particularly those affecting the nervous system, would become much less common than in the past. Unfortunately, this hope has not been realized for a variety of reasons. Vaccinations and the use of antibiotics require a certain degree of medical sophistication and tend to be expensive. Moreover, maintaining an adequate level of hygiene is often difficult in overcrowded areas. These factors explain in part why the prevalence of infections is particularly marked among less affluent populations. In addition, there is increasing opposition to vaccination in certain segments of the population of developed countries. Another key factor is the immunosuppression that accompanies infections with human immunodeficiency virus (HIV) and follows organ transplantations, resulting in a marked resurgence of diseases such as tuberculosis and syphilis, previously considered to be successfully contained. Finally, climate changes and increasing mobility of populations may also contribute to the continuing spread of infectious diseases.

The first series of the Handbook included three volumes published in 1978. They covered bacterial agents (volume 33), viruses (volume 34), and parasitic diseases (volume 35). At the time, HIV infection and acquired immunodeficiency syndrome (AIDS) had not yet been recognized as a problem of epidemic proportion. In the second series, one volume was dedicated to microbial diseases and another to viral infections including AIDS. The very considerable development of the field is reflected by the several volumes dealing with infection in this series. HIV/AIDS was the subject of one of the first volumes of the new series (volume 85). We are now pleased to present a volume dedicated to bacterial infections of the central nervous system. Neurovirology, parasitology, fungal infections, and tropical neurology will be covered in future volumes.

The new volume covers advances in the field of bacterial infections and includes a number of new topics. It provides insight into the pathophysiological mechanism of bacterial CNS infections and covers the main principles of modern antimicrobial therapy as well as the bases for new therapeutic strategies for bacterial infections. There is considerable emphasis on new diagnostic techniques, particularly imaging and new laboratory tests. The volume was edited by Karen L. Roos and Allan R. Tunkel. As series editors, we reviewed all the chapters in the volume and made suggestions for improvement, but we are delighted that the volume editors and chapter authors produced such scholarly and comprehensive accounts of different aspects of bacterial infections. Hence we hope that the volume will appeal to clinicians and neuroscientists alike. Significant new advances continue to occur, leading to new insights that demand a critical appraisal. Our goal is to provide basic researchers with the foundations for new investigations. We also hope that clinicians will gain from this volume a thorough understanding of the clinical features and management of the many neurological manifestations of bacterial infections. In addition to the print form, the Handbook series will soon be available electronically on Elsevier's Science Direct site. This should make it more accessible to readers and should also facilitate searches for specific information.

We wish to express our deep gratitude to the two volume editors and to the numerous authors who contributed their time and expertise to summarize developments in their field and helped put together this outstanding volume. As always, we are also grateful to the team at Elsevier – and in particular to Mr. Michael Parkinson and Mr. Timothy Horne in Edinburgh – for their unfailing and expert assistance in the development and production of this volume.

Michael J. Aminoff
François Boller
Dick F. Swaab

Preface

Bacterial infections of the central nervous system (CNS) are often challenging in terms of establishing the etiologic diagnosis, initiating antimicrobial therapy, and managing complications. Many of these infections continue to be important causes of morbidity and mortality, such that a rapid approach to management is critically important to increase the likelihood of a good neurological outcome. Furthermore, the increased numbers of immunocompromised patients (e.g., following transplantation or infection with human immunodeficiency virus) have further complicated diagnosis and management.

Recent decades have witnessed profound advances in the approach to the patient with bacterial CNS infections. Advances in neuroimaging techniques, such as computed tomography and magnetic resonance imaging, have greatly improved the ability to diagnose CNS structural lesions and monitor their response to therapy. Nucleic acid amplification tests, such as polymerase chain reaction (PCR), have aided in the identification of infectious agents that are not routinely isolated using conventional culture techniques. With the emergence of bacterial strains resistant to standard antimicrobial agents, there is a need for newer agents that effectively cross the blood–brain barrier and eradicate the infecting pathogen. Adjunctive therapy, specifically with dexamethasone, has improved morbidity and mortality in patients with bacterial meningitis and is now part of standard practice guidelines for the management of this important infection. Furthermore, the successful approach to bacterial CNS infections is multidisciplinary and often includes neurologists, neurosurgeons, and specialists in infectious diseases.

This volume includes four chapters that elucidate the general approach to the patient with a suspected bacterial CNS infection. The topics covered include the characteristic neuroimaging appearance of specific bacterial infections and the limitations of neuroimaging; cerebrospinal fluid analysis with an emphasis on the use of newer diagnostic tests; the pathogenesis and pathophysiology of bacterial CNS infections, an understanding of which may lead to the development of other specific adjunctive strategies; and the principles of antimicrobial therapy. Other chapters review specific disease entities, including meningitis, focal CNS infections (e.g., brain abscess, subdural empyema, and epidural abscess), the neurological complications of endocarditis, suppurative venous sinus thrombosis, infections in the neurosurgical patient, and CNS diseases caused by selected infectious agents and toxins. The contributors are recognized experts in their fields, and have extensive clinical and investigative interests. Our goal was to create a comprehensive treatise to be used by physicians who care for patients with bacterial infections of the CNS.

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Handbook of Clinical Neurology, Vol. 96 (3rd series)
Bacterial Infections
K.L. Roos and A.R. Tunkel, Editors

Chapter 1

Pathogenesis and pathophysiology of bacterial CNS infections

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INTRODUCTION

A bacterial infection of the central nervous system (CNS) is a life-threatening condition with high mortality, particularly in the case of bacterial meningitis. Antibiotic therapy and vaccines have changed the face of bacterial CNS infections, but outcome is still unfavorable and associated with permanent neurological dysfunction in many survivors. A key factor that contributes to this insufficient therapeutic success is our incomplete understanding of the pathogenesis and pathophysiology of bacterial CNS infections. A central role of the host's inflammatory response in causing cerebral complications and associated morbidity and mortality has been increasingly recognized. The prototypical bacterial CNS infection that illustrates this is bacterial meningitis, where two-thirds of meningitis-related deaths are attributable primarily, or in part, to CNS complications (van der Flier et al., 2003). The remainder is believed to result from systemic complications (Pfister et al., 1993).

The focus of this chapter is to summarize the current knowledge of the following pathophysiologic steps of CNS infections: (1) mucosal colonization by the pathogen; (2) interaction of microbes with and crossing of the blood–brain or blood–choroid barrier; (3) microbial survival and growth within the CNS; (4) induction of CNS inflammation; (5) pathophysiologic alterations in the CNS; and (6) subsequent development of neuronal damage.

The most important conditions caused by bacterial invasion of the CNS are bacterial meningitis, (meningo)encephalitis, brain abscess, epidural abscess, and subdural empyema (Ziai and Lewin, 2007). The clinical presentation and treatment options are covered in the later chapters. Here, the most prevalent bacterial CNS infections are briefly summarized (Fig. 1.1).

Bacterial meningitis

Bacterial meningitis is both the most common and most serious bacterial infection of the CNS. It is characterized by acute purulent infection of the meninges affecting the pia, the arachnoid, and subarachnoid space (van de Beek et al., 2006). The inflammatory reaction may not only involve the meninges and the subarachnoid space but also the brain parenchymal vessels (vasculitis) and the parenchyma itself and contributes to the development of neuronal injury. Systemic complications, including septic shock, pneumonia, and disseminated intravascular coagulation, also contribute to unfavorable outcome.

Brain abscess

A brain abscess is a focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule (Sharma et al., 2000). The term cerebritis is used to describe the early nonencapsulated correlate. Once infection is established, the brain abscess evolves through a series of stages. The dynamics of this process depend on the infectious organism and the immunocompetence of the host.

The early cerebritis stage is characterized by a central core of necrosis, perivascular accumulation of inflammatory cells, and edema (Fig. 1.1). During the late stage of cerebritis, growth of the necrotic center can be observed due to frank pus formation. During

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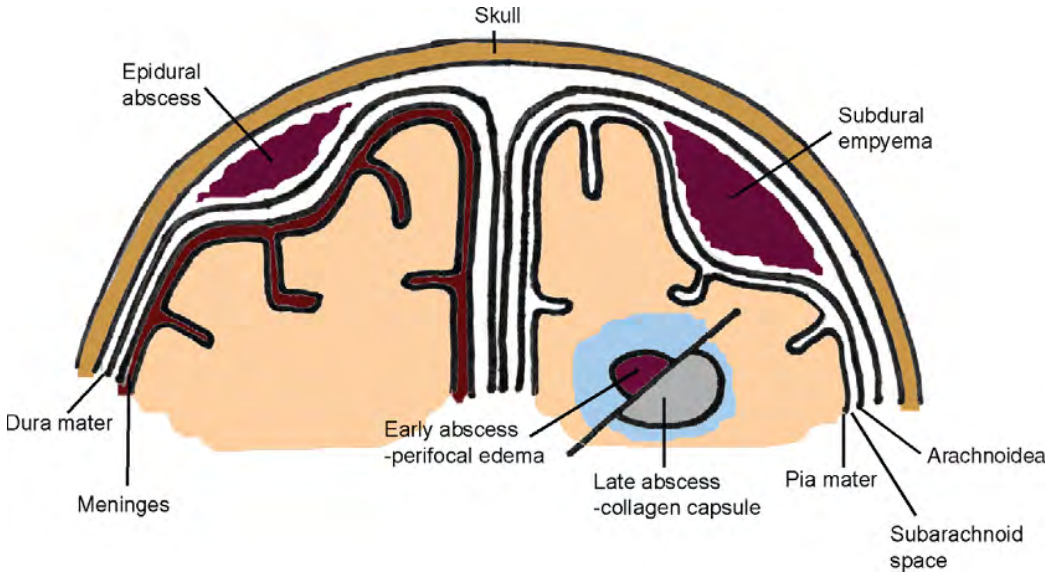

Fig. 1.1. Schematic coronal view illustrating the sites of common bacterial central nervous system infections. (Adapted from Ziai and Lewin, 2007.)

the early abscess stage, the capsule formation occurs: this can be seen as a ring-enhancing structure on neuroimaging. Finally, the late capsule formation stage evolves, and this is characterized by regression of edema and a dense collagenous capsule and marked gliosis surrounding the capsule (Fig. 1.1).

Epidural abscess

A cranial epidural abscess is a suppurative infection occurring in the virtual space between the inner skull surface and the dura (Fig. 1.1). An epidural abscess may occur as a complication of craniotomy or skull fracture, or as a result of infection of the frontal sinuses, middle ear, mastoid, or orbit. Since the dura is tightly adherent to the inner skull table, the infection has to separate the dura from the skull table in order to cause an epidural abscess.

Subdural empyema

A subdural empyema is a collection of pus between the dura and arachnoid membranes (Fig. 1.1). The most frequent cause is a frontal sinusitis, either alone or in combination with ethmoid and maxillary sinusitis. In these conditions, the subdural empyema results from either retrograde spread of infection from septic thrombophlebitis of the mucosal veins draining the sinuses or contiguous spread of infection to the subarachnoid space from osteomyelitis in the posterior wall of the sinuses. Less frequently a subdural empyema may develop as a complication of a neurosurgical procedure. Often, there is concomitant epidural empyema, cortical thrombophlebitis, or intracranial abscess. Involvement of veins can also result in venous cortical infarction.

Suppurative thrombophlebitis

Suppurative intracranial thrombophlebitis is a septic venous thrombosis of cortical veins and sinuses. It can occur as a complication of bacterial meningitis, of subdural empyema or epidural abscess, or of infections of the facial skin, the paranasal sinuses, the middle ear, or the mastoid.

Ventriculitis

Ventriculitis is an infection of the ventricular system of the brain. It occurs as a complication of meningitis or as a primary process, often associated with implantation of a cerebrospinal fluid (CSF) shunt, external ventricular drain, or other intracranial devices.

PATHOGENESIS OF BACTERIAL CNS INFECTIONS

Most understanding of the pathophysiology of CNS infections is derived from human autopsy studies and from experimental models of bacterial meningitis. Hence, the current understanding will be covered with regard to knowledge obtained from clinical and experimental studies of bacterial meningitis.

Most prevalent pathogens of bacterial meningitis

Here, the most common causative agents of bacterial meningitis and the current understanding of their pathogenetic mechanisms leading to mucosal colonization, dissemination, and traversal of the blood–brain and blood–choroid barrier are described.

Streptococcus pneumoniae

S. pneumoniae is a gram-positive, α-hemolytic, catalase-negative, and optochin-sensitive bacterium. It is the most frequent cause of community-acquired bacterial meningitis, except in the neonatal period (Weisfelt et al., 2006a).

In *S. pneumoniae*, surface components, of which more than 500 are known to date, are major adherence factors (Oggioni et al., 2006). A variety of choline-binding proteins expressed on the cell surface, such as pneumococcal surface adhesin A (PsaA) and choline-binding protein A (CbpA; also called PspC, SpsA, or Hic), function as adhesins to host cells. PsaA and CbpA are produced by virtually all clinical isolates of *S. pneumoniae* and contribute to their virulence (Gosink et al., 2000). Several studies have shown that immunization with these proteins can protect against infection with multiple pneumococcal serotypes and prevent nasopharyngeal carriage (Kayhty et al., 2006). Moreover, in mice lacking CbpA, the most frequent Cbp, *S. pneumoniae* is not capable of colonizing the nasopharynx (Rosenow et al., 1997). Further factors supporting nasopharyngeal colonization include neuraminidase NanA and immunoglobulin (Ig) A protease. NanA decreases viscosity of the mucus or exposes other cell surface receptors by cleaving *N*-acetylneuraminic acid from mucin, glycolipids, glycoproteins, and oligosaccharides (Tong et al., 2000). IgA protease is a zinc metalloprotease which inactivates IgA, an important component of the mucosal host defense (Reinholdt and Kilian, 1997).

Adherence of pneumococci to mammalian cells is affected by phase variations, in which colonial morphology of the pathogen shifts from opaque to transparent (Fig. 1.2). Differences in colony opacity correlate with differences in virulence (Weiser et al., 1994). The transparent phenotype is more capable of colonizing the nasopharynx, whereas the opaque phenotype shows increased virulence during systemic infections. Transparent, invasive bacteria harbor significantly greater amounts of the pneumococcal adhesins CbpA and more cell wall choline, the natural ligand for the platelet-activating factor (PAF) receptor, which is expressed on endothelial cells following inflammatory activation (Cundell et al., 1995).

A key virulence factor is pneumolysin, which is a product of *S. pneumoniae* that binds to cholesterol in cell membranes, forming oligomers and creating transmembrane pores (Hirst et al., 2004). Pneumolysin triggers different proinflammatory reactions and can activate the classical complement pathway (Boulnois et al., 1991; Houldsworth et al., 1994). On the other hand, pneumolysin also interferes with cellular functions of the immune system, including the respiratory burst of polymorphonuclear leukocytes, chemotaxis,

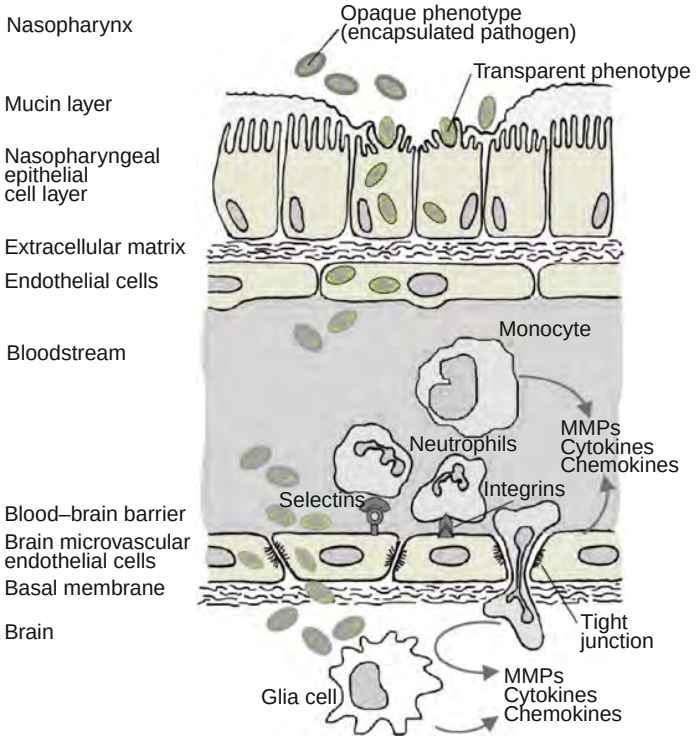

Fig. 1.2. Schematic representation of pathogenetic steps involved in the development of bacterial meningitis. MMP, matrix metalloproteinase.

and bactericidal activity (Paton and Ferrante, 1983). Moreover, it was reported that, *in vitro,* pneumolysin is capable of inducing caspase-independent apoptosis in neurons and microglia via apoptosis-inducing factor (AIF) and mitochondrial damage (Braun et al., 2002, 2007).

Neisseria meningitidis

N. meningitidis is a gram-negative diplococcus that accounts for approximately a quarter of all cases of bacterial meningitis and for up to 60% of cases in children and young adults (Stephens et al., 2007). It is also the cause of large epidemics in various parts of the globe, particularly in sub-Saharan Africa ("meningitis belt"). Thirteen serogroups of *N. meningitidis* based on different capsular polysaccharide structures are identified, among which six serogroups (A, B, C, W-135, Y, and X) are associated with significant pathogenetic potential (Rosenstein et al., 2001). The surface structures include capsular polysaccharides, outer-membrane proteins, and endotoxins; all of these are major virulence factors.

The occurrence of meningococcal disease is influenced by the pathogenetic potential of the bacteria and the susceptibility of the human host (Stephens, 2007). *N. meningitidis* is a frequent commensal, isolated in the nasopharynx of 8–20% of healthy individuals (Caugant et al., 1994). Meningococcal carriage and acquisition are influenced by age, close contacts, and cofactors such as smoking and co-infections (Tzeng and Stephens, 2000). Meningococci are passed on by respiratory secretions and saliva or by inhalation of aerosolized droplets. Acquisition of meningococci may be transient, lead to colonization, or result in invasive disease. Once meningococci reach human epithelial cells, a series of interactions with host epithelial cells occurs, leading to attachment to the epithelial surface, microcolony formation, and/or epithelial cell invasion (Stephens et al., 1983). Meningococcemia is characterized by widespread vascular injury with endothelial necrosis, disseminated intravascular coagulation, and perivascular hemorrhage (Rosenstein et al., 2001).

Group B streptococcus (*Streptococcus agalactiae*)

Group B streptococcus (GBS) is a gram-positive diplococcus and is responsible for severe sepsis (early-onset disease) and meningitis (late-onset disease) in neonates (Clarke and Heyderman, 2006). It is a common inhabitant of the maternal genital and gastrointestinal tracts and colonizes approximately 20% of pregnant woman. GBS is acquired through vertical transmission, either *in utero* or during passage through the birth canal. Transmission may also occur horizontally in the nursery or at home. The frequency of GBS meningitis in individuals >50 years of age, particularly in the context of underlying chronic diseases, is increasing.

GBS are classified serologically based on cell wall polysaccharides (Ia, Ib, Ia/c, II, III, IV, V, VI, VII, and VIII). While all serotypes can cause infections, subtype III is detected most frequently.

GBS adhere to a variety of human cells, including vaginal epithelium, placental membranes, respiratory tract, and blood–brain barrier epithelium (Tamura et al., 1994). Adhesion to epithelial cells is mediated by cell wall-associated lipotechoic acid and GBS surface proteins (Wibawan et al., 1992). GBS was shown to bind to extracellular matrix components, including fibronectin, fibrinogen, and laminin, in order to facilitate mucosal colonization (Tamura and Rubens, 1995). This is mediated by ScpB, a homologue of the Lra1 adhesin family, and the surface-anchored protein FbsA. Moreover, GBS has developed strategies for penetrating and traversing host cell barriers, and for avoiding immunological clearance and an inflammatory reaction (Doran and Nizet, 2004). GBS can traverse placental membranes and infect the fetus within the amniotic cavity, leading to placental membrane rupture and premature delivery. GBS β-hemolysin/cytolysin (β-H/C) is directly cytolytic for human brain endothelial cells and contributes to the disruption of the blood–brain barrier (Doran et al., 2003). Avoidance of immunological clearance by GBS is mediated by its polysaccharide capsules (Doran and Nizet, 2004).

Escherichia coli

Escherichia coli is the most common gram-negative organism that causes meningitis during the neonatal period (Kim, 2003). In about 80% of cases, *E. coli* strains with the K1 capsular polysaccharides are isolated. The development of *E. coli* K1 meningitis is a complex and multistage process (Xie et al., 2004). It includes mucosal colonization of the gastrointestinal tract, invasion into the intravascular space followed by intravascular survival and multiplication. *E. coli* K1 is able to achieve a high level of bacteremia based on its defensive structures such as the K1 capsular polysaccharide and O-lipopolysaccharide (Xie et al., 2004). Subsequently, *E. coli* K1 binds to brain microvascular endothelial cells through bacterial surface structures such as OmpA and type 1 fimbriae (FIMH). The bacteria–endothelia interactions induce actin cytoskeleton rearrangement and formation of microvilli-like protrusions to facilitate bacterial internalization into microvascular endothelial cells. *E. coli* K1 is

stored in vacuoles and will enter the subarachnoid space after release at the basal side of the microvascular endothelial cell.

Listeria monocytogenes

L. monocytogenes is a facultative intracellular gram-positive bacillus that can cause sepsis, meningitis, and meningoencephalitis, particularly in immunocompromised patients, neonates, and pregnant women (Wing and Gregory, 2002). Listerial rhombencephalitis is a rare variant that occurs in immunocompetent individuals (Uldry et al., 1993). *L. monocytogenes* is a ubiquitous microorganism found in the gastrointestinal tract of up to 5% of healthy adults. It is found in a wide variety of food, which represents the most frequent source for human infection (Schlech et al., 1983).

L. monocytogenes has a predilection for invading the CNS (Drevets et al., 2004). This occurs by direct invasion of brain endothelial cells during bacteremia, via the intra-axonal route and by phagocyte-facilitated invasion utilizing parasitized monocytes (Antal et al., 2001; Wing and Gregory, 2002). Entry into epithelial cells is facilitated by interaction of the bacteria with cell surface E-cadherin, heparin sulfate proteoglycan receptors, and type I macrophage scavenger receptors (Dunne et al., 1994; Mengaud et al., 1996). After entering cells, *Listeria* escape from phagosomes by entering the cytoplasm via the pore-forming molecule listeriolysin O (LLO) (Kayal and Charbit, 2006). Inside the cell, *Listeria* push against the cell membrane by actin-based propulsion. The resulting protrusion (filopodium) can then be phagocytosed by the adjacent cell and thus lead to further dissemination.

Mechanism of bacterial entry to and infection of the brain

Anatomical barriers of infection

The CNS is protected against bacterial invasion by the bony skull, the leptomeninges, and the blood–brain and blood–choroid barriers (Fig. 1.1).

The blood–brain barrier is a structural and functional unit that separates the systemic circulation from the CNS. It is formed by endothelial cells and their tight junctions, the astrocytic foot processes, and the basement membrane. These endothelial cells are characterized by: (1) tight junctions with extremely high resistance, which limits the amount of paracellular flux; (2) sparse pinocytic activity; and (3) specific transport and carrier systems (Koedel et al., 2002).

The blood–choroid barrier consists of a high density of capillaries, separated from the subarachnoid space by pia mater and choroid ependymal cells. Liquid filters through these cells from blood to generate CSF. The choroid plexus capillaries are fenestrated. Both barriers inhibit the free diffusion of molecules from blood into the CNS (Engelhardt, 2006).

Neuroinvasion of bacteria

Bacterial neuroinvasion can occur either in the context of a systemic disease following bacterial dissemination via the bloodstream (Fig. 1.2) or by contiguous spread from sinusitis or otitis (Kim, 2003). Moreover, direct access of bacteria to the CNS is possible due to local infection, dural defects, after neurosurgery, craniocerebral trauma and invasive neuromonitoring techniques. In addition, *L. monocytogenes* is able to enter the brain by retrograde transport via cranial nerves (Antal et al., 2001).

In this respect, intra- and extracellular bacteria have developed different strategies of how to interact with and cross the blood–brain or blood–choroid barrier, escape the immune system, and replicate within the CNS. Many of the meningeal pathogens produce a polysaccharide capsule that allows them to resist complement-mediated lysis and phagocytosis by leukocytes. These pathogens require a high-density bacteremia for CNS invasion which will result in a high bacterial load within the CSF. Facultative and obligate intracellular bacteria like *L. monocytogenes* require lower densities in the bloodstream and CSF due to their potential to propagate from cell to cell.

Potential routes for bacteria entering the CNS are (Drevets et al., 2004):

1. Intercellular, i.e., passing between cells
2. Transcellular, i.e., passing through cells
3. Leukocyte-facilitated, i.e., Trojan horse-like mechanisms
4. Nonhematogenous, i.e., retrograde transport within cranial nerves.

Inter- and transcellular routes have been described more often than the other mechanisms.

Bacterial multiplication in the cerebrospinal fluid

Host defense mechanisms are severely limited in the subarachnoid space, as neutrophils, plasma cells, complement components, and immunoglobulins are largely excluded by the blood–brain barrier in the normal, uninflamed state (Koedel et al., 2002).

The deficient opsonization due to low concentrations of capsule-specific immunoglobulins and complement factors combined with the paucity of resident macrophages in the CSF favors the survival of pathogens once they have reached the CSF. Lack of optimal

opsonization, primarily due to the lack of capsule-specific antibodies, also greatly reduces the effectiveness of incoming neutrophils (Simberkoff et al., 1980). Even an increase of complement factors during bacterial meningitis, which results from the progressive disturbance of the blood–brain barrier, is insufficient to reduce bacterial titers significantly (Stahel et al., 1997a,b).

Bacteria can multiply within the cerebrospinal fluid almost as efficiently as in culture broth, reaching titers of up to 10^9 cfu/ml. They spread over the entire surface of the brain and spinal cord, and extend into the Virchow–Robins space along penetrating vessels. Replication and autolysis of bacteria in the CSF lead to the release of bacterial components (peptidoglycan fragments of cell wall, lipopolysaccharide) that trigger the inflammatory response in the subarachnoid space by inducing the production and release of inflammatory cytokines and chemokines (Zwijnenburg et al., 2006).

Inflammation

Subarachnoid space inflammation appears as a grayish yellow to green exudate covering the base and convexities of the brain with obvious involvement of cerebral arteries and veins. Histological examination shows that the exudate in acute bacterial meningitis consists predominantly of granulocytes, while there is a mixture of lymphocytes, macrophages, and granulocytes in subacute to chronic forms of meningitis (Wilhelm and Ellner, 1986).

The multiplication of bacteria within the subarachnoid space initiates a complex immune response (Coimbra et al., 2006), as shown in Figure 1.3. Many brain cells, i.e., astrocytes, glial cells, endothelial cells, ependymal cells, and resident macrophages, can produce cytokines and other proinflammatory molecules in response to bacterial stimuli (van Furth et al., 1996; Moreillon and Majcherczyk, 2003). Tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) and interleukin-6 (IL-6) play a role as early-response cytokines. They trigger, often in synergy, a cascade of inflammatory mediators, including other interleukins, chemotactic cytokines (chemokines), PAF, prostaglandins, matrix metalloproteinases (MMPs), nitric oxide, and reactive oxygen radicals (Nathan and Scheld, 2000).

Cytokines

Increased CSF concentrations of TNF-α, IL-1β, IL-6, IL-8 (CXCL8), and IL-10 are found in bacterial meningitis (Lahrtz et al., 1998; Mastroianni et al., 1998; Ostergaard et al., 2000). These cytokines are predominantly proinflammatory, with the exception of IL-10, which downmodulates the production of TNF-α and other proinflammatory cytokines (van Furth et al., 1996). Intracisternal injection of *S. pneumoniae* leads to peak concentrations of TNF-α in CSF approximately 12 hours after infection, with persistently elevated levels for at least 24 hours (Leib et al., 2001). The sustained TNF-α activity in the CSF may be explained by continuous stimulation by products released from bacteria in the CSF or by a positive-feedback loop in the inflammatory cascade.

Administration of TNF-α into the CSF results in pathophysiological changes characteristic of bacterial meningitis, including blood–brain barrier breakdown, generation of a neutrophilic inflammation, and

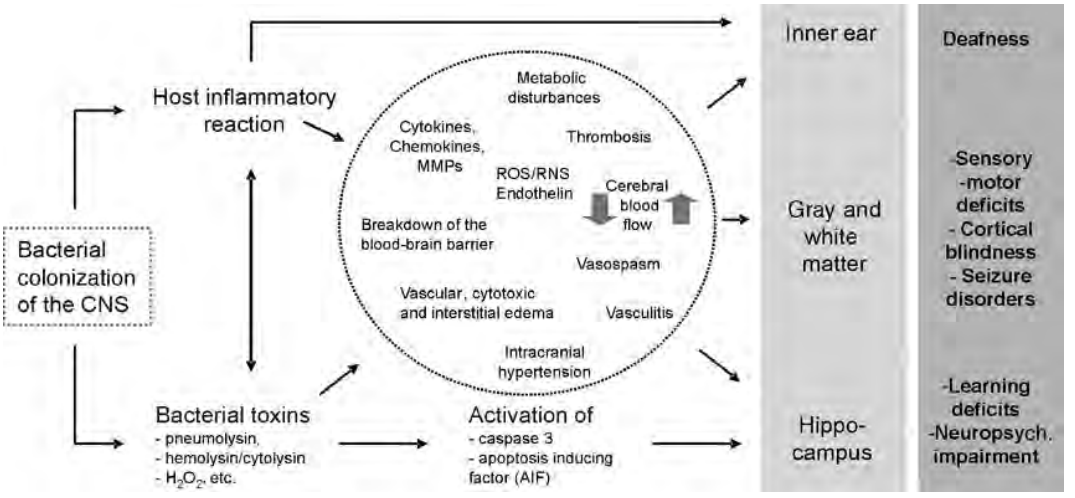

Fig. 1.3. Summary of the development of neuronal damage in bacterial meningitis. This hypothetical cascade highlights the complexity of the pathogenesis and pathophysiology of bacterial central nervous system infections. MMP, matrix metalloproteinase; RNS, reactive nitrogen species; ROS, reactive oxygen species.

increase of cerebral metabolism, oxygen consumption, and cerebral blood flow (CBF) (Rosenberg et al., 1995; Tureen, 1995). TNF-α leads to nuclear factor kappa B (NF-κB) activation in CSF- and brain-resident cells, which in turn regulates the expression of many proinflammatory genes (e.g., for IL-1, TNF-α, IL-6, IL-8, macrophage inflammatory protein-1α (MIP-1α, CCL3), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and intercellular adhesion molecule-1 (ICAM-1)) (Ichiyama et al., 2002). Antibiotics cause rapid lysis of microorganisms and an associated brisk release of bacterial cell wall products, resulting in significantly higher TNF-α concentrations in CSF shortly after initiation of antimicrobial therapy (Mustafa et al., 1990). Recent experimental studies revealed that usage of nonbacteriolytic antibiotics can reduce the proinflammatory response triggered by cell wall components and eventually prevent neuronal damage (Spreer et al., 2003; Grandgirard et al., 2007b).

The proinflammatory cytokine IL-1β is released by mononuclear phagocytes, glial cells, and endothelial cells in the CNS after stimulation by bacterial wall components or TNF-α (Nathan and Scheld, 2000). IL-1β is found in CSF samples of patients with bacterial meningitis, and its concentration is significantly correlated with inflammatory parameters, TNF-α concentrations, and adverse disease outcomes (Mustafa et al., 1989; Ostergaard et al., 2004).

IL-6 is a multifunctional cytokine implicated in a variety of physiological and pathophysiological functions of the brain. It is produced by monocytes, endothelial cells, and astrocytes, essentially in response to IL-1β. IL-6 is present in the CSF during meningitis later than TNF-α and IL-1β, but remains present for longer periods than the former cytokines. Although IL-6 can be detected in the CSF of patients with bacterial meningitis, its presence is not correlated with any of the indices of meningeal inflammation or with severity of disease (Rusconi et al., 1991). IL-6 has a predominantly proinflammatory effect and is a potent inducer of acute-phase proteins, fever, leukocytosis, and activation of the complement and clotting cascades (Gruol and Nelson, 1997). Recent studies in an experimental model documented a dual role of IL-6, in that it promoted blood–brain barrier disruption but also acted as an anti-inflammatory cytokine (Paul et al., 2003). Anti-inflammatory effects of IL-6 include inhibition of TNF-α and IL-1β production *in vitro* and induction of an IL-1-receptor antagonist (Cohen and Cohen, 1996).

IL-8 is the first identified member of a large family of chemokines and increased levels are found in the CSF of patients with bacterial meningitis (Seki et al., 1993; Sprenger et al., 1996). Similar to most chemokines, its primary action is to activate and attract leukocytes to sites of inflammation. Cells shown to produce IL-8 upon stimulation with TNF-α, IL-1β, or bacterial products include monocyte–macrophages, polymorphonuclear leukocytes, endothelial cells, astrocytes, microglia, and neurons. In the context of bacterial meningitis, IL-8 is mainly produced by brain-resident cells and enhances neutrophil adhesion on endothelial cells, a prerequisite for the invasion of leukocytes into the brain (Ostergaard et al., 2000). Several other chemokines are also present in the CSF during bacterial meningitis, and contribute to the composition and intensity of the subarachnoid space cellular infiltrate (Zwijnenburg et al., 2006).

High levels of IL-10 have been found in patients with bacterial meningitis (van Furth et al., 1995). IL-10 is an anti-inflammatory cytokine which inhibits the production of TNF-α, IL-1β, IL-6, and IL-8 *in vitro* and attenuates changes of regional CBF, brain water content, intracranial pressure, and CSF pleocytosis during experimental meningitis (Koedel et al., 1996; Paris et al., 1997). Hence, in experimental cerebral listeriosis, IL-10 was shown to prevent an overshoot of inflammation within the CNS (Deckert et al., 2001). In addition to IL-10, transforming growth factor-β (TGF-β) has also been suggested to downregulate inflammatory activity within the CNS (Malipiero et al., 2007). Neutrophil granulocytes in the CSF of patients with bacterial meningitis were reported to have increased mRNA transcripts for TGF-β (Ossege et al., 1996). TGF-β was shown to interfere with TNF-α production, oxygen radical formation, and the adhesiveness of polymorphonuclear leukocytes to endothelial cells (Fontana et al., 1992).

MMPs and related proteases

The MMPs comprise endopeptidases that serve as effectors of cell migration, tissue remodeling, and cytotoxicity by degradation of extracellular matrix (ECM) components (Gasche et al., 2006). MMPs are synthesized as inactive zymogens and can be activated by conformational changes that disrupt a Zn^{2+}-binding cysteine switch. MMPs not only function as effectors of tissue remodeling but also interact with the cytokine network (Leppert et al., 2001). Cytokines such as TNF-α, IL-1β, and IL-2 modulate the expression and regulation of MMPs. In return, MMPs and related metalloproteinases can act as sheddases or convertases as they transform membrane-bound cytokines, cytokine receptors, and adhesion molecules to their soluble forms. ADAM-10 and ADAM-17 (TNF-α-converting enzyme (TACE)), membrane proteins containing a disintegrin and a metalloproteinase domain, are highly

efficient sheddases of TNF-α and TNF receptors. This makes them integral components in the network of MMPs and cytokines (Echchannaoui et al., 2007).

MMPs appear to play a central role in the development of bacterial meningitis (i.e., breakdown of the blood–brain barrier, intrathecal production of cytokines, and accumulation of blood-derived leukocytes in the CSF) (Paul et al., 1998; Leib et al., 2000). Studies in a rat model of pneumococcal meningitis documented a 100–1000-fold transcriptional induction of MMP-3, -8, -9, -12, -13, and -14, but not of MMP-2 and -7, in brain parenchymal tissue (Leib et al., 2001). In a clinical study, MMP-13, MMP-9 and MMP-8 were found to be upregulated in CSF from children with bacterial meningitis (Leppert et al., 2000; Lindberg et al., 2006). CSF levels of MMP-9 were significantly higher in those children who developed neurological sequelae than in those who recovered fully, thus identifying high CSF levels of MMP-9 as a risk factor for the development of neuronal damage (Leppert et al., 2000).

Tissue inhibitors of metalloproteinases (TIMPs), the specific endogenous inhibitors of MMPs, form complexes with pro- and activated forms of MMPs and inhibit the enzymatic activity. Similar to MMPs, TIMPs are also regulated by a network of different signaling molecules (Gasche et al., 2006).

The imbalance of MMP-9 and its inhibitor TIMP-1 were shown to play a key role in the degradation of the neurovascular basement membrane and development of neuronal damage within the cortex (Sellner and Leib, 2006). Treatment with MMP inhibitors led to a significant reduction of mortality and seizure incidence, and reduced the extent of cortical damage (Leib et al., 2000). Moreover, doxycycline, an antibiotic with anti-inflammatory and MMP-inhibitory properties, was shown to reduce blood–brain barrier disruption and cortical brain injury in the neonatal model of pneumococcal meningitis (Meli et al., 2006). In addition to these effects, the combined inhibition of MMP and TACE led to a reduction of hippocampal apoptosis and preserved learning capacity of animals that recovered from bacterial meningitis (Leib et al., 2001).

Neutrophil extravasation

Neutrophil migration into the CSF is a key step of the protective immune response against invading microbes (Zwijnenburg et al., 2006). In response to cytokines, chemokines, and other chemotactic stimuli, neutrophils penetrate the microvascular basement membrane, leaving the bloodstream to accumulate in the CSF, where they produce the profound CSF pleocytosis characteristic of bacterial meningitis. Blocking of leukocyte entry was shown to increase bacteremia and decrease survival in an experimental model of pneumococcal meningitis (Brandt et al., 2005). However, invasion of leukocytes may contribute to the deleterious effects of inflammation within the brain with development of neuronal damage (Grandgirard and Leib, 2006).

The entry of blood-derived neutrophils into the CSF requires several major steps. The initial step in the adhesion cascade is the tethering and rolling of leukocytes along the endothelium. This is mediated by adhesion molecules of the selectin family (L-, E-, and P-selectin) and their respective ligands which are upregulated on the endothelial cell surface in response to proinflammatory stimuli (Tang et al., 1996). Treatment with fucoidin, a selectin blocker inhibiting leukocyte rolling, has been shown to attenuate the pleocytosis in experimental pneumococcal meningitis (Granert et al., 1994). After this initial tether, the leukocyte rolls along the vessels with greatly reduced velocity and is exposed to chemotactic factors presented on the endothelial surface (Engelhardt, 2006). Chemokines bind to and activate G-protein coupled receptors of the leukocyte surface, leading to activation of adhesion molecules of the integrin family. These integrins (α and β chain) are constitutively expressed on leukocytes in an inactive conformation (Springer and Wang, 2004). Activated integrins allow firm adhesion of leukocytes to the vessel wall by binding to ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1), which are upregulated by proinflammatory molecules. In experimental meningitis, an antibody against ICAM-1 was shown to reduce leukocyte counts within the CSF (Weber et al., 1995).

The final step is the transmigration of leukocytes through vessel walls along a chemotactic gradient. Several studies have reported increased levels of chemokines in the CSF during bacterial meningitis (Lahrtz et al., 1998; Zwijnenburg et al., 2006). Particularly ELR+ CXC chemokines and, to a lesser extent, CC chemokines are upregulated. Neutrophils are attracted by IL-8, an ELR+ CXC chemokine, and a correlation of CSF leukocytes and IL-8 in CSF was reported (Ostergaard et al., 1996). CXCL5 can also exert chemotactic activity on neutrophils and is found in the CSF of children with bacterial meningitis (Zwijnenburg et al., 2003). Antibodies against IL-8 and CXCL5, respectively, were shown to reduce chemotactic activity of purulent CSF (Spanaus et al., 1997; Zwijnenburg et al., 2003). Other chemokines increased during bacterial meningitis are CXCL1, CCL2, CCL3, and CCL4 (Sprenger et al., 1996; Spanaus et al., 1997; Lahrtz et al., 1998).

The extent of neutrophil extravasation during meningitis, as measured by CSF pleocytosis, can be reduced experimentally by nitric oxide synthase

(NOS) inhibitors (Koedel et al., 1995). The underlying mechanisms by which NO supports neutrophil extravasation during meningitis are not clear. The complement factors C3a and C5a are also potent chemoattractants. While normal CSF contains very low concentrations of these factors, they are increased in CSF of patients with bacterial meningitis and activation of the complement cascade is detected (Buchanan and Macnab, 1972; Ernst et al., 1984). Treatment with the C1 inhibitor, which regulates the initiation phase of the classical pathway, was associated with less pronounced meningeal leukocyte infiltration (Zwijnenburg et al., 2007). MMPs also contribute to the early increase of the blood–brain barrier permeability by degradation of the basal membrane of the neurovascular matrix during meningitis (Sellner and Leib, 2006). In a rat model of meningococcal meningitis, disruption of the blood–brain barrier, increased intracranial pressure, and CSF pleocytosis were paralleled by the occurrence of MMP-9 activity in the CSF (Paul et al., 1998).

The precise pathways of leukocyte passage across the blood–brain barrier in bacterial meningitis are still not clear. It is generally thought that leukocyte passage occurs via the paracellular route, but morphological studies have reported that leukocytes may also traverse endothelial cells via transcellular pathways (Engelhardt, 2006). The paracellular route may alter the molecular organization of the tight junction complex, including breakdown of occludin and reorganization of the actin cytoskeleton, eventually leading to increases in blood–brain barrier permeability (Bolton et al., 1998). In addition to separation of intercellular tight junctions, increased blood–brain barrier permeability also results from increased pinocytosis of endothelial cells (Cipolla et al., 2004; Lossinsky and Shivers, 2004).

Selected pathophysiological mechanisms and cerebral consequences

Cerebral blood flow

Bacterial meningitis is associated with marked changes in CBF. During the early phase of the disease, an increase in blood flow is observed, while in advanced meningitis, CBF is reduced (Ries et al., 1997; Moller et al., 2004; Lu et al., 2006). Morphological changes underlying these CBF alterations include the narrowing of large and small arteries and arterioles, most likely as a result of vasospasm (Ries et al., 1997). In addition to focal changes in the vasculature, pathophysiological alterations during meningitis lead to a global reduction of CBF in advanced meningitis. Parameters contributing to global CBF reduction in meningitis are the loss of CBF autoregulation, increased intracranial pressure, and systemic hypotension. CBF autoregulation impairment has been documented in bacterial meningitis, both in experimental models and in clinical studies (Tureen et al., 1990; Moller et al., 2000, 2004). Superimposed on global cerebral hypoperfusion are brain regions with focal hypoperfusion caused by vasculitis of large and small arteries traversing the inflamed subarachnoid space. This form of vasculitis is thought to be mainly responsible for ischemic damage leading to permanent neurological sequelae (Ment et al., 1986; Koedel et al., 1995).

Nitric oxide plays a crucial, albeit complex role in modulating CBF during meningitis, with experimental studies suggesting a phase-dependent role at the level of the cerebral vasculature (Klein et al., 2006). Early in the disease, the vasodilatative effect of NO contributes to the hyperemia induced by subarachnoid space inflammation. Later, when CBF progressively declines under the influence of vasoconstrictive factors, NO produced in the vasculature has some protective effects against ischemia. Thus, attempts to downmodulate NO production during meningitis are potentially dangerous, despite the evidence that NO contributes to some of the potentially harmful changes, such as CSF inflammation, brain edema, and intracranial pressure.

There is growing evidence that reactive oxygen species (ROS) and reactive nitrogen species (RNS) also play a critical role in modulating CBF during meningitis. The likely cellular sources of ROS include polymorphonuclear leukocytes, endothelial cells, and activated microglial cells. Interestingly, the cerebral vasculature shows evidence of marked oxidative alterations during experimental pneumococcal meningitis in infant rats, while oxidative damage to the brain parenchyma itself has not been documented conclusively to date (Schaper et al., 2002). Oxidative damage to the vasculature can be inhibited by treatment with antioxidants. The same antioxidants have been shown to prevent CBF reductions and reduce cerebral ischemic damage in these models (Auer et al., 2000; Christen et al., 2001).

ROS and RNS can chemically react and form peroxynitrite ($ONOO^-$), which is a strong oxidant that exerts cytotoxic effects on endothelial and vascular smooth-muscle cells (Szabo, 2003). In addition, the reaction leads to the loss of the vasodilatative biological effect of NO. Nitrotyrosine residues on proteins as a marker for the presence of peroxynitrite were detected in the meninges, the cortical blood vessels penetrating the subarachnoid space, and on inflammatory cells in the brains of patients with bacterial meningitis and in animal models (Kastenbauer et al., 1999, 2002). Furthermore, pretreatment with the peroxynitrite scavenger urate attenuated meningeal inflammation, blood–brain barrier

disruption, and intracranial hypertension (Kastenbauer and Pfister, 2002). These data suggest that the cerebral vasculature is exposed to significant oxidative stress during meningitis, which in turn contributes to CBF reduction and cerebral ischemia.

Endothelins are potent vasoconstrictory peptides and increased levels are found in the CSF of patients with bacterial meningitis (Koedel et al., 1997). The formation and release of endothelins are triggered by cytokines and NO, and they are produced in the CNS by vascular endothelial cells, glial cells, and neurons. In experimental pneumococcal meningitis, treatment with an endothelin antagonist significantly prevented the reduction of CBF induced by the infection and concomitantly reduced the extent of cerebral ischemia (Pfister et al., 2000).

Brain edema

The development of cerebral edema, which may be vasogenic, cytotoxic, or interstitial, is a hallmark of the cerebral involvement during meningitis.

Vasogenic cerebral edema is primarily a consequence of increased blood–brain barrier permeability, which leads to extravasation of macromolecules and serum into the brain parenchyma. Vascular endothelial growth factor (VEGF) was shown to contribute to blood–brain barrier disruption and subsequent vascular brain edema. This protein is a potent vascular permeability factor which is produced by inflammatory cells and increased CSF levels were reported in patients with bacterial meningitis (van der Flier et al., 2001).

Cytotoxic edema results from an increase in intracellular water following alterations of the cell membrane and loss of cellular homeostasis with influx of potassium and calcium into the cell. Cytotoxic mechanisms include ischemia and the effect of excitatory amino acids (Dijkhuizen et al., 1999). Secretion of antidiuretic hormone also contributes to cytotoxic edema by producing hypotonicity of extracellular fluid and increasing the permeability of the brain vasculature to water (Kaplan and Feigin, 1978).

Interstitial edema occurs by an increase in CSF volume, either through increased CSF production (increased blood flow in the choroid plexus) or decreased resorption secondary to increased CSF outflow resistance across the arachnoid villi system of the sagittal sinus (Scheld et al., 1980). Interstitial edema is believed to be the pathogenetic basis for the occurrence of hydrocephalus complicating meningitis.

Recently, the bidirectional water channel aquaporin-4 has been found to play an important role in brain–water homeostasis. In bacterial meningitis, aquaporin-4 appears to facilitate water movement into brain astroglia in cytotoxic edema, and water movement out of the brain in vasogenic edema (Papadopoulos and Verkman, 2005).

Cerebral complications and neuronal damage

The neuropathology of bacterial meningitis includes subarachnoid space inflammation, vasculitis, brain edema, and evidence of injury to cortical and subcortical brain structures. Frequent sites of neuronal injury include the cortex, the hippocampus, and the inner ear (Fig. 1.3).

Necrotic brain injury

Cortical injury in the context of bacterial meningitis will lead to focal sensorimotor deficits, seizure disorders, and cortical blindness (Weisfelt et al., 2006b; Hoogman et al., 2007). Areas of cortical injury are characterized by focal ischemic necrosis. The neuronal loss is associated with a marked reaction of astrocytes and microglia (Leib et al., 1996). An autopsy study revealed the presence of arterioles with leukocyte infiltration of the vessel wall, extravasation of leukocytes into the surrounding nervous tissue, and fibrin thrombus obstructing the lumen (Nau et al., 2004). Microvascular injury, thrombosis of vessels, and loss of autoregulation in combination with changes in CBF were shown to be associated with this type of brain damage. An involvement of MMPs is suggested, since cortical lesions are associated with increased gelatinolytic activity and specific MMP inhibition led to a reduction of this injury (Leib et al., 2000; Sellner and Leib, 2006). Other experimental treatments recently shown to reduce the extent of cortical injury include different antioxidants, the nonbacteriolytic antibiotic daptomycin, the antibiotic doxycycline, and brain-derived neurotrophic factor (Auer et al., 2000; Bifrare et al., 2005; Meli et al., 2006; Grandgirard et al., 2007b).

Hippocampal injury

Hippocampal injury is documented in approximately 75% of patients dying from the disease and in corresponding animal models. This type of injury is present in the dentate gyrus of the hippocampus and may cause learning deficits and neuropsychological sequelae. Individuals surviving infant and childhood meningitis tend to show deficits in their academic performance (Grimwood et al., 2000; de Louvois et al., 2007). Apoptosis is based on morphological criteria in Nissl-stained brain sections (condensed, fragmented nuclei) and the detection of fragmented DNA

(i.e., TUNEL stain) (Bifrare et al., 2003). Recently, it was shown in an infant rat model of pneumococcal meningitis that particularly immature neurons, e.g., neuronal stem cells and/or their progeny in the dentate gyrus, are affected (Braun et al., 2007; Grandgirard et al., 2007a). These progenitor cells in the subgranular zone of the dentate gyrus are implicated in the acquisition of new memory. Furthermore, involvement of activated caspase-3, an effector caspase which is responsible for executing the cell death program, has been implicated in the apoptotic death of neurons, as shown in animal studies and corresponding human autopsy studies (Nau et al., 1999; von Mering et al., 2001; Gianinazzi et al., 2003). Confirming the findings in animal models, brain sections of 20 patients who died from bacterial meningitis showed apoptotic neurons with immunoreactivity for precursor and active forms of caspase-3 in the dentate gyrus (Nau et al., 1999).

A second form of hippocampal neuronal damage, which is linked to AIF and characterized morphologically by uniformly shrunken nuclei forming clusters of damaged cells, is predominantly found in the lower blade of the dentate gyrus in infant rats (Bifrare et al., 2003). This form of hippocampal damage is the preferential pattern of neuronal injury observed in meningitis caused by GBS in this model. Criteria for classical apoptosis, such as formation of apoptotic bodies and positive staining for activated caspase-3, as well as morphological criteria for necrosis, e.g., cell swelling, loss of cellular structures, are absent. *In vitro* studies revealed that pneumolysin can induce this type of injury in neurons and microglia through mitochondrial damage and subsequent release of AIF (Braun et al., 2001, 2007).

Several adjunctive treatment strategies have proven effective in attenuating apoptotic death of hippocampal neurons. These include exogenous brain-derived neurotrophic factor, inhibitors of caspases and of MMPs or neutralization of TNF-α (Braun et al., 1999; Leib et al., 2001; Bifrare et al., 2005). However, treatment with dexamethasone in experimental pneumococcal and *E. coli* meningitis aggravated hippocampal injury and subsequent learning impairment (Leib et al., 2003; Spreer et al., 2006).

Inner-ear damage

Unilateral or bilateral hearing impairment is the most common neurological sequela following meningitis and is detected in 5–30% of patients, depending on the infecting pathogen (Kastenbauer and Pfister, 2003; van de Beek and de Gans, 2004). Studies in models of meningitis indicate that hearing loss is the result of direct damage of the inner ear by the inflammation. Histopathological examination of the temporal bone from rats with bacterial meningitis showed a dense inflammatory cell infiltrate throughout the subarachnoid space extending to the inner ear. However, no close correlation could be found between the extent of hearing loss and the magnitude of CSF pleocytosis or the amount of bacteria in the CSF (Kesser et al., 1999). Magnetic resonance imaging studies in humans with meningitis have documented inflammatory involvement of the inner ear, suggesting that the animal models reflect the clinical situation (Dichgans et al., 1999). The density of spiral ganglion neurons is markedly decreased and correlates with the severity of permanent hearing loss (Klein et al., 2003b). Toxic effects of the meningeal pathogen (e.g., pneumolysin from *S. pneumoniae*) and of inflammatory mediators appear to be responsible for the cytopathic effects (Kastenbauer et al., 2001). Interestingly, antioxidant treatment could reduce hearing loss while efficacy of dexamethasone was limited in an infant rat model of pneumococcal meningitis (Klein et al., 2003a; Coimbra et al., 2007).

CONCLUDING COMMENTS

Bacterial infections of the CNS are severe, often life-threatening illnesses with a complex pathophysiology. Much has been learned about the infecting pathogens, the epidemiology and pathogenesis of these infections, the limited protection yet severely harmful effects of the host's inflammatory response, and about the mediators and pathways of cerebral damage. Nevertheless, progress with regard to treatment and improved outcome has been slow, and few pathophysiological insights have been translated into novel therapeutic approaches. Moreover, interference with the complex network of cytokines, chemokines, and other inflammatory mediators including proteolytic enzymes and oxidants may be a double-edged sword, as has already been documented in several experimental studies. An even more detailed understanding of the multistep process from bacterial survival within the bloodstream to colonization and CNS invasion, to the induction of an inflammatory response and the induction of neuronal damage, is undoubtedly desirable. However, it must be recognized that much of the cascade of events that ultimately leads to brain injury is already well under way when the patient comes to medical attention. Therefore, efforts to understand and support the reparative capacity of the brain, an area that thus far has received limited attention, may be as important as further unraveling the mechanisms that lead to damage.

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Chapter 2

Principles of antimicrobial therapy

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INTRODUCTION

A governing principle in the treatment of infectious diseases is summarized by the aphorism "the right drug for the right bug," a statement that is as complex as it is simple. This aphorism is particularly critical when considering infections involving the central nervous system (CNS) for two main reasons: (1) the blood–brain barrier (BBB) limits the penetration of antimicrobial agents and, perhaps more importantly, immune effectors into the CNS; and (2) the nature of infections of CNS tissues engenders greater morbidity and mortality than infections at other sites. In this chapter, we will discuss the important factors involved in choosing the "right drug" for infections involving the CNS, including antimicrobial pharmacokinetic (PK) and pharmacodynamic (PD) properties, and the impact of adjunctive glucocorticoids on the treatment of CNS infections. These basic principles of antimicrobial therapy in bacterial CNS infections (specifically bacterial meningitis and bacterial brain abscess) are reviewed in detail in the following sections.

BACTERIAL MENINGITIS

Meningitis is defined as inflammation of the meninges, and is manifested by an increased number of white blood cells in cerebrospinal fluid (CSF). When bacterial meningitis is first suspected in a patient, the causative organism is rarely known, except in the broader sense of epidemiological clues such as host risk factors, exposure history, and the incidence of specific pathogens as causes of bacterial meningitis (e.g., *Neisseria meningitidis* among college dormitory residents). Consequently, the initial choice of antimicrobial therapy is empiric and includes antibacterial agents with very broad spectra of *in vitro* activity against many of the possible causative organisms. The antimicrobials chosen may subsequently be modified based on laboratory studies, such as Gram's stain or culture of the CSF, specifically to treat the involved pathogen. Many of the factors contributing to the clinician's decisions regarding antimicrobial therapy are common to both empiric and pathogen-specific antimicrobial regimens, including the ability of antimicrobials to cross the BBB, the bactericidal properties of those antimicrobials in CSF, the impact of meningeal inflammation on CSF antimicrobial concentrations, and the antimicrobial spectra of the chosen agents. These factors are, to a large degree, influenced by the PK and PD properties of antimicrobial agents, so some knowledge regarding the PK/PD parameters of relevant antimicrobials is important in drug selection.

Pharmacokinetics of antimicrobial agents in bacterial meningitis

PK parameters are defined by drug properties involving the interaction between the host and the drug, and can be considered in the context of four different processes: absorption, distribution, metabolism, and elimination. All of these processes interact with each other to influence the availability of active antimicrobial agents at the site of the invading organism and, therefore, the ability of the drug to treat the pathogen.

Absorption

Antimicrobials are typically administered via either the enteral route (e.g., by mouth) or the parenteral route (e.g., intravenously). For some infections, the route of administration matters little with respect to the clinical outcome. However, the intravenous route is heavily favored in the treatment of bacterial meningitis for

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several reasons: (1) the intravenous route bypasses variables that influence gastrointestinal absorption of an antimicrobial, such as gut motility or splanchnic blood flow; (2) the intravenous route may avoid drug–drug or drug–food interactions that interfere with the enteral absorption of an antimicrobial (e.g., chelation of fluoroquinolones by divalent cations); and (3) the intravenous route results in the rapid achievement of peak drug concentrations in the blood, thus favoring optimal bactericidal concentrations of the antimicrobial in CSF. Although some newer antimicrobials, such as moxifloxacin, have excellent oral bioavailability, an appropriate spectrum of activity, and achieve therapeutic CSF concentrations after oral administration, there are currently few clinical studies to support a recommendation for their routine use as oral agents for bacterial meningitis.

Distribution

Once administered, antimicrobial agents are partitioned throughout compartments of the body based on biochemical features (hydrophobicity, molecular weight, pK_a), sequestration, protein binding, and host determinants that influence the access of a drug to specific areas of the body (Hessen and Kaye, 2004). The extent to which the BBB excludes antimicrobial penetration into CSF is a major issue for choosing appropriate antimicrobial therapy. Although many drugs are able to cross the BBB due to their biochemical properties, protein pumps in the choroid plexus are also capable of directly removing drugs from the CSF (de Lange, 2004). The choroid plexus–blood barrier, also known as the blood–CSF barrier (BCSFB), is similar to the BBB with respect to low permeability, but is only one-third of the size of the BBB. However, ependymal cells of the choroid plexus have been shown to express at least two members of the ATP-binding cassette (ABC) family of transport proteins, P-glycoprotein (P-gp) and multidrug resistance-related protein 1 (MRP1) (de Lange, 2004). The best characterized of these pumps, P-gp, was originally discovered in studies of tumors resistant to chemotherapeutic agents, as these drugs are often substrates of P-gp and are subject to removal from the site of action due to the energy-dependent activity of P-gp (de Lange, 2004). P-gp is active as an efflux pump in the BBB, but is oriented toward CSF at the BCSFB. However, MRP1 is oriented toward the blood at both the BCSFB and BBB, and may contribute to removal of substances from the CSF. Fluoroquinolones have been shown to be substrates of MRP1 in cell types outside the CNS and brain endothelial cells *in vitro*, but the exact roles of MRP1 and P-gp on antimicrobial concentrations in the CSF have yet to be fully investigated (Tamai et al., 2000). Probenecid, a pharmacological inhibitor of organic acid transporters, increases penicillin and cephalosporin CSF concentrations when given during experimental meningitis in animals, but its clinical utility in this regard is limited by lack of data (Dacey and Sande, 1974).

Hydrophilic antimicrobials (β-lactams, vancomycin) generally do not cross the uninflamed BBB well, while drugs that are hydrophobic at physiological pH (7.4) are more able to cross the BBB into CSF (Sinner and Tunkel, 2004). Examples of hydrophobic antimicrobials include the fluoroquinolones, rifamycins, and chloramphenicol. The pK_a of these antimicrobials thus determines their degree of hydrophobicity; antimicrobials with pK_a values near physiological pH will have a neutral, or near-neutral, electrostatic charge and will more easily cross the BBB. However, once these drugs cross into the lower pH of infected CSF, many will gain a net positive charge, thus trapping these agents in the CSF. Hydrophilic agents depend on paracellular movement across tight and adherens junctions, while hydrophobic antimicrobials are able to cross the BBB via transcellular routes. Conditions that alter the paracellular permeability of the BBB may significantly alter the ability of hydrophilic agents to cross the BBB; inflammation of the BBB can significantly increase the BBB permeability to β-lactam antimicrobials (~5–10-fold), while resolution of inflammation of the BBB may substantially decrease the penetration of β-lactams into the CSF (Lutsar et al., 1998).

In addition to the effect of hydrophobicity, the molecular weight of an antimicrobial may substantially influence the penetration of the drug across the BBB. As might be expected, antimicrobials with small molecular weights (e.g., sulfonamides, rifampin, fluoroquinolones) are better able to penetrate the CSF than other drugs (e.g., daptomycin) (Sinner and Tunkel, 2004).

Protein binding may significantly affect the clinically important availability of free (i.e., nonprotein-bound) drug, largely based on the biochemical properties of the specific antimicrobial. While this is predominantly a factor in determining the amount of free drug capable of crossing the BBB, protein binding may also play a role once a drug has crossed into the CSF, as infection-induced inflammation usually results in an increased concentration of proteins in the CSF, and may thus reduce the activity of highly protein-bound drugs at the site of infection.

Once an agent has crossed the BBB into the CSF, additional factors may influence the antimicrobial activity of that specific agent. Infected CSF is more acidic than serum, thus altering the net electrostatic charge of drugs that reach the CSF (Sinner and Tunkel, 2004); aminoglycosides rely on an active, charge-dependent

transport system to achieve antimicrobial activity in pathogenic bacteria (Taber et al., 1987). The lower pH of infected CSF significantly reduces the penetration of aminoglycosides into bacteria by inhibiting the first energy-dependent phase of aminoglycoside transport into the bacterial cytosol, thus diminishing their ability to function as antimicrobials in the CNS (Taber et al., 1987). Table 2.1 displays the CSF:serum concentration ratios for various antimicrobials commonly used to treat bacterial meningitis (Lutsar et al., 1998; Rodriguez-Cerrato et al., 2001).

Metabolism

Most antimicrobial agents do not undergo significant chemical changes in the CSF. The peripheral metabolism of antimicrobials has a much greater impact on the amount of active drug in the CSF.

Elimination

As noted above, the activity of specific membrane-bound protein pumps carries clinically important implications for the concentration of antimicrobials in the CSF. This hypothesis has yet to be clinically proven, but does have some biological weight, given the impact of these ABC transporters on specific cancer therapies. Most antimicrobials, perhaps with the exception of the quinolones, have increased elimination half-lives in CSF when compared with blood (Nau et al., 1998). The half-lives of quinolones in CSF are comparable to their serum half-lives (McCoig et al., 1999). Unfortunately, most of the PK/PD data on antimicrobials used for the treatment of meningitis are derived from animal models, predominantly rabbits, rather than humans. However, the limited data available from both rabbits and humans are fairly comparable, suggesting that rabbits represent a useful animal model with respect to use of antimicrobials for human bacterial meningitis.

Table 2.1

Cerebrospinal fluid penetration for selected antimicrobials used to treat bacterial meningitis

Antibiotic	C_{csf}:C_{serum} (%), with inflamed meninges (values are for humans unless otherwise noted)
β-lactams	
Penicillin	5–10
Ampicillin	13–14
Cefotaxime	10.1
Ceftriaxone	1.5–9
Cefepime	10
Imipenem	8.5
Meropenem	21
Aminoglycosides	
Gentamicin	0–30
Netilmicin	21–26
Quinolones	
Ofloxacin	42–72
Moxifloxacin	34–57*
Ciprofloxacin	26
Trovafloxacin	23
Others	
Vancomycin	7–14
Rifampin	7–56
Trimethoprim/sulfamethoxazole	<41

Modified from Lutsar et al. (1998).
*Rabbit model (Rodriguez-Cerrato et al., 2001).

PHARMACODYNAMICS OF ANTIMICROBIAL AGENTS IN BACTERIAL MENINGITIS

Pharmacodynamics entails the interactions that occur between the antimicrobial agent and the pathogen, and, although separate from PK properties, is dependent on these processes with respect to localizing antimicrobials at sites of infection. There are several PD properties of antimicrobials relevant to bacterial meningitis, including bactericidal/bacteriostatic activity, time- versus concentration-dependent killing, and postantimicrobial effect (PAE). Additionally, the impact of corticosteroid therapy on antimicrobial CSF penetration and bacterial killing will be reviewed.

Bactericidal/bacteriostatic activity

The potency of a specific antimicrobial against a particular pathogen is usually defined by an *in vitro* measure of antimicrobial activity known as the minimal inhibitory concentration (MIC). The MIC can be measured in several different ways in the clinical microbiology laboratory; a standardized definition of MIC is the minimum concentration of an antimicrobial required to prevent a 10-fold increase in the bacterial density of an initial bacterial inoculum, generally set at 10^5 colony-forming units (cfu)/ml, incubated overnight, but other methods more loosely define MIC as the lowest concentration required to inhibit *visible* growth of bacteria after overnight incubation (Levison, 2004). A related parameter, the minimal bactericidal concentration (MBC), is defined as the lowest concentration of antimicrobial able to reduce an initial inoculum (10^5 cfu/ml in most situations) by at least 3 $\log_{10}$ after overnight incubation (Levison, 2004). An antimicrobial with a MBC less than or equal to fourfold greater than the MIC for a specific bacterium is considered *bactericidal* against that organism, while

bacteriostatic agents have MBC:MIC ratios much greater than bactericidal agents (Levison, 2004). Some examples of bactericidal agents (under most circumstances) include β-lactams, vancomycin, and the fluoroquinolones, while examples of bacteriostatic agents include linezolid, the macrolides, and the tetracyclines. There are exceptions to these classifications and it should be noted that the bactericidal or bacteriostatic activity of any individual agent depends on the specific organism being considered. For example, while many β-lactams are bactericidal for meticillin (formerly methicillin)-sensitive *Staphylococcus aureus* (MSSA), these agents are bacteriostatic for *Enterococcus faecium*. Another important factor influencing bactericidal/bacteriostatic activity is the variability of MICs and MBCs among different isolates of bacteria belonging to the same species. As a consequence, antimicrobial susceptibility studies usually report the MIC_{50} and/or the MIC_{90} for multiple isolates of a bacterial species; these MIC values correspond to the MICs for 50% and 90% of isolates, respectively. The MIC_{90} values are relevant when determining the most appropriate empiric antimicrobial therapy for pathogens invading the CNS because the concentration of the chosen agents must exceed the MICs for most, if not all, of the potential isolates present in the population from which the patient presents.

The choice of using a bactericidal or a bacteriostatic agent in the treatment of most infections is often less important in the host with a normal immune response, as host immune defenses are capable of clearing the infection even when antimicrobial concentrations fall below the MIC for the invading pathogen. However, as alluded to earlier, the CSF represents a site of physiological immune suppression. The BBB tightly regulates the movement of leukocytes and immunologically active molecules into the CSF. As a consequence, few leukocytes are normally present in CSF and there is a significantly reduced concentration of complement components and immunoglobulins (Sinner and Tunkel, 2004). These features influence bacterial proliferation in the CSF, allowing poorly checked growth and the achievement of high bacterial concentrations during the course of bacterial meningitis. In one study, experimental inoculation of pneumococci into the CSF of rabbits resulted in a peak bacterial concentration of approximately 10^9 cfu/ml, which was unaltered by the presence or absence of leukocytes in the CSF (Ernst et al., 1983). Examination of bacterial counts in children with meningitis revealed values between 10^4 and 10^9 cfu/ml, with 25% of CSF samples $>10^7$ cfu/ml (Bingen et al., 1990). Thus, there is a plausible biological reason why a bactericidal antimicrobial would be preferable to a bacteriostatic agent for the treatment of bacterial meningitis. To test this hypothesis, Scheld and Sande (1983) compared the ability of two antimicrobials, ampicillin and chloramphenicol, to achieve a microbiological cure (defined as sterile CSF after 5 days of treatment) of experimental pneumococcal meningitis in rabbits. Two strains of *Streptococcus pneumoniae* were used: strain 1 had an MIC for chloramphenicol of 16 μg/ml, strain 2 had an MIC for chloramphenicol of 2 μg/ml, while both strains had ampicillin MICs of <0.125 μg/ml. Table 2.2 displays the cure rates as they relate to the peak CSF antimicrobial concentration.

Comparable cure rates were achieved when the mean peak CSF concentration exceeded the MBC, but not when the peak concentration was below the MBC. The observation that bactericidal activity influences the clinical outcome of bacterial meningitis has also been made in clinical trials, where antimicrobials (e.g., cefuroxime) unable to achieve CSF concentrations approximating their MBCs demonstrated poorer clinical outcomes than antimicrobials, with CSF concentrations exceeding their respective MBCs (Friedrich et al., 1980; Lebel et al., 1989; Peltola et al., 1989; Schaad et al., 1990).

Table 2.2

Bactericidal versus bacteriostatic therapy in experimental pneumococcal meningitis

Inoculum	Drug	Dose (mg i.m. t.i.d.)	MBC (μg/ml)	Mean peak CSF concentration (μg/ml)	Cure rate (%)
Strain 1	Ampicillin	250	≤0.125	6.6	77
	Chloramphenicol	375	16	4.4	17
	Chloramphenicol	1000	16	32	64
Strain 2	Ampicillin	250	≤0.125	6.8	80
	Chloramphenicol	375	2	4.9	70

Modified from Scheld and Sande (1983).
i.m., intramuscularly; t.i.d., three times a day; MBC, minimal bactericidal concentration; CSF, cerebrospinal fluid.

While bactericidal activity is observed for many antimicrobials that achieve infection site concentrations slightly above their respective MBCs, experimental models of meningitis have shown that bactericidal activity is achieved in the CSF only when antimicrobial concentrations are 10–30 times the MBC of the pathogen (Täuber et al., 1984a, 1989). The exact reason for this difference is not known, but has been attributed to factors such as the reduced pH of infected CSF (6.5–7.0), the sensitivity of specific antimicrobials to the inoculum effect, and the presence of slowly growing bacteria that are less susceptible to antimicrobials (e.g., β-lactams) whose mechanism of action depends on the rate of bacterial cell division (Lutsar et al., 1998; Sinner and Tunkel, 2004). The inoculum effect is observed when the concentration of antimicrobial required to inhibit growth varies directly with bacterial density; as bacterial density increases, so does the concentration of antimicrobial required to inhibit growth, thus creating a "moving MIC." This effect is relevant to CSF infections, where the initial bacterial density may be as high as 10^9 cfu/ml. Because the standard MIC is derived from an original bacterial density of 10^5cfu/ml, antimicrobials (e.g., the β-lactams) that demonstrate an inoculum effect must achieve CSF concentrations well above the standard MIC in order to inhibit bacterial growth.

Bacterial killing

Two PD properties have been used to characterize the killing of bacteria by bactericidal antimicrobials: time-dependent and concentration-dependent killing. These broad categories are not mutually exclusive, but are generally useful properties to consider when determining the dosing and administration intervals for antimicrobials. Time-dependent killing refers to the observation that certain antimicrobials, such as the β-lactams or vancomycin, do not kill bacteria more rapidly at concentrations significantly greater than the MBC for the pathogen, but continue to kill bacteria as long as the antimicrobial concentration remains above the MIC. The parameter most often used to assess time-dependent killing is "time above MIC" ($t >$ MIC), and many studies have found that antimicrobials achieving a $t >$ MIC for at least 40% of the dosing interval correlate well with favorable clinical outcomes (Lutsar et al., 1997). However, a study of ceftriaxone given once or twice daily to treat experimental pneumococcal meningitis in rabbits demonstrated that sterilization of the CSF was achieved only when CSF ceftriaxone concentrations remained above the MBC ($t >$ MBC) for 95–100% of the initial 24 hours of therapy (Lutsar et al., 1997). This observation lends itself directly to the issue of dosing intervals for time-dependent antimicrobials; a logical approach to the delivery of these antimicrobials is to provide a continuous infusion that achieves antimicrobial concentrations above the MIC for the entire course of therapy, as opposed to intermittent dosing that achieves these concentrations for only part of the dosing interval. In practice, continuous infusion of time-dependent antimicrobials may result in better clinical outcomes, as supported by a meta-analysis of randomized, controlled trials comparing continuous versus intermittent administration of the same antimicrobial agent (Kasiakou et al., 2005). However, most of these trials addressed infections outside the CNS and few data are available for infusion strategies in patients with bacterial meningitis. A clinical study in Marseille, France, examined CSF penetration of vancomycin administered by continuous infusion to mechanically ventilated patients with or without meningitis and compared the minimal and maximal vancomycin concentrations in CSF with those achieved by intermittent infusion (Albanese et al., 2000). Although this study demonstrated higher CSF concentrations of vancomycin among patients with meningitis (48% versus 18%), there was no significant difference between vancomycin CSF concentrations based on the infusion strategy. This study was small, however, examining vancomycin CSF penetration in only 13 patients, thus limiting the power of this study to detect real differences in clinical outcomes. An experimental pneumococcal meningitis study in rabbits of intermittent versus continuous intravenous infusion of penicillin G did not find a difference in bacterial clearing from the CSF beyond the second hour of therapy (Sande et al., 1981). Perhaps more importantly, the only parameter that determined the time to CSF sterilization in this study was the initial bacterial density, suggesting that the inoculum effect with penicillin G may play a bigger role than time-dependent killing in CSF sterilization.

Concentration-dependent killing describes the increase in bacterial killing achieved with increasing concentrations of the antimicrobial above and beyond the MBC. That is, the higher the concentration of antimicrobial above the MIC, the greater the rate of bacterial killing. Antimicrobials exhibiting this property include the fluoroquinolones and aminoglycosides. Several parameters have been used to reflect concentration-dependent killing, including the C_{max}/MIC (C_{max} being the peak concentration of the antimicrobial), the area under the curve (AUC), and the AUC:MIC ratio (also known as AUIC). The parameter that best correlates with *in vitro* and *in vivo* efficacy varies with antimicrobial classes and specific agents. In theory, both the dose and dosing interval can influence the clinical efficacy of concentration-dependent

antimicrobials, depending on which parameter (C_{max}/MIC, AUC, AUIC) best predicts bacterial killing with a specific antimicrobial. For example, in the experimental rabbit pneumococcal meningitis model, trovafloxacin killing best correlated with the AUC:MBC ratio (McCoig et al., 1999). Importantly, bacterial regrowth in this model occurred when the CSF trovafloxacin concentration fell below the MBC, an observation consistent with the need for bactericidal activity when treating bacterial meningitis.

Aminoglycosides are able to cross the BBB and achieve concentrations in the CSF that approximate 15–30% of serum concentration, a percentage that is on the higher end of CSF penetration relative to other antimicrobials. However, CSF concentrations of aminoglycosides administered via the intravenous route achieve concentrations that are only on par with the MBC for most meningeal pathogens, and this is reflected in a poor clinical response to aminoglycosides in patients with bacterial meningitis, despite the bactericidal activity these agents demonstrate *in vitro* (Kaiser and McGee, 1975; McCracken et al., 1980). When aminoglycosides are administered intraventricularly or intrathecally, much higher CSF concentrations are achieved, although limited clinical data are available to gauge the success of this route of administration to outcome. In a small study of six patients with gram-negative bacillary meningitis and/or ventriculitis, aminoglycoside (tobramycin or gentamicin) concentrations were measured in the lumbar, cisternal, and ventricular CSF during intravenous aminoglycoside therapy or after intraventricular or intrathecal administration (Kaiser and McGee, 1975). The CSF concentrations of aminoglycosides administered intravenously were <1 μg/ml, with corresponding serum values ranging from 2 to 7.5 μg/ml. In contrast, administration of 5–10 mg aminoglycoside intrathecally resulted in lumbar CSF peak concentrations of 27–81 μg/ml, with values near 10 μg/ml 24 hours after administration, but low ventricular CSF concentrations (0–2.1 μg/ml). Intraventricular administration, via Rickham or Ommaya reservoirs, produced ventricular CSF aminoglycoside peak concentrations of 12.8–40 μg/ml and lumbar CSF peak concentrations of 11.5–27.5 μg/ml, with CSF concentrations at both sites of 4–6 μg/ml at 24 hours after administration. These data suggest that the intraventricular route is superior to the intrathecal route with respect to achieving CSF aminoglycoside concentrations above the MBCs for most meningeal pathogens. It should be noted that a Cochrane systematic review of intraventricular antimicrobials in neonates with bacterial meningitis concluded that intraventricular antimicrobials may increase mortality, although this conclusion was based on the results of a single trial (Shah et al., 2004). No clinical trials addressing the use of intraventricular or intrathecal aminoglycosides in adults have been published at the time of this writing, though case reports have been published describing the successful clinical use of these routes to treat bacterial meningitis and/or ventriculitis (Kaiser et al., 1980; Shah et al., 2004). Given the increasing resistance of bacterial pathogens to available antimicrobials, these routes of administration deserve a more critical assessment.

Postantimicrobial effect

PAE is the term used to describe the ability of an antimicrobial to inhibit regrowth of bacteria after exposure and subsequent removal of the agent. This phenomenon is relatively easy to study *in vitro* because the investigator can manipulate the presence or absence of the antimicrobial. However, the removal of an antimicrobial from the site of an infection *in vivo* depends on many factors, thus complicating assessment of PAE in both clinical and experimental studies. *In vivo* PAE is most commonly gauged by measuring bacterial regrowth when the antimicrobial concentration at the site of infection has fallen below the MIC for the invading organism, known as the post sub-MIC effect. The PAE differs among antimicrobial classes and is an important consideration when choosing antimicrobial therapy for specific types of infections, such as those in neutropenic patients and in patients with bacterial meningitis. β-lactams usually have a short PAE, while aminoglycosides and fluoroquinolones usually have a long PAE, though these generalizations vary with the bacterial species and site of infection. For example, β-lactams have a long PAE with most gram-positive organisms *in vitro*, but a short PAE with gram-negative bacteria; the carbapenems are an exception, however. In an experimental rabbit model of pneumococcal meningitis, ampicillin had a much longer PAE in the CSF than the *in vitro* PAE of this drug in broth culture (6–12 versus 4–6 hours, respectively) (Tauber et al., 1984b). This prolonged PAE *in vivo* has been attributed to several factors, including antimicrobial-related damage to bacterial cell walls, enhanced phagocytosis, and slow removal from the CSF of residual antimicrobial. Scanning electron microscopy of pneumococci in CSF removed 3 hours after exposure to ampicillin does indeed appear to show that they are morphologically altered, supporting the concept that ampicillin-related damage to the cell wall may impair bacterial replication in the absence of the drug (Sande et al., 1981). Notably, injection of a β-lactamase into CSF is associated with rapid resumption of bacterial growth, an observation consistent with the presence of residual ampicillin suppressing bacterial regrowth in the CSF (Täuber et al., 1984b). This also suggests that a true PAE (i.e., delayed regrowth upon removal

of drug) does not exist for ampicillin *in vivo*. Rather, the delay in pneumococcal regrowth in CSF, when the ampicillin concentration falls below the MIC *in vivo*, is due to slow clearance of residual ampicillin from the CSF (i.e., a true post sub-MIC effect).

There are limited data on the *in vivo* or *in vitro* PAE for other antimicrobial classes in the CSF, including the fluoroquinolones and aminoglycosides. An *in vitro* study of the PAE of trovafloxacin against *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and serogroup B *Neisseria meningitidis* in both broth medium and pooled human CSF demonstrated that, after exposure of these organisms to trovafloxacin at four times the respective MICs for 1 hour, the mean PAE for these organisms in broth ranged from 0.57 to 5.83 hours, while the mean PAE in pooled CSF ranged from 0.47 to 6.00 hours (Tessier et al., 2000). The presence of CSF did not alter the PAE of trovafloxacin for these meningitis pathogens, but it is difficult to comment on the implications of this information for the proper use of quinolones in bacterial meningitis, particularly since these drugs achieve excellent CSF concentrations, are bactericidal, and have CSF half-lives comparable to their serum half-lives. A similar study examined the effect of pooled human CSF on the PAEs of gentamicin, ciprofloxacin, or cefotaxime against *Escherichia coli* (Zhanel et al., 1992). Bacteria in log-phase growth were inoculated into broth medium or broth supplemented with human CSF and exposed to one of these antimicrobials for 2 hours at a concentration of twice the MIC. The addition of pooled CSF prolonged the PAEs for all of these antimicrobials when compared with broth alone. More data are needed from clinical studies and experimental animal models to shed light on the importance of PAE in bacterial meningitis and what role this parameter should have in selecting appropriate antimicrobial agents, and dosing intervals, for the treatment of this disease.

CORTICOSTEROID EFFECTS ON ANTIMICROBIAL CSF PENETRATION AND BACTERIAL KILLING

Bacterial growth and death in the CSF both result in the release of proinflammatory bacterial products, such as peptidoglycan or lipopolysaccharide (LPS) that worsen CNS inflammation. For example, LPS activates Toll-like receptor 4 signaling in a wide variety of cells, ultimately leading to nuclear factor kappa B (NF-κB)-mediated transcription of proinflammatory genes like tumor necrosis factor-α (TNF-α) (Lu et al., 2008). Such inflammation mediates breakdown of the BBB and brain edema, with subsequent morbidity and/or mortality for the host. Both animal experiments and clinical trials have demonstrated a beneficial role for the early use of glucocorticoids to inhibit inflammation and brain edema during bacterial meningitis (Paris et al., 1994; de Gans and van de Beek, 2002; Nguyen et al., 2007). However, the reduced inflammation associated with glucocorticoids is also associated with reduced permeability at the BBB, thus potentially affecting the penetration of hydrophilic antimicrobials and immune cells into the CNS, leading to decreased clearance of bacteria from the CSF. Table 2.3 displays data on the effects of corticosteroids on CSF antimicrobial concentrations and bacterial clearance from CSF; this

Table 2.3

The effects of corticosteroids on cerebrospinal fluid (CSF) antimicrobial concentrations and bacterial clearance

Antimicrobial agent	Bacterium	Decreased CSF antimicrobial concentration?	Altered bacterial clearance?
Ampicillin (Scheld and Brodeur, 1983)	PSSP	Yes	No
Gentamicin (Scheld and Brodeur, 1983)	*E. coli*	Yes	No
Vancomycin (Ahmed et al., 1999)	PRSP	Yes	Yes – reduced
Vancomycin (Ahmed et al., 1999)	CRSP	Yes	No
Rifampin (Paris et al., 1994)	PRSP	No	No
Rifampin (Kaojarern et al., 1991)	MTb	No	NE
Ceftriaxone (Paris et al., 1994)	iCRSP	No	Yes – reduced
Trovafloxacin (Paris et al., 1995)	PRSP	No	No
Isoniazid (Kaojarern et al., 1991)	MTb	No	NE
Pyrazinamide (Kaojarern et al., 1991)	MTb	No	NE
Streptomycin (Kaojarern et al., 1991)	MTb	No	NE

Modified from Lutsar et al. (1998).

PSSP, penicillin-sensitive *Streptococcus pneumoniae*; *E. coli*, *Escherichia coli*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; CRSP, cephalosporin-resistant *Streptococcus pneumoniae*; MTb, *Mycobacterium tuberculosis*; iCRSP, intermediately cephalosporin-resistant *Streptococcus pneumoniae*; NE, not evaluated.

table includes data from both humans with bacterial meningitis and animals with experimental meningitis. The data in Table 2.3 for vancomycin and ceftriaxone are from *in vivo* studies of experimental meningitis in rabbits and are concerning in light of the increased incidence of invasive disease caused by both penicillin- and ceftriaxone-resistant pneumococci (Buke et al., 2003; Ricard et al., 2007). Current Infectious Diseases Society of America guidelines for the empiric treatment of suspected pneumococcal meningitis recommend a combination of vancomycin and ceftriaxone (or cefotaxime), along with early initiation of dexamethasone (Tunkel et al., 2004).

Fortunately, the clinical data available do not suggest that these observations for ceftriaxone and vancomycin in experimental meningitis translate into clinical failures or less favorable clinical outcomes in patients with pneumococcal meningitis treated with these antimicrobials (Buke et al., 2003; Ricard et al., 2007). A prospective, double-blind, randomized multicenter study in Europe of adjunctive dexamethasone therapy for adults with bacterial meningitis demonstrated a reduction in mortality among patients receiving the steroid (relative risk of death 0.48, 95% confidence interval 0.24–0.96, $P = 0.04$) (de Gans and van de Beek, 2002). A similar prospective study among adults in Malawi, 90% of whom were infected with human immunodeficiency virus (HIV), failed to demonstrate a benefit to adjunctive dexamethasone for bacterial meningitis, but did not find a difference in antimicrobial efficacy in those receiving steroids (Scarborough et al., 2007). Interestingly, a prospective, randomized, double-blind study of adjunctive dexamethasone for adults in Vietnam with bacterial meningitis found clinical benefits supporting dexamethasone use among patients with microbiologically proven bacterial meningitis (Mai et al., 2007). A cautionary note, however, is warranted because the vast majority of pneumococcal isolates in these three trials were cephalosporin- and vancomycin-susceptible.

BACTERIAL BRAIN ABSCESS

Brain abscesses are most commonly complications of infections at other anatomical sites, usually of the head, leading to contiguous spread to the brain, or less often from hematogenous dissemination (e.g., from a lung abscess) or direct inoculation (e.g., from trauma) (Calfee and Wispelwey, 2000). Approximately 20% of brain abscesses are considered cryptogenic. The nature of the primary infection has a major influence on the specific organisms causing the formation of a brain abscess. For example, brain abscesses developing from primary dental infections commonly involve oral commensal organisms such as streptococcal species and oral anaerobes. As a consequence, a vigorous search should be made to discover a primary source of infection, both to treat this process and to guide empiric antimicrobial therapy. As with other types of abscesses, drainage is the primary therapy for brain abscesses and aspiration should always be performed when possible. A major benefit of drainage is the potential for identifying the specific microbiological culprits; drainage specimens should be sent to the clinical microbiology laboratory for bacterial (aerobic and anaerobic), fungal, and mycobacterial stains and cultures. A thorough review of brain abscesses can be found in this volume. This chapter will focus on factors involved in the selection of appropriate empiric antimicrobial therapy for bacterial brain abscess. Microbiological information, when available, should be used to tailor subsequent antimicrobial therapy, with these notable caveats: (1) anaerobes are commonly implicated in brain abscess, but are notoriously difficult to culture in the laboratory; and (2) the ability of specific antimicrobial agents to cross the BBB must be considered when tailoring therapy based on culture data.

EMPIRIC ANTIMICROBIAL THERAPY FOR BACTERIAL BRAIN ABSCESS

As stated above, the bacteria found in brain abscesses correspond to predisposing conditions such as pathogenesis of infection, host immunity, or events leading to direct inoculation. These predisposing conditions must be considered when designing an empiric antimicrobial regimen for patients with brain abscesses. Table 2.4 delineates a number of predisposing conditions, their associated bacteria, and an empiric antimicrobial recommendation. Common themes among these recommendations are the use of agents with good CNS penetration, and the use of agents with activity against streptococci and/or anaerobes; the latter theme is based on the high frequency with which these organisms are isolated from brain abscesses, regardless of the predisposing condition. The third-generation (ceftriaxone, cefotaxime) and fourth-generation (cefepime) cephalosporins have good penetration into brain tissue, but less is known about their penetration into brain abscess cavities. High-dose cefotaxime (3 grams intravenously every 8 hours) does result in concentrations of cefotaxime, and its active metabolite desacetylcefotaxime, that approximate those in the serum and above the MICs for relevant pathogens, with the exception of gram-negative anaerobes (Sjolin et al., 1991). Ceftizoxime, another third-generation cephalosporin, also achieves therapeutic concentrations in brain abscess pus (Guglielmo et al., 1997).

Table 2.4

Empiric antimicrobial therapy for brain abscess

Predisposing condition	Common pathogens	Empiric antimicrobial regimen
Otitis media or mastoiditis	Streptococci, *Bacteroides* spp., *Prevotella* spp., Enterobacteriaceae	Metronidazole + cephalosporin*
Sinusitis	Streptococci, *Haemophilus* spp., Enterobacteriaceae, *Bacteroides* spp., *Staphylococcus aureus*	Metronidazole + cephalosporin* ± vancomycin†
Dental infection	*Fusobacterium* spp., *Prevotella* spp., *Bacteroides* spp., streptococci	Metronidazole + penicillin
Direct inoculation (trauma, surgery)	*Staphylococcus* spp., Enterobacteriaceae, streptococci, *Clostridium* spp.	Vancomycin + cefepime + metronidazole
Lung infections (abscess, empyema), bronchiectasis	*Actinomyces* spp., streptococci, *Fusobacterium* spp., *Bacteroides* spp., *Prevotella* spp., *Nocardia* spp.	Metronidazole + penicillin, + trimethoprim-sulfamethoxazole if *Nocardia* spp. suspected
Endocarditis	*Staphylococcus aureus*, streptococci	Vancomycin‡ + gentamicin
Congenital heart disease	Streptococci, *Haemophilus* spp.	Cephalosporin*
Unknown	Streptococci, *Staphylococcus* spp., *Haemophilus* spp., fastidious anaerobes	Metronidazole + vancomycin + cephalosporin*

Modified from (Tunkel, 2005).
*Ceftriaxone, cefotaxime or cefepime.
†If meticillin-resistant *Staphylococcus aureus* (MRSA) suspected.
‡If meticillin-sensitive *Staphylococcus aureus* is the etiology of endocarditis, nafcillin should be used instead of vancomycin.

Among other β-lactams, penicillin reaches pus in brain abscesses, although only at consistently therapeutic concentrations when the total daily dose exceeds 24 million units (De Louvois et al., 1977). The penetration of nafcillin or ampicillin into brain abscess pus is variable and poorly studied, but case reports have reported successful treatment of brain abscesses using these β-lactams (Boom and Tuazon, 1985; Akova et al., 1993). Limited data show that vancomycin is also able to achieve therapeutic concentrations in a brain abscess cavity (Levy et al., 1986). The carbapenems imipenem and meropenem both penetrate into brain parenchyma well; both of these drugs have excellent antimicrobial spectra with respect to bacteria commonly associated with brain abscess, including *Nocardia* species. One retrospective study reported a high rate of clinical cure with imipenem compared with standard chemotherapy (100% versus 87%), with a low rate of drug-associated adverse events (Asensi et al., 1996). This study also included limited measurements of imipenem in brain abscess pus and reported concentrations for imipenem above the MICs for bacterial isolates in these abscesses. However, there is concern regarding the induction of seizures with imipenem in a patient population already at increased risk for seizures due to the presence of a brain abscess.

The remaining classes of antimicrobials noted in Table 2.4 include an aminoglycoside (gentamicin), a sulfonamide combined with trimethoprim, and metronidazole. The aminoglycosides probably do not achieve therapeutic concentrations in brain abscess cavities, and the lower pH present in an abscess cavity would most certainly impair entry of the aminoglycosides into bacteria, thus interfering with their antimicrobial activity. Owing to their small molecular size, sulfonamides cross the BBB quite well, but direct measurements of sulfonamide concentrations in brain abscess cavities are not available. Trimethoprim also crosses the uninflamed BBB quite well, but at a different rate than sulfamethoxazole, a finding with unclear clinical significance; no data are available regarding the concentration of trimethoprim in brain abscess pus, but clinical case reports and case series support the use of trimethoprim-sulfamethoxazole for the treatment of brain abscesses caused by *Nocardia* species (Mamelak et al., 1994). Metronidazole achieves excellent penetration into brain abscess cavities, of the order of 16–45 μg/ml, concentrations that are severalfold greater than the MICs for most anaerobes associated with brain abscesses, and metronidazole resistance is low among contemporary anaerobic isolates (Ingham et al., 1977). These concentrations are obtained even when metronidazole is given via the oral route. For these reasons, metronidazole should be used in virtually all patients with brain abscess.

DURATION OF ANTIMICROBIAL THERAPY FOR CNS INFECTIONS

Little information is available addressing the appropriate duration of therapy for most types of CNS infection. Some experimental and clinical data are available for the effective duration of bacterial meningitis, especially for meningitis caused by *N. meningitidis*. For nonmeningococcal meningitis, the recommended duration of therapy is 10–14 days, but this duration is based more on historical practice and less on solid experimental studies or clinical trials (Tunkel et al., 2004). A single clinical trial in children with acute meningitis prospectively compared 7 versus 10 days of ceftriaxone therapy to determine whether the shorter duration is comparable to the recommended 10-day course (Singhi et al., 2002). Children were randomized to receive either 7 or 10 days of ceftriaxone and a clinical scoring system was used to determine whether additional ceftriaxone therapy was needed at the 7- or 10-day treatment mark, respectively. The baseline characteristics, CSF findings, and microbiology were similar between the two groups. The "treatment failure rate" was based on the clinical scoring system and was comparable between each group (~25%), as were the causes for classification as a "treatment failure." Two earlier trials evaluated the duration of ceftriaxone therapy for children with meningitis based on the specific etiological agent: 4 days for *N. meningitidis*, 6 days for *H. influenzae*, and 7 days for *S. pneumoniae*, all compared with standard duration (8–10 days) of therapy (Kavaliotis et al., 1989; Martin et al., 1990). No significant clinical differences were noted in both of these trials between those who received short- versus standard-course therapy. These studies suggest that, in selected children with nonmeningococcal meningitis, the duration of ceftriaxone therapy may be as short as 6–7 days. However, no studies have adequately examined the appropriate duration of antimicrobial therapy with antimicrobials other than ceftriaxone, nor have there been studies to evaluate the appropriate duration of therapy for penicillin- or cephalosporin-resistant pneumococci. Thus, the duration of therapy for nonmeningococcal bacterial meningitis in children must be guided by clinical response and microbiological information. The implications of these trials for the duration of treatment in adults with nonmeningococcal meningitis remain unclear.

In addition to the two trials mentioned above with respect to meningococcal meningitis, Nathan et al. (2005) performed a prospective, randomized, open-label, clinical trial of short-course therapy for epidemic meningococcal meningitis among patients >2 months old in sub-Saharan Africa. These investigators compared a single dose of ceftriaxone 100 mg/kg intramuscularly (i.m.) with a single dose of i.m. chloramphenicol (100 mg/kg), with allowance for a second dose of either drug in cases considered treatment failures after the initial 24–48 hours of therapy. The primary outcome was death or clinical failure at 72 hours posttreatment. There were no significant baseline differences between those randomized to either antimicrobial. Intention-to-treat analysis demonstrated equivalent treatment failure rates between each group (~9%). This failure rate is comparable to prior trials of longer (3–4 days) duration therapy for meningococcal meningitis and supports the notion that meningococcal meningitis can be treated with substantially shorter courses of effective antimicrobial therapy than nonmeningococcal bacterial meningitis. The applicability of these trial results to other clinical settings, such as meningococcal meningitis in more developed countries, is unclear; single-dose therapy is likely hazardous in settings where nonmeningococcal pathogens predominate. However, further studies should be done to establish the safety and efficacy of limited-duration therapy ($\leq$ 3 days) for meningococcal meningitis.

Available information to guide the duration of antimicrobial therapy for brain abscess is limited. The recommended duration for most bacterial brain abscesses is 6–8 weeks with intravenous antimicrobials, followed by 2–6 months of oral antimicrobials. However, the optimal duration has not been established experimentally or clinically, and existing data suggest that the duration should be guided by clinical and radiographic response, as well as the nature of the involved pathogens.

SUMMARY

We have discussed important factors involved in choosing appropriate antimicrobial regimens for the treatment of bacterial meningitis and brain abscess to illustrate common themes relevant to the treatment of these diseases. We have limited this review to these conditions for two main reasons: (1) the principles involved in optimal antimicrobial therapy for these diseases likely apply to other CNS infections, such as viral and fungal diseases; and (2) little pharmacological information is currently available for other types of CNS infections. Many of the studies addressing the relevant pharmacological and microbiological aspects of antimicrobial therapy for CNS infections have been performed in experimental animal models and, as a result, the information derived from these studies may be different when examined in appropriate human studies. Our current understanding of appropriate antimicrobial therapy for CNS infections may be summarized as follows:

1. Choose bactericidal antimicrobials that effectively cross the BBB to achieve CSF concentrations well above the MBC ($\geq$ 10-fold) for the suspected bacterial pathogen(s).
2. Take into consideration the relevant PD parameters underlying the bactericidal activity of the antimicrobials used to treat bacterial meningitis, such as $t >$ MBC or AUC/MBC.
3. Tailor the antimicrobial regimen based on microbiological information, once available. However, with respect to brain abscess therapy, keep in mind that anaerobes are commonly involved, but difficult to culture, and consider including antianaerobic therapy even if the bacterial cultures do not grow anaerobes.
4. Treat bacterial meningitis caused by nonmeningococcal pathogens for 7–10 days, but monitor clinical progress to determine whether the patient should continue on a more prolonged antimicrobial course. Meningococcal meningitis may be treated with 3–4 days of effective antimicrobial therapy, again with the caveat that the patient's clinical course should dictate duration of therapy.
5. Treat brain abscess, preferably after aspiration/drainage, for at least 6 weeks with intravenous antimicrobials. Base decisions regarding duration of antimicrobials for brain abscess on the clinical response (e.g., improved symptoms, lack of new neurological findings) and radiographic changes (e.g., reduction in cavity size).

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Chapter 3

Lumbar puncture and cerebrospinal fluid analysis

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The lumbar puncture (LP), a century-old procedure, is the enduring procedure for the evaluation of suspected central nervous system (CNS) disorders. The analysis of cerebrospinal fluid (CSF) is key in the diagnosis of several infectious and noninfectious neurological syndromes. The assays that can be performed on the CSF range from routine laboratory tests, such as cell count with differential and protein concentration, to advanced molecular diagnostics and cytokine determinations. The role of screening cranial imaging has been prospectively evaluated and recommendations by the Infectious Diseases Society of America (IDSA) now exist for indications for obtaining a head computed tomography (CT) scan prior to LP. The diagnostic accuracy of meningeal signs has recently been challenged and should not be routinely used to determine the need to perform an LP or not in an individual with suspected meningitis. The most important and commonly available CSF tests in the clinical setting are reviewed in this chapter and novel CSF assays that could potentially have an impact on patient management are discussed. Clinical models that have been derived to help clinicians differentiate viral from bacterial meningitis are also described.

THE VENTRICLES AND THE CEREBROSPINAL FLUID

The CNS consists of the brain and spinal cord, which are well protected from the outside environment by the skull and the spinal canal that form a continuous bony and fibrous shield (Gray and Alonso, 2002). The meninges protect the CNS, and consist of three layers: the outermost dura mater, the middle arachnoid layer, and the inner pia mater. The dura layer is thick, tough, and composed of hypocellular fibrous tissue that adheres to the skull except where it invaginates into the cranial cavity to form septa (falx cerebri, falx cerebelli, tentorium cerebelli, and diaphragma sella) (Greenlee and Carroll, 1997; Gray and Alonso, 2002). Below the foramen magnum, the dura and periosteum diverge and are separated by a fat-filled epidural space (Greenlee and Carroll, 1997). The middle arachnoid layer is very thin and avascular, and closely adheres to the dura mater by specialized fibroblasts. The inner pia mater is a vascular and delicate membrane, continuous with the brain and spinal cord, but is separated from the neural tissue by the subpial space. It is the pia mater which projects into the ventricles as villi and loose connective tissue stroma to form the choroid plexus, which in turn is responsible for the formation of CSF.

Between the arachnoid layer and the pia mater is the subarachnoid space, which contains CSF. The arachnoid gives off projections of filaments into the subarachnoid space. This gives the space a spider-like appearance, consisting of a trabecular meshwork crossed by nerves, small arteries known as rete mirable, and bridging veins which connect the meningeal veins with the deeper intracranial venous system (Greenlee and Carroll, 1997).

The subarachnoid space extends from the basal cisterns surrounding the brainstem superiorly, to its termination opposite the level of the second sacral vertebra (Greenlee and Carroll, 1997). The subarachnoid space is dilated in certain locations due to the variation in the contour of the brain and skull, forming pockets of CSF called cisterns. The largest and most important of the cisterns is the cisterna magna, which surrounds the brainstem and cerebellum at the base of the skull. The cistern magna may be used to obtain CSF (Greenlee and Carroll, 1997).

The choroid plexus located in the ventricular system produces approximately 500 ml of CSF/day, with

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150 ml present in the ventricular system at any time (Jerrard et al., 2001). The choroid plexus of the lateral, third, and fourth ventricles produces 70% of the CSF, at a rate of approximately 20 ml/h, and is recycled four to five times daily (Jerrard et al., 2001; Cinque and Linde, 2003). CSF flows from the lateral ventricles into the third ventricle via the foramina of Monroe, and then through the cerebral aqueduct into the fourth ventricle. The CSF circulates through apertures in the fourth ventricle, the lateral foramina of Luschka and the medial foramen of Magendie, to the subarachnoid space. Once the CSF enters the subarachnoid space it flows both cephalad toward the cerebral hemispheres and caudally toward the spinal cord, ultimately being absorbed by the arachnoid villi in the dural sinuses located along the superior sagittal sinus and intracranial venous sinuses and returned to the venous circulation (Jerrard et al., 2001).

The subarachnoid space is normally a closed system, and head trauma increases the risk of bacterial meningitis (Tunkel, 2001). Leakage of CSF manifesting as CSF rhinorrhea or otorrhea may occur after a basilar skull fracture and indicates that the dura has been torn.

THE LUMBAR PUNCTURE

The procedure

CSF was described by the Egyptians in 1500 by Ebers papyrus (Frederiks and Koehler, 1997) and Hippocrates alluded to hydrocephalus in *Water in the Head*. Lumbar puncture is 120 years old and ascribed to Quincke, who first performed the procedure in 1891 on children suffering from headaches in hopes of relieving their symptoms. Soon thereafter, CSF examination became the standard diagnostic method for evaluating patients with meningitis (Frederiks and Koehler, 1997). Examination of the spinal fluid is critical to the diagnosis of meningitis, subarachnoid hemorrhage (SAH), demyelinating diseases, and leptomeningeal metastasis (Strauss et al., 2006).

Thrombocytopenia and coagulation defects are typically corrected with platelet infusions and fresh frozen plasma prior to LP. The platelet count should be $\geq$ 50 000 cells/μl and the international normalized ratio $<$1.5. One study of 941 children with leukemia who had platelet counts less than 50 000 cells/μl had no hemorrhagic complications from LP (Howard et al., 2000). There were only 29 children with a platelet count less than 10 000 cells/μl, however, and the safety of performing an LP with a platelet count of less than 10 000 cells/μl is unknown. The needle should not be inserted through an area of soft-tissue infection as this may insert bacteria into the CSF.

The LP is generally performed with the patient in the lateral recumbent position with the knees flexed toward the chest and the neck slightly flexed, as demonstrated in Figure 3.1 (Strauss et al., 2006). It is helpful to have another person assist with positioning of the patient, especially with children and neonates. The patient's back should be at the edge of the bed and the patient's shoulders and pelvis perpendicular to the bed. The opening pressure can be measured only when the patient is in the lateral recumbent position. Lumbar puncture can also be performed with the patient sitting upright on the edge of the bed and bending forward over a bed stand or sitting with the feet supported and the chest resting on the knees. Performing a LP on an active child may prove difficult and conscious sedation may be required. The person performing the LP should ideally be sitting comfortably.

The spinal cord ends as the conus medullaris typically at the L1–L2 level in adults, and slightly lower in children at the L3–L4 level. The landmarks used are the anterior superior iliac crests, which correlate with the L4–L5 interspace. The needle may be inserted between the L3–L4, L4–L5, or L5–S1 interspaces (Strauss et al., 2006). Insertion above the L3 level may puncture the conus medullaris and should not be done. A sterile technique should be followed, including hand washing, gloves, gown, and mask. After the anterior superior iliac spine is identified, the spinous process superior to the interspace is palpated. The needle should be inserted 1 cm below this and directed in a horizontal position toward the umbilicus to an approximate depth of 2 cm (Strauss et al., 2006). In children, the needle should be directed slightly cephalad toward the umbilicus. Prior to inserting the spinal needle, 2–3 ml of lidocaine is injected subcutaneously and then deeper, allowing 1–2 minutes for lidocaine to take effect. During the LP, if bone is encountered, the needle should be withdrawn to the subcutaneous layer and reinserted at a slightly different angle. The needle is inserted until a "pop" is felt, indicating penetration of the subarachnoid space. The stylet is then removed and CSF obtained. A manometer should be attached if there is an indication to measure the opening pressure. If no CSF is obtained, rotate the needle as part of the dura may be blocking the hole of the needle. If this does not work, reinsert the stylet and advance the needle, stopping frequently to withdraw the stylet (Strauss et al., 2006). If these techniques do not work, a different site should be identified and a new needle inserted.

Role of head CT scan prior to lumbar puncture

It has become routine practice to obtain a cranial CT scan prior to performing an LP in patients with suspected meningitis. This is done to rule out an intracranial mass, hydrocephalus, or edema that could

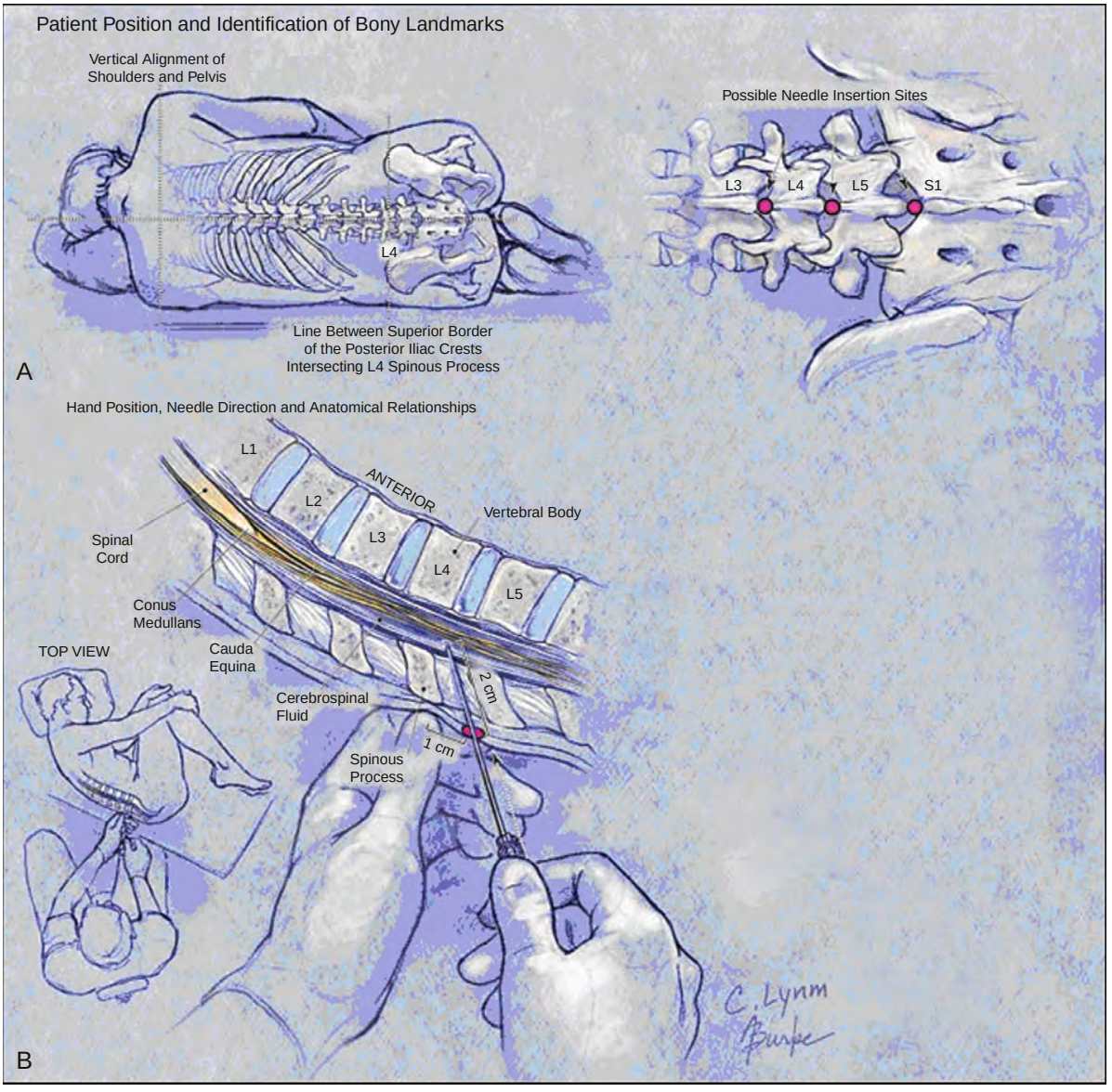

Fig. 3.1. Anatomical considerations during lumbar puncture. Lumbar puncture is performed with the patient in the lateral recumbent position. To avoid rotation of the vertebral column, align the patient's shoulders and pelvis in a plane perpendicular to the bed. A line connecting the superior border of the posterior iliac crests intersects the L4 spinous process or the L4–L5 interspace. Insert the lumbar puncture needle in the midline of the L3–L4, L4–L5 (most commonly), or the L5–S1 interspace. These interspaces are below the end of the spinal cord, which terminates at the level of L1. Angle the needle towards the patient's umbilicus and advance it slowly. The needle will penetrate the ligamentum flavum, dura, and arachnoid to enter the subarachnoid space, where cerebrospinal fluid is located. (Reprinted from Strauss et al. (2006), with permission from JAMA.)

theoretically place the patient at risk of cerebral herniation after CSF removal during the LP. However, considerable controversy in the literature and clinical practice exists as to whether this should be a routine procedure or should be done only in selected patients (Bilaniuk et al., 1978; Bodino and Lylic, 1982; Addy, 1987; Davidson and Carty, 1993). Performing a head CT should not delay treatment, however, and antibiotics should be administered as soon as the diagnosis is suspected.

Herniation of the brain is the consequence of severe cerebral edema or acute hydrocephalus, and can occur in acute bacterial meningitis and other CNS infections (Petito and Plum, 1974; Horwitz et al., 1980; Hart et al., 1988; Haslam, 1991). Clinically this is manifested

by coma, fixed and dilated pupils, and decerebrate or decorticate posturing.

It has been reported since 1909 that performing an LP can precipitate cerebral herniation in a patient with increased intracranial pressure. The literature addressing this issue has been conflicting and inconclusive. In 1933, Schaller reviewed 103 patients with increased intracranial pressure who underwent LP; approximately 80% of the patients had intracranial tumors. Four of the 103 patients died after the LP, although it was documented by autopsy that only one of the four patients who died had evidence of cerebral herniation. The patient with evidence of cerebral herniation had a large posterior fossa glioma and had undergone five large-volume LPs to decrease the intracranial pressure.

In a retrospective series to investigate the incidence of herniation after LP in the setting of increased intracranial pressure, 418 of 1053 patients who had an LP had papilledema (Korein et al., 1959). Only five (1.2%) had a possible complication within the first 48 hours following the LP. The authors concluded that LP in the setting of increased intracranial pressure was relatively safe even with papilledema. Several problems with the existing literature exist:

1. The LPs that were performed in earlier studies were done with large-bore needles (12–16 G).
2. Large quantities of CSF (30–50 ml) were removed (Sencer, 1956; Korein et al., 1959; Rinaldi and Peach, 1969). This is in contrast to today, when a 20- or 22-G needle is used for diagnostic analysis of approximately 5–10 ml of CSF.
3. The timing of herniation was not reported in all studies.
4. Not all deaths after LP were due to proven herniation. In fact, necropsy results in the majority of patients who died after LP revealed no brain herniation (Korein et al., 1959; Duffy, 1969; Long et al., 1969).

Prospective evaluations of the need for obtaining a head CT scan for CNS infection have been done in children (Cabral and Flodmark, 1987; Gower et al., 1987). In a series of 41 children with bacterial meningitis, there were no clinically significant CT abnormalities that were not suspected by neurological assessment (Cabral and Flodmark, 1987). Similar findings have been observed in other studies (Stovring and Snyder, 1980; Packer et al., 1982; Kline and Kaplan, 1988; Pike et al., 1990; Tallon, 1994). CT scan should be considered in any child with bacterial meningitis with a depressed level of consciousness; new-onset, prolonged, or partial seizures; focal neurological examination; enlarging head circumference; evidence of continuing infection; or recurrence of disease (Riordan et al., 1993).

In a recent prospective study of 301 adults with suspected meningitis, baseline clinical features were evaluated prior to obtaining a head CT (Hasbun et al., 2001). These clinical features were then used to identify those unlikely to have abnormal CT findings. Baseline features that were associated with an abnormal finding on head CT were: age $\geq$ 60 years, immunocompromised state (i.e., human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), immunosuppressive therapy, or transplantation), a history of CNS disease, and a history of seizure within 1 week before presentation. Neurological features associated with an abnormal head CT were an abnormal level of consciousness, an inability to answer two consecutive questions correctly or to follow two consecutive commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, and abnormal language (i.e., aphasia). None of the features were present at baseline in 96 (41%) of the 235 patients who underwent cranial CT, and the CT scan was normal in 93 of these 96 patients, yielding a negative predictive value (NPV) of 97%. Of the three patients with an abnormal CT scan, only one had a mild mass effect on CT, and all three subsequently underwent LP, with no evidence of brain herniation 1 week later. Based on these findings, the IDSA has set guidelines for adults with suspected meningitis who should undergo CT prior to LP (Table 3.1). This predictive model, however, has not yet been externally validated on a different patient population.

Table 3.1

Recommended criteria for adult patients with suspected bacterial meningitis who should undergo computed tomography (CT) of the head prior to lumbar puncture (Tunkel et al., 2004)

Criterion	Comment
Immunocompromised state	HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation
New-onset seizure	Within 1 week of presentation
Papilledema	Presence of venous pulsations suggests absence of increased ICP
Abnormal level of consciousness	
Focal neurological deficit	Includes dilated nonreactive pupil, abnormalities of ocular motility, abnormal visual fields, gaze palsy, hemiparesis

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ICP, intracranial pressure.

Role of meningeal signs in suspected meningitis

The meningeal signs, which are nuchal rigidity, Kernig's sign, and Brudzinski's sign, have been used for over a century to evaluate patients with suspected meningitis in the Emergency Room and physicians have relied on them to make a decision to perform or not perform an LP on an individual patient. To determine the diagnostic accuracy of the meningeal signs, a recent study evaluated 297 adults with suspected meningitis who were prospectively evaluated before LP was done. Kernig's sign (sensitivity, 5%; likelihood ratio for a positive test result (LR (+)) 0.97), Brudzinski's sign (sensitivity, 5%; LR (+) 0.97), and nuchal rigidity (sensitivity, 30%; LR (+) 0.94) did not accurately discriminate between patients with meningitis (≥ 6 white blood cells (WBCs)/mm^3 of CSF) and patients without meningitis (Thomas et al., 2002). The meningeal signs had a very poor sensitivity and their absence should not defer the performance of LP. The decision to perform an LP on those suspected of having meningitis is largely based on a combination of clinical signs and symptoms at presentation (e.g., fever, chills, vomiting, photophobia, and severe headache in children and adults) (Saez-Llorens and McCracken, 2003). The triad of fever, stiff neck, and altered mental status was present in only 44% of patients in a prospective study involving 696 patients with confirmed meningitis (van de Beek et al., 2004). However, at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status were found in 95% of patients. A rash was noted in 26% of the patients, mostly in those infected with *Neisseria meningitidis*, and was described as petechial 89% of the time. Focal neurological deficits were present in 33%, of whom 14% were comatose. A seizure occurred in 5% of patients prior to presentation.

Post-lumbar puncture headache

There are a number of complications reported with LP, although most of them are uncommon. Infection may occur if the needle is inserted through infected soft tissue, such as cellulitis. Bleeding may occur from a traumatic LP. More serious bleeding can occur when an emergent LP is performed in patients with thrombocytopenia or other coagulation defects. The development of intraspinal lumbar epidermoid tumors is an extremely rare complication that may occur after introduction of tissue cores through the spinal needle into subarachnoid space. Backache and pain over the site of puncture may also occur.

The most frequent complication is the post-LP headache (Tunkel, 2001; Ahmed et al., 2006; Strauss et al., 2006). Post-LP headache is more common in the 18–30 years age group, young women with a lower body mass index, and in pregnant women (Ahmed et al., 2006). The diagnosis is a clinical one, and it is usually defined as a bilateral headache that develops within 7 days of an LP and disappears within 14 days (Olsen et al., 2004). The headache characteristically worsens upon sitting up and improves by lying down. It is thought that the headache is the result of a piece of dura being withdrawn with the needle, thus leaving a tract for CSF to escape, creating a hole for persistent CSF leakage and a decrease in CSF volume and pressure (Ahmed et al., 2006). The chance of this occurring is decreased if the stylet is reinserted prior to removal of the needle (Strupp et al., 1998; Spriggs et al., 1992). While the exact mechanism for producing the headache is unknown, it may be related to increased gravitational traction on sensitive meningeal vascular coverings as a result of CSF volume depletion. However, the volume of CSF removed has not been associated with an increased incidence of post-LP headache (Ahmed et al., 2006). Another possibility is the activation of adenosine receptors as a result of decreased CSF volume, which would cause cerebral vasodilatation and stretching of pain-sensitive cerebral structures (Ahmed et al., 2006).

The incidence of post-LP headache is not affected by the volume of CSF removed, hydration (oral or intravenous), the position of the patient (lying on the side or sitting up), or the opening pressure (Kuntz et al., 1992; Evans et al., 2000). In a review of four studies comparing bed rest with immediate mobilization post-LP, no significant increase in the incidence of headache occurred in those patients who were mobilized post-LP (Strauss et al., 2006).

Factors associated with the development of a post-LP headache include the type and size of the needle, the direction of the bevel, the replacement of the stylet, and the number of LP attempts. Atraumatic needles which have a blunt end, as compared with the standard Quincke needle, are recommended by the American Academy of Neurology to reduce the incidence of post-LP headaches (Armon and Evans, 2005). The blunt end separates the dura fibers rather than cutting them and is associated with a decreased incidence of headache (Strauss et al., 2006). The tip of the blunt needle needs to be passed 0.5 mm into the subarachnoid space before fluid can be obtained, and paresthesias may develop as a result of impingement of the stretched cauda equina by the tip of the needle (Ahmed et al., 2006). The stylet should always be reinserted prior to removal of the needle as this has been shown to reduce the incidence of post-LP headache (Strupp et al., 1998). Smaller needles have also been shown to decrease the incidence of post-LP headache. The

incidence of a headache with the standard 20–22 G needle is 40%. The incidence of headache with a needle size between 16 and 19 G is 70%, and only 12% with a needle size between 24 and 27 G. Using a needle smaller than 22 G is impractical for a diagnostic LP as the flow rate is slow (it may take >6 minutes to collect 2 ml CSF), and obtaining an opening pressure is difficult (Ahmed et al., 2006). The direction of the bevel should be parallel to the long axis of the spine to decrease the incidence of headache. If the patient is lying on his/her side, the bevel should face up. If the patient is seated, the bevel should be facing the superior iliac crest. This way the needle will separate the dural collagen fibers, which run along the long axis of the spine, rather than cutting them (Lybecker et al., 1990). The number of LP attempts may correlate with an increase in post-LP headache, but this has not been conclusively demonstrated (Strauss et al., 2006).

Several techniques to treat post-LP headache exist, including the instillation of blood or dextran into the epidural space. A "blood patch" may be used, where 20–30 ml of the patient's blood is removed and then immediately placed into the epidural space. The patient is then asked to lie still in the supine position for 1–2 hours prior to mobilization. This works in about 70–98% of patients and can be repeated if necessary. It is thought to work by forming a clot and sealing the CSF leak. Contraindications include the presence of fever, local infection at the site of the LP, and bleeding disorders (Turnbull and Shepherd, 2003). Injecting 20 ml of dextran 40 into the epidural space may treat those who do not respond to a blood patch. Dextran is thought to raise the epidural pressure and reduce the CSF leak (Barrios et al., 1989). Caffeine acts as a cerebral vasoconstrictor and blocks adenosine receptors, which are also involved in the post-LP headache. Both oral and intravenous forms may be used; however, there have been only a few studies and case reports researching the use of caffeine, and a properly designed randomized controlled study has yet to be completed. Epidural saline has been less well studied, and intravenous hydration has not been shown to have an effect on post-LP headache. Surgical closure of the dural gap is the last resort (Ahmed et al., 2006).

CEREBROSPINAL FLUID ANALYSIS

Evaluation of CSF is essential for any suspected CNS infection, and there have been numerous investigations into various data obtained from CSF, as detailed below. The amounts of CSF needed for various studies are included in Table 3.2. Reference values for CSF are detailed in Table 3.3 and further described in the text.

Table 3.2

Minimal volumes of cerebrospinal fluid (CSF) required for common diagnostic tests*

Test	CSF required
Cell count and differential	0.5–5.0 ml
Glucose and protein	0.5 ml
Bacterial culture	3–5 ml[†]
Mycobacterial culture; fungal culture (including acid-fast smear and India ink preparation)	~ 20 ml[‡]
Mycobacterial polymerase chain reaction (PCR)	0.1–1 ml[§]
Viral culture and/or PCR	1–2 ml[¶]
Cryptococcal antigen	0.5 ml
Venereal Disease Research Laboratory (VDRL)	0.5 ml
Oligoclonal bands	2 ml + serum[#]

Adapted from Fishman (1992) and Greenlee and Carroll (1997).
*Volumes represent minimum quantity of CSF and may vary between hospitals.
[†]As little as 0.5 ml may be submitted for culture if there is difficulty obtaining fluid, but greater volume improves yield on culture.
[‡]Yield on culture for acid-fast bacilli and fungi is generally poor unless larger volumes of CSF are obtained (20 ml or more in adults).
[§]Bonington et al. (1998). This is not currently a test approved by the The Food and Drug Administration.
[¶]Thomson and Bertram (2001).
[#]Serum (2–5 ml) drawn before or after lumbar puncture should be submitted for electrophoresis along with CSF.

Opening pressure

The CSF opening pressure is obtained with the patient in the lateral decubitus position. The normal pressure in adults ranges from 50 to 180 mmH_2O (3.8–15 mmHg) (Fishman, 1992). Values less than 100 mmH_2O are considered normal, and over 200 mmH_2O abnormal. In bacterial meningitis the opening pressure is usually between 200 and 500 mmH_2O (Tunkel, 2001). The mean opening pressure in neonates and preterm infants is typically lower than that of adults, with a mean of 100 mmH_2O and 95 mmH_2O, respectively.

Appearance

Once CSF is obtained, it is centrifuged down to give a supernatant. The yellow or sometimes pinkish discoloration of this supernatant is termed xanthochromia, and is used to distinguish between a bloody or traumatic tap and SAH. The discoloration is from degradation products of hemoglobin from lysis of red blood cells. Normal CSF is clear and colorless, but as few as 200 WBCs/mm^3, 400 red blood cells (RBCs)/mm^3, or bacterial concentrations of $>10^5$ colony-forming

Table 3.3

Reference values for cerebrospinal fluid (CSF)

CSF parameter	Children and adults	Term infant	Bacterial meningitis	Viral meningitis
Opening pressure*	50–180	100	>180	<180
WBC count/mm^3	≤ 5	≤ 8	1000–5000	100–1000
% PMNs	0	60	≥ 80%	Unusual
Protein (mg/dl)	≤ 45	20–170	100–500	50–100
Glucose (mg/dl)	45–80	34–119	≤ 40	Normal
Serum:CSF glucose ratio	0.6	0.81	<0.4	>0.6
Gram's stain	–	–	60–90%	–
Culture	–	–	70–85%	–

*Opening pressure is in mmH_2O.
WBC, white blood cell; PMNs, polymorphonuclear leukocytes.

units (cfu)/ml, can produce a cloudy, turbid CSF (Greenlee and Carroll, 1997). Xanthochromia usually develps 2–4 hours after RBCs have entered the subarachnoid space (Greenlee and Carroll, 1997), which is why some experts suggest waiting at least 6 hours after the onset of headache when a subarachnoid bleed is suspected, to avoid a false-negative result (Seehusen et al., 2003). Up to 90% of patients will have xanthochromia within 12 hours of an SAH (Fishman, 1992). Xanthochromia may be obvious after obtaining CSF in a clear plastic tube, or be visualized when the vial of CSF is placed next to a vial of clear water against a white background, but should be confirmed using spectrophotometry when suspecting SAH. CSF in a traumatic tap should clear as the CSF is collected in serial vials, but the CSF does not clear in cases of SAH. Xanthochromia is not pathognomonic for SAH. Xanthochromia may be detected in CSF from patients who have had a recent LP with introduction of red blood cells into the subarachnoid space. Graves and Sidman (2004) added whole blood to clear CSF at varying concentrations from 5000, 10 000, 20 000, 30 000, to 40 000 RBCs/μl. Xanthochromia was observed within 2 hours and sooner in samples with greater than 10 000 RBCs/μl added. Other causes of xanthochromia are shown in Table 3.4, and xanthochromia may be a result of elevated CSF protein concentration (>150 mg/dl), or systemic hyperbilirubinemia (serum bilirubin >10–15 mg/dl) (Tunkel, 2001).

Table 3.4

Different colors of cerebrospinal fluid (CSF) and their causes

Color of CSF	Causes
Yellow	Blood breakdown products
	Hyperbilirubinemia (total bilirubin >10–15 mg/dl)
	CSF protein (>150 mg/dl)
	>100 000 RBCs/mm^3
Orange	Blood breakdown products
	High carotenoid ingestion
Pink	Blood breakdown products
Green	Purulent CSF
	Hyperbilirubinemia
Brown	Meningeal melanomatosis

RBCs, red blood cells.
Adapted from Seehusen et al. (2003).

Cell count

One of the most useful and common markers to differentiate bacterial meningitis from viral meningitis is the type of WBCs present in the CSF. Typical findings are shown in Table 3.3. Prior oral antibiotic use, which can decrease the yield of the Gram's stain and culture, has little effect on the cellular response, making the cell count with differential an invaluable tool (Kacica and Lepow, 1994). In children and adults, the normal WBC count is 0–5 cells/mm^3, with counts greater than 5 cells/mm^3 consistent with meningitis. The normal WBC count is higher in neonates, with counts up to 8 cells/mm^3, and in some reports up to 32 cells/mm^3 (Sarff et al., 1976; Feigin et al., 1992). By 1 month of age, the CSF should contain fewer than 10 WBCs/mm^3 (Greenlee and Carroll, 1997). There should not be any neutrophils in the CSF of adults, but the CSF of infants may have 60% neutrophils. Once CSF is obtained it should be sent immediately to the laboratory for analysis, as the WBC count may decrease by 50% in 2 hours (Steele et al., 1986).

The WBC count is usually between 1000 and 5000/mm^3 in untreated bacterial meningitis (Tunkel, 2001), and a WBC greater than 2000 cells/mm^3 is a predictor of bacterial infection (Spanos et al., 1989). Viral meningitis typically has fewer than 100 cells/mm^3, although one review found 4% of cases of viral meningitis with a pleocytosis of greater than 1000 cells/mm^3 (Karadanis and Shulman, 1976).

Bacterial and viral meningitis cause a pleocytosis, typically with bacteria causing a neutrophilic predominance and a virus causing a lymphocytic predominance. In the early stages of meningitis this may not be as clear, as a neutrophilic pleocytosis may accompany early viral meningitis or encephalitis (Cinque and Linde, 2003). Up to two-thirds of early enteroviral meningitis cases have a neutrophilic predominance (Rice et al., 1995). Within 12–24 hours there is usually a shift from a neutrophilic predominance to a lymphocytic predominance, which is the basis for the recommendation that a repeat LP be performed in suspected viral meningitis with a CSF neutrophilic pleocytosis on initial LP (Feigin et al., 1992). In 10% of cases of acute bacterial meningitis, a lymphocytic predominance may be seen, usually in cases of *Listeria monocytogenes* meningitis and in newborns with gram-negative bacillary meningitis (Tunkel and Scheld, 1995). A lymphocytic pleocytosis is seen in meningitis due to viruses, *Mycobacterium tuberculosis, Borrelia burgdorferi, Treponema pallidum,* fungi, as well as in neoplastic and drug-induced meningitis (Cinque and Linde, 2003). Eosinophilic meningitis is defined as >10 eosinophils/mm^3 or in the total CSF count >10% eosinophils. This should raise the suspicion of *Coccidioides immitis* meningitis or a parasitic infection, although a number of other conditions may cause eosinophilic meningitis, as shown in Table 3.5 (Weller and Liu, 1993).

Glucose concentration

Low CSF glucose concentration, termed hypoglycorrhachia, although characteristic of bacterial meningitis, may occur by a variety of mechanisms. Mycobacteria and fungal species cause hypoglycorrhachia, and, less frequently, viral pathogens such as mumps, enterovirus, lymphocytic choriomeningitis virus, herpes simplex virus (HSV), and herpes zoster infections may cause hypoglycorrhachia as well. In addition, carcinomatous meningitis is typically associated with a decreased CSF glucose concentration (Greenlee and Carroll, 1997). Patients with bacterial meningitis, who have been treated with oral antibiotics prior to LP, may have a normal CSF glucose concentration (Greenlee and Carroll, 1997). Elevated CSF glucose concentration is a reflection of serum glucose and is seen in patients with diabetes mellitus: there is no intrinsic CNS pathological process that causes CSF glucose concentration to be elevated.

Table 3.5

Causes of eosinophilic meningitis

Parasitic infection
Viral meningitis
Fungal meningitis
Rickettsial meningitis
Ventriculoperitoneal "shunt" (with or without active infection)
Malignancy
Drug reaction

The normal range for CSF glucose concentration is a reflection of serum glucose. Typically, the CSF glucose concentration is two-thirds the serum glucose concentration, or a ratio of CSF glucose to serum glucose of 0.6, with a ratio of 0.5 considered abnormal. This ratio is higher in preterm and term infants, with 0.6 or lower being abnormal. In adults, the normal serum glucose is 70–120 mg/dl, which corresponds to a CSF glucose concentration of 45–80 mg/dl (Greenlee and Carroll, 1997). During infection, glucose metabolism and transport are altered. Bacteria and leukocytes metabolize glucose (Fishman, 1992; Tunkel, 2001). In general, it takes 2–4 hours for the CSF and serum to equilibrate (Fishman, 1992). Therefore, it is important to measure the serum glucose at the same time as the CSF glucose is obtained because hyperglycemia and hypoglycemia may alter the CSF glucose concentration and affect the interpretation.

Protein concentration

Under normal circumstances, most proteins do not cross the blood–brain barrier and their CSF concentration level is low. Proteins typically gain access via pinocytic vesicles and are excluded by tight junctions between cells of the arachnoid membrane and capillary endothelial cells in the choroid plexus (Pardridge et al., 1986). During infection, the tight junctions break down and the number of pinocytic vesicles is increased (Quagliarello et al., 1986; Tunkel, 2001). The normal CSF protein concentration for adults and neonates is listed in Table 3.3. Values above these norms are considered abnormal, although nonspecific. The CSF protein concentration taken alone has minimal diagnostic value and should be interpreted in the context of other CSF results. A SAH will increase the protein concentration by 1 mg/dl for every thousand RBCs (Greenlee and Carroll, 1997).

Gram's stain

Gram's stain examination is recommended for all patients suspected of having meningitis as it is fast, inexpensive, and fairly reliable. A positive result is useful in guiding initial antimicrobial therapy. Various reports of Gram's stain sensitivity suggest a range from 50% to 90%. The specificity approaches 100% (Durand et al., 1993; van de Beek et al., 2004). The CSF concentration of bacteria does alter the likelihood of visualizing an organism: fewer than or equal to 10^3 cfu/ml yields a positive Gram's stain 25% of the time, concentrations 10^3–10^5 cfu/ml yield a positive Gram's stain 60% of the time, and $>10^5$ cfu/ml yields a positive Gram's stain result more than 97% of the time (La Scolea and Dryja, 1984). There are also reports that, even with a negative culture, the Gram's stain may be positive 10–15% of the time (Durand et al., 1993). One review found the sensitivity of the Gram's stain without prior antibiotic use to be 75–90%, but decreased to 40–60% when antibiotics were used prior to LP (Thomson and Bertram, 2001). Prior antibiotic therapy is unlikely to alter other biochemical and cellular tests such as glucose concentration, protein concentration, and cell count (Flitch and van de Beek, 2007). Care must be taken to make sure the sample was not contaminated with skin flora, or mishandled in the laboratory, both of which may lead to erroneous results (Tunkel, 2001). Preparation of the specimen is important, particularly the use of cytospin cytocentrifugation, which greatly increases the probability of obtaining a positive Gram's stain (Chapin-Robertson et al., 1992). The sensitivity of the Gram's stain also varies by pathogen: *Streptococcus pneumoniae* is detected 90% of the time, *Haemophilus influenzae* 86%, *Neisseria meningitidis* 75%, and gram-negative bacilli only 50% of the time. *Listeria monocytogenes* is detected less than 50% of the time (Greenlee and Carroll, 1997).

CSF with negative Gram's stain

A frequently encountered problem in the Emergency Room is what to do in cases of a negative Gram's stain. If the CSF cell count and glucose concentration are suggestive of bacterial meningitis, antimicrobial and adjunctive therapy should be initiated and continued until bacterial meningitis has been ruled out.

Latex agglutination

Bacterial antigen tests have fallen out of favor as a positive result rarely alters therapy, and the test performance is similar to the Gram's stain (Thomson and Bertram, 2001). In addition, the antigen detection tests are less sensitive than bacterial culture, and their diagnostic accuracy varies from institution to institution (Greenlee and Carroll, 1997). Antigens for common meningeal pathogens are available, including: *H. influenzae* type b, *S. pneumoniae, N. meningitidis, Escherichia coli,* and *S. agalactiae*. The range of sensitivities varies from 50% to 100%. The latex agglutination test, when positive, establishes the diagnosis of bacterial meningitis due to a specific pathogen, but a negative test never rules out bacterial meningitis (Chapin-Robertson et al., 1992).

CSF cultures

Bacterial culture

Culture of CSF remains the gold standard for diagnosing bacterial meningitis, and is positive in 70–85% of patients with bacterial meningitis (Durand et al., 1993; Roos et al., 1997). The amount of CSF required for bacterial culture is around 3–5 ml and it usually takes at least 48 hours to finalize identification of the meningeal pathogen (Greenlee and Carroll, 1997). CSF is routinely cultured on 5% sheep blood agar, chocolate agar, and enriched broth (Gray and Alonso, 2002). It is important to inoculate the specimens quickly to ensure growth of fastidious organisms, including *H. influenzae, N. meningitidis,* and anaerobes (Greenlee and Carroll, 1997).

Mycobacterial culture

The isolation of *Mycobacterium tuberculosis* in culture of CSF is difficult with positive cultures in the range of 52–78% (Greenlee and Carroll, 1997). Ideally mycobacterial cultures require at least 20 ml of CSF (Greenlee and Carroll, 1997). Up to 6 weeks' incubation time is required to see growth of the organism. Rapid broth culture using the mycobacterial growth indicator tube has standardized detection and reduced detection times for *M. tuberculosis* to less than 3 weeks (Thomson and Bertram, 2001).

CSF adenosine deaminase has been shown to be a useful marker to differentiate tuberculosis from non-tuberculosis meningitis. In one study of 117 patients with tuberculous meningitis, and 104 patients with non-infectious neurological disorders, adenosine deaminase 11.39 units/l/min or higher had an 82% sensitivity and 83% specificity for tuberculous meningitis (Kashyap et al., 2006).

Fungal culture

The diagnosis of fungal meningitis is made by identification of the organism in culture, which, aside from

cryptococcal meningitis, is very difficult. In general the yield of a positive CSF culture may be increased by collecting 15–20 ml of CSF and large volumes of CSF should be obtained if fungal meningitis is suspected (Dismukes et al., 1987). In cryptococcal meningitis, culture is positive in almost 80% of those with AIDS due to the high number of organisms present in CSF (Sanchez-Portocarrero et al., 2000). Cultures are positive in 90% of cryptococcal meningitis without HIV (Diamond and Bennett, 1974; Snow and Dismukes, 1975).

The cryptococcal antigen test is positive in over 90% of HIV-infected patients and slightly less in nonimmunosuppressed patients. A positive titer is usually considered when it is 1:8 or greater, and is present in both serum and the CSF (Snow and Dismukes, 1975). False-positive tests can result from rare infections due to the fungus *Trichosporon beigelii* or the bacterial genera *Stomatococcus* or *Capnocytophaga* (Westerink et al., 1987). Nonetheless, the cryptococcal polysaccharide antigen test is a very useful screening test as it is quick and reliable (Powderly et al., 1994).

For other causes of fungal meningitis, the yield of culture is much lower. Cultures are positive in coccidioidal meningitis in 30–50%, and less in cases of *Blastomyces* and *Histoplasma capsulatum*, and they may also take several weeks to identify the fungus (Perfect, 1997). Other fungi such as *Sporothrix* and Zygomycetes also present a challenge in diagnosis since the yield of positive CSF culture is less than 50% (Perfect, 1997). *Histoplasma capsulatum* meningitis is difficult to culture, and fungal stains are rarely positive. Cisternal aspiration or repeated spinal taps may be required if the initial cultures are negative and clinical suspicion is high. Many cases are diagnosed by CSF *H. capsulatum* capsular polysaccharide antigen. At least three fungal blood cultures should be performed in all cases of suspected *Histoplasma capsulatum* meningitis (Wheat et al., 2005).

Viral culture

Sending CSF for viral culture is still done, and is useful for enteroviral meningitis and primary HSV meningitis, but most other viruses do not grow in culture of CSF.

Polymerase chain reaction (PCR)

Classic PCR uses enzymes to replicate a single or a few copies of pieces of DNA by several orders of magnitude, generating millions or more copies of DNA. Specific regions of the DNA strand are amplified, such as a single gene, part of a gene, or a noncoding sequence. The sample containing DNA is heated to denature the double-stranded DNA, which separates it into two single strands. Cooling the sample allows primers designed specifically with the nucleic acid sequence, such as those of typical viral or bacterial pathogens, to anneal or bind to the opposing DNA sequence if present. Reheating the sample in the presence of a thermostable DNA polymerase and single nucleotides will synthesize new pieces of DNA. This cycle is then repeated allowing amplification of DNA. For RNA viruses, the RNA is first converted to DNA by reverse transcriptase RT-PCR prior to amplification (Tang and Persing, 1999).

There are a variety of PCR methods used today, including "multiplex" and "nested" PCR. Multiplex PCR has the advantage of detecting one or more organism in the same PCR reaction. This is done by using two or more primer pairs, each specific for a single agent. In nested PCR, products from the first amplification are reamplified from a second set of primers that is nested between the first set. This essentially overcomes nonspecific amplification (i.e., of contaminants) and increases the sensitivity of detection. The use of reference DNA molecules added to a PCR reaction reveals possible inhibitors of amplification, such as substances that are already present in the samples (Podzorski and Persing, 1995).

The amplified products are usually subjected to electrophoresis in an agarose gel stained with ethidium bromide, which separates the products based on size. Labeled DNA probes are then employed that have complementary strands to the target DNA.

Bacterial PCR

The use of PCR in bacterial meningitis is expected to be beneficial in patients pretreated with antibiotics, and in patients where the LP is delayed for hours or days after antibiotic therapy is initiated, both of which can lower the yield of the Gram's stain and culture. PCR may also be helpful in the identification of difficult-to-culture and fastidious organisms (*Mycobacterium tuberculosis, Brucella*).

Laboratory tests using both broad-range bacterial primers for PCR (Radstrom et al., 1994; Kotilainen et al., 1998; Backman et al., 1999; Lu et al., 2000; Rantakokko-Jalava et al., 2000; Margall Coscojuela et al., 2002; Nikkari et al., 2002; Saravolatz et al., 2003; Xu et al., 2003; Schuurman et al., 2004) and organism-specific PCR (Cherian et al., 1998; Taha, 2000; Corless et al., 2001) have been found to be sensitive and specific in detecting meningeal pathogens. Broad-range PCR has a number of advantages as it can detect a number of gram-positive and gram-negative species, as well as infrequent pathogens causing meningitis (Yamamoto, 2002). Specimens would need to be confirmed by a species-specific PCR once positive.

One of the more appealing uses of PCR is its rapid detection methods. Real-time PCR has the advantage over conventional PCR in that it uses fluorescent probes to detect the amplified product in the same reaction vessel, with results available in less than 1 hour. Studies involving real-time PCR for *Neisseria meningitidis* (Guiver et al., 2000; Corless et al., 2001), *Haemophilus influenzae* (Corless et al., 2001), *Streptococcus pneumoniae* (Corless et al., 2001), and penicillin-resistant *S. pneumoniae* (Kearns et al., 2002) show sensitivities close to that of culture. One study evaluated 70 patients with primers derived from conserved regions of the bacterial 16S RNA gene and found a sensitivity and specificity of 100% and 98.2% respectively, and a positive predictive value (PPV) and NPV of 94.4% and 100% respectively. The authors concluded that this test could be used as an adjunct test with bacterial culture, but culture for antimicrobial sensitivities would still be needed. Negative results, which could be known in less than 2 hours, would be useful in excluding a diagnosis of meningitis (Saravolatz et al., 2003). This would allow the physician to discontinue antibiotics sooner than the 24–48 hours it takes for a culture to become positive.

Contamination of a PCR specimen may cause false-positive results which can be encountered by improper handling or contaminated work equipment from previous PCR reactions. An ultraviolet light and uracil DNA glycosylase (UNG) can be used in these cases (Longo et al., 1990; Espy et al., 1993). UNG degrades products from previous amplifications but not native nucleic acid templates, by substituting 2′-deoxyuridine, 5′-triphosphate (dUTP) for 2′-deoxythymidine, 5′-triphosphate (dTTP) in the amplification mixture and pretreating all subsequent mixtures with UNG prior to amplification (Cinque and Linde, 2003). Broad-range PCRs frequently use a *Taq* polymerase which is known to be a frequent contaminate (Schuurman et al., 2004). The 16S rRNA gene, which is frequently targeted in broad-range PCR because it is shared by the most common bacterial pathogens, lends to potential contamination with skin flora such as staphylococci (Yamamoto, 2002). False-negative tests may be seen when there is poor sensitivity of the laboratory assay, or a bloody tap leading to a high number of erythrocytes which may inhibit amplification.

Viral PCR

PCR has become the diagnostic modality of choice for detecting HSV (Aurelius et al., 1991; Anderson et al., 1993; Puchhammer-Stockl et al., 1993; Whitley and Lakeman, 1995; DeBiasi and Tyler, 2004). Numerous studies have shown sensitivities greater than 90%, with specificities near 100% (DeBiasi and Tyler, 2004). Viral cultures are not routinely recommended for adults, as they are positive in less than 5%. In infants and neonates, viral cultures may be positive for HSV in 25–40% (Nahmias et al., 1982; Skoldenberg et al., 1984). Results of PCR must be interpreted in the context of the clinical presentation, duration of illness, and prior use of antiviral therapy. A negative PCR for HSV does not rule out HSV infection. False-negative results may occur in the setting of a bloody tap or in the presence of xanthochromia. Porphyrin, a heme degradation product of RBCs, inhibits the PCR and gives a false-negative result (Aurelius et al., 1991). While this is not common, there are two studies that found approximately 1% inhibitory activity to HSV PCR in samples from CSF that was bloody (Lakeman and Whitley, 1995; Mitchell et al., 1997). Obtaining CSF samples early in the course of illness, usually less than 72 hours, may result in false-negative tests thought be related to limited viral replication (Rozenberg and Lebon, 1991). One study found that three of 11 patients with an initially negative PCR for HSV in CSF on days 1–3 of illness became positive upon repeat LP on days 4–7 of illness (Weil et al., 2002). Thus, in patients with a high suspicion for HSV infection and an initial negative HSV PCR, antiviral therapy should be continued and a repeat LP performed between days 4 and 7 of illness. In cases where CSF is not obtained until weeks after the onset of symptoms or the HSV PCR is negative, intrathecal HSV-specific antibody may be used to make a retrospective diagnosis (DeBiasi and Tyler, 2004). Antibodies in the CSF to HSV are usually absent early in the course of illness and not recommended in these stages, but usually become positive by 2 weeks of illness (DeBiasi and Tyler, 2004). False-negative HSV PCR may also occur in patients previously treated with acyclovir, or in whom the collection of CSF is obtained much later after the onset of neurologic symptoms (Aurelius et al., 1991; Rozenberg and Lebon, 1991; Lakeman and Whitley, 1995).

Antiviral therapy can decrease the detection of HSV DNA in the CSF of patients (Cinque and Linde, 2003). PCR usually remains positive during the first week of therapy (Lakeman and Whitley, 1995). HSV PCR has been found to be positive for at least 5 days after the start of antiviral therapy (Skoldenberg, 1996). One study reviewed the presence of detectable HSV DNA in CSF after treatment: HSV DNA was detected in 100% of patients within 10 days of treatment, 30% of patients between 11 and 20 days, and 19% within 21–40 days (Revello et al., 1997). Other reports have also found viral genomes persisting in the CSF for 2 weeks or longer after the initiation of antiviral therapy (Lakeman and Whitley, 1995; Wildemann et al., 1997).

PCR is also useful for the diagnosis of neonatal HSV infection. In one series of, HSV DNA was detected in the CSF in 76% (26 of 34) of infants with CNS disease, 94% (13 of 14) with disseminated infection, and 24% (seven of 29) with skin, eye, or mouth involvement (Kimberlin et al., 1996). Quantitative analysis of HSV DNA is also useful in neonatal HSV encephalitis. Neonates with disseminated infection had a higher viral load in their sera, and patients with CNS infection had a higher viral load in the CSF. The viral load was significantly higher in the serum of patients who died later. Neonates with HSV type 2 infection had more CNS involvement and neurological impairment, together with a high viral load in the CSF, than did HSV type 1 patients (Kimura et al., 2002).

Mycobacterium tuberculosis PCR

The diagnosis of tuberculous meningitis can be difficult as the organism is difficult to grow in culture, and culture may take up to 6 weeks to be positive (Greenlee and Carroll, 1997). Nucleic acid amplification testing (NAAT) by PCR has received interest in the hope that it may be a rapid, sensitive, and specific test for tuberculous meningitis. One of the more frequently used PCR techniques detects a nucleotide sequence of IS61100 present in the genome of *M. tuberculosis*. Investigators prospectively studied 677 CSF samples in patients with clinically suspected tuberculous meningitis (Rafi et al., 2007). All culture-positive samples ($n = 136$) were positive (100%) by the PCR assay. In those patients with clinically suspect (culture-negative) tuberculous meningitis, the assay was positive in 70% ($n = 541$). In another study which evaluated 57 CSF samples from suspected cases of meningitis, microscopy, culture, and PCR had a sensitivity of 3.3%, 26.7%, and 66.7% respectively (Desai et al., 2006). PCR assays used on respiratory specimens in the diagnosis of pulmonary tuberculosis were used on CSF samples in patients with definite or probable tuberculous meningitis, with positive results in nine of 15 patients using PCR (Bonington et al., 1998). In contrast, in some studies the sensitivity of PCR has been as low as 33% (Nguyen et al., 1996) and as high as 91% (Liu et al., 1994).

CSF defensin and lactoferrin

While not a routinely tested assay, endogenous antimicrobial molecules play a role in host defense. Two of these antimicrobial molecules, defensin and lactoferrin, were found to be significantly higher in a prospective study of 19 children with bacterial meningitis compared with 31 children with aseptic meningitis, and 32 controls (Maffei et al., 1999). The utility of CSF defensin and lactoferrin as a diagnostic tool or therapeutic monitoring assay has yet to be determined.

DIFFERENTIATING BACTERIAL FROM VIRAL MENINGITIS

Laboratory tests

Lactic acid

While not a frequently utilized test, elevated CSF lactate levels may be more useful than glucose in postoperative neurosurgical patients in predicting bacterial meningitis. In one retrospective study of 74 neurosurgical patients, an elevated lactate level greater than 4 mmol/l was more sensitive than the CSF:serum glucose ratio (<0.4) in identifying bacterial meningitis (Strauss et al., 2006). An elevated CSF lactate >2 mmol/l has been reported due to seizures, meningitis or encephalitis, cerebral ischemia, malignancy, and other metabolic disorders (Chow et al., 2005). In general, the test does not add a great amount of additional information, and therefore is rarely used clinically (Tunkel, 2001).

Rapid detection of *Streptococcus pneumoniae*

A rapid immunochromatographic membrane assay has been used to diagnose *S. pneumoniae* from urine samples of patients, with sensitivities between 64% and 86% and specificities greater than 95% (Binax NOW *Streptococcus pneumoniae* Urinary Antigen Test, Binax, Portland, ME, USA) (Henney, 1999; Genne et al., 2006). Other less sensitive bacterial antigen tests are targeted at the capsular antigen. Binax NOW detects *S. pneumoniae* C-polysaccharide, which is found in the cell wall and is common to all serotypes (Marcos et al., 2001). The use of the Binax NOW antigen test on CSF to diagnose pneumococcal meningitis has been evaluated in patients with meningitis, and appears to be both sensitive and specific for pneumococcal meningitis (Marcos et al., 2001; Samra et al., 2003).

CSF cortisol

Bacterial meningitis results in a systemic and intrathecal inflammatory reaction. As such, investigators have looked at various serum and CSF inflammatory markers, such as C-reactive protein (CRP), procalcitonin, cytokines, interleukins, and cortisol.

Elevated serum cortisol levels have been found to be predictors of poor outcome in pediatric patients (Singhi and Bansal, 2006) with bacterial meningitis and in patients with sepsis (Annane et al., 2000). The relationship of endogenous steroids and inflammatory cytokines, including CSF cortisol and CSF cytokines,

to the severity of disease was evaluated in a prospective case–control study involving 47 patients aged 16 years or older with bacterial meningitis (Holub et al., 2007). There was a significant difference ($P < 0.001$) between CSF cortisol levels in patients with bacterial meningitis (133 nmol/l) compared with those with aseptic meningitis (17 nmol/l) and healthy controls (10 nmol/l). A CSF cortisol concentration of 46.1 nmol/l (88% sensitive; 100% specific) was the optimal cutoff to distinguish bacterial from aseptic meningitis. In addition, the authors found elevated CSF cortisol to be a marker of disease severity. Elevated cortisol levels are not a specific finding of bacterial meningitis and can be found in other disorders such as multiple sclerosis, Alzheimer's disease, depression, and posttraumatic stress disorder (Holub et al., 2007).

Procalcitonin

Procalcitonin is a calcitonin propeptide synthesized by C cells of the thyroid gland and released from leukocytes of the peripheral blood (Taskin et al., 2004). It has been used as a marker of severe inflammation (Ernst et al., 2007). One of the advantages of procalcitonin is that it is released during infections caused by bacteria, fungi, and parasites, but is normal or only slightly elevated in viral infections (Meisner, 1996).

Serum levels of procalcitonin have been used to differentiate bacterial from viral meningitis (Tunkel et al., 2004). In a prospective study of 151 patients (age 35 ± 15 years) with confirmed meningitis, there were 18 patients with bacterial meningitis and 133 with nonbacterial meningitis. CRP and procalcitonin levels, CSF WBC and absolute neutrophil counts, CSF glucose-to-blood glucose ratio, and CSF protein concentrations were significantly higher in the bacterial meningitis group. Only serum procalcitonin (sensitivity 87%, specificity 100%, PPV 1.0, NPV 0.99) was better than the Emergency Room physician (sensitivity 89%, specificity 77%, PPV 0.31, NPV 0.96) at identifying bacterial from nonbacterial meningitis (Ray et al., 2007).

In a study of 59 consecutive children hospitalized for meningitis (Gendrel et al., 1997), a serum procalcitonin concentration >5.0 µg/l was 94% sensitive and 100% specific for the diagnosis of bacterial meningitis. In adults, serum concentrations >0.2 ng/ml had a sensitivity and specificity of up to 100% for the diagnosis of bacterial meningitis (Viallon et al., 1999). Dubos et al. (2006) looked at a number of different biological markers to distinguish between bacterial and viral meningitis in the Emergency Room, and found that serum procalcitonin >0.5 ng/ml (89% sensitive, 86% specific) along with CSF protein concentration 0.5 g/l or greater (86% sensitive, 78% specific) had the best predictive value to distinguish between bacterial and aseptic meningitis in children (Dubos et al., 2006).

Another prospective study involving 45 adult patients evaluated the predictive value of procalcitonin in both serum and CSF (Jereb et al., 2001). A serum procalcitonin level >0.5 ng/ml had a PPV for bacterial meningitis of 100% and an NPV of 93%, while corresponding values for CSF procalcitonin were 100% and 74%, respectively. Routine use of procalcitonin is not an official recommendation of the IDSA as the assay is not readily available in all laboratories (Tunkel et al., 2004).

Procalcitonin in the CSF may also be elevated in patients with Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia as well as encephalitis and meningitis (Ernst et al., 2007).

C-reactive protein

CRP is an acute-phase reactant released from the liver in response to an inflammatory reaction, such as meningitis. CRP is released within 6 hours of insult and peaks after 36 hours. One of the functions of CRP is to recognize foreign pathogens and phospholipid components of damaged cells, resulting in activation of the classical complement pathway (Volanakis, 2001; Ray et al., 2007).

Measurement of serum CRP concentration may be helpful in patients with CSF findings consistent with meningitis, with a negative Gram's stain result such that the physician is considering withholding antimicrobial therapy. A normal CRP has a high NPV in the diagnosis of bacterial meningitis (Tunkel et al., 2004).

Clinical models

The presentation of bacterial and viral meningitis may be very similar, and differentiating between the two through CSF analysis may not always be clearcut.

A number of prediction models have been designed to help the clinician differentiate between bacterial and viral meningitis. Spanos and colleagues (1989) found individual predictors of bacterial meningitis in adults as follows: CSF glucose concentration less than 34 mg/dl (1.9 mmol/l); CSF/blood glucose ratio less than 0.23; CSF protein concentration >220 mg/dl; CSF leukocyte count >2000 cells/mm^3; or a neutrophil count >1180/mm^3. In a retrospective study of 144 patients, a CSF absolute neutrophil count of more than 1000/mm^3 was predictive of bacterial meningitis, but neither a CSF glucose concentration less than 2 mmol/l nor a CSF protein concentration greater than 2 g/l was predictive of bacterial meningitis on logistic regression analysis (Brivet et al., 2005).

In 151 adult patients over 16 years of age with acute meningitis, the CSF WBC count (median 494 versus 98 cells/mm^3), CSF neutrophil count (median 428 versus 20 cells/mm^3), and protein concentration (2.45 g/l versus 0.75 g/l) were significantly ($P < 0.05$) higher in the bacterial meningitis group than in the nonbacterial meningitis group, respectively (Ray et al., 2007). However, none of the diagnostic indicators of bacterial meningitis were more efficient than the diagnosis of the Emergency Room physician, with the exception of serum procalcitonin level.

In a pediatric study of patients aged 1 week to 14 years, a CSF glucose concentration less than 20 mg/dl or a CSF-to-serum glucose ratio less than 0.3 was found to be strongly predictive of bacterial meningitis. A CSF-to-serum glucose ratio greater than 0.3 excluded most cases of bacterial meningitis. Other studies have shown a CSF-to-serum glucose ratio less than 0.4 to be accurate for diagnosing bacterial meningitis (Briem, 1983; Lindquist et al., 1988).

To help clinicians differentiate bacterial from viral meningitis, the records of a cohort of 696 children aged 29 days to 19 years admitted to the hospital with a diagnosis of meningitis (bacterial and viral) from 1992 to 2000 were reviewed (Nigrovic et al., 2002). The patients were randomly divided into a derivation set (two-thirds of patients) to identify the clinical predictors, which were then applied to the validation set (one-third of patients) and tested for accuracy. There was a total of 125 (18%) children with bacterial meningitis, and 571 (82%) with aseptic meningitis. The clinical predictors of bacterial meningitis were the following: CSF Gram's stain showing bacteria, CSF protein concentration $\geq$ 80 mg/dl, peripheral absolute neutrophil count $\geq$ 10 000 cells/mm^3, seizure before or at the time of presentation and CSF absolute neutrophil count $\geq$ 1000 cells/ mm^3 (Table 3.6). Patients with none of these clinical predictors were given a bacterial meningitis score of 0 and were identified as at low risk for bacterial meningitis. A bacterial meningitis score of 0 had an NPV of 100% for bacterial meningitis, and had a specificity of 73%. A bacterial meningitis score of $\geq$ 2 had a sensitivity of 87% for bacterial meningitis, and a PPV of 87%.

Table 3.6

Nigrovic bedside meningitis score

Predictor	Score
CSF Gram's stain showing bacteria	2
CSF protein $\geq$ 80 mg/dl	1
Peripheral absolute neutrophil count $\geq$ 10 000 cells/mm^3	1
Seizure before or at time of presentation	1
CSF absolute neutrophil count $\geq$ 1000 cells/mm^3	1

CSF, cerebrospinal fluid.

Nigrovic and colleagues (2007) then performed a follow-up study to validate the bacterial meningitis score externally. This was a large retrospective cohort study involving 3295 patients aged 29 days to 19 years evaluated in 20 US academic medical centers with CSF pleocytosis (CSF $\geq$ 10 white blood cells/μl). In the validation study there were 121 (3.7%) patients with bacterial meningitis and 2518 (96.3%) patients with aseptic meningitis. Two patients out of 1714 classified as very low risk with a bacterial meningitis score of 0 had bacterial meningitis (NPV 99.9%). The sensitivity for a bacterial meningitis score $\geq$ 1 was 98.3% with a specificity of 61.5%, corresponding to a positive likelihood ratio of 2.56 and a negative likelihood ratio of 0.03. However, the study had a number of limitations. Patients were excluded if they had received antibiotics within 72 hours of the LP, required hospitalization regardless of risk of meningitis, were critically ill, were immunosuppressed, had a ventricular shunt device or recent neurosurgery, or had purpura. These were similar to the exclusion criteria in the original study. Of note, the investigators did not develop a prediction rule between patients with a positive and those with a negative Gram's stain. The authors did note this as a limitation, since prediction rules for bacterial meningitis are needed only if the Gram's stain is negative. If the Gram's stain is positive, the diagnosis of bacterial meningitis is virtually ruled in (Strauss et al., 2006).

Universal application of bedside decision rules is not always applicable, as demonstrated in a retrospective study on children with meningitis (De Cauwer et al., 2007). When the authors of this study applied the bacterial meningitis score to the children with bacterial meningitis in their study ($n = 21$), five (23.8%) children lacked all the criteria of the bacterial meningitis score, and therefore would have been considered as low-risk patients and would not have been treated properly. These authors developed a bedside meningitis score that consisted of serum CRP, CSF glucose concentration, and CSF protein concentration, resulting in a bacterial meningitis score from 0 to 3 points, as shown in Table 3.7. The frequency of patients with different scores is shown in Table 3.8. In this study, the physician started antibiotics in 41 of 71 patients. Use of the De Cauwer bacterial meningitis score would have resulted in only 16 of 71 children with viral meningitis receiving antibiotics.

For the management of children with suspected meningitis, Oostenbrink et al. (2001, 2002) developed a diagnostic decision rule to guide decisions on the

Table 3.7

Bedside meningitis score

Value	Score	PPV, NPV
CRP, serum >2 mg%	1	62.5, 98.3
CSF glucose >52 mg%	1	57.1, 7.3
CSF protein >100 mg%	1	100, 88.7
Total score	3	

PPV, positive predictive value; NPV, negative predictive value; CRP, C-reactive protein; CSF, cerebrospinal fluid.
(Reproduced with permission from De Cauwer et al. (2007).)

Table 3.8

Frequencies of patients meeting the different scores for the bacterial meningitis score

Score	Viral meningitis (number of patients)	Bacterial meningitis (number of patients)
0	54	0
1	12	7
2	4	6
3	0	8
Total patients	71	21

use of LP and empirical antibiotic treatment in children with meningeal signs, which was subsequently validated (Oostenbrink et al., 2004). The original study evaluated 360 children aged 1 month to 15 years with meningeal signs, and logistic regression analysis was utilized to identify predictors for bacterial meningitis, which are shown in Table 3.9. The authors concluded that children with a score of 9.5 or more should undergo LP (Oostenbrink et al., 2001). The authors then prospectively validated their study among 226 children in four Dutch hospitals (Oostenbrink et al., 2004). Using the same score of 9.5 on the validation set resulted in missing two children with bacterial meningitis, both of whom had a score of 8.5. The authors then adjusted the original threshold for the indication of an LP from 9.5 to 8.5, and applied it to the entire study population of 586 children (360 from the derivation set and 226 from the validation set). None of the 205 children with a score of less than 8.5 points had bacterial meningitis; 13% with a score of 8.5–14.9 had meningitis; 52% with a score of 15.0–19.9 had meningitis, and 87% with a score of greater than 20.0 had meningitis (Oostenbrink et al., 2004).

Table 3.9

Oostenbrink clinical scoring algorithm

Risk factor	Points
Duration of main problem in patient history	1.0/day (maximum 10)
Vomiting in history	2.0
Physical examination findings	
Meningeal irritation	7.5
Cyanosis	6.5
Petechiae	4
Disturbed consciousness	8
Serum C-reactive protein (mg/l)	
<5.0	0
5.0–9.9	0.5
100–149	1.0
150–199	1.5
>200	2.0
Total clinical risk score	_____

SUMMARY

Examination of the CSF is the gold standard for the diagnosis of meningitis. There are a number of laboratory tests, in addition to CSF cell count, glucose concentration, Gram's stain, and bacterial culture, that are useful in identifying the organism and in differentiating between bacterial and viral meningitis. These laboratory tests can be used in combination with the clinical presentation to determine which patient should be treated for bacterial meningitis while awaiting the result of CSF Gram's stain and bacterial culture.

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Chapter 4

Bacterial meningitis

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INTRODUCTION

Bacterial meningitis is initially an acute purulent infection of the meninges and subarachnoid space. It is a complex disorder in which injury is caused, in part, by the causative organism, and in part, by the host's own inflammatory response. The inflammatory reaction involves the meninges, the subarachnoid space, the brain parenchyma, and the cerebral arteries and veins. The incidence of bacterial meningitis is estimated at 5–10 cases per 100,000 persons per year (van de Beek et al., 2004, 2006a). There are approximately 25,000 cases of bacterial meningitis annually in the USA. This disease is more common in developing countries. In the meningitis belt of Africa, a region that extends from Ethiopia in the east to Senegal in the west, there are outbreaks of bacterial meningitis every 8–12 years with attack rates of 500–1000 cases per 100,000 persons. In 1996, 152,813 cases were reported to the World Health Organization with 15,783 deaths (Rosenstein et al., 2001).

Bacterial meningitis is a neurological emergency that requires prompt recognition and initiation of therapy.

ETIOLOGY

The most common organisms that cause meningitis are bacteria with a polysaccharide capsule. The host's initial response to a bacterial infection is to mount an antibody response. The inability to develop sufficient concentrations of antibody to the capsular polysaccharide results in invasive disease. Patients with defective humoral immunity are unable to mount an antibody response to a bacterial infection, and they are therefore unable to control infection caused by encapsulated bacteria. Young age, old age, and congenital or acquired immunodeficiency states are associated with antibody deficiency or dysfunction. Congenital or acquired splenic dysfunction, or complement deficiency or dysfunction, increases the risk of infections caused by polysaccharide-encapsulated pathogens (Overturf, 2003).

In neonates, the most common pathogens are group B streptococci (*Streptococcus agalactiae*), gram-negative bacilli (*Escherichia coli*, *Enterobacter* species, *Klebsiella pneumoniae*, *Citrobacter diversus*), and *Listeria monocytogenes* (Mulder and Zanen, 1984; Saez-Llorens and McCracken, 1990; Moreno et al., 1994; Synnott et al., 1994). Beyond the neonatal period, *S. pneumoniae* is the most common causative organism of community-acquired meningitis (Schuchat et al., 1997). In children and adolescents aged 2–18 years, *Neisseria meningitidis* and *Streptococcus pneumoniae* are the most common pathogens of bacterial meningitis. *L. monocytogenes* is the most common cause of bacterial meningitis in patients with defective cell-mediated immunity (i.e., hematological malignancy, pregnancy, organ transplantation, human immunodeficiency virus (HIV) infection, chronic corticosteroid therapy) (Armstrong and Wong, 1982; Brouwer et al., 2006). *L. monocytogenes* is an intracellular parasite, the eradication of which depends on an intact T-lymphocyte-macrophage system.

The development of vaccines has affected the etiology of meningitis. In 1986, *Haemophilus influenzae* was the most common cause of bacterial meningitis, followed by *S. pneumoniae* and *N. meningitidis* (Wenger et al., 1990). *H. influenzae* type b (Hib) was the leading cause of bacterial meningitis among children prior to the routine vaccination of all infants with the Hib conjugate vaccine. Hib continues to cause meningitis in older adults, and non-b *H. influenzae* is

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an emerging pathogen (Dworkin et al., 2007). The US Advisory Committee on Immunization Practices recommends immunization with a tetravalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine for all 11–18-year-olds (Snape et al., 2008). The vaccine does not contain serogroup B, which is responsible for one-third of cases of meningococcal disease (Gardner, 2006). Toddlers are immunized with the MenACWY vaccine beginning at age 2 months in the UK and in Canada (Snape et al., 2008). Serogroup A meningococcal disease is important in Africa and Asia and responsible for the largest epidemics of meningitis. Serogroups B and C cause the majority of cases in Europe and the USA, and serogroup Y meningococcal disease is increasing in the USA (Salzman and Rubin, 1996; Martin and Spratt, 1999; Rosenstein et al., 2001). Infants are also vaccinated with a 7-valent pneumococcal conjugate vaccine. Conjugate vaccines confer protection by inducing bactericidal antibodies against the capsular polysaccharide. The incidence of pneumococcal meningitis caused by serotypes in the vaccine has decreased with the use of the vaccine, but there is emergence of nonvaccine serotypes (specifically serotypes 19A, 22F, and 3B) (Hsu et al., 2009). Of 77 cases of pneumococcal meningitis in children between 2001 and 2004 reported from 20 US medical centers, 62% were due to nonvaccine serotypes (Nigrovic et al., 2008).

In nonindustrialized countries, such as sub-Saharan Africa, Hib and *S. pneumoniae* continue to cause bacteremia and meningitis in children (Berkley et al., 2005). There are epidemics of meningococcal disease in Saudia Arabia and sub-Saharan Africa (Gardner, 2006).

Underlying and associated conditions for pneumococcal meningitis include pneumonia, sinusitis, otitis, chronic illness (malignancy, diabetes mellitus, renal failure, alcoholism, chronic immunosuppressive therapy, liver disease), and asplenia (Kastenbauer and Pfister, 2003; Weisfelt et al., 2006a). *S. pneumoniae* is the most common cause of meningitis following traumatic head injury in association with the formation of a dural sinus fistula. Risk factors for meningococcal disease include crowded conditions where the risk of nasopharyngeal colonization is high (college dormitories, primary and secondary schools, and military barracks), concomitant upper-respiratory tract infection, asplenia, congenital or acquired deficiency in the terminal common complement pathway (C3 and C5 to C9), immunoglobulin deficiency, and active and passive smoking (Gardner, 2006). Risk factors for invasive *H. influenzae* disease include advanced age, chronic lung disease, and HIV infection (Schuchat and Messonnier, 2007).

Although *S. pneumoniae* is the most common causative organism of community-acquired meningitis, predisposing and associated conditions put the individual at risk for meningitis due to other organisms. Meningitis in patients with otitis, mastoiditis, or sinusitis may be due to *Streptococcus* spp., gram-negative anaerobes, *Staphylococcus aureus, Haemophilus* spp., or Enterobacteriaceae. Meningitis complicating endocarditis may be due to viridians streptococci, *S. aureus, Streptococcus bovis,* the HACEK group (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*), or enterococci. The most common organisms causing meningitis in a patient who has undergone a neurosurgical procedure, with the exception of a shunting procedure, are gram-negative bacilli and staphylococci. Coagulase-negative staphylococci and *Staphylococcus aureus* are the most common pathogens causing cerebrospinal fluid (CSF) shunt infections.

Recurrent bacterial meningitis occurs in patients with previous head trauma and a skull fracture or dural CSF leak, patients who have had a splenectomy, those with congenital defects such as meningomyelocele, and those with parameningeal foci of infection (Adriani et al., 2007).

PATHOGENESIS AND PATHOPHYSIOLOGY

The pathogenesis and pathophysiology of bacterial CNS infections are described in Chapter 1, and will be reviewed here as they pertain to the clinical features and management of bacterial meningitis.

Neisseria meningitidis is transmitted by direct contact with large-droplet respiratory secretions and initially colonizes the nasopharynx. There is a short time interval of 10 days or less between the acquisition of the organism and clinical infection (Gardner, 2006). Seventy percent of secondary household cases occur within the first week of the index case. Following colonization of the nasopharynx, the meningococci penetrate the mucosal barriers and enter the bloodstream (Salzman and Rubin, 1996). *Streptococcus pneumoniae* also initially colonizes the nasopharynx. The most important antecedent illnesses for pneumococcal meningitis are pneumonia, acute otitis media, and acute sinusitis.

Host defense against invasive meningococcal and pneumococcal disease depends on the presence of serum bactericidal antibodies and an intact complement system.

Listeria monocytogenes infection is typically acquired by foodborne transmission from coleslaw,

raw vegetables, processed meats, unpasteurized milk, and soft cheeses (Brouwer et al., 2006). The neonate becomes infected from the mother's genitourinary tract, and meningitis in the newborn is usually associated with sepsis.

Bacteria in the bloodstream can gain access to the CSF through the choroid plexus of the lateral ventricles. The multiplication and lysis of bacteria in the subarachnoid space leads to the release of bacterial cell wall components, such as peptidoglycan and lipopolysaccharide, that induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, ependymal cells, and white blood cells in the CSF space. The inflammatory cytokines that have been most extensively studied in bacterial meningitis are interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α). A number of pathophysiological consequences result from the presence of the inflammatory cytokines in CSF. TNF-α and IL-1β act synergistically to alter the permeability of the blood–brain barrier. The alteration in blood–brain barrier permeability during bacterial meningitis results in vasogenic cerebral edema and allows leakage of serum proteins and other molecules into the CSF, contributing to the formation of a purulent exudate in the subarachnoid space. The purulent exudate obstructs the flow of CSF through the ventricular system and diminishes the resorptive capacity of the arachnoid granulations in the dural sinuses. This leads to obstructive and communicating hydrocephalus and interstitial edema. The exudate also surrounds and encases the cranial nerves and narrows the diameter of the lumen of the large arteries at the base of the brain, and inflammatory cells infiltrate the arterial wall (vasculitis). This, in combination with the alterations in cerebral blood flow that occur in this infection, results in cerebral ischemia, focal neurological deficits, and stroke. Cerebral blood flow is initially increased and then decreases due to a loss of autoregulation. Systemic hypotension due to septic shock can lead to global cerebral hypoperfusion. Vasculitis causes areas of focal hypoperfusion and ischemic infarction. Cerebral ischemia resulting from alterations in cerebral blood flow causes cytotoxic edema. The combination of interstitial, vasogenic, and cytotoxic edema leads to raised intracranial pressure and coma. In addition, bacteria and the inflammatory cytokines induce the production of excitatory amino acids, reactive oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that induce massive apoptosis of brain cells, especially in the dentate gyrus of the hippocampus.

GENETICS

Genetic factors are major determinants of susceptibility to infectious diseases. All individuals have single-base pair alterations (single-nucleotide polymorphisms) in genes controlling the host response to microbes. In sepsis, identified alterations include single-nucleotide polymorphisms in TNF receptors, IL-1 receptors, Fcγ receptors, and Toll-like receptors. Extreme phenotype studies have identified genetic correlates of increased susceptibility in the complement system and the signaling cascade following Toll-like receptor and IL-1 receptor activation (Brouwer et al., 2009). These polymorphisms are rare in the normal population but are associated with a substantial increase in susceptibility. Particular subgroups of patients with a genetic predisposition to more severe illness, potentially mediated through their innate immune response, are possible and further work in this area may help design rationale adjunctive therapy (van de Beek and de Gans, 2006).

CLINICAL MANIFESTATIONS

Neonates

The signs of meningitis in the neonate are nonspecific and include irritability, lethargy, poor feeding, vomiting, diarrhea, temperature instability (fever or hypothermia), respiratory distress, apnea, and seizures (Saez-Llorens and McCracken, 1990). Newborns may have a bulging fontanel, but the classic sign of meningeal irritation, nuchal rigidity, is rarely present in the newborn with meningitis (Volpe, 1987; Saez-Llorens and McCracken, 1990).

Children

The possibility of bacterial meningitis should be considered in every child with fever, vomiting, photophobia, lethargy, or an altered mental status and signs of meningeal irritation. Fever (≥38.5°C) is present in 80–94% of children with bacterial meningitis (Gururaj et al., 1973; Valmari et al., 1987).

The presentation of meningitis in children is either that of a subacute infection or an acute fulminant illness. Children with a subacute presentation have fever, lethargy, and nuchal rigidity that progresses over one to several days and that is often preceded by an upper-respiratory tract infection or an otitis media (Klein et al., 1986). Children with meningitis may also present with an illness that has been progressive over 24–72 hours or a fulminant illness that develops over several hours.

Once meningococci have invaded the bloodstream, clinical disease may present as a meningococcemia or meningitis. The most common initial symptoms of

infection are fever, chills, malaise, nausea, vomiting, and headache. Petechial or maculopapular lesions are present in approximately 50–60% of patients and may be the first sign of meningococcemia. *N. meningitidis* can be isolated from blood cultures in 75% of patients, but meningococcal sepsis occurs in only 5–20% of patients (Rosenstein et al., 2001; Heckenberg et al., 2008). Patients may present with meningococcal meningitis without meningococcemia; as such, the characteristic rash of meningococcemia may not be part of the presentation (Salzman and Rubin, 1996).

Nuchal rigidity may be absent early in the course of the illness: therefore the absence of nuchal rigidity should not exclude the diagnosis of bacterial meningitis (Valmari et al., 1987). Nuchal rigidity is present when there is resistance to passive flexion of the neck. Brudzinski's sign is positive when passive flexion of the neck results in flexion of the hips and knees. Both Brudzinski's sign and Kernig's sign are typically performed with the patient in the supine position. To examine the patient for Kernig's sign, the thigh is flexed on the abdomen, with the knee flexed; the leg is then passively extended. When meningeal inflammation is present, the patient resists leg extension. Nuchal rigidity and Brudzinski's and Kernig's sign are observed in fewer than 50% of children with bacterial meningitis.

Adults

The majority of adults with community-acquired bacterial meningitis present with at least two of the following four symptoms: headache, fever, nuchal rigidity, and altered mental status (van de Beek et al., 2004). In one series of 352 episodes of community-acquired pneumococcal meningitis in patients 16 years of age and older, the triad of fever, neck stiffness, and altered mental status was present in 59% (206 of 352) (Weisfelt et al., 2006a). In a prospective study of 297 adults with suspected meningitis, Kernig's sign and Brudzinski's sign had a poor sensitivity (5%) but a high specificity (95%) in patients with a CSF pleocytosis of $\geq$6 white blood cells/μl (Thomas et al., 2002). Eighty of 297 patients had a CSF pleocytosis, but only 24 had nuchal rigidity (sensitivity 30%). Nuchal rigidity was absent in 148 of the 217 patients without a CSF pleocytosis (specificity 68%). The major limitation of this study was that only 18 patients had microbiological evidence of infection: three patients had bacterial meningitis, nine had viral meningitis, and six had fungal meningitis. It should be emphasized that fever (present in 95%), headache, stiff neck, or an altered level of consciousness will be present in nearly every patient with bacterial meningitis (Durand et al., 1993; van de Beek et al., 2004). In the Dutch Meningitis Cohort Study, 246 of 258 patients (98%) with CSF culture-proven meningococcal meningitis had two of the four signs (fever, stiff neck, altered level of consciousness, and headache) (Heckenberg et al., 2008). Symptoms of fever, headache, photophobia, nausea, and vomiting, even in the absence of stiff neck, should raise a suspicion of meningitis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the triad of fever, headache, and stiff neck is bacterial or viral meningitis, fungal meningitis, tuberculous meningitis, drug-induced aseptic meningitis, carcinomatous or lymphomatous meningitis, aseptic meningitis associated with inflammatory diseases (systemic lupus erythematosus, sarcoidosis, Sjögren's syndrome), and when the temperature is normal or only moderately raised and the onset of headache is acute, subarachnoid hemorrhage (Schut et al., 2008). When impaired consciousness, focal neurological deficits, or new-onset seizures are added to the classic triad, the differential diagnosis includes viral encephalitis, intracranial venous thrombosis, tick-borne bacterial infections (depending on geography: *Borrelia* and *Ehrlichia* infections in North America and Europe, Rocky Mountain spotted fever in North America), brain abscess, and subdural empyema. The differential diagnosis in HIV-infected patients who present with meningeal signs includes meningitis caused by *Cryptococcus neoformans*, *Mycobacterium tuberculosis,* and *Treponema pallidum*. Focal brain lesions with mass effect and edema are most commonly caused by *Toxoplasma gondii*, primary central nervous system lymphoma, and *M. tuberculosis*. Patients with tuberculous meningitis tend to have a longer duration of illness (>6 days), frequently have an abnormal chest radiograph, and often have a lymphocytic CSF with a low glucose concentration. The search for acid fast bacilli in the CSF requires diligence and time.

DIAGNOSIS AND MANAGEMENT

Given the high mortality of acute bacterial meningitis, starting treatment and completing the diagnostic process should be carried out simultaneously in most cases. The first step is to evaluate vital functions and obtain two sets of blood cultures, which typically should not take more than 1–2 minutes, and send C-reactive protein and serum procalcitonin if available. At the same time, the severity of the patient's condition and the level of suspicion for the presence of bacterial meningitis should be determined. Timing is

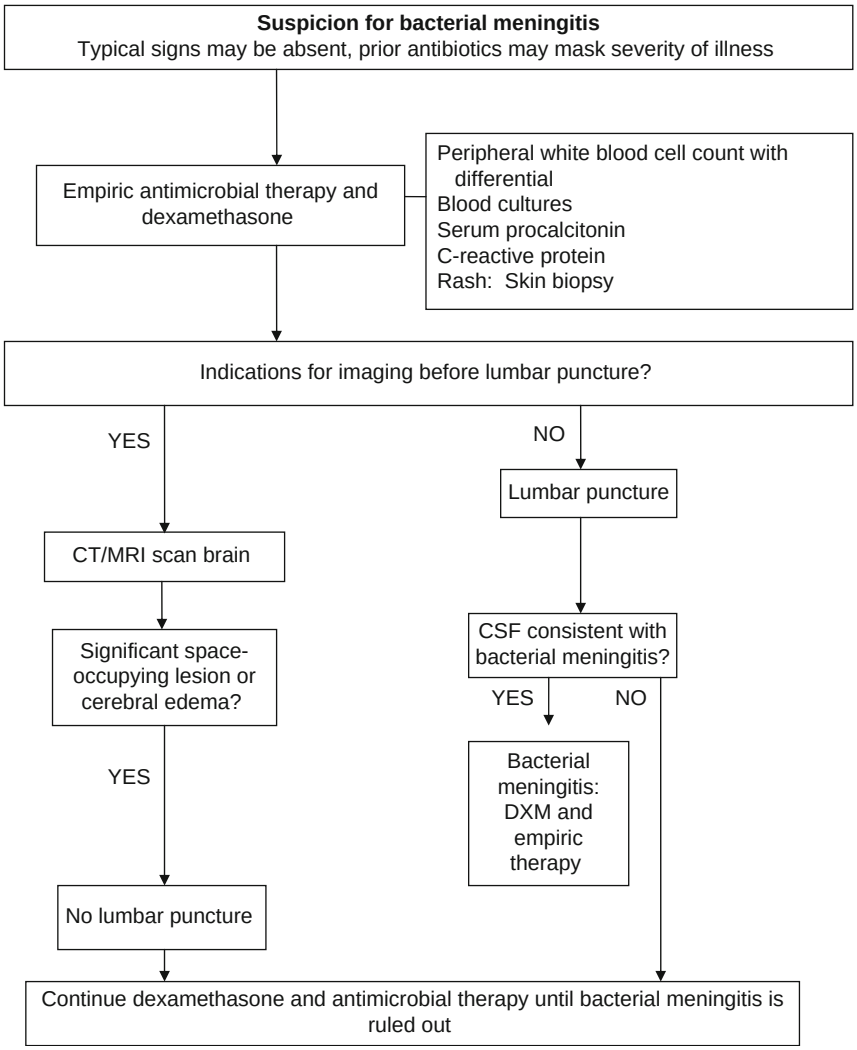

Fig. 4.1. Algorithm for the management of a patient with suspected bacterial meningitis. See Table 4.1 for indications for neuroimaging prior to lumbar puncture. PCR, polymerase chain reaction; CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; DXM, dexamethasone.

critical: the first step in the management of acute bacterial meningitis is to obtain blood cultures and start antimicrobial therapy and adjunctive dexamethasone when indicated (Fig. 4.1).

Recommendations for cranial computed tomography (CT) and fears of herniation are based on the observed clinical deterioration of a few patients in the several to many hours after lumbar puncture and the perceived temporal relationship of lumbar puncture and herniation, but proving a cause-and-effect association is very difficult based on the available data (Fitch and van de Beek, 2007). Therefore, it is reasonable to proceed with lumbar puncture without a CT scan if the following are not present: new-onset seizures, signs that are suspicious for space-occupying lesions (papilledema or focal neurological signs – not including cranial nerve palsy), or moderate to severe impairment of consciousness. A CT scan should also be obtained prior to lumbar puncture in the patient with an immunocompromised state. Other contraindications to lumbar puncture include local skin sepsis at the site of puncture, a clinically unstable patient, and signs suggestive of spinal cord compression. Lumbar puncture may also be harmful in patients with coagulopathy, because of the chance of needle-induced subarachnoid hemorrhage or of the development of spinal subdural and epidural hematomas. Contraindications for (immediate) lumbar puncture are provided in Table 4.1. In patients with suspected bacterial meningitis who are CT-scanned before lumbar puncture, initial therapy consisting of adjunctive dexamethasone (10 mg intravenously in adults) and empirical antimicrobial therapy should always be started without delay, even before sending the patient to the CT scanner.

Table 4.1

Contraindications for immediate lumbar puncture

Obtain neuroimaging prior to lumbar puncture if any of the following is present:
- Altered level of consciousness
- Focal neurological signs, not including cranial nerve palsy
- Papilledema
- Immunocompromised state
- New-onset seizures

Other contraindications for lumbar puncture
- Skin infection at lumbar puncture site
- Septic shock
- Spinal cord compression
- Anticoagulant therapy or severe coagulopathy

Spinal fluid analysis

Frank turbidity of CSF instantly suggests bacterial meningitis. Microscopic examination of CSF for white cells, red cells, and organisms, the measurement of glucose and protein concentrations, and culture are important investigations in any case of possible meningitis. The CSF abnormalities characteristic of bacterial meningitis include an opening pressure >180 mmH_2O, a polymorphonuclear pleocytosis, a low glucose concentration, and an elevated protein concentration. The CSF should be examined promptly after it is obtained because white blood cells in the CSF begin to disintegrate after about 90 minutes. Normal CSF does not contain polymorphonuclear leukocytes; however, following centrifugation, an occasional polymorphonuclear leukocyte may be seen. A glucose concentration of <40 mg/dl occurs in approximately 58% of patients with bacterial meningitis. A normal CSF-to-serum glucose ratio is 0.6. A CSF-to-serum glucose ratio of less than 0.31 is seen in approximately 70% of patients with bacterial meningitis. Gram's stain is positive in identifying the organism in 60–90% of cases of bacterial meningitis (Marton and Gean, 1986). However, the probability of detecting bacteria on a Gram's stain specimen depends on the number of organisms present. Most smears will be positive when the CSF bacterial concentration is $>10^5$ colony-forming units (cfu)/ml. Only 25% of smears are positive when the bacterial concentration is 10^3 cfu/ml or less (Klein et al., 1986). Latex agglutination tests, which detect the antigens of common meningeal pathogens, are no longer routinely available or recommended for the rapid determination of the bacterial etiology of meningitis.

CSF polymerase chain reaction (PCR) assays have been developed to detect bacterial nucleic acid in CSF, and are now available for the detection of *N. meningitidis* and *Streptococcus pneumoniae*. There is also a 16S rRNA conserved-sequence broad-based bacterial PCR that has been developed. PCR will not replace culture as culture is critical for antimicrobial sensitivity testing. The availability of bacterial and enteroviral PCR will change the initial management of the patient with the classic triad of meningitis – fever, headache, and stiff neck – provided the results are available within a few hours. Given the uncertainty about the sensitivity and specificity of PCR, a positive or negative result will need to be interpreted in combination with the results of the CSF cell count and glucose concentration, and confirmed by Gram's stain and culture (bacteria), and culture or serology (enteroviruses). Table 4.2 provides a list of recommended tests on CSF for bacterial meningitis and the major infections in the differential diagnosis.

The CSF lactate concentration is, in general, nonspecific and the measurement of the CSF lactate concentration is not recommended for patients with suspected community-acquired bacterial meningitis. The CSF lactate concentration, however, does appear to be valuable for the diagnosis of bacterial meningitis

Table 4.2

Cerebrospinal fluid diagnostic studies for meningitis

Cell count with differential
Glucose and protein concentration

Stains and cultures
- Gram's stain and bacterial culture
- India ink and fungal culture
- Viral culture
- Acid-fast smear and *Mycobacterium tuberculosis* culture

Antigens
- Cryptococcal polysaccharide antigen
- *Histoplasma capsulatum* polysaccharide antigen

Polymerase chain reaction (PCR)
- Broad-range bacterial PCR
- Specific meningeal pathogen PCR
- Reverse transcriptase PCR for enteroviruses
- PCR for herpes simplex virus type 1 and 2
- PCR for West Nile virus
- PCR for Epstein–Barr virus
- PCR for varicella-zoster virus
- PCR for *M. tuberculosis*
- PCR for HIV RNA

Antibodies
- Herpes simplex virus (serum:CSF antibody ratio of $<20:1$)
- Varicella-zoster virus IgM, and IgG antibody index
- Arthropod-borne viruses (West Nile virus IgM)
- *Borrelia burgdorferi* antibody index
- *Coccidioides immitis* complement fixation antibody

HIV, human immunodeficiency virus; IgM, immunoglobulin M; RNA, ribonucleic acid.

in postoperative neurosurgical patients. In the postoperative neurosurgical patient, empiric antimicrobial therapy should be initiated if the CSF lactate concentration is $\geq$ 4.0 mmol/l (Tunkel et al., 2004).

The peripheral white blood cell count, C-reactive protein, and sedimentation rate are usually elevated in patients with bacterial meningitis, with the possible exception of immunosuppressed patients. Measurement of C-reactive protein may be helpful in patients with CSF findings consistent with meningitis, based on the data that a normal C-reactive protein has a high negative predictive value in the diagnosis of bacterial meningitis (Tunkel et al., 2004). Serum procalcitonin can be helpful in the differential diagnosis of meningitis due to either bacteria or viruses (Viallon et al., 1999) but is not routinely available. Procalcitonin is a polypeptide that increases in patients with severe bacterial infections. Elevated serum concentrations of procalcitonin can be used to differentiate between bacterial and viral meningitis in patients in whom the CSF Gram's stain is negative.

Gram's stain

N. meningitidis is a biscuit- or kidney-shaped gram-negative diplococcus. *S. pneumoniae* is a gram-positive lancet-shaped diplococcus which tends to associate in pairs rather than in short chains. *L. monocytogenes* is a gram-positive rod that may have the appearance in gram-stained preparations of a diphtheroid and be discounted by the laboratory as a contaminant. The organism may also be misidentified as *S. pneumoniae*. Group B streptococcus is a gram-positive diplococcus. *Staphylococcus aureus* is a gram-positive coccus.

ANTIMICROBIAL THERAPY

The initial management of the patient with suspected acute bacterial meningitis is empiric antimicrobial and adjunctive therapy begun immediately after obtaining blood for bacterial culture. Respiratory isolation for the first 24 hours of antimicrobial therapy is recommended only for patients with suspected meningococcal meningitis. Respiratory isolation is not required for patients with meningitis due to other bacteria. This determination can be made by CSF Gram's stain.

The choice of antibiotic for empirical therapy (that is, before the organism is known) is based on the possibility that a penicillin- and cephalosporin-resistant strain of *Streptococcus pneumoniae* is the causative organism, and on the patient's age and any associated conditions that may have predisposed to meningitis. Recommendations for empiric therapy of bacterial meningitis are listed in Table 4.3. Empiric therapy

Table 4.3

Recommendations for empiric antimicrobial therapy of bacterial meningitis

Predisposing condition	Bacterial pathogen	Antibiotic
Neonate	Group B streptococcus, *Escherichia coli* *Listeria monocytogenes*	Ampicillin plus cefotaxime or an aminoglycoside
Children and adults – community-acquired	*Streptococcus pneumoniae* and *Neisseria meningitidis*	Third- or fourth-generation cephalosporin plus vancomycin
Otitis, mastoiditis, sinusitis	*Streptococcus* spp., gram-negative bacilli, *Staphylococcus aureus, Haemophilus* spp	Third- or fourth-generation cephalosporin plus vancomycin plus meropenem or metronidazole
Adults over the age of 55	*Streptococcus pneumoniae,* gram-negative bacilli, *Neisseria meningitidis, Listeria monocytogenes, Haemophilus influenzae*	Third- or fourth-generation cephalosporin plus vancomycin plus ampiciilin
Endocarditis	Viridans streptococci, *Staphylococcus aureus, Streptococcus bovis,* HACEK group, enterococci	Third- or fourth-generation cephalosporin plus vancomycin
Immunosuppressed	*Streptococcus pneumoniae, Listeria monocytogenes, Haemophilus influenzae*	Third- or fourth-generation cephalosporin plus vancomycin plus ampicillin
Postneurosurgical	Staphylococci, gram-negative bacilli	Vancomycin plus meropenem or vancomycin plus ceftazidime
Intraventricular device	Staphylococci, gram-negative bacilli	Vancomycin plus meropenem or vancomycin plus ceftazidime

HACEK, *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*. Appropriate third-generation cephalosporins are cefotaxime and ceftriaxone.

of bacterial meningitis in neonates <1 month of age should include a combination of ampicillin and cefotaxime. Empiric therapy in infants older than 1 month of age, children, and adults up to the age of 55 should be based on the possibility that penicillin and cephalosporin-resistant pneumococci are the causative organisms of the meningitis, and include a third- or fourth-generation cephalosporin, either ceftriaxone (pediatric dose 100 mg/kg/day in a 12-hour dosing interval; adult dose 2 grams every 12 hours) or cefepime (pediatric dose 150 mg/kg/day in an 8-hour dosing interval; adult dose 2 grams every 8 hours) plus vancomycin (pediatric dose 40–60 mg/kg/day in a 6- or 12-hour dosing interval; adult dose 45–60 mg/kg/day in an 8-hour dosing interval). Ampicillin should be added to the empiric regimen for coverage of *L. monocytogenes* in individuals over the age of 55 years, and in individuals with impaired cell-mediated immunity due to a chronic illness, organ transplantation, pregnancy, acquired immunodeficiency syndrome (AIDS), malignancy, or immunosuppressive therapy, if they have not been on trimethoprim-sulfamethoxazole prophylactic therapy. Gentamicin is added to ampicillin in critically ill patients with *L. monocytogenes* meningitis. Empiric therapy is modified for pre-existing or associated conditions as recommended in Table 4.3. Prior to or with the first dose of antibiotic, dexamethasone (infants and children 2 months of age and older: 0.15 mg/kg of body weight intravenously every 6 hours for 2–4 days; adults 10 mg intravenously every 6 hours for 4 days) should be administered. Dexamethasone is administered either 15–20 minutes before the first dose of an antimicrobial agent or with the first dose of an antimicrobial agent. Adjunctive therapy with dexamethasone before or with the first dose of antimicrobial therapy improves the outcome and reduces mortality in adults with acute community-acquired bacterial meningitis (Girgis et al., 1989; de Gans and van de Beek, 2002; van de Beek et al., 2007a).

Empiric therapy in the postneurosurgery patient should include a combination of vancomycin plus meropenem or vancomycin plus ceftazidime.

In countries with very low rates of pneumococcal penicillin resistance (such as the Netherlands), penicillin can still be used safely as a first-line agent (van de Beek et al., 2002a). In the UK, the addition of vancomycin is also not considered necessary and is not recommended unless the patient presents from one of the geographic regions associated with high-level ceftriaxone resistance, such as Spain, Southern Africa, and the USA (Schut et al., 2008).

In patients in whom herpes simplex virus encephalitis is suspected, acyclovir 10 mg/kg every 8 hours is added to the empiric regimen. Doxycycline 100 mg every 12 hours can be added to the empiric regimen during tick season if tickborne bacterial infections are suspected. Doxycycline is relatively contraindicated in pregnant and lactating women and in children younger than 8 years of age.

Once the bacterial pathogen is isolated and the sensitivity of the organism to the antibiotics is confirmed by *in vitro* testing, antimicrobial therapy is modified accordingly. Table 4.4 lists the recommended antibiotic therapy based on meningeal pathogen and Table 4.5 lists the recommended dose.

Table 4.4

Recommendations for specific antibiotic therapy in bacterial meningitis

Microorganism	Antibiotic
Streptococcus pneumoniae	
Penicillin-susceptible (MIC <0.1 mg/l)	Penicillin G or ceftriaxone (or cefotaxime or cefepime)
Penicillin-intermediately susceptible (MIC 0.1–1.0 mg/l)	Ceftriaxone (or cefotaxime or cefepime or meropenem)
Penicillin-resistant (MIC >1 mg/l) or Cefotaxime or ceftriaxone (MIC ≥1 mg/l)	Cefepime (or cefotaxime or ceftriaxone) plus **vancomycin**
Neisseria meningitidis	**Penicillin G or ampicillin** Ceftriaxone or cefotaxime for penicillin-resistant strains
Listeria monocytogenes	**Ampicillin** Ampicillin plus gentamicin (see text)
Streptococcus agalactiae (group B streptococci)	**Ampicillin** or penicillin G or Cefotaxime
Escherichia coli and other Enterobacteriaceae	**Ceftriaxone or cefotaxime or cefepime**
Pseudomonas aeruginosa	**Ceftazidime** or Cefepime or **Meropenem**
Staphylococcus aureus	
Meticillin-susceptible	**Nafcillin or oxicillin**
Meticillin-resistant	**Vancomycin**
Staphylococcus epidermidis	**Vancomycin** or Linezolid
Haemophilus influenzae	**Ceftriaxone or cefotaxime or cefepime**

Recommended antimicrobial agents are in **bold**.
Maintain vancomycin serum trough concentrations of 15–20 mg/l.
MIC, minimum inhibitory concentration.

Table 4.5

Recommended doses for the antibiotics commonly used in the treatment of bacterial meningitis

Antibiotic agent	Total daily dosage (dosing interval in hours)
Ampicillin	Neonate: 150 mg/kg/day (q 8 hours) Infants and children: 300 mg/kg/day (q 6 hours) Adult: 12 g/day (q 4 hours)
Cefepime	Infants and children: 150 mg/kg/day (q 8 hours) Adult: 6 g/day (q 8 hours)
Cefotaxime	Neonate: 100–150 mg/kg/day (q 8–12 hours) Infants and children: 225–300 mg/kg/day (q 6–8 hours) Adult: 8–12 g/day (q 4–6 hours)
Ceftriaxone	Infants and children: 80–100 mg/kg/day (q 12 hours) Adult: 4 g/day (q 12 hours)
Gentamicin	Neonate: 5 mg/kg/day (q 12 hours) Infants and children: 7.5 mg/kg/day (q 8 hours) Adult: 5 mg/kg/day (q 8 hours)
Meropenem	Infants and children: 120 mg/kg/day (q 8 hours) Adult: 6 g/day (q 8 hours)
Nafcillin	Neonates: 75 mg/kg/day (q 8–12 hours) Infants and children: 200 mg/kg/day (q 6 hours) Adult: 9–12 g/day (q 4 hours)
Penicillin G	Neonates: 0.15–0.2 mU/kg/day (q 8–12 hours) Infants and children: 0.3 mU/kg/day (q 4 hours) Adult: 24 million units/day (q 4 hours)
Rifampin	Infants and children: 10–20 mg/kg/day (q 12–24 hours) Adults: 600–1200 mg/day (q 12 hours)
Vancomycin*	Neonates: 20–30 mg/kg/day (q 8–12 hours) Infants and children: 40–60 mg/kg/day (q 6 hours) Adults: 45–60 mg/kg/day (q 6–12 hours)
Chemoprophylaxis	
Neisseria meningitidis	Rifampin 600 mg twice daily for 2 days or Ceftriaxone 250 mg intramuscular or Ciprofloxacin 500 mg orally

*Intraventricular vancomycin administration: children 10 mg/day, adults 20 mg/day.

The duration of therapy of bacterial meningoencephalitis is dependent on the meningeal pathogen. Bacterial meningitis due to *S. pneumoniae*, *H. influenzae*, and group B streptococci is usually treated with intravenous antibiotics for 10–14 days. Meningitis due to *N. meningitidis* is treated for 5–7 days. Meningitis due to *L. monocytogenes* or Enterobacteriaceae is treated for 3–4 weeks. Current recommendations are that all patients with pneumococcal meningitis have CSF re-examined 48 hours after antimicrobial therapy has been initiated if they have not had the appropriate clinical response to determine that the organism is being treated effectively.

Patients with clinically suspected meningococcal meningitis have to be isolated for the first 24 hours after initiation of antibiotic therapy. Chemoprophylaxis for meningococcal meningitis is recommended for every person who has had close contact with the index patient. Rifampin is recommended in a dose of 600 mg every 12 hours for 2 days for adults. A single dose of ciprofloxacin 500 mg is as effective as rifampin. Rifampin and ciprofloxacin should not be prescribed during pregnancy. Ciprofloxacin is not recommended for children and adolescents less than 18 years of age, or in selected counties of North Dakota and Minnesota because of reports of ciprofloxacin-resistant strains (Wu et al., 2009). Pregnant and lactating women and children under 2 years of age may be given intravenous or intramuscular ceftriaxone (a single injection of 250 mg for adults and 125 mg for children). If the index patient was treated with penicillin G, chemoprophylaxis with rifampin is recommended before discharge from the hospital.

MONITORING OF THE PATIENT AFTER ADMISSION

Patients who are diagnosed with acute bacterial meningitis are at risk for various neurological and systemic complications, and to detect them patients should be admitted to a critical care unit where the following should be monitored: vital signs (blood pressure, heart rate, respiratory rate, temperature), oxygen saturation, level of consciousness, presence or absence of focal neurological signs or symptoms, pupillary diameter, and certain laboratory parameters, including C-reactive protein, leukocyte count with differential, electrolytes, urea and creatinine (Schut et al., 2008). Analysis of arterial blood gases and measurement of serum lactate are important in patients in whom septic shock is suspected and the platelet count and coagulation tests are important in those in whom disseminated intravascular coagulation is suspected. Core body temperatures exceeding 40°C should be treated with antipyretic agents and cooling blankets if necessary to avoid excessive fluid loss (van de Beek et al., 2006b).

Systemic complications

Septic shock is an important predictor of poor outcome and may manifest in several ways: hypotension (systolic blood pressure <90 mmHg or a reduction of

>40 mmHg from baseline) despite adequate fluid resuscitation, tachycardia (>100 beats/min), tachypnea (>20 breaths/min), core body temperature >38°C or <36°C, drowsiness, and oliguria (Schut et al., 2008). Dyspnea, labored breathing, agitation, followed by progressive drowsiness, tachycardia, scattered crackles on pulmonary auscultation, and hypoxemia (as documented by arterial blood gas analysis) point to the diagnosis of adult respiratory distress syndrome.

Hyponatremia (serum sodium less than 135 meq/l) on admission is found in 30% of patients with culture-proven acute bacterial meningitis (Brouwer et al., 2007). Most episodes of hyponatremia resolve within a few days without specific treatment, and hyponatremia does not influence outcome. The cause of hyponatremia is unclear but may be from cerebral salt wasting, the syndrome of inappropriate antidiuretic hormone secretion (SIADH), or from too aggressive fluid resuscitation. Patients with bacterial meningitis who develop hyponatremia should not automatically be assumed to have SIADH and be fluid-restricted. Instead, the goal of fluid management should be to maintain a normovolemic state.

Hypernatremia occurs in 7% of patients with culture-proven bacterial meningitis (van de Beek et al., 2007b). Patients with sodium levels >146 meq/l (2% of patients) are more likely to have seizures before admission than those with lower levels. Hypernatremia is independently predictive of unfavorable outcome and mortality; however, it is unclear whether this is because it reflects severe disease or directly contributes to the poor outcome.

The coexistence of bacterial meningitis and arthritis has been described in several studies; it occurs in 7% of patients overall, more in meningococcal meningitis (12%: Weisfelt et al., 2006b). It is caused either by hematogenous bacterial seeding of joints (septic arthritis) or by immune-complex deposition in joints (immunomediated arthritis). The treatment of acute bacterial arthritis requires antibiotics and joint drainage.

Neurological complications

The most commonly recognized complications of meningitis are diffuse and focal brain edema, hydrocephalus, seizures, arterial and venous cerebrovascular complications (vasculitis with ischemia and stroke, intraparenchymal bleeding, subarachnoid hemorrhage, and venous sinus thrombosis), myelitis, cranial nerve palsies, and hearing loss (Kastenbauer and Pfister, 2003) (Figs 4.2 and 4.3).

Cerebrovascular complications may present as focal neurological deficits, seizures, or a deterioration in the level of consciousness. Cerebral infarction due to arterial occlusion complicates bacterial meningitis in 10–15% of patients, and venous infarction due to septic venous thrombosis occurs in 3–5% (Kastenbauer and Pfister, 2003; van de Beek et al., 2006a; Weisfelt et al., 2006c). Infarction of paramedian thalamic or brainstem nuclei due to septic arteritis of basal vessels or septic venous thrombosis may rarely cause coma and this devastating complication may develop late (approximately 10 days) in the course of treatment. Arteritis of small and medium-sized arteries and inflammatory involvement of veins are probably caused by tissue-destructive agents, such as oxidants and proteolytic enzymes, released by activated leukocytes. Treatment

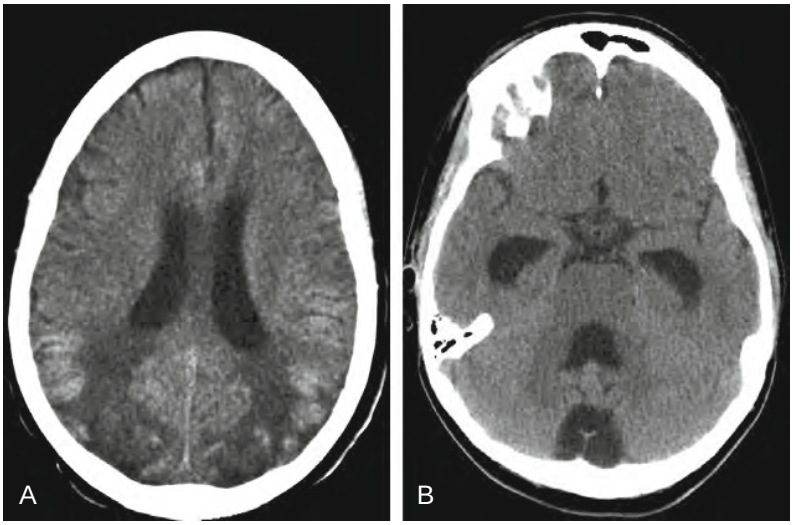

Fig. 4.2. Cranial computed tomography in bacterial meningitis. (A) Hypodensities in bilateral occipital areas due to edema. (B) Hydrocephalus with enlargement of the entire ventricular system.

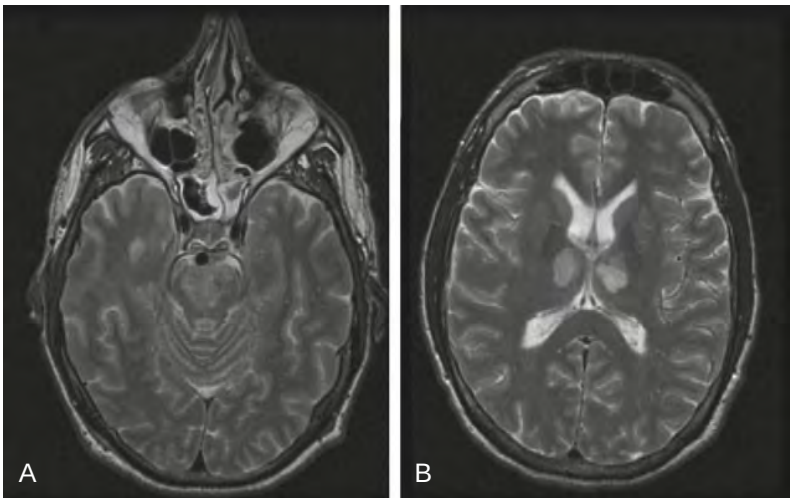

Fig. 4.3. Magnetic resonance imaging in patients with bacterial meningitis. (A) T2 proton density-weighted images showing hyperintense signal of the brainstem indicating edema. (B) T2 proton density-weighted image showing hyperintense signal of the thalami indicating edema due to bilateral infarctions.

is mainly supportive and these patients have a poor outcome (Schut et al., 2008).

Seizures occur frequently in patients with bacterial meningitis (Zoons et al., 2008). These patients tend to be older, are more likely to have focal abnormalities on brain CT and to have *S. pneumoniae* as the causative microorganism, and they have a higher mortality. The high mortality warrants a low threshold for starting antiepileptic therapy in those with clinical suspicion of seizures.

Cognitive impairment occurs frequently in adults who survive bacterial meningitis (van de Beek et al., 2002b). Over the years, patients tend to report fewer complaints, but the cognitive impairment does not seem to improve (Hoogman et al., 2007).

PROGNOSIS

Patients suspected of having bacterial meningitis should be treated with antimicrobial and adjunctive therapy as quickly as possible. A delay in administering antibiotics longer than 6 hours after arrival in the Emergency Room has been associated with increased mortality (Proulx et al., 2005). In a retrospective study on timing of antibiotic therapy and clinical outcome, the authors determined that the treatment of bacterial meningitis before it advances to a high level of clinical severity improves clinical outcome (Aronin et al., 1998). The authors of this study were able to determine arrival time in the Emergency Room, administration of the first dose of effective antibiotics, and prognostic stage on arrival in the Emergency Department and at the time of the administration of antimicrobial agents. There were 269 patients with community-acquired microbiologically proven bacterial meningitis. This study was conducted by the review of medical records between 1970 and 1995. Patients who arrived in the Emergency Department in stage I or II but advanced to stage III at the time of initial antibiotic therapy had significantly more adverse clinical outcomes than those who remained in the original prognostic stage. The authors concluded that treatment of bacterial meningitis before advancement of disease severity improves clinical outcome and should be the major therapeutic goal for physicians treating patients with bacterial meningitis (Aronin et al., 1998).

A risk score for unfavorable outcome based on initial presentation in adults with bacterial meningitis has been developed (Weisfelt et al., 2008). The risk score was developed to help physicians make decisions about the level of care (ward or intensive care unit), and to counsel family members. The authors caution that the risk score must not lead to a bias by the treating physician and that ultimately outcome is the result of the clinical course and therapeutic interventions. The risk score combines age with tachycardia (heart rate greater than 120 beats/min), low CSF leukocyte count (<1000 cells/mm^3), Glasgow Coma Scale, results of CSF Gram's stain, and cranial nerve palsies. Unfavorable outcome occurred in 34% of patients (237 of 696) and 21% died (143 of 696).

Recurrent bacterial meningitis

Recurrent bacterial meningitis occurs in 5% of community-acquired bacterial meningitis cases, and most patients have a predisposing condition, particularly head injury and CSF leak: only occasionally is there

impairment of humoral immunity (Adriani et al., 2007). In patients with no apparent cause of recurrent meningitis or known history of head trauma, the high prevalence of remote head injury and CSF leakage justifies an active search for anatomical defects and CSF leakage. Detection of β-2 transferrine in nasal discharge is a sensitive and specific method to confirm a CSF leak, and thin-slice CT of the skull base is best to detect small bone defects. It should be borne in mind however that the detection of a small bone defect does not prove CSF leakage. Surgical repair has a high chance of success with low mortality and morbidity.

SUMMARY

Bacterial meningitis is a neurological emergency. Empiric antimicrobial and adjunctive therapy should be initiated as soon as a single set of blood cultures has been obtained. Clinical signs suggestive of bacterial meningitis include fever, headache, meningismus, vomiting, photophobia, and an altered level of consciousness. The peripheral white blood cell count with a left shift, an elevated serum procalcitonin and C-reactive protein, and a CSF pleocytosis with a predominance of polymorphonuclear leukocytes, and a decreased glucose concentration are predictive of bacterial meningitis. Patients with documented bacterial meningitis and those in whom the diagnosis is a strong possibility should be admitted to the intensive care unit. Timely recognition of bacterial meningitis and initiation of therapy are critical to outcome (Aronin et al., 1998; Miner et al., 2001; Proulx et al., 2005).

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Chapter 5

Brain abscess

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Brain abscess is a focal area of purulent exudate surrounded by a well-developed capsule in the brain parenchyma. Characteristics of brain abscesses vary widely due to the multitude of pathogens and the numerous means of inoculation of the brain. However, left untreated, a bacterial brain abscess is fatal (Calfee and Wispelwey, 2000). In 1893, Scottish surgeon Sir William MacEwen published his experiences with surgical treatment of patients with brain abscess (Canale, 1996). This led to a significant reduction in mortality as some patients were cured by drainage of the abscess. Development of antibiotics in the 1900s led to a further reduction of morbidity and mortality. The widespread use of diagnostic radiographic imaging and stereotactic brain biopsy has further reduced mortality to less than 10% in many case series over the last 30 years (Calfee and Wispelwey, 2000).

EPIDEMIOLOGY

Despite an increase in the incidence of brain abscess in developed nations, the disease remains relatively rare. Because of the rarity, no large epidemiological studies have been performed. Thus, the incidence and population distribution of bacterial brain abscesses can only be estimated from the few published case series. In the 1980s the annual incidence of bacterial brain abscess in the USA was estimated at 1500–2500 (Rosenblum et al., 1986; Mampalam and Rosenblum, 1991; Wispelwey et al., 1991). This correlates with an annual incidence of roughly one case in 100 000–150 000 individuals. Studies from the 1970s and earlier reported brain abscess in 0.18–1.3% of all autopsy cases (Nicolosi et al., 1991). The population of the USA in 1970 was roughly 208 million (US Bureau of the Census, 1973). There were approximately 1.92 million deaths in the USA in 1970 (National Center for Health Statistics, 2007). Based on autopsy data reporting abscesses in 0.18–1.3% of all autopsies, between 3400 and 25 000 brain abscesses would be expected in the USA in 1970 for an annual incidence of 1.6–12 cases per 100 000 persons.

A large retrospective epidemiological study of patients in Olmsted County, Minnesota, reported an incidence of 1.3 cases of brain abscess per 100 000 person-years. The study found 38 cases of intracranial abscess over a 47-year period (Nicolosi et al., 1991). This correlates with an annual incidence of roughly one brain abscess per 100 000 persons per year or 0.001% of the general population. Other studies report higher measured or estimated rates, which increased over time – thought to be due to better surveillance and detection with head computed tomography (CT) (Samson and Clark, 1973; Nielsen et al., 1982; Garvey, 1983; Chun et al., 1986; Duel et al., 1991). The number of cases diagnosed in the USA every year is about 1500–2500 (Mamelak et al., 1995), which is close to 1 in 100 000 incidence.

ETIOLOGY

Although the majority of bacterial brain abscesses are caused by a few species of bacteria, many bacteria have been reported to cause brain abscess. Because the predisposing risk factors for developing an abscess largely affect which organisms are isolated, determining the overall incidence of individual bacteria is difficult. Case series reviewing all causes of bacterial abscess report *Streptococcus* spp. as the most commonly isolated organisms from abscess material, blood cultures, or both (Gortvai et al., 1987; Calfee and Wispelwey, 2000; Lu et al., 2002; Kao et al., 2003; Roche et al., 2003; Hakan et al., 2006; Prasad et al., 2006; Tonon et al., 2006; Tseng et al., 2006; Carpenter et al., 2007;

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Lee et al., 2007). The most common *Streptococcus* species identified were the *S. milleri* group including *S. intermedius*, *S. constellatus*, and *S. anginosus*. *Staphylococcus aureus* was isolated frequently, especially in the subgroup of patients with abscess after trauma or neurosurgical procedure (Mathisen and Johnson, 1997; Calfee and Wispelwey, 2000; Lu et al., 2002; Carpenter et al., 2007; Saeed et al., 2007). The majority of isolates are aerobic organisms, but anaerobic bacteria were isolated in as many as 23% of patients with abscess (Hakan et al., 2006). The most common anaerobes isolated were *Peptostreptococcus* (Kao et al., 2003; Hakan et al., 2006), *Bacteroides*, and *Fusobacterium* (Calfee and Wispelwey, 2000; Lu et al., 2002; Kao et al., 2003; Prasad et al., 2006). In most series, multiple organisms were identified in 14–24% of patients in whom abscess material cultures were positive (Lu et al., 2002; Kao et al., 2003; Roche et al., 2003; Hakan et al., 2006; Prasad et al., 2006; Tseng et al., 2006; Lee et al., 2007). Abscesses arising from otogenic or mastoid origin are more likely to be mixed infections (Osenbach and Loftus, 1992; Lu et al., 2002). No organism is identified in the abscess material in 19–42% of patients and appears to be related to the empirical use of antibiotics before surgery (Mathisen and Johnson, 1997; Calfee and Wispelwey, 2000; Lu et al., 2002; Kao et al., 2003; Roche et al., 2003; Hakan et al., 2006; Prasad et al., 2006; Tonon et al., 2006; Tseng et al., 2006; Lee et al., 2007). A list of pathogens known to cause brain abscess is given in Table 5.1.

Table 5.1

Bacteria known to cause brain abscess

Aerobic bacteria	Gram-positive	Streptococci
		Streptococcus milleri group
		Streptococcus sanguis
		Streptococcus salivarius
		Streptococcus pneumoniae
		Other *Streptococcus* spp.
		Staphylococci
		Staphylococcus aureus
		Other *Staphylococcus* spp.
		Other gram-positives
		Arcanobacterium spp.
		Brevibacterium spp.
		Corynebacterium spp.
		Nocardia asteroides
	Gram-negative	Enterobacteriacae
		Escherichia coli
		Enterobacter cloacae
		Proteus spp.
		Salmonella typhimurium
		Other gram-negatives
		Eikenella spp.
		Haemophilus influenzae
		Haemophilus parainfluenzae
		Haemophilus paraphophilus
		Acinetobacter spp.
		Pseudomonas spp.
Anaerobic bacteria	Gram-positive	*Actinomyces* spp.
		Clostridium spp.
		Peptostreptococcus spp.
		Streptococcus spp.
	Gram-negative	*Bacteroides* spp.
		Fusobacterium spp.

PATHOGENESIS AND PATHOPHYSIOLOGY

A brain abscess is a focal area of purulent exudate surrounded by a well-developed capsule in the brain parenchyma. An abscess arises as an inflammatory response to a local infection of the brain, called cerebritis. The infection begins after inoculation of the brain, which requires breakdown of the blood–brain barrier. The best-described methods of inoculation are direct extension from a neighboring structure, hematogenous spread from a distant site, and direct inoculation from penetrating head trauma or neurosurgical procedures. The causative organism can be predicted if the mode of inoculation is known (Table 5.2) (Mathisen and Johnson, 1997; Ali et al., 2005). Brain abscess from any cause requires significant interruption of the normal defense of the brain and thus remains rare. Although abscesses have been described as complications of existing cerebral damage (Biller et al., 1985; Chen et al., 1995; Inamasu et al., 2002; Emmez et al., 2007; Tsai et al., 2008), the majority of cases occur in patients without existing brain lesions (Mathisen and Johnson, 1997). Additionally, most patients do not have an underlying systemic, hematological, or immune condition that would predispose them to cerebritis or abscess.

Extension from a neighboring structure requires either erosion through the cranial bones or retrograde transit through valveless emissary veins into the brain (Mathisen and Johnson, 1997). The initial infection may arise in the paranasal or mastoid sinuses, the middle ear, or the oral cavity. When the infection spreads from the middle ear or mastoid sinuses, the abscess usually forms in the temporal lobe or cerebellum and the most common pathogens are streptococci, Enterobacteriaceae, *Bacteroides* spp., *Haemophilus* spp., and *Pseudomonas aeruginosa*. Abscesses arising from the

Table 5.2

Abscess site and pathogen characterized by the source of infection

Source of infection	Site of abscess	Causative organism
Paranasal sinusitis	Frontal lobe	Aerobic streptococci (usually *Streptococcus milleri* group) Anaerobic streptococci *Staphylococcus* species *Haemophilus* species *Bacteroides* species *Fusobacterium* species
Otitis media	Temporal lobe, cerebellum	*Streptococcus* species *Haemophilus* species Enterobacteriaceae *Bacteroides* species *Pseudomonas aeruginosa*
Metastatic spread	Frequently multiple abscesses in multiple areas of the brain, any lobe may be involved	Depends on source: Endocarditis *Staphylococcus aureus* Viridans streptococci Urinary tract Enterobacteriaceae Pseudomonadaceae Intra-abdominal *Streptococcus* species Enterobacteriaceae Anaerobes Lung abscess *Streptococcus* species *Actinomyces* species *Fusobacterium* species
Penetrating trauma	At the site of trauma	*Staphylococcus aureus* *Clostridium* species Enterobacteriaceae
Postoperative	At the site of surgery	*Staphylococcus epidermidis* *Staphylococcus aureus* Enterobacteriaceae Pseudomonadaceae

paranasal sinuses and oral cavity occur in the frontal lobes and are most commonly caused by anaerobic and aerobic (usually *milleri* group) streptococci, *Bacteroides* spp., *Haemophilus* spp., *Fusobacterium* spp., and staphylococci. Although sinus and middle-ear infections are the most common cause of bacterial brain abscess, the incidence has declined with the routine treatment of sinusitis and otitis media. Dental infections have been thought to be a source of intracranial infections since Hollin et al. presented two cases in the 1960s (Hollin and Gross, 1964; Hollin et al., 1967). However, because of the high incidence of oral infections in adults (especially periodontal disease), a brain abscess in the setting of oral infection may have arisen from another source and other mechanisms for brain abscess formation should be considered (Corson et al., 2001; Mylonas et al., 2007). Abscesses forming after penetrating trauma or neurosurgical procedure arise at the site of the wound and are usually caused by *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci, Enterobacteriaceae, *Clostridium* spp., and *Pseudomonas* spp. (Gortvai et al., 1987; Mathisen and Johnson, 1997; Ali et al., 2005). Hematogenous spread of bacteria from distant sites is the least common cause of brain abscess, accounting for less than 10% of all brain abscesses (Roche et al., 2003; Carpenter et al., 2007). The most common sites of primary infection are cardiac, especially due to congenital heart disease (Yang, 1989; Park and Neches, 1993; Takeshita et al., 1997), intra-abdominal infections, osteomyelitis, urinary tract infections, and skin infections (Roche et al., 2003; Ali et al., 2005). About 20–30% of brain abscesses are idiopathic and no other site of infection is found (Mathisen and Johnson, 1997).

When bacteria gain access to the brain parenchyma, the ensuing infection will progress to cerebritis and abscess in a predictable manner regardless of the infecting organism. The progression can be grouped into four stages based on the radiographic findings, which correlate well with the pathological findings (Table 5.3) (Britt et al., 1981). In the early cerebritis stage (days 1–3), there is a focal area of edema and inflammation composed of polymorphonuclear leukocytes, plasma cells, lymphocytes, and macrophages. As the inflammation progresses, coagulative necrosis forms in the central core and grows rapidly. The margins of the inflammation are ill defined and there is no distinct evidence of capsule formation. By the late cerebritis stage (days 4–9), the necrotic center has reached its maximal size and a collection of macrophages and fibroblasts congregates around the border of the inflammation. There is a marked increase in vascular proliferation and the early signs of capsular formation are present. Fibroblasts and reticular fibers develop a thin wall around the necrotic core as the cerebritis progresses toward abscess formation. In the early abscess stage (days 10–14), the thin wall of reticular fibers develops into a mature collagen capsule and the inflammatory milieu consists mainly of fibroblasts and lipid-laden macrophages on the inner surface of the capsule. The inner core of necrosis is smaller in the abscess stage than in the cerebritis stages. Beyond day 14, the abscess has matured and the surrounding edema begins to regress. The mature abscess is characterized by an inner

Table 5.3

Pathological findings in the four stages of abscess formation

Stage	Pathological findings
Stage 1 (days 1–3)	Focal edema and inflammation composed of polymorphonuclear leukocytes, plasma cells, lymphocytes, and macrophages with or without coagulative necrosis in the central core; ill-defined margins without distinct evidence of capsule formation
Stage 2 (days 4–9)	Well-defined area of inflammation with a large necrotic core, surrounded by a collection of macrophages and fibroblasts; marked increase in vascular proliferation, and early signs of capsular formation
Stage 3 (days 10–14)	Smaller area of necrotic core surrounded by fibroblasts and lipid-laden macrophages and a mature collagen capsule
Stage 4 (beyond day 14)	Inner core of necrosis, surrounded by a layer of inflammatory cells inside a dense collagen capsule; marked gliosis and reactive astrocytes with decreasing edema

core of necrosis, surrounded by a layer of inflammatory cells inside a dense collagen capsule. Surrounding the capsule is a margin of marked gliosis with a large number of reactive astrocytes (Enzmann et al., 1979; Britt et al., 1981; Garvey, 1983; De Girolami et al., 1999; Tunkel, 2000; Nguyen et al., 2004; Ali et al., 2005).

CLINICAL FEATURES

The clinical presentation of a patient with a brain abscess varies greatly depending on the size, location, and number of abscesses. While a minority of patients will have focal neurological deficits, the majority of signs and symptoms are nonspecific. In a number of case series, headache was the most common symptom and reason for seeking medical attention, occurring in at least half of all patients and nearly all patients who can give a history (Mathisen and Johnson, 1997; Roche et al., 2003; Carpenter et al., 2007). Confusion or diminished level of consciousness is the second most common symptom at presentation and can occur in up to 50% of patients (Roche et al., 2003; Carpenter et al., 2007). Fever may not be present and is not reliable in making a diagnosis. Most series report about 50% of patients will have fever at presentation, though some series report fever in as few as 20% and other series in as many as 79% of patients (Chun et al., 1986; Grigoriadis and Gold, 1997; Lu et al., 2002; Kao et al., 2003; Roche et al., 2003; Hakan et al., 2006; Prasad et al., 2006; Tonon et al., 2006; Carpenter et al., 2007). Depending on the location of the abscess, seizures or focal neurological deficits are common signs. Nausea and vomiting are also frequent, especially in the setting of increased intracranial pressure (ICP). Other signs of elevated ICP, including papilledema and decreased level of consciousness, may also be present and would indicate an immediate need for medical attention. A variety of other nonspecific signs and symptoms, including malaise, meningismus, and photophobia, may be present in patients with brain abscess, but are rarely the presenting complaint (Roche et al., 2003; Carpenter et al., 2007).

DIAGNOSIS

Because the clinical features of patients with brain abscess are nonspecific, diagnosis is made primarily with neuroimaging. Before the routine use of CT, morbidity and mortality were significantly higher in operated and medically managed patients. Rosenblum et al. (1978) reported 44% mortality among 18 consecutive patients with brain abscess in the 4 years prior to routine use of CT and no mortality in the 20 consecutive patients who were diagnosed using CT. Other studies confirm the benefit of CT in improving outcomes (Miller et al., 1988; Tekkok and Erbengi, 1992). Prior to the routine use of brain imaging, diagnosis required suspicion of a focal intracerebral infectious process. Because the presenting signs and symptoms of brain abscess are often nonspecific, differentiating brain abscess from other central nervous system processes was difficult. Additionally, in the absence of focal neurological deficits, localization of the abscess would be difficult or impossible. The routine use of CT solved these problems, allowing for accurate diagnosis and localization of brain abscess. Furthermore, CT can identify multiple lesions and help to determine which patients are poor surgical candidates (Rosenblum et al., 1978).

Because CT scans can be obtained quickly and easily at most institutions, the brain CT is the imaging modality of choice for initial evaluation of suspected brain abscess. Brain CT may be less sensitive than brain magnetic resonance imaging (MRI) in detecting early cerebritis; however, most patients present more than 3 days after infection, thus increasing the yield on brain CT (Enzmann et al., 1979; Henson and Ferraro, 1993; Roche et al., 2003). In experimental models, brain abscesses follow a predictable pattern on brain CT. In the early stages of cerebritis (days 1–3 after inoculation), the infected portion of the brain appears as a hypodensity on unenhanced CT. Following the administration of intravenous contrast, there may be a faint, irregular, thin rim of enhancement surrounding the hypodensity. Delayed scans 30–60 minutes after the administration of intravenous contrast reveal diffusion of the contrast agent into the hypodense area of cerebritis. As the lesion progresses into the late cerebritis stage (days 4–9), the region of hypodensity grows and the area of enhancement reaches its maximum size. The enhancing rim is more prominent than in the early cerebritis stage, but remains irregularly shaped. Delayed scans continue to reveal diffusion of contrast into the hypodense area of cerebritis. Progression of the lesion into the abscess stages (Fig. 5.1) is characterized by a thicker, well-demarcated ring of enhancement around an isodense or hypodense center. The ring of enhancement is smaller in the abscess stage than in the cerebritis stages. Additionally, delayed scans do not show diffusion of contrast into the central area of necrosis (Enzmann et al., 1979; Britt et al., 1981).

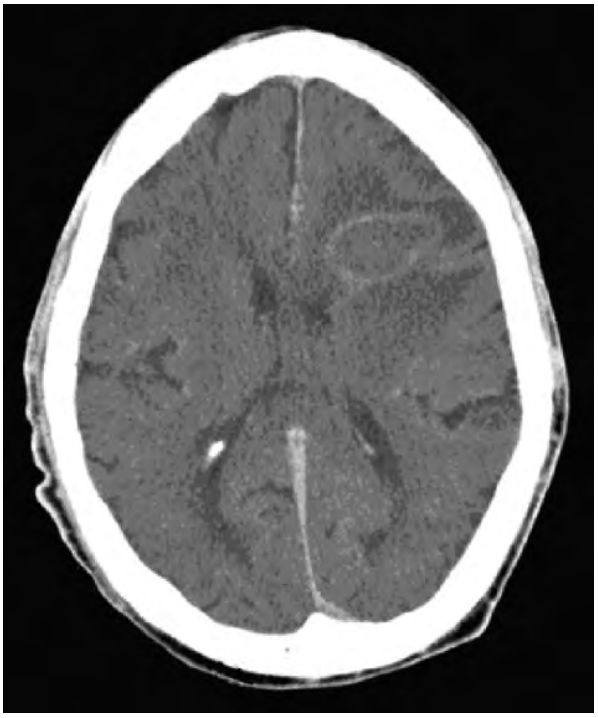

Fig. 5.1. Contrasted head computed tomography scan showing ring enhancement of a brain abscess with surrounding hypodense region of edema.

Though useful in early detection of brain abscess, brain CT imaging is not always diagnostic. Primary and metastatic neoplasms in the central nervous system have an appearance similar to brain abscess on contrasted brain CT. Although the clinical picture often helps to differentiate the two, brain abscesses are not uncommonly misdiagnosed as neoplasms based on the initial brain CT and clinical presentation (Mathisen and Johnson, 1997). Although some features may help predict a brain abscess, in one study investigators reported only 86% accuracy in differentiating the various causes of a ring-enhancing lesion on brain CT (Coulam et al., 1980).

MRI of the brain can supplement and potentially replace brain CT for the diagnosis of brain abscesses. Although still nonspecific in the first 1–2 days of infection, the multiple modalities of MRI can reliably stage cerebritis and abscess (Table 5.4) and can differentiate brain abscess from other intracranial pathologies such as infarct and neoplasm (Haimes et al., 1989). In the acute cerebritis stage, T1-weighted MRI reveals a hypointensity and T2-weighted MRI shows a hyperintensity in the region of the infected brain. In the late cerebritis stage, the lesion develops an iso- to hyperintense rim on T1-weighted imaging and iso- to hypointense rim on T2-weighted imaging. After administration of intravenous gadolinium, there is partial or complete enhancement of the rim on T1-weighted imaging with or without extension of the contrast into the central core of the lesion. There may also be patchy restriction on diffusion-weighted imaging (DWI) during the late cerebritis stage. As the cerebritis progresses to an abscess, the rim of enhancement becomes smaller and better circumscribed without extension into the central core (Figs 5.2–5.4). The restricted diffusion on DWI becomes uniform and involves the entire central core (Fig. 5.5).

Magnetic resonance spectroscopy may be helpful in confirming a diagnosis of brain abscess. A brain abscess has large amounts of lactate, but this is nonspecific and is found in necrotic brain tumors (Nguyen et al., 2004). Acetate is also seen in brain abscesses and appears to be more specific than lactate. The presence of acetate is not seen in necrotic brain tumors and indicates a bacterial infection (Kim et al., 1997; Martinez-Perez et al., 1997; Nguyen et al., 2004).

Though imaging techniques greatly aid in the diagnosis of bacterial brain abscesses, definitive diagnosis can be made only with a biopsy. Obtaining purulent

Table 5.4

Radiographic findings in cerebritis and abscess

Imaging modality	Early cerebritis	Late cerebritis	Early abscess	Late abscess
T1W MRI without contrast	Hypointense lesion	Hypointense central zone, iso- to hyperintense rim, hypointense edema		
T1W MRI with contrast	Nodular or no enhancement	Partial or complete enhancement of the rim with extension into the central zone	Thin, smooth, well-circumscribed rim of enhancement without extension into the central zone	Same as early abscess
T2W MRI	Hyperintense lesion	Iso- to hyperintense central zone, iso- to hypointense rim, hyperintense edema	Hyperintense central zone, hypointense rim, hyperintense edema	Loss of hypointense rim, otherwise same as early abscess
FLAIR MRI	Hyperintense lesion	Iso- to hyperintense central zone, iso- to hypointense rim, hyperintense edema	Hyperintense central zone, hypointense rim, hyperintense edema	Same as early abscess
DWI/ADC MRI	No restricted diffusion, possible T2 shine-through	Patchy restricted diffusion in the central zone with T2 shine-through	Uniform restricted diffusion in the central zone	Same as early abscess

T1W, T1-weighted; MRI, magnetic resonance imaging; T2W, T2-weighted; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

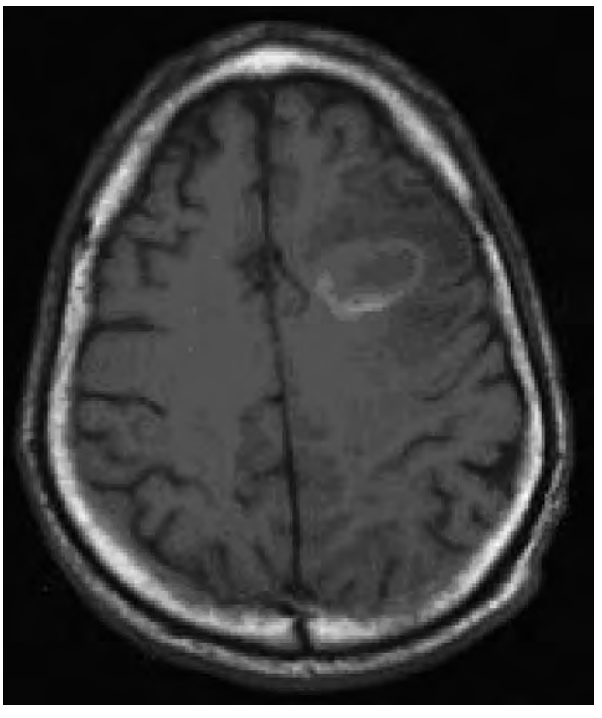

Fig. 5.2. Contrasted T1-weighted magnetic resonance imaging shows ring enhancement of the abscess and hypointense surrounding edema.

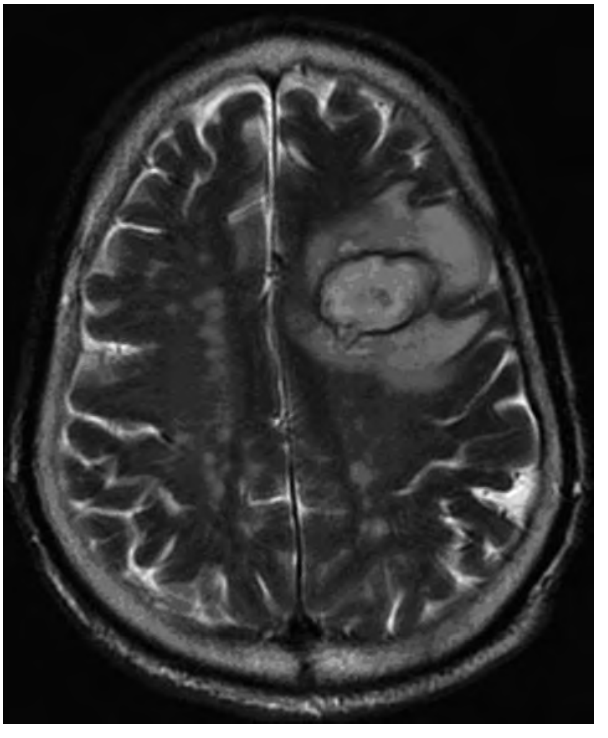

Fig. 5.3. T2-weighted magnetic resonance imaging of brain abscess shows a hyperintense necrotic core with a hypointense capsule, surrounded by hyperintense edema.

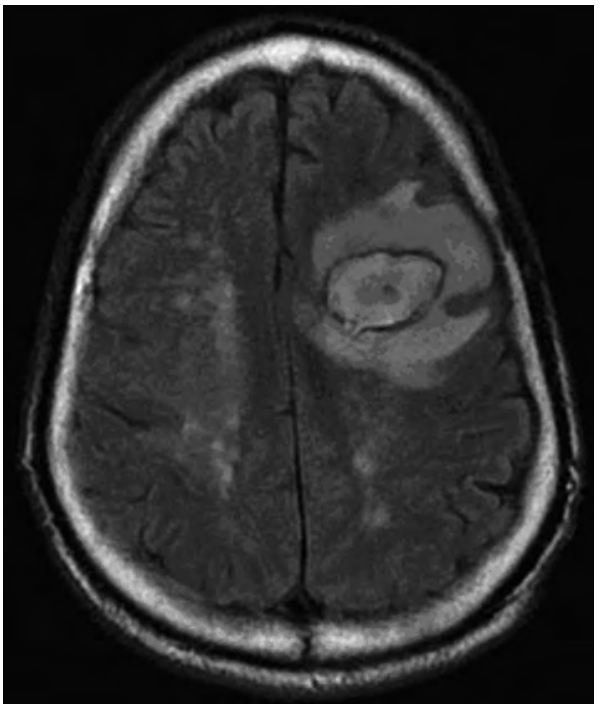

Fig. 5.4. Fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging of brain abscess shows a hyperintense necrotic core with a hypointense capsule, surrounded by hyperintense edema.

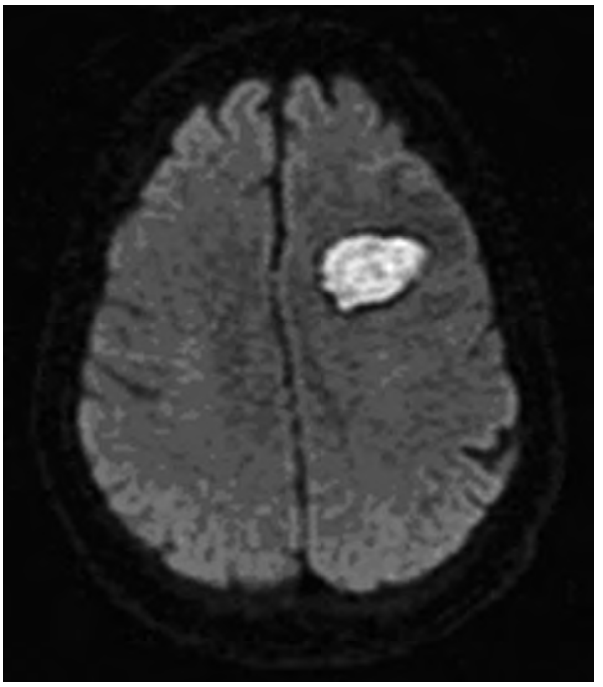

Fig. 5.5. Diffusion-weighted imaging (DWI) shows restricted diffusion in the necrotic core of the abscess.

material via needle aspiration or surgical excision confirms the diagnosis of abscess. Determining the cause of the abscess requires microbiological techniques. Culture and Gram's stain of the purulent material may reveal one or more pathogens causing the abscess. The ability of these tests to confirm a diagnosis in multiple recent case series was 58–81% (Calfee and Wispelwey, 2000; Lu et al., 2002; Kao et al., 2003; Roche et al., 2003; Hakan et al., 2006; Prasad et al., 2006; Tonon et al., 2006; Tseng et al., 2006; Lee et al., 2007), but approaches 100% in older series (de Louvois et al., 1977; Mathisen et al., 1984). Treating the patient with intravenous antibiotics appears to correlate with a lower diagnostic yield from culture and Gram's stain of the abscess material. Obtaining blood cultures or getting a culture of the abscess before initiating empirical antibiotic therapy will likely increase the chances of identifying the pathogen, which will enable the clinician to tailor the antibiotic regimen to the specific organism. Every attempt to make a definitive diagnosis should be made, but only if it can be done without significantly delaying antimicrobial therapy.

Other laboratory data, although supportive of an infectious process, are not helpful in making a diagnosis of bacterial brain abscess. The most common abnormalities in laboratory data include an elevated blood leukocyte count, elevated erythrocyte sedimentation rate, and elevated protein and leukocyte count in the spinal fluid. Spinal fluid may contribute to the diagnosis of a central nervous system infectious process, but is generally avoided as the risk of cerebral herniation outweighs the potential benefit (Chun et al., 1986). Furthermore, the combination of radiographic findings, neurosurgical intervention, and microbiological laboratory data obviates the need for a lumbar puncture.

MANAGEMENT

The initial approach to a brain abscess is CT-guided stereotactic aspiration of the abscess for Gram's stain, culture, and antimicrobial sensitivity testing immediately prior to the initiation of empiric antimicrobial therapy (Ali et al., 2005). In patients who are not good surgical candidates, or in patients where the abscess is located in deep or eloquent parts of the brain, empirical antibiotics are started and surgical aspiration is deferred (Rosenblum et al., 1980). When antibiotics and aspiration do not control the infection, excision of the abscess can be a definitive treatment. Excision is used only when less invasive techniques have failed because of the risk for permanent neurological deficit with surgery. Excision is contraindicated when the abscess is located in deep or eloquent parts of the brain.

Empiric antibiotics should be started after aspiration of the abscess or immediately at the time of diagnosis in patients who are not candidates for aspiration. Empiric therapy is based on predisposing and associated conditions, and location that predict the etiological organism (Tables 5.2 and 5.5). Sinusitis-associated abscesses are usually caused by streptococci and anaerobes, but can be caused by *Haemophilus* and *Staphylococcus* species as well. In sinusitis-associated abscesses, empirical antibiotics consist of metronidazole for anaerobic coverage and either penicillin G for streptococcal coverage or a third- or fourth-generation cephalosporin to cover both streptococci and *Haemophilus* species. Vancomycin is added if meticillin (formerly methicillin)-resistant *Staphylococcus aureus* is suspected. In otitis-associated abscesses, the most common causative organisms are streptococci, Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Bacteroides* spp. Empirical therapy of otitis-associated abscesses includes penicillin G for streptococci, metronidazole for *Bacteroides* species, a cephalosporin for Enterobacteriaceae, and either ceftazidime or meropenem if *Pseudomonas aeruginosa* is suspected. A brain abscess from penetrating head trauma is most commonly caused by *S. aureus*, *Clostridium* species, and Enterobacteriaceae. Empirical therapy of abscesses due to penetrating head trauma includes a third- or fourth-generation cephalosporin and vancomycin. A brain abscess that occurs as a complication of a neurosurgical procedure is usually caused by staphylococci, Enterobacteriaceae, or *Pseudomonas* species. Empirical antimicrobial therapy for an abscess complicating a neurosurgical procedure should include vancomycin and either meropenem or ceftazidime (Ali et al., 2005).

Once the causative microorganism is identified, the antibiotic regimen can be modified accordingly (Table 5.6). All antibiotics are given intravenously and should be continued for 6–8 weeks. A head CT or MRI should be performed at least every 2 weeks to follow the progress of treatment. If the abscess

Table 5.5

Empirical therapy for bacterial abscess and empyema

Population/etiology	Treatment
Unknown etiology	Third- or fourth-generation cephalosporin plus vancomycin plus metronidazole
Sinusitis-associated	Metronidazole plus either penicillin G or a third- or fourth-generation cephalosporin ± vancomycin*
Otitis-associated	Metronidazole plus penicillin G plus cephalosporin†
Penetrating head trauma	Third- or fourth-generation cephalosporin plus vancomycin
Postneurosurgery	Vancomycin plus meropenem or ceftazidime

*If meticillin-resistant *Staphylococcus aureus* is suspected.
†If *Pseudomonas aeruginosa* is suspected, use cefepime or meropenem.

Table 5.6

Antibiotics for specific bacteria in brain abscess or empyema (recommendations are in bold)

Pathogen	Antibiotic
Bacteroides fragilis	**Metronidazole 2000 mg/day (500 mg every 6 hours)**
Enterobacteriaceae (e.g. *Klebsiella, Escherichia coli, Proteus*)	**Ceftriaxone 4 g/day (2 g every 12 hours)** or **Cefotaxime 12 g/day (2 g every 4 hours)** or **Cefepime 6 g/day (2 g every 8 hours)** or Meropenem 6 g/day (2 g every 8 hours)
Haemophilus influenzae	**Ceftriaxone or cefotaxime**
Nocardia asteroides	**Trimethoprim-sulfamethoxazole 15–20 mg/kg/day of trimethoprim component (5–6.67 mg/kg every 8 hours)**
Pseudomonas aeruginosa	**Meropenem** or Cefepime or Ceftazidime 6 g/day (2 g every 8 hours)
Staphylococci	
Meticillin-susceptible	**Nafcillin or oxacillin 12 g/day (2 g every 4 hours)**
Meticillin-resistant	**Vancomycin 45–60 mg/kg/day IV (every 6–12 hours)**
Streptococcus spp.	**Penicillin G 20–24 million units/day (3–4 million units every 4 hours)** or **Ceftriaxone or cefotaxime or cefepime**

enlarges after 2 weeks of intravenous antibiotics or fails to decrease in size after 4 weeks of antibiotic treatment, further neurosurgical intervention is required (Kastenbauer, 2003). A brain abscess caused by *Nocardia asteroides* usually requires complete excision to obtain a cure, and 6–12 months of trimethoprim-sulfamethoxazole.

Corticosteroids can decrease antibiotic penetration into the abscess and slow the formation of the abscess wall, so they should be avoided if possible. In patients with increased ICP, mass effect, or significant edema, a short course of dexamethasone 10 mg every 6 hours for 3–7 days is recommended (Schroeder et al., 1987). An epileptogenic focus can develop in the area of the brain involved by the abscess. Seizures occur in approximately 50% of patients during the initial hospitalization and in 70–90% of patients after discharge (Mathisen and Johnson, 1997; Calfee and Wispelwey, 2000). Present recommendations are to treat all patients empirically with an antiepileptic medication (Mathisen and Johnson, 1997; Calfee and Wispelwey, 2000; Ali et al., 2005). There are insufficient data to determine the optimal duration of therapy. Certainly patients with a markedly abnormal electroencephalogram should continue treatment, potentially indefinitely (Mathisen and Johnson, 1997). Patients who have not had a seizure and who have a normal electroencephalogram several months after completion of antibiotic therapy may be candidates for slow weaning off antiepileptic medications (Mathisen and Johnson, 1997; Ali et al., 2005).

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Chapter 6

Cranial epidural abscess and subdural empyema

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INTRODUCTION

Intracranial epidural abscess and subdural empyema are relatively uncommon amongst neurological disorders. Although the actual incidence is not known, they are seen in association with particular circumstances. Familiarity with these syndromes, and how they differ from more common infectious conditions, such as meningitis, is essential for proper timely recognition and management. It is generally felt that the incidence of these conditions has declined, attributed to computed tomography (CT) and magnetic resonance imaging (MRI) and antibiotic therapies that allow for management of the predisposing conditions that can result in these infections.

EPIDEMIOLOGY

Cranial epidural abscess, as discussed below, is classically the consequence of frontal sinusitis with osteomyelitis of the frontal bone producing a visible swelling known as Pott's puffy tumor. Percivall Pott (1714–1788), a surgeon at St Bartholomew's Hospital, London, did much to develop neurosurgical treatments and influence the field by basing intervention on the changing status of the patient (Flamm, 1992; Tattersall and Tattersall, 2002). A few eponymous diseases persist in the modern medical era, including Pott's puffy tumor and Pott's disease (osteomyelitis of the spine with spinal cord compression). Pott advocated early trephination of the "puffy tumor," recognizing it was a collection of "matter" (as opposed to blood) that may be relieved or prevented. This was surgically sound reasoning, even though Pott did not fully appreciate the infectious nature of this condition or spinal osteomyelitis in the era before bacteriology (Flamm, 1992).

The frequency of epidural infections is difficult to determine accurately. Navendra Nathoo and colleagues, at their referral center in Durban, South Africa, serving an area of over 9 million people, have published their experience with these intracranial infections (Nathoo et al., 1999a,b). They found 82 cases of cranial epidural infection that would estimate the annual incidence at less than one per million (Nathoo et al., 1999b). In another series at a US community hospital, cranial epidural abscess constituted two of 31 cases (6%) of intracranial infection seen over a 7-year period (Harris et al., 1987). A review of publications from 1970 through 2005 shows an increase in the number of reported cases of epidural abscess, suggesting an increasing incidence (Kombogiorgas and Solkani, 2006). CT and MRI have certainly increased the ability to recognize this disease. It may also be that these uncommon cases are of significant clinical interest in the eyes of the treating physicians and are increasingly more often reported.

Cranial epidural abscess is more common in late childhood or adolescence with a mean age of 17 years (Singh et al., 1995; Nathoo et al., 1999b). The age range is from 1 month of age to late adulthood. Some of the adult cases are the result of immunocompromised states, but most are otherwise healthy adults.

Subdural empyema has a predilection for younger ages as well (Nathoo et al., 1999b; Hartman et al., 2004). Most cases are reported in patients 11–20 years of age, but subdural empyema can occur throughout life, with the underlying source related to the paranasal sinuses or otogenic in origin, as is the case for cranial epidural abscess. Meningitis can rarely be complicated by the occurrence of subdural empyema more often in children or the elderly (Nathoo et al., 1999b). In a prospective study of 86 patients with bacterial meningitis from 15 to 81 years of age, no cases of subdural empyema were reported. The age range for that study perhaps explains the absence of this complication (Pfister et al., 1993).

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In Nathoo's series, 699 cases of subdural empyema were evaluated at their center from 1983 through 1997 (Nathoo et al., 1999a). An estimate of incidence in that area would be one case per 193,000 people per year. According to the authors, this is in an area that has struggled with adverse socioeconomic conditions, and, until recently, a lack of resources for many people (Nathoo et al., 1999a). This presumably would result in a higher rate of disease if compared with more resource-rich areas. In comparison with a more common disease such as community-acquired bacterial meningitis, in a US study in a population of just over 10 million from 1985 to 1995, the annual incidence was 2.4 per 100,000 persons (Schuchat et al., 1997).

Interestingly, all of the space-occupying central nervous system infections (spinal epidural abscess, cranial epidural abscess, brain abscess, and subdural empyema) demonstrate a male:female ratio that ranges from 1.5 to 3.0:1.0 (Bok and Peter, 1993; Singh et al., 1995; Nathoo et al., 1999a; Hartman et al., 2004; Kastenbauer et al., 2004a,b). This is a remarkably consistent finding.

ETIOLOGY

Epidural abscess and subdural empyema develop as a logical consequence of the anatomic relationship of these spaces, and, of course, the infectious organisms. A brief review of these anatomic relationships is essential to an understanding of the pathogenesis and clinical presentation of these syndromes.

The cranial dura mater is a double-layered, densely packed, thick sheet of cells that lines the cranial cavity and is clinically referred to as the pachymeninges. The dura mater itself is relatively avascular and a naturally formidable barrier to infection. The skull also has its periosteal coverings, on the external surface (pericranium) and the internal surface (endocranium), respectively (Carpenter, 1991). It is erroneous to refer to the dura as distinct from the internal periosteum as it is so tightly adhered and inseparable (Smith, 1978). Therefore, clinical disorders that are coined "epidural" are actually anatomically external to the internal periosteal lining. The term "subperiosteal" abscess or empyema is also used, predominantly in the otolaryngology literature, and is more anatomically accurate. The cranial dura is tightly adhered to the skull at the cranial sutures, at the cranial base, and at the neural foramina where the dura becomes contiguous with the epineurium of the cranial nerves. Over the cranial vault, the dura is relatively less adherent in the adult, such that it is more susceptible to separation, resulting in a true space (Smith, 1978).

The inner layer of the dura mater also forms the falx cerebri and the tentorium cerebella, collectively referred to as the dural septa. At the base of these septa, the superior sagittal sinus and transverse sinuses are formed and these are anatomically within the "intradural" or intralamellar space (Smith, 1978) (Fig. 6.1).

The delicate, avascular arachnoid mater is adherent to, but more easily separated from, the internal surface of the dura and forms the noncommunicating subdural space (Carpenter, 1991). The arachnoid villi (pacchionian bodies) traverse the dura to protrude into the venous sinuses. The dura mater is also traversed by

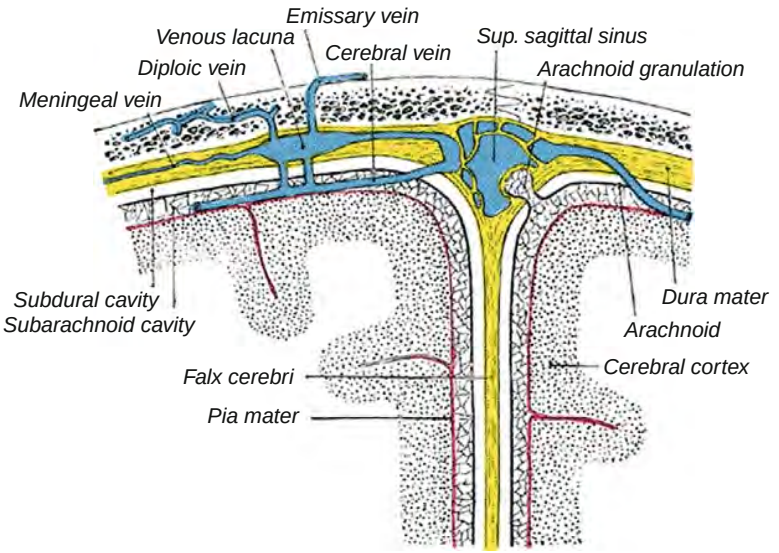

Fig. 6.1. Sagittal cross-section through the skull showing the relationship of skull to the meninges and meningeal spaces as labeled. The anatomy of the diploic veins is important to note as they relate to the pathogenesis of subdural empyema. Reproduced from Figure 769 Gray's Anatomy, 20th US edn., published 1918 (public domain).

cortical veins draining into the sinuses that span the subarachnoid space and the cerebrospinal fluid (CSF) it contains. Furthermore, the external layer of dura (and internal periosteum) is crossed by valveless diploic veins from the skull and emissary veins from the scalp that also cross the subaponeurotic space, and frontal sinus (Kombogiorgas and Solkani, 2006).

The cranial dura mater is contiguous with the spinal dura below the foramen magnum and below this level an actual separation of the bony periosteum occurs, creating a true epidural space.

The aerated sinus cavities of the skull are a source for intracranial infection given that sinus and middle-ear infections are relatively common and their anatomic proximity. The maxillary sinuses are anterior to the middle cranial fossa and are separated from the orbit laterally by the perpendicular plate of the ethmoid bone. These sinuses also lie inferior to the frontal cranial fossa separated by the cribriform plate of the ethmoid with its fenestrations. The frontal sinus cavity is an enlargement within the medullary cavity of the frontal bone. The sphenoid sinus of the posterior aspect of the nasopharynx lies between the venous blood-filled cavernous sinuses, and collectively these structures are anterior to the prepontine cistern and brainstem proper.

These paranasal sinuses (frontal, maxillary, ethmoid, and sphenoid) are lined by columnar ciliated epithelium and are normally sterile, although transient colonization from mouth flora may occur. The maxillary sinuses and the sphenoid sinus drain into the nasopharynx via their respective ostia. Secretory immune function via immunoglobulin A and local cell-mediated immune function are additional local defenses against infection. Infectious sinusitis results from the introduction of pathogens and disturbance of one or more of these three host factors (patent ostia, intact functioning epithelium, and local immune function) (Chow and Vortel, 1992).

The middle and inner ear are within the aerated mastoid air cells. There is essentially a pre-existing path via the internal acoustic meatus to the dura and potentially the subarachnoid space. In the newborn, the eustachian tube is wider and more horizontal than later in life, creating a path to the middle ear; and only a thin cartilaginous sheet from the squamous to the petrous portion of the temporal bone prevents meningeal extension (Smith, 1978).

PATHOGENESIS AND PATHOPHYSIOLOGY

Based on the anatomical structures discussed, there is a formidable barrier that prevents infections of the epidural or subdural space and its avascular nature makes these locations less than hospitable. Clinical infection requires a process and pathogen that is, by itself, sufficiently invasive or disruptive of the barrier. Paranasal sinusitis and otomastoiditis are the most common source of epidural and subdural infection.

Frontal sinusitis can directly cause frontal osteomyelitis by erosion of bone by the organisms (Davidson and McComb, 2006). If the outer table of the bone is involved, then the suppuration is subgaleal (under the galeal aponeurosis) and causes a Pott's puffy tumor appearance (Fig. 6.2). Similar erosion of the inner table

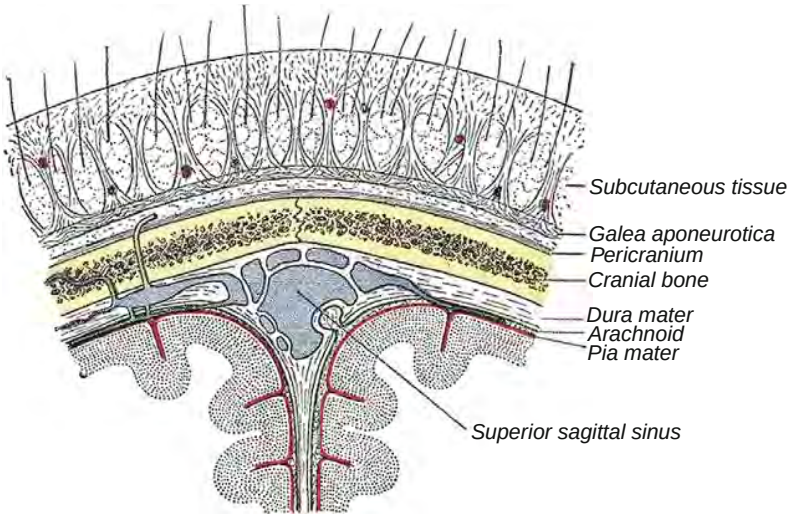

Fig. 6.2. Sagittal cross-section of the skull and its coverings, as in Fig. 6.1. The galea aponeurosis (galea aponeurotica) is shown. Reproduced from Figure 769 Gray's Anatomy, 20th US edn., published 1918 (public domain).

results in suppuration that is subperiosteal, causing cranial epidural abscess. Expansion of this epidural process is by lateral progression of the osteomyelitic bone and by the suppuration dissecting the periosteum from the bone at the lateral margins of the abscess. This mass grows slowly due to the rigidity of the pachymeninges and bone, has a convex or lentiform shape, and does not significantly deform underlying brain unless it is quite large (Kastenbauer et al., 2004a). Some patients who present with frontal osteomyelitis and epidural abscess have had prior sinus surgery, sometimes years before, suggesting that anatomical disruption may predispose to later complications with subsequent sinusitis (Marshall and Jones, 2000). However, the history of sinus disease alone may explain the need for the surgery and intracranial complications.

The ethmoid and sphenoid sinuses can result in the same intracranial complications. Infectious cavernous sinus thrombosis often occurs from extension from these paranasal sinuses or other infections from the middle third of the face (Dolan and Chowdhury, 1995). Maxillary sinusitis rarely extends intracranially, with the exception of odontogenic maxillary sinusitis that has an increased tendency for intracranial spread (Dolan and Chowdhury, 1995).

The drainage of the emissary and diploic veins may cause intracranial focal infections by propagation of septic thrombophlebitis or emboli (Fig. 6.1) (Rich et al., 2000; Kuckowski et al., 2005). These sinogenic intracranial infections often occur in the absence of osteomyelitis, supporting this mechanism. The frontal sinuses may be particularly susceptible to spread infection due to its rich network of diploic veins and, in adolescents, rapid growth of the frontal sinuses (Germiller et al., 2006). This is the prevailing mechanism by which subdural empyema forms. After bacterial seeding of the subdural space occurs, a robust inflammatory response occurs and typically the process progresses rapidly (Morgan and Williams, 1985). The leptomeninges offer little resistance to the expansion of the suppuration and subdural empyemas can become quite large over the convexities, the falx cerebri or tentorium cerebella, and can extend bilaterally along dural septa (Shapiro, 1997). Intracranial subdural empyema may even extend from the infratentorial space caudally into the spinal canal (Pompucci et al., 2007). Local meningeal irritation is present that becomes diffuse meningitis if a breach to the subarachnoid space occurs. Septic thrombosis of involved bridging cortical veins creates cortical inflammation and vascular congestion, causing ischemia and edema within the brain parenchyma. The mass effect of the subdural empyema, the inflammation that occurs, and the secondary effects on the underlying brain are responsible for clinical signs and deficits that are observed. Understanding this pathogenesis, it is apparent why the mortality of this condition was almost universally fatal in the preantibiotic era (Wackym et al., 1990).

This mechanism of emissary and diploic vein thrombophlebitis not only causes epidural abscess or subdural empyema, but can also result in the formation of intracranial septic thrombophlebitis, brain abscess, or meningitis. More than one of these manifestations may be present in the same patient. One series reported 219 patients with intracranial complications of sinus disease causing subdural empyema in 127 (58%), epidural abscess in 17 (8%), and 15 patients (7%) had both manifestations. In that same series, 38 patients (17%) had parenchymal brain abscess and 15 patients (7%) had brain abscess and subdural empyema (Singh et al., 1995). In another series, 17.6% of patients had simultaneous epidural and subdural empyema (Nathoo et al., 1999a). In another series of 25 patients, epidural abscess alone occurred in nine patients and simultaneously with subdural empyema in another three patients. Epidural and subdural collections were also found with brain abscess in one patient each. Meningitis occurred in six patients, three with coincident subdural empyema (Germiller et al., 2006). The precise factors that determine which clinical presentations occur in a given individual are not known.

Otomastoiditis can also result in intradural complications by the similar mechanisms of direct extension and venous septic thrombophlebitis or emboli. In a series of 130 patients with mastoiditis, cholesteatomas were present in 74 of these cases, representing acute-on-chronic disease. Of these, 33 (45%) had intradural extension compared with only four (7%) intracranial complications in 56 noncholesteatomatous cases (Mathews and Marus, 1988). Similar to paranasal sinusitis, chronic or acute-on-chronic inflammation increases the likelihood of intracranial infection. Epidural or subdural extension is more likely to be infratentorial or temporal lobe in location as a consequence of middle-ear or mastoid disease (Mathews and Marus, 1988; Vehnkatesh et al., 2006).

The mechanical disruption that is caused by trauma and neurosurgical intervention can understandably result in epidural or subdural empyema. Penetrating trauma is an obvious risk, especially open depressed skull fractures involving the nasal sinuses. The reported incidence of epidural abscess after a clean craniotomy is about 1% (Shapiro, 1997). Halo devices and pins have been reported to result in epidural or subdural infection but this is very rare (Dill et al., 1995). One series of 41 cases of epidural abscess and subdural empyema found that 27 (66%) of these were postoperative neurosurgical infections and more likely to occur in older patients, have evidence of a wound infection, and have a gram-negative rod as a pathogen (Hlavin et al., 1994).

The majority of postoperative infections result from skin organisms such as *Staphylococcus aureus* and *S. epidermidis* as well as gram-negative rods, including *Pseudomonas* spp. (Greenlee, 2003). There have been a few reports of an uncommon skin anaerobe, *Propionibacterium acnes,* in association with dural allografts (Jallo et al., 1999; Barkhoudarian et al., 2005).

Rarely there are cases that are apparently from hematogenous dissemination. Hematogenous seeding of a pre-existing subdural hematoma, without neurosurgical manipulation, can occur with the microbiology determined by the source of infection (Khan and Chan, 1981; Bakker et al., 1995; Dill et al., 1995; Kawamoto et al., 1998). Rarer still, based on frequency of reports in the literature, is primary hematogenous seeding of the subdural space without known pre-existing subdural disease or as a result of meninigitis (Meschia et al., 1994; Dill et al., 1995; Ulloa-Gutierrez et al., 2005).

Seeding of the subdural space from meningitis occurs infrequently. Subdural fluid collections are a common manifestation of meningitis, more common in children, occurring in 48 of 107 (45%) children who had repeat CT scanning (Friedland et al., 1992). In most cases, the fluid is sterile and is resorbed on its own. In that series of the children receiving intervention for the subdural collection, at least five were subdural empyema. Meningitis secondarily infecting a subdural effusion, resulting in an empyema, has been estimated to occur in about 2% of pediatric cases (Dill et al., 1995).

The two most common organisms that cause acute bacterial sinusitis are *Streptococcus pneumoniae* and *Haemophilus influenzae* (Piccirillo, 2004). Although these organisms are common causes for bacterial meningitis, they are not the more common pathogens for epidural abscess or subdural empyema (Schuchat et al., 1997; van de Beek et al., 2006). In chronic sinusitis the common pathogens are respiratory tract anaerobes (*Bacteroides* spp., *Fusobacterium* spp., peptostreptococci), and anaerobic and microaerophilic streptococci (Chow and Vortel, 1992).

The most common organisms cultured from cranial epidural abscess and subdural empyema are anaerobic and microaerophilic streptococci (*Streptococcus milleri* group), Enterobacteriaceae (i.e., *Proteus*), and other anaerobes (Yoshikawa et al., 1975; Hartman et al., 2004; Kastenbauer et al., 2004a). Culture-negative cases are more common in subdural empyema, about 27–29% of the cases, and may represent anaerobic organisms due to the difficulty in culturing these organisms (Yoshikawa et al., 1975; Hartman et al., 2004). Surgical cultures demonstrate multiple organisms in 15–54% of cases (Nathoo et al., 1999a; Germiller et al., 2006). As mentioned above, neurosurgical cases are often skin organisms such as *S. aureus* (including meticillin (formerly methicillin)-resistant) and *S. epidermidis,* and with nosocomial infection in frequently hospitalized patients, gram-negative organisms, or enterococci (Dill et al., 1995; Kastenbauer et al., 2004a). In one series, meticillin-resistant *S. aureus* (MRSA) was the cause in 12 of 90 (13%) patients (Bok and Peter, 1993).

Historically, *Streptococcus milleri,* and related streptococci (i.e., *S. anginosus*), were classified as *milleri*-group streptococci as a useful clinical designation for these microaerophilic, α-hemolytic organisms that cause pyogenic disease (particularly abscess) and are commensal organisms found in oral flora. Viridans group streptococci and related species, also commensal organisms found in the upper respiratory tract, are not very virulent but a pathogen in certain diseases such as endocarditis (Willett, 1992). The *milleri*-group and related organisms are now classified under the broader heading *Anginosus* species group (Bisno and Ruoff, 2005). However, many clinicians and the medical literature continue to refer to the more familiar terminology. To add to the confusion, the gram-positive cocci that are obligately anaerobic are mostly classified as *Peptococcus* spp. or *Peptostreptococcus* spp. (Bisno and Ruoff, 2005). These laboratory distinctions are less relevant as clinically these groups of organisms behave similarly to normal flora that are potentially pathogenic, microaerophilic, or anaerobic, and are common causes of clinical suppurative disease, particularly abscess.

Other less common organisms that have been described (incomplete list) are too numerous to list completely, but include *Salmonella* spp., *Klebsiella* spp., *Escherichia coli*, *Serratia marcescens*, *Citrobacter* spp., *Campylobacter* spp., and *Clostridium perfringens* (Mendelsohn et al., 1989; Meschia et al., 1994; Hartman et al., 2004; Kastenbauer et al., 2004a). Atypical bacteria causing epidural and subdural infections, such as *Mycobacterium tuberculosis* and *Actinomyces* (an organism with bacterial and mold-like properties) have been reported (Kirsch and Stears, 1970; van Dellen et al., 1998; Cayli et al., 2001).

Invasive fungal sinusitis can extend intracranially, into the orbit and structures of the eye. Fungi or molds such as *Aspergillus fumigatus*, *Pseudallescheria boydii,* and *Rhizopus* spp. can occur in otherwise healthy patients but these are more common in immunocompromised patients (deShazo et al., 1997). Mucormycosis, a zygomycosis-like *Rhizopus*, is notoriously invasive and is often fatal if not treated early, before vascular invasion occurs (deShazo et al., 1997). Invasive "rhinocerebral" mucormycosis may also proceed slowly if contained within the sinuses, causing a Pott's puffy tumor appearance. Acute decompensation can occur after months of symptoms, presumably at the time of epidural extension or vascular invasion (Effat et al., 2005).

CLINICAL FEATURES

The clinical features, presentation, and outcome of cranial epidural abscess and subdural empyema mostly differ, despite the similar clinical microbiology and underlying conditions.

Cranial epidural abscess in most cases is well contained by the intact dura and progresses slowly. The typical patient is an adolescent boy with an acute exacerbation of chronic sinus disease. When the source of the infection is trauma, neurosurgery, or dental infection, adult patients are as likely as adolescents to develop an epidural abscess.

Fever is the most common symptom present in 57% of cases, although, as is the case with brain abscess, the number of patients without fever is notable. The Pott's puffy tumor appearance is contingent upon the presence of a subgaleal collection of fluid and reported in 30–47% (Nathoo et al., 1999a; Germiller et al., 2006). About 40% of patients will have unilateral or bilateral periorbital edema due to extension into the soft tissues of the frontal bone osteomyelitis. Localized headache, often subacute in duration, occurs in about 40% of cases (Nathoo et al., 1999a). Localized scalp tenderness may also be present. These symptoms are often present for 1–2 weeks (median of 9–12 days) but there are many instances of 2–4 months of headache and frontal swelling (Nathoo et al., 1999a; Marshall and Jones, 2000; Germiller et al., 2006). Meningismus occurs in about one-third of cases. Focal neurological signs are less common, with seizures occurring in about 10% and even fewer patients with neurological deficits like hemiparesis (Nathoo et al., 1999a). A sinocutaneous fistula can be found at presentation even without prior surgical intervention (Marshall and Jones, 2000; Davidson and McComb, 2006).

In a patient with active or chronic frontal sinusitis, incidental trauma may result in Pott's puffy tumor presentation, likely a hastened presentation by fracture of already weakened bone from osteomyelitis (Maheshwar et al., 2001). In this situation, it may be wrongly assumed that the trauma is responsible for the swollen appearance.

As mentioned above, focal neurological signs are uncommon in cranial epidural abscess. A notable syndrome of orbital pain, lateral rectus palsy and otitis media, known as Gradenigo's syndrome, occurs from inflammation of the petrous apex and the dura, whether by extension from the middle ear or by direct extension from the eustachian tube (Adelstein, 1931). These patients have a fairly unique presentation of fever, retro-orbital pain, and intorsion of the eye ipsilateral to the otitis. Furthermore, about 10% of cases may have both epidural and subdural empyema at presentation, usually from inward extension from the epidural to subdural space. As expected, these cases may present subacutely, but then assume a faster clinical course more typical for subdural empyema.

Subdural empyema patients may present after days to weeks of symptoms but most present at about 7–12 days (Nathoo et al., 1999a; Adame et al., 2005; Germiller et al., 2006). Many patients experience nonspecific signs of infection and complain of malaise, headache, and fever. If oral antibiotic therapy is prescribed for diagnosed sinusitis or otitis, temporary improvement can occur and prolong the time to clinical presentation. A more acute, fulminant syndrome of diffuse and focal neurological signs often follows.

Most patients are febrile at presentation (63–77%), with associated headache and meningismus in over half of the cases (Dill et al., 1995; Nathoo et al., 1999a). Obtundation, lethargy, or some decreased mental status is common in 50–80% of patients (Wackym et al., 1990; Hartman et al., 2004; Adame et al., 2005; Vehnkatesh et al., 2006). In one series, one-third of patients were obtunded or comatose on admission (Singh et al., 1995). Infants may have bulging of the fontanel as a sign of raised intracranial pressure (Adame et al., 2005). Papilledema may be seen, but is not reliably present despite the intracranial mass effect (Dill et al., 1995). Hemiparesis, the result of mass effect over the convexity, is apparent in over 50% of cases (Nathoo et al., 1999a; Hartman et al., 2004). Overall, the location of the subdural is over the convexity in half of the cases, over the convexity and parafalcine in another quarter of cases, parafalcine only in about 20% of cases, and tentorial or infratentorial in the rest (Nathoo et al., 1999a). Seizures are common in subdural empyema, and occur in up to 48% of cases (Hartman et al., 2004). Patients with mainly falcine empyema may have predominantly leg symptoms such as weakness or jacksonian seizures (Dill et al., 1995). Infratentorial empyema does not reliably cause signs that would localize well to the cerebellum or brainstem, but may be suspected when preceded by otitis or recent mastoid surgery (van de Beek et al., 2007).

DIAGNOSIS

Routine serum studies may not be specific, but often support the diagnosis of an infectious syndrome. Leukocytosis with neutrophilic predominance is found in over 75% of patients. Comparing patients with subdural empyema with those with uncomplicated sinusitis, significant elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (mean 82 versus 10.3 mm/h and 18.1 versus 3.0 mg/dl respectively) are reported (Adame et al., 2005). Case reports of epidural abscess often demonstrate elevated ESR and CRP levels (Davidson and McComb, 2006; Kombogiorgas and Solkani, 2006). Blood cultures are rarely helpful and intraoperative cultures establish the diagnosis far more reliably (Kastenbauer et al., 2004a; Vehnkatesh et al., 2006).

The diagnosis of intracranial epidural abscess is not made by lumbar puncture. Owing to the separation of

the process from the subarachnoid space, the CSF cultures are typically sterile with nonspecific inflammatory changes (Kastenbauer et al., 2004a). In one review, one of 12 patients experienced a clinical deterioration as a result of the lumbar puncture (Nathoo et al., 1999a). Overall, the information gained is limited, with some potential risk from the procedure, and the treatment and microbiological diagnosis are frequently surgical.

With subdural empyema, lumbar puncture may be helpful at times but the potential for harm is real, given the issues of mass effect. Lumbar punctures are sometimes done at the time of presentation when the diagnosis appears to be bacterial meningitis (without abscess or empyema). As a rule, suspected meningitis with focal neurological findings, a deceased level of consciousness, or new partial seizures warrants antibiotics and brain imaging prior to lumbar puncture. As already discussed, these findings are often present with subdural empyema. In a large review, 40% of patients with subdural empyema underwent "inappropriate" lumbar punctures at referral hospitals. Lumbar puncture was attributed to deterioration in 12% and caused a few deaths (1.1% of those who had the procedure) (Nathoo et al., 1999a). Given the clinical progression of this condition, at times rapid, coincident decline with lumbar puncture is also possible. Meningitis may be the cause of the subdural effusion or empyema, as is more common in children, or the empyema may escape detection by CT imaging. In these cases, the CSF analysis has been pursued with varied results. Cultures or Gram's stain of CSF are positive in 2–6% of cases (Hartman et al., 2004).

Nonetheless, the risk of this procedure is to be balanced with what important information may be gained from lumbar puncture in these patients. The causative organism is usually diagnosed from specimens at the time of surgery, not CSF. Often the CSF shows nonspecific abnormalities that are consistent with virtually any parameningeal inflammatory process (Smith, 1978; Darouiche et al., 1992; Hartman et al., 2004).

Plain films (roentgenograms) have historically been used in the diagnosis of sinus disease and its complications, and provide a clue to the correct diagnosis in some circumstances and in resource-limited settings (Rich et al., 2000). If CT or MRI is available, then sinus or skull films are superfluous.

Prior to the mid-1970s with the evolution of CT scanning, the diagnosis of all intracranial mass lesions was clearly more difficult. The ability to image more accurately not only intracranial mass, but also sinus disease and skull anatomy, has directly aided the management of patients with cranial epidural and subdural infections. The estimated mortality from subdural empyema has been reduced from 50% to 10% by CT alone (Rich et al., 2000).

CT imaging of the head is a reliable means of imaging most patients, especially with cranial epidural abscess. The abscess itself is convex to the brain with the inflamed dura appearing as a thick rim of enhancement around the hypodense fluid collection (Fig. 6.3). In addition, the integrity of the frontal sinus, the presence and extent of sinus or mastoid disease, and the presence of orbital involvement can usually be determined. CT is very reliable, with large case series correctly identifying

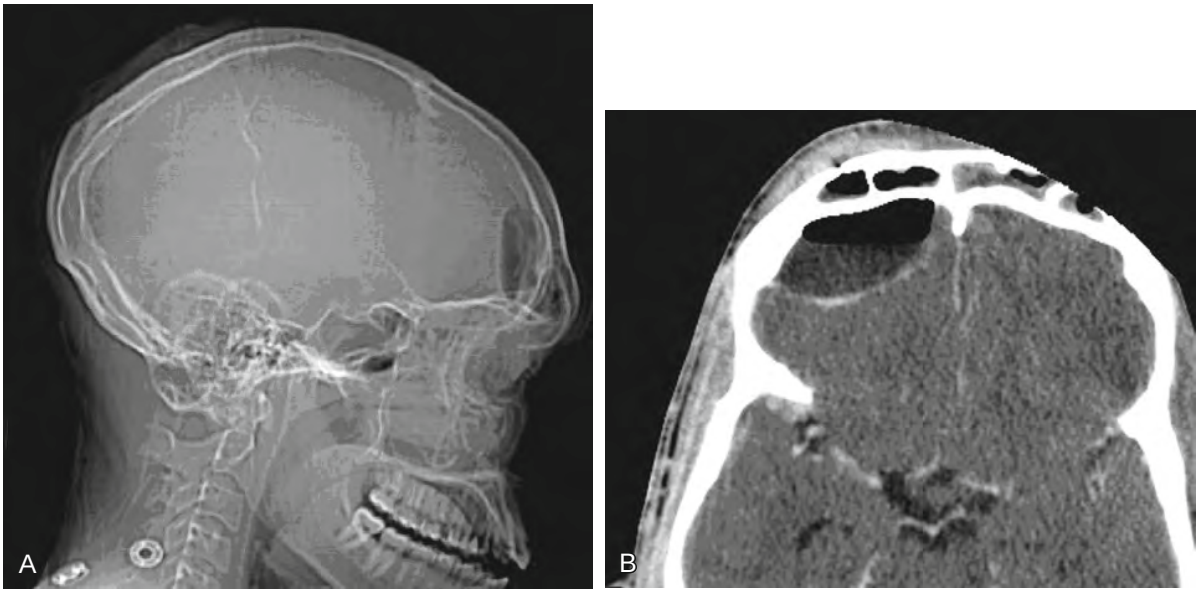

Fig. 6.3. Computed tomography scout film (A) and axial (B) images showing cranial epidural abscess with subgaleal extension causing a Pott's puffy tumor appearance. This patient had previously suffered a fracture of the frontal sinus and presented later with this complication. Note the lack of mass effect near the midline and premesencephalic cistern, despite the size of the epidural air fluid collection.

all 82 cases of epidural abscess and 699 cases of subdural empyema (Nathoo et al., 1999a,b). In contrast, a series of 25 patients since 1999 reported a sensitivity of only 63% (Germiller et al., 2006). Overall, with modern CT scanning, subdural abscess is usually identified, but may escape discovery when performed early in the evolution of the abscess (smaller in size), especially in the infratentorial compartment (Rich et al., 2000; van de Beek et al., 2007).

MRI is obviously superior to CT due to improved resolution, fewer artifacts, and multiplanar images (Fig. 6.4). Cranial epidural abscess and the associated frontal osteomyelitis are better visualized. Orbital invasion can be determined, in particular with fat saturation images (Tsuchiya et al., 2003). In addition, the diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) images add to the diagnostic value of localized intracranial infections. In brain

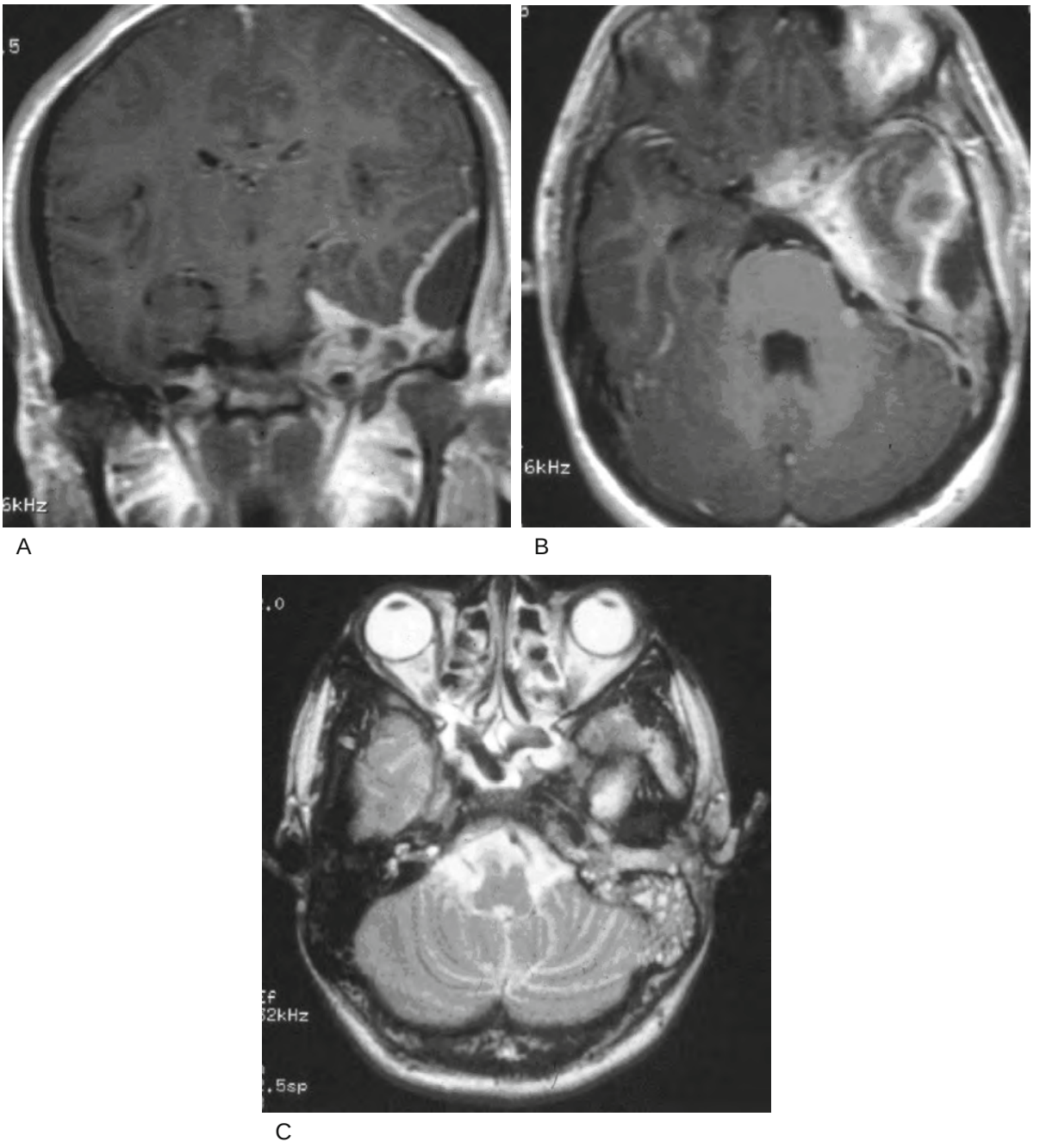

Fig. 6.4. T1 coronal (A) and axial (B) images, and T2 axial image (C) of mastoiditis resulting in epidural abscess. In this patient extension along the sphenoid wing and adjacent high signal changes in the brainstem have occurred.

abscess and subdural empyema, there is consistently restricted diffusion (high signal) of the abscess cavity with corresponding low signal on ADC due to the cellularity of the cavity (Guzman et al., 2002; Leuthardt et al., 2002; Wong et al., 2004). This finding improves the ability to differentiate other cystic structures, which have low signal on DWI, from infection. This can reliably make the important distinction between subdural effusion and subdural empyema, particularly in children with meningitis (Wong et al., 2004).

MRI also allows for better imaging of brain edema, mass effect, and vascular structures. Particularly with subdural empyema there is often underlying brain injury by these mechanisms. In particular, MR venography (MRV) can often visualize thrombosis of the dural sinuses and cortical bridging veins (Rich et al., 2000). As discussed above in the pathogenesis of these conditions, patients may have simultaneous brain abscess or coincident cranial epidural abscess and subdural empyema that is best defined by MRI (Fig. 6.5).

MANAGEMENT

Prompt recognition and treatment with a combined medical and surgical approach are essential to reduce the morbidity and mortality of these conditions.

Patients with cranial epidural abscess and subdural empyema require hospitalization with close supervision. Subdural empyema patients, in particular, can progress quickly and admission to an intensive care unit setting is recommended initially, even if the patient appears stable.

The source of the infection, and therefore the likely pathogens, determines the empiric therapy to be used. Of course, isolation and identification of the organism allow for more focused antibiotic therapy.

Metronidazole is the antibiotic that treats anaerobic infections. Given the difficulties in culturing anaerobes, and the high rate of polymicrobial abscess and empyema, anaerobic coverage should be maintained in most cases even if another organism is cultured. The exception would be a clinical syndrome and source of infection that is almost certainly monomicrobial. If *S. aureus* is present or suspected, treatment with a regimen containing vancomycin is recommended due to an increased incidence of resistant organisms (Daum, 2007).

The rationale for antibiotic choice is also determined by issues such as good tissue penetration, effectiveness at an acidic pH, and bactericidal activity. For these reasons, certain antibiotics such as aminoglycosides and chloramphenicol (limited activity

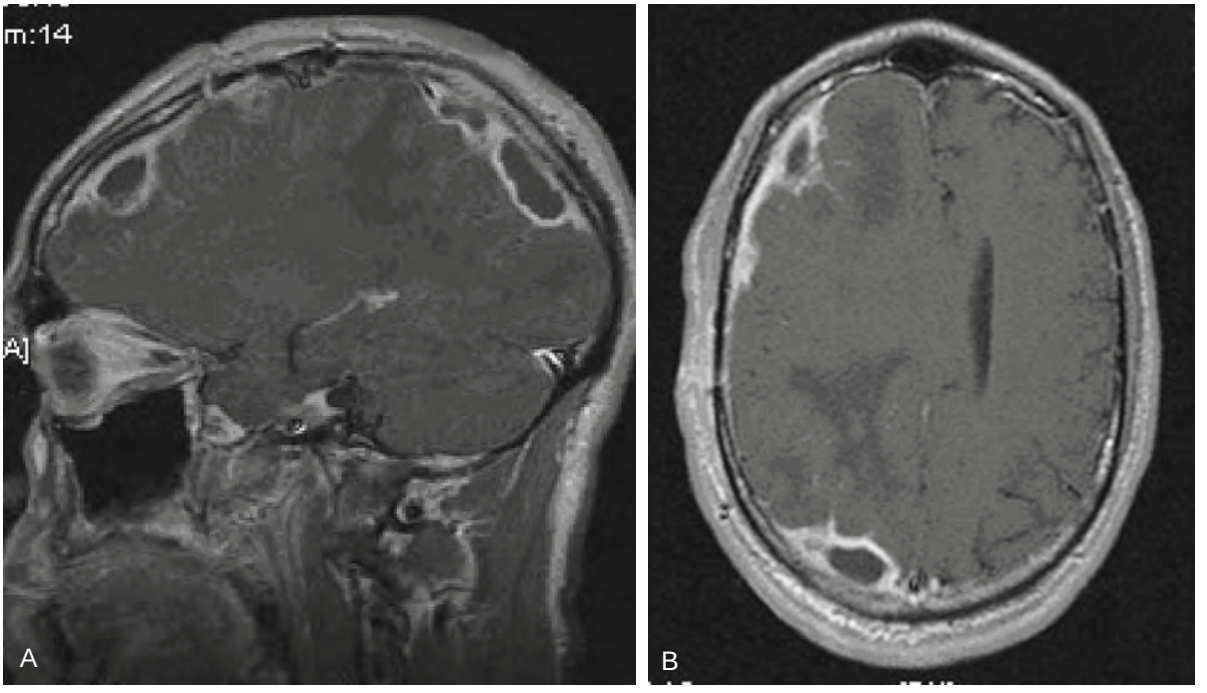

Fig. 6.5. This 45-year-old man was admitted after being hit by an automobile causing concussion and facial trauma. A pressure bolt was placed, showing normal pressures. The bolt fell out 2 days later and a suture was placed on the scalp prior to discharge. He was admitted 10 days later with progressive headache and purulent discharge from the scalp. Surgical cultures grew *Staphylococcus aureus* (meticillin-sensitive). Note the dural enhancement and underlying edema and mass effect in the T1 postcontrast images (A–C) and T2 images (D).

Continued

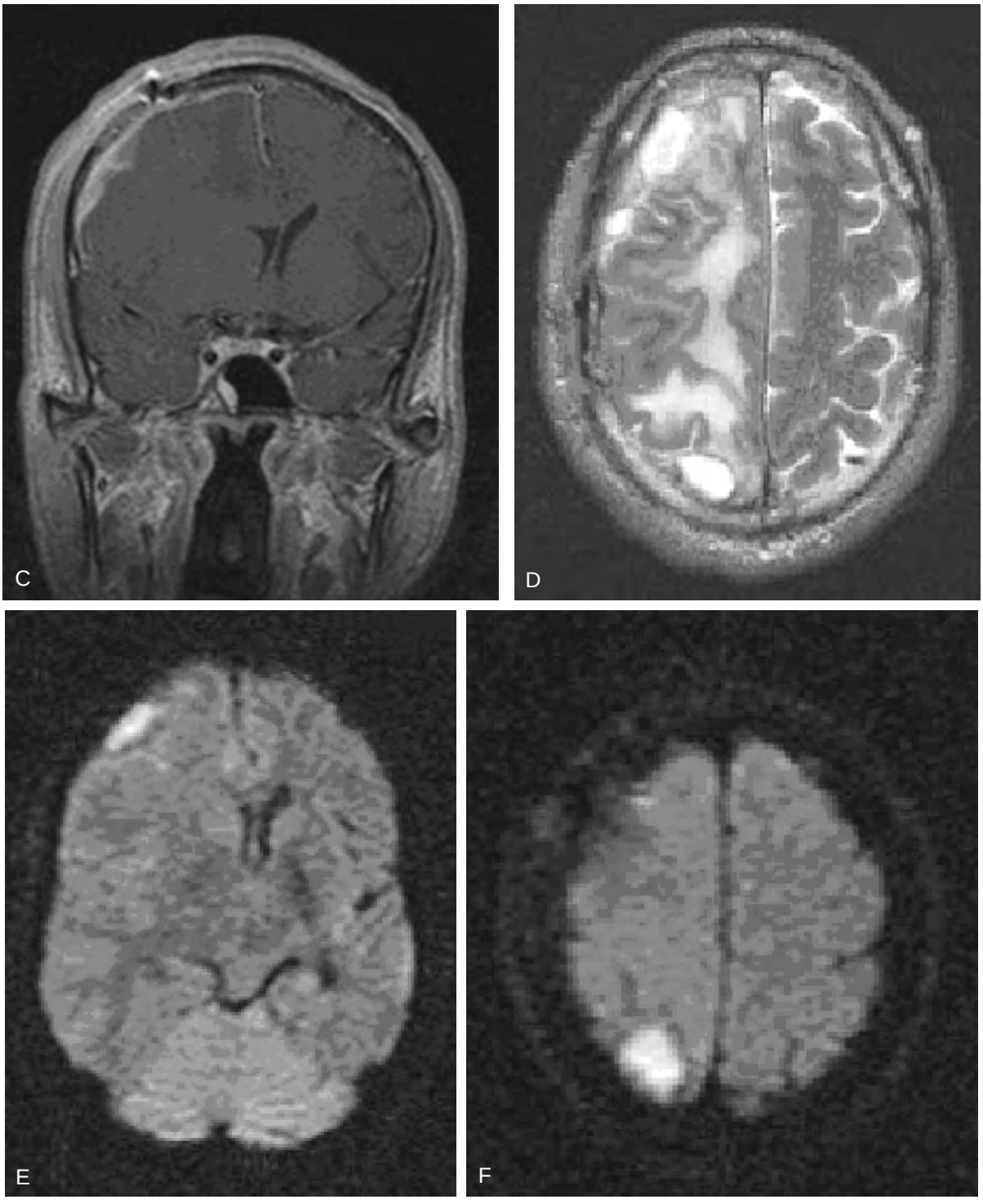

Fig. 6.5 Cont'd. The multifocal fluid collections illustrate the relative ease of spread in the subdural space. The diffusion-weighted images (E, F) show increased signal (restricted diffusion) consistent with abscess.

at low pH) that also have other toxicities are not used as often. Vancomycin is used to cover resistant organisms (meticillin-resistant *S. aureus*).

Suggested empiric regimen includes vancomycin, ceftazidime or cefepime, and metronidazole (Table 6.1). Serum trough vancomycin levels should be followed and dose adjusted accordingly. Penicillin-allergic patients are treated with the same regimen, unless the allergy is known to be life-threatening, due to an acceptably low rate of cephalosporin cross-reactivity. If a sensitive streptococcus or staphylococcus is the pathogen, then vancomycin can be switched to nafcillin with metronidazole, except in penicillin-allergic patients. If a cephalosporin is not tolerated, then alternative regimens can be used, substituting aztreonam or trimethoprim/sulfamethoxazole. Meropenem is a broad-spectrum antibiotic that can be used as monotherapy, but, if MRSA is suspected, vancomycin should be added. Owing to issues of penetration, dosing of antibiotics for central nervous system infections is often higher than doses to treat other organ infections and underdosing is a common clinical mistake (Table 6.2). It is imperative that the patient is receiving the correct drugs and the correct dose, and all the doses under close supervision.

The duration of therapy is not concrete or studied in particular for these diseases. With frontal bone osteomyelitis, treatment durations of 4–6 weeks are expected. Brain abscess treatment duration is suggested for up to 6–8 weeks (Kastenbauer et al., 2004b). Further consideration is based upon the organism and its susceptibilities (which are not typically done for anaerobic bacteria). Host factors, in particular immunocompromised patients, may necessitate longer treatment courses or chronic suppressive therapy after initial treatment. Cases due to *Mycobacterium tuberculosis* are rare but have been reported: in these cases 9–12 months of four-drug therapy (isoniazid, rifampin, ethambutol, pyrazinamide), followed by 4–7 months of isoniazid plus rifampin, is suggested (Cayli et al., 2001; Blumberg et al., 2003).

Invasive fungal disease, classically mucormycosis following diabetic ketoacidosis, has a characteristic black painless ulcer or eschar and this appearance requires prompt therapy. Treatment is amphotericin B 1.0–1.5 mg/kg/day (before fungal culture results) with a total dose of 2500–4000 mg required in immunocompromised patients (deShazo et al., 1997). Posaconazole, an orally absorbed widely distributed antifungal agent, has shown encouraging results in open-label use after failure of conventional antifungal regimens for invasive fungal disease due to zygomycoses (which includes mucormycosis). Of the 24 patients treated, 11 had rhinocerebral disease with the entire group demonstrating complete response in 79% of the treated subjects (Greenberg et al., 2006).

Table 6.1

Suggested empiric therapy for cranial epidural abscess and subdural empyema

Site/origin	Common pathogens	Suggested empiric therapy
Paranasal sinuses	Aerobic and anaerobic *Streptococci* spp. *Haemophilus* spp. *Bacteroides* spp.	Vancomycin + metronidazole + third- or fourth-generation cephalosporin
Otogenic and odontogenic	*Proteus* spp. *Streptococcus* spp. Enterobacteriaceae *Bacteroides* spp.	Vancomycin + metronidazole + ceftazidime
Hematogenous	Depends on source, usually monomicrobial	Vancomycin + metronidazole + cefotaxime
Penetrating trauma postneurosurgical	*Staphylococcus aureus* and other species (especially MRSA) Enterobacteriaceae *Pseudomonas*	Vancomycin + ceftazidime or cefepime

MRSA, meticillin (formerly methicillin)-resistant *Staphylococcus aureus*.

Corticosteroids have been used to manage issues of cerebral edema and are rarely used as part of a nonsurgical cure of subdural empyema (van de Beek et al., 2007). The rationale and success of corticosteroids in community-acquired meningitis are well established; however, their routine use or clear benefit is difficult to determine in epidural abscess and subdural empyema (de Gans, van de Beek, and the European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators, 2002). The use of corticosteroids is an individual case decision. Nonetheless, intracranial pressure must be managed. The surgical interventions discussed below may be adequate, and, if needed, ventriculostomy externalizing CSF flow can be used to manage hydrocephalus. Other conventional and practical measures to manage elevated intracranial pressure should be used. Seizures are common and seizure precautions should be in place: if seizures occur, anticonvulsant treatment should be initiated.

There are patients with successful treatment of subdural empyema by medical therapy alone who had only mild deficits and were closely observed on antibiotic therapy (Mauser et al., 1985; Leys et al.,

Table 6.2

Typical dosing of antimicrobials for central nervous system (CNS) infections*

Antibiotic	CNS infection dosing*	Other information
Vancomycin	15 mg/kg IV q 8–12 hours	Monitor trough levels to maintain 15–20 μg/ml
Metronidazole	500 mg IV q 6–8 hours	
Ceftazidime or cefepime	2 g IV q 8 hours	Cefepime gives better gram-positive coverage
Nafcillin	2 g IV q 4 hours	In place of vancomycin and cephalosporin if sensitive gram-positive organism
Aztreonam	2 g IV q 8 hours	Gram-negative coverage if cephalosporin allergy. Monitor liver and renal function
Trimethoprim/sulfamethoxazole	5 mg/kg IV q 6–8 hours	Gram-negative coverage if cephalosporin allergy *Nocardia* treatment of choice
Meropenem	2 g IV q 8 hours	Broad-spectrum antibiotic, can be used as monotherapy except for MRSA (add vancomycin)
Amphotericin B	1.0 mg–1.5 mg/kg IV daily	Give test dose prior to first full dose. Monitor renal function and electrolytes
Posaconazole	800 mg p.o. divided 2–4 times daily	Preliminary data show efficacy as salvage after amphotericin B

*Based on typical adult with normal renal function; adjust dose if necessary.
MRSA, meticillin (formerly methicillin)-resistant *Staphylococcus aureus*.

1986; van de Beek et al., 2007). These reports are noted, but the standard of care is combined medical and surgical therapy that has made cranial epidural abscess and subdural empyema survivable diseases.

The surgical treatment of cranial epidural abscess and subdural empyema is debridement of the abscess and of the infected sinus cavity if not spontaneously draining. Simultaneous otolaryngology and neurosurgical procedures done promptly at the time of recognition, and under the same anesthesia, are suggested.

In the treatment of frontal sinusitis and osteomyelitis, cranialization of the sinus cavity by burr hole or craniotomy is performed with trephination of the sinus. Subgaleal fluid collections (Pott's puffy tumor) can be removed at the same procedure. Removal of osteomyelitic bone is usually performed; this may require cranioplasty at a later time (Shapiro, 1997). Occasionally, postoperative drain placement is done that can be irrigated if necessary and later removed.

Subdural empyema can be more extensive, and the use of single or multiple burr holes in addition to craniotomy has been used successfully. The advantages of craniotomy include removal of pus from a larger area, as there may be pockets of pus over the hemisphere. Burr holes are a less extensive procedure, sometimes with drain placement, and occasionally patients may undergo craniotomy as a second procedure if worsening occurs. At times, a burr hole with small craniectomy may be used, as with parafalcine empyema. Some authors advocate the use of burr holes, citing similar outcomes with either procedure in a nonrandomized sample (Bok and Peter, 1993). Factors such as consciousness level at presentation, age of the patient, and sepsis are known to influence patient outcomes and also influence the choice of procedure (Morgan and Williams, 1985; Hartman et al., 2004). Having acknowledged potential biases and differences in case and procedure selection, pooling a large number of studies, the overall craniotomy mortality is 10%, compared with 23% for burr holes (Hartman et al., 2004).

In the pre-CT era, subdural empyema consistently had a mortality rate in the range of 25–40%, and, in publications by 1983, rates as low as 1% (typically 8–22%) were reported (Mathews and Marus, 1988; Hartman et al., 2004). Mortality and outcome with subdural empyema are predicted well by level of consciousness at presentation. If the patient presents in coma, mortality rates as high as 57–80% are reported, whereas those who present conscious or "drowsy" have a mortality of 0–7% (Dill et al., 1995; Singh et al., 1995). Advanced age is associated with greater mortality; however, given the demographics of this disease, most deaths occur in adolescents (Bok and Peter, 1993; Dill et al., 1995). Hemiparesis is the most common sequela amongst survivors, classified as mild to moderate in up to 42% of cases and severe in another 5–25% of cases (Hartman et al., 2004). Short-term sequelae that resolved in follow-up were seen in one-third of cases in a series where fewer

than 10% of cases had lasting neurological disability. Epilepsy as a consequence of subdural empyema occurred in 17% of cases in a large series but has been reported in up to 42% in the post-CT era (Nathoo et al., 1999a; Hartman et al., 2004).

By contrast, the mortality from bacterial cranial epidural abscess is significantly lower and had achieved rates as low as 3.7% in the 1960s as a result of improved antibiotic therapies, before the era of CT (Kombogiorgas and Solkani, 2006). Mortality is uncommon in the current era for patients who have infection isolated to the epidural space (Nathoo et al., 1999a; Marshall and Jones, 2000; Kastenbauer et al., 2004a). Morbidity is limited as well with these patients as they infrequently have focal neurological deficits as part of the syndrome. Cosmetic issues may occur based on the extent of infected bone and the surgical intervention used.

Although the treatment of bacterial cranial epidural abscess and sinus disease can be successful, the mortality of invasive fungal sinusitis is 30–80%, with intracranial extension representing the higher end of this mortality range (deShazo et al., 1997). Posaconazole, as discussed above, shows promise, demonstrating complete response in 79% of the treated subjects after failure of conventional antifungal regimens (Greenberg et al., 2006).

The best management and outcome from cranial epidural abscess and subdural empyema rely on recognition of the syndrome, prompt intracranial imaging, and a combined medical and surgical approach. A child or adolescent who appears to worsen despite oral antibiotic therapy is an immediate concern. A command of the neuroanatomical relationships and clinical understanding of the microbiology allow for proficient care of these patients.

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Chapter 7

Spinal epidural abscess and subdural empyema

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SPINAL EPIDURAL ABSCESS

Currently affecting up to 0.04% of hospitalized patients, spinal epidural abscess has become increasingly more prevalent in the past three decades as a result of the aging population, increasing spinal instrumentation, escalating use of vascular access, and spread of illicit drug use (Nussbaum et al., 1992; Rigamonti et al., 1999; Akalan and Ozgen, 2000; Pereira and Lynch, 2005; Darouiche, 2006). Although still considered relatively rare, spinal epidural abscess is a serious condition that poses major challenges, as the diagnosis is often elusive and treatment is suboptimal despite advances in medical knowledge, imaging techniques, and surgical interventions. There are only 25 reported series, with each series of at least 20 cases of spinal epidural abscess, in the medical literature (Heusner, 1948; Baker et al., 1975; Kaufman et al., 1980; Danner and Hartman, 1987; Curling et al., 1990; Hlavin et al., 1990; Darouiche et al., 1992; Nussbaum et al., 1992; Wheeler et al., 1992; Khanna et al., 1996; Rigamonti et al., 1999; Akalan and Ozgen, 2000; Lu et al., 2002; Soehle and Wallenfang, 2002; Tang et al., 2002; Joshi et al., 2003; Khan and Hussain, 2003; Sorensen, 2003; Zafonte et al., 2003; Davis et al., 2004; Curry et al., 2005; Pereira and Lynch, 2005; Savage et al., 2005; Siddiq et al., 2005; Bostrom et al., 2008). This chapter addresses the pathogenesis, microbiology, clinical manifestations, diagnosis, treatment, and outcome of bacterial spinal epidural abscess.

PATHOGENESIS

Most patients with spinal epidural abscess have at least one predisposing condition, including an underlying disease (e.g., alcohol abuse, diabetes mellitus, or human immunodeficiency virus (HIV) infection), a potential local or systemic source of infection (e.g., osteomyelitis, skin and soft-tissue infection, urinary tract infection, sepsis, indwelling vascular access, injection drug use, nerve acupuncture, tattooing, epidural analgesia, or nerve block), and/or spinal abnormality or intervention (e.g., degenerative joint disease, trauma, surgery, anesthetic injection, or placement of stimulators or catheters) (Hlavin, 1990; Nussbaum et al., 1992; Chowfin et al., 1999; Sillevis Smitt et al., 1999; Soehle and Wallenfang, 2002; Tang et al., 2002; Alcock et al., 2003; Philipneri et al., 2003; Davis et al., 2004; Huang et al., 2004; Lin and Greco, 2005; Pereira and Lynch, 2005; Bang and Lim, 2006; Grewal et al., 2006; Rauchwerger et al., 2008). Bacteria arising from the vascular space, urinary tract, skin, soft tissue, muscle, or bone reach the epidural space via either hematogenous dissemination or contiguous spread in about one-half and one-third of cases, respectively; the source of infection is not identified in the remaining patients. Likewise, infection that originates in the spinal epidural space can either disseminate via the bloodstream or extend locally to those other bodily sites that could also serve as a source of infection (Fig. 7.1).

Epidural infection can cause injury to the spinal cord either directly via mechanical compression or indirectly as a result of vascular occlusion secondary to septic thrombophlebitis. The remarkable degree of neurological improvement in some patients after decompressive laminectomy supports mechanical pathophysiology, but thrombosed levels are observed in some postmortem examinations (Browder and Meyers, 1941). Furthermore, infarction of the spinal cord, as reflected by altered cord signal on magnetic resonance imaging (MRI), can be caused not only by vascular occlusion due to septic

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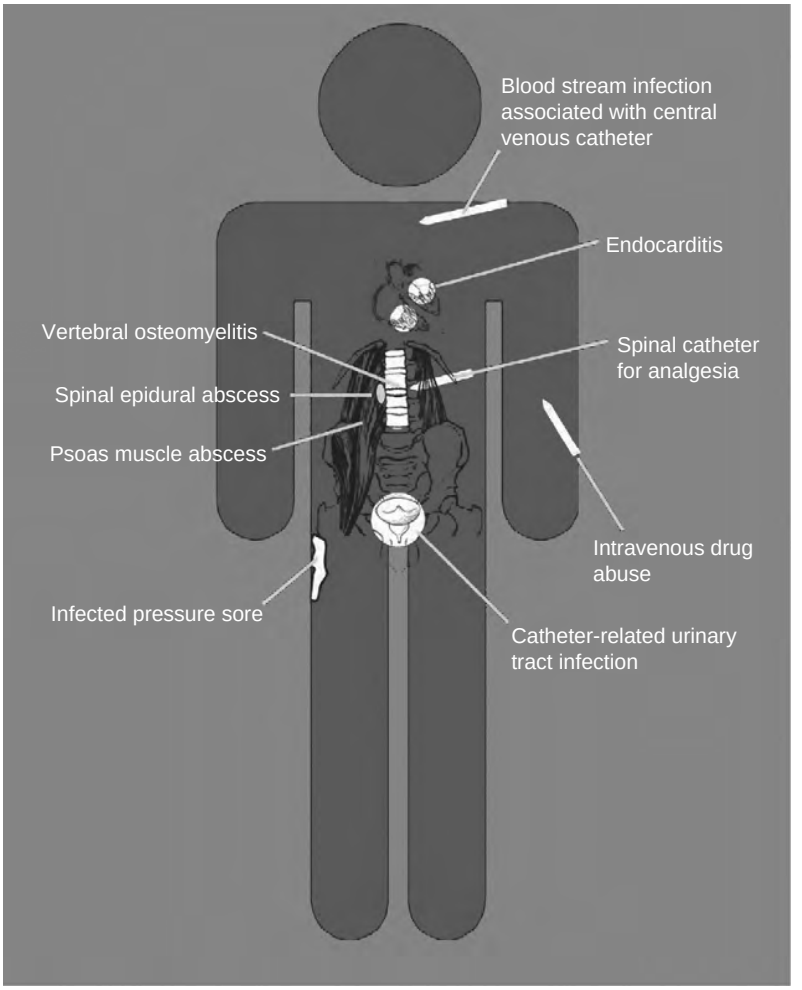

Fig. 7.1. Common causes and/or complications of spinal epidural abscess. Spinal epidural abscess can arise from or result in a number of infections at distant or adjacent sites, including the vascular space, urinary tract, skin, soft tissue, and bone.

thrombophlebitis, but also by profound compression. Although experiments in rabbits revealed a primary role for mechanical compression (Feldenzer et al., 1988), other animal models showed an additive adverse impact of compression and ischemia on neurological function. Therefore, the principal mechanism of cord damage in patients with spinal epidural abscess remains elusive and may differ between patients.

MICROBIOLOGY

Since most conditions that predispose to the formation of spinal epidural abscess allow for invasion by skin flora, *Staphylococcus aureus* causes about two-thirds of all cases of spinal epidural infection (Rigamonti et al., 1999; Reihsaus et al., 2000; Khan and Hussain, 2003). Although meticillin (formerly methicillin)-resistant *S. aureus* (MRSA) accounted for only 15% of staphylococcal spinal epidural infections just a decade ago (Rigamonti et al., 1999), the proportion of abscesses caused by MRSA has since escalated rapidly, and in some geographic areas, has already exceeded 50% of cases (Darouiche, 2006). The risk of MRSA infection is particularly high in patients with a vascular prosthesis or an implantable spinal device, and in whom the abscess develops within a few weeks after spinal injection or surgery. Coagulase-negative staphylococci (usually *S. epidermidis*) may be isolated in patients with spinal procedures, including placement of catheters for analgesia, steroid injection, or surgery. Less common causative pathogens include gram-negative bacilli such as *Escherichia coli*, which often originates from infection or instrumentation of the urinary tract, and *Pseudomonas aeruginosa*, which typically is cultured from injection drug users or patients with severe burns (Kaufman et al., 1980; Curling et al., 1990; Chowfin et al., 1999; Reihsaus et al., 2000; Soehle and Wallenfang, 2002; Fradet et al., 2005; Pereira and Lynch, 2005;

Asakage et al., 2006). Spinal epidural abscess is much less likely to be caused by anaerobic bacteria (Lechiche et al., 2006; Crema et al., 2007), *Bartonella henselae* (Hussain and Rathore, 2007), *Brucella* spp. (Guzey et al., 2007), *Actinomyces* species (Honda et al., 2008), *Nocardia* species (Reihsaus et al., 2000), tuberculous and nontuberculous mycobacteria (Curling et al., 1990; Reihsaus et al., 2000; Lu et al., 2002; Pereira and Lynch, 2005), fungi (including *Candida*, *Aspergillus*, and *Sporothrix* species) (Curling et al., 1990; Hlavin et al., 1990; Reihsaus et al., 2000; Khan and Hussain, 2003), and parasites (*Echinococcus* and *Dracunculus* species) (Reihsaus et al., 2000).

CLINICAL MANIFESTATIONS

The staging system outlined in Table 7.1 delineates the progression of symptoms and physical findings of spinal epidural abscess: stage 1, spinal pain; stage 2, pain radiating from the spine along the affected nerve root; stage 3, weakness and sensory deficit below the level of the lesion, and/or bladder and bowel dysfunction; and stage 4, paralysis (Darouiche, 2006). Both the duration of clinical manifestations prior to hospital admission (range, 1 day to 2 months) and the rate of progression from one stage to another (neurological deficit and eventual paraplegia can evolve in a matter of hours to days) are highly variable (Darouiche et al., 1992). Patients with spinal epidural abscess at stage 2 or higher that affects the cervical spine may have neck pain radiating down the upper extremities, whereas those with an epidural abscess located in the lumbar spine may suffer from low back pain radiating down the lower extremities. Patients with stage 2 thoracic epidural abscess, however, can have a more enigmatic clinical presentation that includes chest or abdominal pain, complaints that are frequently caused by other more common conditions (Bremer and Darouiche, 2004); the three most common presenting manifestations are back pain (affecting three-quarters of patients), fever (present in almost half of patients), and neurological deficit (detected in about one-third of patients) (Rigamonti et al., 1999; Akalan and Ozgen, 2000; Reihsaus et al., 2000). However, this classic clinical triad of back pain, fever, and neurological deficit is present in only the minority of the patients (Davis et al., 2004). Spinal epidural abscess more commonly affects posterior rather than anterior and thoracolumbar rather than cervical areas because infection is more likely to develop in larger epidural spaces that contain infection-prone fat (Danner and Hartman, 1987; Darouiche et al., 1992; Akalan and Ozgen, 2000). The escalating use of spinal interventions for pain management has led to a disproportionate increase in the occurrence of lumbar epidural infection (Khan and Hussain, 2003). Although spinal epidural abscesses extend over an average of three or four vertebrae (Danner and Hartman, 1987; Hlavin et al., 1990; Darouiche et al., 1992; Khanna et al., 1996; Lu et al., 2002; Tang at al., 2002; Darouiche, 2006), they rarely affect the entire spine with resultant panspinal infection (Rigamonti et al., 1999; Solomou et al., 2004).

Table 7.1

Stages of spinal epidural abscess

Stage 1	Spinal pain at the level of the affected spine
Stage 2	Nerve root pain radiating from the involved spinal area
Stage 3	Weakness, sensory deficit, and/or bladder or bowel dysfunction
Stage 4	Paralysis

DIAGNOSIS

Although spinal epidural abscess can be suspected based on abnormal clinical findings and laboratory data, the diagnosis is confirmed only by imaging studies, intraoperative observations, and cultures of epidural material. Inflammatory markers (e.g., erythrocyte sedimentation rate and C-reactive protein) are almost uniformly elevated and leukocytosis is detected in about two-thirds of patients with spinal epidural abscess (Hlavin et al., 1990; Darouiche et al., 1992; Nussbaum et al., 1992; Soehle and Wallenfang, 2002; Tang et al., 2002); however, neither the presence nor the degree of elevation of these laboratory tests is specific for diagnosis. Bacteremia, causing or arising from spinal epidural abscess, is detected in about 60% of patients (Danner and Hartman, 1987; Curry et al., 2005), more so in those infected with *S. aureus* than with other organisms (Danner and Hartman, 1987; Hlavin et al., 1990; Darouiche et al., 1992; Khanna et al., 1996). The presence of *S. aureus* bloodstream infection does not establish the source of infection because *S. aureus* causes most cases of not only spinal epidural abscess, but also other mimicking conditions such as vertebral osteomyelitis, disc space infection, sepsis, and endocarditis. Although analysis of cerebrospinal fluid (CSF) yields high protein concentrations and pleocytosis with either polymorphonuclear or mononuclear predominance in about three-quarters of patients, these abnormal findings are only suggestive of parameningeal inflammation and not specific for epidural infection (Darouiche, 2006). Gram's stain of CSF is usually negative and CSF cultures are positive in less than one-quarter of patients, although blood cultures usually yield the infecting pathogen in almost all

patients with a positive CSF culture (Darouiche et al., 1992). Since CSF analysis after lumbar puncture yields minimal additional information and is associated with a slight potential risk of causing neurological deterioration if performed below the level of complete spinal subarachnoid block, it should not be routinely done unless the patient first undergoes myelography (Hollis et al., 1986; Danner and Hartman, 1987; Hlavin et al., 1990; Darouiche et al., 1992).

A plain roentgenograph or computed tomography (CT) scan of the spine may reveal disc narrowing and bone lysis, indicating the presence of disc space infection and osteomyelitis (which coexist with spinal epidural abscess in up to 80% of patients), and a radionuclide scan (e.g., technetium, gallium, or indium) may show increased uptake to help localize the affected body site. However, the findings of these imaging tests are neither sensitive nor specific for spinal epidural abscess and should not preclude the need to perform more diagnostic radiological studies (Khan and Hussain, 2003). MRI with intravenous gadolinium is the imaging modality of choice for diagnosing spinal epidural abscess because it is less invasive, detects infection of tissues adjacent to the epidural space (Fig. 7.2), delineates both the paraspinal and longitudinal extension of the abscess (which is essential for planning surgery), and may help differentiate between infection and malignancy based on the imaging appearance and signal intensity (Parkinson and Sekhon, 2004). In situations where MRI is not available or cannot be performed, the more invasive imaging study that comprises myelography followed by CT scan of the spine should be considered because of its high sensitivity (more than 90%) in diagnosing spinal epidural abscess (Hlavin et al., 1990; Rigamonti et al., 1999).

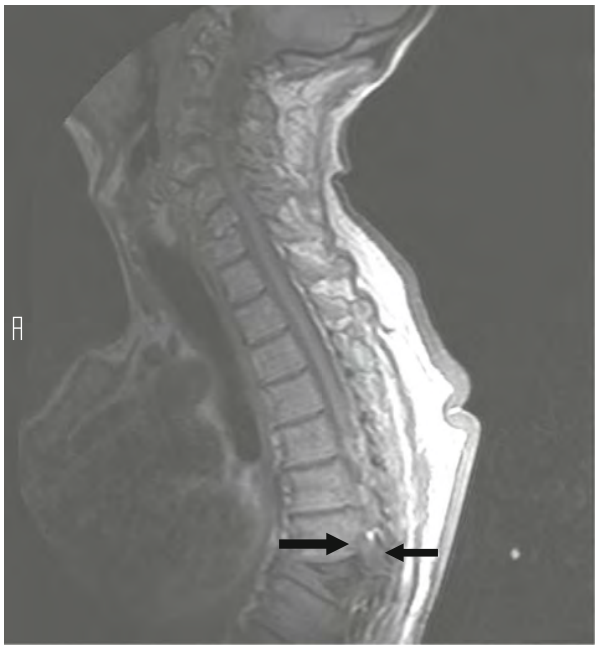

Fig. 7.2. Imaging findings of vertebral osteomyelitis and spinal epidural abscess. Magnetic resonance imaging of the thoracic spine with intravenous gadolinium demonstrates osteomyelitis of the T8 vertebral body (arrows) and spinal epidural abscess caused by *Staphylococcus aureus*. The severe kyphosis provides a local abnormality of the spine that has low resistance to infection.

Although the incidence of spinal epidural abscess continues to increase, it remains a relatively rare condition that may manifest with nonspecific clinical and laboratory findings and is often misdiagnosed upon presentation, particularly in neurologically intact patients (i.e., stages 1 and 2) (Darouiche et al., 1992; Tang et al., 2002; Davis et al., 2004). More common infectious (osteomyelitis, disc space infection, meningitis, urinary tract infection, sepsis, and endocarditis) and noninfectious (intervertebral disc prolapse, degenerative joint disease, spinal tumor, demyelinating illness, transverse myelitis, and spinal hematoma) conditions are frequently considered instead of spinal epidural abscess at the time of initial evaluation (Hlavin et al., 1990; Darouiche et al., 1992; Reihsaus et al., 2000).

TREATMENT

The results of retrospective studies overwhelmingly support the consensus that surgical drainage together with systemic antimicrobial agents is the treatment of choice (Heusner, 1948; Baker et al., 1975; Danner and Hartman, 1987; Hlavin et al., 1990; Darouiche et al., 1992; Nussbaum et al., 1992; Rigamonti et al., 1999; Lu et al., 2002; Curry et al., 2005; Pereira and Lynch, 2005). Since the preoperative neurological stage is the most important predictor of the final neurological outcome and because the rate of progression of neurological impairment is difficult to predict (as some patients may become paralyzed within hours after the onset of neurological deficit), decompressive laminectomy should be done as an emergency (Darouiche et al., 1992; Akalan and Ozgen, 2000; Lu et al., 2002; Davis et al., 2004).

Because of the rare occurrence of and serious outcome in patients with spinal epidural abscess, it is both impractical and ethically prohibitive to conduct prospective randomized clinical trials to compare different approaches of treatment. Few retrospective studies have reported similar outcomes in patients who were managed with antimicrobial therapy alone compared with those who received combined medical–surgical treatment (Sørensen, 2003; Curry et al., 2005; Savage et al., 2005; Siddiq et al., 2005). However, in some medically treated patients who had no or minimal neurological impairment (Sørensen, 2003; Curry et al., 2005; Savage et al., 2005)

or smaller-sized abscesses (Siddiq et al., 2005), neurological deterioration occurred despite appropriate antimicrobial therapy (Danner and Hartman, 1987; Hlavin et al., 1990; Darouiche et al., 1992; Wheeler et al., 1992; Curry et al., 2005). The true benefit of nonsurgical therapy is difficult to assess since successfully treated cases may have been selectively reported (Wheeler et al., 1992) and failed attempts at conservative management are rarely published (Harrington et al., 2001).

In clinical scenarios where decompressive laminectomy is refused by the patient, contraindicated because of high operative risk, unlikely to reverse paralysis that had existed for more than 24 hours (Darouiche et al., 1992; Rigamonti et al., 1999) to 36 hours (Heusner, 1948; Danner and Hartman, 1987), or considered impractical because of panspinal infection, patients may be treated medically. Since it is impractical to perform decompressive laminectomy along the entire spine in patients with panspinal epidural abscess, less extensive surgery that consists of limited laminectomy, or laminotomy with cranial and caudal insertion of epidural catheters for drainage and irrigation, may be considered (Hollis et al., 1986). Nonsurgical therapy may also be considered in neurologically intact patients if the microbial etiology is identified and the patient's clinical condition is closely monitored, particularly when the radiological epidural abnormality can be explained by inflammatory findings (including postoperative changes) that are not caused by a true abscess. Although emergency decompressive laminectomy is not indicated in patients with paralysis for longer than 24–36 hours, surgical drainage may still need to be done to cure the epidural infection and control sepsis.

Antimicrobial therapy should be guided by the results of cultures of blood or CT-guided needle aspiration of the abscess (Lyu et al., 2002; Rust et al., 2005). Because of the potentially serious consequences of this infection and pending the results of cultures, empiric antimicrobial therapy should provide coverage not only against staphylococci (usually with vancomycin to treat the possibility of MRSA) but also against gram-negative bacilli (usually a third- or a fourth-generation cephalosporin, such as ceftazidime or cefepime, respectively), particularly in the presence of documented or suspected gram-negative bacterial infection of other sites such as the urinary tract. Since vancomycin is less active *in vitro* than β-lactam agents against meticillin (formerly methicillin)-susceptible *Staphylococcus aureus* (MSSA), nafcillin or cefazolin is preferred for treatment of documented MSSA infection. The usual duration of antimicrobial therapy is at least 6 weeks because vertebral osteomyelitis exists in most patients with spinal epidural abscess. Since noncompliance and limited bioavailability may have an adverse impact on oral therapy, intravenous administration of antimicrobial agents is preferred.

The patient's condition, neurological function, status of sepsis, and imaging findings should be closely monitored after initiating therapy regardless of the type of treatment. In patients with spinal epidural abscess associated with an infected spinal cord stimulator, it is important to remove the entire stimulator system (including the subcutaneously placed generator and epidural electrodes) to decrease the likelihood of recurrence of the implant-related epidural infection (Arxer et al., 2003; Rauchwerger et al., 2008). Subsequent development of an immunocompromising condition, or intake of immunosuppressive agents, may result in recurrence of spinal epidural abscess long after completion of antimicrobial therapy (Harrington et al., 2001). Patients with unexplained persistent or recurrent epidural infection may be assessed for rare sources of infection, such as intestinal spinal fistula for thoracolumbar abscess or esophageal tear for cervical abscess. Although glucocorticoid therapy has been sporadically reported to be associated with an adverse outcome in patients who already have a spinal epidural abscess (Danner and Hartman, 1987), these agents may be beneficial in reducing swelling while awaiting surgical decompression in patients with progressive neurological compromise, particularly if they are already receiving antimicrobial therapy that is active against the infecting pathogen. There have been anecdotal reports of using hyperbaric oxygen therapy to improve healing of wounds associated with spinal epidural abscess (Baechli et al., 2008), but the impact of this adjunctive therapeutic option is not well determined.

OUTCOME

The outcome of spinal epidural abscess is governed by the following two essential principles: (1) the neurological status of the patient immediately prior to surgery (Heusner, 1948; Baker et al., 1975; Danner and Hartman, 1987; Hlavin et al., 1990; Darouiche et al., 1992; Lu et al., 2002; Darouiche, 2006); and (2) the final neurological condition in patients in whom the spinal epidural abscess is adequately decompressed is as good as or better than the preoperative condition unless a perioperative complication occurs. Accordingly, patients who are operated upon in stage 1 or 2 are expected to remain neurologically intact and may have fewer complaints of spinal and radicular pain. Likewise, patients who undergo surgical decompression when they are in stage 3 may regain their baseline neurological function, experience a lesser degree of weakness, or remain weak after surgery. The neurological outcome in patients who have stage 4 spinal epidural abscess is dependent on the

period of time from the onset of paralysis to surgery. In general, patients who are operated upon within 24–36 hours of the onset of paralysis are likely to regain some neurological function postoperatively, whereas paralysis is likely to be irreversible in most patients who do not undergo decompressive laminectomy within 24–36 hours after they have become paralyzed. There are no published data comparing the postoperative outcome in patients who have been paralyzed for different periods of time during the 24–36-hour surgical window. It is possible, however, that earlier surgery in some patients with virulent infection and rapid deterioration of neurological condition may be associated with a better outcome.

In patients with rapid deterioration of neurological function, the time from admission to accurate diagnosis may indirectly reflect a worse outcome (Danner and Hartman, 1987; Darouiche et al., 1992). The degree of leukocytosis (Soehle and Wallenfang, 2002), level of elevation of the erythrocyte sedimentation rate (Lu et al., 2002) or C-reactive protein (Soehle and Wallenfang, 2002), and MRI findings related to the length of the abscess and extent of spinal canal stenosis (Tung et al., 1999) were reported to correlate with outcome. However, these potential relationships were assessed only by univariate analyses that did not consider the pretreatment neurological status and, therefore, need further study.

About one out of 20 patients with spinal epidural abscess die, usually because of uncontrolled sepsis, evolution of meningitis, or underlying illnesses (Darouiche, 2006). Since patients may continue to regain some neurological function up to 1 year after the onset of spinal cord damage, the final neurological outcome and functional capacity of patients should be assessed at that time. The most common complications of spinal cord injury are urinary tract infection, pressure sores, deep vein thrombosis, and pulmonary infection (Soehle and Wallenfang, 2002). The outcome of spinal epidural abscess can be optimized by providing well-coordinated multidisciplinary care by various health care providers, including emergency medicine physicians, hospitalists, internists, infectious diseases physicians, neurosurgeons, orthopedic surgeons, urologists, neurologists, nurses, and physical and occupational therapists.

Practices that could improve outcome

Since irreversible paralysis, the most fearsome complication of spinal epidural abscess, continues to affect 4–22% of patients (Baker et al., 1975; Danner and Hartman, 1987; Darouiche et al., 1992; Khanna et al., 1996), it is crucial to implement practices that could improve outcome. Although bacterial virulence and host characteristics may contribute to a worse outcome, delayed diagnosis and suboptimal management are the usual culprits. About half (range, 11–75%) (Tang et al., 2002; Davis et al., 2004) of patients with spinal epidural abscess may be initially misdiagnosed but, fortunately, not all diagnostic delays lead to worsening of neurological function and progression of sepsis. Even though cases diagnosed in a timely manner may still be improperly treated, suboptimal management often follows a delay in diagnosis. Table 7.2 addresses some diagnostic and therapeutic shortcomings and the recommended practices that could enhance the likelihood of rapid diagnosis and proper treatment, thereby resulting in better outcome of this serious infection.

Table 7.2

Shortcomings and recommended practices for improving outcome of spinal epidural abscess

Diagnostic shortcoming	Recommended practice
Ascribe all clinical and laboratory findings to vertebral osteomyelitis	Recognize that osteomyelitis commonly coexists with epidural abscess
Order imaging studies of an area that is not affected by epidural infection	Utilize the level of spinal tenderness and neurological deficit to localize the abscess
Unable to evaluate sensorimotor function in patients with altered mental status	Assess for presence of depressed reflexes and bladder and bowel dysfunction
Identify only one of multiple nonadjacent spinal epidural abscesses	Suspect other abscesses if bacteremia persists or neurological level changes after surgery
Therapeutic shortcoming	**Recommended practice**
Request nurses or clerks to call consultations for patients with suspected or documented epidural abscess	Communicate directly with consultants to ensure timely multidisciplinary treatment
Treat *Staphylococcus aureus* bacteremia without attempting to determine the source of infection	Consider spinal and paraspinal sources of bacteremia as indicated
Decompress epidural abscess but keep in place a spinal stimulator associated with the infection	Remove the implant to increase the chance of curing the infection

SPINAL SUBDURAL EMPYEMA

Most cases of subdural empyema are cranial and only a small portion affect the spinal area. As Table 7.3 shows, spinal subdural empyema and epidural abscess share some common characteristics as both are considered serious and emergency conditions, most commonly caused by *S. aureus*, best assessed by MRI, and require combined medical–surgical treatment. However, spinal subdural empyema and epidural abscess differ with regard to the incidence (fewer than 100 cases of spinal subdural empyema have been reported compared with several hundred cases of spinal epidural abscess), anatomic location (subdural empyema arises in the space between the dura and arachnoid, whereas the epidural abscess forms above the dura), source of infection (subdural empyema usually evolves secondary to disseminated infection from a distant site, but both metastatic spread and local extension contribute significantly to the development of spinal epidural abscess), and clinical manifestations (radicular pain and symptoms of cord compression are common to both entities, but spinal pain is more prominent with epidural abscess) (Vural et al., 2005).

Although most traumatic collections of fluid in the subdural space represent sterile hematoma rather than empyema (Greiner-Perth et al., 2007), a subdural hematoma occasionally becomes infected (Hoshina et al., 2008). Local interventions such as epidural injection (Volk et al., 2005), placement of dural grafts that are mostly infected by *Propionibacterium* (Barkhoudarian et al., 2005), dural tear (Wu et al., 2004), and acupuncture (Chen et al., 2004) can facilitate the evolution of subdural empyema. In patients with spinal epidural abscess, there exists a low but potential risk of inducing meningitis or subdural infection if the lumbar puncture needle traverses the epidural abscess (Hollis et al., 1986; Danner and Hartman, 1987; Hlavin et al., 1990; Darouiche et al., 1992). Likewise, meningitis can lead to subdural empyema via either direct spread or by translocation of organisms on the needle used to access the CSF (Dinleyici et al., 2007).

Spinal subdural empyema is a medical emergency that optimally requires treatment with proper antimicrobial agents and surgical drainage. Since the usual organisms that are isolated include *S. aureus*, streptococci, coagulase-negative staphylococci, and gram-negative bacilli, empiric antimicrobial therapy should include coverage against both gram-positive and gram-negative bacteria pending the results of cultures. Unless a patient is allergic to β-lactam agents, vancomycin should not be used for treatment of meticillin-sensitive staphylococci or streptococci. Rarely, spinal subdural empyema is caused by nonbacterial infections such as *Candida* species (Carter et al., 2008), tuberculosis (Alessi et al., 2003), and *Plasmodium falciparum* (Dwarakanath et al., 2004). Although the optimal duration of medical therapy is not clear, intravenous systemic antimicrobial agents are usually administered for 3–4 weeks, and up to 6 weeks if osteomyelitis is also present. As in patients with spinal epidural abscess, there exist few anecdotal reports of successful treatment of subdural empyema with antimicrobial therapy alone. However, since antimicrobials alone do not usually sterilize the subdural empyema, laminectomy is recommended in patients who can tolerate surgery to drain the purulent material in a timely fashion in an effort to preserve neurological function and control sepsis. Regardless of the modality of treatment, however, the clinical condition, microbiological findings, and imaging abnormalities should be closely monitored.

Table 7.3

Comparison of spinal epidural abscess and spinal subdural empyema

Characteristic	Subdural empyema	Epidural abscess
Type of condition	Serious emergency	Serious emergency
Reported cases	Fewer than 100	Several hundreds
Anatomic location	Between the dura and arachnoid	Above the dura
Source of infection	Metastasis from a distant site	Both metastatic and local spread
Most common pathogen	*Staphylococcus aureus*	*Staphylococcus aureus*
Clinical presentation	Radicular pain and cord compression	Spinal pain, radicular pain, and cord compression
Diagnostic imaging of choice	Magnetic resonance imaging	Magnetic resonance imaging
Optimal treatment	Antimicrobials plus surgical drainage	Antimicrobials plus surgical drainage

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Chapter 8

Suppurative intracranial thrombophlebitis

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INTRODUCTION

The first description of intracranial venous sinus thrombosis is believed to have been reported by Duncan, in 1821, involving a case of cavernous sinus thrombosis detected at autopsy (Chisolm and Watkins, 1920). Ribes, in 1825, described thrombosis of the superior sagittal sinus, the left transverse sinus, and a parietal cortical vein in an autopsied cancer patient who died after a 6-month illness characterized by severe headache, seizures, and delirium. An additional case of transverse sinus thrombosis detected at autopsy was described by Hooper in 1826. Bircher, in 1893, first described successful surgical treatment of cavernous sinus thrombosis (Pirkey, 1950), and Hoffman, in 1897, reported the successful surgical treatment of septic transverse sinus thrombosis (Stuart et al., 1951). Intracranial venous thrombosis was recognized as a cause of childhood epilepsy by Money in 1887 and of infantile hemiplegia by Gowers in 1888. Isolated septic thrombophlebitis of cortical veins, without venous sinus occlusion, was identified by Hoffman in 1897 (Stuart et al., 1951).

Until the latter half of the 20th century, intracranial venous thrombophlebitis remained a significant diagnostic challenge (Merwarth, 1942; Stuart et al., 1951). Maneuvers such as the Tobey–Ayer test, developed as a means of assessing transverse sinus patency based on cerebrospinal fluid (CSF) dynamics, were unreliable in many cases (Tobey and Ayer, 1925; Jahrsdoerfer and Fitz-Hugh, 1968). Precise diagnosis became possible with the development of angiography and venography, and for many years these remained a diagnostic gold standard (Krayenbühl, 1967; Smith, 1968; Blauenstein and Levy, 1969). Noninvasive diagnosis became possible in some cases through use of radionuclide scanning in the 1970s (Go et al., 1973) and in a larger number of patients, with the advent of computed tomography (CT) (Kingsley et al., 1978; Wendling, 1978). Reliable noninvasive imaging of the intracranial venous system, however, awaited the development of magnetic resonance imaging (MRI), MR venography, and, more recently, CT venography (Eick et al., 1981; Ford and Sarwar, 1981; Hickey et al., 1982; McArdle et al., 1987; Tsai et al., 1995; Casey et al., 1996; Leach et al., 2006; Linn et al., 2007; Stracke et al., 2007).

Until the 1930s, suppurative intracranial thrombosis remained a devastating, often fatal disease with occasional surgical successes. This changed with the introduction of sulfonamides as treatment for this condition, followed by penicillin in 1941 (Shaw, 1952). Heparin was first used as treatment in 1941 (Shaw, 1952). Antibiotic therapy and heparin remain the treatments of choice in most patients. Within the last several years, however, endovascular treatment involving clot disruption and thrombolytic agents has been used increasingly in the treatment of patients who deteriorate in the face of antibiotics and anticoagulation (Kourtopoulos et al., 1994; Niwa et al., 1998; Wasay et al., 2006; Albers et al., 2008).

EPIDEMIOLOGY

Prior to World War II, infections were a major cause of intracranial thrombophlebitis (Courville, 1934; Stuart et al., 1951; Southwick et al., 1986). The incidence of suppurative intracranial venous thrombosis declined significantly following the introduction of antibiotics, along with improved surgical techniques to deal with sinusitis and otitis and with refinement of techniques to provide adequate parenteral hydration (Southwick et al., 1986). By 1966, Weber, in his review of 63 cases of intracranial venous and venous sinus thrombosis, identified only four as being of infectious origin. Krayehbühl, in his 1967 review of cerebral venous and venous sinus thrombosis, associated 30 of 73 cases with infection. Of these, however, only 11 were associated with pericranial infections

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and seven with bacterial meningitis; the remainder were associated with systemic infections and may at least in part have represented sterile thrombosis as a consequence of dehydration or a hypercoagulable state (Krayenbühl, 1967). Bousser et al., in their 1985 review, identified an infectious cause of cerebral venous thrombosis in only four of 38 cases, with an additional four cases being associated with Behçet's disease. Southwick et al. (1986) were able to identify only 19 cases occurring at Massachusetts General Hospital over a period of 36 years from 1948 to 1984 and found only 136 cases in the literature during that same period. Daif et al., in a 1995 series of 40 patients in Saudi Arabia, calculated a hospital frequency of seven per 100 000 admissions, with the ratio of venous thromboses to arterial strokes being 1:62.5. In this series, infection (including Behçet's disease) was present in only three of 40 patients. Recent studies from Portugal, Canada, and the USA indicate that intracranial venous and venous sinus thrombosis from all causes accounts for 0.22 per 100 000 hospital admissions overall; for 0.67/100 000 admissions in infants and children under the age of 18; and for 11.6/100 000 admissions for pregnant women (Lanska and Kryscio, 2000; Deveber et al., 2001; Ferro et al., 2001). Of these, only a minority of cases are of infectious origin. Thrombosis of cortical and other veins still occurs as a complication of bacterial meningitis (Kastenbauer and Pfister, 2003). Suppurative thrombophlebitis of venous sinuses, on the other hand, is now the least common of the major focal intracranial infectious processes, occurring less frequently than intracranial epidural abscess, subdural empyema, brain abscess, or meningitis.

ETIOLOGY

Septic intracranial venous sinus thrombosis most commonly arises as a consequence of infection in the paranasal sinuses and less frequently following infections of the middle ear or mastoid. In each case, the infection usually results in septic thrombophlebitis of local veins, followed by extension to the intracranial venous circulation via emissary veins (Bleck and Greenlee, 2000a,b). Cortical vein or venous sinus thrombosis may also occur during bacterial or less frequently, tuberculous or fungal meningitis (Pfister et al., 1992; Kastenbauer and Pfister, 2003). Superior sagittal sinus thrombosis has been reported as a complication of calvarial tuberculosis (Sundaram and Sayed, 2007). Occasional cases may develop following craniofacial trauma or surgery. The most common isolate from cases of septic intracranial venous thrombosis associated with pericranial infections is *Staphylococcus aureus*, which will be found in approximately two-thirds of cases and is particularly common in cases of cavernous sinus thrombosis (Southwick et al., 1986; Southwick, 1995) (Table 8.1). *Fusobacterium* species, in particular *F. necrophorum*, are important agents in otitis and mastoiditis. These organisms are

Table 8.1

Major reported organisms in suppurative intracranial thrombophlebitis

	Cavernous sinus	Lateral sinus	Superior sagittal sinus	Internal jugular vein
Sites of primary infection	Face, nose, paranasal sinuses	Middle ear; mastoid	Paranasal sinuses; bacterial meningitis	Orpharyngeal infections (otitis; intravenous drug abuse)
Major organisms*	*Staphylococcus aureus*	*Staphylococcus aureus* *Fusobacterium* spp. *Proteus* spp.	*Streptococcus pneumoniae*† β-hemolytic streptococci *Klebsiella* spp.	*Fusobacterium necrophorum*
Less common organisms	Streptococci *Streptococcus pneumoniae* Gram-negative bacilli *Bacteroides* spp. *Fusobacterium* spp.‡ *Rhizopus* spp.§	*Escherichia coli* *Bacteroides fragilis* Anaerobic streptococci	*Staphylococcus aureus* *Pseudomonas* spp. *Trichinella* spp.	Other *Fusobacterium* spp. *Staphylococcus aureus* Viridans streptococci *Porphyromonas asaccharolytica*

*It is important to keep in mind that multiple organisms may be present and should be considered in developing provisional treatment.
†*S. pneumoniae* is also the major organism associated with isolated cortical vein thrombosis in cases of bacterial meningitis.
‡*Fusobacterium* spp. is most closely associated with otitis and mastoiditis. It is most closely associated with Lemierre's syndrome followed by lateral sinus thrombosis, but has been associated with cavernous sinus thrombosis.
§In particular in diabetics or patients infected with human immunodeficiency virus (HIV).

associated most closely with transverse sinus and internal jugular vein thrombosis, but may also cause suppurative cavernous sinus or superior sagittal sinus thrombosis (Chirinos et al., 2002; Bentham et al., 2004). The organisms may also cause suppurative thrombophlebitis resulting from dental or pharyngeal infection (Jones et al., 1990; Bader-Meunier et al., 1994; Klinge et al., 2002; Giridharan et al., 2004; Brown and Wallwork, 2007). Less frequent organisms include streptococci, including anaerobic and microaerophilic species, *Streptococcus pneumoniae*, and gram-negative organisms, including *Haemophilus influenzae, Listeria monocytogenes*, and *Bacteroides* species (Southwick et al., 1986). Polymicrobial infections may also occur. The most frequent organism where septic venous thrombophlebitis occurs as a complication of bacterial meningitis is *S. pneumoniae*, but cortical vein thrombosis may also occur during severe meningitis due to other gram-positive and gram-negative agents (Robinson et al., 1968; Jones et al., 1990; Pfister et al., 1993). In diabetics or other immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS), *Rhizopus* (*Mucor*) may cause cavernous sinus thrombosis as part of an extremely destructive nasofacial infection which may also involve the carotid arteries (Press et al., 1988; Van et al., 1988; Onerci et al., 1991; Mandava et al., 2001). Rare cases of intracranial venous sinus thrombosis have been associated with *Trichinella* infestation (el Koussa et al., 1994). Aseptic venous sinus thrombosis, in particular involving the superior sagittal sinus, may occur in patients with Behçet's disease (Alper et al., 2001; Saltik et al., 2004; Bir et al., 2005; Yazici et al., 2007).

PATHOGENESIS AND PATHOPHYSIOLOGY

Anatomy of the cerebral veins and venous sinuses

Drainage of venous blood from the central nervous system occurs via a complex network of cerebral veins. These empty into dural venous sinuses which, in turn, empty predominantly into the systemic circulation via the internal jugular veins. Additional routes of venous drainage are provided by venous plexuses at the base of the brain which connect with the deep veins of the face and neck, and by veins which cross the frontal bone to anastomose with veins in paranasal sinuses and the orbital region of the face (Figs 8.1 and 8.2). The venous sinuses and the superficial and deep veins are extensively interconnected, and there is also communication of superficial veins and venous sinuses with the extracranial venous system via emissary veins which cross the skull. The intracranial venous system is a low-pressure system, unlike the cerebral arteries, and neither intracranial veins nor venous sinuses have valves. Because of these anatomical features, the direction of venous flow may reverse in response to hemodynamic changes and even with change in position (Toole, 1999). Merwarth, in a classical review of cerebral venous anatomy and physiology, likened the intracranial venous system to an enormous sponge (Merwarth, 1942).

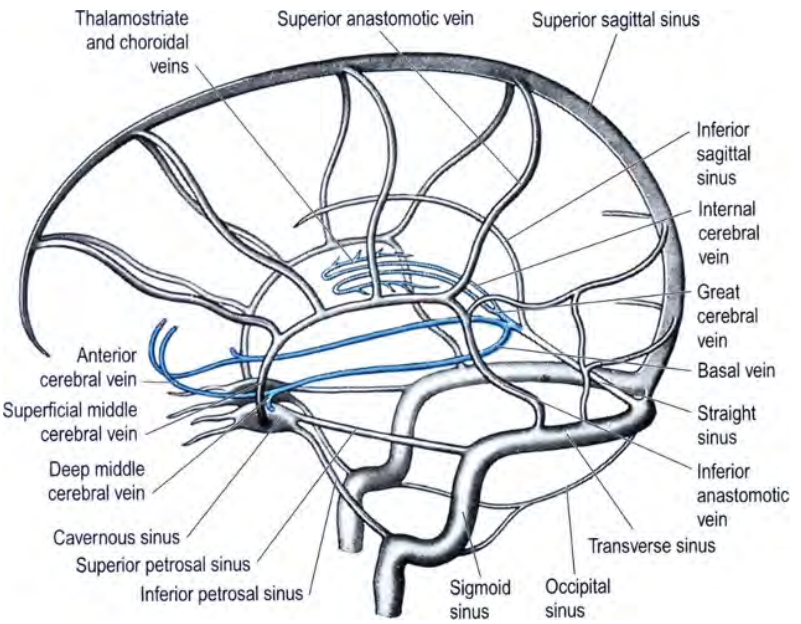

Fig. 8.1. The major cerebral veins and venous sinuses. (Reproduced from Crossman and Standring (2005a), with permission of the publisher.)

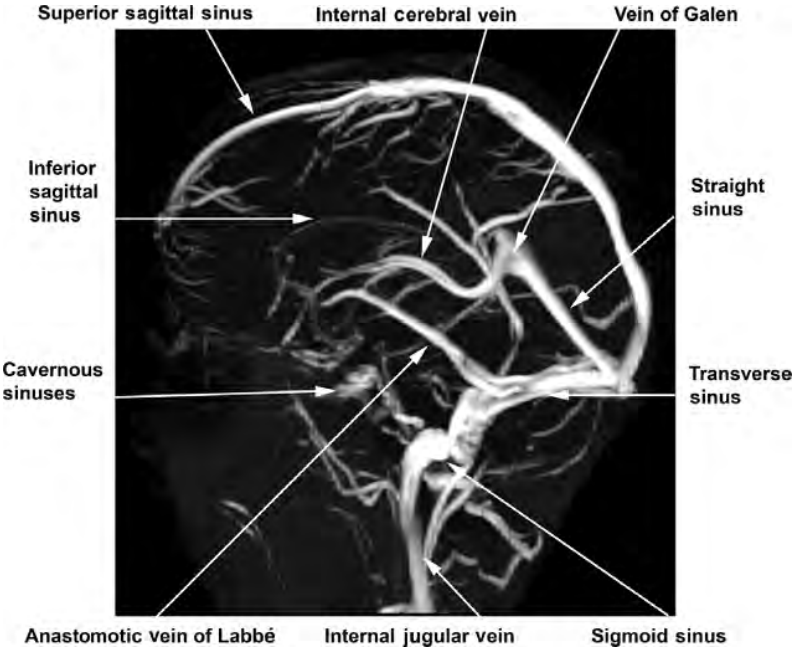

Fig. 8.2. Normal magnetic resonance venogram showing the major cerebral veins and venous sinuses. (Courtesy of Dr. Karen Salzman.)

The cerebral veins

The cerebral veins are divided into superficial and deep groups. In both humans and animals, patterns of venous drainage are extremely variable. For this reason, although certain larger veins are consistent enough to have received specific names (Fig. 8.1), venous drainage is basically regional.

Superficial cerebral veins

The superficial veins lie in troughs in the cerebral sulci, roughly following but superficial to arteries, and are divided about a watershed area above the sylvian fissure into veins which drain upward into the superior sagittal sinus and veins emptying downward into the basilar venous sinuses (Dowman, 1926; Merwarth, 1942; Swanson and Fincher, 1954; Parsons, 1967). The superolateral surface of the cerebral cortex is thus drained by cerebral veins which empty into the superior sagittal sinus, with their terminal 1–3 cm lying within the walls of the sinus itself (Gillilan, 1962). Much of the remainder of the lateral portion of the cerebrum is drained by one or more superficial middle cerebral veins (sylvian veins) which empty into the cavernous sinuses. The sylvian veins also connect with the superior sagittal sinus via the greater anastomotic vein of Trolard and with the transverse sinuses through the lesser anastomotic veins of Labbé. The major vein draining the superolateral surface of the brain, the rolandic vein, follows the central sulcus to empty into the superior sagittal sinus but may also communicate with the sylvian veins. Veins of the frontal pole and interior surfaces of the frontal lobes drain upward into the superior sagittal sinus and downward into the cavernous and sphenopalatine sinuses or into the sylvian veins. The portions of the temporal and occipital lobes lying at the base of the brain usually drain via inferior cerebral veins into the transverse sinus. The medial surface of the occipital lobes, including the calcarine cortex, drains into the great cerebral vein of Galen.

Deep cerebral veins

Deep venous drainage of the cerebral hemispheres, including the basal ganglia and thalamus, is supplied by veins which join the septal and choroidal veins to form the internal cerebral vein (Figs 8.1 and 8.2). Additional deep veins join veins supplying the insula to form the basal vein of Rosenthal. The internal cerebral veins and the basal vein of Rosenthal merge to form the great cerebral vein of Galen. Cerebellar veins drain predominantly into the transverse and superior petrosal sinuses and into the vein of Galen but may also empty into the internal cerebral veins, or into the transverse, superior petrosal, or occipital sinuses. The pons and upper medulla drain into the inferior petrosal sinus. The lower portion of the medulla drains inferiorly into the marginal sinus or directly into vertebral veins.

The transcerebral venous system

The superficial and deep cerebral veins are connected by an extensive system of small-caliber veins which roughly follow the course of the corona radiata (Kaplan, 1959). These small veins fall into three groups: (1) an anterior group which connects the rostral cerebral cortex to veins draining the anterior portions of the basal ganglia and thence the septal veins; (2) a middle group which joins with veins draining the basal ganglia to form the terminal vein; and (3) a group of veins which converge ventral to the atrium of the lateral ventricle (Schlesinger, 1939; Kaplan, 1959).

Venous sinuses

The venous sinuses are endothelium-lined channels whose outer walls are comprised of the cranial dura. The dural venous sinuses are without muscular tissue and are held open by the tension of the dura and its attachment to the overlying skull. The venous sinuses, like the cerebral veins, have no valves (Crossman and Standring, 2005a). Although the venous sinuses are thought of as single-lumen channels, this is not always the case: during development, the venous sinuses arise as venous plexuses. This plexiform structure persists in the cavernous sinuses and may be present throughout life in other venous sinuses as well. The sinuses most frequently involved by suppurative processes are the cavernous sinus, the superior sagittal sinus, and the transverse sinuses.

The cavernous sinuses

These are the venous sinuses most frequently involved by infectious processes. The cavernous sinuses (Figs 8.1 and 8.2) are plexiform channels which lie on either side of the sella turcica and extend backward along the sphenoid bone from the superior orbital fissure to the apices of the petrous portion of each temporal bone, surrounding the sphenoid sinus and the pituitary gland (Figs 8.1 and 8.2) (Crossman and Standring, 2005a). The cavernous sinuses, unlike the other dural sinuses, are not completely embedded within the dura. In some individuals, the walls of the sphenoid sinus may be incomplete, and the cavernous sinuses may be separated from the sphenoid sinus by only a thin wall of soft tissue (Harris and Rhoton, 1976; Lew et al., 1983). The cavernous sinuses are traversed by the intracranial portions of the internal carotid arteries and their sympathetic plexuses and also contain, covered by a layer of endothelial cells, cranial nerves III, IV, and VI, as well as the ophthalmic and maxillary divisions of cranial nerve V. The two cavernous sinuses are connected through intercavernous sinuses and receive venous drainage from the superficial middle cerebral veins, the superior and inferior ophthalmic veins, and veins from the hypophyseal plexus.

The transverse (lateral) sinuses

This is the venous sinus most commonly involved by infections involving the middle ear and mastoid. The transverse sinuses (Figs 8.1 and 8.2) begin beneath the occipital protuberance to run laterally along the line of attachment of the tentorium cerebelli and empty into the internal jugular vein through S-shaped sigmoid sinuses. The superior sagittal sinus drains predominantly into the right transverse sinus, so that, in most individuals, the right transverse sinus drains supratentorial structures. Although there is extensive individual variation, the left transverse sinus serves as a route of venous drainage from the cerebellum and brainstem structures.

The superior sagittal (longitudinal) sinus

This extends posteriorly along the vertex from the frontal pole to drain into the transverse sinuses. The wall of the superior sagittal sinus (Figs 8.1 and 8.2) contains lateral lakes into which the parameningeal veins empty. The superior sagittal sinus is the major route of venous drainage for cerebral veins on the top half of the lateral and medial surfaces of the brain. In addition, the proximal one-third of the sinus also contains the majority of the arachnoid villi which provide drainage of CSF into the venous circulation.

Other venous sinuses

A number of smaller venous sinuses also exist. These are less common sites of septic intracranial venous thrombosis, except as a consequence of infection of the cavernous, superior sagittal, or transverse sinuses. The inferior sagittal sinus is formed within the free edge of the falx cerebri by the confluence of veins draining the falx cerebri and empties into the straight sinus. The sphenoparietal sinus connects both to the cavernous sinus and to the superior sagittal sinus. The inferior petrosal sinus extends from the posterior inferior end of the cavernous sinuses to the sigmoid sinuses. The base of the brain is drained by a basilar venous plexus. The hypophysis is also surrounded by a dense venous plexus which is similar in structure to the cavernous sinuses.

Emissary veins

These are veins which cross the skull to connect the cerebral veins and venous sinuses with veins draining the sinuses, face, scalp, and pharyngeal structures (Crossman and Standring, 2005b). The emissary veins serve as an alternative route of intracranial venous drainage but also represent the major route by which

Table 8.2

The major emissary veins

Emissary vein or sinus	Point of entry into cranium	Associated intracranial venous sinus	Associated extracranial veins
Mastoid emissary vein	Mastoid foramen	Sigmoid sinus	Posterior auricular vein; occipital vein
Parietal emissary vein	Parietal foramen	Superior sagittal sinus	Scalp veins
Venous plexus of the hypoglossal canal	Hypoglossal canal	Sigmoid sinus	Internal jugular vein
Posterior condylar emissary vein	Posterior condylar canal	Sigmoid sinus	Veins of occipital triangle
Venous plexus of the foramen ovale	Foramen ovale	Cavernous sinus	Pterygoid plexus
Veins of foramen lacerum	Foramen lacerum	Cavernous sinus	Pharyngeal veins Pterygoid plexus
Vein of emissary sphenoidal foramen (of Vesalius)	Emissary sphenoidal foramen	Cavernous sinus	Pharyngeal veins Pterygoid plexus
Internal carotid venous plexus	Carotid canal	Cavernous sinus	Internal jugular vein
Petrosquamous sinus		Transverse sinus	External jugular vein
Nasal emissary vein	Foramen caecum	Superior sagittal sinus	Nasal veins
Occipital emissary vein	Occipital protruberance	Confluence of sinuses	Occipital vein
Occipital sinus	Foramen magnum	Occipital sinus	Vertebral venous plexuses

In addition, multiple smaller veins cross the skull to connect with the superficial venous system. The most important of these are the veins connecting with superficial veins draining the facial triangle, nasal mucosa, sinuses, middle ear, and mastoid.

infectious agents gain access to cerebral veins and venous sinuses. The most important of the emissary veins in terms of infections are those which connect intracranial venous structures with veins draining the sinuses, middle ear, and mastoid. Multiple other emissary veins exist; these vary in distribution from patient to patient (Table 8.2).

Pathogenesis and mechanisms of injury

Suppurative intracranial thrombophlebitis is most frequently the result of pericranial infection. The local infection causes septic thrombophlebitis of veins draining the infected area, with subsequent intracranial extension of the infected thrombus along emissary veins. Occasionally, the infection may also spread directly through haversian channels in bone. Prior to 1945, the most common site of primary infection involved what has been termed the "facial triangle" or "muzzle area": the medial third of the face, including nose, orbits, soft palate, and tonsils (Southwick et al., 1986; Southwick, 1995). At present, infection most often originates in the sphenoidal, ethmoidal, and frontal sinuses, with a smaller number of cases following otitis or mastoiditis and occasional cases occurring after craniofacial trauma or surgery. In most cases, infection of intracranial veins and venous sinuses occurs near the site of primary infection: suppurative cavernous sinus thrombosis is usually associated with sinusitis and less frequently with otitis or mastoiditis. Thrombosis of the superior sagittal sinus is usually associated with sinusitis or meningitis. Thrombosis of the transverse sinuses is usually the result of spread of infection from middle ear or mastoid (Kinal and Jaeger, 1960). Suppurative thrombophlebitis of cortical veins, in the absence of venous sinus thrombosis, is most commonly the result of bacterial meningitis or subdural empyema (DiNubile et al., 1990; Kastenbauer and Pfister, 2003), but has also been reported as a complication of tuberculous meningitis (Poltera, 1977). In a minority of cases, suppurative intracranial thrombophlebitis may be the result of hematogenous spread of organisms from a distant site of infection (Jinbayashi et al., 1997).

Initial septic thrombosis of emissary veins preceding intracranial venous thrombosis may be asymptomatic or may produce local pain. The pain caused by the septic thrombus, however, is often obscured by pain from the accompanying sinusitis or otitis. In rare cases, septic thrombosis of emissary veins may produce venous necrosis at the interface between skull and dura, causing a venous epidural hemorrhage (Rajput and Rozdilsky, 1971; Moonis et al., 2002). Extension

of the thrombotic process intracranially may cause only transient neurological findings and may also be silent except for its interference with CSF reabsorption. Occlusion of the anterior third of the superior sagittal sinus, where most CSF reabsorption occurs, may result in hydrocephalus without other neurological signs (Kristensen et al., 1992). Hydrocephalus may also occur as a result of transverse or sigmoid sinus occlusion where the contralateral sinus is hypoplastic or otherwise compromised (Symonds, 1956). So long as collateral venous drainage is sufficient, thrombosis of intracranial veins or venous sinuses may not result in focal neurological findings. Where the thrombotic process outstrips venous collateral reserve, however, subarachnoid or parenchymal hemorrhage, cerebral edema, or infarction may result (Fig. 8.3). The presentation here may mimic arterial stroke, or brain abscess, often with impairment of consciousness, focal or generalized seizures, and increased intracranial pressure. Venous infarcts do not follow typical arterial patterns and are frequently hemorrhagic, due both to increased venous pressure and also to infection and necrosis of vessel walls (Fig. 8.3). Focal neurological findings include hemiparesis which may involve the face and hand if veins over the cerebral convexity are involved. Thrombosis of veins along the falx cerebri may produce unilateral leg weakness which can become bilateral if propagation of the thrombus involves the veins of the contralateral hemisphere. Because of the extensive anastomotic connections between cortical veins, focal thrombosis may not produce a corresponding neurological deficit at the outset, and signs may develop in a fluctuating or stuttering fashion as additional veins become compromised. Suppurative intracranial thrombophlebitis may be a source of septic emboli to lungs or other tissues and may also be accompanied by other intracranial processes, including epidural abscess, subdural empyema, meningitis, and brain abscess, as well as by distant septic embolization (Bleck and Greenlee, 2000a,c). Carotid involvement within an infected cavernous sinus may cause vasospasm, occlusion, or mycotic aneurysm (Parsons, 1967; Southwick et al., 1986; Quisling et al., 2003).

CLINICAL FEATURES

Suppurative intracranial thrombophlebitis is often thought of in terms of syndromes representing involvement of specific veins or venous sinuses (Table 8.3). It must be kept in mind, however, that the suppurative process may involve multiple cortical or deep veins as well as more than one venous sinus. Furthermore, clinical findings may vary over time, as additional veins or venous sinuses are involved, and may also fluctuate on

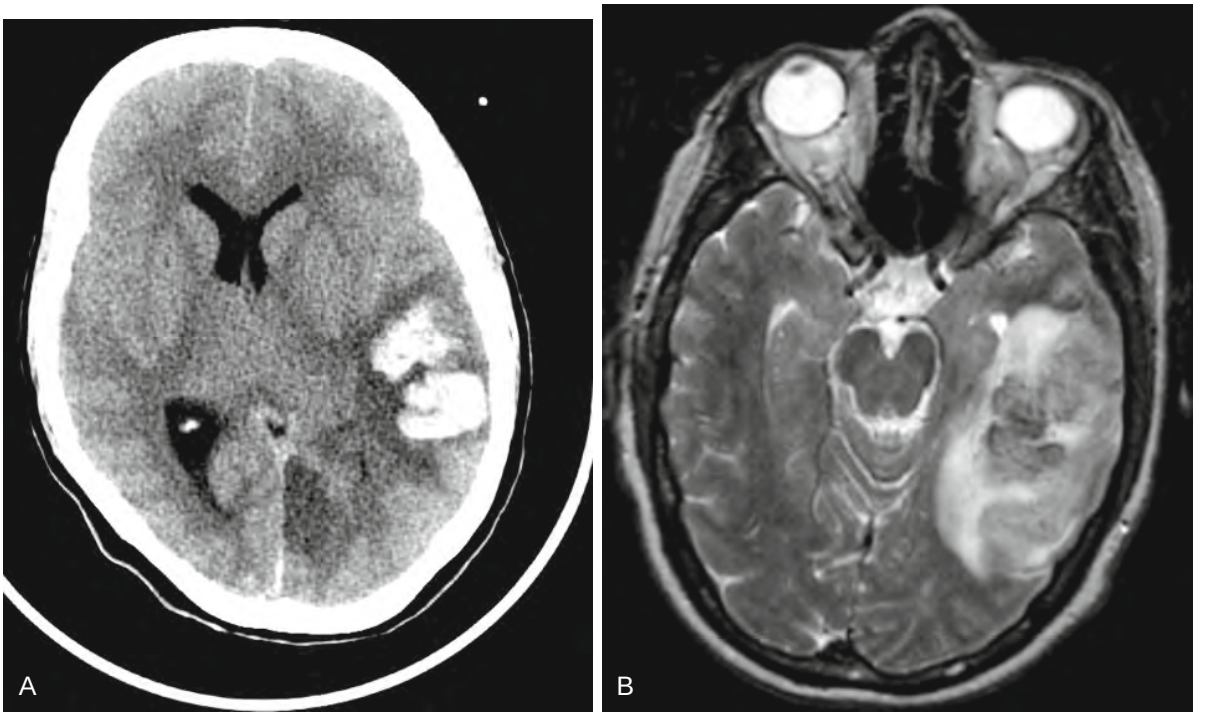

Fig. 8.3. Cerebral infarct of venous origin shown (A) on computed tomography (CT) and (B) on magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR) sequence. Both CT and MRI show hemorrhagic infarct with surrounding edema. The infarct does not involve a typical arterial distribution. (Courtesy of Dr. Karen Salzman.)

Table 8.3

Symptoms of suppurative intracranial venous sinus or cerebral vein thrombosis

Structure involved	Associated infection	Anatomical structures affected	Classical findings
Cavernous sinus	Paranasal sinuses, especially frontal, ethmoid, or sphenoid; infections of "facial triangle" or mouth	Venous drainage from orbit and eye; cranial nerves III, IV, V, and VI, within cavernous sinus Internal carotid arteries	Unilateral periorbital edema; exophthalmos, chemosis. Examination shows venous engorgement of retinal vessels or papilledema, palsies of extraocular muscles, diminished pupillary reactivity, frequently diminished corneal reflex, and impaired sensation in V1 and V2 distributions of cranial nerve V. Involvement of the internal carotid artery within the sinus may cause arterial occlusion. Identical findings may develop in the contralateral eye following spread of thrombosis to the contralateral cavernous sinus
Lateral sinus	Otitis media or mastoiditis; rarely pharyngitis	Cranial nerves V and VI. Venous route of CSF drainage (venous supply of temporal lobe, jugular bulb, cranial nerves IX, X, and XI at jugular foramen)*	Onset of symptoms may be gradual. Findings include ear or mastoid pain, lateral rectus palsy, facial pain and altered facial sensation. Increased intracranial pressure with papilledema may develop if the contralateral lateral sinus is hypoplastic or compromised (temporal lobe seizures)
Superior sagittal sinus	Infections of face, scalp, subdural, or epidural spaces Meningitis	CSF reabsorption (anterior one-third of the superior sagittal sinus). Venous drainage from medial and superolateral portions of cerebral hemispheres	Bilateral leg > arm weakness with corticospinal tract signs in legs > arms. Motor findings may be bilateral, complex, and variable. Intracranial hypertension may be present in isolation if thrombosis is confined to anterior third of sinus
Superior petrosal sinus	Otitis media or mastoiditis	Trigeminal ganglion (venous drainage from temporal lobe)	Ipsilateral pain or sensory deficit (temporal lobe seizures)
Inferior petrosal sinus	Otitis media or mastoiditis	Cranial nerves V and VI at tip of petrous bone	"Gradenigo syndrome": ipsilateral facial pain and sensory deficit with ipsilateral lateral rectus palsy

Table 8.3

Continued

Structure involved	Associated infection	Anatomical structures affected	Classical findings
Internal jugular vein thrombosis (Lemierre's syndrome)	Oropharyngeal infections, otitis, illicit use of intravenous drugs	Intracranial venous drainage	Pharyngeal or neck pain, neck swelling, septic pulmonary emboli.[†] Retrograde extension of the thrombus may involve cavernous sinus, sigmoid sinus, or other intracranial venous structures
Deep cerebral veins	Not usually due to infection	Venous drainage from basal ganglia and thalami	Acute onset of coma, decerebrate posturing, and extrapyramidal alteration in muscle tone

*Brackets indicate structures affected or symptoms produced by extension of the sinus thrombosis into cortical veins.
[†]Pulmonary emboli may arise from other thrombosed venous sinuses but are especially common in internal jugular vein occlusion.
CSF, cerebrospinal fluid.
Adapted from Bleck and Greenlee (2000a).

an hour-to-hour basis depending upon variations in venous hemodynamics. The clinical picture may also be influenced by the presence of concomitant parameningeal infection, meningitis, or brain abscess. In general, findings include fever, headache with or without signs of meningeal irritation, alteration in consciousness, and focal or generalized seizures. Papilledema is often present but may be absent early in the course of infection. Cranial nerve VI palsy may be present due to increased intracranial pressure. Proptosis or deficits involving cranial nerves III, IV, V, or VI suggest involvement of the cavernous sinus. Bousser et al., in their 1985 review of patients with cerebral venous thrombosis, including both infectious and noninfectious cases, reported headache in 74% of patients, papilledema in 45%, hemiplegia in 34%, seizures in 29%, confusion or coma in 26%, and dysphasia in 1%. One of their patients exhibited multiple cranial nerve palsies, and one showed cerebellar incoordination. Cough with production of bloody sputum may indicate pulmonary emboli from involved intracranial veins (Southwick et al., 1986). Because suppurative intracranial thrombophlebitis is currently an unusual disorder, overall estimates of mortality from suppurative intracranial thrombophlebitis in the modern age are difficult to obtain, and most modern series include small numbers of suppurative cases with a much larger number of cases of noninfectious origin. Dentali et al., in a review of published studies between 1966 and 2005, gave an overall mortality of 5.6%, but with a range 0–15.2% (Dentali et al., 2006). The presence of infection, however, constituted a hazard ratio of 3.34 (Dentali et al., 2006). Prognosis is much more grave in cortical vein or sinus thrombosis complicating bacterial meningitis and also where there is thrombosis of the deep cerebral veins (Pfister et al., 1992; Crawford et al., 1995; Kastenbauer and Pfister, 2003). The clinical syndromes associated with specific venous structures are discussed in the following sections.

Suppurative cavernous sinus thrombosis

The cavernous sinuses are the structures most frequently involved in septic venous sinus thrombosis (Fig. 8.4). This is in contrast to cases occurring due to noninfectious venous sinus thrombosis, which most frequently affect the superior sagittal sinus in adults and the superior sagittal or transverse sinuses in children (Schell and Rathe, 1988; Saw et al., 1999; Terazzi et al., 2005; Dalgic et al., 2008; Teksam et al., 2008; Wasay et al., 2008). Prior to 1945, as mentioned above, the most common sites of primary infection involved the medial third of the face, including nose, orbits, soft palate, and tonsils (Southwick et al., 1986), with a smaller number of cases resulting from sinusitis, otitis, or mastoiditis (Shaw, 1952; Southwick et al., 1986; Southwick, 1995). Facial or otitic infections may still lead to cavernous sinus thrombophlebitis. Since the advent of antibiotics, however, episodes of cavernous sinus thrombosis secondary to facial infections, otitis, or mastoiditis have become infrequent, and the most common sites of infection have become the sphenoid,

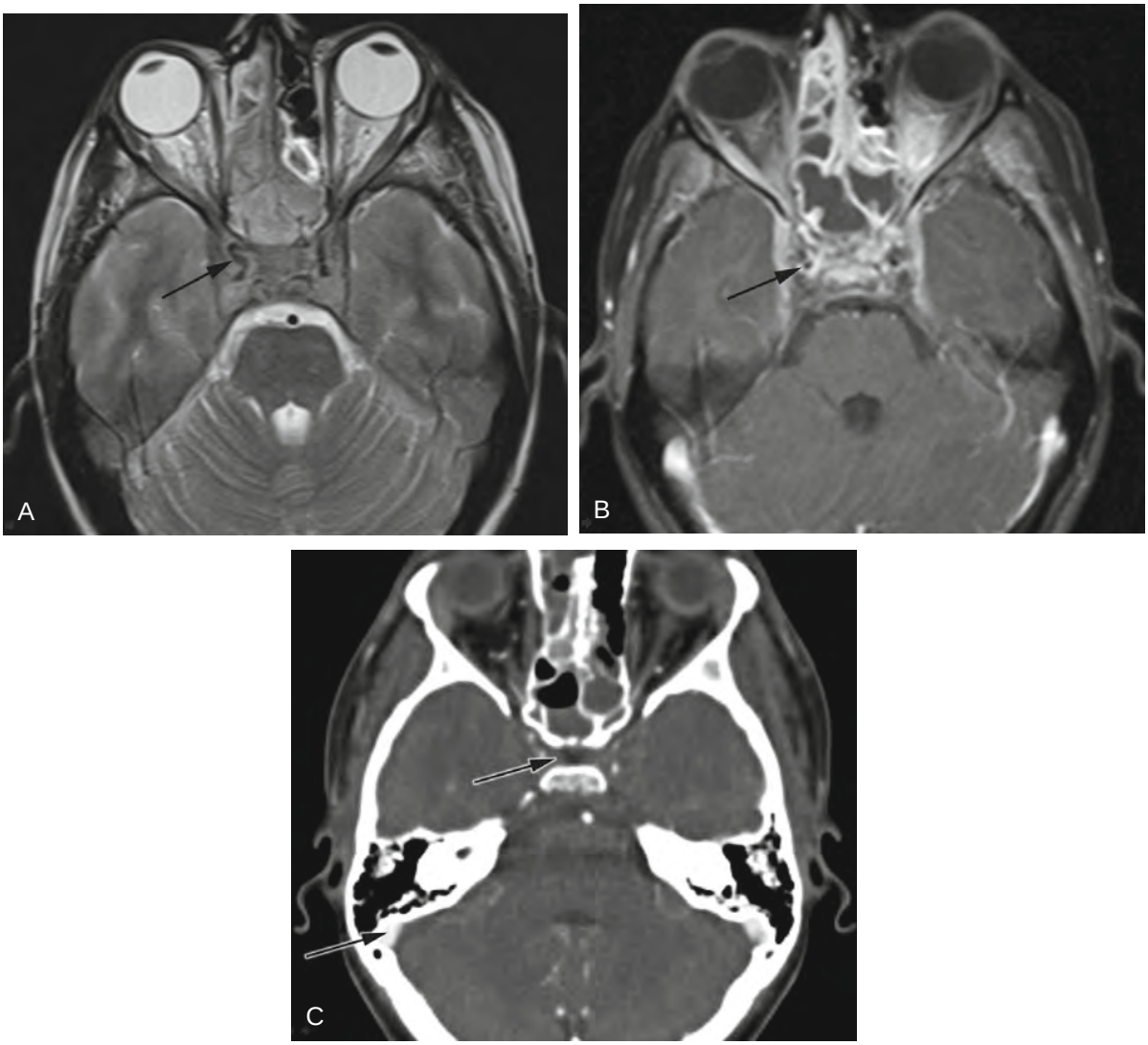

Fig. 8.4. Cavernous sinus thrombosis. (A) T2-weighted magnetic resonance imaging (MRI). There is extensive sinusitis involving frontal, ethmoidal, and sphenoidal sinuses. There is altered signal within the cavernous sinus. The carotid arteries are narrowed within the sinus (arrow). (B) Gadolinium-enhanced T1-weighted MRI showing extensive sinusitis and irregular enhancement within the cavernous sinus. Narrowing of the carotid arteries is again seen (arrow). (C) Computed tomography venogram. Contrast is seen within the sigmoid sinuses posterior to the petrous portion of the temporal bone (arrow) but is absent within the cavernous sinus (arrow). (Courtesy of Dr. H. Christian Davidson.)

ethmoidal, and, to a lesser degree, frontal sinuses (Sofferman, 1983; Southwick et al., 1986; DiNubile, 1988; Thatai et al., 1992; Southwick, 1995; Chen et al., 2006; Pavlovich et al., 2006). A small number of cases result from primary dental infections, trauma, or complications of surgery (Coll et al., 1994; Ahmmed et al., 1996; Sadun et al., 1996). Spread of infection from facial infections usually occurs via the pterygoid venous plexus and superior or inferior ophthalmic veins (Southwick et al., 1986). Spread from sphenoidal or ethmoidal sinuses can occur either through emissary veins or directly through haversian channels in bone. *S. aureus* is the major isolate in up to 70% of cases, with a lesser number of cases being caused by aerobic and anaerobic streptococci, *S. pneumoniae, H. influenzae, Fusobacterium* species or *Bacteroides* (Southwick et al., 1986; Southwick, 1995). In diabetics or other immunosuppressed patients, including patients with AIDS, *Rhizopus*, as mentioned above, may cause cavernous sinus thrombosis as part of an extremely destructive nasofacial infection. Rare similar cases have also been associated with *Aspergillus* (Deveze et al., 2005).

Eagleton, in 1926, described clinical criteria suggesting the diagnosis of cavernous sinus thrombophlebitis. These included generalized sepsis; venous obstruction

of the retina, conjunctiva, and eyelid; paresis of the third, fourth, and sixth cranial nerves; meningeal irritation; and proptosis. These criteria hold true at present as well, although evidence of systemic sepsis is much more frequently lacking. Onset of symptoms is frequently abrupt. Engorgement or thrombosis of the facial veins may occur. The initial symptoms are usually diplopia, reflecting involvement of cranial nerve III within the wall of the cavernous sinus, photophobia, and eye pain. Orbital edema, progressive exophthalmos, loss of the pupillary light reflex, and papilledema may occur. The ocular symptoms seen in cavernous sinus thrombosis may be mimicked by orbital cellulitis. Orbital cellulitis, however, will usually not cause papilledema or as severe toxic symptoms, will not usually result in abnormal spinal fluid, and is readily discriminated from cavernous sinus thrombophlebitis by MRI.

Involvement of cranial nerves III, IV, and VI may produce ophthalmoplegia and a midposition fixed pupil. Involvement of cranial nerve V fibers may cause loss of the corneal reflex, and diminished sensation over the face. Impedance of retinal venous return may cause papilledema, retinal hemorrhages, and visual loss (Gupta et al., 1990; Sud et al., 1990; Arat et al., 2004). Similar findings may develop in the opposite eye as the infection spreads to the contralateral cavernous sinus. Involvement of the carotid artery within the sinus may cause arterial vasospasm or occlusion (Fig. 8.5), with ensuing arterial ischemia and stroke (Van et al., 1988; Endo et al., 1989; Hoshino et al., 2007). In one reported case, blindness in septic cavernous sinus thrombophlebitis resulted from optic nerve compression by an enlarging carotid mycotic aneurysm (Quisling et al., 2003); and one case has been reported of visual loss due to what was thought to represent recurrent embolization from focal carotid arteritis in the setting of septic cavernous sinus thrombosis (Gupta et al., 1990). Further propagation of septic thrombophlebitis, in particular where there is delay in diagnosis, will result in a widely variable pattern of cortical venous thrombosis, at times with involvement of other venous sinuses. As in cases where other venous sinuses are involved, suppurative cavernous sinus thrombophlebitis may be accompanied by epidural abscess, subdural empyema, meningitis, or brain abscess (Chang et al., 2003; Kamouchi et al., 2006; Munckhof et al., 2008). Death in preantibiotic days was almost invariable (Yarington, 1961). Shaw, in a 1952 review of 35 cases of septic cavernous sinus thrombophlebitis treated with penicillin, found a mortality rate of 8.6%, with 43% of surviving patients having significant neurological sequelae, including blindness or lesser degrees of visual impairment and palsies of cranial nerves III, IV, V, and VI (Shaw, 1952). In his series, nine patients developed orbital abscesses, five developed brain abscesses, and 25 patients had evidence of septic pulmonary embolization. Despite advances in imaging techniques, antibiotic therapy, and surgical methodology, mortality and morbidity in more recent series have been as high as 20–30% (Miller, 1991; Ebright et al., 2001; Chen et al., 2006).

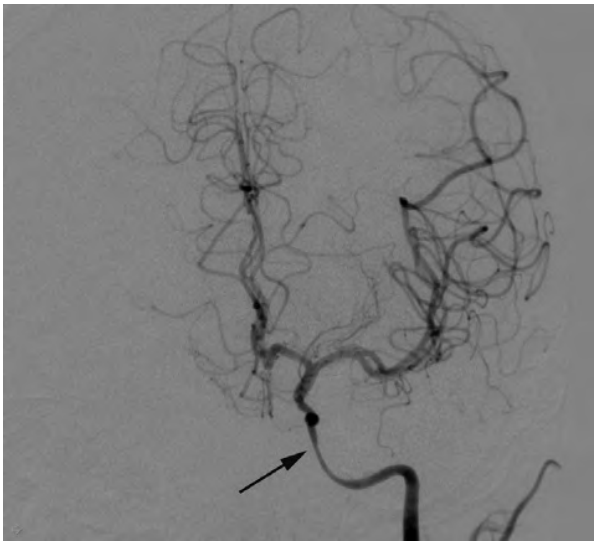

Fig. 8.5. Carotid arteriogram in cavernous sinus thrombosis showing spasm of the petrous portion or the internal carotid artery (arrow). (Courtesy of Dr. H. Christian Davidson.)

Transverse (lateral) sinus thrombosis

The transverse sinuses are the second most frequent intracranial venous sinuses to be involved by septic processes (Fig. 8.6). Southwick et al., in their 1986 case series and review, identified four cases at their own institution and collected 60 others from the literature, as compared with a total of 96 cases of cavernous sinus thrombophlebitis. Middle ear and mastoid are the major predisposing sites of infection: infection may be acute or chronic and either symptomatic or silent (Southwick et al., 1986). Courville, based on pathological studies prior to the advent of antibiotics, estimated that intracranial complications of otitis media caused 25 out of every 1000 deaths (Courville, 1934). By 1955, this had dropped to 25 out of every 10 000 cases (Teichgraeber et al., 1982). Reduction in numbers of cases has paralleled increasingly effective antibiotic therapy. Nonetheless, the condition still occurs, and prior treatment with antibiotics may make the diagnosis more difficult (Teichgraeber et al., 1982). Before 1940, the majority of cases of transverse sinus thrombosis

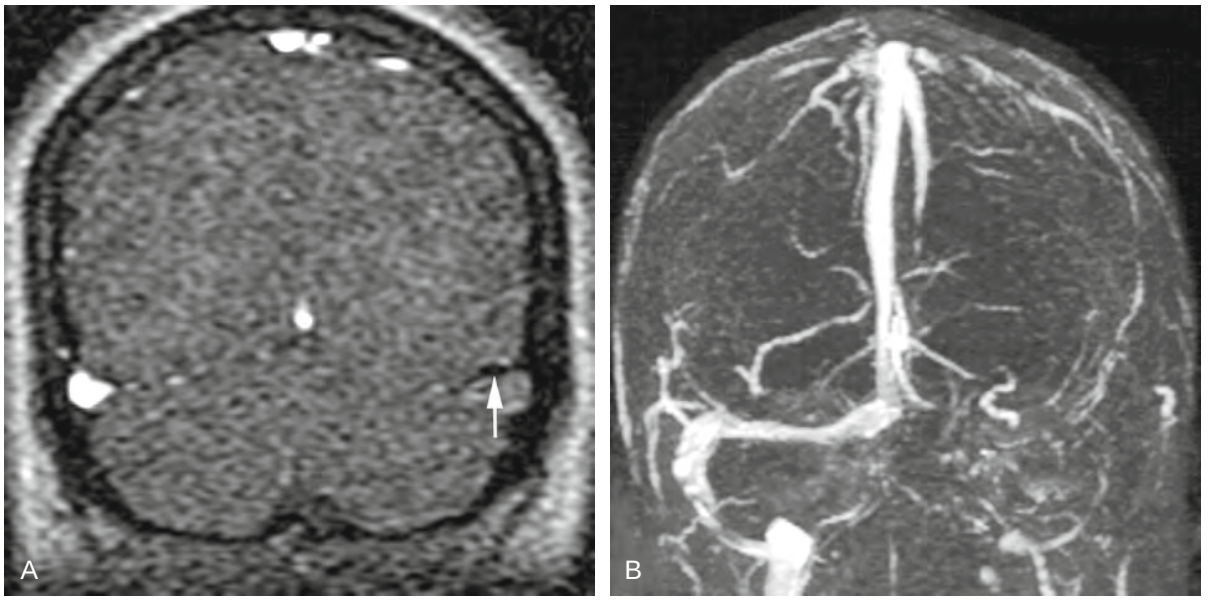

Fig. 8.6. Transverse sinus thrombosis. (A) Magnetic resonance (MR) angiogram source image showing absence of the left transverse sinus (Arrow). (B) Absence of the sinus is also demonstrated on the MR venogram. (Courtesy of Dr. Karen Salzman.)

were associated with β-hemolytic streptococci. At present, this organism accounts for a minority of cases, with the majority of cases being caused by *S. aureus*, anaerobic or microaerophilic streptococci, gram-negative enteric organisms including *Pseudomonas*, and anaerobes such as *Bacteroides. Fusobacterium* species, especially *F. necrophorum*, have been increasingly implicated as causative agents (Jahrsdoerfer and Fitz-Hugh, 1968; Teichgraeber et al., 1982; Holzmann et al., 1999; Giridharan et al., 2004). As in septic cavernous sinus thrombosis, multiple organisms may be present (Jahrsdoerfer and Fitz-Hugh, 1968).

Transverse sinus thrombosis should be suspected in any patient presenting with high fever or systemic signs of sepsis in the setting of acute otitis. The diagnosis should also be suspected in the patient who has mild or intermittent fever in the setting of chronic otitis and a draining ear, or in the individual who develops fever, headache, or stiff neck following apparently successful treatment of acute otitis (Teichgraeber et al., 1982). Prior to the advent of antibiotics, transverse sinus thrombosis was predominantly a condition of childhood and was most commonly seen in the setting of acute otitis (Boies, 1932; Teichgraeber et al., 1982). At present, the condition occurs somewhat more frequently in adults in the setting of chronic infection, and may be accompanied by cholesteatoma, malignant otitis externa, or skull base osteomyelitis (Nadol, 1980; Teichgraeber et al., 1982; Mathews, 1988; Manolidis and Kutz, 2005; Singh et al., 2005). The likelihood of transverse sinus thrombosis may be increased by the presence of diabetes mellitus or other immune-deficient state (Teichgraeber et al., 1982). In contrast to suppurative cavernous sinus thrombosis, in which onset of symptoms is often abrupt, transverse sinus thrombosis is more frequently characterized by a more gradual course. In preantibiotic days, severe generalized or occipital headache, loss of visual acuity, vomiting, fever, and hemiparesis were common symptoms, and examination frequently showed mastoid tenderness, a recurring "picket fence" fever, weight loss, and anemia (Boies, 1932; Teichgraeber et al., 1982; Southwick et al., 1986). At present, fever may or may not be present and usually does not have the spiking pattern seen in preantibiotic days (Teichgraeber et al., 1982). Fever remains an important diagnostic clue, however, as do ear pain and mastoid or sternomastoid tenderness (Teichgraeber et al., 1982) Headache, nausea, and vomiting remain common presenting symptoms, but diplopia is less frequent (Southwick et al., 1986). Occasional patients may present with vertigo (Southwick et al., 1986). Otoscopic abnormalities are present in up to 98% of cases associated with otitic infections, and posterior auricular swelling and pain (Griesinger's sign) is present in 49% of patients (Southwick et al., 1986). Cranial nerve VI palsy may be present in up to 37% of patients, due to compression of the nerve by the inferior petrosal sinus in Dorello's canal (Southwick et al., 1986). Other localizing signs are frequently absent. The triad of suppurative otitis, cranial nerve VI palsy, and cranial nerve V irritation resulting in retroorbital and temporoparietal pain (Gradenigo's syndrome), suggesting the presence of inflammation along the

petrous ridge, should always raise the question of transverse sinus thrombosis (Southwick et al., 1986; Bleck and Greenlee, 2000a; Motamed and Kalan, 2000; Sherman and Buchanan, 2004). Patients may also exhibit altered mental status, loss of visual acuity, horizontal nystagmus, and nuchal rigidity (Southwick et al., 1986). In most cases, papilledema is absent (Teichgraeber et al., 1982). Hemiparesis, although reported, is now unusual (Southwick et al., 1986), and the presence of focal motor, sensory, or cerebellar signs should raise concern about extension of the process into other veins as well as the possibility of subdural empyema or brain abscess. At present, the most common intracranial complications of transverse sinus thrombosis are meningitis and communicating ("otitic") hydrocephalus, followed by cerebellar abscess (Jahrsdoerfer and Fitz-Hugh, 1968; Teichgraeber et al., 1982; Southwick et al., 1986; Southwick, 1995). Hydrocephalus is more likely to develop with thrombosis of the right transverse sinus, since this sinus usually provides the drainage for the superior sagittal sinus (Southwick et al., 1986). Extension of the thrombus into the internal jugular vein may also occur (Jahrsdoerfer and Fitz-Hugh, 1968), and distant embolization may result in pulmonary infarcts or pulmonary abscesses which may at times be multifocal and bilateral (Jahrsdoerfer and Fitz-Hugh, 1968). Despite the advent of antibiotics, transverse sinus thrombosis still carries a significant mortality (Goldenberg, 1985; Syms et al., 1999; Giridharan et al., 2004). Southwick et al., in their review of cases reported between 1940 and 1984, found an overall mortality of 12%. Mortality in the period 1956–1984, well after the advent of antibiotics, was 10%, with no deaths occurring between 1976 and 1984, after the advent of CT scanning. During that period eight of 10 patients made a full recovery (Southwick et al., 1986). Mortality and morbidity are increased in patients presenting with altered consciousness or where there is delay in diagnosis.

Superior sagittal sinus thrombosis

Superior sagittal sinus thrombosis is more frequently associated with hypercoagulable states including malignancy, pregnancy, and ulcerative colitis (Fig. 8.7). Suppurative thrombophlebitis of the superior sagittal sinus, however, is uncommon and occurs significantly less frequently than does septic thrombosis of the cavernous or transverse sinuses. Southwick et al., in their 1986 review of septic thrombosis of the dural venous sinuses, identified only seven cases of superior sagittal sinus thrombosis from their own institution between 1940 and 1984, with an additional 23 cases from the literature. In contrast to thrombophlebitis of the cavernous or transverse sinuses, the majority of cases of septic superior sagittal sinus thrombophlebitis

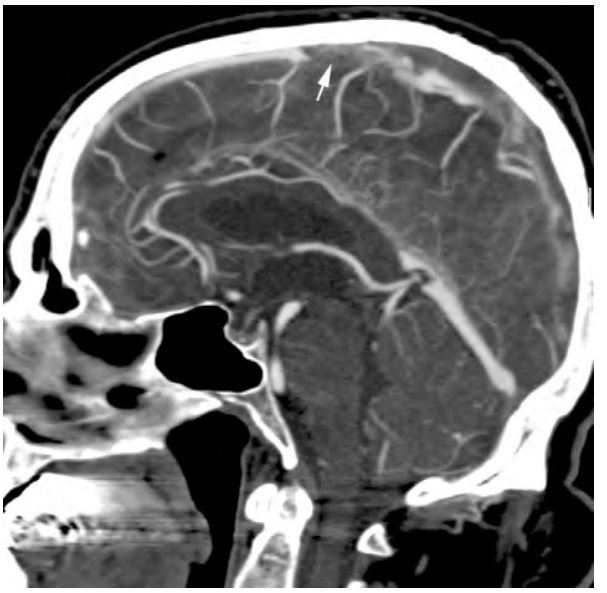

Fig. 8.7. Computed tomography venogram showing thrombosis of the superior sagittal sinus. (Courtesy of Dr. Karen Salzman.)

occur in the setting of meningitis (Southwick et al., 1986; Southwick, 1995; Kastenbauer and Pfister, 2003), with a smaller number of cases occurring as a complication of sinusitis (Southwick et al., 1986). Cases may occasionally follow head trauma, craniofacial infections, or dental surgery (Strauss et al., 1973; Tovi and Hirsch, 1991; Luo et al., 2001). A minority of cases result from spread of septic thrombosis from an involved transverse sinus (Stuart et al., 1951; Poltera and Jones, 1973). Prior to the availability of antibiotic therapy, most cases of septic superior sagittal sinus thrombophlebitis were due to *S. pneumoniae* or *H. influenzae*. *S. pneumoniae* remains the most common organism associated with this condition, with a minority of cases due to *S. aureus*, β-hemolytic, microaerophilic, or anaerobic streptococci, *Klebsiella* species, or *Pseudomonas* species (Southwick et al., 1986). Rare cases have been associated with trichinosis, but it is not clear that this organism had directly infected the superior sagittal sinus in these cases (el Koussa et al., 1994). Onset of symptoms is usually rapid, occurring over 1–2 days, and may be fulminant, in particular in cases associated with bacterial meningitis. Symptoms may also, however, develop over a period of weeks: this occurs more frequently in cases arising from sinusitis and may be insidious where the thrombus involves only the anterior portion of the sinus (Southwick et al., 1986). Headache, often with nausea or vomiting, is the most common symptom but may be masked by the pain of an accompanying meningitis or sinusitis. In most cases,

especially in those associated with meningitis, there is rapid progression to clouding of consciousness followed by coma, often with focal or generalized seizures which may be refractory to anticonvulsant therapy (Southwick et al., 1986; Southwick, 1995). Examination will reveal high fever and alteration of mental status, stupor, or coma in 65–70% of patients (Southwick et al., 1986). Approximately one-quarter of patients overall will have nuchal rigidity or other signs of meningeal irritation; this figure is higher in cases caused by meningitis. In the series by Southwick et al., 43% of patients exhibited hemiparesis (Southwick et al., 1986). Because the superior sagittal sinus drains blood from the lateral and medial surfaces of the hemispheres, including motor areas for both legs, a variety of other motor findings may be present, including spastic paraparesis or paraplegia (Southwick et al., 1986). Obstruction of CSF reabsorption in the anterior portion of the superior sagittal sinus may result in communicating hydrocephalus. Brainstem compression may result from downward herniation caused by the accompanying meningitis; hydrocephalus; and cerebral edema; venous cerebral infarction; and/or hemorrhage. These findings are most frequently seen in cases associated with bacterial meningitis and less so in cases related to sinusitis in which only the anterior portion of the sinus is involved (Southwick et al., 1986). Papilledema is present in only a minority of patients, however, and progression of neurological findings following superior sagittal sinus occlusion may occur so rapidly that profound impairment or death may occur before papilledema can develop (Southwick et al., 1986). Mortality in the series collected by Southwick et al. was 78% (Southwick et al., 1986). Pathological examination has demonstrated microscopic evidence of meningitis in approximately one-third of cases. In 92% of cases there is thrombosis of the entire superior sagittal sinus (Adams et al., 1948; Toomey and Hutt, 1949; Stuart et al., 1951; Kalbag and Woolf, 1967; Krayenbühl, 1967), and in over 40% of cases one or more additional venous sinuses are also occluded (Stuart et al., 1951; Ata, 1965; Poltera and Jones, 1973; Strauss et al., 1973). Rarely, thrombi may extend into the internal jugular vein (Ata, 1965). Cortical venous thrombosis may be found in up to 50% of fatal cases, almost always associated with edema or hemorrhagic infarction (Stuart et al., 1951; Askenasay et al., 1962; Krayenbühl, 1967; Poltera and Jones, 1973; Strauss et al., 1973; Southwick et al., 1986).

Suppurative thrombophlebitis of other dural sinuses

Thrombosis of other dural sinuses is unusual and most frequently occurs in the setting of occlusion of the cavernous, transverse, or superior sagittal sinus. Suppurative thrombophlebitis of the inferior petrosal sinus may occur as a complication of otitis media with spread of infection through the tegmen tympani. Involvement of the superior petrosal sinus may follow otitis media or mastoiditis, but may also follow spread of infection from the inferior petrosal sinus or the cavernous sinus (Stehbens, 1972). Thrombosis of the superior petrosal sinus may impair venous drainage from the temporal lobe resulting in temporal lobe congestion or venous infarction or may involve the trigeminal ganglion. Resultant symptoms may include temporal lobe seizures or, following involvement of the trigeminal gangion, ipsilateral facial pain or sensory deficit (Bleck and Greenlee, 2000a). Thrombosis of the inferior petrosal sinus may, like transverse sinus thrombosis, produce Gradenigo's syndrome (Bleck and Greenlee, 2000a). Occlusion of the straight sinus or the vein of Galen is uncommon and almost always secondary to extension of a thrombus from the superior sagittal sinus or the transverse sinus (Stehbens, 1972). Rarely, thrombosis of the vein of Galen may occur during infections in the neonatal period, but is extremely rare in older infants, children, or adults (Stehbens, 1972). Sigmoid sinus occlusion has been reported secondary to Lemierre's syndrome, discussed below (Repanos et al., 2006).

Internal jugular vein thrombosis and Lemierre's syndrome

Lemierre's syndrome represents occlusion of the internal jugular vein with septic pulmonary emboli and at times systemic sepsis (Edibam et al., 2000; Shaham et al., 2000; Dool et al., 2005; Kuduvalli et al., 2005; Ravn et al., 2006; Wang et al., 2007; Hagelskjaer and Prag, 2008). The condition is most frequently associated with oropharyngeal infections but has also been reported secondary to otitis or to intravenous injection of illicit drugs (Chirinos et al., 2002; Brown and Wallwork, 2007; Hagelskjaer and Prag, 2008; Monteiro and Thompson, 2008) and may be associated with occult disorders of blood coagulation (Riordan, 2007). The majority of cases are caused by *Fusobacterium necrophorum* or rarely other fusobacteria. Occasional cases have been attributed to *S. aureus*, viridans streptococci, and *Porphyromonas asaccharolytica* (Tsai et al., 1999; Venglarcik, 2003; Kuduvalli et al., 2005; Morizono et al., 2005; Riordan, 2007; Hagelskjaer and Prag, 2008). Approximately 10% of cases follow infectious mononucleosis (Boz et al., 2005; Matten and Grecu, 2006; Garimorth et al., 2008). Typical symptoms include pharyngeal pain, neck pain or swelling, and evidence of systemic sepsis or septic pulmonary embolization. The condition may be complicated by symptomatic or asymptomatic occlusion of the cavernous or sigmoid sinuses, or by thrombosis of other

intracranial venous sinuses (Bentham et al., 2004; Repanos et al., 2006; Brown and Wallwork, 2007).

Suppurative thrombophlebitis of superficial cortical veins

Septic thrombophlebitis of cortical veins is a common accompaniment of suppurative dural sinus thrombosis and often accounts for the focal neurological deficits which occur. Isolated septic thrombophlebitis of cortical veins, on the other hand, is uncommon and is almost always a complication of bacterial meningitis (DiNubile et al., 1990; Pfister et al., 1992; Kastenbauer and Pfister, 2003). Because of the enormous anastomotic reserve of the intracranial venous system, symptoms and signs, in contrast to those seen with arterial thromboses, may fluctuate markedly over relatively short periods of time (Merwarth, 1942). Adams et al. (1948), in a series prior to antibiotics, found cerebral thrombophlebitis in four of 14 patients who died following *H. influenzae* meningitis. Swartz and Dodge (1965) identified thrombosis of small cortical veins near areas of infarction in five of 30 patients with meningitis coming to autopsy. DiNubile et al. (1990), in a case series spanning 24 years following the advent of antibiotics, were able to document only 10 cases unrelated to superior sagittal sinus thrombosis. Of these, four had occurred in the setting of otitis and subsequent meningitis; three occurred following sinusitis (accompanied by meningitis in one patient); two patients had subdural empyemas; and one patient had cavernous sinus thrombosis and meningitis (DiNubile et al., 1990). Causative organisms were *Escherichia coli* in one patient (a neonate); *S. pneumoniae* in five patients (including three of the four patients with otitis media); and *Pseudomonas aeruginosa* in one immunocompromised patient. Multiple organisms including *Streptococcus milleri* and three other species of streptococci, *Bacteroides melaninogenicus*, and *Fusobacterium nucleatum* were identified in one patient with a concomitant subdural empyema. All patients who could be evaluated had abnormal mental status, and all had seizures and/or focal neurological deficits. Overall incidence of cortical vein thrombosis at autopsy in cases of meningitis without superior sagittal sinus thrombosis was 5%, although the incidence rose to 10% if seizures or focal neurological deficits were present. Mortality in this series was 50% (DiNubile et al., 1990).

Suppurative thrombophlebitis of deep cerebral veins

Infectious processes only infrequently cause deep venous thrombophlebitis, and clinical findings described in the literature represent, in general, those seen in patients without infection. Thrombosis of deep cerebral veins is more commonly seen in women (Crawford et al., 1995). The classical presentation reflects involvement of venous drainage from basal ganglia and thalami and is characterized by the acute onset of coma, decerebrate posture, and extrapyramidal alteration in muscle tone (Crawford et al., 1995). Occlusion of one or more venous sinuses may be seen in up to half of the cases (Crawford et al., 1995). Over 50% of patients suffer a fatal course or are left with severe disability (Crawford et al., 1995).

Systemic complications of suppurative intracranial venous thrombophlebitis

Suppurative thrombosis of intracranial sinuses may result in systemic sepsis and may also serve as a source of single or multifocal pulmonary emboli or pulmonary abscesses (Jahrsdoerfer and Fitz-Hugh, 1968). Although septic pulmonary embolization may occur in the setting of known or suspected venous sinus thrombosis, it may also be a sign of occult dural sinus occlusion (Jahrsdoerfer and Fitz-Hugh, 1968; Hawkins, 1985). Although pulmonary infarcts and lung abscesses are the most frequent embolic complications of septic intracranial venous occlusion, emboli may also involve other structures. In the preantibiotic era (and prior to development of modern imaging techniques), sites of distant septic embolization included subcutaneous tissues and large joints (Meltzer, 1935). Paradoxical arterial septic embolization through a patent foramen oval has not been reported. However, Del Sette et al. (2007) have reported a patient with a patent foramen ovale in whom nonseptic intracranial venous sinus thrombosis was thought to have been the source of an embolic stroke.

DIAGNOSIS

Suppurative intracranial thrombophlebitis must be suspected in any patient presenting with focal neurological deficits or evidence of increased intracranial pressure in the setting of infections involving face, nares, sinuses, middle ear, or mastoid. Suppurative intracranial thrombophlebitis should thus be included in a list of differential diagnoses which also includes epidural abscess, subdural empyema, brain abscess, and meningitis, keeping in mind that more than one of these conditions may be present. Cavernous sinus thrombosis should be strongly suspected in any patient developing proptosis and abnormalities of extraocular muscle function – in particular involving cranial nerve III – in the setting of infection involving the facial triangle, nose, or sinusitis. Transverse sinus thrombosis, in particular, should be suspected in the setting of otitis or mastoiditis with accompanying Griesinger's sign or Gradenigo's syndrome. Isolated cortical vein thrombosis

should be suspected in any patient with meningitis who develops focal neurological abnormalities or seizures. Sagittal sinus thrombosis and transverse sinus thrombosis may produce focal findings but may also be silent except for the development of hydrocephalus or occurrence of distant embolization.

Blood and CSF studies

Routine blood studies may provide evidence of host response to infection with neutrophilic pleocytosis and elevated erythrocyte sedimentation rate or C-reactive protein. Spinal fluid examination will reveal elevated pressure in the majority of patients but may sometimes be normal (Teichgraeber et al., 1982; Southwick et al., 1986; DiNubile et al., 1990; Durand et al., 1993; Southwick, 1995). Although the test may provide both false positives and false negatives, elevation of serum D-dimer levels to >500 ng/ml is suggestive of the diagnosis (Lalive et al., 2003). CSF examination may give one of two pictures. In many cases, CSF findings will resemble those seen in bacterial meningitis, with neutrophilic pleocytosis, elevated protein concentration, and decreased glucose concentration (Southwick et al., 1986; Southwick, 1995). Other cases, however, may show findings much more suggestive of a parameningeal process, with mixed or lymphocytic pleocytosis, varying degrees of elevated protein concentration, and normal glucose concentration (Southwick et al., 1986; Southwick, 1995). Red blood cells may be present where there has been subarachnoid or cerebral hemorrhage. In a minority of cases, CSF may be normal (Southwick et al., 1986; Southwick, 1995). Blood, and where possible, CSF cultures should be obtained in all patients; these will yield one or more infectious organisms in approximately 70% of cases (Southwick et al., 1986; Southwick, 1995). Cultures may be negative, however, in particular in patients already on antibiotic therapy. The causative agents involved in suppurative venous thrombophlebitis vary with the primary site of infection (Table 8.1).

Radiological diagnosis

Specific diagnosis of venous sinus obstruction became possible with development of catheter angiography and venography, and initial noninvasive diagnosis of venous sinus or cortical vein thrombosis began with the widespread availability of CT. Cases described in the literature do not make a clear distinction between suppurative and bland thrombotic processes. In general, contrast-enhanced CT displays three groups of findings: (1) hyperintense signal within the lumen of the sinus representing the clot itself; (2) evidence of venous collaterals resulting from the occlusion, including the "empty delta sign"; and (3) signs of brain parenchymal involvement, including hemorrhage and cerebral edema (Virapongse et al., 1987). Intralumenal clot, edema, and hemorrhage – all visible on unenhanced CT – are the most common findings, with intraluminal clot being seen in about 25% of cases (Virapongse et al., 1987). The "empty delta sign," seen on contrast-enhanced scans, is present in approximately 30% of patients. This finding is thought to represent congestion of small veins surrounding the thrombosed sinus. The empty delta sign is most often seen in cases of superior sagittal sinus thrombosis but has also been reported in transverse sinus thrombosis (Virapongse et al., 1987). The empty delta sign may be absent acutely, however, and is lost over time (Shinohara et al., 1986; Davies and Slavotinek, 1994; Tang et al., 2008). Increased signal within the involved sinus, representing the actual thrombus, may be seen in approximately 25% of cases (Virapongse et al., 1987).

The advent of MRI and then of CT angiography and venography revolutionized diagnosis of both venous sinus and cortical vein thrombosis, such that MRI and MR or CT venography are currently the diagnostic procedures of choice in detecting venous sinus thrombosis. Each of these modalities provides important information. Blood, like other anatomical structures, responds to magnetic fields with alteration in signal. Circulating blood, however, passes out of the plane of imaging by the time the sequence is obtained and thus results in a "flow void" of absent signal, whereas stationary blood is hyperintense on T1-weighted images, representing the actual clot (Wasay and Azeemuddin, 2005). Both diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) imaging can provide important additional information about both ischemia and cerebral edema. MR venography is extremely useful in showing detailed venous anatomy and will demonstrate an area of decreased or absent signal in the area of the clot (Wasay and Azeemuddin, 2005). Recent work suggests that diagnostic accuracy of MR venography, in particular in chronic cases, may be increased by the use of a fibrin-specific contrast agent (Wasay and Azeemuddin, 2005; Stracke et al., 2007). CT venography appears to have a degree of sensitivity and specificity equalling that of MRI. CT venography is often better tolerated by patients than is MR venography and is less prone to imaging artifacts (Wasay and Azeemuddin, 2005; Rodallec et al., 2006; Linn et al., 2007). False-negative results occasionally occur with all of these modalities, however, and MR or CT studies may need to be followed by catheter angiography/venography in cases in which venous sinus thrombosis is suspected but noninvasive studies are unrevealing. Patients with suppurative intracranial thrombophlebitis are usually severely ill and may have difficulty remaining

still for any of these studies. In such cases, the use of midazolam with careful monitoring may be essential to obtain an adequate study.

MANAGEMENT

Management of suppurative intracranial thrombophlebitis involves antibiotic therapy directed against the offending organism or organisms, treatment of the thrombus itself, treatment of its direct complications, and treatment of associated infectious or other conditions; these latter may be confined to the central nervous system or may be systemic. Because suppurative thrombophlebitis is an unusual condition, controlled trials do not exist for any of these areas of treatment, and therapeutic approaches are derived from those used in other central nervous system infections or in intracranial thrombophlebitis in the absence of infection.

Antibiotic therapy

Because an infected thrombus may contain more than one organism, a reasonable approach is to begin treatment with three agents, one directed against meticillin (formerly methicillin)-resistant *Staphylococcus aureus* or other gram-positive agents, one directed against gram-negatives, and one directed against anaerobic organisms such as *Bacteroides* or *Fusobacterium*. Such a regimen should include vancomycin, a third-generation cephalosporin such as cefotaxime or ceftriaxone, and metronidazole, with consideration of the use of chloramphenicol in patients unable to tolerate metronidazole. Ceftazidime or meropenem may be used in place of cefotaxime or ceftriaxone if *Pseudomonas* is a suspected organism, and consideration should be given to the use of gentamicin or tobramicin where gram-negative infection is likely. Antibiotic therapy may be refined on the basis of cultures. However, failure to isolate more than one organism does not necessarily exclude polymicrobial infection and, in particular, may not exclude the presence of anaerobic agents which are difficult to culture. Controlled data on duration of antibiotic therapy do not exist, but treatment is usually continued for a minimum of 4 weeks.

A different approach to antibiotic therapy is required in the patient presenting with intracranial venous sinus thrombosis complicating nasopharyngeal infection due to *Rhizopus*. As previously noted, this infection is by far most common in the setting of uncontrolled diabetes or diabetic ketoacidosis. Treatment here almost always involves both antibiotic therapy and surgical intervention, at times with use of hyperbaric oxygen. Amphotericin B, used in conventional form, liposomal form, or as amphotericin B lipid complex, has been most frequently used. Limited recent cases suggest that the newer antifungal agents, voriconazole and posaconazole, may also be effective, as may liposomal nystatin (Mileshkin et al., 2001; Munir and Jones, 2007; Scheinfeld, 2007). Amphotericin B preparations have been used in the treatment of central nervous system aspergillosis with variable results. The newer agents, voriconazole and itraconazole, have shown some efficacy in *Aspergillus* infections, but their utility in intracranial venous thrombophlebitis due to this organism has not been established (Elter et al., 2006; Wandroo et al., 2006).

Anticoagulation

Heparin was introduced as treatment for venous sinus thrombosis over 50 years ago (Stansfield, 1942) and has been used both to prevent clot propagation and to prevent distal embolization (Southwick et al., 1986). In retrospective studies the drug has been shown to improve morbidity and mortality, such that its use for aseptic venous sinus thrombosis is now routine in many centers (Levine et al., 1988; Einhaupl et al., 1991, 2006; Shafqat et al., 2006; Albers et al., 2008; Ferro and Canhao, 2008; Masuhr and Einhaupl, 2008). Studies with its use in suppurative intracranial venous conditions are more limited. Southwick, in a limited series derived from his own experience and from the literature, found that use of heparin reduced mortality from 36% to 14% in septic cavernous sinus thrombosis, but discouraged its use in transverse sinus or superior sagittal sinus thrombosis because of the risk of hemorrhage (Southwick et al., 1986; Southwick, 1995). Holzmann et al. (1999) reported its use in six children with septic transverse sinus thrombosis, all of whom recovered. In this study, however, all children also underwent thrombectomy, and therapeutic anticoagulation was achieved in only two patients. More recent case analyses discussing the use of heparin in intracranial venous sinus thrombosis do not differentiate between septic and aseptic cases. Einhaupl et al. (1991), in a placebo-controlled study of 20 patients, noted that, of 10 patients treated with heparin, eight made a complete recovery and two had slight residual deficits, as compared with only one complete recovery, six patients with residual neurological deficits, and three deaths in patients receiving placebo. In an accompanying retrospective study, mortality in patients with an accompanying intracranial hemorrhage treated with heparin was 15% as compared with 69% in similar patients not receiving anticoagulation (Einhaupl et al., 1991). Current recommendations are for use of unfractionated heparin in venous sinus thrombosis, including those cases in which hemorrhage is present (Einhaupl

et al., 2006; Shafqat et al., 2006; Albers et al., 2008; Ferro and Canhao, 2008; Masuhr and Einhaupl, 2008). Treatment with low-molecular-weight heparin has also been used; however, a placebo-controlled trial, using the low-molecular-weight compound nadroparin, although yielding slightly better results in the treatment group, did not reach statistical significance (Stam et al., 2002). Use of heparin in patients with large hemorrhages should be approached with some caution, and in such cases use of unfractionated heparin rather than low-molecular-weight compounds should be strongly considered because of its shorter half-life and reversibility. In many centers, heparin is used to obtain a partial thromboplastin time of 2–2.5 normal where hemorrhage is absent or 1.25–1.5 times control where hemorrhage is present. In both instances, consideration should be given, at least during the acute period, to monitoring the patient with serial CT scans to detect increasing hemorrhage size. Heparin should be followed by oral anticoagulation with warfarin once the patient is stable, aiming for an international normalized ratio of 2–3 (Jahrsdoerfer and Fitz-Hugh, 1968; Einhaupl et al., 2006; Ferro and Canhao, 2008). Anticoagulation is usually continued for 3–6 months (Einhaupl et al., 2006; Ferro and Canhao, 2008). MR or CT venography may be used to follow evolution of the thrombus and recanalization of the sinus over time.

Thrombectomy, thrombolysis, and endovascular therapy

Surgical thrombectomy has been used for many years in cases of transverse sinus thrombosis and has also been employed where the process involves the superior sagittal sinus (Kobayashi et al., 2004). Internal jugular vein ligation, once frequently employed in transverse sinus thrombosis, is not usually performed. In recent years, surgical thrombectomy has often been accompanied by thrombolytic therapy (Kourtopoulos et al., 1994; Ekseth et al., 1998). Endovascular therapy using mechanical clot disruption, tissue plasminogen activator, or urokinase has also been used increasingly in place of surgery (Dowd et al., 1999; Opatowsky et al., 1999; Chow et al., 2000; Novak et al., 2000; Curtin et al., 2004; Kirsch et al., 2007; Tsai et al., 2007; Stam et al., 2008). Controlled data indicating the superiority of thrombolysis over heparin anticoagulation do not yet exist, and a reasonable approach would be to consider use of endovascular treatment in cases in which there is deterioration or progression of neurological deficit despite heparin therapy (Einhaupl et al., 2006; Albers et al., 2008).

Treatment of complications

Suppurative intracranial thrombophlebitis does not exist in isolation. Infections of the face, sinuses, or mastoid may require surgical drainage or debridement in addition to antibiotic therapy. Systemic infection may require antibiotic therapy. Surgical drainage may be needed for pulmonary or other distant abscesses. Seizures may require acute therapy with diazepam or lorazepam followed by intravenous fosphenytoin, levatiracetam, or other intravenously administered agents. Cases of refractory seizures may require more aggressive treatment, including induction of pentobarbital coma. Subsequent maintenance anticonvulsant therapy may be required in many patients and should be continued for 6–12 months.

Hydrocephalus and cerebral edema are major therapeutic concerns. The risk of hydrocephalus should be kept in mind, in particular where the thrombosis involves the superior sagittal or transverse sinuses. In such cases, it may be important to monitor ventricular size by CT or MRI, with ventricular shunting if needed. Where shunting is required, anticoagulants should be briefly discontinued to allow shunt placement. Cerebral edema may be of major concern, in particular where accompanied by hemorrhage. In this situation, monitoring of intracranial pressure is invaluable. Hyperventilation or mannitol may be used as an emergency to control swelling, but should not be used over a longer duration. Dexamethasone, although shown to be of value in bacterial meningitis, is of unknown value in suppurative intracranial thrombophlebitis in the absence of meningeal infection (de Gans and van de Beek, 2002). Hanley et al. (1988) have reported two cases of noninfectious sagittal sinus thrombosis, cerebral hemorrhage, and intracranial hypertension treated with pentobarbital coma. Hemicraniectomy may be life-saving in cases with severe brain swelling (Einhaupl et al., 2006; Ferro and Canhao, 2008).

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Chapter 9

Infections of the central nervous system in the neurosurgical patient

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INTRODUCTION

Infection of the central nervous system (CNS) in the neurosurgical patient, although infrequent, can increase morbidity and mortality. CNS infection may complicate placement of a shunt or drainage catheter, craniotomy, craniocerebral injury, or dural puncture. The highest risk of postoperative infection is associated with a ventricular shunt, followed by spinal fusion and laminectomy, craniectomy, brain biopsy, and peripheral nerve surgery (Gaynes et al., 2001; McClelland and Hall, 2007).

SHUNT INFECTIONS

Ventricular shunts, to relieve increased intracranial pressure (ICP) associated with hydrocephalus, were first introduced in 1952. Shunts, temporary or permanent, are also placed to deliver medication or intermittently monitor ICP (Nulsen and Spitz, 1952). Shunts can be internalized or externalized; the latter are useful if temporary access or drainage is required or anticipated. The most common type of internalized shunt is the ventriculoperitoneal (VP) shunt; other types include ventriculoatrial (VA) and ventriculopleural shunts. Ventricular shunts consist of a ventricular catheter, a valve to regulate flow, and a catheter draining into the peritoneum, atrium or pleural space; an optional access reservoir may be placed at the cranial end of the shunt. Externalized devices may be positioned within the epidural, subdural, intraparenchymal, or intraventricular spaces to monitor and reduce ICP.

The diagnosis of iatrogenic infection – meningitis or ventriculitis – due to a shunt requires the following criteria: (1) nomeningitis or ventriculitis prior to shunt placement; (2) negative cerebrospinal fluid (CSF) culture at time of shunt placement; (3) presence of shunt $\geq$ 24 hours prior to positive CSF culture; and (4) positive CSF culture obtained from shunt or lumbar puncture (LP) (Mayhall et al., 1984). Of 3331 ventricular shunt placements reported to the National Nosocomial Infections Surveillance system between 1992 and 2002, 139 (4.2%) developed infection (National Nosocomial Infections Surveillance (NNIS) System Report, 2002). In children being treated with shunts for hydrocephalus, CNS infection occurred in 7.8–10.4% (Dallacasa et al., 1995; Kulkarni et al., 2001). Children are more likely than adults to acquire shunt infection, perhaps due to longer hospital stay, higher skin bacterial concentrations, immature immune system, or more adherent strains of bacteria (Pople et al., 1992; Bayston, 1994). Shunt infection in children has not been associated with gender, birth weight, or presence of other infections during the period of shunt surgery (Dallacasa et al., 1995). Fetal ventriculitis has been reported in ventriculoamniotic shunting performed for treatment of fetal hydrocephalus (Bland et al., 1983).

Some indications for shunt placement are associated with higher rates of shunt infection: ventricular shunt for patients with neurocysticercosis (NCC) are frequently complicated by bacterial shunt infection. Fifteen percent of people with NCC have cysts in the ventricular system, with the majority located in the fourth ventricle (Cuetter et al., 1997). Many of these patients require shunt placement to relieve hydrocephalus. One study reported that 47 (68%) of 69 patients with NCC required one or more CSF shunt revisions; fourteen were due to development of meningitis (Colli et al., 1986).

Factors associated with increased risk of shunt infection include: postoperative CSF leak; younger age,

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especially prematurity (<40 weeks' gestation); exposure to perforated surgical gloves; and surgery for shunt revision (Dallacasa et al., 1995; Tuli et al., 2000; Kulkarni et al., 2001; McGirt et al., 2002). The incidence of shunt infection is similar for shunts draining into the peritoneum or atrium, but is slightly increased for three-piece, rather than one-piece, shunt systems (Raimondi et al., 1977; Borgbjerg et al., 1998). Shunts without a valve have similar rates of CNS infection as shunts with a valve, and rates of CNS infection and shunt failure are similar for different shunt valve types: the standard differential-pressure valve; the Delta valve (Medtonic PS Medical, Goleta, CA) that reduces siphoning in the upright position; and the Orbis-Sigma valve (Cordia, Miami, FL) that provides a variable, flow-limiting resistance (Schoenbaum et al., 1975; Drake et al., 1998). At the distal draining end of the shunt, malfunction can result in cerebral edema, and formation of an abdominal pseudocyst in patients with shunt infection has been reported (Bryant et al., 1988; Owen and Pittman, 2003).

Fewer shunt infections occur when neurosurgeons who have more experience placing ventricular shunts perform the procedure: in a study of 840 shunts placed over 25 years at the Johns Hopkins Hospital, the shunt infection rate varied between surgeons from 1.8% to 50% (George et al., 1979). A more recent study confirmed a higher prevalence of shunt infections when inserted by less experienced surgeons: residents had a shunt infection rate of 11.5%, whereas specialists had a rate of only 2.2% (Lund-Johansen et al., 1994). Some risk factors for infection vary by shunt type.

Risk of shunt infection by shunt type

Intracranial pressure monitors

An ICP monitor is often used to provide a quantitative measure of ICP or cerebral perfusion pressure when physical examination alone is not a reliable measure of neurological status, such as following open or closed head injury or neurosurgery. An ICP monitor may be placed within the subdural space, parenchyma, or ventricle. The most common complications associated with ICP monitor placement are hemorrhage and infection, with CNS infection occurring in 2.9–10.3% of patients. Risk factors for infection include placement in patients with open head injury or hemorrhage, intraventricular monitor placement, presence of CSF leak, concurrent infection outside the CNS, and presence of monitoring device for longer than 5 days (Aucoin et al., 1986; Clark et al., 1989; Martinez-Manas et al., 2000; Rebuck et al., 2000). Unlike increased rates of CNS infection complicating shunts placed by less experienced surgeons, CNS infection rates following insertion of subdural or parenchymal ICP monitors are similar, regardless of whether a neurosurgeon, general surgeon, or midlevel practitioner performs the procedure (Kaups et al., 1998; Harris et al., 2002). The incidence of CNS infection is not reduced by the administration of prophylactic antibiotics while a monitor is in place (Aucoin et al., 1986; Rebuck et al., 2000).

External ventricular drain

The external ventricular drain (EVD) catheter is an alternative method for monitoring and controlling elevated ICP. Although CNS infection rates as high as 27% have been reported in patients undergoing EVD placement, highest rates of infection occurred in patients who had an EVD in place for an average of 8.1 days, and had not received prophylactic antibiotics (Wyler and Kelly, 1972). Other studies have noted infection rates between 4.5% and 12.5% (Smith and Alksne, 1976; Kanter et al., 1985). Risk factors for CNS infection include placement of EVD following intraventricular hemorrhage, presence of hemorrhagic CSF, duration of EVD exceeding 5 days, and perhaps increased number of drain manipulations (Narayan et al., 1982; Mayhall et al., 1984; Stenager et al., 1986).

Lumbar drains

Lumbar drains are most often placed to treat communicating hydrocephalus following subarachnoid hemorrhage, and for normal-pressure hydrocephalus. Hydrocephalus complicates the clinical course in 20–31% of patients with subarachnoid hemorrhage, 40% of whom will improve within 1 day without intervention (Hasan et al., 1989, 1991). The incidence of meningitis following lumbar drain placement varies from 0% to 25.6%, and is highest when placed in patients after subarachnoid or intraventricular hemorrhage (Huang et al., 1993; Raquet and Mann, 1993; Coplin et al., 1999). Meningitis following lumbar drain placement typically occurs within 24 hours of drain placement. Although CSF pleocytosis (white blood cell (WBC) count $\geq$ 11 cells/mm^3) is not a risk for development of meningitis, the majority of patients who develop meningitis typically have an increasing CSF WBC count in the days preceding diagnosis (Coplin et al., 1999).

Lumboureteral shunt

Although lumboureteral shunts are rarely used because a functioning kidney must be sacrificed and resultant electrolyte disturbances and dehydration are common, these shunts are occasionally used for patients who have failed multiple standard shunts (Irby et al., 1993).

An additional infectious complication of this specific type of shunting is meningitis due to ascending urinary tract infection (Ferrera et al., 1994).

Etiology

Shunt infection is most often caused by nonpathogenic skin (commensal) flora that colonize the shunt device. Coagulase-negative and -positive staphylococcal species are most often responsible (Huebner and Goldmann, 1999). Other organisms isolated from infected shunts include α- (viridans) and β-hemolytic streptococci, *Propionibacterium acnes,* a commensal pleomorphic gram-positive anaerobic rod, *Pseudallescheria boydii,* and *Mycobacterium fortuitum* (Beeler et al., 1976; Berenguer et al., 1989; Chan et al., 1991). *Staphylococcus aureus* is the organism most commonly isolated from shunt infections in children (Bayston, 1994). In one study, fungal infection accounted for 17% of shunt infections in premature babies undergoing VP shunt placement for treatment of hydrocephalus: fungi isolated included *Candida albicans, C. parapsilosis, C. tropicalis,* and *Torulopsis glabrata* (Chiou et al., 1994). *Neisseria gonorrhoeae* has been reported in a fetus with a ventriculoamniotic shunt who developed ventriculitis (Bland et al., 1983). The etiologies and associated frequencies of isolation of organisms associated with shunt infection are listed in Tables 9.1 and 9.2.

Possible mechanisms for development of shunt infection include: (1) bacterial contamination at the time of surgery; (2) extension of skin infection into the surgical site; (3) hematogenous spread of infection from another site; and (4) ascending infection from the distal catheter tip (Kaufman et al., 1990). A study of 108 shunt placements comparing perioperative surgical site cultures with CSF cultures obtained from 13 subsequent shunt infections found only one infection with similar isolates, suggesting contamination at the time of surgery may not be a common cause of shunt infection (Thompson et al., 2007).

The presence of foreign material, such as a shunt catheter, diminishes the host immune system's ability to adhere to and phagocytose bacteria, while increasing certain bacteria's ability to adhere to the catheter (Borges, 1982). *S. aureus, S. epidermidis*, and some *Corynebacterium* species are able to form an extracellular biofilm, also referred to as "slime," that enhances adherence to shunt material and decreases susceptibility to antibiotic therapy (Diaz-Mitoma et al., 1987; Bayston et al., 1994). This biofilm "slime" is a mucoid

Table 9.1

Risk of central nervous system infection and etiological agents in patients with a ventricular shunt

Reference	Number of patients	Infection rate	Etiological agents
Davis et al. (1999)	1193	3.2%	*Staphylococcus aureus* (37.8%) *Staphylococcus epidermidis* (32.4%) *Klebsiella* spp. (5.4%) *Escherichia coli* (5.4%) *Pseudomomas* spp. (5.4%) *Streptococcus* spp. (5.4%) *Bacillus* spp. (1.4%) *Enterobacter* spp. (1.4%) *Candida* spp. (1.4%) *Enterococcus* spp. (1.4%) Diphtheroids (1.4%) *Haemophilus influenzae* (1.4%)
Enger et al. (2003)	161	2.7%	*Staphylococcus epidermidis* (77.8%) *Staphylococcus aureus* (11.1%) *Candida* spp. (11.1%)
Kulkarni et al. (2001)	299	10.4%	*Staphylococcus aureus* (48.4%) Coagulase-negative staphylococci (38.7%)
McClinton et al. (2001)	81		*Staphylococcus epidermidis* (33%) *Staphylococcus aureus* (33%) Gram-negative rods (25%)
Pople et al. (1992)	294	9.4%	Coagulase-negative staphylococci (67%)
Schoenbaum et al. (1975)	289	27.0%	*Staphylococcus epidermidis* (50%) *Staphylococcus aureus* (25.5%)

Table 9.2

Risk of central nervous system infection and etiological agents in patients with an external ventricular drain

Reference	Number of patients	Number of infections (%)	Etiological agents
Alleyne et al. (2000)	308	12 (4.0%)	Coagulase-negative staphylococci (33.3%) *Pseudomonas aeruginosa* (33.3%) *Acinetobacter calcoaceticus* (8.3%) *Bacillus cereus* (8.3%) *Enterobacter cloacae* (8.3%)
Aucoin et al. (1986)	41	9 (21.9%)	*Klebsiella pneumoniae* (33.3%) *Staphylococcus aureus* (16.7%) Coagulase-negative staphylococci (8.3%) *Enterobacter cloacae* (8.3%) *Serratia marcescens* (8.3%) *Escherichia coli* (8.3%) Mixed (16.7%)
Friedman and Vries (1980)	66	0 (0%)	NA
Kanter et al. (1985)	65	9 (13.8%)	Coagulase-negative staphylococci (55.6%) Enterococcal spp. (22.2%) *Serratia marcescens* (11.1%) Viridans streptococci with coagulase-negative staphylococci and *Acinetobacter* (11.1%)
Khanna et al. (1995)	100	4 (4.0%)	*Staphylococcus epidermidis* (50%) *Staphylococcus aureus* (25.5%) *Klebsiella pneumoniae* (25%)
Mayhall et al. (1984)	172	19 (11.0%)	Coagulase-negative staphylococci (32%) *Staphylococcus aureus* (5%) *Streptococcus faecalis* (5%) *Streptococcus mitis* (5%) *Enterobacter aerogenes* (11%) *Enterobacter cloacae* (11%) *Acinetobacter calcoaceticus* (11%) *Escherichia coli* (5%) *Klebsiella pneumoniae* (5%) *Serratia marcescens* (5%) *Providencia stuartii* (5%)
Ohrstrom et al. (1989)	256	27 (10.6%)	Coagulase-negative staphylococci (55.6%) *Staphylococcus aureus* (33.3%) *Klebsiella pneumoniae* (7.4%) *Acinetobacter calcoaceticus* (3.7%)
Paramore and Turner (1994)	161	9 (5.6%)	*Staphylococcus epidermidis* (55.6%) *Klebsiella pneumoniae* (22.2%) *Enterobacter aerogenes* (11%) *Proteus mirabilis* (11%) *Staphylococcus aureus* (11%) (co-infection)
Smith and Alksne (1976)	64	3 (4.5%)	*Staphylococcus epidermidis* (42.9%) *Staphylococcus aureus* (42.9%)

Table 9.2

Continued

Reference	Number of patients	Number of infections (%)	Etiological agents
Stenager et al. (1986)	87	15 (17.2%)	*Staphylococcus epidermidis* (80%) Viridans streptococci (6.7%) *Acinetobacter calcoaceticus* (6.7%)
Winfield et al. (1993)	184	13 (7.1%)	Coagulase-negative staphylococci (38.5%) *Enterococcus* (30.8%) *Serratia marcescens* (7.7%) Alpha-hemolytic streptococci (7.7%) *Acinetobacter* (7.7%)
Wyler and Kelly (1972)	70	11 (15.7)	*Staphylococcus epidermidis* (45.5%) *Staphylococcus aureus* (27.3%) Viridans streptococci (18.2%)

NA, not applicable.

substance composed of glycosaminoglycans, regulated by bacterial icaA, icaC, and icaD genes (Arciola et al., 2002). *Staphylococcus* species unable to produce biofilm may be less likely to produce shunt malfunction and may be curable with antibiotics alone. Although polymerase chain reaction (PCR) assays can detect biofilm-forming strains of bacteria, these assays are not readily available in most hospitals (Younger et al., 1987; Arciola et al., 2002).

Shunt malfunction is often caused by obstruction of the catheter by adjacent inflammation, growth of tissue into the catheter lumen, or degradation or migration of the catheter (Del Bigio, 1998). Over 50% of shunts will develop malfunction in 10–12 years after placement (Sainte-Rose et al., 1991; Barnes et al., 2002).

Clinical features

Symptoms of CNS shunt infection typically develop within 6 months of device placement and are often similar to those occurring in patients with shunt malfunction: headache, drowsiness, and vomiting (Gardner et al., 1985). In patients who develop shunt infections within the first postoperative month, inflammation along the subcutaneous shunt tract is often present (Haines and Taylor, 1982). In children, shunt infection is usually preceded by fever, irritability, and shunt malfunction (Odio et al., 1984). In children with fungal ventriculitis, onset of symptoms may occur 1–12 months after shunting and clinical manifestations may be more subtle and insidious (Chiou et al., 1994).

While only one-third of patients with shunt infection will develop signs of meningeal irritation, virtually all will have fever (Schoenbaum et al., 1975). In addition to fever, shunt infection is more likely than shunt malfunction to produce seizures, serum C-reactive protein greater than 7 mg/l, elevated CSF protein concentration, hypoglycorrachia, and CSF neutrophilic pleocytosis (Barnes et al., 2002; Lan et al., 2003; Schuhmann et al., 2005). Other symptoms infrequently reported with shunt malfunction include: cranial nerve palsies, hemiparesis, visual deficits, and rigidity (Jamjoom and Wilson, 1988; Molia et al., 1996; Lee et al., 1999; Barnes et al., 2002). When CSF pleocytosis is present, patients with shunt malfunction are more likely to have a predominance of eosinophils, rather than neutrophils (Lan et al., 2003).

Diagnosis

CSF examination should be performed in all patients with suspected shunt infection. Unfortunately, aseptic meningitis can occur following shunt placement and may mimic infectious meningitis. Studies attempting to differentiate between aseptic and infectious meningitis in patients with shunts found no patient with aseptic meningitis had a CSF WBC count >7500 cells/μl or glucose concentration <10 mg/dl (Forgacs et al., 2001). In children, increased risk of shunt infection and higher number of shunt revisions were associated with CSF eosinophilia (defined as $\geq 8\%$ eosinophils of the total CSF WBC count), in the absence of peripheral eosinophilia or parasitic infection (Tung et al., 1991). Both shunt infection and shunt malfunction may be associated with increased CSF protein concentration (Brydon et al., 1996). Accumulation of fluid along the shunt tract or at the operative site is highly suggestive of CNS infection, but occurs in less than 10% of patients with VP shunt infection (Davis et al., 1999).

Bacterial and fungal cultures of CSF, in addition to blood cultures, should be obtained from all patients

with suspected shunt infection, preferably before antibiotics are initiated. Culture of CSF obtained from the shunt is more likely to identify the causative organism than culture of CSF from a lumbar or ventricular tap (Myers and Schoenbaum, 1975; Schoenbaum et al., 1975; Noetzel and Baker, 1984). Blood cultures are more likely to identify the causative organism in patients with VA rather than VP shunts (Schoenbaum et al., 1975). In patients with shunt infection, CSF broth cultures identify the causative organism in up to 25% of patients with negative routine plate cultures (Dunbar et al., 1998). In children with VP shunt infection, Gram's stain of CSF was positive in 46% of cases and blood cultures in 29% (Odio et al., 1984). The rate of positive CSF culture obtained from the shunt declined from 96% to 53% in patients who received antibiotics prior to obtaining CSF culture (Myers and Schoenbaum, 1975). Routine monitoring of CSF cultures in patients with EVD has not identified infection prior to development of clinical symptoms of infection (Hader and Steinbok, 2000).

Special mention should be made of organisms that are typically considered contaminants in patients who do not have a CNS shunt: *Propionibacterium* species and coagulase-negative staphylococci. Shunt infection by *Propionibacterium* species and coagulase-negative staphylococci is common, and should always be considered pathogenic. Shunt infection by *Propionibacterium* species almost always occurs in the setting of fever and CNS symptoms, such as seizure or cognitive impairment (Everett et al., 1976). CSF examination usually demonstrates mild pleocytosis (24–315 cells/mm^3) and variable CSF protein or glucose concentrations. As *Propionibacterium* species grow slowly, the laboratory should be asked to hold CSF cultures for at least 14 days before issuing a final negative report.

Imaging of the brain with computed tomography (CT) or magnetic resonance imaging (MRI) is most useful when earlier postoperative scans are available for comparison. Although no comprehensive review of neuroimaging findings associated with shunt infection has been published, case series have reported increased or decreased ventricular size, as well as abscess formation, in patients with shunt infection (Gower et al., 1990; Jones et al., 1993; Butler and Khan, 2001). Increased ventricular size is often encountered in patients with shunt infection or shunt malfunction, with reports noting increased ventricular size in 66–84% of children with shunt malfunction (Iskandar et al., 1998; Barnes et al., 2002). Focal encephalitis of the dorsal midbrain, confirmed by MRI, has been described with shunt infection by *P. acnes* (Camarata et al., 1990). Ultrasound has been used to diagnose neonatal ventriculitis following VP shunt placement; increased echogenicity of ventricular fluid was a typical finding, with echogenicity in a fine homogeneous pattern or with strand-like material and coarse particles (Brown and Thorp, 1984).

Management

When shunt infection is suspected, antibiotics should be started after obtaining CSF and blood cultures and then adjusted according to the antibiotic sensitivity of the pathogen detected. Initial antibiotic treatment of a presumptive shunt infection should include antibiotic coverage for the most likely pathogenic organism. Recommended dosages of antibiotics are listed in Table 9.3. In most patients with shunt infection, *S. epidermidis* or *S. aureus* will be the causative organism, and should be adequately treated by vancomycin in combination with ceftazidime, cefepime, or meropenem (Tunkel et al., 2004). For children, vancomycin

Table 9.3

Antibiotic dosages for treatment of shunt infection

Antibiotic	Adult dosage	Pediatric dosage
Vancomycin	30–60 mg/kg IV daily q 8–12 hours	15 mg/kg IV q 6 hours
Rifampin	600 mg twice daily	10–20 mg/kg PO q day
Cefotaxime	3 g IV q 8 hours	75–100 mg/kg IV q 8 hours
Ceftriaxone	2 g IV q 12 hours	40–50 mg/kg IV q 12 hours
Cefepime	2 g IV q 8 hours	50 mg/kg IV q 8 hours
Meropenem	2 g IV q 8 hours	40 mg/kg IV q 8 hours
Gentamicin (preservative-free)	4–8 mg intraventricular q day	1–2 mg intraventricular q day
Amikacin	5 mg/kg IV q 8 hours	10 mg/kg IV q 8 hours
	30 mg intraventricular q day	30 mg intraventricular q day
Amphotericin B	0.5–0.8 mg/kg IV q day	0.5–0.8 mg/kg IV q day

Data from Pickering et al. (1978), Tunkel et al. (2004), and Wen et al. (1992).

alone should suffice, unless gram-negative bacilli are identified on CSF examination. When gram-negative rods are detected, treatment should include a third- or fourth-generation cephalosporin, such as cefepime. If enteric coliforms or *Pseudomonas* species are identified by culture, some experts recommend administration of intraventricular preservative-free gentamicin (Pickering et al., 1978; Wen et al., 1992). Infection with *Mycobacterium fortuitum* has been successfully treated with oral ofloxacin in combination with intrathecal and systemic amikacin (Chan et al., 1991). Successful treatment of fungal shunt infection usually requires shunt removal and administration of systemic amphotericin B; intrathecal administration should be considered for patients who do not respond to systemic therapy (Chiou et al., 1994).

Treatment of an infected shunt device with antibiotics alone, even if delivered systemically and through the infected device, is not as effective as antibiotic treatment followed by replacement of the infected device (James et al., 1980). Most experts recommend administration of antibiotics with concomitant externalization of the shunt; once the CSF is sterilized, antibiotics can be discontinued and the drain replaced by a new shunt (Table 9.4). Simultaneous removal of an infected shunt with placement of a new shunt in a different location prior to completion of antibiotic treatment has been associated with higher rates of reinfection (Gardner et al., 1985). Regardless of manner of treatment, shunt infection can recur, typically does so within 6 months, and is usually caused by the original infecting organism – most often *S. epidermidis* (Kestle et al., 2006). In patients who receive a complete course of antibiotics followed by shunt replacement, repeat shunt infection occurs in 17–52% (Renier et al., 1984; Meirovitch et al., 1987). Higher mortality rates have been associated with CSF glucose <20% of serum glucose value, increasing Acute Physiology and Chronic Health Evaluation (APACHE) III score, and CNS infection due to gram-negative organisms (Federico et al., 2001).

Perhaps the most difficult aspect of treating a shunt infection is determining when symptoms are due to infection rather than shunt malfunction. As mentioned previously, no test, other than CSF culture identifying a pathogenic organism, can differentiate between shunt infection, aseptic meningitis, and shunt malfunction. Some experts recommend initiating empiric antibiotic treatment when infection is suspected, and discontinuing if CSF cultures are negative after 2–3 days (Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy, 2000). Table 9.5 lists the clinical and laboratory findings favoring shunt infection over malfunction.

Prevention

A recent meta-analysis of the prophylactic use of antibiotics for intraventricular shunt placement by the Cochrane Collaboration found a decreased rate of shunt infection in patients receiving antibiotics for 24 hours; no additional benefit accompanied longer duration of antibiotic administration (Ratilal et al., 2006). Other studies have reported that the use of

Table 9.4

Shunt replacement and recurrent shunt infection

Study	Shunt type	Device removed? (no. of patients)	Antibiotics	Outcome
Odio et al. (1984)	VP	No (13)	Yes	3 relapses
		Immediate (37)	Yes	2 reinfections
		Delayed (9)	Yes	No relapses
				3 reinfections
				1 reinfection
Schoenbaum et al. (1975)	VA	No (28)	Yes	4 died
		Yes (12)		19 relapses or continued infection
		Revised (5)		1 death
				No reinfections
				3 re-infections
Wyler and Kelly (1972)	EVD	No	Yes (44)	4 infections
			No (26)	7 infections

VP, ventriculoperitoneal; VA, ventriculoatrial; EVD, external ventricular drain.

Table 9.5

Factors favoring central nervous system (CNS) infection over aseptic meningitis or shunt malfunction

Factor	CNS infection	Malfunction or aseptic
Onset of symptoms	<6 months after procedure	
Clinical	Fever	Somnolence
	Seizure	Similar symptoms with prior episode of malfunction
	Shunt tract tenderness	
Laboratory	CSF neutrophilic pleocytosis	CSF eosinophilia
	CSF cell count >7500 cells/μl	
	CSF glucose <10 mg/dl	
	CSF lactate level ≥4 mmol/l	
	Serum C-reactive protein >7 mg/l	
Imaging	Meningeal enhancement; abscess formation	Increased ventricular size

CSF, cerebrospinal fluid.

prophylactic antibiotics before and after ventricular shunt placement reduces the rate of shunt infection, but only in institutions where the shunt infection rate is higher than 5% (Langley et al., 1993; Haines and Walters, 1994). The benefit of prophylactic antibiotics administered pre- or postoperatively for EVD catheters is unclear. The Cochrane Collaboration and other studies have not detected a significant effect upon incidence of postprocedural infection (Blomstedt, 1985; Alleyne et al., 2000; Ratilal et al., 2006). A randomized study of perioperative injection of 10 mg of vancomycin into the EVD did not enroll enough patients to determine whether this approach reduced the incidence of CNS infection (Bayston et al., 1990). Regardless of shunt type, if prophylactic antibiotics are administered they should cover *S. epidermidis* and *S. aureus*.

Antibiotic-impregnated shunt (AIS) catheters offer another potential mechanism of decreasing shunt infections. An *in vitro* study demonstrated that clindamycin and rifampin reduced catheter colonization without inducing antibiotic resistance (Bayston et al., 1989). However, a recent *in vivo* study comparing shunt infection rates in 86 patients receiving AIS catheters impregnated with clindamycin and rifampin with 126 patients with non-AIS catheters did not demonstrate a significant difference in shunt infection (Ritz et al., 2007). Other studies have demonstrated a reduction, but not elimination, of shunt infections in patients receiving AIS shunts (Govender et al., 2003; Aryan et al., 2005; Sciubba et al., 2005). The Cochrane Collaboration meta-analysis suggested AIS reduced the incidence of shunt infection, but requested additional clinical trials to confirm this potential benefit (Ratilal et al., 2006).

POSTCRANIOTOMY CENTRAL NERVOUS SYSTEM INFECTION

Epidemiology

Potential postcraniotomy CNS infections include meningitis, bone flap infection, epidural or brain abscess, and subdural empyema. Infectious meningitis complicates fewer than 5% of craniotomies, but is more common in patients who undergo repeat resection surgery for recurrent glioma, neurosurgical procedures traversing areas of bacterial colonization, such as the paranasal sinuses, longer duration of external ventricular drainage or ICP monitoring and higher American Society of Anesthesiologists score – a preoperative risk of surgical site complications (Tenney et al., 1985; Mollman and Haines, 1986; Blomstedt, 1992; Kourbeti et al., 2007).

Aseptic (noninfectious or "chemical") meningitis is another potential complication of any neurosurgical procedure, and can produce symptoms identical to infectious meningitis. Aseptic meningitis, by definition, requires negative CSF Gram's stain and culture, as well as recovery of the patient without administration of antibiotics (Finlayson and Penfield, 1941; Carmel et al., 1974). Aseptic meningitis has been reported after craniotomy, suboccipital craniotomy, and posterior fossa surgery in children (Finlayson and Penfield, 1941; Carmel et al., 1974).

Etiology

The etiology of infectious meningitis is usually related to direct contamination from surrounding skin or sinuses and is typically caused by coagulase-negative or -positive staphylococcal species – similar to those

species causing CNS shunt infection (Ferrera et al., 1994). The etiology of aseptic meningitis in postneurosurgical patients is not completely understood: one hypothesis is that release of red blood cells or other material during surgery produces meningeal inflammation. This hypothesis is supported by experimental injections of saline, air, casein, or blood into the subarachnoid space that produced symptoms of meningitis and a neutrophilic pleocytosis, the latter persisting for 3–4 weeks (Jackson, 1949).

Clinical findings

Signs of meningeal irritation, such as headache, nuchal rigidity, or discomfort, and change in level of consciousness can occur in patients with infectious or aseptic meningitis. In a study of 70 patients undergoing craniotomy, paranasal or spinal surgery, bacterial meningitis was more common in those with fever (temperature $\geq$ 39.4°C) and purulent or nonpurulent wound drainage (Forgacs et al., 2001). Transient loss of consciousness showed a trend towards significant association with bacterial meningitis, but headache and neck stiffness were no more common in patients with bacterial than aseptic meningitis. Infection was also more common in patients who developed postoperative seizure or neurological deficit, CSF leak or infection outside the CNS (Ross et al., 1988; Forgacs et al., 2001).

Diagnosis

Both infectious and aseptic meningitis are characterized by spiking fevers, stiff neck, and headache; thus, differentiating between infectious and noninfectious causes of meningitis can be difficult. Other than identification of an organism in CSF by Gram's stain or culture, no single assay or clinical symptom or sign is able to predict the presence of CNS infection with certainty. One study of meningitis occurring in patients following neurosurgery noted patients with aseptic meningitis did not have marked pleocytosis (CSF WBC count >7500 cells/μl) or depressed glucose concentrations (<10 mg/dl); unfortunately, marked CSF abnormalities were rarely present in patients with bacterial meningitis either, and there was no statistically significant difference between CSF WBC count or glucose concentration in patients with bacterial and aseptic meningitis (Forgacs et al., 2001).

In patients with bacterial meningitis following craniotomy, elevation of CSF lactate level $\geq$4 mmol/l was a sensitive and specific predictor of bacterial meningitis (Leib et al., 1999). Elevations in CSF lactate during bacterial meningitis result from a combination of bacterial production, anaerobic metabolism, and lactate released by neurons and glial cells associated with brain edema induced by meningitis (Salord et al., 1994; Tureen, 1995).

All patients with suspected meningitis should have blood and CSF samples sent for Gram's stain and culture, in addition to routine studies. Although identification of an organism on Gram's stain of the CSF is sufficient for diagnosis of infectious meningitis, up to 70% of patients with positive CSF culture will have a negative Gram's stain (Ross et al., 1988). In addition, although use of CSF lactate level has not been studied prospectively, this assay may prove useful in differentiating between infectious and aseptic meningitis. Neuroimaging should not be used to differentiate between chemical or infectious meningitis, as inflammation and contrast enhancement can be seen in up to 80% of postcraniotomy patients without CNS infection (Burke et al., 1990).

Management

Unfortunately, it is not possible to distinguish between infectious and aseptic meningitis rapidly in the postoperative neurosurgical patient using tests presently available. An antibiotic with activity against *S. aureus* and α- and β-hemolytic streptococci should be administered to any postoperative neurosurgical patient with clinical or laboratory evidence of meningitis, especially in the setting of marked pleocytosis (CSF WBC count >7500 cells/μl), CSF lactate level $\geq$4 mmol/l, or high fever (temperature $\geq$39.4°C). If the patient did not receive antibiotics prior to obtaining CSF, and the CSF culture remains negative after 2–3 days, antibiotics can be discontinued (Bayston et al., 2000).

Prevention

Elemental iodine kills a broad spectrum of organisms, including bacteria, fungi, and viruses, but has not yet been tested for prophylaxis against postneurosurgical infection in humans. A study of craniectomized rats with irrigation of brain tissue with an elemental iodine solution demonstrated no evidence of brain infection after challenge with either *S. aureus* or *S. epidermidis* (Choi et al., 2003). In addition, there was no evidence of cortical injury due to irrigation. In a study of children who underwent posterior fossa surgery, initiation of dexamethasone therapy immediately following surgery was associated with a decrease in the occurrence of chemical meningitis from 70% to 30.5% and was not associated with an increase in bacterial meningitis (Carmel and Greif, 1993).

SKULL FRACTURES AND PENETRATING CRANIOCEREBRAL INJURIES

Compound depressed skull fractures are commonly associated with traffic accidents, falls, or assault and by definition include laceration of the skin over a downwardly displaced skull fragment. Penetrating craniocerebral injuries may be due to shrapnel from acts of war or violence. High-velocity bullets, shrapnel, and stones from explosive devices most often produce damage at the convexity of the skull (83%) and less often at the base (13%) (Levi et al., 1990). For patients who sustain head injuries during combat, those with open head injuries have higher rates of CNS infection than those with closed head injuries. Risk of CNS infection is not increased if retained shrapnel is present, although one case of CNS abscess associated with retained shrapnel 53 years after penetrating craniocerebral injury has been reported (Marquardt et al., 2000).

From World War I to the war in Iran, the incidence of CNS infection following penetrating craniocerebral injury has declined, but the mortality associated with such infection has remained fairly stable. During World War I, the majority (58%) of patients with penetrating craniocerebral injuries contracted CNS infection, and 83% of these patients died (Whitaker, 1918). Coincident with the introduction of antibiotics, CNS infections complicating penetrating craniocerebral injury during World War II decreased to less than 25% of cases, but still carried a morbidity of up to 50% (Haynes, 1945; Rowe and Turner, 1945). From the Korean and Vietnam wars to recent conflicts, CNS infections have continued to complicate 6–15% of penetrating craniocerebral injuries, and approximately 40% of these patients will die (Carey et al., 1974; Taha et al., 1991; Aarabi et al., 1998).

Etiology

Factors associated with higher rates of CNS infection following compound depressed skull fracture include dural tear, free bone fragments, and delayed presentation for treatment greater than 8 hours (Rehman et al., 2007). Higher rates of CNS infection following penetrating craniocerebral injuries include multilobar damage, penetration of the ventricles, inadequate debridement, incomplete dural closure, CSF fistula, retained bone fragments, coma, and delay in evacuation from the field (Cushing, 1918; Ascroft, 1943; Haynes, 1945; Rish et al., 1981). Even following the advent of antibiotics, rates of CNS infection remain higher in patients who sustain open head injuries.

Of 964 patients admitted following penetrating craniocerebral injuries due to military projectiles to a hospital in Iran, 105 (11%) developed a CNS infection (Aarabi et al., 1998). The most frequent infection was meningitis (82 cases), but cerebritis (three cases) and intracerebral abscess (20 cases) were also reported. The most common etiological agent was *Klebsiella pneumoniae*. Increased risk of CNS infection was associated with CSF fistulas, injuries penetrating the ventricles or paranasal sinuses, but not with retained bone fragments. Infection rate was lowest in patients who sustained penetrating injuries that did not pass through and exit the skull, or disrupt more than one dural membrane. A study of penetrating wounds of the brain sustained during warfare in Lebanon during 1982–1985 found higher mortality associated with a Glasgow Coma Scale of ≤ 4 upon arrival to the hospital, high-velocity bullet wounds, penetration of the ventricles or multiple lobes, and presence of shock (Levi et al., 1990). No CNS infection was detected over 6 years of follow-up in 23 patients with retained bone fragments.

Treatment and prevention

A review of prophylactic or therapeutic use of antibiotics following penetrating craniocerebral injuries found support for prophylactic use of broad-spectrum antibiotics (Bayston et al., 2000). This group also found evidence of reduced risk of CNS infections when bone fragments or metal shrapnel were removed, but recommended removal only if additional CNS damage could be avoided.

DURAL PUNCTURE

Complications of LP include post-LP headache, cranial neuropathy, subdural or epidural bleeding, nerve root irritation, low back pain, and herniation of the brain or spinal cord (Evans, 1998). Meningitis has been reported after dural puncture performed for diagnostic or therapeutic purposes, during spinal anesthesia and myelography (Domingo et al., 1994; Lurie et al., 1999; Yaniv and Potasman, 2000).

Although LP can potentially introduce an infection into the CNS, the occurrence is rare: only 75 cases of meningitis due to LP have been reported over the past 50 years (Baer, 2000). In a study of 5000 patients who underwent spinal or epidural anesthesia, only one case of meningitis occurred (Yaniv and Potasman, 2000). While community-acquired meningitis has a mortality rate between 3% and 29%, only three deaths have been reported due to iatrogenic meningitis following LP, suggesting iatrogenic meningitis following LP may be more readily recognized and treated earlier, or may be less severe due to less virulent organisms (Schlech et al., 1985; Wenger et al., 1990).

Some patient populations with an increased risk of bacteremia, such as women in labor and immunocompromised patients, may also have an increased risk of contracting meningitis following a dural puncture procedure (Yaniv and Potasman, 2000). Whether risk of meningitis during LP is higher in a bacteremic patient without other risk factors is not completely known (Wintergerst et al., 1986). In a study of bacteremic rats, meningitis occurred only in rats that underwent dural puncture; those rats that received one dose of antibiotics prior to dural puncture did not develop meningitis (Carp and Bailey, 1992). In a study of bacteremic patients, no statistically significant difference in incidence of meningitis was noted between patients who did or did not undergo LP, suggesting infection is not introduced by dural puncture or by introduction of contaminated blood with the needle (Eng and Seligman, 1981).

Etiology

Although no study has demonstrated introduction of skin flora directly through an LP needle, clusters of cases of meningitis following LP or epidural catheter placement performed by the same operator suggest organisms may be introduced through the needle or catheter via disruption of sterile technique or by droplet transmission of bacteria from operator to patient (de Jong and Barrs, 1992; Gelfand and Abolnik, 1995; Schneeberger et al., 1996). Iatrogenic meningitis caused by droplet transmission of *Streptococcus salivarius* from operator to patient is supported by a study of two patients who developed meningitis following spinal anesthesia and by a study that used PCR assay to identify identical isolates of *S. salivarius* in CSF of patients who developed meningitis following LP, with a throat swab of the neurologist who performed the LP (Veringa et al., 1995; Couzigou et al., 2003). An alternative hypothesis for bacterial contamination of the CSF during dural puncture is the increase in blood–brain barrier permeability induced by decreased CSF pressure after LP (Baumann and Koch, 1952). One study on animals injected intravenously with bacteria prior to LP demonstrated that meningitis followed in only those animals that had an LP (Weed et al., 1920).

As with any procedure that disrupts the dura, CNS infection complicating LP is most often caused by commensal skin flora, most often the α- and β-hemolytic streptococci. Cultures of skin around LP sites have detected *Streptococcus* species and other bacteria, consistent with the hypothesis that patients who develop postdural puncture meningitis acquire the organism from skin via introduction with the spinal needle (Nachamkin and Dalton, 1983). Culture of spinal needles immediately after dural puncture revealed bacterial contamination in 17.9% of the needles, most by coagulase-negative staphylococci (87.5%) (Raedler et al., 1999). The most frequently identified species of α-hemolytic streptococci from patients with iatrogenic meningitis include: *S. salivarius, S. mitis*, and *S. sanguis* (Blackmore et al., 1993). Meningitis caused by α-hemolytic streptococci most often occurs after a procedure requiring prolonged dural penetration, such as spinal anesthesia or myelography, but is uncommon during short procedures such as LP (Moen, 1998).

The majority of epidural abscesses following temporary epidural catheters are due to *Staphylococcus aureus* (Sarubbi and Vasquez, 1997). Other organisms isolated following epidural catheter placement include *Mycobacterium fortuitum* cultured from an epidural abscess in a patient who underwent epidural injection for low back pain 3 months previously (O'Brien and Rawluk, 1999), and *Pseudallescheria boydii* from an epidural abscess in a patient who received epidural anesthesia (Berenguer et al., 1989).

Clinical features

As with infectious meningitis complicating neurosurgical procedures, symptoms of meningitis complicating LP are similar: headache, meningismus, and altered mental status. When infection occurs, it typically does so within the first day (Eng and Seligman, 1981). Epidural abscess after placement of a temporary epidural catheter typically occurs later – 5 days following placement – with most patients developing fever, low back pain, and neurological deficits. A study of 22 patients with epidural abscess detected lower limb sensory deficits in 50%, lower limb weakness or paralysis in 41%, bladder dysfunction in 36%, and meningismus in 18% (Sarubbi and Vasquez, 1997).

Diagnosis

Diagnosis of iatrogenic meningitis following dural puncture can be problematic; elevated CSF WBC count may accompany infection, chemical meningitis, or trauma. A study of CSF from patients who underwent spinal anesthesia noted pleocytosis in 65% of patients at 24 hours, 30% at 48 hours, and 18% at 72 hours; the highest cell count in this study was 1950 cells/mm^3 (Backer-Grundahl, 1934). Distinguishing between an infectious or noninfectious etiology of meningitis should be based on CSF examination and culture (Geiseler et al., 1980; Spanos et al., 1989; Durand et al., 1993).

Management

When iatrogenic meningitis is suspected, antibiotic therapy should be directed against the most likely etiological agents, α- or β-hemolytic streptocci, then adjusted once antibiotic sensitivities are known. In a study of antibiotic sensitivities of viridans group streptococci, less than half were highly susceptible to penicillin therapy, and most had intermediate or high resistance to penicillin; *Streptococcus mitis* most often demonstrated the highest level of penicillin resistance. (Doern et al., 1996). In addition, 15–20% of α-hemolytic streptococci were resistant to ceftriaxone (Doern et al., 1996). Therefore, when iatrogenic meningitis is suspected, ceftazidime or cefepime, as well as an additional antibiotic such as vancomycin, should be administered.

Prevention

The incidence of post-LP CNS infection is low and adherence to sterile technique reduces the risk of introduction of infectious agents into the subarachnoid, arachnoid, or epidural space (Gorelick and Biller, 1986). Although proper sterile technique can reduce introduction of skin flora into the spinal canal, performance of an LP through an infected lumbar area increases the risk of introducing infection and should be avoided: an alternative is use of cisternal puncture to obtain CSF.

If prolonged presence of a catheter in the epidural space is anticipated, wearing a face mask may reduce the introduction of α-hemolytic streptococci. Studies have isolated oral flora, such as α-hemolytic streptococci, from agar culture plates placed 30 cm from subjects who spoke while not wearing surgical masks, but not from any plates near subjects who spoke while wearing masks (Philips et al., 1992). In 2005, the Healthcare Infection Control Practices Advisory Committee recommended use of face masks for operators placing a catheter or injecting material into the spinal or epidural space (Siegel et al., 2007). Some experts also recommend wearing face masks during LP if the operator will be talking.

XENOGRAFTS

Transplantation of neural tissue from species other than humans (xenografts) was recently introduced for diseases such as Parkinson's disease, Huntington's disease, and epilepsy; ventral mesencephalon and lateral ganglionic eminence cells from fetal pigs are examples of such xenografts. Although porcine endogenous retrovirus (PERV) can infect human cells *in vitro*, one small study suggested *in vivo* transmission of PERV to recipients of porcine xenografts does not occur; this study examined peripheral blood mononuclear cells from patients receiving xenografts, as well as *in vitro* exposure of xenograft to human cell culture, and found no evidence of PERV transmission (Dinsmore et al., 2000). To date, no atypical infections have been reported in humans receiving intracranial xenograft transplant.

CONCLUSION

Infection of the nervous system in the postoperative neurosurgical patient is infrequent, but, when suspected, should be treated urgently with antibiotics. Clinical presentation of CNS infection in any postoperative neurosurgical patient may mimic clinical symptoms caused by a noninfectious etiology, such as shunt malfunction or aseptic meningitis. Evaluation of CSF formula and cultures of CSF and blood, in concert with clinical evaluation, provides the highest likelihood of detecting CNS infection. Given the widespread usage of sterile technique and perioperative antibiotics, future reductions in the rate of postoperative infectious complications are likely to be small; antibiotic-impregnated catheters may provide an additional reduction.

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Chapter 10

Rickettsial and ehrlichial infections

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Rickettsial diseases generally include infections caused by organisms of the genera *Rickettsia* (spotted fever rickettsioses, typhus fever group), *Orientia* (scrub typhus), *Coxiella* (Q fever), *Ehrlichia* and *Anaplasma*. Rickettsiae are pleomorphic obligate intracellular coccobacilli, and have many epidemiological, clinical, and laboratory features in common. Most rickettsial diseases are transmitted by arthropod vectors, including ticks, mites, fleas, and lice. Humans are usually incidental hosts of rickettsial infection, with the important exception of epidemic typhus in which humans are the principal or reservoir host, and the human body louse is the vector. Clinical features of rickettsial infections often include fever, headache, myalgias, and rash.

Central nervous system (CNS) involvement has been described in most rickettsial infections (Marrie and Raoult, 1992). Headache is often the earliest and most commonly reported symptom in patients with rickettsial infections, and is present in more than 80% of cases (Harrell, 1953). Of the rickettsial diseases, Rocky Mountain spotted fever (RMSF) and epidemic typhus most frequently present with neurological manifestations (Silpapojakul et al., 1991). The epidemiology, clinical manifestations, and treatment of the various rickettsiae are provided in Tables 10.1 and 10.2, and are discussed in detail below.

SPOTTED FEVER GROUP

The spotted fever group of rickettsial diseases is composed of RMSF and other members of the genus *Rickettsia* causing spotted fevers such as rickettsialpox and various forms of "tick typhus." However, RMSF is the most virulent of the rickettsiae in the spotted fever group.

Rocky Mountain spotted fever

Etiology and epidemiology

Rickettsia rickettsii, the causative agent of RMSF, is an obligate intracellular pathogen. RMSF is the most common fatal tick-borne disease in the USA (CDC, 2004); anywhere between 100 and 1000 cases are reported annually. The disease has been reported throughout the continental USA, with the exception of Maine and Vermont, as well as in Alaska (Walker, 1995). Between 1981 and 1991, the states with the highest incidence of RMSF were Oklahoma, North Carolina, Virginia, Maryland, Georgia, Missouri, Arkansas, Montana, and South Dakota (CDC, 1991). In the northern hemisphere, the majority of infections are reported between the months of April and September, when tick bites are most likely to occur. Along the southern Atlantic coast and south-eastern and south central USA, the American dog tick (*Dermacentor variabilis*) is the primary vector for *R. rickettsii.* In the western region of the USA, the vector is usually the wood tick (*Dermacentor andersoni*). Outside the USA, RMSF has been reported in Canada, Mexico, and Central and South America (Sexton and Kaye, 2002). Rural and suburban populations are more likely to be infected than urban residents due to heavier infestations of the tick vectors. The incubation period ranges from 2 to 14 days (mean 7 days) after a tick bite (Thorner et al., 1998).

RMSF should be considered in the differential diagnosis of any patient with compatible clinical features

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Table 10.1

Epidemiological and clinical features of *Rickettsia* and *Ehrlichia* causing human disease

Disease	Agent	Cases/year (USA)	Geography	Mode of infection/vector	Reservoir	Rash
Spotted fever group						
Rocky Mountain spotted fever	*Rickettsia rickettsii*	2000	North America, Central America, and South America	Tick	Rodents	Rash initially maculopapular, then petechial (often begins on ankles or wrists)
Typhus group						
Epidemic typhus/ Brill–Zinsser disease	*Rickettsia prowazekii*	<10	North, Central and South America, Europe, Asia, Africa	Human louse, rat louse	Humans, eastern flying squirrels (USA)	Maculopapular rash (begins in axillae, spreading peripherally)
Murine typhus	*Rickettsia typhi*	<50	Worldwide; in USA, endemic foci southern California, Texas, Hawaii	Rat flea	Rodents	Similar to epidemic typhus
Other						
Q fever	*Coxiella burnetii*	100–200	Worldwide, most common in rural areas	Inhalation of infectious aerosols from milk, urine, feces, amniotic fluid of infected animals; rarely tick-borne	Cattle, sheep, goats, cats, dogs, wildlife	Rare
Ehrlichioses						
Human monocytotrophic ehrlichiosis (HME)	*Ehrlichia chaffeensis*	150–200	USA (south-east and south-central regions)	Lone star tick (*Ambylomma americanum*)	Deer	Variably macular, papular, petechial. Seen in ~60% pediatric cases, ~20% adults
Human ewingii ehrlichiosis (HEE)	*Ehrlichia ewingii*	<20	USA (south-east and south-central regions)	Lone star tick (*Ambylomma americanum*)	Deer, canines	Not reported
Human granulocytotrophic anaplasmosis (HGA)	*Anaplasma phagocytophilum*	300–500	USA (north-east, north-central, and pacific north-west states), Europe, Asia	Blacklegged ticks (*Ixodes scapularis* and *Ixodes pacificus*)	Deer, rodents	Macular, rare

Table 10.2

Diagnostic testing for rickettsial and ehrlichial infections

Syndrome	Serology	IHC of biopsy samples	PCR (blood or CSF)	Culture	Blood smears
Spotted fever group					
Rocky Mountain spotted fever	+	+	Research only	n/a	n/a
Typhus group					
Epidemic typhus	+				
Murine typhus	+				
Other					
Q fever	Acute: phase II antibodies Chronic: phase I antibodies	+	+		
Ehrlichioses					
Human monocytotrophic ehrlichiosis (HME)	+		+	Research only	Morulae in monocytes
Human ewingii ehrlichiosis	+ (reacts with assay for HME)		+	Research only	Morulae in granulocytes
Human granulocytotrophic anaplasmosis (HGA)	+		+	Research only	Morulae in granulocytes

IHC, immunohistochemical staining; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; n/a, not applicable.

and exposure to a grassy or wooded area where ticks may be present (Walker, 1995). Dogs may carry ticks into households and yards, and canine exposure is an additional risk factor for infection (Walker, 1995; Paddock et al., 2002). Household and family clusters of infection have been identified in areas with large populations of infected ticks (Jones et al., 1999; CDC, 2004). The absence of a history of a reported tick bite should not dissuade a clinician from including RMSF in the differential diagnosis, as 30–40% of individuals diagnosed with RMSF did not recall a specific exposure (Kirk et al., 1990). This is especially true in pediatric patients, as shown in a recent study of 92 children with RMSF, in whom only 49% recalled a recent tick bite (Buckingham et al., 2007).

Pathophysiology

Transmission of rickettsiae occurs as a tick feeds on the blood of its host. After entry into the body, there is hematogenous dissemination of the rickettsiae, which then multiply within and disrupt the endothelial cells of capillaries and arterioles; the smooth-muscle cells of the tunica media may also be infected. Vasculitis is the pathological hallmark of RMSF and many of the clinical manifestations are a direct result of the vascular inflammation. For instance, the rash seen in patients with RMSF is a result of small-vessel vasculitis. Many of the CNS manifestations are due to loss of integrity of the small vessels in the brain, resulting in hemorrhage into the subarachnoid space. Subsequent meningeal irritation and an accompanying perivascular mononuclear infiltrate develop. Multifocal glial nodules and arteriolar microinfarcts are the most characteristic pathological lesions within the CNS (Lillie, 1941). Autopsy studies of RMSF cases have demonstrated that rickettsial vasculitis can result in focal neurological damage in the brain and spinal cord as well as myocarditis and vasculitis in the lungs, kidney, and spleen (Walker and Mattern, 1980).

Clinical manifestations

General clinical features

RMSF is characterized by the classic triad of fever, headache, and rash in a patient with a recent tick bite. Most patients with RMSF, however, do not present with this classic triad, and initial symptoms are often nonspecific, such as fever, malaise, lethargy, and headache. Symptoms of RMSF vary in severity from mild to severe; in some cases, the course may progress rapidly to multisystem organ involvement and death. Although the rash is often absent in the first few days of the illness, 85% of patients will develop a skin eruption by the fifth day of fever. Characteristically, the rash begins with small, blanching pink macules that evolve to a maculopapular appearance. The skin findings most commonly begin on the ankles, wrists, and forearms, and then spread to other parts of the body, typically sparing the face. The palms and soles are variably involved. In many instances, however, the rash is atypical and may be localized or even completely absent in up to 10% of cases (Sexton and Corey, 1992). In severe cases, skin necrosis and gangrene of the digits can be a late complication of RMSF. Acute renal failure, coagulopathy, and cerebral edema are also well-recognized complications. Peripheral edema, usually periorbital at first and then becoming generalized, is characteristic of RMSF and may suggest the diagnosis. Hepatosplenomegaly accompanied by liver dysfunction, including coagulation defects, is variably present. In fulminant disease, shock and coma can occur.

Data from many studies suggest that no specific pattern of clinical manifestations or laboratory abnormalities is adequately sensitive to diagnose or exclude RMSF. The differential diagnosis of RMSF includes a number of other illnesses associated with fever and rash. These include meningococcemia, enteroviral infections, scarlet fever, toxic shock syndrome, Kawasaki syndrome, Epstein–Barr virus infection (infectious mononucleosis), syphilis, typhoid fever, rat bite fever and other tick-borne diseases, as well as a variety of noninfectious syndromes.

Neurological features

CNS complications are described in approximately one-quarter of cases (Kaplowitz et al., 1981; Marrie and Raoult, 1992). The headache of RMSF is usually intense and refractory to nonnarcotic analgesics. Progressive restlessness, irritability, confusion, and delirium may also occur, and general or focal neurological impairment including vertigo, seizures, hemiparesis, and ataxia may be present (Marrie and Raoult, 1992). In a recent study of almost 100 children hospitalized with RMSF, 33% had altered mental status, 18% photophobia, 17% seizures, and 10% coma (Buckingham et al., 2007). Acute temporary hearing impairment has been described, but permanent auditory disruption is uncommon (Kelsey, 1979). Ophthalmic features in all rickettsial disorders are similar (Raab et al., 1969; Smith and Burton, 1977) and may include photophobia, conjunctivitis, petechiae on the bulbar conjunctiva, exudates and retinal venous engorgement, papilledema, and ocular palsies. Only one case of Guillain–Barré syndrome associated with RMSF has been reported (Toerner et al., 1996). Residual neurological impairment is not unusual in RMSF – these include learning disabilities, behavioral problems, aphasia, and impairment of fine motor skills (Rosenblum et al., 1952; Harrell, 1953; Gorman et al., 1981).

Diagnosis

Laboratory abnormalities are common in severe disease, including hyponatremia and thrombocytopenia, sometimes as a manifestation of disseminated intravascular coagulopathy (DIC) (Elghetany and Walker, 1999). The cerebrospinal fluid (CSF) may show a mild lymphocytic pleocytosis, and the CSF protein concentration has been reported to be elevated in 30–50% of patients (Kim and Durack, 1997). The CSF cell counts and chemistries may suggest bacterial meningitis, and the dermal petechiae may mimic meningococcemia. Magnetic resonance imaging (MRI) of the brain variably reveals increased signal intensity in the distribution of perivascular spaces, which resolves with clinical improvement (Baganz et al., 1995).

Serological testing remains the gold standard for diagnosis of RMSF. The immunofluorescence assay (IFA) is the most commonly used and most practical test for RMSF (Lochary et al., 1998; Sexton and Kaye, 2002), and is available through most state health departments and many commercial laboratories. Immunofluoresence testing for immunoglobulin (Ig) G or IgM antibodies can be used to make a presumptive diagnosis of acute infection, although these antibodies are often undetectable in the early phase of the illness. Either seroconversion or a fourfold or greater rise in IgG antibody titer between paired serum specimens is generally considered to be confirmatory for RMSF (Thorner et al., 1998). Importantly, the IFA for RMSF and other members of the spotted fever group (e.g., *R. akari*) may cross-react, and therefore a positive IFA cannot distinguish between these related bacteria. The Weil–Felix test is no longer recommended, as it is neither sensitive nor specific for the diagnosis of RMSF (Thorner et al., 1998).

Direct immunofluorescent antibody or immunohistochemical (IHC) staining of skin biopsies is 70–90% sensitive for patients with RMSF and a rash. Molecular

assays for *R. rickettsii* DNA can be performed on serum, whole blood, or tissue specimens, but are currently available only at specialized research laboratories. Polymerase chain reaction (PCR) is more likely to be positive in tissue samples than from blood or serum samples, as the bacteria are trophic for endothelial cells. IHC staining of antigens in formalin-fixed biopsy or autopsy tissue can also be used to diagnose RMSF. In patients who expire prior to seroconversion, IHC staining of tissue can be a useful diagnostic tool (Paddock et al., 1999).

Treatment

Doxycycline is the drug of choice for treating RMSF. For adults, the recommended dose is 100 mg per dose administered twice daily (orally or intravenously). For children weighing <45.4 kg (100 lb), 2.2 mg/kg body weight per dose administered twice daily (orally or intravenously) is recommended. Doxycycline has excellent bioavailability, with equivalent serum concentrations following both oral and parenteral administration (Hongo and Bloch, 2006). Most experts agree that the benefit of using doxycycline in treating RMSF outweighs the potential risk of staining of teeth in pediatric patients (CDC, 2006). Intravenous therapy is often indicated for hospitalized patients. Oral therapy is acceptable for inpatients who are not vomiting or obtunded, and for patients who can be managed as outpatients. Oral absorption of doxycycline is significantly decreased when given with divalent cations, and therefore should not be given concurrently with antacids, sucralfate, or multivitamins (Hongo and Bloch, 2006). The optimal duration of treatment has not been established, but current recommendations for RMSF are to treat for at least 3 days after the fever subsides and until evidence of clinical improvement is noted, which typically results in a minimum total course of 5–7 days. Severe or complicated disease usually requires longer treatment durations.

Since seroconversion in patients with RMSF may be delayed for 2–3 weeks following onset of symptoms, therapy should be administered when the diagnosis is suspected based on clinical and epidemiological findings, such as a history of tick bite or compatible laboratory findings such as thrombocytopenia or elevated liver enzymes, rather than awaiting serological confirmation. With early treatment, the prognosis for full recovery from RMSF is excellent. Neurological sequelae, including mild intellectual impairment (Wright, 1972), may occur if therapy is postponed (Miller and Price, 1972; CDC, 2000). The case fatality rate is 2–10% in patients treated early in the course of illness, but may be as high as 25–30% in untreated patients (Dalton et al., 1995; Thorner et al., 1998).

Other spotted fever group rickettsiae

Etiology and epidemiology

In the USA, there are three other species of spotted fever group rickettsiae besides RMSF: *R. akari* (mite-borne/rickettsialpox), *R. felis,* and *R. parkeri* (Paddock et al., 2004). Outside the USA, other spotted fever group rickettsiae forms of "tick typhus" include boutonneuse fever (Marseille fever or Mediterranean spotted fever, *R. conorii*), North Asian or Siberian tick typhus (*R. sibiraca*), oriental spotted fever (*R. japonica*), and Queensland tick typhus (*R. australis*). With the advent of new molecular techniques, many novel *Rickettsia* species have been described since the early 1990s: *R. africae* in Africa and the West Indies, *R. japonica* in Japan, *R. helvetica* in Europe and Asia, and *R. parkeri* in the USA (Raoult, 2004). Altogether, the spotted fever group rickettsiae include at least 30 different genotypes and 15 distinct species known to cause disease in humans.

Clinical features

The other spotted fever group infections closely resemble RMSF with abrupt onset of high fever, myalgias, prostration, and headache. One important exception is that the rash follows a different distribution than in patients with RMSF and classically begins in the axillae before spreading to involve the entire trunk. Additionally, in some of these other rickettsiae, an eschar may be present (Parola et al., 2005), which is infrequent in RMSF. Little is known about the frequency and spectrum of neurological involvement for these infections.

TYPHUS FEVER GROUP

The typhus fever group consists of epidemic (louse-borne) typhus, Brill–Zinsser disease (relapsing louse-borne typhus), and murine (flea-borne) typhus.

Epidemic typhus

Etiology and epidemiology

Epidemic typhus and Brill–Zinsser disease are caused by *Rickettsia prowazekii*. Unlike most other rickettsial infections, humans are considered to be the primary reservoir for *R. prowazekii*. Epidemics of typhus fever occur by human-to-louse-to-human *R. prowazekii* transmission, typically after rubbing or scratching skin that is contaminated with infective louse feces. Only the body louse, *Pediculus humanis corporis*, plays a role in the transmission of this infection. The body louse lives in clothing and requires daily blood meals and body warmth to survive. Infestation occurs when blankets and clothing are not changed or washed on a regular basis. Epidemics of typhus are often associated with war and squalid living

conditions (Zinsser, 1935). During World War I, 25–30 million cases of epidemic typhus ("trench fever") occurred in Russia alone, including 3 million deaths (Patterson, 1993; Raoult and Roux, 1999). There have been outbreaks of louse-borne typhus in the last three decades involving refugee camps, jails, and other unsanitary living conditions (Perine et al., 1992; Raoult et al., 1997; Tarasevich et al., 1998; Mokrani et al., 2004), including almost 24 000 cases in Burundi in 1997. In some instances, thousands of individuals were affected and mortality rates exceeded 10% (Raoult et al., 1997). Typhus is rare in the USA, with fewer than a dozen cases reported each year (Marrie and Raoult, 1992). The incubation period is usually 7–14 days. Brill–Zinsser disease is a relapsing form of louse-borne typhus that may occur years to decades after the primary attack (Raoult et al., 1998).

Rarely, *R. prowazekii* infection occurs in a nonepidemic pattern associated with a nonhuman reservoir. In the 1970s, a sporadic form of typhus was noted in Florida and Virginia associated with flying squirrels (*Glaucomys volans*) (Bozeman et al., 1975). Most sporadic cases are reported during colder months of the year and are theorized to result from the tendency of squirrels to nest in the attics of homes during the fall and winter. The exact mechanism of transmission from squirrels to humans is not specifically known, but it is believed that vectors (fleas or lice) or airborne transmission may be responsible. Transmission of *R. prowazekii* from flying squirrels to humans is suggested by the isolation of the agent from squirrels and the high frequency of patients who either had handled squirrels or reported squirrel infestation in their residence.

Pathophysiology

Infection occurs via skin entry following deposition of rickettsiae in arthropod feces, with inoculation after scratching. Similarly to RMSF, the rickettsiae spread through the bloodstream, infecting endothelial cells. The severity of clinical illness depends on the degree of vasculitis following the endothelial injury. In epidemic typhus, perivascular infiltration often occurs in the leptomeninges leading to CNS involvement; neurological complications are frequently the cause of death (Marrie and Raoult, 1992). Brill–Zinsser disease is a relapsing form of louse-borne typhus that may occur years to decades after the primary attack (Raoult et al., 2004). Presumably the rickettsiae remain dormant in the reticuloendothelial system until a subsequent reactivation occurs. The pathology is similar to RMSF.

Clinical manifestations

General clinical features

The systemic and neurological symptoms of epidemic typhus are similar to RMSF. Almost all patients present with fever and severe headache. In one report, chills (82%), muscle tenderness (70%), arthralgias (50%), and anorexia (48%) were also described (Perine et al., 1992). Respiratory symptoms, including cough and dyspnea, may occur as well (Raoult et al., 1997). In a case series of 60 patients in Africa, 38% reported a dry hacking cough but few had significant pulmonary complications (Perine et al., 1992).

The clinical characteristics of sporadically occurring *R. prowazekii* infection (i.e., squirrel-associated) are similar to epidemic louse-borne typhus. Of 30 cases described in the USA, fever (100%), headache (81%), rash (66%), myalgias (42%), and confusion (44%) were common manifestations (CDC, 1982). Unlike epidemic typhus, however, there have been no documented fatalities among patients with sporadic *R. prowazekii* infection.

Neurological features

Neurological manifestations of typhus, often described as an agitated delirium (the word "typhus" is derived from the Greek word *typhos* meaning stupor), have been reported in many cases and, if untreated, can progress to coma and death (Marrie and Raoult, 1992). A severe headache is almost always present. Neurological complications include seizures, confusion, and coma. In an outbreak involving nine individuals in a Burundi jail, neurological involvement was common and included mental confusion (six patients), coma (three patients) and seizures (one patient) (Raoult et al., 1997). In Brill–Zinsser disease, the symptoms are similar to the primary attack, although generally milder.

Diagnosis

Laboratory findings of epidemic typhus vary considerably. One study of 58 hospitalized patients with typhus found that the white blood cell count was normal in 83%, low in 3%, and high in 14%. Platelet counts were decreased in 43%. Eighty percent had elevated lactate dehydrogenase and over half had a mild elevation of aspartate transaminase. Proteinuria and hematuria were also frequently detected (Perine et al., 1992).

Serology is the standard diagnostic test, but lacks specificity as there is cross-reactivity among typhus-group rickettsioses (Svraka et al., 2006). Indirect IFA is the most commonly available method. As in RMSF, a fourfold or greater rise in IgG antibody titers between paired serum specimens is diagnostic. PCR methods have been developed but have mostly been used in epidemiological studies of vectors (Svraka et al., 2006).

Treatment

Doxycycline is the drug of choice for treatment of epidemic typhus, with dosing and administration considerations similar to those described for RMSF. Duration

of therapy will depend on the severity of the illness and is typically about 1 week. In a large outbreak setting, such as occurred in Burundi, a single dose of 200 mg doxycycline was often sufficient (WHO, 1997). The response to therapy is usually rapid. In an outbreak setting, delousing is also necessary.

Murine typhus

Etiology and epidemiology

Murine, or flea-borne typhus, is caused by *Rickettsia typhi*. Murine typhus is considered to be one of the most prevalent rickettsial infections worldwide (Azad, 1990), and was one of the most common causes of febrile illness in American military personnel during the Vietnam war (Miller et al., 1974). Prior to 1950, several thousand cases of murine typhus were reported each year in the USA (Pratt, 1958). Endemic foci often exist around port cities and adjacent coastal areas (Azad, 1990). In the USA, endemic foci of the infection are found in California, Texas, and Hawaii (CDC, 1992). *R. typhi* is transmitted to humans by the rat flea, *Xenopsylla cheopis*, with human infection occurring most often in warmer climates, typically in late summer and early fall. Many other animals, such as other rodents, skunks, opossums, shrews, and cats, can serve as hosts for *R. typhi* and its arthropod vectors (Azad, 1990). The flea acquires infection from the blood of a rat or other host species, and excretes rickettsiae in feces. Human infection occurs after exposure of abraded or flea-bitten skin to infective flea feces. Unlike many other arthropod-borne infections, murine typhus can be acquired in households because the transmission cycle includes commensal rats and fleas (Azad, 1990). Similar to many tick-borne illnesses, individuals are often unaware of a flea bite; in one study, only 39% of cases reported either a flea bite or exposure to fleas (Dumler et al., 1991). The incubation period between exposure and clinical disease varies from 6 to 14 days.

Pathophysiology

Although murine typhus is typically a benign disease, fatalities occur in 1–4% of adult cases (Whiteford et al., 2001). In severe cases, prominent vasculitis may be found in the lungs, kidneys, heart, liver, and CNS (Walker et al., 1989).

Clinical manifestations

General clinical features

The clinical manifestations of murine typhus are similar to, but generally less severe than, epidemic typhus and RMSF, and the onset of symptoms is generally more gradual (Miller et al., 1974). The illness is characterized by fever (often prolonged), headache, myalgia, and sometimes a maculopapular or petechial rash (Gelston and Jones, 1977). When present, the rash often begins in the axillae and spreads to the trunk. Splenomegaly and hepatomegaly may also be present. Many *R. typhi* infections are likely misdiagnosed because of the clinical and laboratory similarities to viral infections or Kawasaki's disease (Bitsori et al., 2002), although consideration of murine typhus is increased if a history of flea bite or flea exposure is elicited (Whiteford et al., 2001). Children may present with atypical symptoms, and the classic triad of fever, headache, and rash is only seen in about half of pediatric patients (Whiteford et al., 2001).

Neurological features

In one report of 58 cases of murine typhus, the headache (noted in 80% of cases) was described as "constant pressure" and was exacerbated by physical activity (Miller et al., 1974). Other than headache, there is considerable variability in the frequency of neurological manifestations of murine typhus, ranging from 2% to 20% of cases (Allen and Saitz, 1945; Bitsori et al., 2002). Meningitis and encephalitis are occasionally reported (Gelston and Jones, 1977; Bitsori et al., 2002; Galanakis et al., 2002). Less commonly, focal symptoms, such as papilledema, focal seizures, and hemiparesis, have been described (Miller and Beeson, 1946; Masalha et al., 1998). In a large study of 70 patients in southern Texas, CNS abnormalities other than headache were uncommon; confusion (six patients), seizures (three patients), stupor (three patients), and ataxia (one patient) occurred infrequently (Dumler et al., 1991). In the pediatric population, the frequency of neurological manifestations is also variable. In a large case series of pediatric patients, neurological signs such as ataxia (one of 59, 2%) and stupor (5/61, 8%) were rarely identified (Whiteford et al., 2001).

Occasionally, systemic signs and symptoms may be minimal, and neurological manifestations may be the primary clinical manifestations of *R. typhi* infection. A purely neurological syndrome was observed in five of 34 patients in a case series by Masalha et al., four patients with nuchal rigidity and one patient with altered mental status. Other neurological symptoms included bilateral papilledema (three patients), cranial nerve palsy (one patient) and nystagmus (one patient). None of these five patients had rash or other systemic manifestations (Masalha et al., 1998).

Diagnosis

Laboratory findings in patients with murine typhus often indicate vascular damage and include elevation of liver function tests (38–82%) and low serum albumin (87%), as well as a decrease in the white blood cell (37%) and platelet (43%) counts (Whiteford et al., 2001).

Although early administration of appropriate antimicrobial therapy for murine typhus is often empiric, serology can be used for confirmation of infection. IFA is the best method for diagnosis and positive titers are seen in 60% of patients by 2 weeks from onset of illness and in nearly all patients by 4 weeks (Whiteford et al., 2001). A fourfold rise in antibody titer by IFA between acute and convalescent sera is diagnostic of acute infection.

Treatment

As in other rickettsial diseases, doxycycline is the treatment of choice. Recovery even without antimicrobial therapy is the general rule, with a mortality rate of only 1–2% in untreated patients (Dumler et al., 1991).

Q Fever

Etiology and epidemiology

Q fever is caused by *Coxiella burnetii,* a small gram-negative bacterium and an obligate intracellular pathogen. *C. burnetii* is a worldwide zoonosis. Unlike other rickettsiae which are typically transmitted by arthropods, *Coxiella* is usually spread by inhalation, although it may also occur following ingestion of contaminated dairy products or tick bite. The primary reservoirs for the infection are cattle, goat, and sheep, but many other animal species can harbor the organism. Infection in animals is usually not clinically apparent. Occasional outbreaks in research laboratories that use sheep or cattle have also been reported. Pets, such as dogs and cats, have also been the source of infection in some cases. The organism can be found in urine, feces, milk, and placental tissue ("afterbirth"). Individuals living in rural areas, especially those with contact with farm animals, generally have the highest risk. However, animal contact is not necessary for infection since *C. burnetii* can be transmitted over long distances by wind. The incubation period for Q fever is 9–39 days.

Pathophysiology

Inhalation of aerosolized microorganisms results in proliferation within the lung, leading to bacteremia. Onset of clinical symptoms correlates with bloodstream invasion, and severity may be dependent on the inoculated dose of the microorganism and the characteristics of the infecting strain (Maurin and Raoult, 1999). The route of acquisition may influence presentation, such that aerosolized pathogens may result in pneumonia while ingestion of contaminated milk favors development of hepatitis (Maurin and Raoult, 1999).

Clinical manifestations

General clinical features

Illness caused by *C. burnetii* is generally characterized as either acute or chronic. In acute infections, more than one-half of individuals are asymptomatic. Of those with symptoms, most are self-limited with "flu-like" illness or pneumonia. Fever and headache almost always accompany the illness. Occasionally, a granulomatous hepatitis, myocarditis, or pericarditis can occur. Unlike other rickettsial infections, a rash rarely, if ever, occurs. Endocarditis is the most frequent manifestation of chronic illness.

Neurological features

Severe headache is the most common neurological manifestation in Q fever. Characteristically, it is described as the worst headache a patient has ever experienced and tends to persist throughout the course of illness (Clark et al., 1951). Major clinical syndromes of neurological involvement include meningoencephalitis, meningitis, myelitis, and peripheral neuropathy as well as behavioral and psychiatric disturbances. The prevalence of neurological manifestations (other than headache) in Q fever cases varies considerably, ranging from 2% to 22% (Clark et al., 1951; Reilly et al., 1990; Bernit et al., 2002).

In a study from the 1940s which included 180 cases of Q fever in California, disorientation and confusion were observed in 7% of patients (Clark et al., 1951). In a recent study of 1269 patients identified with acute Q fever, 29 (2.2 %) were identified with neurological symptoms other than headache. Interestingly, many patients had fever but only one-third had "flu-like" illness and only three had a concurrent pneumonia. Three major neurological syndromes were described: meningoencephalitis (eight patients), meningitis (eight patients), and myelitis or peripheral neuropathy (four patients). Of patients diagnosed with Q fever-associated encephalitis, symptoms were diverse and included abnormal behavior, confusion, and focal neurological deficits.

Other reported neurological manifestations of Q fever include hemiparesis (Ferrante and Dolan, 1993), aphasia (Cameron et al., 1990; Ferrante and Dolan, 1993), ataxia (Cameron et al., 1990; Diaz Ortuno et al., 1990), seizures (Brooks et al., 1986), tinnitus (Ferrante and Dolan, 1993), facial nerve palsy (Drancourt et al., 1991), extrapyramidal symptoms (Gallaher, 1961), blindness and optic neuritis (Schuil et al., 1985; Shaked and Samra, 1989), and behavioral abnormalities (Schwartz, 1974; Bernit et al., 2002).

Diagnosis

Lumbar punctures are often done in cases of Q fever due to the severity of headache and frequency of meningeal signs. The CSF white blood cell count may be elevated. In a large case series of Q fever patients in Australia, only two of 26 patients who underwent lumbar puncture had pleocytosis, while an increased protein concentration was seen in 14 of 26 (Spelman, 1982). In contrast, of 33 patients with Q fever in France who underwent lumbar puncture, pleocytosis was observed in 70% and elevated protein in 30% (Bernit et al., 2002). Coombs-negative hemolytic anemia is sometimes observed (Spelman, 1982). Neuroimaging in patients with Q fever is generally normal.

Serology is the preferred method for diagnosis of Q fever. During acute infection, phase II antibodies are elevated, whereas phase I antibodies are high in chronic Q fever. IFA or complement fixation methods are most commonly used. A fourfold or greater increase in titers between acute and convalescent samples is considered diagnostic for Q fever; a single titer of 1:256 or greater with a compatible clinical presentation is classified as probable Q fever (Marrie and Raoult, 1992). PCR and immunostaining of tissues are available in specialized research laboratories.

Treatment

Although many cases of Q fever will resolve without therapy, doxycycline for 15–21 days is the treatment of choice for acute Q fever (Raoult, 1993). The addition of a fluoroquinolone should be considered in patients with neurological involvement or in chronic Q fever (Drancourt et al., 1991). Full recovery almost always occurs but residual neurological sequelae have been reported, including weakness, paresthesias, recurrent meningismus, and peripheral neuritis (Reilly et al., 1990; Marrie and Raoult, 1992).

EHRLICHIOSIS

Ehrlichiosis refers to symptomatic human infection with any of the bacteria in the family Anaplasmataceae. The three species responsible for the majority of human infections in the USA include *Ehrlichia chaffeensis,* the cause of human monocytotrophic ehrlichiosis (HME), *E. ewingii,* the cause of human ewingii ehrlichiosis (HEE), and *Anaplasma phagocytophilum*, the cause of human granulocytotrophic anaplasmosis (HGA, formerly known as human granulocytic ehrlichiosis or HGE). Clinically, these three syndromes present similarly, with fever, headache, leukopenia, thrombocytopenia, and elevated liver enzymes. Symptoms typically begin a median of 9 days following a tick bite, with the majority of patients seeking medical attention within the first 4 days of illness (Fishbein et al., 1994). Neurological manifestations are most frequently reported with HME.

More than 90% of cases occur between April and September, corresponding to periods of abundant tick populations and human outdoor recreation. The incidence of HGA and HME is highest in males and in adults older than 60 years of age (Demma et al., 2005). This may reflect the higher proportion of symptomatic infections in the elderly, as studies conducted in endemic areas have documented *E. chaffeensis* seroprevalence as high as 20% among children without a prior history of clinical disease (Marshall et al., 2002).

Differences in the geographic distribution of the ehrlichioses are best understood with respect to the ecological niche of the specific tick vector. Both *E. chaffeensis* and *E. ewingii* are transmitted primarily by the lone star tick, *Ambylomma americanum*, which predominates in south-eastern and south-central USA. In contrast, *A. phagocytophilum* is transmitted by *Ixodes* species ticks, which are widespread throughout the northern and mid-Atlantic regions of the USA. HGA, in contrast to the other two ehrlichioses, is not restricted to the USA, with cases occurring in Europe and Asia.

Laboratory confirmation of *Ehrlichia* infection at the time of the acute illness is hindered by the limited availability of rapid diagnostic tests such as PCR, and the absence of detectable serum antibody at the onset of clinical illness (Childs et al., 1999). As adverse outcomes are more common if treatment is delayed (Paddock et al., 2001; Hamburg et al., 2008), it is important that empiric therapy be initiated for any patient with compatible clinical and laboratory findings. All three of the ehrlichial illnesses discussed below are treatable with doxycycline.

Human monocytotrophic ehrlichiosis

Etiology and epidemiology

HME is caused by the bacterium *Ehrlichia chaffeensis*. HME was first described in 1986, with more than 2300 cases reported to the Centers for Disease Control and Prevention (CDC) in the ensuing 19 years (Dumler et al., 2007). While the average incidence of HME in the USA is estimated at 0.7 cases/million population, this is thought to be a significant underestimation of the true burden of disease (CDC, 2006). Active surveillance in endemic areas has suggested rates of HME of 300–400 cases per 100 000 (Standaert et al., 2000; Olano et al., 2003). The true incidence of human

infection with *E. chaffeensis* is likely much higher, as two-thirds of incident infections are either asymptomatic or minimally symptomatic (Yevich et al., 1995).

The geographic distribution of HME is directly related to that of the lone star tick vector, which is endemic throughout the south-eastern USA. The white-tailed deer, the principal reservoir for *E. chaffeensis*, is prevalent throughout this region. States with the highest reported rates of HME include Mississippi, Oklahoma, Tennessee, Arkansas, and Maryland (Demma et al., 2005). There have been case reports of patients co-infected with both *E. chaffeensis* and *R. rickettsii*, which, although spread by different tick vectors, share a common geographic distribution (Sexton et al., 1998).

Among cases of HME reported to the CDC between 2001 and 2002, 61% were male, and 95% of cases self-identified as white race (Demma et al., 2005). The median age for infection was 53 years; however, the age-specific incidence was highest in the group aged 70 years and above. While cases were reported year-round, the greatest number of cases occurred during the period of May through August.

Pathophysiology

Ehrlichia chaffeensis is transmitted through the saliva of the *A. americanum* vector tick. A tick attachment is recalled in 72% of patients with HME (Olano et al., 2003). The duration of attachment required to transmit infection is unknown, but based on experimental data for other ehrlichial infections, is thought to be at least 24 hours. Following transmission, the bacteria are ingested by monocytes, where they multiply in cytoplasmic membrane-bound vacuoles called morulae. These morulae may be visualized following Wright stain of the buffy coat smear as basophilic intracytoplasmic inclusion bodies, and may be useful for early diagnosis as well as for distinguishing HME from HGA or HEE, where the morulae are found in neutrophils.

Ehrlichia have evolved mechanisms to evade host cell detection, and survive for prolonged periods intracellularly (Rikihisa, 2006). Most of the clinical manifestations associated with the ehrlichioses are thought to be due to cytokine activation, particularly tumor necrosis factor-α, rather than direct bacterial invasion (Ismail and Walker, 2005).

Clinical manifestations

General clinical features

HME is a more severe disease than the other two ehrlichioses, with 42% of cases requiring hospitalization, and a case fatality rate of 3% (Demma et al., 2005). Up to 17% of patients develop life-threatening complications, with severe disease and death more common in immunocompromised patients (Paddock et al., 2001). Several studies have reported an association between the use of sulfonamide antibiotics and severe clinical manifestations (Peters et al., 2000); whether this represents a causal relationship is unknown. A study of HME among transplant patients found no difference in severity of illness among patients taking prophylactic sulfa antibiotics (Thomas et al., 2007).

Fever is an almost universal symptom (97%), followed by headache (80%), myalgias (57%), and arthralgias (41%) (Dumler et al., 2007). A skin eruption is relatively common among children with HME, occurring in 66% of pediatric cases compared with 21% of adults (Olano et al., 2003; Schutze et al., 2007). The rash of HME can be maculopapular, petechial, or be characterized by diffuse erythroderma (Fichtenbaum et al., 1993), but typically spares the face, palms, and soles. Nausea, vomiting, abdominal pain, and cough are variably present.

Neurological features

The most frequent neurological manifestation of HME is meningitis or meningoencephalitis; CNS involvement is identified in approximately 20% of patients (Ratnasamy et al., 1996; Hongo and Bloch, 2006), and in some cases may be associated with seizures and coma (Paddock et al., 2001). Uncommon complications include cranial nerve palsy, with onset after initiation of effective antimicrobial therapy being reported (Everett et al., 1994; Carter and Miller, 1997; Grant et al., 1997). Long-term neurological sequelae in children are uncommon, but include cognitive delays, fine motor impairment, and persistent foot drop (Schutze and Jacobs, 1997). Subjective neurocognitive deficits following meningoencephalitis have also been reported in adults (Harkess et al., 1990).

Diagnosis

Although the clinical manifestations of *E. chaffeensis* infection are nonspecific, laboratory abnormalities provide important clues to the diagnosis. A prospective cohort study of patients in an endemic area presenting with a febrile illness following a tick bite found a significantly lower white blood cell count (mean 4.6×10^9 cells/μl), neutrophil count (mean 2.6×10^9 cells/μl), and platelet count (mean 172×10^9 cells/μl) among patients with HME than in non-infected patients (Olano et al., 2003). Elevated transaminases are present in 83% of cases (Dumler et al., 2007). In pediatric patients, mild hyponatremia may be seen in 50% of cases (Schutze, 2006), but this finding has been less frequently noted among infected adults.

Among patients with HME who undergo lumbar puncture, CSF pleocytosis is identified in approximately 60% (Ratnasamy et al., 1996). While most samples have a lymphocytic predominance, a neutrophilic or mixed picture is found in a third of cases (Ratnasamy et al., 1996). The CSF white blood cell count is typically <100 cells/mm^3, and the protein concentration may be mildly elevated (Schutze et al., 2007). Morulae are rarely identified in CSF monocytes by Giemsa stain (Ratnasamy et al., 1996; Berry et al., 1999). Neuroimaging may be normal, or may show leptomeningeal enhancement (Standaert et al., 1998). Bilateral medial temporal lobe enhancement has been reported in a patient with PCR evidence of *E. chaffeensis* and *A. phagocytophilum* coinfection (Young and Klein, 2007). Electroencephalogram may show nonspecific slowing (Eng et al., 1990; Ratnasamy et al., 1996). Although pathological review of brain tissue from patients with HME is limited, one study reported atypical lymphoid infiltration of the leptomeninges and Virchow–Robin space, with sparing of the brain parenchyma (Grant et al., 1997), while others have not shown CNS pathology (Ratnasamy et al., 1996).

An insensitive but rapid method for diagnosing HME is identification of morulae in the cytoplasm of peripheral monocytes. Microscopy of a buffy coat smear stained with Wright or Giemsa stain allows visualization of morulae in up to 20% of HME cases, but is highly dependent on the skills and patience of the microscopist (Hamilton et al., 2004; CDC, 2006). Morulae may rarely be visualized in monocytes recovered from the CSF (Dunn et al., 1992; Berry et al., 1999; Schutze et al., 2007).

Seroconversion or a fourfold rise in IgG titers to *E. chaffeensis* on serum collected at the time of illness and a convalescent sample >2 weeks after onset is considered diagnostic of HME infection. Acute serology is positive in less than 50% of cases at presentation (Childs et al., 1999); therefore, a negative initial titer does not exclude a diagnosis of HME, and should not delay initiation or continuation of antibiotic treatment. A single elevated titer is difficult to interpret, as antibody to *E. chaffeensis* may remain detectable for a prolonged period of time following infection. Serological cross-reactivity between the different *Ehrlichia* species is common. While patients with HGA may have an elevated titer to *E. chaffeensis*, the absolute value is typically lower than the titer to *A. plasmacytophilum*.

PCR of whole blood is commercially available, and allows rapid diagnosis of infection in up to 85% of cases (Standaert et al., 2000). The diagnostic yield is highest early in the course of infection, prior to directed antimicrobial treatment. While PCR of CSF may be positive, the sensitivity is lower than for whole blood, likely due to the significantly lower volume of infected cells (Bloch et al., 2005).

Treatment

Doxycycline is the recommended treatment for HME at an adult dose of 100 mg orally twice daily; the pediatric dose for children <45.4 kg (100 lb) is 2.2 mg/kg twice daily. Doxycycline remains the treatment of choice in pediatric patients, despite the risk of dental discoloration in this age group.

Response to treatment of HME is typically rapid, and fever persisting >72 hours after initiation of treatment strongly suggests an alternative diagnosis. While no studies have specifically addressed duration of treatment, most authorities advocate continuing antimicrobial therapy for 3–5 days after resolution of fever (CDC, 2006), and perhaps longer (e.g., total of 10–14 days) if there is CNS involvement (Hongo and Bloch, 2006).

Human ewingii ehrlichiosis

Etiology and epidemiology

HEE is caused by the bacterium *Ehrlichia ewingii*. *E. ewingii* was initially thought to be a canine pathogen, until a series of four human cases was described in 1999 (Buller et al., 1999). The epidemiology of HEE remains poorly defined due to the lack of a specific serological assay for this organism and the absence of a dedicated reporting system for this infection. Most infections reported to date have occurred in patients with human immunodeficiency virus (HIV) infection (Paddock et al., 2001) or who are immunosuppressed following organ transplantation (Thomas et al., 2007).

Amblyomma americanum, the primary vector for *E. chaffeensis*, is also the vector for *E. ewingii*. Most cases of HEE have been reported in Tennessee, Missouri, and Oklahoma. However *E. ewingii* infection in deer, dogs, and ticks has been described throughout the range of the lone star tick, suggesting that human infection with this pathogen might be more widespread than previously appreciated (CDC, 2006; Mixson et al., 2006).

Clinical manifestations

General clinical features

Little is known of the clinical spectrum of HEE due to the paucity of reported cases. Symptoms appear to be similar to those described for HME and HGA. Despite the fact that the majority of HEE infections have occurred in immunocompromised hosts, the clinical manifestations appear to be milder (Paddock et al., 2001; Thomas et al., 2007). Findings of leukopenia,

thrombocytopenia, and abnormal liver enzymes are variably present (Buller et al., 1999; Paddock et al., 2001; Thomas et al., 2007).

Neurological features

Headache is a frequent symptom in HEE, and may be associated with meningitis, but the frequency of this finding and the spectrum of neurological manifestations are unknown. There is one report of neutrophilic pleocytosis in a patient with HEE (Buller et al., 1999).

Diagnosis

A diagnosis of HEE is suggested by visualization of intracytoplasmic morulae in neutrophils in a patient with residence in or travel to an area endemic for HME (rather than HGA). Morulae may be visualized in both blood and, rarely, CSF (Buller et al., 1999). While there is no specific serological assay for *E. ewingii*, there is significant serological cross-reactivity with *E. chaffeenesis* (Buller et al., 1999). It is conceivable that, in the absence of visualization of morulae in granulocytes or confirmatory PCR for *E. ewingii*, a proportion of cases meeting serological criteria for HME actually represent HEE infection. A specific PCR for *E. ewingii* exists, but is limited to research laboratories. Similar to the PCR for *E. chaffeensis* and *A. phagocytophilum*, sensitivity is maximal early in the course of the illness, prior to antimicrobial therapy.

Treatment

There are no randomized trials evaluating treatment of *E. ewingii*; however, doxycycline is considered the treatment of choice in both adults and children. When therapy with this agent is started promptly, outcomes are uniformly excellent (Buller et al., 1999; Thomas et al., 2007). Considerations in dosing and administration of doxycycline are discussed in the section on HME management.

Human granulocytotrophic anaplasmosis

Etiology and epidemiology

HGA is caused by the bacterium *A. phagocytophilum*. In the early 1990s, patients from Michigan and Wisconsin with a febrile illness similar to HME were described (Bakken et al., 1994). These cases were distinguishable by the presence of inclusion bodies in granulocytes rather than monocytes, causing this syndrome initially to be termed human granulocytic ehrlichiosis (HGE). After isolation of the human granulocytic ehrlichiosis agent, *Anaplasma phagocytophilum*, the syndrome was renamed human granulocytotrophic anaplasmosis, or HGA.

More than 2900 cases of HGA have been reported to the CDC between 1994 and 2005, with the annual number of cases of HGA exceeding that of HME at an estimated annual incidence of 1.6 cases per million population in the USA. Active surveillance in endemic areas has identified incidence rates of >50 cases per 100 000 population (Bakken et al., 1996). As with *E. chaffeensis*, serosurveys suggest asymptomatic disease is common (Bakken et al., 1998).

A. phagocytophilum is transmitted by *Ixodes* species ticks: *Ixodes scapularis* in New England and north-central USA and *Ixodes pacificus* in the western USA. Deer, elk, and wild rodents are thought to serve as reservoirs (CDC, 2006). These ticks also serve as vectors for *Borrelia burgdorferi* (the causative agent of Lyme disease) and various *Babesia* species (agents of human babesiosis); co-infections have been reported (Nadelman et al., 1997). The highest average incidence of HGA during 2001–2002 occurred in Rhode Island, Minnesota, Connecticut, New York, and Maryland (Demma et al., 2005), areas that also consistently report high rates of Lyme disease.

Demographics of patients with HGA resemble those of HME. The median age is 51 years, with more than 95% of cases in whites, and a slight male predominance (Demma et al., 2005). Cases occur year-round, with a peak incidence during June and July, perhaps reflecting the shorter arthropod season in these northern states.

Pathophysiology

A. phagocytophilum is transmitted through the saliva of the tick vector. The duration of attachment required to transmit infection has been studied experimentally, where a minimum of 36 hours is required for bacterial passage (Katavolos et al., 1998). Following transmission, the organisms are phagocytized and form morulae inside neutrophils, and can be visualized by Wright stain of the buffy coat smear. Granulocytic inclusion bodies are not specific for HGA, as these may also be seen with *E. ewingii* infection.

Clinical manifestations

General clinical features

HGA resembles HME with respect to the frequency of fever, headache, and myalgias, but rash is uncommon, noted in fewer than 10% of patients (Dumler et al., 2007). As with HME, leukopenia, thrombocytopenia, and elevations in transaminases are important clues to the diagnosis. HGA tends to be a less severe illness than HME, although life-threatening complications, including acute respiratory distress syndrome, acute renal failure, and hemodynamic collapse, have been reported.

Neurological features

CNS involvement is uncommon in HGA, with meningoencephalitis reported in approximately 1% of cases (Dumler et al., 2007). In contrast, a number of different peripheral nervous system manifestations have been described, including brachial plexopathy, cranial nerve palsies, and demyelinating polyneuropathy (Horowitz et al., 1996). Bilateral facial nerve palsy has also been reported (Lee et al., 2000). Recovery of neurological function may be delayed over several months (Horowitz et al., 1996). As the geographic distribution of *Borrelia burgdorfori* is similar to *A. phagocytophilum*, and because Lyme disease may present with similar neurological findings, patients should be tested for co-infection.

Diagnosis

Lumbar puncture is performed less frequently for HGA than for HME. Reported CSF abnormalities include lymphoctyic pleocytosis and moderate elevation in protein concentration (Lee et al., 2000).

Granulocytic morulae may be visualized in 25–75% of cases of HGA (Dumler et al., 2007). Antibodies to *A. phagocytophilum* are present in a minority of cases at the time of clinical illness, with convalescent serum allowing a retrospective diagnosis (Wormser et al., 2006). Serological cross-reactivity occurs between *A. phagocytophilum* and *E. chaffeensis*; however, differentiation of HGA from HME can be accomplished based on the absolute titer, leukocyte trophism, and geographic region. PCR of whole blood allows for a rapid and specific diagnosis of HGA, with positive results in 60–70% of cases (Bakken et al., 2001). There have been anecdotal reports documenting detection of *A. phagocytophilum* nucleic acid in CSF (Young and Klein, 2007); however, the sensitivity of CSF PCR compared with that of whole blood has not been evaluated.

Treatment

Therapeutic considerations for HGA are similar to those for HME (see HME management section), with doxycycline remaining the drug of choice for both pediatric and adult cases. If co-infection with *B. burgdorferi* is suspected based on characteristic skin findings or elevated antibodies, doxycycline should be continued for at least 10 days for adults (Wormser et al., 2006). In *B. burgdorferi*- co-infected children <8 years of age, doxycycline should be continued until the patient is afebrile for 3 days, with the remainder of the 14-day course completed with an alternative agent active against *B. burgdorferi* (e.g., amoxicillin or cefuroxime axetil) to minimize the risk of dental discoloration (Dumler et al., 2007). Patients who fail to respond to doxycycline monotherapy after 72 hours should be evaluated for an alternative diagnosis or the possibility of *Babesia* co-infection. Pregnant patients with ehrlichial infection represent a particular challenge, as doxycycline is contraindicated. In this population, as well as in patients with a specific contraindication to doxycycline, rifampin (adults: 300 mg twice daily; children <45.4 kg (100 lb) 10 mg/kg twice daily) may be substituted (Buitrago et al., 1998; Dhand et al., 2007).

SUMMARY

Rickettsial diseases represent a clinically homogeneous group of infections characterized by fever, headache, myalgias, variable presence of a rash, and a broad spectrum of neurological manifestations. Epidemiological information including time of year, geography, history of arthropod exposure, and animal contact gives important clues to the diagnosis, and should be actively elicited. Abnormalities in hematological indices and liver function tests should also increase suspicion for illness. Delay in initiation of doxycycline therapy while awaiting laboratory confirmation of infection has been associated with progressive neurological impairment and death. Clinicians should maintain a low threshold to initiate empiric therapy for rickettisal diseases in any patient with neurological findings and compatible exposures, signs, or laboratories, as these syndromes represent readily treatable causes of neurological dysfunction.

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Chapter 11

Mycobacterial infections

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The clinical expression of disease caused by *Mycobacterium tuberculosis,* one of the most important infectious agents worldwide, differs between children and adults (Idriss et al., 1976; Kennedy and Fallon, 1979; Katti, 2004). Most adult tuberculosis cases result from reactivation of dormant organisms from a remote infection (Ogawa et al., 1987), whereas childhood tuberculosis usually reflects the pathophysiological events surrounding the initial infection (Kent et al., 1993; Marais et al., 2006). Children are particularly prone to extrapulmonary tuberculosis, especially tuberculous meningitis (TBM), because of their relative inability to contain the infection at sites beyond the lung (Lincoln et al., 1960). Although the most common extrapulmonary manifestation of tuberculosis in children is lymphadenitis, the second most common is meningitis (Curless and Mitchell, 1991; Ussery et al., 1996). Tuberculous meningitis is uniformly fatal if untreated, but early detection and treatment, combined with appropriate surgical intervention, greatly improve the outcome.

Although TBM is the most common central nervous system (CNS) complication of tuberculosis in children, tuberculomas occur commonly among persons living in certain high-incidence regions of the world (Caldarelli et al., 1988a,b). In some developing countries, tuberculoma is among the most common causes of "brain tumor." These space-occupying lesions can arise early in the infection, but more commonly appear during long-standing infections. In developed countries, tuberculoma is often a paradoxical reaction occurring during the treatment of TBM (Chambers et al., 1984; Afghani and Lieberman, 1994; Ajay et al., 1996).

Most human mycobacterial CNS infections are due to *M. tuberculosis*. *M. bovis*, the cause of bovine tuberculosis, causes a small percentage of cases, particularly in developing countries. The bacillus Calmette–Guérin (BCG)-*M. bovis* can cause CNS infections in immunocompromised children. Although nontuberculous mycobacteria (NTM) have been associated with CNS disease, these infections are quite rare (O'Brien et al., 1987). Prior to the 1980s there was a small number of reports of CNS disease caused by NTM (Lincoln and Gilbert, 1972). By 1997, only 56 cases had been reported, with 48 occurring in patients with acquired immunodeficiency syndrome (AIDS) as part of a disseminated infection (Stone et al., 1992; Cegielski and Wallace, 1997). Meningitis, ventriculitis, subdural empyema, and brain abscess due to NTM have been described (Flor et al., 1996; Saritsiri et al., 2006). In the absence of culture confirmation, the diagnosis of NTM CNS infection cannot be established (Florakis et al., 2003; Marie et al., 2003; Konde et al., 2006; Griffith et al., 2007).

The terminology used to describe the stages and presentations of tuberculosis can be confusing. *Exposure* means that the person has had significant contact with an adult or adolescent with infectious pulmonary tuberculosis. The contact investigation – examining those persons in close contact with a suspected case of tuberculosis with a tuberculin skin test, chest radiograph, and physical examination – is the most important activity to prevent tuberculosis, especially in children. *Infection* occurs when a person inhales droplet nuclei containing tubercle bacilli, which become established within the lung and associated lymphoid tissue. The hallmark of tuberculosis infection is a reactive tuberculin skin test or a positive interferon-gamma release assay (IGRA). Tuberculosis *disease* indicates overt signs, symptoms, or radiographic manifestations of *M. tuberculosis* infection. Not all infected persons have the same risk of developing disease. An immunocompetent adult with untreated tuberculosis infection has a 5–10% lifetime risk of disease, with one-half of the risk occurring in the first 2–3 years after infection. In contrast, an adult

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with untreated infections caused by *M. tuberculosis* and human immunodeficiency virus (HIV) has a 5–10% annual risk of developing tuberculosis. Historical studies suggest that as many as 40% of the infants and young children with untreated tuberculosis infection develop tuberculosis disease within 1–2 years, and they more commonly develop TBM.

EPIDEMIOLOGY

The risk of tuberculosis infection is determined by the likelihood of contact with an adult with contagious tuberculosis (Bidstrup et al., 2002). By contrast, the risk of tuberculosis disease depends on immunological and genetic factors. Age represents one of the most important risk factors. Approximately 60% of childhood tuberculosis cases occur among infants and children less than 5 years of age, with most children being under 3 years of age (World Health Organization, 2007). The age range from 5 to 14 years is often called the "favored age" because such children have the lowest rates of tuberculosis disease in any population (Nelson and Wells, 2004). In contrast to the male predominance in adult tuberculosis, the gender ratio in children is about 1:1. In adults, most disease occurs among the elderly in developed countries and among young adults in developing countries (Cain et al., 2007).

Certain persons are more likely to develop tuberculosis infection. Most individuals are infected with *M. tuberculosis* in the home, but clusters of tuberculosis infection and disease have been centered in hospitals, homeless shelters, residential facilities, elementary and high schools, nursery schools, family day-care homes, churches, school buses, and stores.

Although the number of TBM cases varies greatly throughout the world, they consistently account for 5–10% of all extrapulmonary tuberculosis cases. In the USA in 2007, 170 cases of meningeal tuberculosis were reported to the Centers for Disease Control and Prevention, representing 6.3% of all extrapulmonary cases of tuberculosis (Centers for Disease Control and Prevention, 2008). The majority of these cases occurred in children.

The incidence of TBM increases in children with recent measles, and persons with alcoholism and malignancies and those given immunosuppressive agents. HIV infection has had a profound effect on the epidemiology of tuberculosis among adults and children (Rana et al., 2000; Caws et al., 2006). HIV-infected adults with tuberculosis may transmit *M. tuberculosis* to children, some of whom will develop tuberculosis disease. Children with HIV infection may be at increased risk for progressing from tuberculosis infection to disease. Most of the disease in HIV-infected children is pulmonary tuberculosis. When CNS disease occurs in HIV-infected patients, the disease progresses somewhat more rapidly and is more severe at diagnosis than in immunocompetent patients (Berenguer et al., 1992; Dube et al., 1992; Yechoor et al., 1996; Havlir and Barnes, 1999; Katrak et al., 2000; Vander Woert et al., 2006). Tuberculoma appears to be rare among children with HIV infection. However, some adults with pulmonary tuberculosis and HIV infection have experienced tuberculoma as a paradoxical reaction to institution of antituberculosis and anti-HIV chemotherapy, the so-called immune reconstitution inflammatory syndrome (IRIS) (Crump et al., 1998; Lawn et al., 2005, 2007). Unfortunately, both pulmonary and CNS tuberculosis in HIV-infected children and adults can resemble other opportunistic infections, making the diagnosis of tuberculosis difficult. Persons with HIV infection and severe acute CNS disease may require empiric antituberculosis chemotherapy until an alternate diagnosis can be established (Narita et al., 1998).

PATHOGENESIS AND PATHOPHYSIOLOGY

Tuberculous meningitis usually arises as a complication of the primary infection, although the portal of entry for *M. tuberculosis* is typically the lung (Phypers et al., 2006). The precise number of tubercle bacilli necessary to establish infection is unknown. During the evolution of the pulmonary lesion and the accelerated, hypersensitivity-induced caseation, tubercle bacilli spread from the lung via the bloodstream and lymphatic system to many parts of the body with high blood flow. The most commonly affected sites are the liver, spleen, lymph nodes, pleura, brain, and meninges. This process can involve large numbers of bacilli, which leads to disseminated tuberculosis disease, or small numbers, which causes scattered, microscopic tuberculous foci. The metastatic foci are initially unapparent, but they can be the origin of extrapulmonary tuberculosis and reactivation pulmonary tuberculosis.

Before the 1930s, TBM was thought to result from direct hematogenous seeding of the subarachnoid space. However, the classic studies of Rich and McCordock (1933) challenged this assumption. Based on animal models, and on clinical and histopathological data from humans, and experimental data from animal models, Rich and McCordock postulated that TBM arises in two stages. First, tuberculous lesions form in the brain or in the meninges from hematogenous dissemination of bacilli early in the infection. Meningitis then develops via discharge of bacilli and associated antigens from an adjacent caseous focus into the subarachnoid space

either immediately after infection or after a latent period of weeks to years. Occasionally, the inciting lesion may be in the spinal cord, vertebrae, middle ear, or skull (Gokalp and Ozkal, 1981). It is generally accepted that a caseating vascular focus, the "Rich focus," in the brain cortex or meninges is the key pathway for the tubercle bacilli to enter the subarachnoid space (Rock et al., 2008). Many children develop TBM in association with miliary tuberculosis (Change et al., 1998; Van den Bosch et al., 2004), but recent papers have concluded that this massive dissemination of tubercle bacilli simply increases the chance that a Rich focus will develop (Donald et al., 2005; Jain et al., 2006).

In immunocompetent persons, mycobacterial antigens produce an intense immune reaction, not unlike the reaction to a large dose of purified protein derivative (PPD) in a skin test-positive person (Kim, 2003). As a result, inflammatory changes occur with accumulation of cells, hyperemia, edema, capillary damage, exudate, and fibrosis. This inflammatory reaction may damage nerves, block the circulation of cerebrospinal fluid (CSF), or occlude small blood vessels, producing multiple cerebral infarcts (Goel, 2004).

Serous tuberculous meningitis develops when a tuberculous focus adjacent to the subarachnoid space causes a lymphocytic reaction without the actual seeding of tubercle bacilli (Lincoln, 1947). Before effective chemotherapy, serous meningitis was readily differentiated from true TBM because the former was the only nonfatal form of tuberculous meningitis. Today, this distinction is no longer possible because treatment is begun immediately. Cases of transient aseptic meningitis have also been ascribed to tuberculosis (Emond and McKendrick, 1976; Zinneman and Hall, 1976).

Tuberculomas may originate from small areas of necrosis surrounded by a few epithelioid giant cells that form in or just below the cortex. These lesions start to enlarge and aggregate, producing a macroscopic nodule that does not rupture into the subarachnoid space. The organisms stimulate a local hypersensitivity reaction with edema and polymorphonuclear infiltration in adjacent brain tissue (Shaharao et al., 2004). Alternatively, well-vascularized granulation tissue, containing lymphocytes, histiocytes, epithelial, and plasma cells, may appear. Occasionally, these lesions may stimulate extensive necrosis, causing a tuberculous brain abscess. In a tuberculous brain abscess, there is an encapsulated collection of pus containing viable bacilli without formation of disseminated tubercular granulomas (Whitener, 1978; Henrickson and Weisse, 1992; Kumar et al., 2002).

The pathology of TBM depends on the age of the patient, the severity of the infection, the patient's state of immunity, the duration of illness, and the type of treatment. Although the major pathological changes involve the basilar meninges, lesions of brain parenchyma, due to extension of the inflammatory process or vasculitis, are present in most cases. As TBM progresses, a thick exudate, consisting of lymphocytes and plasma cells, fills the interpeduncular, pontine, and other basilar cisterns (John and Douglas, 1975). Tissue, especially the subependymal area, underlying tuberculous exudate shows edema, perivascular infiltrates, and microglial reaction. The convexities of the brain are relatively unaffected. The exudate surrounds the cranial nerve roots and the major blood vessels at the base of the brain and may affect the choroid plexus.

Vasculitis, an important feature of tuberculous meningitis, can involve large, medium, and small arteries as well as veins, causing complete or partial vascular occlusion. Vessels near the circle of Willis are often involved. Ischemia and hemorrhagic infarction involving basal ganglia, hypothalamus, or brainstem are potential complications (Hsieh et al., 1992). Occasionally, intracranial venous sinuses can thrombose. Involved arteries, usually the middle or anterior cerebral, show inflammatory, proliferative, and degenerative changes. Adventitial involvement, consisting of cellular infiltration with or without tubercle formation and necrosis, represents an extension of the tuberculous process from the subarachnoid space (Macgregor and Green, 1937).

Communicating hydrocephalus, often present in patients with tuberculous meningitis who have survived more than several weeks, results from blockage of the basal cisterns by the exudate early on, or from arachnoid adhesions in later stages of disease. Less frequently, occlusion of the aqueduct or blockage of outlet foramina causes obstructive hydrocephalus. Aqueductal narrowing results from edema of the midbrain or compression of the brainstem by the surrounding exudate. In high-prevalence areas for tuberculosis, a child with unexplained hydrocephalus is occasionally found to have TBM.

Mature tuberculomas consist of firm grayish-white, unencapsulated nodules with lobulation and a central area of caseation. They are often surrounded by satellite lesions and occasionally become a grape-like granulomatous cluster. Most lesions are 2–40 mm in diameter, although lesions up to 8 cm in diameter have been reported. Tuberculomas are usually found in the frontal lobes in adults and in the cerebellum in children (Ira, 2005). Less common features include liquefaction and abscess formation, calcification, or invasion of surrounding bone.

CLINICAL FEATURES

In the pretherapy era, TBM had a relentless progressive course and inevitably resulted in death. However, during the past four decades, the clinical presentation

has become increasingly varied, and atypical cases are now more common, particularly in developed countries. The onset of TBM in children is often gradual, occurring over a period of 1–3 weeks, and seems in some cases to be precipitated by a viral infection, a fall, or a blow to the head (Delage and Dusseault, 1979; Maree et al., 2007). Occasionally, the onset is abrupt and marked by a convulsion or rapid progression of neurological deficits.

The clinical course of TBM can be divided into three stages, as defined by the British Medical Research Council (Farinha et al., 2000). The first stage, reflecting meningeal inflammation, consists of personality change, irritability, anorexia, listlessness, and some fever. These nonspecific features can be recognized as being caused by TBM only in retrospect (Waecker and Connor, 1990; Donald et al., 1996). After 1–2 weeks, the disease passes into the second stage. Here, signs and symptoms of increased intracranial pressure and cerebral insults appear, including drowsiness, stiff neck, cranial nerve palsies (especially of the third, sixth, and seventh nerves), anisocoria, vomiting, *tache cérébrale*, absence of abdominal reflexes, and focal or generalized convulsions. A psychiatric presentation of TBM occurs rarely (Kocen and Parsons, 1970; Udani and Dastur, 1970; Udani et al., 1971). In older children and adults, headache and vomiting may be the major features of stage II, and the presence of headache in a patient with miliary tuberculosis correlates highly with meningeal involvement (Verdon et al., 1996; Sutlas et al., 2003). Occasionally, macrocephaly or tense fontanel can be observed in infants (Yaramis et al., 1998). As many as 10% of patients do not experience fever.

The third stage of tuberculous meningitis is characterized by severe neurological deficits, including coma, autonomic instability, and rising fever. Papilledema may be noted but it is not a universal finding. Hemiplegia may occur at the onset of disease or at a later stage, but usually correlates with ischemic infarction in the territory of the middle cerebral artery. Monoplegia, an uncommon event, results from a vascular lesion occurring at an early stage of disease. Quadriplegia, caused by bilateral infarction or severe edema, occurs in only very advanced cases.

Occasional cases of TBM are associated with chorea, hemiballism, athetosis, generalized tremors, myoclonus, or ataxia (Riela and Roach, 1982; Bakikian et al., 1985). Inflammation of the spinal meninges may result in radiculomyelopathy, and organization of this exudate may cause spinal block with slow progression to paraplegia or quadriplegia (Naidoo et al., 1991). In rare cases, vascular lesions may result in acute transverse myelitis. Tuberculous encephalopathy, characterized by diffuse cerebral involvement with convulsions, stupor, or coma without significant signs of meningitis, occurs mainly in children and adults with HIV infection (Thwaites et al., 2005).

Stage III, associated with progressive cerebral dysfunction, produces apathy and irritability that evolve into lethargy, confusion, stupor, and coma. Signs of meningeal irritation may disappear, but fever usually persists. The terminal illness is characterized by deep coma, decerebrate or decorticate posturing, and extreme rigidity or spasm. Eventually, the pupils become dilated and fixed, the pulse rapid, and the respiration irregular. Brainstem dysfunction may be the result of infarction or transtentorial herniation caused by increased cranial pressure.

A tuberculoma usually presents with the symptoms and signs of a space-occupying lesion (Bagga et al., 1988). The clinical features depend on the size and location of the tuberculomas and the pressure they exert on adjacent structures (Berthiei et al., 1987). Headache, seizures, paralysis, personality changes, and other focal neurological problems occur frequently. The exact signs and symptoms of tuberculomas depend on their anatomic location. For instance, the rare occurrence of a tuberculous pituitary lesion can mimic a pituitary tumor, causing visual changes and many neuroendocrine effects, including diabetes insipidus and panhypopituitarism (Dutta et al., 2006). Because children are more prone to developing infratentorial lesions, ataxia or the sudden onset of severe neurological dysfunction is more commonly associated with tuberculomas in children than in adults. Some tuberculomas are clinically silent. Several reports have demonstrated asymptomatic tuberculomas in children with TBM or only apparent pulmonary tuberculosis when a magnetic resonance imagery (MRI) scan of the brain was performed. Spinal tuberculomas are rare but serious complications of CNS tuberculosis (Bhagwati, 1979; MacDonnell et al., 1990; Lin et al., 1994; Muthukumar et al., 2007).

DIAGNOSIS

Fungal meningitis, partially treated bacterial meningitis, and viral meningitis or encephalitis are among the conditions most often confused with TBM (Table 11.1). Additional considerations are focal parameningeal infections, such as brain abscess, unusual cases of bacterial meningitis, malignant infiltration, sarcoidosis, neurocysticerosis, and meningitis or encephalitis that result from embolic complication of infective endocarditis (Pretell et al., 2005). As a general rule, any patient who presents with meningitis and basilar inflammation, vasculitis or stroke, cranial nerve involvement, or hydrocephalus should be considered to have TBM until proven otherwise. Antituberculosis chemotherapy should be started

Table 11.1

Differential diagnosis of tuberculous meningitis

Bacterial infection	Untreated or partially treated meningitis, brain abscess, leptospirosis, brucellosis, cat-scratch disease (bartonellosis)
Viral infection	Herpes simplex, mumps, lymphocytic choriomeningitis virus
Fungal infection	Cryptococcosis, histoplasmosis
Protozoal infection	Naegleria, toxoplasmosis
Vascular	Embolic, infectious endocarditis, sinus thrombosis, stroke by any cause, systemic vasculitis syndromes
Collagen vascular	Systemic lupus erythematosus, polyarteritis
Other	Sarcoidosis, metastatic carcinoma, lymphoma or leukemia, acute hemorrhagic leukoencephalopathy

empirically while the true cause of the illness is being determined.

The complete approach to evaluation of a patient with suspected TBM is shown in Table 11.2. The key to establishing the diagnosis of TBM is often detecting another focus of tuberculosis disease. The most common other focus is pulmonary tuberculosis. Although one study found that chest radiographs in children were frequently normal, other studies have shown that up to 90% of children with TBM have an abnormal chest radiograph. The most common radiographic findings are hilar or mediastinal adenopathy in association with pulmonary infiltrates or atelectasis caused by bronchial obstruction due to the enlarged lymph nodes. One study of TBM in children revealed abnormal chest radiographs in 87% of patients, with 33% having hilar adenopathy, 33% pulmonary infiltrates, 20% a miliary pattern, and 1% with pleural effusions. Most adults with TBM have a normal chest radiograph as their initial tuberculosis infection occurred years previously. However, adults with untreated HIV infection frequently have concomitant pulmonary and meningeal involvement.

Whenever TBM is suspected, it is critical to evaluate the adolescent and adult contacts of the patient immediately to determine if any has evidence of contagious pulmonary tuberculosis (Doerr et al., 1995). Tuberculin skin testing may be part of this evaluation, and chest radiographs should be obtained on close contacts. Obtaining from the family a history for possible exposure to tuberculosis is important, but this history can be unrevealing.

Table 11.2

Evaluation of a patient with suspected tuberculous meningitis

Medical history	Exposure to a person with known tuberculosis or suggestive symptoms
	Previous tuberculin skin test results
	History of immune suppression
	Results of tuberculin skin tests and chest radiographs of close contacts*
Physical examination	Complete neurological examination, especially cranial nerves
	Funduscopic examination for choroid tubercles or papilledema
	Reticuloendothelial and lymphatic systems
Laboratory and other tests	Tuberculin skin test on IGRA
	Chest radiograph (posterior–anterior and lateral)
	Serum electrolytes
	Lumbar puncture: pressure, cell count and differential, cytology, protein, glucose, acid-fast stain and mycobacterial culture (5–10 ml is best)
	Nucleic acid amplification – "experimental"

*This is a critical step for children, often the most productive in identifying tuberculosis as the cause of the illness. IGRA, Interferon-gamma release assay.

In a study in Houston, Texas, 30 of 31 children with TBM had an initially negative family history for tuberculosis. However, in most of these cases, an adult family member with tuberculosis was discovered after it was suspected that the child had TBM.

General laboratory evaluations

The erythrocyte sedimentation rate is elevated in up to 80% of cases of TBM, but this has no diagnostic value. Most children with TBM have a fairly normal complete blood count and differential; while anemia is more common, leukopenia and thrombocytopenia are rare in the absence of disseminated tuberculosis. Potential abnormalities in the electrolyte content of extracellular fluids include low serum sodium and chloride levels with low or normal potassium levels.

High levels of antidiuretic hormone (the syndrome of inappropriate antidiuretic hormone (SIADH) secretion) may cause hypotonic expansion of the extracellular fluids (Doxiadis et al., 1954). Because vomiting and dehydration often accompany TBM, the electrolyte disturbances usually include severe hypochloremia (Cotton et al., 1991). In patients with aseptic meningitis, the presence of SIADH suggests a tuberculous etiology.

Tuberculin skin test and interferon-gamma release assay

The placement of the Mantoux intradermal skin test, although fairly simple and routine in a cooperative adult, can be challenging in a frightened, young child. A wheal of 6–10 mm should be raised after injection of the purified protein derivative (Huebner et al., 1993). The test is interpreted 48–72 hours after placement, with measurement and recording of the amount of induration (not erythema). The amount of induration considered to be a positive skin test depends on the risk of tuberculosis infection and the risk of tuberculosis infection progressing to tuberculosis disease. In general, induration of greater than 5 mm should be considered positive for a person with clinical or radiographic signs of tuberculosis disease, including TBM. Unfortunately, many studies have shown that up to 50% of children with tuberculous meningitis have no reaction to a Mantoux tuberculin skin test. Serious tuberculosis disease itself is immunosuppressive and can prevent the patient from displaying a reaction to tuberculin. In addition, TBM, often an early complication of tuberculosis infection, may appear before delayed hypersensitivity has developed. In immunocompetent hosts, anergy to tuberculin may be specific or part of a generalized anergy. Control skin tests using other antigens are rarely helpful in patients with TBM because most patients have global anergy. Reaction to other antigens does not preclude the presence of tuberculosis. Many of the patients with TBM who initially have negative tuberculin skin tests develop reactive skin tests as they improve on effective chemotherapy. Patients with underlying immune deficits, especially patients with HIV infection, may have a persistently negative tuberculin skin test despite tuberculous infection or disease.

Previous inoculation with BCG vaccine can pose problems in the interpretation of a subsequent tuberculin skin test. However, most patients who received a BCG vaccine as an infant lose their ability to react to the tuberculin skin test after several years. Many experts agree that a skin test interpretation in children who received a BCG vaccine more than 3 years previously should be the same as if they had never received the vaccine, especially if tuberculosis disease is suspected clinically. Several studies have shown that the clinical and laboratory manifestations of TBM tend to be similar in children with and without a previous BCG vaccination (Guler et al., 1998; Kumar et al., 2005b).

A new class of tests called IGRA has recently been developed to diagnose tuberculosis infection. Like the tuberculin skin test, they cannot distinguish between tuberculosis infection and disease. These tests measure *in vitro* the patient's immune response to two or three antigens that are found on *M. tuberculosis*, but are not found on most other mycobacteria, including BCG-*bovis* and the *Mycobacterium avium* complex. One test measures whole blood interferon-gamma levels while the other measures the number of lymphocytes that produce interferon-gamma. While both tests are more specific than the tuberculin skin test, they have a similar sensitivity. There are currently few reports of the use of these tests to diagnose TBM, and it is unclear whether they are more likely to be positive in cases of TBM when the tuberculin skin test is negative. However, a negative IGRA and/or negative tuberculin skin test should never dissuade the clinician from considering TBM in a patient with a compatible clinical presentation.

Cerebrospinal fluid examination

Lumbar puncture in TBM usually reveals an elevated opening pressure and clear, colorless CSF. A pellicle or cobweb clot may appear on standing (Sumi et al., 2002). Most patients have a moderate degree of pleocytosis, usually less than 500 cells/mm^3: a CSF white blood cell count greater than 1000 cells/mm^3 is rare in TBM. Although polymorphonuclear cells may predominate early in the course, most cells are usually lymphocytes at the time of the lumbar puncture.

The spinal CSF protein level usually ranges between 100 and 500 mg/dl (Hooker et al., 2003). It increases gradually as the disease progresses but can increase abruptly if spinal block occurs. The protein level from a concomitant ventricular specimen may be normal as the blockage and inflammation are occurring distal to the lateral ventricle. Initial protein values above 300 mg/dl correlate with a poor prognosis in adults with TBM, but a similar association has not been shown in children. In advanced stages, when spinal block is well formed, the fluid may be xanthochromic, with protein content exceeding 1000 mg/dl. The CSF glucose concentration is usually below 40 mg/dl or 50% of the simultaneous blood glucose measurement. However, the CSF glucose concentration rarely falls below 20 mg/dl in cases of TBM. The low CSF glucose distinguishes TBM from most other causes of meningitis except the bacterial etiologies.

The CSF changes in TBM reflect an intrathecal tuberculin reaction and depend on the sensitivity of the patient and the amount of the antigens in the CSF (Jeren and Beus, 1992). Occasionally, the CSF white blood cell count may be below 40 cells/mm^3, and the protein content may show only a small increase. In such patients, the findings may be wrongly interpreted to exclude TBM. In other cases, TBM produces a strong reaction to tuberculin antigens with high CSF white blood cell count and a predominance of polymorphonuclear cells. Most patients with isolated tuberculoma have normal CSF examinations. Rare patients will have increased numbers of cells or protein, depending on the location of the tuberculoma(s).

Microscopic examination of the spinal fluid for acid-fast bacilli is the most important procedure for the early diagnosis of TBM. The frequency with which organisms are seen varies widely, but depends on the amount of CSF that is sampled and the time devoted to searching for the organisms. Some studies report detection of organisms in over 90% of consecutive adult cases of TBM. The most effective technique appears to be to centrifuge 10–20 ml of CSF for 30 minutes and prepare a thick smear from the pellicle. In most series of TBM in children, the acid-fast bacilli stain of CSF has been positive in fewer than 20% of cases, and the organism has been isolated from the CSF in 10–50% of patients, depending on the quantity of fluid cultured and the laboratory facilities (Thwaites et al., 2004b). When possible, the CSF should be cultured on traditional media and in liquid radiometric media to enhance detection of organisms.

Because the initial CSF examination may not be diagnostic in patients with TBM, repeated lumbar punctures may yield valuable results, especially when the clinical presentation is delayed or unusual (Thwaites et al., 2002). Slowly rising CSF protein levels associated with a decreasing glucose concentration and a shift in white blood cells from neutrophils to lymphocytes over a period of days to weeks suggests TBM. It is not unusual for acid-fast bacilli to be demonstrated on a second or third CSF specimen even after the patient has received antituberculosis chemotherapy.

Many attempts have been made to develop a rapid test for the diagnosis of TBM, often involving detection of specific antigens, but most have been unsuccessful (Mardh et al., 1983; Chandramuki et al., 1985; French et al., 1987). Serological assays lack sufficient sensitivity or specificity to be used routinely (Chandramuki et al., 1989). Studies using measurement of adenosine deaminase have also been disappointing, with reported sensitivity and specificity in adults ranging from 44% to 100% and from 71% to 100%, respectively (Ribera et al., 1987; Gambhir et al., 1999; Choi et al., 2002; Corral et al., 2004; Jakka et al., 2005). The bromide partition test, which can sometimes differentiate tuberculous from other causes of meningitis, measures the ratio of serum to CSF bromide 24 hours after oral administration of sodium bromide. In patients with tuberculous meningitis, the ratio falls below 1:6, indicating an increase in the permeability of the blood–CSF barrier. Unfortunately, this test can be positive in bacterial meningitis, neurosyphilis, and some cases of viral meningeoencephalitis.

Nucleic acid amplification

Polymerase chain reaction (PCR) techniques, the first ones using the mycobacterial insertion element IS6110 as the DNA marker for *M. tuberculosis* complex organisms, have sensitivity and specificity of more than 90% compared with the sputum culture for detecting pulmonary tuberculosis in adults (Pfyffer et al., 1996). However, test performance varies even among reference laboratories. Use of PCR in childhood tuberculosis has been more limited. Compared with a clinical diagnosis of pulmonary tuberculosis in children, the sensitivity of PCR has ranged from 25% to 83% and the specificity has varied from 80% to 100%. Unfortunately, a negative PCR never eliminates tuberculosis as a diagnostic possibility, and false-positive results can occur.

The sensitivity of nucleic acid amplification tests for the diagnosis of TBM has ranged between 33% and 90% (Kox et al., 1995; Bonington et al., 1998, 2000; Brienze et al., 2001; Baker et al., 2002; Cheodore and Jamieson, 2002; Pai et al., 2003; Cloud et al., 2004; Johansen et al., 2004; Thwaites et al., 2004a; Desia et al., 2006; Rafi et al., 2007). Although most studies have shown a high specificity, false-positive results from CSF analysis have occurred (Noordhock et al., 1994; Caws et al., 2000; Rafi and Naghily, 2003). Other nucleic acid amplification techniques, such as ligase chain reaction amplification, have yielded similar results (Miorner et al., 1995; Gamboa et al., 1998; Quan et al., 2006). In general, decisions concerning treatment should not be made solely on the basis of these tests (Takahashi et al., 2005, 2007). However, a positive nucleic acid amplification test of CSF may suggest tuberculosis when it is otherwise difficult to confirm (Folgueira et al., 1994), especially if antituberculosis chemotherapy has already been given.

Neuroimaging studies

Neuroimaging by computed tomography (CT) or MRI cannot establish the diagnosis of TBM, but can help exclude other CNS disorders and may provide clues regarding CNS tuberculosis (Bernaerts et al., 2003). CT in TBM often shows dilated ventricles, exudates,

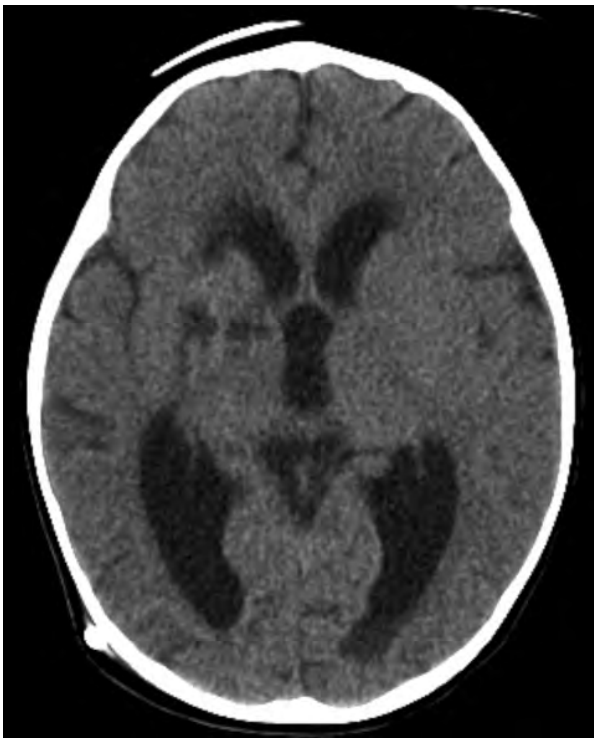

Fig. 11.1. A noncontrasted computed tomography scan showing the communicating hydrocephalus that is typical of the second clinical stage of tuberculous meningitis.

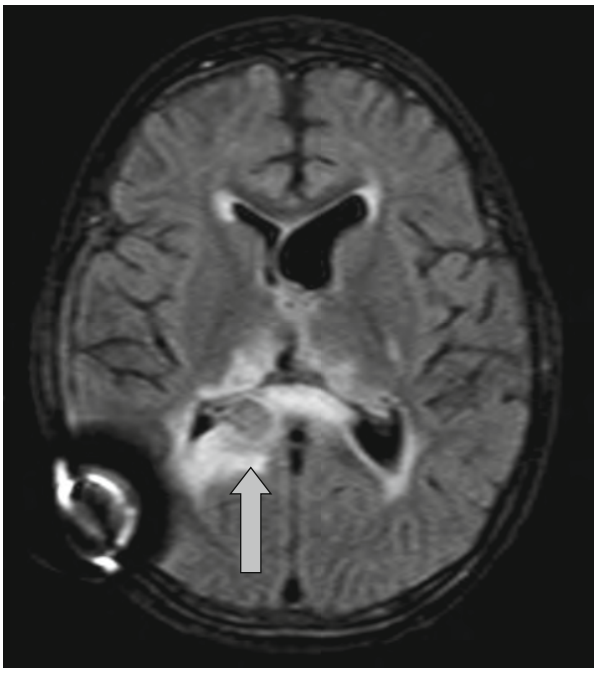

Fig. 11.2. This magnetic resonance image demonstrates distorted ventricular anatomy and a tuberculoma (arrow) with surrounding edema. Culture of the cerebrospinal fluid was positive for *Mycobacterium tuberculosis*.

and thickened meninges, particularly in the basilar areas of the brain (Fig. 11.1). Ischemia associated with TBM manifests as hypodense areas, usually in the basal ganglia or adjacent to the sylvian fissure (Jinkins, 1991). Hydrocephalus associated with TBM may be present initially but can worsen during the early months of therapy. Progression of hydrocephalus may indicate the need for shunting of CSF. MRI has advantages over CT by allowing better visualization of the base of the brain, a common site of pathology in TBM, as well as improved detection of ischemic lesions (Gupta et al., 1994; Jinkins et al., 1995; Kim et al., 1995).

Kumar et al. (1996) identified basal meningeal enhancement, ventriculomegaly, infarcts, and tuberculomas to distinguish TBM from pyogenic meningitis (Fig. 11.2). Andronikou et al. (2004) found that several characteristics of basilar enhancement were found in up to 90% of childhood cases of TBM (Andronikou and Weiselthaler, 2004). However, there have been no definitive studies of the effect of treatment on specific radiographic features of TBM, due largely to the variability of the response (Wallace et al., 1991; Andronikou et al., 2005; Pryzbojowski et al., 2006). The long-term sequelae of TBM often include meningeal calcifications and areas of atrophy (Andronikou et al., 2006).

Neuroimaging of tuberculomas reveals one or several mass lesions, involving the posterior fossa of young children and the frontal or parietal lobes of cerebral cortex in adults (Fig. 11.3) (Tandon and Bhargava, 1985). Although a target sign – a central nidus of calcification surrounded by a ring of enhancement and/or edema – is common with tuberculomas, it is not a specific sign (Bargallo et al., 1996). In tuberculoma of a shorter duration, the surrounding edema is often substantial. An important phenomenon that has been defined better since the advent of CT and MRI is the paradoxical development of tuberculomas in patients undergoing therapy for TBM (Teoh et al., 1987). These lesions may not be present at the initial diagnosis, but develop after chemotherapy is started. They appear to reflect an immunological phenomenon caused by intensification of inflammation as organisms are killed and mycobacterial antigens are released into the surrounding tissues. Paradoxical tuberculomas should be suspected in any patient undergoing treatment for TBM who has the sudden or gradual onset of focal neurological deficits, seizures, or any other new neurological abnormalities. Formation of tuberculomas has been described as part of the IRIS which occurs in some HIV-infected individuals being treated for tuberculosis after highly effective antiretroviral therapy is started. This phenomenon should be suspected in any such patient who unexpectedly develops seizures or focal neurological findings.

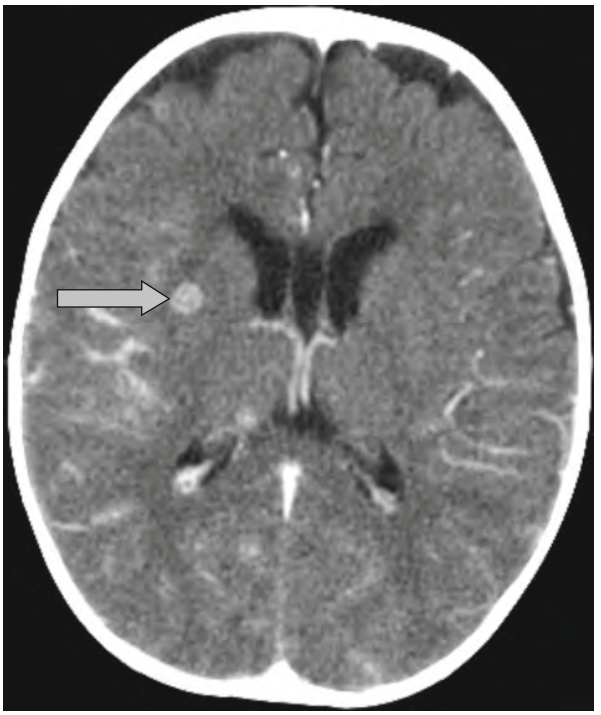

Fig. 11.3. An isolated tuberculoma (arrow) in a patient recovering from tuberculosis meningitis.

MANAGEMENT

Despite effective antituberculosis drugs, morbidity and mortality rates from TBM remain high throughout the world. Early death and poor clinical response are usually caused by failure to recognize the disease and begin appropriate therapy in the early stages. Because it is so difficult to find specific evidence of *M. tuberculosis* in a patient with TBM, initial therapy is usually empiric, based on the epidemiological, clinical, laboratory, and radiographic data. As a rule of thumb in tuberculous meningitis, start treatment first, ask questions later.

Antituberculosis drugs vary in their CSF penetrance, a necessary requirement for successful treatment of TBM (Ellard et al., 1993). Drugs used to treat tuberculosis, their doses, and most common adverse effects are listed in Table 11.3. Isoniazid diffuses readily into the spinal fluid in the presence or absence of meningeal inflammation, with CSF concentrations approximately 20–90% of serum levels (Donald et al., 1992). The CSF levels far exceed the minimal inhibitory concentration for susceptible strains. Rifampin penetrates poorly into the CSF in the absence of meningeal inflammation. However, in patients with TBM, the CSF concentration of rifampin is approximately 10–20% of the serum level and exceeds the minimal inhibitory concentration by several times (D'Oliveira, 1972; Nau et al., 1992). Pyrazinamide crosses well into the CSF, achieving levels between 50% and 100% of simultaneous serum levels (Ellard et al., 1987; Donald and Seifart, 1988).

Little or no ethambutol is detected in the CSF of patients with normal meninges; however, in those with TBM, CSF concentrations are 10–50% of serum levels. Although little or no streptomycin or aminoglycosides are detectable in the CSF in the absence of meningeal inflammation, patients with TBM have CSF levels that reach 20% of serum concentrations. As a result, streptomycin and other aminoglycosides may be effective drugs for the treatment of TBM, but are less effective in the treatment of tuberculoma without CNS inflammation. An important secondary drug for treatment of TBM is ethionamide, which penetrates well into the CSF of patients with or without meningeal inflammation (Donald and Seifart, 1989). Cycloserine also penetrates into the CSF well but has less antituberculous activity than ethionamide. The fluoroquinolones have been used in cases of multidrug-resistant (MDR) TBM (Alangaden and Lerner, 1997; Padayatchi et al., 2006). Intrathecal and intraventricular administration of various antituberculosis drugs has been used in difficult and drug-resistant cases of TBM, but is rarely used today (Vincken et al., 1992).

Clinical trials of antituberculosis therapy in children who suffer from most cases of TBM have been problematic because of the difficulty in obtaining positive cultures. Several major studies of 6-month therapy in children with pulmonary tuberculosis have been reported using at least three drugs in the initial phase of treatment. The most common regimen is 6 months of isoniazid and rifampin supplemented during the first 2 months with pyrazinamide (American Thoracic Society, 2003). For pulmonary tuberculosis, the overall success rate with this regimen has been greater than 98% and the incidence of clinically significant adverse reactions less than 2%. Drugs are administered daily during an initial period of 2 weeks to 2 months; subsequent medication can be given twice weekly under directly observed therapy, where a health care worker directly observes the administration of medication to the child.

Unfortunately, the incidence of drug-resistant tuberculosis is increasing in the USA and throughout the world (Zignol et al., 2006; Raviglione and Smith, 2007; Shah et al., 2007). As many as 10% of *M. tuberculosis* isolates in the USA are resistant to at least one antituberculosis drug, most often isoniazid. The three-drug regimen noted earlier may not be successful in cases of severe pulmonary tuberculosis when isoniazid resistance is present. As a result, the US Centers for Disease Control and Prevention has recommended that a fourth

Table 11.3

Drugs used for the treatment of tuberculosis in children and adults. First-line agents are above the gray bar; drugs used primarily for drug-resistant tuberculosis are shown below the bar

	Daily dose		Biweekly dose						
Agent	Children (mg/kg/day)	Adult maximum dose	Children (mg/kg/day)	Adult maximum dose	Drug interactions*	Toxicities	CNS penetrance†	Monitoring parameters	Hepatic or renal dosing necessary
Isoniazid	10–15	300 mg	20–30	900 mg	+	Hepatitis, peripheral neuropathy	100%	‡	§
Rifampin	10–20	600 mg	10–20	600 mg	++	Hepatitis	10–20%	‡	§
Pyrazinamide	30–40	2 g	50	2 g	–	Gout, rash	100%	‡	§ Renal
Ethambutol	20	2.5 g	50	2.5 g	–	Optic neuritis	Minimal¶	‡	§ Renal
Amikacin	15–30	1 g	There are few data available on the efficacy of biweekly dosing of second-line agents		–	Nephrotoxicity, ototoxicity	Low	Baseline and monthly creatinine, drug levels, and hearing screen	Renal
Capreomycin	15–30	1 g			–	Nephrotoxicity, ototoxicity	Minimal¶	Baseline and monthly creatinine and hearing screen	Renal
Kanamycin	15–30	1 g			–	Nephrotoxicity, ototoxicity	Low	Baseline and monthly creatinine and hearing screen	Renal
Streptomycin	20–40	1 g			–	Ototoxicity, nephrotoxicity	Minimal	Baseline and monthly creatinine and hearing screen	Renal

Ethionamide	15–20	1 g	–	Hepatotoxicity, GI distress, hypersensitivity reactions, hypothyroidism, peripheral neuropathy, optic neuritis	100%	Consider baseline ALT and TSH	§ Renal
Levofloxacin	7.5–10[†]	1 g[†]	++	Arthropathy, CNS stimulation	16–20%		Renal
Ciprofloxacin	20–30[†]	1.5 g[†]	++	Arthropathy, CNS stimulation	10%		Renal
Cycloserine	10–20	1 g	–	Rash, seizures, psychosis	100%	Monthly neuropsychiatric evaluation; serum levels available	Renal
Para-aminosalicylic acid (PAS)	200–300	10 g	+	Hepatotoxicity, GI distress, hypersensitivity reactions, hypothyroidism	10–50%[¶]	Baseline ALT, TSH; check monthly if used >3 months	Renal

[*]For drug interactions: – minimal interactions; + few interactions; ++ multiple interactions.
[†]Percentage of serum levels reached in cerebrospinal fluid.
[‡]Routine baseline laboratory evaluation not necessary except in children with known underlying hepatic disease.
[§]Can be used, but with more frequent monitoring, in patients with underlying hepatic disease.
[¶]Only marginally efficacious for tuberculous meningitis.
GI, gastrointestinal; CNS, central nervous system; ALT, alanine aminotransferase; TSH, thyroid-stimulating hormone.

antituberculosis drug be added to the initial regimen of all cases of tuberculosis. In some regions of the world, close to one-third of *M. tuberculosis* isolates are MDR, being resistant to at least isoniazid and rifampin. The treatment of MDR TBM is extremely challenging and, unfortunately, often unsuccessful.

Controlled treatment trials for extrapulmonary tuberculosis, including TBM and tuberculomas, have not been performed (Donald et al., 1998). Early studies showed that treatment with isoniazid and rifampin for 12 months was generally effective in patients with drug-susceptible TBM (Ramachandran et al., 1986). A study from Thailand showed that a 6-month regimen including pyrazinamide for TBM led to few deaths and better outcomes than did longer regimens that did not contain pyrazinamide (Jacobs et al., 1992).

Most experts recommend starting four antituberculosis drugs in a patient with suspected TBM to guard against unknown drug resistance, using isoniazid, rifampin, and pyrazinamide. Streptomycin, kanamyacin, or amikacin is used as the fourth drug, although some experts use ethionamide (Phuapradit and Veijajiva, 1987). The fourth drug can be discontinued when it becomes known that the *M. tuberculosis* isolate causing the disease is susceptible to all drugs.

The duration of therapy for TBM in children is controversial. Although it has been shown that 12 months is effective, many experts have shown that regimens between 6 and 9 months are equally effective (van Loenhout-Rooyackers et al., 2001). Directly observed therapy should always be used in the outpatient treatment of TBM (Weis et al., 1984). The treatment of drug-resistant TBM is very difficult and should be guided by an infectious disease expert (DeVincenzo et al., 1999; Daikos et al., 2003; Caminero, 2006; Byrd and Davis, 2007; Kapp, 2007). The regimen must be tailored to the exact drug susceptibility profile of the infecting organism. Few experts currently recommend intrathecal and intraventricular antituberculosis therapy unless traditional treatment is failing or cannot be given successfully (Berning et al., 2001).

The optimal medical treatment of tuberculoma has not been established. Superficial tuberculomas are amenable to surgical therapy and may be best treated with a combination of surgical excision and chemotherapy (Arseni, 1958; Bouchama et al., 1991). However, many tuberculomas have been cured with medical therapy alone (Domingo and Peter, 1989). Most experts recommend an initial three- or four-drug regimen with a total length of therapy of 6–9 months.

Supportive measures for treatment of CNS tuberculosis can be very important. Careful fluid and airway management as well as aggressive anticonvulsive therapy may be necessary. Fluid restriction and diuretics may be helpful when inappropriate antidiuretic hormone secretion results in cerebral edema. Nutritional support, good nursing care, and early rehabilitation with physical therapy are also helpful to the patient with TBM.

Corticosteroids have been used widely in the treatment of TBM (O'Toole et al., 1969; Dooley et al., 1997; Simmons et al., 2005). One well-controlled, small investigation failed to show a significant difference between treated patients and controls (Kumarvelu et al., 1993), whereas several other studies have shown that patients in early and advanced stages of TBM benefit from corticosteroid therapy (Escobar et al., 1975; Girgis et al., 1991; Schoeman et al., 2001; Thwaites et al., 2007). A Cochrane review failed to demonstrate much benefit from corticosteroid therapy for TBM (Prasad et al., 2000). However, most experts agree that it is best to use corticosteroids early, especially if the diagnosis has been reasonably established and the patient's condition is critical (Kaojaren et al., 1991). Corticosteroids are usually given for 4–6 weeks and then tapered over a period of several weeks as the patient improves (Schoeman et al., 1997; Thwaites et al., 2004c, 2005).

When acute hydrocephalus develops, insertion of a ventriculostomy may be life-saving (Bullock and Van Dellen, 1982; Clark et al., 1986; Nadvi et al., 2000; Agrawal et al., 2005; Yadav et al., 2006). Neuroendoscopy also has been used successfully to manage hydrocephalus (Husain et al., 2005). There have been several series showing that placement of a ventriculoperitoneal shunt is appropriate and effective when hydrocephalus complicates TBM (Mathew et al., 1998; Lamprecht et al., 2001; Kemaloglu et al., 2002). This approach should be considered when hydrocephalus leads to extreme symptoms or when the clinical condition deteriorates despite use of corticosteroids or diuretics. Shunt placement does not lead to peritoneal tuberculosis. Older studies used acetazolamide to decrease CSF production, but the results were generally poor (Visudhiphan and Chiemchanya, 1979).

The prognosis of TBM relates directly to the clinical stage of disease at presentation and onset of therapy (Humphries et al., 1990). Most patients treated in stage I have a normal outcome. By contrast, most patients diagnosed in stage III will die or have severe neurological sequelae. Some individuals diagnosed in stage II have a good outcome, whereas others have persistent neurological deficits (Misra et al., 1996; Saitoh et al., 2005). The current mortality rate of TBM with adequate therapy is 10–20% in developed countries, but may be as high as 30–40% in developing countries. In general, the prognosis is worse for infants, the elderly, malnourished patients, and patients with disseminated disease or with markedly elevated intracranial pressure (Schoeman et al., 1985, 1991, 2000).

Visual and auditory impairments are the most common late sequelae. Impaired vision is usually due to edema compressing the optic nerve or chiasm, but is occasionally secondary to raised intracranial pressure. Hearing loss results from nerve damage induced by basilar exudates. Unfortunately, the use of streptomycin or other aminoglycosides can contribute to diminished hearing after TBM. Early audiometry is essential to be sure that appropriate therapy can be continued. Although most cranial nerve abnormalities resolve with appropriate therapy, there are reports of persistent oculomotor, abducens, or facial nerve deficits (Palur et al., 1991).

Motor deficits after TBM, more common in children than in adults, have been reported in 10–25% of survivors (Leiguarda et al., 1988; Schoeman et al., 2002). Seizures, although common in the acute stage of the illness, occur as late sequelae in fewer than 10% of patients. Mental or behavioral impairments occur most often in those with marked meningitis under the age of 3 years. Children who had TBM-induced hydrocephalus and required shunting tend to remain shunt-dependent. Overall, 10–50% of children who survive TBM have neurological sequelae.

Endocrinopathies may become evident months or years after recovery from TBM (Lam et al., 1993). They are more common in adults but can occur in young or older children. They are due to progressive scarring of either the hypothalamus or the adjacent basal cisterns. The most common forms are obesity, hypogonadism, sexual precocity, diabetes insipidus, and growth retardation.

CONCLUSION

Tuberculous meningitis will persist as long as untreated tuberculosis infection occurs. In the USA, preventing tuberculosis infection and disease relies mainly on contact investigation and tuberculin skin testing (American Thoracic Society, 2005). Children can acquire tuberculosis infection only if they are in contact with an infectious adolescent or adults. The resurgence of tuberculosis in the USA during the 1980s and 1990s showed that, when contact investigations were done poorly, an increased number of children developed tuberculosis disease, including TBM.

All countries except the Netherlands and the USA have used BCG vaccines to prevent complications of tuberculosis infection in children. This vaccine does not reliably prevent tuberculosis infection, but it is between 50% and 80% effective in preventing serious forms of tuberculosis, such as meningitis, for 5 years after vaccination of infants (Camargos et al., 1988; Bhattacharjee et al., 1993; Rodrigues et al., 1993; Colditz et al., 1995; Mittal et al., 1996; Awasthi and Moin, 1999; Kumar et al., 2005a; Trunz et al., 2006). This vaccination understandably remains a cornerstone of the World Health Organization tuberculosis disease prevention programs for children.

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Chapter 12

Spirochetal infections

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NEUROSYPHILIS

Epidemiology

Syphilis

The peak reported incidence of early (primary and secondary) syphilis in the general population of the USA was about 400/100 000 population in the 1940s. Since that time, there has been a steady fall, dropping to 2.1/100 000 by 2000 (Centers for Disease Control and Prevention, 2001). Despite this, syphilis remains an important health problem in certain geographic areas and subgroups of the population, which include African American and Hispanic males (Centers for Disease Control and Prevention, 1997), and men having sex with men (MSM) (Peterman and Furness, 2007; Zetola et al., 2007). The incidence of syphilis in the USA is higher in certain states such as Florida, California, and New York (Centers for Disease Control and Prevention, 1988). Unprotected sex with infected subjects remains the single most important risk factor. Furthermore, up to 8% of healthy adults had serological evidence of prior exposure to *Treponema pallidum* (Traviesa et al., 1978); this increases to 11% in adults admitted to inner-city hospitals (Carey et al., 1995) and to 19% in adults admitted to psychiatric hospitals (Roberts et al., 1992). Reports in the early 1990s revealed that one in 200 patients admitted to neurology wards had active syphilis (van de Ree et al., 1992), and one in 200 cases of dementia were caused by syphilis (Powell et al., 1993).

Neurosyphilis

Fortunately, only some patients with syphilis develop neurosyphilis. The estimated frequency depends on the stage of syphilis when the cerebrospinal fluid (CSF) is examined, the risk of the population, prior treatment with antimicrobial therapy, and the diagnostic criteria. Neurosyphilis is defined as any direct or indirect evidence of the presence of *T. pallidum* in the CSF or brain parenchyma. Before the availability of penicillin, the risk of progression to symptomatic neurosyphilis in untreated syphilis was estimated to be about 6% (Hahn and Clark, 1946). However, the risk of progression increases to 23–87% if the CSF is abnormal (Moore and Hopkins, 1936; Hahn and Clark, 1946). Conversely, if the CSF is normal during early syphilis, the risk of progression to symptomatic neurosyphilis is minimal (Merritt, 1940; Hahn and Clark, 1946). The risk of progression is also minimal if the nontreponemal serology is negative or fixed positive at a low titer 2 years after treatment with penicillin (Lukehart and Holmes, 1991). However, the risk of progression increases if patients with latent syphilis become infected with human immunodeficiency virus (HIV) (Holtom et al., 1992) or become pregnant (Jones and Harris, 1979). The risk of progression to symptomatic neurosyphilis is two to three times greater for whites than for blacks, and two times greater for males than females (Lukehart and Holmes, 1991). Age at time of infection also affects the risk. In a study of untreated syphilitic patients, none of the males older than 40 years at the time of early infection developed symptomatic neurosyphilis (Clark and Danbolt, 1964). If symptomatic neurosyphilis develops early, the risk of progression to the more severe late symptomatic forms of neurosyphilis increases; in one study of patients with untreated acute syphilitic meningitis, two-thirds progressed to late symptomatic neurosyphilis (Merritt et al., 1946). In the postpenicillin era, symptomatic neurosyphilis was responsible for up to 10% of hospital admissions with acute psychiatric (Roberts et al., 1992) or neurological illnesses (van Eijk et al., 1987). Although treatment with

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penicillin has dramatically reduced the incidence of neurosyphilis, the percentage of cases of syphilis with symptomatic neurosyphilis remains stable at about 20% (Merritt et al., 1946; Luger et al., 1987).

Co-infection with HIV

A significant percentage of patients infected with HIV have serological evidence of exposure to *T. pallidum* – up to 35% in some series. One study of 151 patients from Germany who were co-infected with HIV and *T. pallidum* found that 17% had primary syphilis, 36% secondary syphilis (including 7% with the malignant ulcerated variant), 25% latent syphilis, and 17% neurosyphilis, mostly meningovascular and gummatous (Schofer et al., 1996). Paretic or tabetic neurosyphilis occurs only rarely in the context of HIV infection (Gue et al., 1993). The risk of neurosyphilis in patients co-infected with HIV and *T. pallidum* is 2–27%, and is asymptomatic in most patients. The risk of progression from early syphilis to symptomatic early neurosyphilis in HIV-positive MSM is 2% (Centers for Disease Control and Prevention, 2007a). In many instances, patients are found to be HIV-infected only after they develop neurosyphilis (Musher et al., 1990). There is no difference in CD4 lymphocyte counts between HIV-infected patients with or without neurosyphilis (Bordon et al., 1995); severe syphilitic meningitis can occur in HIV-infected patients with normal CD4 counts (DiNubile et al., 1992). However, some forms of syphilis are more common in patients co-infected with HIV, including syphilitic meningitis (Katz et al., 1993). Some studies (Holtom et al., 1992; Musher et al., 1992) and case reports (Berry et al., 1987) suggest that the course of syphilis in HIV-infected patients may be more protracted. This has not been confirmed, however, in prospective studies (Lukehart et al., 1988; Hutchinson et al., 1991; Gourevitch et al., 1993; Rolfs et al., 1997; Rompalo et al., 2001).

Etiology

Syphilis is a multisystem infectious disease caused by the spirochete *Treponema pallidum* subspecies *pallidum* (Norris and the *Treponema pallidum* Polypeptide Research Group, 1993). *T. pallidum* is an obligate parasite of humans and no other natural reservoirs are known. In most cases *T. pallidum* is sexually transmitted by direct inoculation at cutaneous or membranous sites, but it can also be transmitted transplacentally after the fourth month of gestation or by blood transfusion. *T. pallidum* replicates locally at the site of inoculation, where it causes a painless chancre (primary syphilis), and then disseminates hematogenously to the skin and other tissues, resulting in rash and lymphadenopathy (secondary syphilis). Spirochetemia occurs more commonly early after the infection, but can occur throughout the disease (Stokes et al., 1944; Wendel et al., 1991) even after antimicrobial treatment (Dunlop, 1985). Early infection may be followed by latent infection, which may progress to neurological, cardiovascular, or gummatous complications. Latency represents smoldering infection in immunologically isolated regions, including the central nervous system (CNS), eyes, and dense connective tissues (Sell and Norris, 1983). Only about one-third of patients with untreated latent syphilis progress to symptomatic neurosyphilis; this may be explained by the existence of neurotropic strains of *T. pallidum* (Stokes et al., 1944). In support of this is the observation that neurosyphilis was eight times more frequent in parents of children with congenital neurosyphilis and that the concordance rate for conjugal paretic neurosyphilis was as high as 57% (Stokes et al., 1944).

Pathogenesis and pathophysiology

Pathology

Infection of the CNS by *T. pallidum* triggers a prominent inflammatory response in the host that is mainly leptomeningeal and perivascular (Escobar and Nieto, 1972). The inflammatory cells are lymphocytes, plasma cells, macrophages, and a few mast cells. Lymphocytes predominate in acute meningeal and meningovascular forms, and plasma cells predominate in paretic forms. The leptomeningeal and perivascular infiltrate extends to the Virchow–Robin spaces. Brain parenchyma microglia proliferate and activate from a rod-cell stage to a perivascular accumulation of round, fatty debris-filled cells. The meningitis is diffuse with inflammation most marked around blood vessels. Vascular inflammation mainly affects the arterial circulation, including the aorta, branches of the external carotid artery such as the temporal artery (Rosahn, 1947), the internal carotid including the circle of Willis, medium and small-sized arteries, arterioles and capillaries in the leptomeninges and Virchow–Robin spaces, vasa vasorum in larger vessels, and vasa nervorum in cranial nerves. Involvement of the adventitia and arterial wall may damage muscle and elastic fibers in the medial layers and disrupt the internal elastic layer, causing hemorrhage. The inflammation also damages the endothelium with secondary proliferation of subintimal fibroblasts that may lead to progressive thrombosis and luminal occlusion, resulting in ischemia. Various stages of intra-arterial clotting organization can be found. There is often fibrinoid necrosis of the vessel walls with cerebral infarction of the surrounding tissue. Glial nodules can be seen at sites of microinfarction. Inflammation of large and medium arteries is known as Heubner's arteritis or endarteritis obliterans (Escobar and Nieto, 1972);

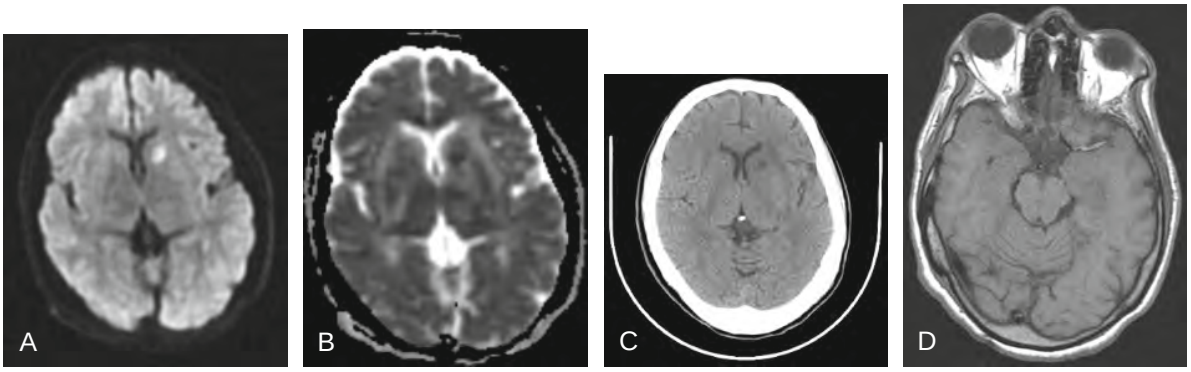

Fig. 12.1. Diffusion-weighted magnetic resonance imaging (A) and acute diffusion coefficient map (B) show an acute infarction in the white matter adjacent to the left caudate nucleus in a 48-year-old black man who was rapid plasma reagin-positive, fluorescent treponemal antibody absorption (FTA-ABS)-positive, and had 90 white blood cells/mm^3 and 159 mg/dl of protein in the cerebrospinal fluid. (C) The appearance of the infarct on head computed tomography; (D) increased signal on the left middle cerebral artery consistent with occlusion.

Heubner's arteritis causes focal neurological deficits in meningovascular syphilis (syphilitic stroke) (Fig. 12.1). Intense proliferation of endothelial and adventitial cells in arterioles of the gray matter and pia mater, in the absence of inflammation, is known as Nissl–Alzheimer's arteritis (Merritt et al., 1946).

In tabetic neurosyphilis, the inflammation is mostly in the middle posterior root zone of Flechsig and around the dorsal roots with interstitial neuritis. Thickening of the vascular adventitia occurs, but perivascular infiltrates are not abundant. In paretic neurosyphilis, the inflammation varies from mild to severe, is more intense in the frontal and temporal lobes and the pre- and postcentral gyri, milder in the dorsal hemispheres and subcortical white matter, and absent in the occipital lobe. Typical Heubner's arteritis has been demonstrated on only a few occasions in paretic neurosyphilis. Chronic inflammation can result in tissue injury, fibrosis, and thickening of meninges and blood vessels. Fibrosis is more severe around the optic nerve and chiasm, in the cervical cord in pachymeningitis cervicalis hypertrophica, in the dorsal spinal cord meninges in tabes dorsalis, and around gummas. Other characteristic findings are vascular intimal hyperplasia and granular ependymitis.

Neuronal loss and degeneration are characteristic of late-stage forms of neurosyphilis (Merritt et al., 1946). Degenerated neurons have shrunken cell bodies with paler and finer Nissl bodies, and a small rim or absent Nissl substance; axons may show ballooning or fragmentation. Other findings may be central chromatolysis, nuclear pyknosis, and clumping of neurofibrils. Neuronal loss can result in cortical atrophy, more prominent in the frontal and temporal lobes, and *ex vacuo* hydrocephalus which is more prominent in the third ventricle and frontal horns. Neuronal cell loss in tabetic neurosyphilis affects dorsal horn nuclei such as the nucleus propius and the nucleus dorsalis of Clarke. This cell loss causes shrinking of the posterior columns and atrophy of the posterior root entry zone and the Lissauer tract. Astrogliosis occurs along the degenerating tracts in tabetic neurosyphilis. Optic nerve atrophy may result in secondary atrophy of the retina and the lateral geniculate body. Nerve fiber degeneration usually begins peripherally and extends to the center of the nerve (Tramont, 1995). Demyelination is seen in paretic neurosyphilis and correlates with the extent of cortical neuronal loss (Escobar and Nieto, 1972), affecting predominantly the fasciculus gracilis bilaterally. Demyelination can also be found in the optic nerve and chiasm. Iron deposition is also common in and around arterioles and capillaries penetrating the cerebral cortex and intracellular in microglia. Iron deposits are presumed to consist of hemosiderin released from circulating red blood cells.

Brain infection

In late forms of neurosyphilis, *T. pallidum* can be found in the cerebral cortex of 25–40% of paretic cases by silver impregnation techniques (Merritt et al., 1946). The spirochetes are mainly found in the frontal areas of the gray matter, becoming very difficult to find after treatment. Treponemes have also been observed free-floating in CSF in meningeal neurosyphilis, in gummatous neurosyphilis (Horowitz et al., 1994), and rarely in tabetic neurosyphilis. The number of organisms in the CNS is low compared with peripheral tissues (e.g., skin).

Immunity

Abundant evidence suggests that *T. pallidum* escapes humoral immune defense despite production of specific antibodies early in the infection. However, research in the rabbit model has shown resistance to reinfection

that may be mediated by phagocytosis and specific antibody (Norris and Sell, 1984; Sell et al., 1985). Although spirochetal multiplication appears to be controlled early during the infection, it appears to recur during late disseminated disease, as suggested by the finding of a high number of spirochetes in the brains of paretic patients. Latent syphilis may represent smoldering infection in immunologically isolated areas, such as the CNS or dense connective tissues.

Clinical features

Acute syphilitic meningitis

Syphilitis meningitis affects mainly young adults and occurred in 0.3–2.4% of patients with syphilis in the pre-penicillin era (Merritt and Moore, 1935). In Merritt's series, 6% of 676 cases of symptomatic neurosyphilis in the period 1932–1942 had acute syphilitic meningitis (Merritt et al., 1946); most cases occurred in the first 2 years after primary infection (Merritt and Moore, 1935; Merritt et al., 1946; Simon, 1985). The onset is subacute and dominated by increased intracranial pressure and acute basilar or vertical meningitis (Merritt and Moore, 1935). Clinical manifestations include delirium, fever, headache, nausea and/or vomiting, seizures, stiff neck, cranial neuropathies (most often of the seventh and eighth cranial nerves), focal neurological deficits, pupillary abnormalities, and communicating hydrocephalus (Merritt and Moore, 1935; Stokes et al., 1944; Katz et al., 1993). Magnetic resonance imaging (MRI) may reveal enhancement of the CSF (Good and Jager, 2000). If untreated, syphilitic meningitis may progress to meningovascular or tertiary neurosyphilis, but occasionally may resolve spontaneously. In the monkey model of neurosyphilis, *T. pallidum* is cleared from the CSF within 8 weeks of intracisternal inoculation (Marra et al., 1991, 1998). Most signs, symptoms, and CSF abnormalities resolve promptly after treatment (Stokes et al., 1944; Merritt et al., 1946), with the exception of advanced hearing loss (Merritt et al., 1946).

Cranial neuropathies

Cranial neuropathies occur in one-quarter of patients with symptomatic neurosyphilis (Smikle et al., 1988). The frequency is highest (up to 50%) in acute syphilitic meningitis (Merritt et al., 1946). Any cranial nerve can be affected with sudden or insidious onset; 40% involved the seventh and/or eighth and 25% the second, third, or sixth cranial nerves (Tramont, 1995). Fifth cranial neuropathy occurred in 12% of cases of acute syphilitic meningitis and was bilateral in 13%, and oropharyngeal dysphagia occurred in 6% and was bilateral in 20% (Hutchinson and Hook, 1990). Half of the patients with acute syphilitic meningitis had multiple cranial neuropathies (Merritt et al., 1946). Most cranial nerve deficits reverse with prompt treatment.

Cerebrovascular disease

Neurosyphilis is an important cause of stroke in the young. In the pre-penicillin era, one-third of patients with meningovascular syphilis were 20–30 years of age and most were younger than 60 years (Merritt et al., 1946). The peak incidence of stroke occurred 4–10 years after primary infection (Merritt et al., 1946), although it can occur as early as a few months after primary syphilis (Merritt et al., 1946; Johns et al., 1987). Meningovascular syphilis is currently the most common manifestation of symptomatic neurosyphilis (Hooshmand et al., 1972; Srinivasan, 1984; Brightbill et al., 1995; Peng et al., 2008). The onset of symptoms is often gradual but can sometimes be sudden. There is often a history of months of prodromal symptoms, including headache, vertigo, memory loss, slow mentation, slow speech, or mood disturbance. The most common manifestations are hemiparesis/hemiplegia and aphasia (Merritt et al., 1946).

Different lacunar syndromes can occur (Merritt et al., 1946; Molin et al., 1992). About 14% of patients with syphilitic strokes have seizures (Kelley et al., 1989). Less common manifestations are choreoathetosis (Jones and Bouchier, 1993) or hemianopia (Stokes et al., 1944). The two most common vascular territories involved are the middle cerebral artery (62%) (Fig. 12.1) and the basilar artery (12%) (Merritt et al., 1946; Britto et al., 1987). Strokes can also occur in the basal ganglia, internal capsule, and the pons (Merritt et al., 1946; Johns et al., 1987; Kase et al., 1988; Labauge et al., 1991; Molin et al., 1992; Tien et al., 1992; Arboix and Marti-Vilalta, 1993). Neuroimaging in HIV-infected patients with syphilitic strokes can show patchy enhancement of the basal ganglia and the territory of the middle cerebral artery (Centers for Disease Control and Prevention, 1993). Magnetic resonance angiography can show abnormalities of the basilar artery (Gallego et al., 1994) or nonspecific vasculopathy (Brightbill et al., 1995). Regular arteriography can show vasculopathy of the circle of Willis (Holland et al., 1986) or distal arterial branches (Holland et al., 1986), segmental dilatation (Liebeskind et al., 1973), multifocal long and smooth segmental narrowing (Holmes et al., 1984; Holland et al., 1986; Brightbill et al., 1995), beading (Liebeskind et al., 1973), or aneurysms (de Villiers and Mitchell, 1985). Untreated meningovascular syphilis results in progressive ischemia with multiple strokes and irreversible neurological deficits. However, effective treatment minimizes the risk of recurrence. Even without treatment

there is a marked tendency for patients to recover and with fewer permanent sequelae than with atherosclerotic strokes (Stokes et al., 1944).

Meningovascular syphilis may also result in stroke of the spinal cord by occlusion of the vertebral, anterior, or posterior spinal arteries (Merritt et al., 1946), or by aortic dissection (Kellet et al., 1997). Of 212 cases of spinal syphilis, 4% corresponded to spinal cord stroke (Stokes et al., 1944). Most strokes occurred at thoracic levels and some may mimic acute transverse myelitis (Merritt et al., 1946; Nabatame et al., 1992). The deficits are usually irreversible (Merritt et al., 1946).

Paretic neurosyphilis

Syphilis may cause dementia, referred to as general paresis of the insane. The peak incidence is 10–20 years after primary infection, but true paresis has been described as early as 8 months (Stokes et al., 1944). Fewer than 2% of cases have latency of less than 5 years (Stokes et al., 1944). The incidence has decreased dramatically since the availability of penicillin (Merritt et al., 1946; Hooshmand et al., 1972). The male-to-female ratio is 2–7:1 and most cases occur in whites. The age at onset is the first to second decades in the juvenile form that follows congenital syphilis, and the fourth to seventh decades in the adult form. Mental development is normal in 60% of cases of juvenile paretic neurosyphilis until the onset of paretic symptoms during puberty (Menninger, 1936). The onset is most often subacute and the course progressive. The disease can affect multiple functions, summarized by the mnemonic PARESIS (personality, affect, reflexes, eye, sensorium, intellect, and speech). Impaired concentration is usually present at onset. Executive dysfunction presents as failure at work or school and motor apraxia. Affective dysfunction presents as emotional lability with depression, agitation, irritability, euphoria, or mania (Dewhurst, 1969; Hoffman, 1982; Bschor et al., 1995). Psychotic manifestations include paranoia (Hoffman, 1982), delusions of grandeur (Dawson-Butterworth and Heathcote, 1970; Ricchieri et al., 1983), and rarely hallucinations (Gastal et al., 1995) or catatonia (Sivakumar and Okocha, 1992).

Other manifestations of frontal lobe dysfunction include impaired personal hygiene and sphincter control, apathy, abulia, behavioral changes, frontal release signs, poor judgment, and careless appearance. Temporal lobe dysfunction presents as posterior aphasia and memory loss. Subcortical disease results in movement disorders such as chorea, intention tremor, and twitching of face and tongue and can result in dysarthria and buccolingual masticatory movements (Roberts and Emsley, 1992). Advanced cases develop motor paresis with facial inexpression (paralytic fascies). Seizures are frequent in the later stages of the disease (Stokes et al., 1944; Dawson-Butterworth and Heathcote, 1970). The electroencephalogram (EEG) is abnormal in 80% of cases (Swartz, 1990) and the MRI is abnormal in 65% (Russouw et al., 1997). MRI abnormalities include cerebral atrophy and foci of increased signal intensity of T2/fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 12.2). Diffuse periventricular white matter lesions may be seen (Ganti et al., 1981; Zifko et al., 1996; Rinkel et al., 1997). Brain atrophy is most marked anteriorly over the frontal and temporal lobes with sparing of central and posterior areas (Godt et al., 1979; Zifko et al., 1996). A few cases have shown focal atrophy of frontal and temporal gyri (Lissauer's dementia paralytica) (Merritt et al., 1946). Single photon emission computed tomography (SPECT) shows marked reduction of the cerebral blood flow mainly in the bilateral frontal and temporal cortex, which can be reversible (Saitoh et al., 1991; Takahashi et al., 1992; Kawai et al., 1994). If untreated, paretic neurosyphilis results in progressive intellectual and motor decline with paralysis and death within 5 years (Merritt et al., 1946).

Tabetic neurosyphilis

Neurosyphilis may cause disease of the spinal cord, roots, and ganglia. The onset of symptoms varies depending on the lesion, from acute in spinal cord infarction to subacute in gummatous spinal cord compression; symptoms may be chronic in hypertrophic spinal pachymeningitis or tabes dorsalis, also known as progressive locomotor ataxia. The site most often involved in tabes dorsalis is lumbosacral and the mechanism is progressive neuronal degeneration secondary to chronic meningitis with vasculopathy and ischemia. The latency from initial infection is 15–30 years. Penicillin has dramatically reduced the incidence of tabes dorsalis (Merritt et al., 1946; Aho et al., 1969; Towpik and Nowakowska, 1970; Heathfield, 1976). Tabes dorsalis peaks in the second decade of life for the juvenile form, and in the fifth to seventh decades for the adult form. The clinical manifestations are those of a posterior myelopathy with involvement of sensory and autonomic tracts and sparing of motor tracts. It is common to find associated abnormalities like cranial nerve and pupillary dysfunction. The onset is usually with paresthesias in girdle or band-like distribution around the trunk and/or the lower extremities that are episodic and of variable intensity. Pain is the most frequent complaint and typically of sudden onset, lancinating, stabbing, or lightning, and recurrent in clusters lasting minutes to hours. Visceral crisis refers to attacks of sudden pain lasting days to weeks,

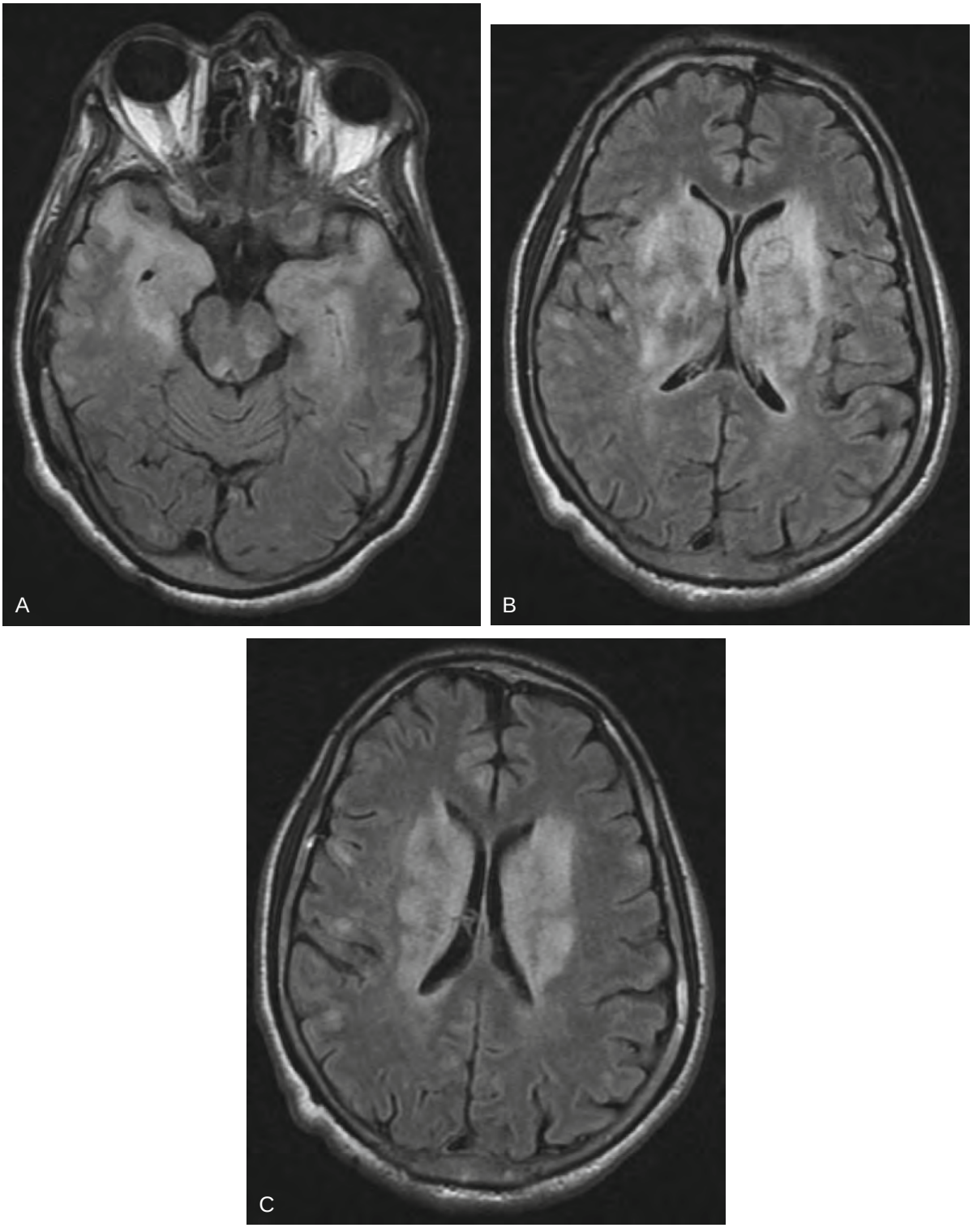

Fig. 12.2. Long TR (fluid-attenuated inversion recovery (FLAIR)) magnetic resonance imaging at the level of the temporal lobes (A), basal ganglia (B), and cerebrum (C) shows extensive signal changes involving both the gray and white matter in a patient with general paresis.

referred to the stomach (nausea and vomiting), bowels (diarrhea or constipation), larynx (hoarseness, stridor), bladder, or uterus (Stokes et al., 1944). On neurological examination, there may be patchy areas of increased sensitivity to pinprick, temperature, or touch and of delayed perception (referred to as Hitzig's zones) or areas of analgesia. Vibratory and position sense loss is frequent over the sacrum and lower extremities. Sensory ataxia with positive Romberg's sign is also frequent (Merritt et al., 1946). Reflexes are decreased or absent. The muscle tone is decreased, resulting in hyperextensible joints. The gait is typically broad-based, stamping, and worse in the dark. Repetitive trauma may result in Charcot's joints (Merritt et al., 1946) and malum perforans (Andrejevic and Jovic, 1970). Charcot's arthropathy of the spine can cause cauda equina syndrome from posterior nerve root compression (Ramani and Sengupta, 1973). Dysautonomia is frequent with orthostatic hypotension, impotence, bladder dysfunction (urinary retention, overflow incontinence), and bowel incontinence.

Syphilitic myelitis

Syphilitic myelitis is a rare inflammatory myelopathy of gradual onset, usually 20–25 years after primary syphilis (Merritt et al., 1946). It has been reported in HIV-infected patients (Berger, 1992). Manifestations include weakness, hyperreflexia, pain, paresthesias, loss of large-fiber sensory modalities in the lower extremities and sensory level in one-third of cases, and urinary retention. The spastic paraparesis or paraplegia is often asymmetric (Merritt et al., 1946; Fisher and Poser, 1977); it may present as transverse myelitis (Harrigan et al., 1984; Lowenstein et al., 1987). Rarely, it can result in amyotrophy with weakness and atrophy secondary to anterior spinal root involvement (Caponnetto et al., 1997). MRI with gadolinium shows heterogeneous enhancement in the superficial portion of the spinal cord (Nabatame et al., 1992). Some patients may develop irreversible paraplegia (Janier et al., 1985). Some authors used the terms Erb's syphilitic spastic paraplegia or syphilitic amyotrophy to describe syphilitic meningomyelitis of the lateral columns with none or mild sensory dysfunction (Boghen, 1972).

Gummatous neurosyphilis

Gummas are rubbery, circumscribed nodules of inflammatory tissue formed as a delayed-type hypersensitivity reaction to the presence of *T. pallidum* in tissues (Lukehart and Holmes, 1991). Gummas usually have central necrosis and increased vascularity. The inflammatory infiltrate consists of epithelioid and multinucleated giant cells and perivascular lymphocytes and plasma cells (Kaplan et al., 1981; Goulon et al., 1986; Berger, 1992). The granulomatous inflammation can be caseating (Inoue et al., 1995) or noncaseating (Goulon et al., 1986). All three meningeal layers may be affected (Stokes et al., 1944). Gummas may occur at any stage of syphilis, but the incidence peaks after 20–30 years of infection. They can occur anywhere in the body (Stokes et al., 1944; Merritt et al., 1946; Kulla et al., 1984). Gummatous neurosyphilis accounted for 0.2% of cases of untreated neurosyphilis in the pre-penicillin era (Merritt et al., 1946). It may be more frequent in patients co-infected with HIV (Brightbill et al., 1995). Cerebral gummas are believed to arise from the pia mater and have both leptomeningeal and dural components, including a dural tail (Berger, 1992; Brightbill et al., 1995; Inoue et al., 1995). Their size varies from microscopic to several centimeters (Merritt et al., 1946), and they can be single or multiple (Punt, 1983; Clavelou et al., 1993; Maurage et al., 1997) and miliary or plaque-like (Stokes et al., 1944). Enhancement may be peripheral, nodular, homogeneous, patchy, or ring-like (Roda et al., 1985; Berger, 1992; Tien et al., 1992; Brightbill et al., 1995; Inoue et al., 1995; Uemura et al., 1995; Pollock et al. 2007). Angiograms show a hypervascular blush surrounding an avascular (necrotic) center (Tsai et al., 1977).

Diagnosis

T. pallidum is difficult to cultivate *in vivo* or in artificial growth media. The only practical way in which syphilis can be diagnosed is to visualize the spirochetes by dark-field microscopy or immunofluorescence in the lesions of early syphilis, or by measuring specific antibodies in serum and/or CSF once the infection disseminates. Two categories of antibodies are searched for: (1) nontreponemal antibodies (reagin), directed against lipidated antigens that cross-react with treponemal antigens; and (2) treponemal antibodies, which are specific for antigens of *T. pallidum*.

Serum nontreponemal antibody tests

The rapid plasma reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) are the standard nontreponemal tests. The RPR measures macroscopic agglutination of cardiolipin-coated charcoal particles by unheated serum; it is sensitive, but not specific, and more useful for screening and to assess the adequacy of therapy. The VDRL measures microscopic agglutination of cardiolipin and lecithin-coated cholesterol particles by heat-inactivated serum into a slide. The RPR and VDRL perform similarly with sensitivity of 70% for the primary, 99% for secondary, and >90% for tertiary forms. False negatives can be common during the first trimester of pregnancy

(Tramont, 1995) and do occur in secondary syphilis due to the prozone phenomenon or in those with HIV infection (Schofer et al., 1996). In general, any strong acute bacterial or viral infection, or vaccination, can transiently (<6 months) falsely elevate nontreponemal serology (Tramont, 1995). Many causes of false-positive nontreponemal serologies have been reported, including systemic lupus erythematosus, rheumatoid arthritis, pregnancy (Salo et al., 1969), injection drug abuse, aging, hypergammaglobulinemia, multiple blood transfusions, chronic liver disease, malaria, leprosy, infectious mononucleosis, HIV infection (Malone et al., 1995), relapsing fever, yaws, pinta, leptospirosis, and rat bite fever; false-positive nontreponemal serologies rarely have titers >1:8 (Lukehart and Holmes, 1991). While the frequency of false positives is <2% when screening populations at risk for syphilis (Lukehart and Holmes, 1991), it can increase up to 11% when screening also includes HIV-infected patients (Terry et al., 1988). HIV-infected patients are also more likely to show increasing titers after adequate therapy (Brown et al., 1985; Hutchinson et al., 1991). In most cases, nontreponemal serology becomes negative with treatment, although a persistently low titer reactive serology is common after treatment of neurosyphilis of more than 1 year's duration.

The nontreponemal titer is highest during early infection and lowest in latent and tabetic syphilis (Stokes et al., 1944; Hahn et al., 1956). When the diagnosis of syphilis is in doubt, it is assumed that high titers are of greater diagnostic significance than low titers (Stokes et al., 1944). Titers tend to be higher in HIV-infected patients (Gourevitch et al., 1993; Malone et al., 1995). However, reagin titers in the blood do not necessarily correlate with disease severity. High titer of blood or CSF nontreponemal serology, with moderate to markedly increased CSF leukocytosis, is characteristic of parenchymatous neurosyphilis. Most positive nontreponemal serologies become nonreactive after successful treatment in 6 months to 2 years in early syphilis (Fiumara, 1980; Brown et al., 1985; Marra et al., 1996b) and by the fifth year in late syphilis (Fiumara, 1979). Persistently positive nontreponemal serologies at high titer after treatment are more frequent in patients infected with HIV (Rampalo et al., 1992; Rolfs et al., 1997; Yinnon et al., 1996).

Serum treponemal antibody tests

The fluorescent treponemal antibody absorption (FTA-ABS) is an indirect immunofluorescent antibody test that uses testis from infected rabbits as the antigen and a standard 1:5 dilution of heat-inactivated serum. Before testing, it is absorbed with "sorbent," which removes antibodies to commensal treponemes that could cause false-positive results. It is sensitive and specific for past or current *T. pallidum* infection and is needed to confirm any positive nontreponemal serological test before the diagnosis of syphilis can be made. The FTA-ABS is positive in 85% of patients with primary syphilis (Marra, 1990) and in nearly 100% of patients with secondary and tertiary syphilis (Swartz, 1990; Tramont, 1995). With few exceptions a negative serum FTA-ABS excludes the diagnosis of disseminated syphilis (Smith and Israel, 1967; Tramont, 1995). However, once positive, it can remain positive for life; the FTA-ABS reverts to negative more often in patients treated during early infection (Romanowski et al., 1991; Mashkilleyson et al., 1996). False-positive serum FTA-ABS occurs in a variety of diseases, including systemic lupus erythematosus (with a weak and/or beaded pattern), relapsing fever, Lyme disease (Magnarelli et al., 1987), yaws, pinta, leptospirosis, and rat bite fever (Tuffanelli et al., 1967).

Other treponemal tests specific for syphilis (past or present) are the *T. pallidum* hemagglutination assays TPHA and MHA-TP that examine agglutination of erythrocytes sensitized with *T. pallidum* antigens by "sorbent"-treated serum in wells of regular (TPHA) or microtiter (MHA-TP) plates. TPHA and MHA-TP are easier to perform than FTA-ABS and have similar sensitivity and specificity (Marra, 1990; Tramont, 1995). False-positive results occur with Epstein–Barr virus infection (Anderson et al., 1994). Other tests are the treponemal immobilization test (TPI), which has sensitivities of 50% in primary syphilis (Marra, 1990), 97% in secondary syphilis (Tramont, 1995), and 95% in late-treated syphilis (Tramont, 1995); it is the gold standard in syphilis serology and can be used to rule out a false-positive FTA-ABS. A serum treponemal immunoglobulin (Ig) M enzyme-linked immunosorbent assay (ELISA) showed a sensitivity of 93% and a specificity of 97% compared with the FTA-ABS (Muller, 1983). A *T. pallidum* sonicate-ELISA and a *T. phagedenis* Reiter filament-ELISA showed sensitivities similar to the TPHA and the FTA-ABS for all forms of syphilis (van Eijk et al., 1986). Western blotting can have very high sensitivity and specificity in early syphilis (Marangoni et al., 1999). When Western blot is used as the gold standard, the specificity and sensitivity of RPR, VDRL, and FTA-ABS are 62% and 92%, 37% and 90%, and 100% and 68%, respectively (Murphy et al., 1999).

Cerebrospinal fluid analysis

CSF examination is indispensable for diagnosis of neurosyphilis and to follow response to treatment. Routine CSF analysis includes cell count, protein and glucose concentrations, and nontreponemal antibody

tests (CSF VDRL). CSF abnormalities precede by months to years the onset of clinical neurosyphilis, but abnormal results do not necessarily indicate that the patient has neurosyphilis. The CSF opening pressure may be increased in acute syphilitic meningitis. The routine CSF analysis can be abnormal during early syphilis in 5–9% of seronegative and 13–23% of seropositive patients (Wile, 1921; Moore and Hopkins, 1936). Systematic examination of the CSF in 39 patients with untreated early syphilis showed that it was abnormal (defined as a positive CSF VDRL or elevated cells and/or protein) in 49% (Marra et al., 1995). Routine CSF analysis is abnormal in 20–78% of patients with secondary syphilis (Wile, 1921; Moore and Hopkins, 1936; Merritt, 1940; Stokes et al., 1944; Hahn and Clark, 1946), 25% with untreated late latent syphilis (Lukehart and Holmes, 1991), and 65% with late symptomatic neurosyphilis (Stokes et al., 1944). In acute syphilitic meningitis (Merritt and Moore, 1935) and active meningovascular syphilis, abnormal CSF is the rule (Zagnoli et al., 1988). The CSF usually normalizes after recommended treatment, but can remain abnormal in a small percentage of patients with early syphilis despite adequate treatment (Zielinski et al., 1977).

Routine CSF analysis can have false-positive and false-negative results. About one-third of patients with early syphilis have treponemes in the CSF despite normal routine CSF analysis (Chesney and Kemp, 1924; Stokes et al., 1944; Lukehart et al., 1988). About 4% of patients with clinical manifestations of neurosyphilis have normal CSF analysis (Tramont, 1995). Rarely, patients with progressive and serious neurosyphilis can have normal CSF (Stokes et al., 1944); this happens more often in cases of tabetic neurosyphilis with gastric crisis and/or Charcot's joints, isolated cranial neuropathies, cerebral gummas, vascular neurosyphilis, or syphilitic myelitis (Stokes et al., 1944). Another problem is the prevalence of CSF abnormalities unrelated to syphilis (false positives), found in 67% and 32% of patients with latent syphilis with or without HIV infection, respectively (Carey et al., 1995).

The CSF cell count is increased in 24% and 67% of patients with untreated early syphilis without or with HIV co-infection, respectively (Lukehart et al., 1988; Marra, 1990), and in 23% and 81% of patients with asymptomatic or symptomatic neurosyphilis, respectively (Hooshmand et al., 1972; Smikle et al., 1988). The median CSF cell count in active neurosyphilis is 24–50 cells/mm^3 (Stokes et al., 1944). Occasionally more than 1000 cells/mm^3 can occur, mainly in acute syphilitic meningitis (Merritt and Moore, 1935). The CSF cell count is higher in HIV-infected patients (Katz et al., 1993), but frequently it is not a result of neurosyphilis. Most cases of asymptomatic neurosyphilis have fewer than 100 cells/mm^3 (Merritt et al., 1946). The CSF cell count in paretic neurosyphilis varies from 8 to 100 cells/mm^3, mainly lymphocytes (Merritt et al., 1946). About one-quarter of cases of neurosyphilis with a negative CSF VDRL have elevated CSF white blood cell (WBC) counts (Smikle et al., 1988). Serial CSF analysis has shown that the cell count fluctuates over time (Stokes et al., 1944; Lukehart and Holmes, 1991). The cell count returns to normal 3–6 months after adequate treatment in most non-HIV-infected patients (Dattner et al., 1951; Marra et al., 1996b). However, in up to 10% of HIV-infected patients, it continues to be elevated 6–12 months after treatment (Nitrini and Spina-Franca, 1987a,b). The CSF cell count should be normal after 2–4 years in all adequately treated cases of neurosyphilis (Lukehart and Holmes, 1991).

CSF protein can be normal or elevated in neurosyphilis. In most cases of asymptomatic neurosyphilis, it is $<$100 mg/dl. CSF protein was elevated in 40% of patients with symptomatic neurosyphilis (Hooshmand et al., 1972) and in 78% of patients with syphilitic meningitis (range 46–200 mg/dl) (Merritt and Moore, 1935). The mean protein concentration is higher in HIV-infected patients (Katz et al., 1993), sometimes as high as 1 g/dl (Lanska et al., 1988). Elevated CSF protein decreases 3–6 months after adequate treatment (Dattner et al., 1951), but may take years to normalize. About 20% of patients with neurosyphilis with negative CSF VDRL have an elevated CSF protein (Smikle et al., 1988). In most cases of neurosyphilis, the concentration of glucose in the CSF is normal, except for some patients with acute syphilitic meningitis (Merritt and Moore, 1935).

The IgG index and/or CSF oligoclonal bands are elevated in about half of the patients with neurosyphilis (Losy and Wender, 1997). Increased IgG index was 70 times more common in symptomatic neurosyphilis than in asymptomatic latent syphilis (Hische et al., 1988). Treatment with high-dose penicillin results in normalization of the CSF IgG index in most cases. However, an elevated index may persist $\geq$12 months after treatment (Hens et al., 1990). Treatment usually increases the IgG index transiently in most patients (Hens et al., 1990).

Treponemal CSF antibodies

Neurosyphilis can be diagnosed by the demonstration of intrathecal antitreponemal antibodies using both nontreponemal (VDRL) and treponemal antigens. However, as in other CNS infections, a major difficulty is the frequent occurrence of blood contamination of the CSF after lumbar puncture. The CSF VDRL is the preferred CSF test in patients with suspected neurosyphilis

because it is less sensitive to blood contamination than the Wassermann test or the FTA-ABS. A false-positive CSF VDRL occurs only if sufficient blood is present as to be seen by the naked eye (Izzat et al., 1971; Davis and Sperry, 1979). The sensitivity of the CSF VDRL in symptomatic neurosyphilis is 27–90% (Hooshmand et al., 1972; Lee et al., 1983; Smikle et al., 1988; Stingl et al., 1990; MacLean and Luger, 1996). False negatives greater than 30% have been documented in modern series of neurosyphilis (Burke, 1972; Hooshmand et al., 1972; Hotson, 1981; Burke and Schaberg, 1985). The sensitivity is particularly low in patients with meningovascular syphilis (Stokes et al., 1944). False negatives also occur in paretic (Stokes et al., 1944; Ch'ien et al., 1970; Dawson-Butterworth and Heathcote, 1970) and gummatous forms (Maurage et al., 1997) and in ocular syphilis (Smith and Israel, 1967). Nontreponemal antibodies may be positive in CSF obtained from the cerebral ventricles at the time of surgery in patients with negative lumbar CSF (Stokes et al., 1944). The specificity of the CSF VDRL is high in healthy people, but decreases in the elderly and the sick (Delaney, 1976; Madiedo et al., 1980; Hart, 1986). Although the titer of the CSF VDRL usually decreases after treatment, it may not become negative for several years and is not necessarily an indication of active infection. A fourfold increase in CSF-VDRL is accepted as an indication of relapse that requires retreatment (Roberts and Emsley, 1995).

The CSF FTA-ABS is more sensitive than the CSF VDRL for the diagnosis of neurosyphilis (Kolar and Burkhart, 1977; Lee et al., 1983; Gendrel et al., 1992; Marra et al., 1995), but it is less specific due to higher susceptibility to blood contamination (Davis and Sperry, 1979) or to diffusion of serum immunoglobulin into the CSF (McGeeney et al., 1979). A negative CSF FTA-ABS rules out neurosyphilis in all stages except early syphilis (Jaffe et al., 1978; Lukehart et al., 1988; Davis and Schmitt, 1989). Clinicians can consider ordering CSF FTA-ABS to support the diagnosis of meningovascular syphilis in stroke patients with a negative CSF-VDRL (Aupy et al., 1982). False-positive CSF FTA-ABS is very rare (<1%) in the general population (Jaffe et al., 1978; Madiedo et al., 1980; Tramont, 1995). The CSF TPHA and the CSF MHA-TP are also highly sensitive and specific (close to 100%) for diagnosis of neurosyphilis (Jaffe et al., 1978; Lukehart et al., 1988).

The demonstration of intrathecal treponemal antibody production is highly suggestive of active neurosyphilis (Luger, 1981; Muller and Moskophidis, 1983; Lee et al., 1986; van Eijk et al., 1987). This can be done using indexes that compare the ratio of antitreponemal to total antibodies in CSF and serum. One such index is the ITpA, which divides the ratios of specific to total IgG in CSF and serum (Prange et al., 1983). A value of 1 (range 0.5–2) means there is no intrathecal antibody production. However, an ITpA index >2 (range 3–430) indicates neurosyphilis (Prange and Ritter, 1986). The IgG ITpA index has a sensitivity of 82% in symptomatic neurosyphilis (Prange et al., 1983; Prange and Ritter, 1986). The ITpA index normalizes with early treatment, but may remain abnormal if the treatment is delayed (Prange et al., 1983). Another index is the TPHA index, which divides the titers of TPHA minus IgG by the mg of total IgG in CSF and serum (Tramont, 1995). A value of 3 or more in patients with a normal blood–brain barrier (BBB) indicates intrathecal antibody production, with normal BBB defined by a serum-to-CSF albumin ratio >144. The TPHA index was positive in 12% of 40 HIV-infected persons with latent syphilis who had a negative CSF VDRL, but otherwise abnormal CSF suggestive of neurosyphilis (Tomberlin et al., 1994). The value of the TPHA index was >100 in all but one patient with active neurosyphilis and decreased to <100 after treatment (Luger, 1981). The sensitivity and specificity of the TPHA index for active neurosyphilis are ≥90 and 100%, respectively (Hagedorn, 1980; Luger et al., 2000).

CSF PCR

T. pallidum DNA can be detected in the CSF of patients with neurosyphilis by polymerase chain reaction (PCR) with a sensitivity of 30–71% (Hay et al., 1990; Noordhoek et al., 1991; Gordon et al., 1994; Moskophidis and Peters, 1996). However, there is a poor correlation between *T. pallidum* CSF PCR and other diagnostic tests for neurosyphilis (Chung et al., 1994). *T. pallidum* CSF PCR is more often positive in patients with untreated symptomatic neurosyphilis. In early syphilis, *T. pallidum* CSF PCR did not provide more information than conventional CSF analysis (Marra et al., 1996a,b). The sensitivity of the PCR is comparable to the rabbit infectivity test (Grimpel et al., 1991; Horowitz et al., 1994), estimated at about 100 treponemes/1 ml of CSF (Noordhoek et al., 1991).

Difficulties in the diagnosis of neurosyphilis

Several factors make the diagnosis of neurosyphilis difficult. The most important is the lack of a satisfactory gold standard for diagnosis. The one used most often is the CSF VDRL because it is specific, simple, and inexpensive, but it has a limited sensitivity. More sensitive tests, such as the CSF FTA-ABS, are very susceptible to blood contamination. Another common problem is the absence of clues as to the syphilitic origin of neurological complaints. Many patients with

neurosyphilis do not report a history of early syphilis, and non-CNS syphilitic lesions are rare in patients with symptomatic neurosyphilis (Stokes et al., 1944). Further complicating the diagnosis is the multiplicity of clinical manifestations of neurosyphilis and the frequent presence of unrelated symptoms (Burke and Schaberg, 1985). Unrelated CSF abnormalities are also frequently observed (Appleman et al., 1988; Holtom et al., 1992; Carey et al., 1995). In many cases of latent syphilis with abnormal CSF, it is uncertain whether the abnormal CSF is a result of neurosyphilis (Graman et al., 1987). Evaluating the response to antimicrobial therapy is also difficult because the serological response may be dissociated from the CSF response (Hahn et al., 1956). The HIV epidemic has further complicated the situation because HIV-infected patients often have erratic serological responses. Finally, widespread use of antimicrobial agents may result in a higher percentage of false-negative nontreponemal serologies (Burke and Schaberg, 1985) and with partially treated patients presenting with *formes frustes* of neurosyphilis (Hooshmand et al., 1972; Joyce-Clarke and Molteno, 1978).

Management of neurosyphilis

Prevention of progression to neurosyphilis

Treatment of early syphilis (1-year duration or less) with penicillin is highly effective in preventing the development of neurosyphilis (Fernando, 1965). Almost no evidence of treatment failure was found by CSF examination in 200 patients with early syphilis treated with 2.4–6 million units of penicillin aluminum monostearate or with benzathine penicillin given over 1–2 weeks (Hotson, 1981). The recommended treatment for early syphilis is 2.4 million units of benzathine penicillin G given intramuscularly (IM) in a single dose. Although prompt recognition and early treatment of syphilis with benzathine penicillin dramatically reduce the incidence of symptomatic neurosyphilis, treatment failures can occur (Tramont, 1976; Al-Samarray and Henderson, 1977; Moskovitz et al., 1982; Bayne et al., 1986; Jorgensen et al., 1986; Weismann and Jorgensen, 1986; van Eijk et al., 1987; Lukehart et al., 1988). In one study, 11% of infants born to mothers with syphilis adequately treated with penicillin had reactive serology and abnormal CSF (IgM FTA-ABS) (Jones and Harris, 1979). The presence of *T. pallidum* in the CSF before treatment does not predict treatment failure (Rolfs et al., 1997). There is no evidence of strains of *T. pallidum* resistant to penicillin. However, the possibility of reinfection should be explored when treatment failure is suspected.

Treatment of neurosyphilis

Progression to symptomatic neurosyphilis is rare in immunocompetent patients with asymptomatic neurosyphilis treated with low doses of nonintravenous penicillin. Therefore, patients with asymptomatic neurosyphilis can be treated with recommended schedules for early syphilis, except for patients who are co-infected with HIV (see below). Accordingly, it is not required to perform lumbar puncture to rule out asymptomatic neurosyphilis in immunocompetent patients with early syphilis. This may also be the case for patients with latent syphilis; when lumbar puncture was done in patients with latent syphilis and those with abnormal CSF were treated with high-dose intravenous (IV) penicillin as opposed to standard therapy for early syphilis, there were no differences in the outcome (Wiesel et al., 1985). However, for late latent syphilis or latent syphilis of unknown duration, the Centers for Disease Control and Prevention (CDC) recommends extension of the treatment with 3-weekly IM injections of 2.4 million units of benzathine penicillin G (total of 7.2 million units) (www.cdc.gov/std/treatment/2006/genital-ulcers.htm#neurosyph).

Patients with symptomatic neurosyphilis should be treated with high doses of IV penicillin as early as possible after onset of symptoms. However, in practice, the treatment is often delayed because most early signs and symptoms are subtle and nonspecific. The most appropriate dose, duration of therapy, and formulations of penicillin are controversial (Musher, 1988). Many early studies of treatment of neurosyphilis with penicillin were done before modern clinical trial methodology was developed and their interpretation is difficult. It appears that duration of therapy ($\geq$8 days) is more important for cure than peak serum concentrations (Kampmeier, 1981). For patients with symptomatic neurosyphilis, the minimum duration of treatment should be 10–14 days, and late forms may require longer treatments. In the pre-penicillin era, treatment was continued until the CSF became normal (Stokes et al., 1944). The minimal effective treponemicidal concentrations of penicillin in serum and CSF are 0.03 and 0.02 μg/ml, respectively (Idsoe et al., 1972). Benzathine penicillin at doses of 2.4 million units/day, or lower, does not consistently provide adequate treponemicidal concentrations in the CSF (Lowhagen et al., 1983; Centers for Disease Control and Prevention, 1988). Despite this, there is evidence that the majority of immunocompetent patients with symptomatic neurosyphilis treated with 2.4 million units of benzathine penicillin given in 2–3-weekly doses show clinical improvement (Short et al., 1966). However, reports of treatment failures advise against this approach (Short et al., 1966; Greene et al., 1980; Folk et al., 1983).

The CDC recommends treatment of symptomatic neurosyphilis with aqueous crystalline penicillin G IV 3–4 million units every 4 hours or by continuous infusion (18–24 million units per day) for 10–14 days (www.cdc.gov/std/treatment/2006/genital-ulcers.htm#neurosyph). For patients with late symptomatic neurosyphilis, some specialists follow the IV treatment by outpatient treatment with benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks. IV penicillin G reliably provides treponemicidal concentrations in the CSF (Mohr et al., 1976; Dunlop et al., 1981; Schoth and Wolters, 1987). A recommended alternative regimen to avoid hospitalization for IV antimicrobials is daily IM injection of 2.4 million units of aqueous procaine penicillin G and oral probenecid 500 mg every 6 hours for 10–14 days (www.cdc.gov/std/treatment/2006/genital-ulcers.htm#neurosyph). However, this regimen does not consistently provide treponemicidal concentrations in the CSF (Lowhagen et al., 1983; Goh et al., 1984; Centers for Disease Control and Prevention, 1988; van der Valk et al., 1988), and there are issues with decreased compliance (Crowe et al., 1997). Another alternative regimen is treatment with 3 grams of amoxicillin given orally twice a day plus 1 gram of probenecid daily for 14 days (Morrison et al., 1985), which reliably achieves treponemicidal concentrations of amoxicillin in the CSF (Faber et al., 1983; Morrison et al., 1985).

The response to treatment should be monitored by serial nontreponemal serology until the titer is negative, or fixed at low level, and by serial CSF examinations at 6-month intervals until the CSF WBC count normalizes. Serial CSF examinations may need to be done more often in HIV-infected patients (Tramont, 1995). Treatment of sexual partners and education about safe-sex practices are equally important. However, treatment failures can occur even after treatment with recommended schedules for neurosyphilis (Sowmini, 1971; Nitrini and Spina-Franca, 1987a; Noordhoek et al., 1991; Stockli, 1992; Trotta et al., 1996). Failure rates of up to 21% have been reported in some series after treatment of symptomatic neurosyphilis with high-dose IV penicillin G. When paretic neurosyphilis improves after treatment, the recovery is gradual over weeks to months (Dattner et al., 1951; Wilner and Brody, 1968). Juvenile paretic neurosyphilis may (Carruthers et al., 1967) or may not (Goeman et al., 1996) improve with penicillin therapy. Most treatment failures in neurosyphilis become apparent in the first 2 years after treatment. For such patients, treatment with larger doses of penicillin and/or for longer periods of time may be necessary.

In patients with confirmed allergy to penicillin, ceftriaxone can be used as an alternative agent for treatment of neurosyphilis. The recommended dose is 2 grams daily either IM or IV for 10–14 days (www.cdc.gov/std/treatment/2006/genital-ulcers.htm#neurosyph). One study showed that HIV-infected patients with early syphilis and asymptomatic neurosyphilis showed similar CSF responses to ceftriaxone and penicillin G (Marra et al., 2000). Ceftriaxone can be safely used in patients allergic to penicillin because the incidence of crossed allergic reactions between cephalosporins and penicillin is minimal (Anne and Reisman, 1995). Although ceftriaxone achieves high CSF concentrations, treatment was associated with a 23% failure rate in HIV-infected patients with latent syphilis or asymptomatic neurosyphilis (Dowell et al., 1992). For patients allergic to penicillin and cephalosporins, and if desensitization cannot be performed and if they are not pregnant or younger than 8 years old, tetracyclines are also an alternative. The recommended dose for tetracycline is 500 mg every 6 hours for 30 days and for doxycycline is 200 mg every 12 hours for 21 days (Yim et al., 1985); these doses result in sufficient CSF concentrations (1.3 μg/ml). However, neurosyphilis may not be prevented by early treatment with tetracyclines and, once established, may not respond to treatment (Folk et al., 1983). Erythromycin is not recommended for neurosyphilis because of unacceptably high rates of treatment failure (Goldmeier and Hay, 1993). However, some of the newer macrolide antimicrobial agents are effective for treatment of early syphilis and for prevention of neurosyphilis; of 100 patients with early syphilis treated with 500 mg of azithromycin daily for 10 days or 500 mg on alternate days for 11 days, none developed symptoms of neurosyphilis or other sites of visceral syphilis at 4-year follow-up, 90% had complete resolution of nontreponemal serology within 4 months, and 40% had negative FTA-ABS within 12 months (Mashkilleyson et al., 1996). However, *T. pallidum* strains resistant to macrolides are known to exist (Goldmeier and Hay, 1993). Chloramphenicol is another alternative for treatment of neurosyphilis in penicillin-allergic patients at a dose of 2 grams daily for 30 days (Romanowski et al., 1983; Nitrini et al., 1984; Tramont, 1995).

Prevention and treatment of neurosyphilis in patients co-infected with HIV

Several case reports suggest that conventional treatment of early syphilis with benzathine penicillin G IM may have reduced efficacy to prevent progression to symptomatic neurosyphilis in patients also infected with HIV (Berry et al., 1987; Johns et al., 1987; Lukehart et al., 1988; Spehn et al., 1988; Musher et al., 1990; Gonzalez-Clemente et al., 1991; Berger, 1992; Gordon et al., 1994). In one study, four of 12 HIV-infected patients developed neurosyphilis despite prior conventional

treatment of early syphilis (Lukehart et al., 1988). In another study, 18% of 56 HIV-infected patients treated with penicillin for early syphilis had serological and/or clinical relapse, seven despite treatment with high-dose penicillin (Malone et al., 1995). Half of the 10 patients relapsed multiple times and 60% of relapses occurred later than 1 year after completing treatment (Malone et al., 1995). Progression and serological relapses can occur in patients co-infected with HIV despite treatment of latent syphilis with ceftriaxone (Dowell et al., 1992). There are also reports of HIV-infected patients who failed treatment with high-dose penicillin for asymptomatic (Malone et al., 1995) and symptomatic (Spehn et al., 1988; Gordon et al., 1994) neurosyphilis. However, since the resolution of all serum and CSF abnormalities is slower in patients infected with HIV (Marra et al., 1996b), this may result in overdiagnosis of treatment failures.

The Jarisch–Herxheimer reaction

The Jarisch–Herxheimer reaction is the abrupt onset of fever, chills, myalgia, headache, tachycardia, hyperventilation, flushing, and mild hypotension 1–2 hours after treatment of a spirochetal infection with penicillin or other antimicrobial agents (Zifko et al., 1994). It is self-limited, peaks at about 7 hours, and lasts for 12–24 hours. It is seen in 70–90% of cases of secondary syphilis and in 10–25% of all cases of syphilis combined (Podesta et al., 1967). The onset is delayed in neurosyphilis, with fever peaking 12–14 hours after treatment (Lukehart and Holmes, 1991). Treatment with anti-tumor necrosis factor (TNF) monoclonal antibodies prevented the Jarisch–Herxheimer reaction in 50% of patients with the related spirochetal disease louse-borne relapsing fever (Fekade et al., 1996) and may be effective in patients with syphilis. In rare cases, the Jarisch–Herxheimer reaction may result in irreversible organ damage (Lukehart and Holmes, 1991). It may be serious in some forms of syphilis, including paretic neurosyphilis, syphilis in pregnancy, and when sites where local inflammation can cause serious functional compromise are affected, such as the eyes, inner ear, and cranial nerves (Brown, 1976).

LYME NEUROBORRELIOSIS

Epidemiology

Lyme borreliosis is endemic throughout North America, Europe, and Asia. Exposure to areas where *Ixodes* ticks are feeding is the single most important risk factor and should be given careful attention when considering the diagnosis. *Ixodes* ticks have a three-host life cycle that spans 2 years: larvae, nymph, and adult. Larval ticks ingest spirochetes from infected reservoir hosts, including small rodents, birds, and reptiles. When larvae ingest spirochetes, they multiply in the tick until the nymph molts (Piesman et al., 1990). At the time that questing nymphs are likely to contact their potential victim, the spirochetes are restricted to the midgut. However, when feeding begins, a pronounced multiplication of spirochetes takes place, in which spirochete numbers increase 300-fold (De Silva and Fikrig, 1995). As spirochetes in the midgut begin to multiply, most cease expression of outer-surface protein A (OspA) and begin expressing OspC, which is essential for the transmission of *Borrelia burgdorferi* to the mammalian host (Tilly et al., 2006, 2007). Although adult ticks feed mainly on deer, they can also transmit infection to humans (Schwan and Piesman, 2002). The seasonal pattern of tick activity, with active feeding and molting beginning in the spring, determines the seasonal pattern of Lyme borreliosis; symptoms typically begin in late spring or summer. Because *Ixodes* ticks prefer the brushy understory of forests or their margins, the illness is more common in individuals with exposure to such areas.

Lyme borreliosis in North America

Lyme borreliosis occurs in both the USA and Canada. In the USA, it is now the most common vector-borne illness. For the period 2003–2005 there were 64 382 Lyme borreliosis cases reported to the CDC, 93% of which occurred in 10 states: Connecticut, Delaware, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin (Centers for Disease Control and Prevention, 2007b) (Fig. 12.3). This corresponds to an average annual incidence for the period 2002–2005 of 29.2/100 000. Although New York reported the largest number of cases (5565 in 2005), the two states with the highest incidence in 2005 were Connecticut (51/100 000) and Delaware (76.6/100 000) (Centers for Disease Control and Prevention, 2007a). Patients were most likely to have disease onset in May (7%), June (25%), July (29%), or August (13%). The median age was 41 years; patient age followed a bimodal distribution (Centers for Disease Control and Prevention, 2007a). *Ixodes scapularis*, the blacklegged tick, is the usual vector in the North-east and Mid-west. It is found throughout the eastern USA, in south-central states, and in southern Ontario and Manitoba, Canada. The percentage of ticks harboring spirochetes may be as high as 79% in some areas (Johnson et al., 1984). Domestic animals are also infected, and Lyme borreliosis has been reported in dogs, cattle, and horses. Both deer and small rodents are important in maintaining disease transmission; Lyme borreliosis is most common in forested and

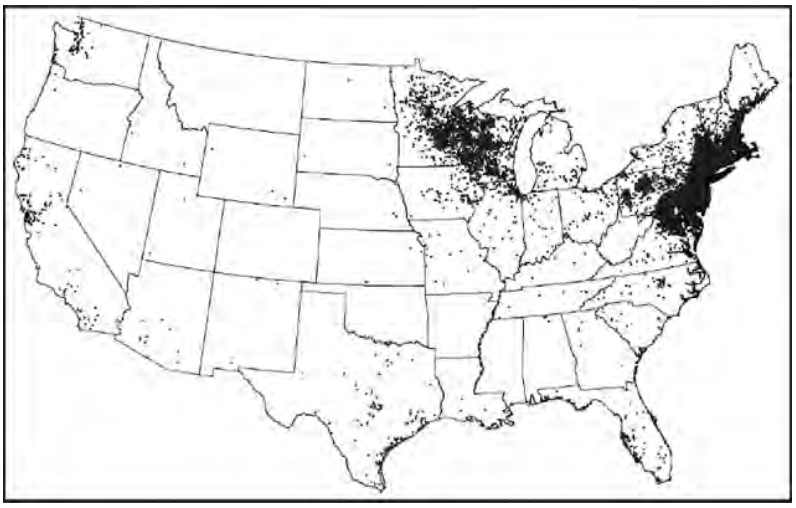

Fig. 12.3. During 2003–2005, the Centers for Disease Control and Prevention (CDC) received reports of 64 382 new cases of Lyme disease from 46 states and the District of Columbia (Centers for Disease Control and Prevention, 2007a). The figure shows the number of newly reported cases by county with one dot placed randomly within the county of patient residence for each reported case.

suburban areas where both are present in large numbers. Both deer and mice are readily infected after being bitten by infected ticks, but do not get the disease. Mice, in particular, remain highly infectious to larval ticks for most of their life span, and, in some areas, almost 90% of mice are infected (Anderson, 1988). Deer, on the other hand, probably serve no reservoir function for natural infection, but, as the preferred host for adult ticks, they are critical for the tick's reproductive success. *Ixodes pacificus*, the western blacklegged tick, is the usual vector on the Pacific Coast (Burgdorfer et al., 1985), and is found along the seaboard from British Columbia to Mexico and on the western slopes of the Sierra Nevada and Cascade Mountains and in Idaho, Nevada, and Utah. Like *I. scapularis*, *I. pacificus* is a three-host tick whose larvae and nymphs feed on a variety of small rodents, lizards, and birds while the adults feed on dogs, foxes, cattle, deer, and humans. In California, where the tick is most abundant, all three stages are active throughout the year. Nymphs of *I. pacificus* rarely attack humans, and fewer than 3% of *I. pacificus* ticks harbor spirochetes in most of the endemic area. Therefore, the frequency of Lyme borreliosis is much lower in the west.

Lyme borreliosis in Europe and Asia

Borrelia burgdorferi infection is widespread and very common throughout Europe and parts of Asia (Santino et al., 1997). *Ixodes ricinus*, the castor bean or sheep tick, is the usual vector (Ackermann et al., 1985; Schmid, 1985). *I. ricinus* favors the brushy edges of forests and clearings with high grass. Nymphs feed on a variety of lizards, ground-feeding birds, and small mammals, and the adults feed on larger wild and domestic animals. Rodents are the most important reservoir. Infection rates for *I. ricinus* are intermediate between *I. scapularis* and *I. pacificus*, ranging from 5% to 43% (Schmid, 1985). *I. ricinus* may serve as a reservoir for *B. burgdorferi* because of transovarial transmission (Krampitz, 1986). However, filial infection rates generally do not exceed 3% (Schmid, 1985). Lyme borreliosis is also endemic in the southern part of the forest zone of Asiatic Russia, in the forested north-eastern regions of China (Heilongjiang and Jilin provinces and widely scattered foci elsewhere), and in Japan (mainly Hokkaido and other eastern parts) (Carlberg and Naito, 1991). The vector in Asia is the taiga tick, *Ixodes persulcatus*. This tick is found in a broad band from the Baltic coast of Germany in the east, where its range overlaps with that of *I. ricinus*, across Eastern Europe and through Asia to Japan. It is found most often in small-leafed deciduous forests, where it feeds on a variety of small mammals and birds as a nymph and attacks cattle, wild ungulates, lagomorphs, and hedgehogs as an adult (Burgdorfer, 1989). All stages feed most actively in late spring and summer. Adult *I. persulcatus* usually transmit the infection to humans (Ai et al., 1990).

Etiology

Lyme borreliosis is caused by infection with different genospecies of *B. burgdorferi*, a slender and irregularly coiled spirochete. Like other spirochetes, it stains

with Giemsa and can be demonstrated in tissues by silver impregnation techniques or immunohistochemistry (Cadavid et al., 2000). All *B. burgdorferi* isolates were originally thought to belong to a single species of *Borrelia* on the basis of DNA hybridization experiments (Schmid et al., 1984). However, analysis of increasing numbers of isolates has led to the division of pathogenic *B. burgdorferi sensu lato* (*B. burgdorferi* complex) into three species: *B. burgdorferi sensu stricto*, *B. garinii*, and *B. afzelii* (Baranton et al., 1992). *B. burgdorferi sensu stricto* was first isolated in North America, where it is the only species of the *B. burgdorferi* complex known to cause disease. In contrast, all three genospecies are found in Europe. Although all three pathogenic genospecies have been isolated or detected by PCR in skin, CSF, and synovial fluid (Wilske et al., 1998), they tend to cause disparate illness patterns; among isolates from European patients, *B. garinii* predominates in Lyme neuroborreliosis whereas almost all isolates from skin lesions are *B. afzelii* (Dressler et al., 1994). In fact, *B. afzelii* is the only known cause of acrodermatitis chronic atrophicans and lymphocytoma benigna cutis, two characteristic dermatological complications of Lyme borreliosis. On the other hand, although *B. burgdorferi sensu stricto* also causes Lyme neuroborreliosis, it appears to be more arthritogenic (Centers for Disease Control and Prevention, 2007a).

All members of the *B. burgdorferi* complex share a number of protein components. These include the 60-kDa heat shock protein that is strongly immunogenic and cross-reactive, with an equivalent antigen from a wide range of bacteria and a 41-kDa flagellar antigen that is similar to the flagellar antigens of other spirochetes. Other highly conserved and immunogenic proteins are the 83-kDa protoplasmic antigen and the 39-kDa family of basic membrane proteins. The three pathogenic genospecies vary in several abundant outer-membrane lipoproteins that are unique to the complex: 31–32-kDa OspA, 33–36-kDa OspB, and 21–22-kDa OspC (Bergstrom et al., 1989; Wilske et al., 1993). The complete genome of the *B. burgdorferi* type strain B31 was sequenced in 1997 (Fraser et al., 1997). It showed a linear chromosome of 910 725 basepairs and 21 linear and circular extrachromosomal DNA elements with a combined size of 610 694 basepairs, the largest number known for any bacterium (Casjens et al., 2000); the total genome size is 1 521 419 basepairs.

Pathogenesis and pathophysiology

Infection

B. burgdorferi first proliferates locally in the skin at the site of the tick bite; dissemination through the skin results in the characteristic skin lesion, erythema migrans (EM) (Duray and Steere, 1988). Within days to weeks, the organism spreads throughout the body; *B. burgdorferi* has been isolated from the bloodstream as early as 4 days after a tick bite and 2 days after the appearance of EM (Benach et al., 1983; Berger et al., 1994). Early during the illness, spirochetes have been demonstrated histologically in skin, bone marrow, spleen, lymph nodes, liver, and testis. Spirochetes likely enter the CNS during early infection; *B. burgdorferi* DNA (Luft et al., 1992) or proteins (Coyle et al., 1993) have been found in the CSF of patients with early disseminated disease, and the organism has been recovered from CSF as early as 18 days after a tick bite (Allal et al., 1986). During hematogenous dissemination, *B. burgdorferi* can cross the placenta; both congenital infection and fetal demise have been reported, and spirochetes can be recovered from, or demonstrated histologically in, sparsely inflamed fetal tissues including the liver, heart, adrenal glands, kidneys, meninges, subarachnoid space, and brain (Schlesinger et al., 1985).

B. burgdorferi preferentially localizes in certain tissues 1–2 months after dissemination, particularly the nervous system, skin, heart, and joints (Duray and Steere, 1988; de Koning et al., 1989). It has also been identified in other tissues such as skeletal muscle (Reimers et al., 1993) and the eyes (Preac-Mursic et al., 1993). Arthritis and neuroborreliosis usually begin weeks to months after illness onset (Nocton et al., 1994). In contrast, acrodermatitis chronica atrophicans usually becomes apparent only years after the initial infection (Asbrink, 1985). Although *B. burgdorferi* has not been cultured from the nervous system of patients with late Lyme neuroborreliosis, improvement after antimicrobial therapy is consistent with the presence of persistent chronic infection. The finding of spirochetes in human brain (Shadick et al., 1994) and CSF months after disease onset (Wokke et al., 1987; Lebech and Hansen, 1992) is further evidence of the ability of *B. burgdorferi* to persist in the CNS.

Inflammation

Humans respond to *B. burgdorferi* infection with a vigorous cellular and humoral immune response characterized by proliferation of lymphocytes and plasma cells, production of increased serum concentrations of antibody, appearance of circulating immune complexes, and hyperplasia of the reticuloendothelial system (lymph nodes, spleen, and bone marrow) (Duray and Steere, 1986, 1988; Duray, 1987, 1989). The T-cell proliferative response occurs first (Dattwyler et al., 1989); once established, it is long-lasting and not related to either disease activity or antimicrobial therapy. The total number of

lymphocytes and T cells is normal but the number of cells in specific T-cell subsets is not. The natural killer cytotoxicity of peripheral blood lymphocytes is subnormal in early disease (Golightly et al., 1988). Suppressor cell activity is increased early in the illness but becomes depressed later, which likely explains the initial delay in the appearance of specific antibody and the eventual vigorous humoral response of established infection (Sigal et al., 1984). Specific antibody is usually not detectable at the onset of EM. The IgM response peaks 3–6 weeks after onset of EM and then declines, although titers may remain high during late disease (Craft et al., 1986). The titer of specific IgM correlates well with total serum concentrations of IgM. At the same time, circulating immune complexes containing IgM, IgG, and complement often appear. Their presence is predictive of subsequent joint or nervous system disease and their concentrations often parallel disease activity (Steere et al., 1977). The appearance of specific IgG antibody is delayed, but measurable amounts are nearly always present during early neurological or joint disease. Once present, specific IgG antibody can persist in high titer for years, even during clinical remission (Craft et al., 1986). Both the early IgM response and the initial IgG response are directed against the 41-kDa flagellar antigen, but the IgG response expands as the disease progresses (Craft et al., 1986). This expanding immune response is not seen in patients with early disease who are treated successfully with antimicrobial agents, and the expansion ceases in patients once adequate treatment is given. Specific antibody does not prevent reinfection.

Pathology

Little is known about the pathology of Lyme neuroborreliosis, particularly in the CNS. The few autopsy and biopsy specimens analyzed have shown lymphocyte and plasma cell infiltration in the meninges and around small vessels in the adjacent gray matter of the brain and spinal cord, accompanied by endothelial swelling and sometimes true vasculitis (Meier and Grehl, 1988; Meurers et al., 1990). Astrogliosis has been reported (Kobayashi et al., 1997). In fatal cases of late Lyme neuroborreliosis from Europe, obliterative inflammatory vasculopathy without vessel wall necrosis, resulting in infarcts in the brainstem with spirochetes in the meninges and around subependymal vessels, has been reported (Kuntzer et al., 1991; Shadick et al., 1994). Examination of the peripheral nervous system has shown perivascular mononuclear cell infiltrates in the nerve roots and dorsal root ganglia (Kohlhepp et al., 1987; Meurers et al., 1990). A similar histological appearance is observed in sural nerves from patients with meningopolyradiculoneuritis, distal axonopathy of late Lyme borreliosis, and the neuropathy that accompanies acrodermatitis chronica atrophicans (ACA) (Halperin et al., 1987). Typical changes include axonal degeneration, loss of large myelinated fibers, perivasculitis with occasional vessel wall infiltration and luminal thrombosis, and pericapillary plasma cell infiltrates in the perineurium and endoneurium. Aggregates of lymphocytes can infiltrate autonomic ganglia and their afferent and efferent rootlets (Duray and Steere, 1988). Interstitial and focal nodular myositis can also occur (Reimers et al., 1989, 1993).

Disease

The mechanisms by which *B. burgdorferi* cause disease are incompletely understood. In most cases, the clinical manifestations are the result of inflammatory response to the local infection. However, *B. burgdorferi* is found in low numbers in blood and tissues, suggesting that some amplification mechanisms are at play. These likely include induction of cytokines and chemokines, shedding of lipoprotein-rich outer-membrane blebs, tissue deposition of immunoglobulin alone or as immune complexes with secondary complement activation, and perhaps autoimmune activation via cross-reactive epitopes between spirochetal and host proteins. Chronic Lyme arthritis unresponsive to antibiotics has been associated with an increased frequency of human leukocyte antigen (HLA) DR4 or, secondarily, HLA DR2 in combination with antibody reactivity to OspA and OspB.

B. burgdorferi lipoproteins are chemotactic for neutrophils (Szczepanski and Benach, 1991) and potent stimulants for the release of cytokines and chemokines via Toll-like receptor 1 (TLR1) (Alexopoulou et al., 2002) and 2 (TLR2) (Hirschfeld et al., 1999). Macrophages release interleukin-1 (IL-1), IL-6, IL-10, and TNF after exposure to *B. burgdorferi* lipoproteins (Radolf et al., 1995). IL-1 may mediate many of the general features of Lyme borreliosis, including fever, fatigue, anorexia, synthesis of acute-phase reactants, and leukocytosis. Within joints, IL-1 may explain the release of collagenase, proteases, prostaglandin E_2, and plasminogen activator from synovial cells and chondrocytes. IL-1 is chemotactic for neutrophils, stimulates antibody secretion, and stimulates T-cell production of IL-2. IL-6 promotes B-cell differentiation, stimulates B cells to release immunoglobulin, is pyrogenic, and stimulates synthesis of acute-phase reactants. Serum and CSF concentrations of IL-6 have been shown to correlate with disease activity in Lyme neuroborreliosis (Weller et al., 1991). TNF induces fever, activates neutrophils, stimulates prostaglandin synthesis, causes eukaryotic cell apoptosis, and promotes resorption of cartilage.

Within the CNS, both the spirochete and the host's reaction to the infection are important for pathogenesis.

Meningitis results from invasion of the CSF and meninges by *B. burgdorferi*; the organism is cultured from CSF and antimicrobials shorten the course (Steere et al., 1983). The evidence that *B. burgdorferi* infects the CNS parenchyma is less convincing (Duray and Steere, 1988; Duray, 1989). No late manifestations of chronic progressive Lyme neuroborreliosis comparable to neurosyphilis occur following untreated acute Lyme neuroborreliosis (Kruger et al., 1989). Vasculopathy via damage of vessel walls directly by *B. burgdorferi* or indirectly via deposition of immune complexes may explain some of the tissue injury both centrally and peripherally (Meier and Grehl, 1988). There is some evidence that Lyme borreliosis may cause CNS demyelination: computed tomography (CT) and MR images from some patients show white-matter disease (Pachner et al., 1989; Tarasow et al., 2001), antibodies to myelin and myelin basic protein have been found in serum and CSF of some patients (Baig et al., 1989), and CSF T cells reactive to myelin basic protein, peripheral myelin, and galactocerebrosides have been found in others (Martin et al., 1988). However, this has not been confirmed in experimental animals (Bai et al., 2004). Demyelination may also occur in the periphery (Corral et al., 1995). Autoimmunity has been suggested by the finding that IgM anti-*B. burgdorferi* antibodies cross-react with central neuronal and peripheral axonal antigens (Sigal and Tatum, 1988; Aberer et al., 1989). Axonal injury has been shown in the periphery by electrophysiology (Halperin et al., 1990; Logigian and Steere, 1992).

The marked heterogeneity in outer-membrane proteins may explain the phenotypic complexity of Lyme borreliosis through differential effects on spirochete–host cell interactions. In vertebrate hosts, *B. burgdorferi* has a predilection for collagenous tissues (Barthold et al., 1991; Cadavid et al., 2000). Binding to several eukaryotic cells has been documented, including epithelial, endothelial, lymphocytic, and neuroglial. There is also evidence of specific adhesion to several extracellular matrix proteins like decorin and fibronectin. *B. burgdorferi* recognizes the widely expressed integrins alpha(v)beta3 and alpha5beta1, the vitronectin and fibronectin receptors, respectively. Variation in outer-surface proteins could be the mechanism underlying variable tissue tropism in spirochetes (Cadavid et al., 1994; Zhang et al., 1997).

Lyme borreliosis

General features

Lyme borreliosis begins in the skin at the site of an infected tick bite with a characteristic rash referred to as EM (Steere, 2001). From the skin, there can be dissemination to multiple organs, most often skin, heart, central and peripheral nervous systems, and joints. For the period 2003–2005 in the USA, of the 32 095 new cases of Lyme borreliosis reported to the CDC that had clinical records available, 70% had EM, 30% arthritis, 8% facial palsy, 3% radiculitis, 2% meningitis, and 1% heart block (Centers for Disease Control and Prevention, 2007a). Early localized disease, if untreated, is often followed within days to weeks by disseminated disease. This, in turn, may be followed months to years later by late disseminated disease. However, there is little pathophysiological evidence to support the traditional differentiation of the complications of Lyme borreliosis as early or late (Wormser, 2006; Wormser et al., 2006). Asymptomatic infection appears to be very common in high-risk populations in endemic areas, including forestry workers (Zhioua et al., 1997), hunters (Nohlmans et al., 1991), and school-aged children (Feder et al., 1995).

Neurological involvement in Lyme borreliosis, known as Lyme neuroborreliosis, is reported in 5–20% of North American cases (Gerber et al., 1996) and in a higher percentage of European patients. Lyme neuroborreliosis can occur without antecedent EM and can be the first manifestation of the disease (Reik et al., 1986). It can be seen early on even when EM is still present (Luft et al., 1992; Kuiper et al., 1994). Neurological signs and symptoms most often develop weeks to months after the beginning of infection. None of the neurological complications of Lyme neuroborreliosis are uniquely early or uniquely late, but all are more likely to occur in the first few months of infection (Halperin, unpublished paper). About two-thirds of cases have concomitant systemic symptoms. The most common manifestations of Lyme neuroborreliosis are cranial neuropathies (especially of the seventh cranial nerve), lymphocytic meningitis, radiculitis, and peripheral neuropathy. They are often present in combination, a condition referred to in Europe as meningopolyradiculoneuritis or Bannwarth's syndrome (Bannwarth, 1941, 1944). Less common manifestations of neurological involvement are myositis, pseudotumor cerebri in children (Belman et al., 1993; Hartel et al., 2002), encephalopathy, and encephalomyelitis (Reik et al., 1979; Steere et al., 1983; Pachner and Steere, 1985; Pachner et al., 1989; Halperin, 1991). Rare cases of sensorineural hearing loss, vertigo, and cerebellitis are occasionally reported.

Cranial neuropathies

About 60% of patients with early Lyme neuroborreliosis have cranial neuropathies. Many cases are not isolated, but are accompanied by CSF pleocytosis ($\leq$80%) or radiculoneuritis (45%). Cranial neuritis usually begins about 3 weeks after onset of EM (Clark et al., 1985). Among all of the manifestations of cranial neuropathy, facial palsy is by far the most common, accounting for

80–90% of cranial nerve palsies and developing in 10% of all patients in one series of almost 1000 cases (Clark et al., 1985; Pachner and Steere, 1985). In fact, unilateral or bilateral facial palsy is the most common neurological complication of Lyme borreliosis. The facial weakness is rapid in onset, often evolving over 1–2 days, and frequently accompanied by slight ipsilateral facial numbness or tingling or ipsilateral ear or jaw pain. The weakness often develops on the same side as an earlier facial EM. Taste is commonly spared, suggesting that the point of involvement is distal to the chorda tympani. Facial palsy is bilateral in about 35% of cases; the two sides are affected asynchronously in most cases, usually within a few days to 3 weeks of each other. Paralysis is total in up to 60% of cases, yet the outcome is favorable in most; complete recovery in 1–2 months is the rule, although recovery may be incomplete in 20% or more patients (Angerer et al., 1993). Because isolated facial palsy can occur without preceding EM, it can be confused with idiopathic Bell's palsy. Indeed, Lyme borreliosis so frequently affects the seventh cranial nerve, it has been identified as the cause in 20–40% of unselected cases of facial palsy in highly endemic areas. During summer months, the percentage becomes even higher, particularly in children, where it may reach 70% (Olsson et al., 1988). Clues to the diagnosis include summer onset, tick exposure, bilateral involvement, and CSF lymphocytosis. MRI may show enhancement of the dura mater and of the seventh and other cranial nerves (Vanzieleghem et al., 1998).

Other cranial nerves may also be involved individually or in combination (Reik et al., 1979; Hansen and Lebech, 1992); visual symptoms are probably the most common. Reported optic nerve abnormalities include papilledema, optic neuritis and perineuritis, and ischemic optic neuropathy (Jacobson et al., 1991). Extraocular muscle weakness and diplopia are usually secondary to abducens nerve palsy, but involvement of the third and fourth cranial nerves also occurs. Other reported cranial nerve deficits include facial sensory loss, vertigo, hearing loss, and, rarely, dysfunction of lower cranial nerves. As with facial weakness, recovery is likely within 2 months, although it may be incomplete. Permanent visual loss, hearing loss, and Argyll Robertson pupils have been reported (Koudstaal et al., 1987).

Meningitis

Meningitis is one of the most common neurological abnormalities in Lyme borreliosis, and may be the first manifestation of the illness (Pachner and Steere, 1985; Pachner, 1995). Meningitis usually follows EM by 2–10 weeks, although only about 40% of patients recall EM. The reported frequency of meningeal symptoms has been quite variable, ranging from 30% to over 90%, depending on the method of ascertainment and country of origin. Children are more likely to be symptomatic than adults (Christen, 1996). Headache is the single most common symptom, affecting 30–90% of patients with CSF inflammation, and usually frontal or occipital, ranging from mild to severe. Neck stiffness is less common, affecting only 10–20% of those with CSF pleocytosis, and, when present, is found only on extreme flexion. Kernig's and Brudzinski's signs are infrequent. Other meningeal symptoms such as photophobia, nausea, and vomiting are intermediate in frequency between headache and neck stiffness. Papilledema has been reported but it is uncommon (Hansen et al., 1987; Hansen and Lebech, 1992). Accompanying systemic symptoms are present in up to two-thirds of cases and include malaise and fatigue (40%), myalgias (30%), fever (30%), arthralgias (20%), and weight loss. Fever is usually low-grade (37.5–38.5°C), but occasionally can be higher. The symptoms usually begin acutely and can last, in untreated cases, from a month to a year or more, often lasting 1–2 months before resolving gradually over weeks. Untreated patients may experience recurrent attacks of meningeal symptoms lasting weeks and alternating with similar several-week periods of milder symptoms. Most patients with symptomatic Lyme meningitis have other manifestations of Lyme neuroborreliosis, particularly facial palsy. When Lyme disease presents as isolated meningitis, it has to be differentiated from other causes of aseptic meningitis. Prospective studies in Germany implicated Lyme borreliosis in 12–40% of cases of isolated aseptic meningitis (Christen et al., 1993). Compared with viral meningitis, patients with Lyme meningitis are less likely to be febrile, but more likely to have been sick for a longer duration of time: median >7 days compared with 2 days for viral meningitis (Shah et al., 2005). Over 90% of children with Lyme meningitis have one or more of the following: EM, papilledema, and cranial nerve palsy (Shah et al., 2005). MRI may show gadolinium enhancement of the leptomeninges and CSF (Demaerel et al., 1994; Good and Jager, 2000).

Several abnormalities are found in the CSF in patients with Lyme meningitis (Wilske et al., 1991; Pachner, 1995; Christen, 1996; Kaiser, 1998). The CSF lumbar pressure is usually normal but may be increased (up to >50 cmH_2O). Expected changes in its contents include a pleocytosis of usually 100–200 cells/mm^3 (up to 4000/mm^3), mostly lymphocytic (>90% lymphocytes in 75% of cases), although plasma cells are also common (average 9%) (Hornig et al., 1984; Maida et al., 1986; Razavi-Encha et al., 1987; Kraft et al., 1989). CSF neutrophils are typically <10% and much lower than

in patients with viral meningitis (Shah et al., 2005). Occasionally, cytology shows prominent immunoblasts and frequent mitoses suggestive of lymphoreticular malignancy, but the cells are polyclonal in origin (Kielich et al., 2000). The CSF protein is usually increased to about 100–300 mg/dl but it is higher (up to 1300 mg/dl) in cases of longer duration. Increases in CSF IgG (90%), IgM (90%), and IgA (75%) and the presence of oligoclonal bands of IgG and specific anti-*B. burgdorferi* antibodies (75–100%) are common, particularly in cases of more then 3 weeks' duration. The CSF glucose is most often normal, but it can be low in cases of longer duration, and values as low as 12 mg/dl have been reported. The CSF abnormalities eventually subside even without treatment. Cell counts peak 3–8 weeks after onset of meningeal symptoms and may take several months to return to normal. The CSF protein falls even more slowly; it may remain elevated after 5–6 months, but is usually normal thereafter. Immunoglobulin abnormalities and specific antibody, on the other hand, can persist for years without evidence of further disease activity (Kruger et al., 1989).

Radiculitis

The symptoms of radiculitis are pain, paresthesias, or hyperesthesias on the trunk or proximal limbs in a dermatomal distribution that typically start 2–4 weeks after EM and may persist for months before resolving spontaneously (Reik et al., 1979; Hansen and Lebech, 1992). They are reported in Lyme neuroborreliosis more often in Europe (78%) than in North America (36%) (Halperin et al., 1990; Deltombe et al., 1996; Halperin, unpublished paper). Unlike adults, painful radiculoneuritis is rare in children; it was diagnosed in only 4% of 169 German children with neuroborreliosis and in none of 71 children from North America (Christen, 1996; Belman et al., 1997). Accompanying meningitis and cranial neuropathy are common and there are almost always CSF abnormalities (≥90%). During this time, the pain may remain localized to the original area, spread to involve additional areas, or move completely to new areas. It ranges from mild and migratory to severe and immobilizing and is described as drawing, stabbing, cutting, burning, or boring in quality. Associated nonradicular back pain under the scapulae or over the spine is common. Within days to weeks, limb weakness appears in about 75% of patients. The weakness can be focal or multifocal, typically asymmetric, and often most marked in the vicinity of the initiating pain. The onset is gradual and may progress over days to weeks. Nerve roots, plexi, and individual nerves may all be involved. A variety of clinical patterns may develop, including motor radiculitis in the extremities, lumbar or brachial plexitis, and mononeuritis simplex (Avanzi et al., 1998) or multiplex (Pachner and Steere, 1985). Widespread depression of deep tendon reflexes may be present. Several cases of the Guillain–Barré syndrome have been reported (Shapiro, 1998), as has paralysis of the diaphragm and the abdominal muscles (Mormont et al., 2001). Weakness may progress quickly to atrophy (Pachner and Steere, 1985). The outcome is favorable in most cases, with the strength usually returning to normal within 2 months. Accompanying meningitis and cranial neuropathy are common.

Actual sensory loss, as opposed to sensory symptoms, is less common than motor weakness. Sensory loss occurs alone in only about 5% of cases. The most common pattern is low cervical or thoracic between T_8 and T_{12}, bilateral, and asymmetric. An intense pain in these areas is followed by dermatomal hypesthesia over one or two segments at about the same time that weakness develops. Less often, loss of superficial sensation occurs in a cutaneous nerve pattern in a paretic limb or distally and symmetrically in the lower extremities. Wherever it occurs, sensory loss usually resolves completely within 1–2 months; residual hypesthesia is rare. Electrophysiological testing of patients with Lyme radiculoneuritis often shows axonal involvement (Halperin et al., 1990). The most commonly reported abnormalities are decreased sensory amplitude with mildly delayed sensory nerve conduction velocity (NCV), slight prolongation of distal motor latency with normal or mildly slowed motor NCV, and decreased amplitude of the compound action potentials. Electromyography (EMG) often shows neurogenic interference patterns and denervation potentials in peripheral nerve and root patterns. Decreased amplitude and prolongation of F waves are consistent with root involvement. Less commonly, there is slowing of motor NCV in the median nerve at the carpal tunnel and of the ulnar nerve at the elbow, but their association with the infection is uncertain. In a few cases, marked slowing of conduction velocity in multiple nerves, multifocal conduction block, and the absence of denervation potentials in weak muscles have suggested primary demyelination (Clavelou et al., 1993).

Encephalopathy

Mild symptoms suggestive of cerebral dysfunction are frequently reported in patients with Lyme neuroborreliosis (Pachner and Steere, 1985; Reik et al., 1986). Patients with the more severe forms of Lyme meningitis often complain of somnolence, emotional lability, depression, impaired memory and concentration, and behavioral changes. These tend to fluctuate in severity for weeks to months in untreated cases before resolving in concert with or independently of the meningeal

symptoms. Cerebral symptoms of this type are less common in Europe and seen in fewer than 20% of patients (Hansen and Lebech, 1992). Many of these patients show abnormalities on the EEG, including focal or generalized slowing and increases in sharp activity. However, brain CT and MRI are almost always normal.

Some patients may develop persistent encephalopathy. Prominent symptoms include incapacitating fatigue accompanied by defects in memory and concentration; however, signs of overt CNS dysfunction are usually absent or mild (Halperin et al., 1989a). This is referred to as chronic Lyme encephalopathy (Krupp et al., 1991; Kaplan et al., 1992; Fallon and Nields, 1994). Cases in both children and adults have been reported. The symptoms begin months to years after the beginning of infection in untreated patients. Bedside tests of mental status are abnormal in 25–50% of cases. Detailed neuropsychological testing is abnormal in about 50%. The most common abnormalities are defects in immediate and delayed memory, learning, attention, concentration, executive function, perceptual motor performance, word-finding difficulties, and verbal fluency. Depression and irritability are also common. Concomitant polyneuropathy is common (70%), with paresthesias and radicular pains and distal sensory loss on examination. Only mild CSF abnormalities may be found; pleocytosis is present in about 5% of cases and increased protein in 20–45%. The IgG index is typically normal and oligoclonal bands are usually absent. Specific antibody in the CSF is present in 40–85% of cases. In addition, the CSF may contain *B. burgdorferi* proteins (Coyle et al., 1993), DNA (Keller et al., 1992), or immune complexes (Coyle et al., 1990). EEG slowing is present in occasional patients. MRI shows multiple punctuate areas of increased signal in the deep cerebral white matter in 15–40% (Halperin et al., 1990; Logigian et al., 1990). It is likely that some subjective complaints are related to depression, fatigue, fibromyalgia, or the psychological stress of having Lyme borreliosis.

Encephalomyelitis

Myelitis is the most common CNS parenchymal complication of infection with *B. burgdorferi*. It is usually transverse, acute or subacute, or progressive, with typical onset during established meningoradiculitis; it was documented in 4% of prospectively studied cases of Lyme neuroborreliosis in Denmark (Hansen and Lebech, 1992). Accompanying CSF pleocytosis is the norm in the acute/subacute cases (95%) and 10% have associated brain involvement (Christen et al., 1993). The most common clinical findings are spastic paraparesis with an attendant sensory level, typically between T_4 and T_{10}. Other presentations include flaccid paraparesis, spastic quadriparesis, partial Brown–Séquard syndrome, and lumbar and cervical sensory levels. Autonomic symptoms, including disturbances of micturition and defecation and impotence, are sometimes seen. In mild cases, the findings may be limited to isolated Babinski's sign and urinary disturbance. Contrast enhancement on the pial surface of the lower thoracic cord and conus medullaris may be seen on MRI (Mantienne et al., 2001) and somatosensory-evoked potentials may be abnormal (Hansen and Lebech, 1992).

Brain parenchymal abnormalities have been reported in 5–10% of North American and 10–20% of European patients in the early phases of Lyme borreliosis (Hansen and Lebech, 1992). There is usually CSF pleocytosis and concomitant or prior radiculoneuritis (55%), radiculomyelitis (10%), or myelitis (1%). Isolated acute encephalitis has been rarely reported as the presenting feature of Lyme borreliosis (Pfister et al., 1993). Symptoms develop over hours to days and may include somnolence, hallucinations, paranoia, catatonia, coma, confusion, irritability, and agitation. Signs reported include hemiparesis, sudden or gradual in onset, hemianopia, alexia without agraphia, dysphasia, pseudobulbar palsy, and the locked-in syndrome. A variety of abnormalities of movement have also been reported, including cerebellar ataxia, chorea, dystonia, athetosis, tremor, and parkinsonism (Reik et al., 1979; Ackermann et al., 1985). Partial complex, focal motor, or generalized convulsions may occur (Mourin et al., 1993). Reported EEG abnormalities include focal or generalized slowing and, in those with seizures, spikes and spike–wave complexes. Several brain abnormalities on CT have been reported, including infarction in the cortex and basal ganglia, large areas of confluent or multifocal white-matter abnormalities, contrast-enhancing areas in the cerebral cortex, and hydrocephalus (Christen et al., 1993). Reported abnormalities on MRI include multiple areas of increased signal in the cerebral white and gray matter and brainstem (Belman et al., 1992; Tarasow et al., 2001). With prompt treatment, recovery may be complete, but the prognosis is not always favorable (Reik et al., 1986).

Rare patients have been reported who develop chronic progressive encephalomyelitis (Hansen and Lebech, 1992; Keller et al., 1992). Among 1200 patients from southern Germany who were examined between 1987 and 1990, only 0.3% had chronic progressive encephalomyelitis (Hofman et al., 1994). Occasional cases have been reported from North America (Steere et al., 1983; Pachner, 1989; Logigian et al., 1990), but they are exceedingly rare (Wormser et al., 2006). Symptoms can begin acutely or gradually, but once started worsen progressively over months to years, either gradually or in a stepwise fashion. These attacks may resemble transient

ischemic attacks or strokes, as in meningovascular syphilis. When the spinal cord is involved, it can mimic progressive forms of multiple sclerosis (Ackermann et al., 1985). The CSF is almost always abnormal (Steere et al., 1983; Pachner, 1989); typical abnormalities include a pleocytosis of 100–200 cells/mm^3, mostly lymphocytes and plasma cells, increased protein of 100–200 mg/dl, and normal or low glucose. Locally synthesized IgA, IgG, and IgM, oligoclonal bands of IgG, and specific anti-*B. burgdorferi* antibody are usually present. Neuroimaging abnormalities are present in most patients and include multifocal periventricular and subcortical white-matter hypodensities, contrast-enhancing infarcts in the internal capsule, lentiform nucleus, and thalamus; communicating hydrocephalus; and cerebral atrophy with intracerebral calcifications (Halperin et al., 1989a; Reik, 1993). Cerebral angiography has shown changes consistent with vasculitis: beading, narrowing, segmental stenoses, poststenotic dilatation, and occlusion of intracranial arteries. Spinal cord MRI can show increased focal or diffuse signal in the cervical spinal cord and lumbar arachnoiditis (Kohler et al., 1988).

Neuropathy

Patients with Lyme neuroborreliosis often have mild, multifocal polyneuropathy (Halperin et al., 1987; Logigian et al., 1990). The symptoms tend to be more severe in cases diagnosed early in the course of disease but milder and more persistent in cases diagnosed late. Intermittent tingling and paresthesias of the extremities are the most common symptoms, beginning months to years after infection. They are usually distal, either symmetric or asymmetric, and can involve the arms, the legs, or both. Concomitant radiculitis occurs in 25–50% of patients. The pain is intermittent, asymmetric, often multifocal, and typically radiates from the spine into the limbs or on to the trunk. Any dermatome can be affected. Physical signs of neuropathy are less frequent. Up to 60% of those with sensory symptoms have a mild stocking/glove distal sensory loss, but distal asymmetric and truncal sensory loss also occurs. The most common abnormality on neurological examination is reduced vibratory sensation of the distal lower extremities. Motor weakness and reflex changes are less common, each occurring in about 10% of cases. Electrophysiological testing is abnormal in most, indicating a patchy, multifocal axonal neuropathy (Halperin et al., 1987; Logigian et al., 1990). Both distal axons and nerve roots are affected. EMG abnormalities are seen in up to 80% of patients. The EMG typically shows denervation, either active or chronic, with prolonged polyphasic motor unit potentials in distal as well as proximal limb and paraspinal muscles. Typical nerve conduction abnormalities include mild slowing of motor or sensory nerve conduction velocities, decreased sensory amplitudes, prolongation of distal motor latencies, decreased compound action potentials, and increased F-wave latencies. Occasional patients have more marked slowing or areas of conduction block (Halperin et al., 1989b). Nerve biopsies may show perivascular lymphocytes.

Axonal neuropathy is common in European patients with ACA, most marked in the vicinity of the skin lesions (Kindstrand et al., 1997, 2002). The most frequent neuropathic symptoms among patients with ACA are mild to severe burning or sharp pains (30%), paresthesias (25%), weakness (7%), and muscle cramps (4%). Physical signs of neuropathy are nearly as prevalent (40%). Typical findings are hypesthesia in about 25% (especially in areas of skin atrophy), impaired vibratory sense (20%), abnormal reflexes (7–40%), weakness (15%), and muscle atrophy (5%). As with symptoms, the signs of neuropathy are often asymmetric and most marked near areas of skin involvement (Kindstrand et al., 2002). Subluxation of small joints in the hands and feet, intermittent arthritis of the knee, and nodular myositis may accompany ACA-associated neuropathy.

Diagnosis of Lyme neuroborreliosis

Lyme neuroborreliosis should be suspected in any patient exposed to endemic areas presenting with aseptic meningitis, cranial neuritis (especially facial nerve palsy), peripheral neuropathy (mononeuritis multiplex), radiculitis, and, rarely, CNS parenchymal abnormalities (Wormser et al., 2006). When these abnormalities follow EM, or accompany or follow arthritis or ACA (in Europe), the diagnosis is straightforward. The difficulty is when Lyme neuroborreliosis occurs without either previous history of skin lesions or arthritis, is delayed (late Lyme neuroborreliosis), or the patient presents with atypical neurological manifestations. In such cases, a rigorous approach to diagnosis is essential. A history of tick bite and onset in summer may alert clinicians to the possibility of Lyme neuroborreliosis. The combination of both peripheral and central neurological abnormalities in patients exposed to endemic areas should also raise the possibility of Lyme neuroborreliosis. The majority of patients with Lyme neuroborreliosis are seropositive. For the few patients with early Lyme neuroborreliosis who are seronegative, a convalescent serological test 2–4 weeks later usually yields positive results (Wormser, 2006; Wormser et al., 2006). Laboratory confirmation is established indirectly by demonstrating specific antibody to *B. burgdorferi* rather than directly, as identification of the spirochetes, or their proteins or nucleic acids, from patients lacks

sensitivity (Nocton et al., 1996). Laboratory testing is not clinically useful if the pretest probability of Lyme borreliosis is less than 0.20 or greater than 0.80. When the pretest probability is between 0.20 and 0.80, sequential testing with ELISA and immunoblot (two-tier test) is the most accurate method for ruling in or ruling out the possibility of Lyme neuroborreliosis. No positive serological test, regardless of titer, reflects disease activity, and the presence of serum reactivity alone is not sufficient to diagnose Lyme neuroborreliosis. Even a truly positive test may indicate only past exposure to *B. burgdorferi*. In highly endemic areas, up to 23% of residents have positive tests for *B. burgdorferi* antibody (Hanrahan et al., 1984) and there may be as many asymptomatic as symptomatic infections (Wilske et al., 1984; Steere et al., 1986). Therefore, the diagnosis of Lyme neuroborreliosis remains primarily a clinical one. However, in the absence of EM or when the neurological manifestations are nonspecific, laboratory support for the diagnosis is required.

Serum antibody tests

The serum of most patients with Lyme neuroborreliosis does contain anti-*B. burgdorferi* antibody. The main exception is during very early disease when the presence of EM is the clue to the diagnosis (Strle et al., 1996; Bunikis and Barbour, 2002). These antibodies can be measured by immunofluorescent assay or ELISA. Most laboratories use the more sensitive and specific ELISA and measure IgM and IgG antibodies separately. In general, the sensitivity of whole-cell ELISA is about 50% for the first few weeks of infection and increases to $\geq$90% thereafter (Dressler et al., 1993). The IgM antibody, directed mainly at the 41-kDa flagellar antigen, first appears 2–4 weeks after the initiation of infection, peaks 3–6 weeks after EM, and then slowly declines, although it can remain elevated for months to years (Craft et al., 1986; Dressler et al., 1994; Bunikis and Barbour, 2002). Serum IgG antibody, also directed against the 41-kDa flagellum, first appears after 4–6 weeks and can remain elevated for years despite clinical remission (Dressler et al., 1994; Bunikis and Barbour, 2002). By the time Lyme neuroborreliosis becomes clinically apparent, serum concentrations of specific IgG are usually raised, while IgM titers may or may not be elevated. Thus, elevated serum titers of specific IgM antibodies indicate acute infection whereas elevated specific IgG antibodies can indicate either active or past infection.

Caution is necessary in interpreting antibody test results in the individual patient, however. Commercially available tests are not standardized (Bunikis and Barbour, 2002; Lange and Seyyedi, 2002) and there is both intra- and interlaboratory variability. When test results are equivocal or weakly positive, a second sample should be sent to a reference laboratory for confirmation. False-positive Lyme ELISA occurs with other past or current spirochetal infections, collagen vascular diseases, or other systemic infections (Hunter et al., 1986; Magnarelli et al., 1987; Bunikis and Barbour, 2002). The specificity of a positive Lyme ELISA should be confirmed by Western blot to rule out false-positive results (Grodzicki and Steere, 1988). This is referred to as a two-tier test. Many normal individuals have antibodies against *B. burgdorferi* antigens that are most likely cross-reacting antibodies against spirochetes of the body's normal flora. Therefore, serum Western blots from normal individuals often show reaction with the 41-kDa flagellin of *B. burgdorferi* and less often with the 60- and 66-kDa antigens. The exclusion of false-positive Western blots is possible because sera from patients with Lyme disease have antibodies reacting with many other *B. burgdorferi* antigens. This is the basis for the recommendations of the interpretation of Lyme Western blots in the USA, which require at least two IgM and at least five IgG bands to be considered positive (Dressler et al., 1993). The sensitivity and specificity of the Lyme Western blot before and after 4 weeks of infection are 30% and 100% for IgM and 80% and 95% for IgG, respectively (Bunikis and Barbour, 2002).

CSF antibody tests

Most patients with Lyme neuroborreliosis have specific antibody in CSF (Morey, 1998; Wormser, 2006; Wormser et al., 2006). The yield of testing for intrathecal antibody in serum antibody-negative patients in North America is very low – about one in 1000 in one study (Carbonaro et al., unpublished paper). However, the yield of CSF-specific antibody in seronegative patients may be higher in Europe: one Swedish study found 91% of patients with Lyme meningitis had positive CSF antibody while only 67% had positive serum antibody (Stiernstedt et al., 1985). However, more recent studies have failed to confirm this (Blanc et al., 2007). CSF antibody testing may be helpful when routine CSF analysis is normal in patients with symptoms suggestive of Lyme neuroborreliosis, and when alternative diagnoses such as multiple sclerosis are being considered. In such cases, a positive CSF antibody test makes it more likely that the symptoms are the result of Lyme neuroborreliosis. However, simply finding specific antibody in the CSF is helpful in only a minority of patients who are seronegative. A recent study of 123 patients with CSF anti-*Borrelia* antibody in France found that another etiology was responsible

for symptoms in 60% of patients (Blanc et al., 2007). Therefore, when testing for *B. burgdorferi*-specific antibody in the CSF, intrathecal synthesis should be requested. For this, paired serum and blood-free CSF samples must be collected, and the total and specific antibody concentrations measured simultaneously by ELISA to calculate an index of specific intrathecal antibody synthesis (Hofstad et al., 1987; Wilske et al., 1991; Kaiser and Lucking, 1993). This requires that serum and CSF first be diluted to the same total IgG concentration before antibody activity is measured. Values of 1.3 or higher are considered positive (Wilske et al., 1986). In a recent study of 123 consecutive patients from France who had signs of neurological involvement, the intrathecal anti-*Borrelia* antibody index had a sensitivity of 75% and a specificity of 97% (Blanc et al., 2007). False-negative results may be caused by CSF antibody bound in antigen–antibody complexes, such that it may not be measurable by routine ELISA (Coyle et al., 1990; Schutzer et al., 1990), or by presentation during early CNS infection (Blanc et al., 2007). An alternative to the antibody index is CSF antibody capture ELISA that requires no dilution and measures the ratio of specific IgG to total IgG directly in CSF samples (Hansen and Lebech, 1991).

CSF PCR

B. burgdorferi DNA can be demonstrated by PCR in the CSF of patients with Lyme neuroborreliosis, even in cases when CSF inflammation and intrathecal antibody production are absent (Christen et al., 1993; Nocton et al., 1996; Ornstein et al., 2001). However, the sensitivity is 40% at best in early Lyme neuroborreliosis and even lower (25%) in late disease (Nocton et al., 1996). This low sensitivity likely reflects the low number of organisms present in the CSF as opposed to the leptomeninges, cranial nerves, and spinal roots, as shown in experimental animals (Cadavid et al., 2000). A proposed advantage of a positive CSF PCR is its indication of active infection, which is not possible with antibody tests.

Treatment of Lyme neuroborreliosis

B. burgdorferi is sensitive to many antimicrobial agents. These include macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin), cephalosporins (ceftriaxone, cefotaxime, and cefuroxime), penicillins (amoxicillin alone or with clavulanate, mezlocillin, oxacillin), and tetracyclines (tetracycline, minocycline, doxycycline). In general, *in vivo* sensitivities parallel those *in vitro*, with the exception of macrolides, which are all less active *in vivo*. The Infectious Diseases Society of America (IDSA) (Wormser et al., 2006) and the American Academy of Neurology (Halperin et al., 2007) recently published updated practice guidelines for the treatment of Lyme neuroborreliosis.

Treatment of early Lyme neuroborreliosis

If a patient is suspected of having Lyme neuroborreliosis, the use of a parenteral antimicrobial agent should be considered. The practice guidelines recommend treatment with parenteral antimicrobials for patients with meningitis, radiculitis, or facial palsy if there is also strong clinical suspicion of CNS involvement (i.e., in association with severe or prolonged headache or nuchal rigidity) (Wormser et al., 2006). If a clinician is unclear about the use of parenteral agents for treatment of a patient with Lyme borreliosis complicated with facial palsy, examination of the CSF may be warranted. Patients with isolated facial palsy and normal CSF examination, and/or lack of clinical signs of meningitis, may be treated with a 14-day course (range 14–21 days) of oral doxycycline (100 mg by mouth twice per day) (Wormser et al., 2006). The first choice for a parenteral antimicrobial agent is once-a-day IV ceftriaxone for both adults (2 grams) and children (50–75 mg/kg/day). In comparison with penicillin, the advantages of ceftriaxone are its excellent CSF penetration and long serum half-life, which permits once-a-day dosing for outpatient management. A potential disadvantage of ceftriaxone is promotion of biliary sludge and increased risk of cholelithiasis. Cefotaxime is the second choice because it has to be administered several times a day (2 grams IV every 8 hours); however, it does not cause the biliary complications associated with ceftriaxone. IV penicillin is also effective (Pachner, 1995; Karlsson et al., 1996; Millner et al., 1996), but it has to be administered multiple times per day (4 million units IV every 4 hours) (Wormser et al., 2006). Patients have failed to improve with IV penicillin, but have responded to IV cephalosporins (Schmutzhard, 1989). Clinical trials in Europe failed to prove that cefotaxime is better than penicillin (Pfister et al., 1989), or that ceftriaxone is better than cefotaxime (Pfister et al., 1991). Doxycycline given orally or IV achieves adequate CSF concentrations and may be as effective as IV penicillin (Dotevall et al., 1988; Karlsson et al., 1996; Dotevall and Hagberg, 1999; Karkkonen et al., 2001). There is increasing evidence that oral doxycycline (200–400 mg divided in two daily doses for 10–28 days) may be a satisfactory alternative for treatment of patients with early Lyme neuroborreliosis who are intolerant to β-lactam antimicrobial agents (Wormser et al., 2006). Since doxycycline is well absorbed orally, IV administration is rarely

necessary. However, it should not be used in children younger than 8 years of age or in pregnant women.

A mild Jarisch–Herxheimer reaction with worsening of pain and fever may occur during the first 24 hours after treatment with parenteral antimicrobial agents in the treatment of Lyme neuroborreliosis (Hassler et al., 1990). Meningismus, radicular pain, and systemic symptoms all improve within days, although there may be residual fatigue, arthralgias, and musculoskeletal pain. Motor deficits improve over weeks, but sometimes incompletely. Antimicrobial agents may not hasten recovery from seventh-nerve palsy (Clark et al., 1985). WBC counts in the CSF are usually lower by the end of treatment, but may take longer before a decrease is seen. CSF protein falls more slowly and may remain elevated for a year or more. Specific CSF antibody can persist for years (Baig et al., 1991). The recommended duration of treatment is 2 weeks, but if symptoms do not improve by the end of the second week or if CSF pleocytosis does not improve, treatment should be continued for 2 additional weeks.

Treatment of late Lyme neuroborreliosis

Patients presenting with late Lyme neuroborreliosis most often have encephalopathy, peripheral neuropathy, or encephalomyelitis. The IDSA practice guidelines recommend treatment with parenteral antimicrobial agents for all patients with late Lyme neuroborreliosis except for ACA-associated neuropathy which can be treated with oral agents. The drug of choice is IV ceftriaxone given for 2–4 weeks. Cefotaxime and penicillin G, also given IV, are valid alternatives (Wormser et al., 2006). In most patients with late Lyme neuroborreliosis, treatment stabilizes the disease, some improve partially, and a few become clinically normal. Recovery is slow and often incomplete with little apparent change during the course of treatment itself (Halperin, 1989a; Logigian and Steere, 1992). CSF pleocytosis typically resolves and the CSF protein concentration decreases within 3 months. Specific CSF antibody can persist for a year or more. Retreatment is not recommended unless relapse is demonstrated by reliable objective measures (Wormser et al., 2006).

The optimal duration of antimicrobial treatment for late forms of Lyme neuroborreliosis is unclear. Because as many as 10% of patients who improve initially following 2 weeks of therapy may have a relapse (Logigian and Steere, 1992), duration of IV therapy is sometimes extended to 4 weeks. A randomized, prospective clinical trial showed higher treatment failures in patients treated for 14 days (5/80) than in patients treated for 28 days (0/63) ($P = 0.07$) (Dattwyler et al., 2005). There is no evidence that treatment for longer than 4 weeks results in greater improvement (Wahlberg et al., 1994; Sigal, 1995; Wormser et al., 2006). In fact, prolonged IV treatment with ceftriaxone can be dangerous, resulting in biliary complications (Centers for Disease Control and Prevention, 1993) or even lead to death or serious morbidity related to catheter-associated bloodstream infection (Patel et al., 2000). Corticosteroids are not recommended in patients with Lyme neuroborreliosis. Although early reports suggested that steroid therapy resolved radicular pain in meningopolyneuritis, subsequent controlled trials showed that the pain resolved almost as quickly with antimicrobial treatment alone (Pfister et al., 1988). Furthermore, steroid use has been associated with subsequent antimicrobial treatment failure during late disease in humans (Dattwyler et al., 1988) and worsening of disease in experimental animals (Cadavid et al., 2000; Straubinger et al., 2000).

NEUROBORRELIOSIS IN RELAPSING FEVER

Epidemiology and etiology

The spirochetes that cause relapsing fever, similar to the spirochetes that cause Lyme disease, are in the genus *Borrelia* (Barbour and Hayes, 1986). Natural vertebrate reservoirs of these organisms include a variety of mammals, but most commonly are rodents. Table 12.1 includes a list of the main relapsing fever *Borrelia* species and an estimate of their geographic ranges.

Table 12.1

Relapsing fever *Borrelia* species pathogenic to humans

Borrelia species	Geographic distribution of disease
Borrelia hermsii	Western North America
Borrelia turicatae	South-western North America and northern Mexico
Borrelia venezuelensis	Central America and northern South America
Borrelia hispanica	Iberian peninsula and north-western Africa
Borrelia crocidurae	North and East Africa, Near/Middle East, south-east Europe
Borrelia duttoni	Sub-Saharan Africa
Borrelia persica	Middle East, Greece, Central Asia
Borrelia uzbekistana	Tajikistan, Uzbekistan
Borrelia recurrentis	Worldwide in the epidemic form

Modified from Barbour and Hayes (1986).

There are two forms of relapsing fever: epidemic and endemic. The epidemic form is caused by *Borrelia recurrentis* and transmitted by the body louse *Pediculus humanus*. Humans are the principal vertebrate hosts for *B. recurrentis*. Large epidemics of louse-borne relapsing fever killed millions of people before the availability of antimicrobial agents. Outbreaks of louse-borne relapsing fever still occur in East Africa (Raoult and Roux, 1999; Houhamdi et al., 2005). Endemic relapsing fever is transmitted by soft-bodied ticks of the genus *Ornithodoros*; therefore, the *Borrelia* species that cause endemic relapsing fever are named for the type of tick involved in transmission. Endemic relapsing fever is still reported in America (Schwan et al., 2003; Guggenheim and Haverkamp, 2005) and Africa (Dupont et al., 1997; van Dam et al., 1999). In the USA, endemic relapsing fever occurs almost exclusively west of the Mississippi river, in particular the mountainous west (*B. hermsii*) and the south-west (*B. turicatae*). Common sites of acquisition of the infection are recreational cabins, caves, and crawl spaces under buildings. Although relapsing fever-like borrelias have been identified in hard-bodied *Ixodes* ticks east of the Mississippi, there is no current evidence that they are pathogenetic to humans (Fukunaga et al., 1996; Scoles et al., 2001; Fraenkel et al., 2002; Bunikis et al., 2004).

Pathogenesis

The recurrent pattern of fever and high bacteremia that characterizes relapsing fever borreliosis is the consequence of antigenic variation of abundant outer-membrane proteins that define the serotype, referred to as variable major proteins (Barbour et al., 1984; Barbour and Hayes, 1986). Although the host's serotype-specific antibody response effectively clears abundant serotypes at times of peak bacteremia (Newman and Johnson, 1984), less abundant serotypes that spontaneously arise by a gene conversion proliferate to cause a relapse. These cycles of relapses and remissions can continue for up to several weeks until the patients are diagnosed and treated, or the ability to escape immune killing finally ends. Residual infection can occur in the brain, as shown in experimental animals (Cadavid et al., 2006; Larsson et al., 2006). The clinical manifestations of the infection are the result of the host's inflammatory response to the infection. Prominent virulence factors of spirochetes include lipoproteins that are potent inducers of inflammation (Vidal et al., 1998) and complement-binding proteins.

Large amounts of cytokines are found in the blood during acute infection, including TNF (13–41 pg/ml), IL-6 (1180–4550 pg/ml), IL-8 (33–110 pg/ml), and IL-10 (2910–9734 pg/ml) (Cooper et al., 2000; Gelderblom et al., 2007). Recent studies in experimental animals indicate that IL-10 plays an important protective role in this infection (Gelderblom et al., 2007). Large amounts of the B-cell chemokine CXCL13 are also found in blood and infected tissues, which is further evidence of the critical role that the B-cell arm of the adaptive immune system plays in this infection (Gelderblom et al., 2007). Similarly, prominent splenomegaly indicates the important contribution of the innate immune system to bacterial clearance via phagocytosis.

Unlike Lyme borreliosis, which is almost never fatal, relapsing fever borreliosis can be fatal, especially the epidemic form. The most consistent findings in the brain at autopsy in fatal cases of relapsing fever borreliosis are edema and hemorrhage, both subarachnoidal and parenchymal (Abdalla, 1969; Perine and Reynolds, 1974; Salih et al., 1977; Ahmed et al., 1980). In many cases, the hemorrhage is widespread and not limited to the brain, with patients presenting wtih epistaxis, hematuria, gastrointestinal bleeding, and skin petechiae; it has been proposed that the bleeding is caused by disseminated intravascular coagulation (Salih and Mustafa, 1977; Salih et al., 1977). There have been comparatively fewer fatal cases of endemic relapsing fever and, consequently, less is known about its pathology in humans. The most common findings on microscopic examination of the brain are meningeal and parenchymal perivascular mononuclear infiltrates with monocytes, lymphocytes, and plasma cells and proliferation of microglia (Belezky and Umanskaja, 1930; Scott, 1944). Other findings include extensive degeneration of the cerebral cortex and ganglion cells, swelling of neurons with chromatolysis and vacuolation, and gliosis. Spirochetes have been demonstrated in the leptomeninges (Fuchs and Oyama, 1969; Yagupsky and Moses, 1985), within the cerebral microvasculature, in the interstitial spaces of the brain, and between neurons in the cortex (Jahnel and Lucksch, 1927). The preferred localization of relapsing fever spirochetes in the brain of experimental animals is leptomeningeal (Cadavid et al., 2001).

Clinical features

The clinical hallmark of relapsing fever borreliosis is two or more episodes of high fever and constitutional symptoms, such as headache and myalgias, spaced by periods of improvement (Southern and Sanford, 1969). While in epidemic relapsing fever the second episode of fever is typically milder than the first, in endemic relapsing fever there are usually multiple febrile periods equal in severity (Southern and Sanford, 1969). The febrile periods last 1–3 days and the afebrile intervals 3–10 days. During febrile periods, numerous

spirochetes readily visible by microscopic examination of blood smears are circulating in the blood, referred to as spirochetemia. However, during afebrile periods, spirochetemia is very low and not detectable microscopically.

Although relapsing fever borreliosis is well recognized as an infection of the blood, it can also result in neurological infection (Cadavid and Barbour, 1998). The most common manifestations of neurological infection are meningitis and facial palsy. Less common are encephalitis, myelitis, radiculitis, and neuropsychiatric disturbances. The frequency of neurological involvement varies according to the species involved, from absent to greater than 50% in some series (Cadavid and Barbour, 1998). The species of relapsing fever borrelias more commonly associated with neurological involvement are *B. duttoni*, *B. turicatae, B. hispanica*, and *B. recurrentis*. It appears that meningismus in endemic relapsing fever is the result of intrathecal infection, while in epidemic relapsing fever it is more often secondary to subarachnoid hemorrhage (Babes, 1916; Chung, 1938; Robinson, 1942). Evidence of CSF inflammation is frequent in patients with meningismus in endemic (Bergeret and Raoult, 1948), but not in epidemic, relapsing fever (Bryceson et al., 1970). The CSF opening pressure is frequently increased in patients with meningismus (Lodewyckx, 1938). The mean CSF WBC count is about 200/mm^3 and the maximum is about 2000/mm^3 (Lodewyckx, 1938; Scott, 1944; Bergeret and Raoult, 1948); CSF leukocytes are predominantly mononuclear. The CSF protein concentration is also increased with a mean of 330 mg/dl and a range of 50–1000 mg/dl (Lodewyckx, 1938; Scott, 1944; Bergeret and Raoult, 1948). Although the CSF glucose is usually normal, it may be low (Horton and Blaser, 1985).

The cranial nerve most frequently involved in relapsing fever borreliosis is the seventh and the most common clinical manifestation is facial palsy. The frequency of facial palsy during infection with *B. duttoni* in East Africa was such that Bergeret and Raoult (1948) suggested that its presence confirmed a diagnosis of endemic relapsing fever. The facial paralysis typically appears during or after the second episode of fever but not during the first. It has been reported with *B. turicatae*, *B. hispanica*, *B. crocidurae*, and *B. duttoni* (Cadavid and Barbour, 1998). The facial paralysis is of sudden onset, usually unilateral, and can be central or peripheral. Lumbar puncture often reveals CSF abnormalities in patients with facial palsy (Taft and Pike, 1945). The facial paralysis usually resolves with or without antimicrobial treatment in 2–9 weeks, but occasionally can persist. Other cranial nerves that can be affected are the eighth, resulting in vertigo, tinnitus, and/or hearing loss or deafness, and the fifth and sixth nerve (Scott, 1944; Bergeret and Raoult, 1948).

Less often manifestations of focal or diffuse cerebral dysfunction can occur in patients with relapsing fever. Their onset is usually delayed until the second or subsequent febrile periods, similar to facial palsy. Extreme somnolence has been reported in both the epidemic (Rijkels, 1971) and endemic (Bergeret and Raoult, 1948) forms. Partial seizures complicated endemic relapsing fever in West Africa (Marques, 1943; Bergeret and Raoult, 1948). Hemiplegia appeared after the second febrile period in several cases of endemic relapsing fever in East Africa, and the majority of CSF examinations revealed leukocytosis (Quin and Perkins, 1946). Hemiplegia has also been reported in children with endemic relapsing fever (Makwabe, 1984). Several other focal neurological manifestations have been reported, including aphasia and ataxia in epidemic relapsing fever and parkinsonism in endemic relapsing fever, with demonstration of spirochetes in the CSF (Raynaud and Pegullo, 1946). There are also reports of transverse myelitis, paraplegia that can be spastic or flaccid, upper-extremity weakness, absent reflexes, radiculitis (either lumbar or cervical), and bladder and bowel involvement (Cadavid and Barbour, 1998). Neuropsychiatric abnormalities, not solely attributable to the fever, can occur in either the endemic or epidemic forms; these include delirium, hallucinations, and mania. Some patients with the endemic form required prolonged or repeated hospitalization because of persistent fatigue and may remain chronically ill (Cadavid and Barbour, 1998). During convalescence, patients can feel mentally depressed, weak, and unable to return to work. Headaches and backaches are common despite normal physical examination. Symptomatic relapses without fever can also occur, manifested as periods of headache, backache, and weakness lasting 24–48 hours (Taft and Pike, 1945).

Diagnosis

The comparatively large number of spirochetes in the blood during relapsing fever borreliosis provides the opportunity for the simplest method for laboratory diagnosis of the infection: Wright stain of a thin blood smear, or dark-field or phase-contrast microscopy of a wet mount of plasma. The blood should be obtained during or just before a febrile peak. Between fever peaks, spirochetes can be demonstrated by inoculations of blood or CSF into culture media (Sigma's BSK-H), or into experimental animals. Enrichment for spirochetes is achieved by using the platelet-rich fraction of plasma or the buffy coat of sedimented blood. Serological assays for Jarisch–Herxheimer are of dubious

utility because the antigenic variation results in hundreds of different serotypes. Therefore, if one serotype or species is used for preparing the antigen that is different from the infecting organism, only antibodies to conserved antigens may be detected. However, since conserved antigens are also present in the Lyme disease spirochete, a standardized ELISA assay with *B. burgdorferi* as antigen, which is widely available, can be used as a screening test for relapsing fever.

Two methods have been used to document the presence of spirochetes in the subarachnoid space of patients with CNS infection. The first is examination of CSF sediment by either bright-field microscopy of Giemsa or Gram-stained fixed specimens, or by dark-field or phase-contrast microscopy of wet mounts (Fuchs and Oyama, 1969). The second method is inoculation of CSF into susceptible animals whose blood is later examined for spirochetemia (Advier et al., 1934). Mouse inoculation is preferred because of its superior sensitivity; microscopic examination of CSF sediment often fails to reveal infection in CSF samples subsequently found infected by animal inoculation (Chung, 1938; Hawking, 1941; Bergeret and Raoult, 1948). Mouse inoculation has been useful to document asymptomatic CSF infection (Leboeuf and Gambier, 1918; Lodewyckx, 1938; Hawking, 1941).

Treatment

Relapsing fever was one of the first diseases treated with the "magic bullet" arsenic compounds of Ehrlich and his colleagues. Penicillin replaced arsenicals for the treatment of relapsing fever in the 1940s (Taft and Pike, 1945). Studies in experimental animals revealed that low doses of penicillin could prevent relapses and brain infection, if treatment was begun during or before the first peak of bacteremia, but was not effective if the treatment was delayed (Lourie and Collier, 1943). Penicillin cured established brain infection in experimental animals only if higher doses were used and for longer periods of time (Schuhardt and O'Bryan, 1945); treatment with penicillin reduced relapse rates from 70–90% to $\leq$5%. Although single injections of IM procaine penicillin G were very effective for epidemic relapsing fever (Perine and Reynolds, 1974; Butler et al., 1979), treatment failures did occur often in patients with the endemic form.

The tetracyclines are most commonly used for treatment of humans with relapsing fever. In general, shorter treatments are needed for the epidemic than for the endemic form; multiple doses of tetracyclines for up to 10 days have sometimes failed to prevent relapses in endemic relapsing fever (Linnemann et al., 1978). Other antimicrobial agents used for tick-borne relapsing fever and louse-borne relapsing fever are macrolides and chloramphenicol. Erythromycin is not as effective as the tetracyclines (Colebunders et al., 1993). If there are symptoms and signs of meningitis or encephalitis in relapsing fever without clinical and/or radiological signs of increased intracranial pressure, the CSF should be examined. The finding of elevation of CSF WBCs and protein demands the use of parenteral agents, such as penicillin G, cefotaxime, or ceftriaxone, for 2 or more weeks. Less obvious is whether to examine the CSF in patients with isolated facial palsy. The cranial nerve involvement in such cases is more likely peripheral and may not be indicative of CNS disease. Moreover, if the treatment would be expected to eliminate spirochetes in the brain or CSF even if the patient is asymptomatic, there may be little to be gained from CSF analysis in cases with isolated facial palsy. However, if oral therapy is being considered for suspected or documented relapsing fever with neurological involvement, it may be prudent to rule out meningeal inflammation by examining the CSF. In the absence of documented brain involvement at the time of diagnosis, the principal aim of antimicrobial therapy is to prevent neurological disease and, for this, treatment with oral agents should be sufficient.

NEUROLEPTOSPIROSIS

Epidemiology and etiology

Leptospirosis is an acute systemic zoonotic disease caused by infection with a number of spirochetes in the *Leptospira* genus (Levett, 2001; Vinetz, 2001). It is the most widespread zoonosis in the world. The disease varies from asymptomatic infection to a rapidly fatal disease. Acquisition by humans is via contact with infected animal body fluids, usually urine. The usual reservoirs are mammals, notably rodents. Most cases are sporadic, but it can assume epidemic proportions when there is excessive flooding, such as during torrential rains (Salkade et al., 2005). The majority of cases occur in young adults and children (Romero et al., 1998). Although leptospirosis occurs during any season, it is more common during the summer (Hubbert and Humphrey, 1968). The etiological agent of Weil's disease is usually *Leptospira interrogans* serovar *icterohemorrhagiae*, while other serovars, including *canicola*, *pomona,* and *copenhageni*, rarely produce jaundice. Various serovars have been implicated in epidemics, including *copenhageni, canicola*, and *lai*. The correlation between the infecting strain and the clinical expression of the disease is rather poor (Vinetz, 2001).

Pathogenesis

Pathogenic leptospiras gain access to humans through the skin or mucosa, and disseminate hematogenously. Leptospiral infection activates the innate immune system via interaction of outer membrane lipoproteins and leptospiral lipopolysaccharide with Toll-like receptors and CD14. Neuroleptospirosis requires migration of leptospiras from the blood into the CNS across the BBB. Although leptospiras are known to attach to endothelial cells, the exact mechanism of BBB crossing remains to be elucidated (de Souza, 2006). Little is also known about the mechanism by which leptospirosis results in neurological and psychiatric complications.

Clinical features

Involvement of the CNS is well documented in patients with leptospirosis, with several different presentations, including stroke, cerebral venous thrombosis, CNS vasculitis, subarachnoid hemorrhage, blindness, optic neuritis, transverse myelitis, cranial neuropathy, psychosis, cerebellitis, encephalitis, and meningitis (Panicker et al., 2001; de Souza, 2006). The most prominent neurological complication of leptospirosis is aseptic meningitis. Before the onset of meningitis, there is typically a nonspecific phase of prodromal symptoms. Leptospiral meningitis occurs more typically in the anicteric form but it is also observed in the icteric form, referred to as Weil's disease (Lecour et al., 1989). In up to 10% of cases, meningitis is the sole clinical manifestation of leptospirosis (de Souza, 2006).

The CSF profile is indistinguishable from that of other spirochetes and viruses, except that elevated CSF protein is more common than in viral meningitis, usually between 50 and 300 mg/dl; elevated CSF protein carries a poor prognosis (Mathew et al., 2006). The CSF WBC count is usually less than 500/mm^3 and the CSF glucose is usually normal (de Souza, 2006). CSF PCR detected leptospiral DNA in the CSF of 40% of patients with aseptic meningitis in Brazil (Romero et al., 1998). Leptospiral meningitis is a benign disease characterized by rapid recovery regardless of therapeutic intervention. However, patients with prolonged symptoms are occasionally reported. Leptospirosis occasionally results in fatal intracerebral hemorrhage (Forwell et al., 1984). Since coagulation tests and platelet counts are relatively normal, it is more likely that bleeding results from either CNS vasculitis or direct injury to the cerebral microcirculation by the spirochete. Leptospiral infection can become chronic by residual infection of the proximal renal tubule, aqueous humor, and subarachnoid space, resulting in chronic nephritis, uveitis, and meningitis, respectively.

Severe cases of leptospirosis usually present with fever, difficulty breathing, hemoptysis, oliguria, anemia, jaundice, and altered consciousness (Salkade et al., 2005; Mathew et al., 2006). Autopsy of fatal cases usually shows massive intra-alveolar hemorrhage, acute interstitial nephritis and/or acute tubular necrosis, and myocarditis. Although lung hemorrhages are usually the cause of death, bleeding also does occur in other organs, including the heart, gastrointestinal tract, brain, pancreas, and adrenal glands (Salkade et al., 2005). Prominent cardiac damage is found in over 50% of fatal cases at autopsy, even if not suspected clinically.

Diagnosis

In the majority of cases of leptospirosis, the diagnosis is done serologically, although spirochetes have been cultured from blood or urine or identified in autopsy material microscopically by silver staining or immunohistochemistry (Hubbert and Humphrey, 1968; Salkade et al., 2005). Confirmation of leptospirosis by serology requires a change in antibody titers between acute and convalescent sera. Commonly used serological tests are the microscopic agglutination test and ELISA for detection of IgM in serum and CSF (Romero et al., 1998). The diagnosis should be suspected in all patients who have been in contact with animals due to their occupation or recreational activities, or have a history of swimming in creeks or irrigation canals.

Treatment

Treatment of leptospirosis consists of antimicrobial agents, with crystalline penicillin being the drug of choice as this reduces the course of illness if given early. It should be started as soon as possible to avoid life-threatening visceral complications (Ragnaud et al., 1994). Doxycycline is another recommended therapy and is also effective if given within the first several days of illness; it may also have a role in prophylaxis (Sperber and Schleupner, 1989). The role of steroids is controversial. The prognosis of neuroleptospirosis is generally good but altered sensorium, high CSF protein, and seizures herald a worse prognosis (Panicker et al., 2001).

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Chapter 13

Neurological complications of bacterial endocarditis

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Infective endocarditis is the fourth leading cause of life-threatening infection (Bayer et al., 1998). Although the incidence has been stable for several decades at 15–60 cases per million, the spectrum of infection has evolved with the decline of rheumatic heart disease and increase in prosthetic valve surgery (Baddour et al., 2005). The increased morbidity and mortality is related to an increase in more serious infections due to *Staphylococcus aureus*, group D *Streptococcus,* and multidrug-resistant species, rather than the traditional etiological agents, such as viridans streptococci (Hoen et al., 2002).

ETIOLOGY

The poor vascularity of the cardiac valves underlies their limited ability to mount an immune response to infection during bacteremia. Predisposing factors for endocarditis include underlying cardiac valvular disease, especially prosthetic and rheumatic, and indwelling cardiovascular medical devices. Risk factors for systemic infection include injection drug use, indwelling catheters, genitourinary infection or manipulation, gastrointestinal disease including colon cancer, burns, chronic skin disorders or infections, poor dental hygiene, alcoholism, cirrhosis, diabetes mellitus, and other immunosuppressive states.

The most common organisms causing infective endocarditis are viridans streptococci, *Streptococcus bovis,* the HACEK group, *Staphylococcus aureus* and community-acquired enterococci. The HACEK microorganisms are all fastidious gram-negative bacilli and include *Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae,* and *K. dentrificans* (Baddour et al., 2005).

PATHOGENESIS AND PATHOPHYSIOLOGY

Neurological complications result when septic embolization occurs from the valvular vegetation producing the key neurological expression of the disease, cardioembolic ischemic stroke. As septic emboli obstruct the arterial lumen or vasa vasorum, a focal arteritis results which can manifest as a septic encephalopathy and spread to result in meningitis, a cerebritis, or brain abscess (Molinari et al., 1973). Fusiform or saccular aneurysmal dilatation occurs when the inflammatory exudate penetrates through the muscularis media into the external elastic membrane, leading to rupture as an intraparenchymal or subarachnoid hemorrhage (Hart et al., 1987).

Systemic embolization and immune-mediated vasculitis as a result of the infection produce many of the other well-recognized clues to the diagnosis. These include splinter hemorrhages, Janeway lesions, and Osler's nodes on the skin of the hands and feet, conjunctival and retinal hemorrhages, Roth's spots, glomerulonephritis, and pulmonary infarcts (Li et al., 2000; Baddour et al., 2005).

CLINICAL FEATURES

Systemic embolization complicates 20–50% of cases and has the most significant impact on survival; 24–50% of those who experience an embolic event will die (Delahaye et al., 1990; Heiro et al., 2000). Risk factors for embolization include large and highly mobile vegetations, the mitral position, and associated antiphospholipid antibodies (Mügge et al., 1989; DiSalvo et al., 2001; Anderson et al., 2003; Homma and Grahame-Clarke, 2003). The frequency of embolization varies by organism, with the highest rates seen with

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S. aureus, Candida, HACEK group, and *Abiotrophia* infection (Baddour et al., 2005).

The neurological manifestations of endocarditis include ischemic stroke, intracranial hemorrhage, transient ischemic attack (TIA), mycotic aneurysm, brain abscess, meningitis, associated manifestations of encephalopathy, headache, seizures, and rarely involvement of peripheral nerves or the spinal cord (Jones et al., 1969; Pruitt et al., 1978; Salgado et al., 1989; Heiro et al., 2000; Ruttmann et al., 2006). The cerebrovascular complications constitute 85–95% of all neurological involvement and have a significant impact on patient management, disability, and mortality.

Stroke is the most common neurological manifestation of infective endocarditis as two-thirds of emboli go to the brain. Stroke is the presenting feature in up to half of cases of endocarditis, with 76% manifesting prior to the initiation of antibiotic therapy (Heiro et al., 2000). Consistent with other types of cardioembolic stroke, the most common destination for these emboli is to branches of the middle cerebral artery producing clinical syndromes of hemiparesis, aphasia, hemisensory deficit, and neglect (Salgado et al., 1989). In one large retrospective series, stroke affected 10% of patients. Ischemic stroke without hemorrhagic transformation accounted for three-quarters of the events, hemorrhagic stroke the remaining one-quarter, but, of these, the majority were hemorrhagic transformations of infarcts with <10% primary intracranial hemorrhages with or without a subarachnoid component (Anderson et al., 2003). Overall, ischemic strokes are threefold more common than hemorrhagic strokes for all settings with the exception of prosthetic valve *S. aureus* endocarditis, where early intracranial hemorrhage predominates (Tornos et al., 1999). In addition to clinically evident infarction, neuroimaging reveals silent infarcts in 10–15% and imaging negative transient ischemic events are diagnosed in 5–10% (Hart et al., 1990; Singhal et al., 2002).

Intracranial hemorrhage is classically thought to be the result of rupture of a mycotic aneurysm, although an aneurysm is documented <15% of the time. In pathological specimens, hemorrhage is more often the result of a septic arteritis that results from embolization to the arterial wall (Fig. 13.1) (Hart et al., 1987). Vascular rupture results in a subarachnoid hemorrhage, a primary intracerebral hemorrhage, a hemorrhagic transformation of an initially bland infarction, or combinations thereof. Intraparenchymal hemorrhages typically involve peripheral aspects of the frontal or parietal lobes, reflecting the tendency of emboli to involve distal branches of the middle cerebral artery.

Intracranial mycotic aneurysms are reported in <2% of clinical series but 5–10% of autopsy cases. This not only reflects their impact on mortality but also suggests clinical underestimation as cerebral angiography, the gold standard for diagnosis, is performed selectively. In one large case series of angiographically documented mycotic aneurysms, only 20% were identified on the basis of contrast-enhanced brain computed tomography (CT) scans (Chapot et al., 2002). Mycotic aneurysms are associated with neuroimaging evidence

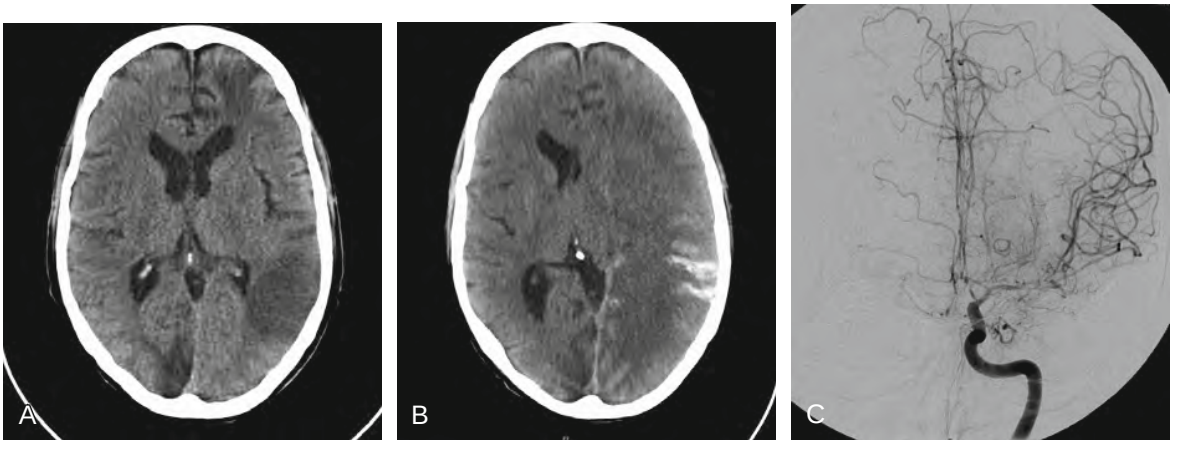

Fig. 13.1. (A) A young man with hypertension, diabetes, and end-stage renal disease on hemodialysis presented with abrupt mental status changes, seizures, and hypotension due to *Staphylococcus aureus* endocarditis from an infected arteriovenous fistula. Noncontrast brain computed tomography (CT) revealed subacute infarcts in the left frontal and temporal parietal lobes and a remote right occipital infarct. (B) He remained hemodynamically unstable despite antibiotic therapy with progressive obtundation and hemiplegia. Repeat CT revealed progression of a holohemispheric infarction with hemorrhagic conversion. (C) Angiography revealed bilateral and diffuse stenosis of the basal cerebral vessels consistent with infectious vasculitis, particularly involving the distal left internal carotid artery and left middle cerebral artery. Lumbar puncture was negative for meningitis.

of infarction (29–35%), intraparenchymal hemorrhage (29–57%), and subarachnoid hemorrhage (21–41%) (Corr et al., 1995; Chapot et al., 2002; Brust et al., 2004).

Extracranial mycotic aneurysms involving peripheral or visceral arteries can also rarely present with neurological manifestations, particularly nerve compression syndromes with bulbar dysfunction from subclavian artery aneurysms (Lee et al., 1998; Tsao et al., 1999), radial neuropathy from brachial artery expansion (Johnson et al., 1983), or spinal syndromes with aortic involvement (Soravia-Dunand and Loo, 1999).

Meningitis represents 6–27% of the neurological manifestations of endocarditis and results from the hematological spread of infected material. Meningitis is more commonly a primary manifestation but also complicates cerebral infarction or intracerebral hemorrhage (Salgado et al., 1987; Heiro et al., 2000). Brain abscess is relatively uncommon, documented in 1–3% of cases (Jones et al., 1969; Pruitt et al., 1978; Salgado et al., 1989; Eishi et al., 1995; Heiro et al., 2000).

Seizures are rarely the sole manifestation of endocarditis and their occurrence should prompt an evaluation for septic embolization that would otherwise have an impact on clinical management. Encephalopathy is described in 20% of series of neurological complications and as an isolated syndrome has been attributed to multifocal ischemic and septic embolization (Pruitt et al., 1978; Singhal et al., 2002).

DIAGNOSIS

Infective endocarditis is often classified as acute or subacute based on the pace of the natural evolution of clinical manifestations. Classically, acute infective endocarditis is fulminant and fatal within days to weeks whereas subacute infective endocarditis smolders with nonspecific systemic symptoms and immunological phenomena in the setting of underlying valvular disease. Although the cast of causative organisms has not substantially changed over the past several decades, their susceptibility to antibiotic therapy has dramatically shifted with the emergence of more virulent organisms and multidrug-resistant organisms (Baddour et al., 2005).

Although developed for epidemiological studies, the Duke criteria have been modified and adapted for clinician use (Durack et al., 1994; Li et al., 2000). High sensitivity and specificity have been demonstrated for multiple populations differing by age and prior injection drug use and involving both native and prosthetic valves. On this basis, a joint Scientific Statement recommends that the modified Duke criteria be used as the main framework to guide the evaluation of patients suspected of infective endocarditis (Baddour et al., 2005). To be classified as a definite case by pathologic criteria requires either culture or histological confirmation of organisms or histological evidence of active endocarditis from cardiac surgery or an embolized vegetation. A menu of clinical criteria allows a diagnosis of "definite" if there are either two major or one major plus three minor or five minor criteria, whereas a diagnosis of "possible" requires one major plus one minor or three minor criteria, as outlined in Table 13.1. Although the Duke criteria provide a framework, they were never meant to supplant clinical judgment. To optimize best outcomes and minimize mortality, the diagnosis of endocarditis must be made promptly, appropriate antibiotic therapy initiated as early as possible, and risk stratification performed to guide adjunctive therapies. As positive blood cultures are a prominent feature of the major criteria, obtaining the appropriate number and frequency of blood cultures prior to the initiation of antibiotic therapy is a key element in confirming the diagnosis and tailoring antibiotic therapy to the sensitivities of the causative organism. At least two sets of blood cultures should be obtained every 24–48 hours until negative (Baddour et al., 2005). Echocardiographic criteria also feature prominently and are essential in identifying high-risk features which would require early surgical intervention. When endocarditis is suspected, a transthoracic echocardiogram should be performed as an emergency, but if negative with a persistent clinical suspicion or if positive with high-risk features, a transesopheal echocardiogram should follow.

Neuroimaging

From a neurological perspective, the presence of major embolic events, most of which affect the central nervous system, represents one of the minor criteria for diagnosis. Although neuroimaging is usually performed to evaluate clinical symptoms, one small prospective study reported evidence of cerebral infarction on CT brain scans in 29% of patients with infective endocarditis (Millaire et al., 1997). Diffusion-weighted magnetic resonance imaging (DWI MRI) is the most sensitive imaging modality and allows for additional information on the temporal profile of involvement (Fig. 13.2). DWI MRI demonstrated acute lesions in 92% of a series of 26 patients with infective endocarditis imaged for the clinical indications of stroke or encephalopathy (Singhal et al., 2002). Multiple lesions were present in 70% of patients: all patients had involvement of more than one arterial territory with all affecting the middle cerebral artery distribution and 41% involving the cerebellum. A pattern of multiple but punctuate dissemination

Table 13.1

Modified Duke criteria for the diagnosis of infective endocarditis

Definite infective endocarditis	
Pathological criteria	Evidence obtained from a vegetation, an embolized vegetation, or an intracardiac abscess specimen demonstrating microorganisms by culture or histology or active endocarditis by histology
Clinical criteria	Two major, or one major and three minor, or five minor criteria
Possible infective endocarditis	One major plus one minor, or three minor criteria
Rejected	Does not fulfill clinical criteria, resolution of syndrome with less than 4 days of antibiotic therapy, no evidence of infective endocarditis at surgery or autopsy, or demonstration of a firm alternative diagnosis

Major criteria

1. Positive blood cultures: microorganisms typical of infective endocarditis* isolated from two separate blood cultures in the absence of a primary focus, or microorganisms consistent with infective endocarditis isolated from two blood cultures drawn >12 hours apart or three blood cultures drawn >1 hour apart
2. Positive blood culture for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer >1:800
3. Echocardiogram positive for infective endocarditis: oscillating intracardiac mass or abscess or new dehiscence of a prosthetic valve or new valvular regurgitation

Note: Serological tests for other difficult-to-cultivate organisms under consideration for addition to the major criteria list.

Minor criteria

1. Predisposition, predisposing heart condition, or injection drug users
2. Fever with temperature >38°C
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
5. Microbiological evidence: positive blood culture but not meeting major criteria or serological evidence of active infection with organism consistent with infective endocarditis

Note: Elevated erythrocyte sedimentation rate or C-reactive protein, new-onset clubbing, splenomegaly, and microscopic hematuria under consideration for addition to the minor criteria list.

*Viridans streptococci, *Streptococcus bovis,* HACEK group (see text), *Staphylococcus aureus,* enterococci.

lesions was associated with a clinical presentation of septic encephalopathy. Follow-up magnetic resonance imaging scans performed for recurrent neurological symptoms were likely to be positive for new lesions and rarely showed new lesions if the patient remained clinically stable (Singhal et al., 2002).

Intra-arterial digital subtraction angiography is the gold standard for the diagnosis of cerebral mycotic aneurysms as their small size and peripheral location are typically poorly visualized by magnetic resonance angiography or contrast-enhanced brain CT scans (Corr et al., 1995). Cerebral mycotic aneurysms typically have an irregular or fusiform shape and involve peripheral branches of the middle cerebral artery but 20–30% can be saccular and proximal (Fig. 13.3).

Lumbar puncture

Prior to the advent of modern neuroimaging, lumbar puncture was performed more commonly as it was one of the only neurodiagnostic studies available to clinicians. In acute endocarditis, CSF culture would often confirm the bacterial diagnosis, especially with *Streptococcus pneumoniae,* but in subacute endocarditis cultures were typically sterile (Greenlee and Mandell, 1973). Lumbar puncture is indicated in the setting of suspected meningitis or in the presence of unremitting headache after fever and bacteremia clear with antibiotic therapy (Salgado et al., 1989). If the patient has depressed consciousness or focal neurological signs or otherwise cannot be adequately examined to exclude a mass lesion from abscess or stroke that could complicate spinal fluid drainage, neuroimaging is recommended prior to lumbar puncture (Hasbun et al., 2001). Cerebrospinal fluid cultures are positive in only 15–25% of cases of meningitis. The most common reason for culture-negative fluid is prior initiation of antibiotic therapy, but it can also reflect an infection with a highly fastidious organism, inadequate microbiological processing, or a parameningeal focus of infection.

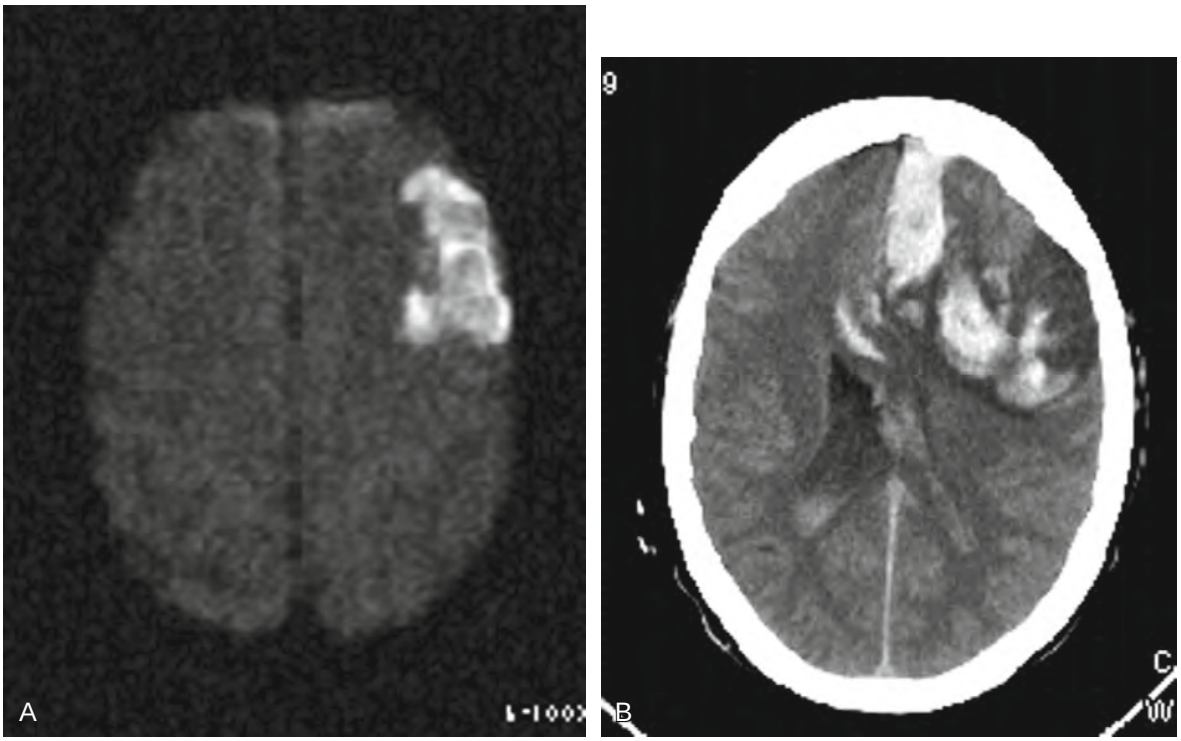

Fig. 13.2. (A) An elderly woman was admitted for an acute Broca's aphasia without systemic symptoms, fever, leukocytosis, or cardiac murmur. Diffusion-weighted magnetic resonance imaging (DWI MRI) confirmed an acute left frontal infarction and aspirin was initiated. (B) She abruptly deteriorated the following day and urgent noncontrast brain computed tomography revealed an intracerebral and intraventricular hemorrhage. She was subsequently diagnosed with *Staphylococcus aureus* endocarditis.

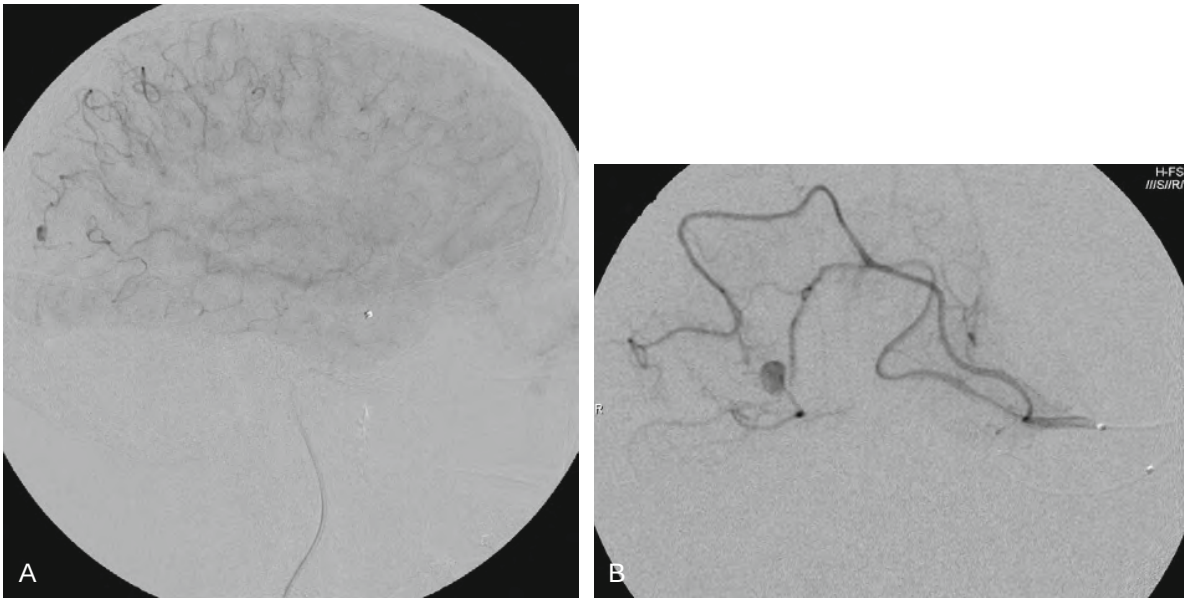

Fig. 13.3. (A) A young man was transferred for cardiac valve replacement after *Staphylococcus aureus* endocarditis. A symptomatic right middle cerebral artery mycotic aneurysm had been previously embolized. Preoperative neurological evaluation included a review of the prior angiogram which was suspicious for an additional aneurysm in the left middle artery territory. Repeat angiography confirmed the additional aneurysm which had enlarged from the prior study. (B) The mycotic aneurysm was successfully embolized with a liquid polymer and the patient went to surgery the following morning.

MANAGEMENT

Antibiotic therapy

The mainstay of treatment is the prompt initiation of appropriate antibiotic therapy and identification of high-risk criteria which would advocate early cardiac surgery. The risk of stroke is greatest prior to the institution of appropriate antibiotic therapy at 6% per day and rapidly declines after 2–3 weeks (Hart et al., 1990). Blood cultures are positive in 95% of cases and define the proper antimicrobial regimen, but initiating antibiotics prior to obtaining blood cultures decreases the yield by 35–40% (Werner et al., 1967). Antibiotic therapy should not be delayed until infection is documented, but rather initiated presumptively after blood cultures have been obtained. Empiric therapy is based on whether the presentation is acute or subacute. If the presentation is acute, the regimen should cover for *Staphylococcus aureus* and include vancomycin until it is known whether the organism is susceptible to nafcillin. If subacute, empiric therapy should include coverage for *Staphylococcus aureus,* viridans streptococci, and enterococci and include vancomycin, and penicillin, ampicillin, or a third- or fourth-generation cephalosporin. Two-week therapy with a combination of penicillin or ceftriaxone plus gentamicin can be curative for endocarditis due to highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis*, but gentamicin is ototoxic, vestibulotoxic, and nephrotoxic. Monotherapy with a third- or fourth-generation cephalosporin for 4 weeks avoids the use of gentamicin (Baddour et al., 2005). For culture-negative endocarditis, empiric therapy is based on whether the patient has a native or prosthetic valve. Empiric antibiotic therapy regimens for adults with culture-negative endocarditis with native valves or remote (>1 year) prosthetic valve surgery, include ampicillin–sulbactam plus gentamicin, or vancomycin plus gentamicin plus ciprofloxacin; rifampin is added if the patient also has a prosthetic valve. For early (<1 year) prosthetic valve surgery, empiric therapy includes vancomycin plus gentamicin plus cefepime plus rifampin (Baddour et al., 2005). The duration of therapy is typically 4–6 weeks for native valves, counting from the first day on which positive blood cultures become sterile (Baddour et al., 2005). Specific recommendations should be obtained by an infectious disease specialist.

Antiplatelet and anticoagulant therapy

There is no evidence that initiating antiplatelet or anticoagulant therapy in the acute period of endocarditis affecting a native or bioprosthetic valve reduces the risk of embolism.

Antithrombotic therapy is associated with an increased risk of intracranial hemorrhage and mortality, particularly with *Staphylococcus aureus* endocarditis (Heiro et al., 2000; Baddour et al., 2005). In a series of 56 patients with left-sided *S. aureus* endocarditis, the most important factor predicting a 73% mortality was the presence of anticoagulant therapy for a prosthetic valve at the time of infection onset (Tornos et al., 1999). In the setting of suspected *S. aureus* infection, or when neurological symptoms suggest embolism, anticoagulant therapy should be promptly discontinued for the first 2 weeks, or until the highest risk of intracranial hemorrhage has passed (Davenport and Hart, 1990; Baddour et al., 2005). At that juncture, if the infection is documented to be under control, intravenous heparin can be initiated pending a surgical decision (Tornos et al., 1999). In the absence of neurological symptoms suggesting embolism and when *S. aureus* is not suspected, oral anticoagulation should be discontinued and replaced with intravenous heparin until a surgical decision is made.

Neuroimaging of mycotic aneurysm

Cerebral angiography is the most accurate diagnostic test to identify mycotic aneurysms as their small size and peripheral location often escape less invasive studies such as contrasted CT scans, CT angiography, or magnetic resonance angiography. However, as cerebral angiography is invasive and mycotic aneurysms are overall uncommon, there is a reluctance to pursue such aggressive diagnostic testing in many patients. Nonetheless, judicious evaluation of high-risk populations is supported as mycotic aneurysm rupture is associated with a mortality of >80%. Recommendations for cerebral angiography in the setting of infectious endocarditis are based on small retrospective case series. In the setting of any subarachnoid or intraparenchymal hemorrhage, cerebral angiography should be performed without delay. In the setting of neurological symptoms consistent with embolic TIA or ischemic stroke that occurs during bacteremia or in the setting of uncontrolled infection, angiography should also be performed, although the optimum timing is controversial. Early study is supported by one study that identified two out of 17 (12%) patients sustaining aneurysm rupturing within 24 hours (Fig. 13.2) of ischemic symptoms, but animal studies suggest that the infected embolus requires at least 24–48 hours to cause sufficient arteritis to produce vessel dilatation (Salgado et al., 1987; Brust et al., 2004).

Historically, repeating cerebral angiography at intervals of 2–3 weeks was recommended to monitor progress during antibiotic therapy. With antibiotic therapy, about 50% of mycotic aneurysms will resolve and 30% will improve. However, 20% will enlarge with

an increased risk of rupture and there are no clear predictive radiographic features (Fig. 13.3) (Salgado et al., 1987). CT angiography or conventional cerebral angiography can be used to follow documented aneurysms. In one small study of five patients, six aneurysms ranging in size from 4 to 10 mm were followed with two (33%) resolving, and four were operated for enlargement or persistence. No new aneurysms were identified (Ahmadi et al., 1993). In another small study, 18 aneurysms in 14 patients were followed with angiography. Aneurysms which ruptured tended to be larger – average size 8.3 mm versus 6 mm. Complete resolution was documented in nine (33%), 17% decreased in size, 33% were unchanged, and 17% increased in size. One patient (7%) suffered an intracranial hemorrhage while on appropriate antibiotic therapy prior to the scheduled 2-week follow-up angiogram (Corr et al., 1995). In a recent study of 28 aneurysms in 17 patients followed by angiography, 10/20 (50%) resolved or regressed and 10/20 (50%) stabilized or enlarged, and, in the latter group, one patient (6%) suffered a delayed aneurysmal rupture after completing the appropriate course of antibiotic treatment (Brust et al., 2004). In addition, there are very rare case reports of *de novo* aneurysms appearing on serial neuroimaging during the course of antibiotic therapy (Ahmadi et al., 1993; Corr et al., 1995; Brust et al., 2004).

Neurosurgical and endovascular therapy

When surgical excision was the only option for treatment of mycotic aneurysms, treatment was recommended for those aneurysms which persisted or enlarged while on medical therapy or prior to systemic heparinization required for cardiac surgery. With advances in endovascular approaches including parent vessel occlusion with cyanoacrylate, embolization of proximal aneurysms, coiling, and neuroform stent placement, treatment is now recommended not only for those requiring early cardiac surgery but also for definitive treatment at the time of diagnosis as a less risky option than the alternative to the 12% risk of precipitous rupture and 6–7% risk of rupture during or after antibiotic treatment (Chapot et al., 2002; Sugg et al., 2006).

Cardiac surgery

Despite improvements in surgical technique, the perioperative risk of cardiac surgery remains increased in infected and unstable patients. However, there are several situations where early cardiac surgery, despite its increased risks, offers patients their best chance for a good outcome when compared with delayed surgery or medical therapy alone. Over the last decade there has been a progressive trend toward earlier surgical intervention; one institution attributed a decrease in in-hospital mortality from 22% to 15% to an increase in early cardiac surgery from 31% to 50% (Hoen et al., 2002). Indications for cardiac surgery in infective endocarditis include heart failure, perivalvular abscesses, intracardiac fistula, valvular obstruction, embolism, vegetations larger than 1 cm, and resistant, persistent, or relapsed infection with medical therapy. Heart failure is a major determinant of in-hospital mortality and more than half of surgical indications are due to heart failure from valvular regurgitation. Although the perioperative mortality is increased from 5–10% to 15–35% with heart failure, surgical candidates still fare better than those with medical therapy alone: their mortality is 55–85% (Olaison and Patterson, 2002). Hemodynamic instability can occur precipitously when endocarditis is complicated by valvular obstruction or dehiscence of a valvular prosthesis or may occur insidiously with progressive valvular insufficiency, particularly with involvement of the aortic valve. Delaying surgery in the setting of a perivalvular abscess or intracardiac fistulae increases the perioperative risk. Elective, but early surgery is recommended when bacteremia persists for >1 week despite appropriate antibiotic therapy or is due to a resistant or difficult-to-treat organism as these patients are more likely to develop large or mobile vegetations with perivalvular infection and systemic embolism; these include fungal infections, such as *Candida* or *Aspergillus* spp., as well as bacterial infections due to *Pseudomonas aeruginosa*, *Achromobacter xylosoxitans*, *Brucella*, or highly resistant enterococci (Delahaye et al., 2004).

The appropriate timing of cardiac surgery in patients with acute ischemic or hemorrhagic stroke remains controversial and is one of the most difficult questions posed to a vascular neurologist. Cardiopulmonary bypass is known to cause cerebral injury through a variety of mechanisms, including macroembolism, microembolism, and poor clearance of microemboli and cerebral hypoperfusion. The baseline risk of ischemic stroke in large series ranges from 6% to 12% for valvular operations not complicated by endocarditis but often combined with coronary revascularization (Wolman et al., 1999). Cardiopulmonary bypass requires systemic heparinization which is recognized to increase the risk of hemorrhagic transformation within a cerebral infarct, particularly when initiated within the first 2 weeks. In addition, cardiopulmonary bypass induces a systemic inflammatory response that disrupts the blood–brain barrier for several days, which would exacerbate cerebral edema associated with a major cerebral infarction or cerebral hemorrhage and could destabilize a mycotic aneurysm, resulting in

rupture. For these reasons, some have advocated delaying cardiac surgery for infective endocarditis in patients with an acute neurological deficit for 2–3 weeks. This approach is supported by several retrospective series culled from surgical databases.

A Japanese multicenter review of 2523 cardiac surgeries for infective endocarditis included 244 patients with preoperative cerebral complications (Eishi et al., 1995). Neurological worsening with increased hospital mortality occurred in 43–46% of those operated within the first week compared with 10–17% of those operated between 2 and 4 weeks. This early risk included the death of one patient with a cerebral hemorrhage operated within 24 hours. Gillinov and colleagues (1996) reviewed the Johns Hopkins experience of 247 cardiac surgeries for left heart infective endocarditis, which included 34 patients with a new neurological deficit; 23 patients with a bland embolic infarct, four patients with a hemorrhagic transformation of an embolic infarct, and three patients with a ruptured mycotic aneurysm which was surgically clipped prior to cardiac surgery. Cardiac surgery performed an average of 22 days after the neurological event was complicated by neurological deterioration in only two (6%) patients.

A retrospective series from Austria described 214 surgical patients, of whom 65 had sustained a preoperative stroke or TIA, who underwent cardiac surgery after a median 4 days (range 0–38 days). The perioperative mortality rate was increased 1.7-fold for stroke patients overall, but was predominantly due to a death rate of 38.9% for those with cerebral hemorrhage or complicated by meningitis or brain abscess, compared with 8.5% for those with uncomplicated ischemic stroke, which included both partial and complete middle cerebral artery syndromes. The patients with cerebral hemorrhage fared poorly: four of six died postoperatively, one from a perioperative recurrent intracranial hemorrhage despite a preoperative craniotomy and three from nonneurological causes. The authors concluded that cardiac surgery should not be delayed for patients with uncomplicated ischemic stroke, including those with major or disabling hemispheric syndromes, for fear of a perioperative intracranial hemorrhage (Ruttman et al., 2006).

A recent prospective multicenter study of 496 patients with endocarditis identified 109 patients with a cerebrovascular complication which included ischemic stroke, intracranial hemorrhage, TIAs, and silent lesions identified by brain CT scan (Thuny et al., 2007). For those patients with a surgical indication, survival was significantly better with surgery than with medical care alone, although the groups were significantly different. Medically treated patients had significantly lower Glasgow Coma Scale scores and greater comorbidities and, among all stroke patients, mortality was largely predicted by poor neurological status and presence of prosthetic valve endocarditis. Perioperative neurological deterioration occurred in four (6.3%) patients, and was confined to patients with a symptomatic stroke preoperatively.

Taken together, these studies confirm that perioperative and in-hospital mortality is increased for those patients with infective endocarditis who experience a symptomatic ischemic stroke or intracerebral hemorrhage. The same risk does not seem to be conferred by TIAs or silent cerebral infarcts identified by surveillance neuroimaging. Stroke patients who undergo cardiac surgery fare better than those managed medically and the risk of neurological deterioration, ranging in small studies from 0% to 17%, is not substantially increased for surgeries performed at 2–4 weeks after stroke onset, particularly for bland ischemic strokes (Borghetti et al., 2006).

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Chapter 14

Whipple's disease of the central nervous system

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INTRODUCTION

George Whipple initially reported the disease bearing his name in 1907, in which he described a 36-year-old male medical missionary with an illness characterized by weight loss and intractable diarrhea (Whipple, 1907). However, extragastrointestinal manifestations were recognized from the first descriptions of this illness as well as in subsequent reports. Whipple's initial observations included all of the essential bowel manifestations of the disease, with pathological features of lipid degeneration involving the intestinal mucosa, and involvement of the mesenteric lymph nodes with argyrophilic rod-shaped microorganisms; this initial description included the name "intestinal lipodystrophy." Whipple also recognized the systemic features of the disease such as polyarthritis, polyserositis, endocarditis, and lymphadenopathy. It was later established that the macrophages involved by this disease contained periodic acid–Schiff (PAS)-positive material, indicative of the presence of glycoprotein. Later, electron microscopic investigations showed that the PAS-positive material consisted of curvilinear-shaped bacilli (Chears and Ashworth, 1961; Yardley and Hendrix, 1961).

ETIOLOGY AND EPIDEMIOLOGY

Identification and characterization of the Whipple's disease agent were performed by molecular techniques using ribosomal RNA sequences amplified from the duodenal tissue of a patient with Whipple's disease (Relman et al., 1992). This sequence was subsequently detected in tissues from patients identified with Whipple's disease, but in none of the patients without the disorder (Relman et al., 1992). The bacterium was discovered to be a gram-positive actinomycete which, at the time, was not closely related to any known genus. Based on this molecular information, the bacillus was named *Tropheryma whippelii*. Subsequent study of this organism utilized molecular cloned sequences derived from extracts of tissue involved by Whipple's disease. Finally, in 2000, the bacterium of Whipple's disease was cultivated (Raoult et al., 2000), and the name was then slightly changed to *Tropheryma whipplei*. The genome of *T. whipplei* has been sequenced and placed in Genbank (Marth and Raoult, 2003). Antibodies were raised against the organism (Relman et al., 1992), and immunohistochemical staining of clinical biopsy specimens was found to be helpful in confirming the presence of disease (Marth and Raoult, 2003). The standard for the diagnosis of Whipple's disease has relied on molecular techniques, specifically using polymerase chain reaction (PCR) amplification of bacterial-specific nucleic acid from involved tissue.

The source of *T. whipplei* and its means of transmission to people are, as yet, unknown. The organism is presumed to be environmental, with ingestion and infection of the gastrointestinal tract as the primary site for disease. One proposed concept is that, although many people are exposed to *T. whipplei*, immune factors are required to predispose to invasive infection; however, no specific immunocompromised state has been associated with disease (Marth and Raoult, 2003; Fenollar et al., 2007). *T. whipplei* replicates in macrophages and other monocytic cells. Humoral responses do not appear to play a role in this disease.

CLINICAL MANIFESTATIONS

General features

Whipple's disease remains a rare disorder. Although no incidence data are available, at least 1000 cases have been reported (Fenollar et al., 2007). It can occur in all

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ages and races, but white middle-aged men have been the predominant group affected. The primary systemic symptoms are weight loss, diarrhea, and abdominal pain. Other systemic symptoms, including serositis, arthritis, lymphadenopathy, and fever, have been identified; cardiac involvement is also well recognized (Enzinger and Helwig, 1963). Fifteen percent of Whipple's disease patients, however, do not have the classical symptoms (Fenollar et al., 2007). There have been several case series that have examined the long-term systemic manifestations of the disease (Fleming et al., 1988); the findings of diarrhea and arthralgia were present in more than two-thirds of those patients (Fleming et al., 1988). Uveitis may be a part of the systemic illness. Laboratory evaluation may show anemia, leukocytosis, an elevated sedimentation rate, and evidence of malabsorption.

Table 14.1

Neurological signs in central nervous system Whipple's disease

Neurological sign	Frequency
Cognitive changes	71%
Supranuclear gaze palsy	51%
Psychiatric signs	44%
Hypothalamic manifestations	31%
Cranial nerve abnormalities	25%
Myoclonus	25%
Seizures	23%
Ataxia	20%
OMM or OFSM	20%

Adapted from Louis et al. (1996).
OMM, oculomasticatory myorhythmia; OFSM, oculo-facial-skeletal myorhythmia.

Neurological disease

Central nervous system (CNS) involvement in Whipple's disease is thought to occur in three circumstances: (1) neurological involvement with systemic disease; (2) neurological relapse in patients treated for systemic disease; and (3) neurological disease without systemic disease. The frequency of neurological involvement is controversial, with estimates ranging from 6% to 63%. One review estimated an incidence of 4% (Fleming et al., 1988) when ophthalmoplegia was included as evidence for neurological involvement. A small autopsy series found CNS disease in 10 of 11 patients studied (Enzinger and Helwig, 1963). Based on a review of 99 patients from seven case series, one-third had neurological signs (Fenollar et al., 2007). Another review documented CNS or eye involvement in 25% of cases (Marth and Raoult, 2003). Neurological involvement without gastrointestinal symptoms has been known for more than 40 years (Lampert et al., 1962; Feurle et al., 1979; Johnson and Diamond, 1980; Grossman et al., 1981); it is estimated that 20% of patients with CNS Whipple's disease will have no systemic symptoms or signs (Louis et al., 1996). Published reviews of neurological Whipple's disease have revealed a strong male predominance approximating 80%, as is also seen in patients with systemic Whipple's disease (Matthews et al., 2005). The mean age of onset of neurological symptoms was 49 years in one series, with a range of 28–64 years (Matthews et al., 2005).

Asymptomatic gastrointestinal involvement in patients with Whipple's disease can be proven at autopsy or by biopsy of the jejunal mucosa (Lampert et al., 1962). Other cases have shown CNS involvement, proven by brain biopsy, even when jejunal biopsy was negative (Halperin et al., 1982; Peters et al., 2002; de Andrade et al., 2007).

The most characteristic primary presentation associated with CNS Whipple's disease is the triad of cognitive changes, ophthalmoplegia, and myoclonus. The complete triad, however, may be present in only 15% of cases (Louis et al., 1996). The myoclonus type that is most specific for Whipple's disease is oculomasticatory myorhythmia (OMM). Other characteristic manifestations include psychiatric, vegetative, cranial nerve, epileptic, or ataxic symptoms (Table 14.1).

The dementia of Whipple's disease usually occurs subacutely to chronically. It may or may not be associated with systemic symptoms of weight loss, diarrhea, arthralgias, and other overt manifestations of systemic disease. Dementia is often associated with prominent behavioral changes (Halperin et al., 1982). Difficulty with working memory may be a prominent feature, correlating with frontal and temporal lobe involvement. Dementia, with prominent vegetative symptoms such as hypersomnolence, autonomic symptoms, or hyperphagia, suggests hypothalamic involvement. Psychiatric signs, typically occurring as part of the cognitive disorder, have been estimated to occur in 44% of patients (Louis et al., 1996).

The eye movement abnormalities typically will begin as vertical conjugate ophthalmoparesis (Finelli et al., 1977; Fleming et al., 1988 Averbuch-Heller et al., 1999) but can evolve into complete ophthalmoplegia (Knox et al., 1995; Louis et al., 1996). This is usually a manifestation of midbrain involvement (Lampert et al., 1962). Typically the vertical gaze palsy is conjugate, and more affected than horizontal gaze. Supranuclear ophthalmoplegia is reported to be the mechanism for conjugate gaze paresis (Averbuch-Heller et al., 1999; Lee, 2002). Individual ophthalmoplegia, with third- or fourth-nerve

involvement, can also be seen, but is usually in addition to conjugate gaze weakness. The pupils may be involved and there is near-light dissociation. Nystagmus is relatively unusual, but may also be seen (Halperin et al., 1982). Uveitis may be part of the ophthalmic involvement (Finelli et al., 1977).

Myoclonus may be generalized, but the most pathognomonic feature of Whipple's disease is OMM. OMM is so rare a disorder that it is felt to be diagnostic of CNS involvement by Whipple's disease (Louis et al., 1996). The clinical constellation consists of rhythmic contractions of the jaw, tongue, and coincident convergent oscillations of both eyes, estimated at a rate of 1–2 Hz (Schwartz et al., 1986). These are often associated with semirhythmic blinking. These movements persist in sleep, unaltered by environmental stimuli (Schwartz et al., 1986). A related movement disorder, oculo-facial-skeletal myorhythmia (OFSM), is defined as convergence of oscillations of the eyes associated with rhythmic movements of the face and proximal extremities that persist into sleep (Adler and Galetta, 1990; Louis et al., 1996). OFSM can be a manifestation of isolated CNS involvement (de Andrade et al., 2007), and, along with OMM, is felt to be a brainstem-generated form of segmental myoclonus.

Ataxia can be a prominent feature of CNS Whipple's disease (Halperin et al., 1982; Matthews et al., 2005) and pathologically is a representation of cerebellar involvement (Lampert et al., 1962). Ataxia, vertical gaze palsy, and hypothalamic vegetative symptoms are strongly suggestive of Whipple's disease. In one series, 55% of the patients presented with cerebellar ataxia as the primary manifestation of disease (Matthews et al., 2005).

Hypothalamic involvement can manifest as hypersomnia, hyperphagia, or personality change (Lampert et al., 1962). Hyponatremia, polydipsia, or impotence may also be seen (Halperin et al., 1982). More rare manifestations of CNS involvement include headache, optic neuropathy, trigeminal neuropathy, or meningitis.

Focal cortical symptoms (hemiplegia, aphasia, alexia, or agraphia) can occur as part of CNS involvement. Unilateral temporal lobe involvement with a mass lesion has been reported (Fig. 14.1) (Halperin et al., 1982). Seizures can manifest as a consequence of cerebral cortical involvement (Koudouris et al., 1963; Finelli et al., 1977); because the temporal lobes are commonly affected by CNS Whipple's disease, partial complex seizures are the most commonly observed.

Polyneuropathy has been reported to be associated with nervous system involvement by Whipple's disease, though PAS-positive material or bacillary profiles may not be found in sural nerve biopsies (Halperin et al., 1982). Myelopathy has been reported, particularly in association with prominent posterior column involvement (Koudouris et al., 1963). Cervical myelopathy has also been reported (Messori et al., 2001). Other unusual clinical manifestations of Whipple's disease

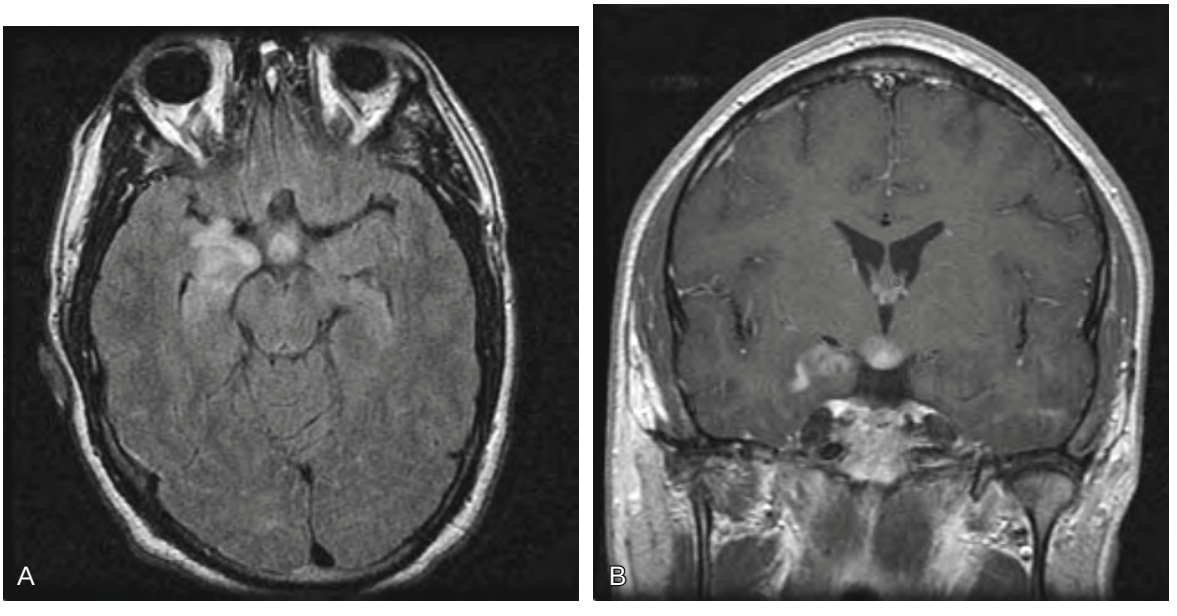

Fig. 14.1. Magnetic resonance imaging (MRI) scan of the brain from a patient with central nervous system Whipple's disease proven by polymerase chain reaction detection of *Tropheryma whipplei* in cerebrospinal fluid. There is abnormal signal in the right mesial temporal and hypothalamic areas on this axial fluid-attenuated inversion recovery (A) and coronal T1-weighted gadolinium-enhanced (B) brain MRI images. There is increased signal and enhancement in the involved areas.

include parkinsonism, hydrocephalus, and myopathy. Hydrocephalus is typically caused by obstruction of the aqueduct of Sylvius or fourth ventricle by granular ependymitis. The myopathy is typically a proximal one, and muscle biopsy is helpful in its evaluation; muscle biopsy has shown type 2 fiber atrophy and variability of fiber size. Muscle interfascicular macrophages show evidence of PAS-positive material (Swash et al., 1977).

DIAGNOSIS

Neuroimaging

Neuroimaging abnormalities are thought to occur in at least half of the patients with CNS Whipple's disease (Louis et al., 1996). Magnetic resonance imaging (MRI) of the brain is the most sensitive neuroimaging study and has most commonly shown focal increased T2 or fluid-attenuated inversion recovery (FLAIR) signal involving the hypothalamus, uncus, and medial temporal lobes (Fig. 14.1A) (Adams et al., 1987). Bright T2 and FLAIR signal abnormalities may also be prominent in the cerebellar peduncles in those patients with associated cerebellar findings (Messori et al., 2001; Lee, 2002). Abnormal signal on FLAIR sequences affecting the thalami, and lentiform and caudate nuclei, has been reported (de Andrade et al., 2007). Hypothalamic involvement can be accompanied by T2 and FLAIR increased signal intensity involving the hypothalamus and fornix areas (Mendel et al., 1999). Parenchymal brain involvement may or may not be associated with postcontrast gadolinium enhancement (Fig. 14.1B) (Mendel et al., 1999).

A longitudinally extensive radiographic cervical myelopathy has been reported in patients with Whipple's disease (Clarke et al., 1998; Messori et al., 2001). The MRI typically shows high T2 signal in the spinal cord over multiple segments, which may partially improve in response to corticosteroid therapy (Clarke et al., 1998). Gadolinium enhancement is often minimal, but at least one proven case has shown extensive gadolinium enhancement (Schroter et al., 2005).

Laboratory investigation

After neuroimaging, cerebrospinal fluid (CSF) analysis is the most specific means of investigating patients for involvement of the CNS by Whipple's disease (Table 14.2). The CSF protein and glucose concentrations, and cell count, may be normal (Koudouris et al., 1963; Halperin et al., 1982). However, the CSF protein concentration was elevated in 46% of cases in one series (Louis et al., 1996). Elevation of CSF intrathecal immunoglobulin synthesis is not usually present. A CSF pleocytosis has also been observed (Adams et al., 1987; Delanty et al., 1999). A review of CSF results of 59 CNS Whipple's disease patients showed that there were five or more leukocytes per microliter in 47% of patients, with a range of 5–900 cells/μl and a mean of 91 cells/μl (Louis et al., 1996). CSF PCR is the confirmatory test of choice (see below).

Table 14.2

Laboratory evaluation of central nervous system Whipple's disease

Test	Finding
Magnetic resonance imaging head	Normal or increased T2 signal, sometimes enhancement; location most common in the hypothalamus, mesial temporal lobes, midbrain, or cerebellum
Cerebrospinal fluid	Normal or mild elevation of protein or cell count
Cerebrospinal fluid polymerase chain reaction for *Tropheryma whipplei*	*Tropheryma whipplei* DNA detected (in most cases)
Small-bowel biopsy	Lipid-laden macrophages and periodic acid–Schiff-positive material in two-thirds of patients

Small-bowel biopsy is the procedure of choice to attempt to identify lipid-laden degeneration of the small bowel in patients with suspected CNS manifestations. Histological staining for PAS-positive material in the macrophages invading the bowel wall tentatively identifies *T. whipplei* on pathological grounds. Electron microscopy of involved tissue can demonstrate the presence of bacillary forms with trilaminar cell walls characteristic of *T. whipplei*. PCR amplification of the *T. whipplei* from the small-bowel biopsy material confirms the disease by molecular means (Lynch et al., 1997). Up to one-third of CNS Whipple's disease cases have negative small-bowel investigations, with histologically negative biopsies and negative PCR analysis. However, a positive small-bowel analysis by PCR identifying *T. whipplei* in the small bowel in a patient with neurological disease is pathologically meaningful. The presence of *T. whipplei* in the intestinal mucosa is rare in patients without other evidence of Whipple's disease (Maiwald et al., 2001).

Neurological involvement can be confirmed by PCR analysis of CSF by amplifying copies of the *T. whipplei*, targeting the 16S rRNA gene (Messori et al., 2001;

Maiwald et al., 2003). This technique has been standardized and is acknowledged as a sensitive means of identifying *T. whipplei* in the CSF of patients with CNS Whipple's disease (Lynch et al., 1997; von Herbay et al., 1997). However, the precise negative predictive value of a PCR study excluding *T. whipplei* as the cause of clinically compatible neurological disease is lacking. It is possible to have *bone fide* CNS Whipple's disease with a negative CSF PCR analysis, but for the patient to respond to appropriate antimicrobial treatment (Peters et al., 2002; Matthews et al., 2005). CSF PCR is, however, the most sensitive and least invasive test to establish the presence of CNS disease.

Some studies have suggested that PCR amplification of the 16S bacterial rRNA gene of *T. whipplei* from CSF is useful for monitoring response to antimicrobial therapy (Ramzan et al., 1997; Pron et al., 1999). More recent work has indicated that a real-time PCR assay, which targets the repeated sequences of the *T. whipplei* genome, has greater sensitivity and no worsening of specificity (Fenollar et al., 2007). Caution with PCR techniques needs to be emphasized because of the significant risk of laboratory contamination; testing for *T. whipplei* by this means is no exception. There are no large series comparing the validity of CSF PCR in patients with pathologically proven CNS disease.

Cultivation of *T. whipplei* from CSF is possible in patients who have CNS Whipple's disease (Maiwald et al., 2003). Successful cultivation has correlated well with the presence of identifiable 16S rRNA demonstrated by PCR amplification from the CSF. Positive PCR from synovial fluid has been used as a means to infer that neurological disease is also caused by *T. whipplei* in the brain (Delanty et al., 1999). Culturing the organism is exceedingly difficult, labor-intensive, and should presently be considered a research tool (Raoult et al., 2000; Maiwald et al., 2003).

The use of PCR amplification from blood is more controversial as an indicator of CNS involvement. Patients with CNS Whipple's disease, proven by brain biopsy, can have positive PCR amplification from blood and brain, but with negative CSF results and a histologically normal small-bowel biopsy (Peters et al., 2002). There are also examples of CNS disease on clinical grounds and by neuroimaging, but with negative CSF PCR for *T. whipplei* and negative bowel biopsy; blood detection of *T. whipplei* by PCR, and clinical and radiographic response to antimicrobial therapy established the diagnosis (Peters et al., 2002; Schroter et al., 2005). These cases suggest that PCR of blood may be another means of diagnosis, although there may be false-positive results. Nervous system involvement, however, can occur when CSF and bowel biopsy findings are negative.

NEUROPATHOLOGY

The first descriptions of pathological changes in the brains of patients with Whipple's disease date back to 1960, when descriptions of presumed neurologically asymptomatic individuals with granular ependymitis were published (Sieracki et al., 1960). Pathological studies were subsequently published, emphasizing the involvement of brainstem and basal brain structures which paralleled the clinical symptomatology (Lampert et al., 1962; Halperin et al., 1982); the neuropathology of a nodular ependymitis infiltration involved the ventricular surface of the brainstem and deep basal brain structures (Sieracki et al., 1960; Lampert et al., 1962). The macrophage response along the ventricles may be innocuous, or may demonstrate a severe reaction which includes a nodular ependymitis with astrocytosis (Lampert et al., 1962).

Gray matter is the most predominantly affected cellular structure of the brain in patients with Whipple's disease (Bruyn, 1988). The cerebral hemispheric gray matter can be diffusely affected with mononuclear perivascular cuffing, abundant foamy macrophages containing PAS-positive material, and reactive astrocytosis (Knox et al., 1995). More commonly, the parenchymal pathology is most densely distributed in the periaquaductal gray matter of the midbrain, the hypothalamus around the third ventricle, mammillary bodies, and deep basal ganglia structures. The colliculi are also commonly involved. Involvement of the periaqueductal midbrain region correlates well with clinical ophthalmoparesis, particularly of vertical eye movements (Finelli et al., 1977). Thalamic involvement is typically seen in the midline, particularly in the dorsal medial nucleus of the thalamus. Cerebellar involvement typically affects the Purkinje cells and regions of the lining of the fourth ventricle. The dentate nucleus is also commonly involved (Lampert et al., 1962). Cerebral cortical involvement can be diffuse (Lampert et al., 1962) or focal (Halperin et al., 1982). In the medulla, the inferior olivary nuclei are commonly involved, but other gray-matter structures may be affected. The most commonly affected cerebral cortical areas are the temporal lobes, and nuclei of the hippocampi and amygdala (Bruyn, 1988).

Spinal cord involvement in Whipple's disease may prominently affect the posterior columns (Koudouris et al., 1963), with similar histological features to those seen elsewhere in the brain. Large numbers of foamy macrophages with PAS-positive structures are found, and can be demonstrated by biopsy of the spinal cord (Clarke et al., 1998). Involvement of the optic nerve or optic chiasm has been reported, as well as leptomeningeal infiltration with associated parenchymal

involvement (Romanul et al., 1977; Peters et al., 2002). The histological abnormalities in the meninges are the same as those seen elsewhere in the parenchyma, with foamy macrophages containing PAS-positive material. Other locations that can be involved pathologically include muscle and pituitary gland.

The histological features are those of parenchymal macrophage clusters containing PAS-positive material (Lampert et al., 1962), characteristically in a perivascular distribution. The affected macrophages will also stain intensely with Gomori methenamine silver (Bruyn, 1988). A macrophage response predominates, but accompanying lymphocytic perivascular infiltration is usual (Halperin et al., 1982). Microglial nodules can be seen (Adams et al., 1987). Multinucleate giant cells can be seen suggestive of granulomatous reaction (Bruyn, 1988). Astrocytosis is present in more chronic lesions.

The PAS-positive material is identifiable in the *T. whipplei* bacillus responsible for Whipple's disease. The bacillus is primarily intracellular in macrophages, but can also be stained in the interstitium. Electron microscopy identifies numerous *T. whipplei* bacillary profiles in infected macrophages (Halperin et al., 1982). Although electron microscopy can be performed to show the presence of bacillary involvement, molecular techniques using PCR for identification of *T. whipplei* sequences are more specific to confirm that brain tissue is infected (Marth and Raoult, 2003; Fenollar et al., 2007).

TREATMENT

Intravenous penicillin, followed by a prolonged course of oral trimethoprim-sulfamethoxazole, had been the regimen of choice in the treatment of CNS Whipple's disease. Tetracycline has also been utilized, but is associated with a high incidence of relapse of disease (Marth and Raoult, 2003). The current treatment recommendation for CNS disease is ceftriaxone 2 grams intravenously every 12 hours for 2 weeks followed by oral trimethoprim-sulfamethoxazole (one tablet double strength twice daily) for 1–2 years (Matthews et al., 2005). In patients with sulfa intolerance, cefixime, minocycline, tetracycline, or oral penicillin has been recommended (Marth and Raoult, 2003). Although patients with neurological disease have a particularly poor prognosis, with average survival thought to be only 4 years (Fenollar et al., 2007), no recent large series of ceftriaxone-treated patients is available to provide data about survival of CNS disease in the modern era. In a recent small series 11 patients with at least 1 year follow-up who were treated in this fashion were alive (Matthews et al., 2005).

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Chapter 15

Neuroimaging of central nervous system infections

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ACUTE PYOGENIC (USUALLY BACTERIAL) MENINGITIS

Meningitis is the most common form of central nervous system (CNS) infection. Microorganisms may reach the leptomeninges through hematogeneous spread (the most common means of entry), local spread from an adjacent focus of infection (e.g., otitis media), perineural spread (rabies, herpes simplex), as well as via direct inoculation (e.g., lumbar puncture, cranial surgery) (Morris and Cshoene, 1999).

Pathologically, acute pyogenic meningitis results in a purulent exudate filling the cisterns and sulci. The pia and arachnoid become congested. The meningeal vessels become engorged and prominent on imaging studies. Similarly, involvement of the ependymal lining of the ventricles results in ventriculitis and/or ependymitis.

Computed tomography (CT)

A normal CT scan is the most common finding in the setting of acute meningitis. In some cases, however, effacement of the basilar or convexity cisterns, or enhancement of the meninges in sulci and cisterns, can be seen (Fig. 15.1). If vasospasm or infarction has occurred, CT angiography may reveal focal arterial narrowing or occlusion (Osborn et al., 2004). In pediatric cases, mild ventricular dilatation and enlargement of the subarachnoid space, particularly in the basal cisterns and along the interhemispheric fissure, can be seen.

Magnetic resonance imaging (MRI)

Abnormalities of meningitis are better visualized on MRI than on CT. On T1-weighted images, the exudate is usually isointense; on T2-weighted images it is mostly hyperintense (Osborn et al., 2004) (Figs 15.1 and 15.2). Precontrast fluid-attenuated inversion recovery (FLAIR) images may be unremarkable or reveal sulcal hyperintensity. Infectious causes of meningitis are usually associated with leptomeningeal enhancement (involving arachnoid and pia) (Fig. 15.2). Postgadolinium FLAIR images are extremely sensitive to leptomeningeal disease and should be included in the imaging protocol in patients with suspected CNS infection (Fig. 15.3). FLAIR images are more sensitive than postcontrast T1-weighted images and are likely to show abnormal meningeal enhancement immediately. Postcontrast T1-weighted images are best obtained after the FLAIR images, thereby allowing a few minutes for abnormal contrast enhancement of the leptomeninges and brain. Such images may or may not reveal enhancement of the exudate within the basal cisterns and sulcal depths (Osborn, 1994; Osborn et al., 2004). However, T1-weighted images are more specific than are FLAIR images with respect to parenchymal enhancement.

Abnormal meningeal enhancement may also be seen in patients following lumbar puncture and has been reported in 1% of patients undergoing uncomplicated lumbar puncture. It has been proposed that cerebrospinal fluid (CSF) leak following lumbar puncture or other operations, such as spinal surgery or spinal anesthesia, results in intracranial hypotension (Krause et al., 1997; Bakshi et al., 1999). Intracranial hypotension is characterized by postural, bilateral headache that occurs mostly after going from the supine to the upright position and disappears or decreases in intensity after resuming the recumbent position. Diffuse meningeal enhancement is probably related to engorgement of meningeal vessels. According to the Monro–Kellie rule, intracranial blood volume and CSF volume fluctuate; thus, reduced CSF volume leads to venous engorgement. In the differential diagnosis of meningeal

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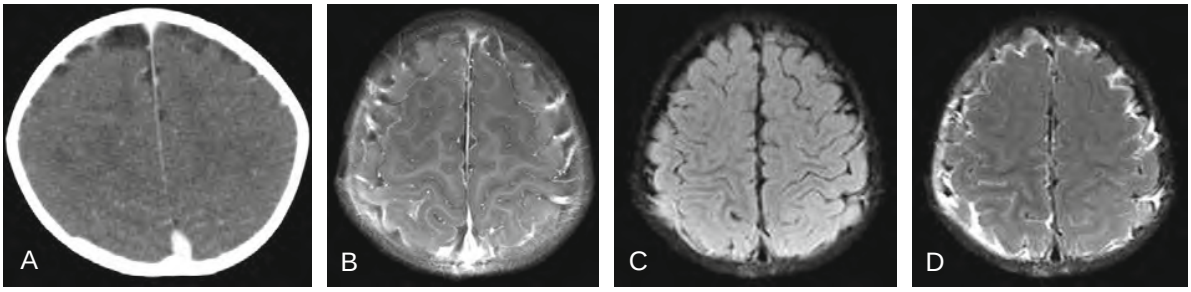

Fig. 15.1. (A) Postcontrast computed tomography shows subtle leptomeningeal enhancement. (B) Postcontrast T1-weighted image shows leptomeningeal enhancement. (C) Precontrast fluid-attenuated inversion recovery (FLAIR) image is unremarkable. (D) Postcontrast FLAIR image demonstrates remarkable leptomeningeal enhancement. (Illustration copyright Truwit.)

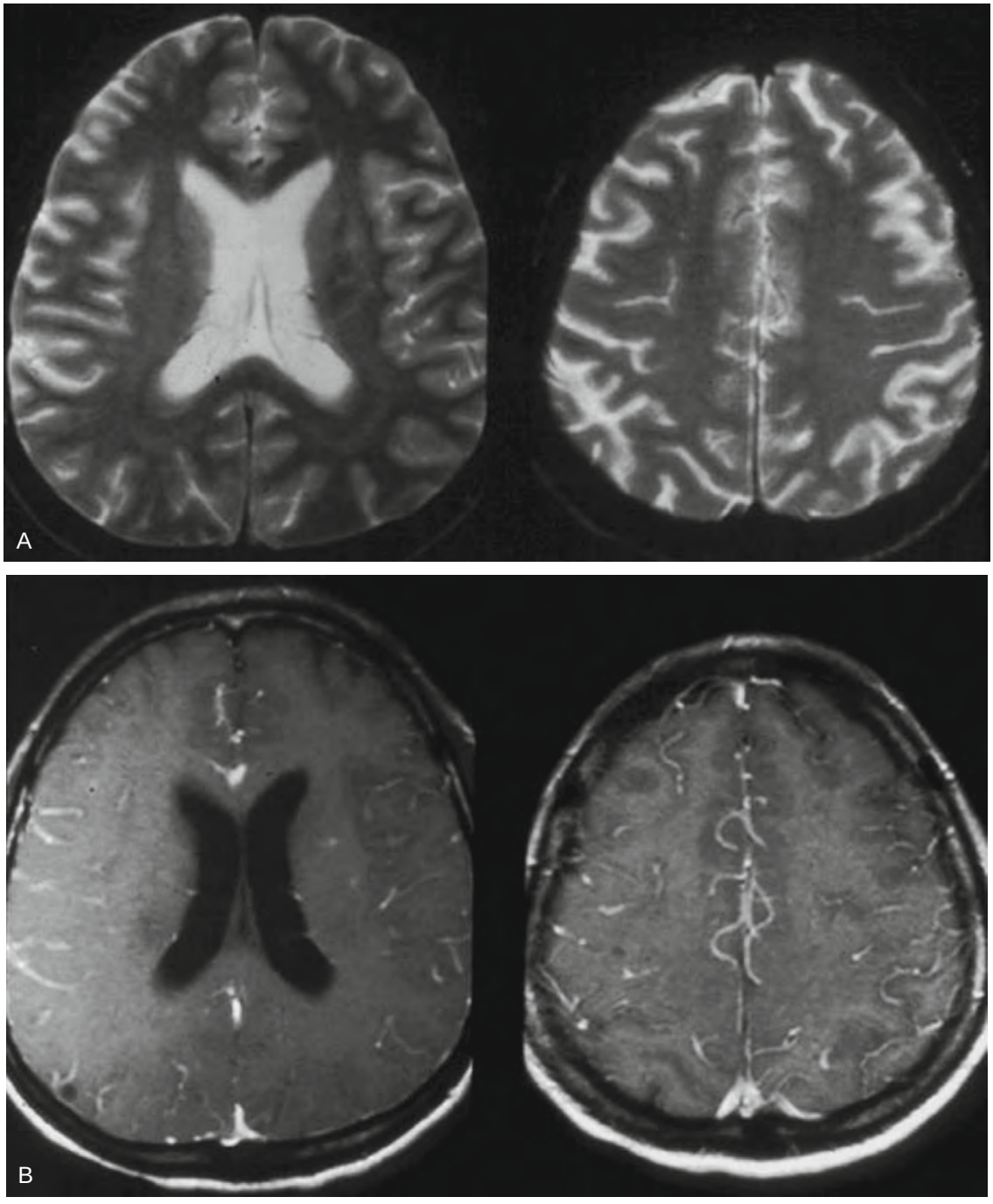

Fig. 15.2. Meningitis: (A) axial T2-weighted images show enlargement of the subarachnoid sulci at the cerebral convexities. (B) Postcontrast images show leptomeningeal enhancement. (Illustration copyright Truwit.)

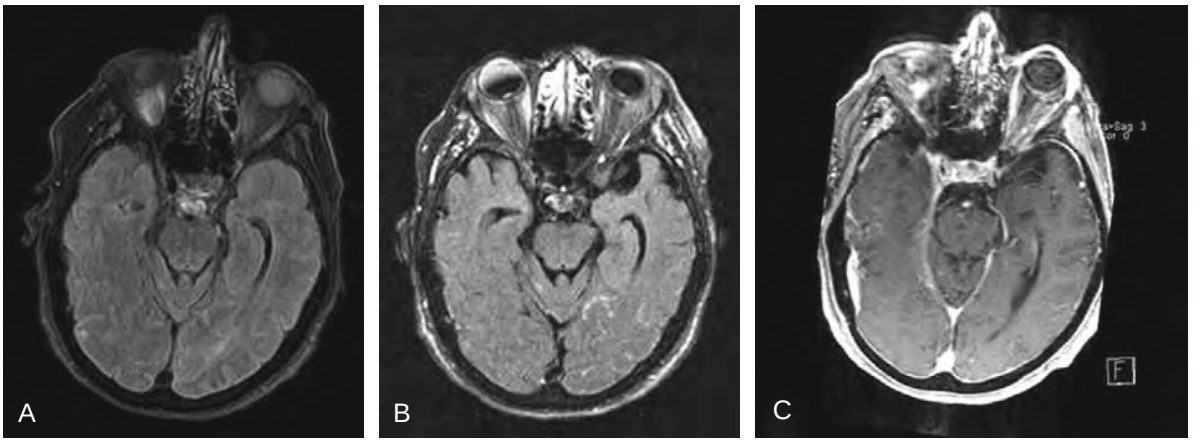

Fig. 15.3. Meningitis: use of postcontrast fluid-attenuated inversion recovery (FLAIR). (A) Axial precontrast FLAIR image is unremarkable. (B) Postcontrast FLAIR image shows leptomeningeal enhancement in the left temporo-occipital region. (C) Contrast-enhanced T1-weighted image was negative for leptomeningeal enhancement. (Illustration copyright Truwit.)

enhancement, cerebral hypotension, primary or secondary to lumbar puncture, should be considered (Krause et al., 1997; Bakshi et al., 1999).

Areas of vasospasm-induced arterial infarction can be detected with diffusion-weighted images. Occasionally, arterial infarcts may become hemorrhagic. Within 12–24 hours, these focal infarctions will be hyperintense on T2-weighted (Fig. 15.4) and FLAIR images, and they may enhance on postcontrast images. In the chronic stage of infarction, cavitation and tissue loss will become

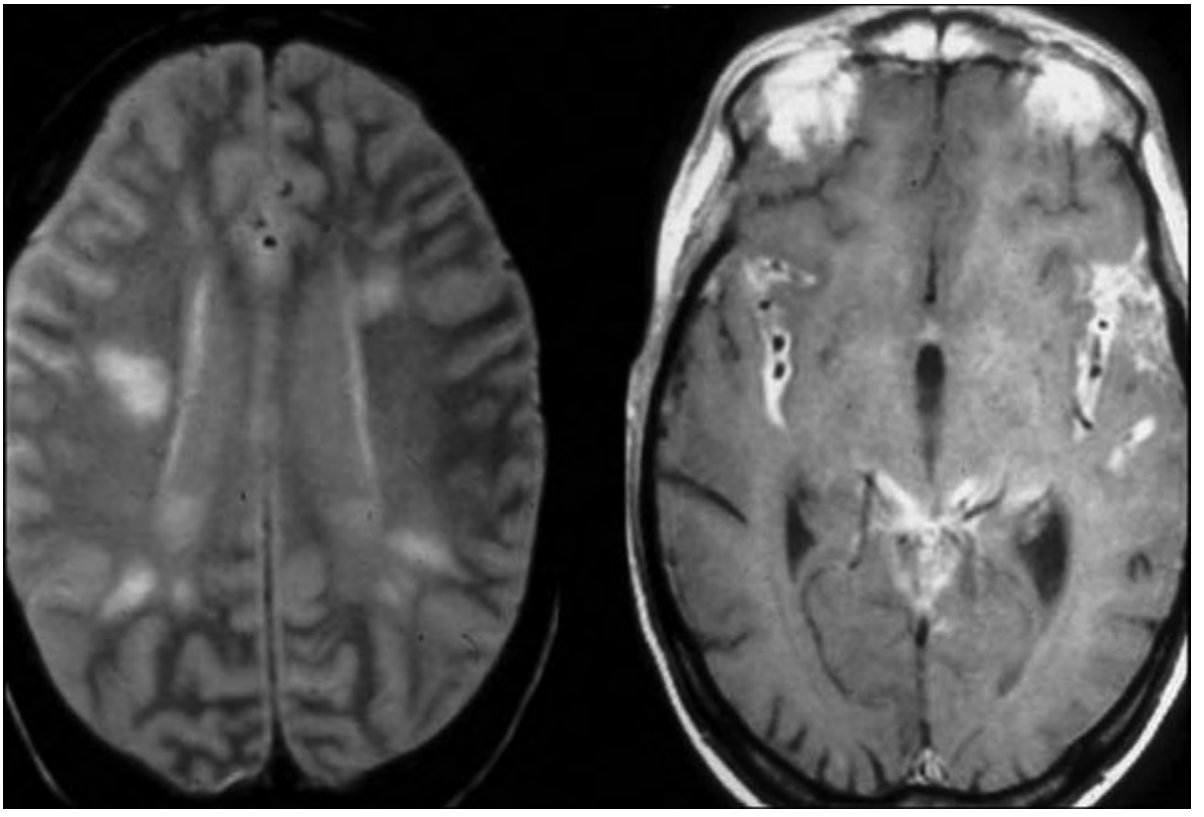

Fig. 15.4. Complications of meningitis. Axial proton density image shows patchy T2 hyperintense areas in the cerebral periventricular white matter, probably representing foci of arterial infarction secondary to meningitis affecting the penetratring arteries of the brain. Postcontrast T1-weighted image of the same patient shows leptomeningeal enhancement most significantly within the quadrigeminal cistern and sylvian fissures. (Illustration copyright Truwit.)

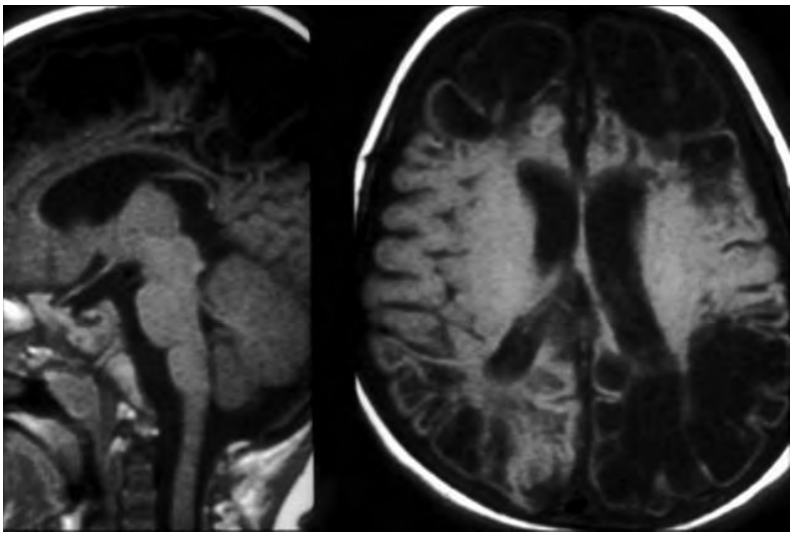

Fig. 15.5. Sequelae of meningitis. T1-weighted sagittal and axial images show multiple patchy areas of tissue loss in the cerebral hemispheres following meningitis. These areas represent old venous infarcts, secondary to meningitis. (Illustration copyright Truwit.)

apparent. Unlike the infarcts secondary to occlusion of penetrating arteries, cortical venous occlusion results in subcortical areas of T2 hyperintensity, usually near the vertex (Goldberg, 1983; Atlas, 2002). In the chronic phase, such venous infarctions may show a pattern of brain injury that appears relatively to spare the overlying cortices yet destroy the underlying brain (Fig. 15.5).

Approximately 10% of patients with meningitis develop parenchymal changes with cerebritis seen in 25% of these cases (Harris and Edwards, 1991; Osborn, 1994). Cerebritis and edema also appear hyperintense on T2-weighted images.

Subdural collections are better evaluated by MRI than CT because of its multiplanar imaging capability. On MR images, subdural effusions appear as crescentic or lentiform-shaped extra-axial fluid collections, isointense with CSF on all sequences. Subdural abscess (empyema), on the other hand, is slightly hyperintense on T1-weighted and proton density images because of a high protein content (Atlas, 2002). More pronounced hyperintensity will be seen on diffusion-weighted images and FLAIR sequences (Fig. 15.6). Postcontrast images may reveal intense and uniform enhancement of the surrounding membrane (Fig. 15.6).

Ventriculitis occurs in the majority of neonates with bacterial meningitis. Nonenhanced CT scans may show areas of subtle hypodensity along the margins of the ventricles. On T2-weighted and FLAIR images, ventriculomegaly and periventricular T2 hyperintensity are mostly present. Postcontrast images show diffuse enhancement along the ventricular margins. Choroid plexitis may also be associated with ventriculitis and is recognized by abnormally swollen choroid plexus. Choroid plexus enhancement itself is not a sign of plexitis. The choroid plexus is a circumventricular organ and thus outside the protective blood–brain barrier, and normally enhances. Its enhancement is to be expected.

EPIDURAL EMPYEMA

Epidural abscess (empyema) typically arises secondary to direct extension from an external source. As such, empyemata are often located adjacent to the frontal sinuses, petromastoid air cells, or areas of penetrating trauma or recent neurosurgery. Similar to subdural empyema, epidural empyemata have slightly higher signal intensity than CSF on CT and MR images. Epidural empyemata are usually lens-shaped or biconvex. As they are extradural, they may cross the falx and/or the tentorium, unlike subdural empyemata which are confined by sutures (Osborn et al., 2004). Thus, epidural empyema may cross the midline; subdural empyemata do not. Importantly, a stripe of T2 hypointense dural signal is seen deep to the empyema. Subdural empyemata are more likely to be associated with concomitant parenchymal edema, whereas in epidural empyema, as the underlying dura forms a strong barrier against intracranial dissemination of infection, the underlying brain is usually normal (Figs 15.7 and 15.8).

Communicating hydrocephalus may develop secondary to obstruction of the subarachnoid space from the purulent exudates; obstructive hydrocephalus may occur with accumulation of exudate at the aqueduct.

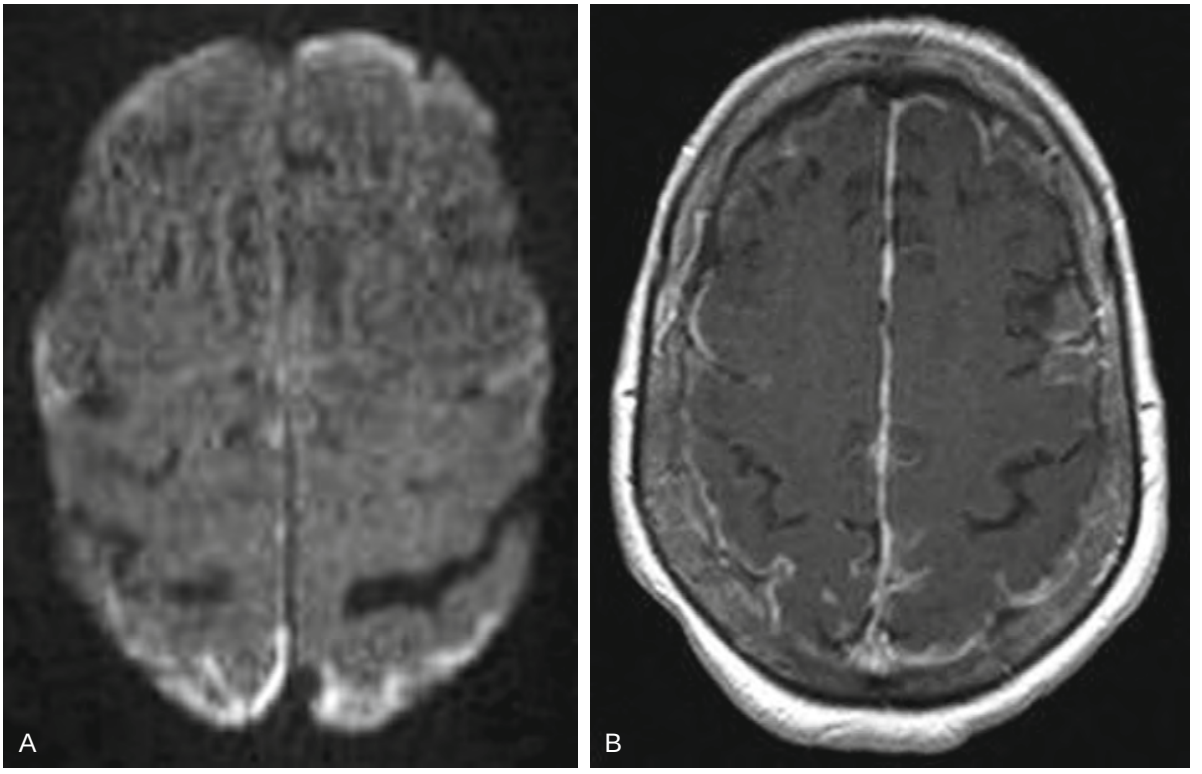

Fig. 15.6. Sequelae of meningitis, empyema, and use of diffusion-weighted image (DWI). (A) DWI shows linear hyperintensities along the bilateral frontoparietal convexities, probably representing areas of empyema. (B) Postcontrast T1-weighted image shows leptomeningeal enhancement. (Illustration copyright Truwit.)

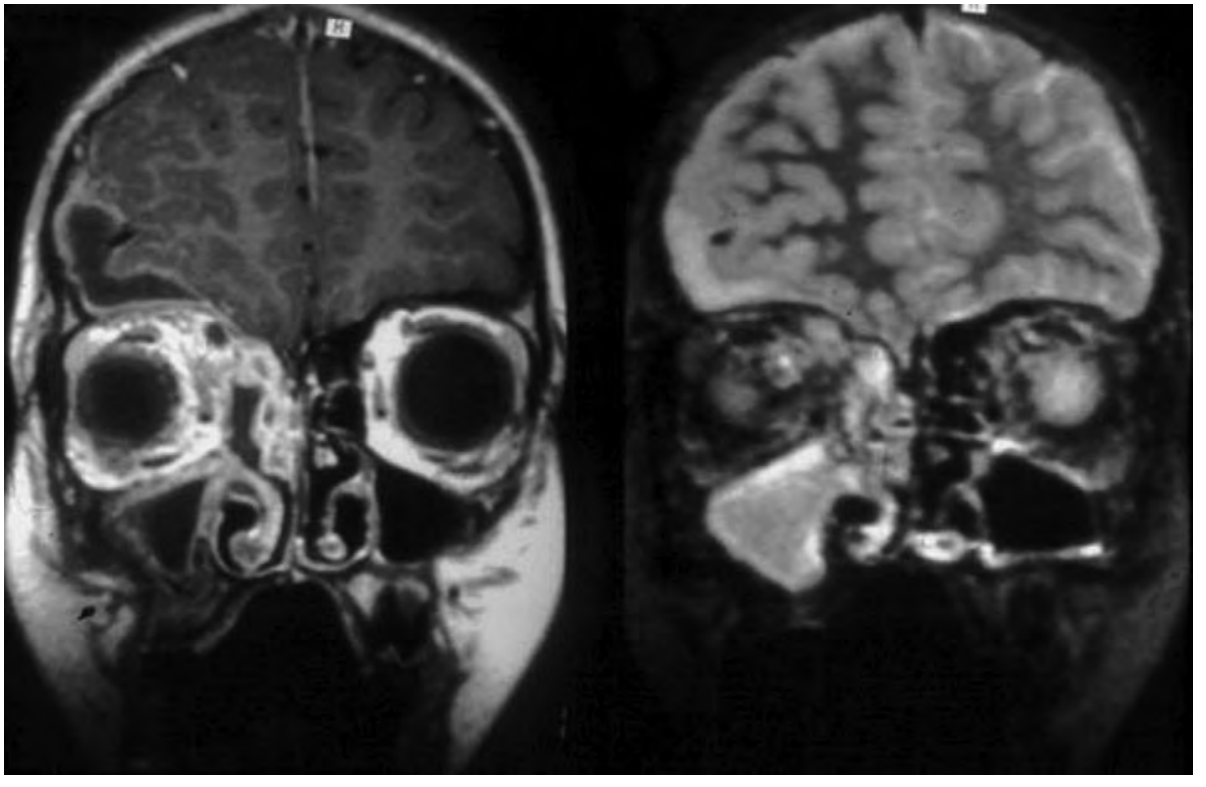

Fig. 15.7. Epidural empyema. Coronal postcontrast T1-weighted and T2-weighted images show right orbitofrontal T2 hyperintense subdural empyema with peripheral linear enhancement. There is also fluid and inflammatory enhancement in the right frontoethmoid recess and in the right maxillary sinus. (Illustration copyright Truwit.)

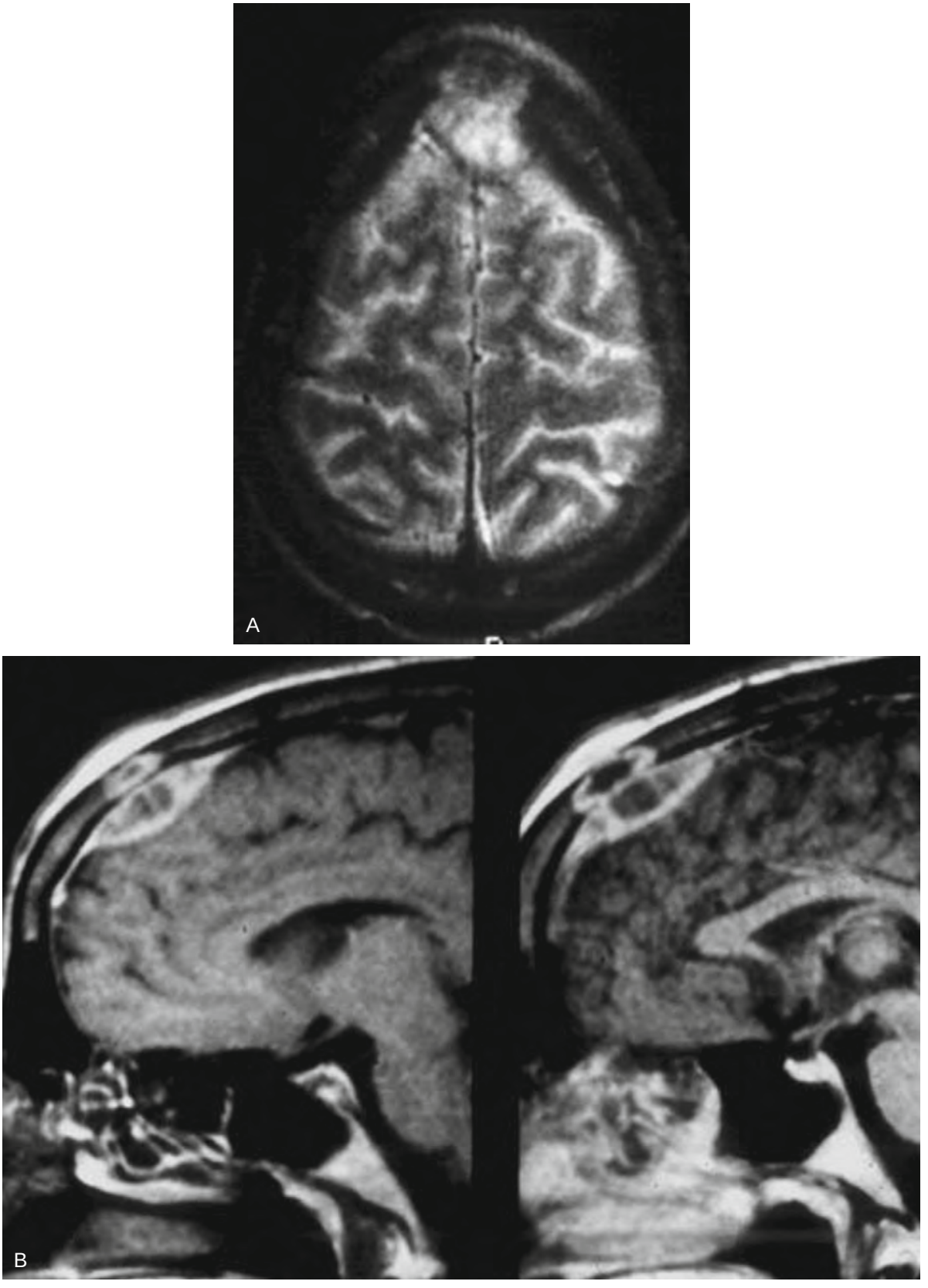

Fig. 15.8. Epidural empyema. (A) T2-weighted axial and (B) postcontrast T1-weighted sagittal images show a T2 hyperintense, peripherally enhancing small bifrontal epidural empyema. There is a T2 hypointense inner rim representing the dura, which is a helpful sign in differentiating epidural from subdural collections. The lentiform shape and crossing-over midline are also useful hints in the differential diagnosis. (Illustration copyright Truwit.)

ACUTE LYMPHOCYTIC MENINGITIS

This disorder is typically viral in origin and is usually self-limited. Enteroviruses are responsible for 50–80% of cases. Signs and symptoms are usually less severe than in cases of pyogenic meningitis. Imaging findings are usually normal. Occasionally, subtle or gross meningeal enhancement may occur on postcontrast CT or MRI (Harris and Edwards, 1991; Morris and Cshoene, 1999).

TUBERCULOUS MENINGITIS

Because of its high mortality rate, involvement of the CNS is one of the most serious forms of tuberculosis (Uysal et al., 2001; Bernaerts et al., 2003). Since the mid-1980s there has been an increase in the number of cases of tuberculosis meningitis in the USA. A significant portion of these patients also suffer from human immunodeficiency virus (HIV) infection (Rajshekhar and Cahndy, 1993; Konsuoglu et al., 1994; Morris and Cshoene, 1999). The gross pathology of tuberculous meningitis reveals a thick, gray gelatinous exudate overlying the basal subarachnoid cisterns (Okagaki, 1989; Osborn, 1994). On microscopic examination, the exudate consists of polymorphonuclear cells and a mixture of lymphocytes and plasma cells. There may also be caseous/noncaseous granulomas and giant cells. Blood vessels within the exudate can be involved directly, by encasement by the exudate, or indirectly, as a reactive endarteritis. They may be affected by both processes, resulting in spasm/arteritis with or without thrombosis and concomitant cerebral infarctions. Arteritis is present in 28–41% of basilar meningitis (Leiguarda et al., 1988; Atlas, 2002). Small lenticulostriate perforating branches are affected, resulting in infarction of the basal ganglia (Post and Hoffman, 1984; Sheller and DesPrez, 1986; Atlas, 2002).

The common neuroradiological findings are basilar meningeal enhancement, hydrocephalus, and infarctions. Tuberculosis and other chronic meningitides have a propensity for the basal subarachnoid cisterns, although generalized disease may also be seen (Okagaki, 1989; Osborn, 1994). Noncontrast CT may show obstruction of the basal cisterns with isoattenuating or slightly hyperattenuating exudate. Postcontrast CT images typically show diffuse basal cisternal enhancement. Homogeneous enhancement of the basal cisterns may extend to the ambient cistern, sylvian cistern, prepontine cistern, and perichiasmatic area (Artopoulos et al., 1984; Chang et al., 1990; de Castro et al., 1995). On MR images, tuberculous exudates result in distension of the affected subarachnoid spaces with hyperintensity (compared with CSF) on T1-weighted images (Bonafe et al., 1985; Morgado and Ruivo, 2005). Postcontrast

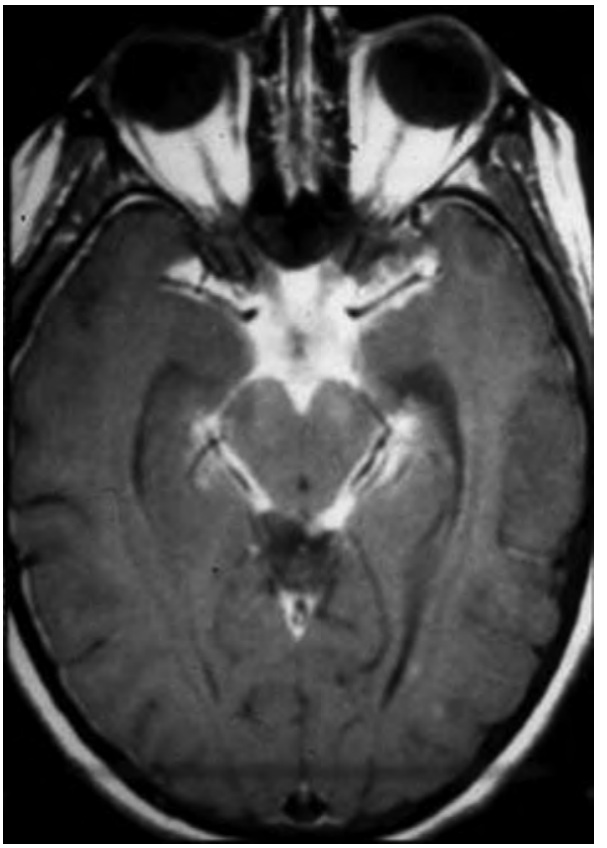

Fig. 15.9. Tuberculous meningitis. Postcontrast T1-weighted magnetic resonance image shows diffuse enhancement of the basal cisterns in a patient with tuberculous meningitis. (Illustration copyright Truwit.)

MR images show diffuse basal cisternal contrast enhancement (Fig. 15.9) and are generally more sensitive than contrast-enhanced CT studies (Jinkins et al., 1995; Harisinghani et al., 2000; Bernaerts et al., 2003). Extension of the inflammation to the ventricles results in ventriculitis and ependymitis with ependymal and choroid plexus engorgement (Villoria et al., 1995; Cho et al., 1998; Bernaerts et al., 2003). Communicating hydrocephalus is another frequent finding secondary to blockage of the basal cisterns. It is present on CT scans in 45–87% of patients at the time of diagnosis (Gupta et al., 1994; Hosoglu et al., 1998) and is considered a sign of poor prognosis (de Castro et al., 1995). Rarely, obstructive hydrocephalus may be seen in cases with focal parenchymal lesions (tuberculomas) resulting in mass effect or entrapment of the ventricle with granulomatous ependymitis (Sheller and DesPrez, 1986; Atlas, 2002). Hydrocephalus may also be seen in bacterial meningitis, although, unlike tuberculous meningitis, it is not progressive. The presence of progressive hydrocephalus should raise a suspicion of tuberculous meningitis (Wallace et al., 1991; Bernaerts et al., 2003).

Cerebral infarction is another possible complication of tuberculous meningitis. Tuberculous vasculitis is initiated either by invasion of the vessel wall by mycobacteria or by extension from arachnoiditis. This results in spasm or thrombosis of the arteries or veins and leads to development of cerebral infarctions. Dastur et al. found infarcts in 41% of autopsy cases (Dastur et al., 1970; Bernaerts et al., 2003). The majority of infarcts were located in the basal ganglia and internal capsule, and were secondary to encasement of the basal perforating arteries. Most of these infarcts were hemorrhagic and led to cavitation (Sheller and DesPrez, 1986; McGuinness, 2000; Bernaerts et al., 2003; Morgado and Ruivo, 2005). Infarction from vasculitis is more common in pediatric patients.

Although both CT and MRI demonstrate the infarcts, MRI allows for earlier detection (Brand-Zawadzki and Kucharezyk, 1987; Morgado and Ruivo, 2005). With the contribution of diffusion-weighted imaging, the age of the infarct can often be determined. Another vascular complication of tuberculous meningitis is intracranial mycotic aneurysm. Although quite rare, it may have devastating sequelae (Leiguarda et al., 1988; Gupta et al., 1994; Morgado and Ruivo, 2005).

Cranial nerve involvement is also common in patients with tuberculous meningitis. Clinically, cranial nerve involvement was observed in 17–70% of patients, with the second, third, fourth, and seventh cranial nerves being most frequently affected (Leiguarda et al., 1988; Wilson and Castillo, 1994; Morgado and Ruivo, 2005). Late sequelae of leptomeningeal tuberculosis include encephalomalacia of the area of cerebral infarction, calcification of the granulomata and hydrocephalus (Jinkins, 1991; Morgado and Ruivo, 2005).

The parenchymal form of tuberculosis results in tuberculomas, mostly located in the corticomedullary junction and periventricular regions. Most are supratentorial. Parenchymal disease can occur with or without meningitis (Sze, 1988; Atlas, 2002; Morgado and Ruivo, 2005). The parenchymal form is more commonly seen in HIV-infected patients.

Tuberculous granuloma (tuberculoma) is the most common form of the parenchymal lesions. The tuberculoma is commonly found in patients with miliary tuberculosis who are neurologically asmpytomatic (Gupta et al., 1997; Bernaerts et al., 2003). Lesions may occur in the spinal cord and brain (Fig. 15.10). In children, they tend to occur in the infratentorial brain, whereas in adults they tend to be supratentorial in location (Villoria et al., 1995; de Castro et al., 1999; Bernaerts et al., 2003). They may develop secondary to hematogeneous spread or may be secondary to extension along Virchow–Robin perivascular spaces. Micrograniulomata form in an area of cerebritis and ultimately a mature noncaseating granuloma develops. In most cases, central caseous necrosis develops. Caseous material is high in lipid content and low in bacilli. Contrast CT studies show small nodular or ring-enhancing lesions (Jinkins, 1991; Morgado and Ruivo, 2005). One-third of patients may demonstrate a "target" sign which appears as a central calcification or punctuate enhancement surrounded by a region of hypodensity with surrounding rim enhancement (Gupta et al., 1990; Morgado and Ruivo, 2005; Van Dyk, 1988). This appearance, although suggestive, is not pathognomonic for tuberculoma. Recent studies suggest that only the target sign with central calcification is pathognomonic, whereas a target sign with a central enhancing dot does not necessarily represent a tuberculoma (Bargallo et al., 1996; Bernaerts et al., 2003).

The MRI features of tuberculomas depend on whether the granuloma is noncaseating or caseating with a solid center, or caseating with a liquid center (Bernaerts et al., 2003). Noncaseating granulomas are usually hypointense relative to brain parenchyma on T1-weighted images and hyperintense on T2-weighted images. After contrast administration, they usually show diffuse contrast enhancement. The caseating granulomas with a solid caseation are usually hypointense or isointense on T1-weighted images and isointense or hypointense on T2-weighted images. The relative hypointensity on T2-weighted images has been postulated to be related to T2 shortening by paramagnetic free radicals produced by macrophages within the caseating granuloma (Gupta et al., 1994; Wilson and Castillo, 1994; Morgado and Ruivo, 2005). In the next stage, central liquefaction of the tuberculoma develops. This is seen as a hypodense core with a dense rim of enhancement on contrast-enhanced CT. These lesions are hypointense on T1-weighted images and hyperintense on T2-weighted images. Postcontrast images show diffuse peripheral contrast enhancement. In this stage, the lesion is indistinguishable from pyogenic abscess or tuberculous abscess (Jinkins et al., 1995; McGuinness, 2000; Bernaerts et al., 2003).

The wall of a caseating granuloma is strikingly hypointense on T2-weighted images and shows avid rim enhancement following contrast administration (Gupta et al., 1990; Desai et al., 1991; Morgado and Ruivo, 2005). Granulomas are usually associated with perilesional edema, the degree of which is variable and thought to be inversely proportional to the maturity of the lesion (Bernaerts et al., 2003).

MR spectroscopy may be useful as it can show prominent lipid peaks in patients with proven tuberculomas. This is probably due to the presence of high lipid content in the granulomas (Gupta et al., 1995, 1996;

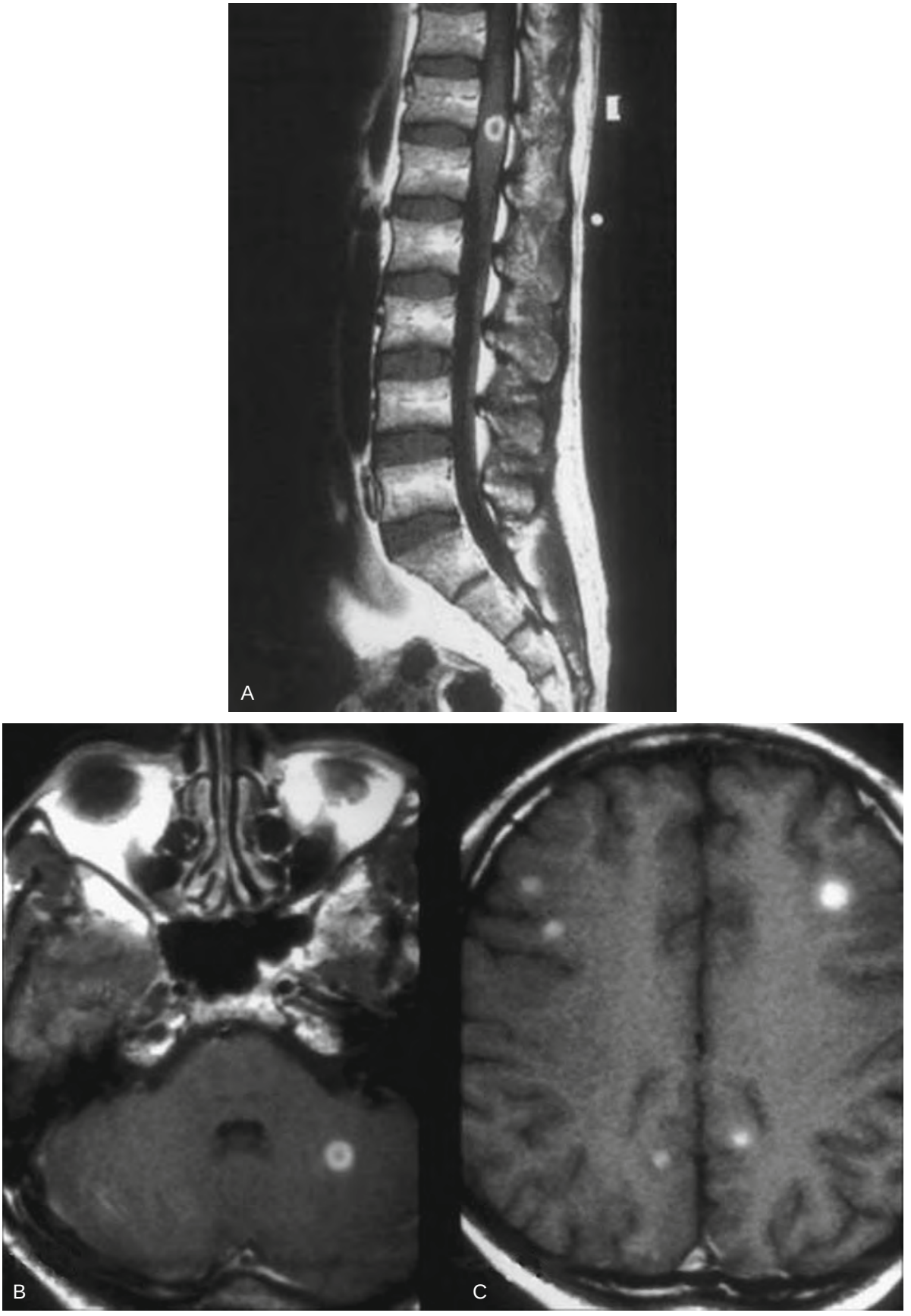

Fig. 15.10. Tuberculoma. (A) Postcontrast sagittal T1-weighted image of lumbar spine and (B, C) postcontrast T1-weighted axial images of the brain show rounded contrast-enhancing tuberculomas. (Illustration copyright Truwit.)

Morgado and Ruivo, 2005). In a T2 hypointense lesion *in vivo* MR spectroscopy showed a lipid peak at 1.3, 2.02, and 3.7 ppm, considered characteristic of tuberculoma (Gupta et al., 1996; Morgado and Ruivo, 2005). Some tuberculomas show central liquefaction. These lesions are hypointense on T1-weighted images, and hyperintense on T2-weighted images with a peripherally enhancing rim. These lesions may be indistinguishable from tuberculous or pyogenic abscess formation. Healed tuberculomas often calcify. Obvious on CT, calcification can be more difficult to detect by MR; gradient echo images are often more useful for the detection of small calcifications.

The activity of tuberculomas may be judged from the degree of contrast enhancement on follow-up CT or MRI studies (McGuinness, 2000; Bernaerts et al., 2003). Occasionally newly developing or enlarging tuberculomas may be seen in patients despite appropriate antituberculous therapy (Gupta et al., 1997; de Castro et al., 1999; Bernaerts et al., 2003). This may be due to therapy-induced destruction of the tuberculoma and liberation of tuberculoprotein, resulting in swelling and inflammation of the related focus (Gupta et al., 1997; Bernaerts et al., 2003). As a consequence, patients on antituberculous therapy who develop signs of increased intracranial pressure or new neurological signs should undergo urgent neuroimaging to exclude the development of new lesions or enlargement of existing lesions, with attention to the development of hydrocephalus (Ravenscroft et al., 2001; Bernaerts et al., 2003).

Tuberculous abscess is uncommon, observed in fewer than 10% of all patients with CNS tuberculosis (Provenzale and Jinkins, 1997; Gupta et al., 2001; Bernaerts et al., 2003; Morgado and Ruivo, 2005). In contrast to caseation which contains a high protein concentration and low numbers of bacilli, the abscess is formed by semiliquid pus with tuberculous bacilli. The wall of a tuberculous abscess is made of an inflammatory neovascular capsule and lacks epitheloid cells of granuloma (Wouters et al., 1985; Morgado and Ruivo, 2005). Tuberculous abscesses are usually larger and show a more accelerated clinical course. The appearance is similar to pyogenic abscess, although tuberculous abscesses are often multiloculated. They are hypointense on CT images and show peripheral thin and uniform rim enhancement with surrounding edema. On MR images, tuberculous abscess has a central T2 hyperintense area with surrounding rim enhancement (Fig. 15.11). On conventional MR studies they can be differentiated from tuberculomas by their greater size (often more than 3 cm in diameter), thin walls, more rapid course, multiloculation, and often

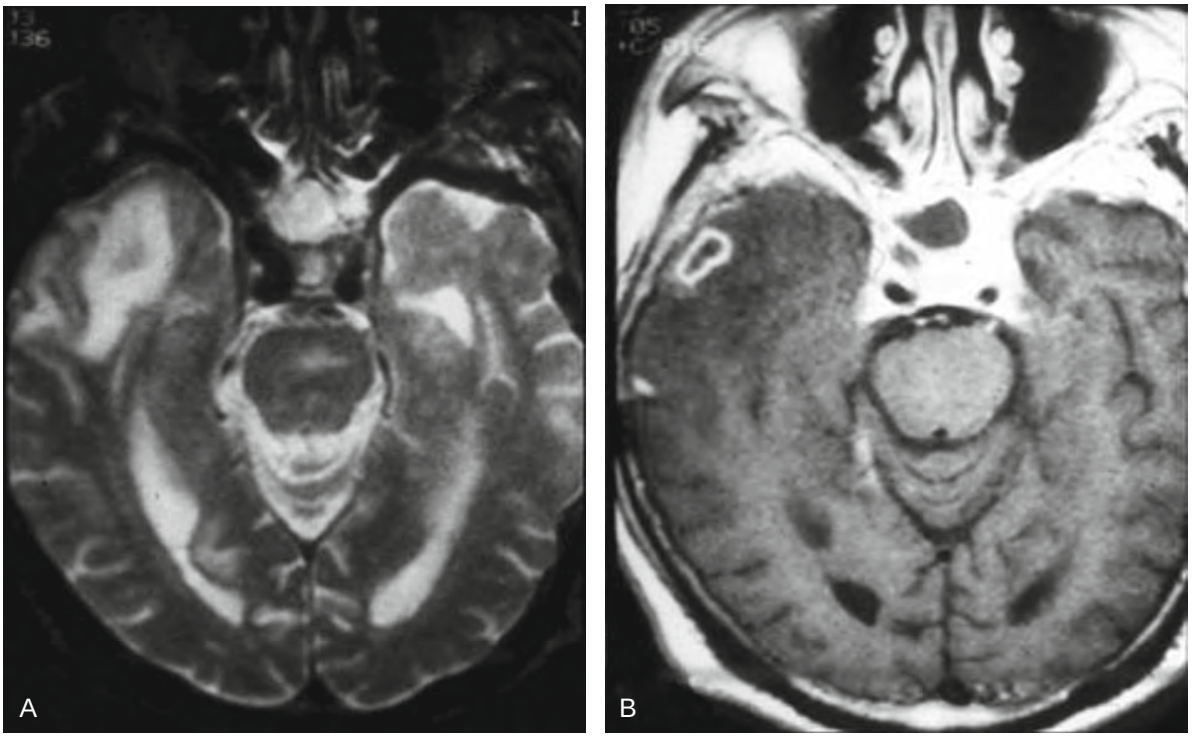

Fig. 15.11. Tuberculous abscess. (A) Axial T2-weighted image shows focus of T2 hyperintensity in the right temporal region consistent with edema. (B) Axial contrast-enhanced T1-weighted image shows rim-enhancing lesion within the center of this edema, consistent with tuberculous abscess. (Illustration copyright Truwit.)

solitary nature (Zimmermann et al., 1987; Bernaerts et al., 2003). In some cases, magnetization transfer (MT) MRI and MR spectroscopy have been helpful. Tuberculous abscesses show low MT ratios compared with pyogenic abscess. On MR spectroscopy, tuberculous abscess shows no evidence of amino acids, which is a spectral hallmark of the pyogenic abscess. Thus, the combined use of these two techniques may help to differentiate tuberculous abscess from pyogenic abscess (Gupta et al., 2001; Morgado and Ruivo, 2005).

CEREBRITIS AND ABSCESS

Cerebritis is the earliest stage of purulent brain infection (Osborn, 1994). There are numerous modes of brain inoculation and infection. Infectious agents may gain access to the CNS via hematogeneous spread. Mastoid and sinus infection may result in direct extension. Patients with untreated dural tears of the anterior frontal fossa may also present with a frontal abscess. Septic thrombophlebitis of the emissary veins in the temporal lobes draining into the cortical veins may result in abscess formation. Cerebral abscesses from dental infections usually contain mixed mouth flora with a predominance of anaerobic bacteria. Infants and children may have additional sources of CNS infection, including meningomyelocele, encephalocele, ectodermal defects, and cyanotic congenital heart disease.

Abscesses occur most commonly within the frontal lobe. Abscesses that occur secondary to hematogenous dissemination of infection are typically located within the gray–white-matter junction. Abscess formation is preceded by cerebritis. There are four main stages in abscess formation:

1. Early cerebritis
2. Late cerebritis
3. Early capsule formation
4. Late capsule formation.

During the early cerebritis stage, a focal area of parenchymal softening is precipitated by the arrival of bacteria to the brain parenchyma. Pathologically there is scattered edema, necrosis without frank tissue destruction, microscopic petechial hemorrhage, vascular congestion, and inflammatory infiltrate (Osborn, 1994). CT is most likely to be normal. MR studies may reveal a focal area of edema with mild mass effect characterized by sulcal effacement or subtle ventricular compression. If there is associated subacute hemorrhage, foci of hyperintense (T1) signal can be seen interspersed in the edematous region. Contrast enhancement is usually heterogeneous or minimal. The early cerebritis stage lasts for 3–5 days. In late cerebritis, the infection becomes more focal, with small, central necrosis. This stage lasts from 4–5 days to 10–14 days. The early capsule stage begins around the end of the second week. Collagen and reticulin start to form a capsule around the liquefied necrotic center. The capsule is initially thin and incomplete, but becomes thicker with increased collagen production (Osborn, 1994). During the late capsule stage, the capsule is complete with three layers, including an inner inflammatory layer of granulation tissue, a middle collageneous layer, and an outer gliotic layer (Osborn, 1994). The collagen layer is usually less well developed on the ventricular side than on the cortical side, likely related to differences in blood supply.

Most patients presenting with clinical findings suspicious for brain abscess undergo either CT or MRI. Imaging features of brain abscess differ with the stage of abscess. Nonenhanced CT may be normal or show a poorly marginated, hypodense focus. Contrast-enhanced CT may show mild patchy enhancement in the early cerebritis stage and irregular peripheral enhancement in the late cerebritis stage. In the early capsule stage, there is usually a ring-enhancing mass with surrounding vasogenic edema. In the late capsule stage, the abscess cavity shrinks and ring enhancement increases in thickness. This enhancement may persist for months (Osborn, 1994). MR findings in brain abscess also differ with the stage of abscess formation. In the early cerebritis stage, there is poorly marginated edema with mild patchy enhancement. At the late cerebritis stage, an obvious rim with perilesional edema is seen. In this stage, there may be irregular but intense rim enhancement. Typically, this is seen as a more pronounced, thick enhancing rim peripherally and a less thick rim at the depth of the abscess. Although not pathognomonic, this may be helpful in differentiating brain abscess from intracranial neoplasm. Satellite lesions are also common at this stage (Osborn, 1994; Osborn et al., 2004). At the early and late capsule stages, there is a T1 isointense/hyperintense, T2 hypointense rim surrounding a necrotic center which is usually isointense with CSF, except on diffusion-weighted images which show characteristic hyperintensity reflecting altered diffusivity.

The signal within the central portion of the abscess strongly depends on the content and to some degree on the pulse sequence. If there is a high proportion of macromolecular components, the central portion appears hyperintense on T1-weighted images due to T1 shortening. Diffusion-weighted images show restricted diffusion. Visibility of abscess rim in the noncontrast studies is probably related to the various components of the capsule, including collagen, hemorrhage, or

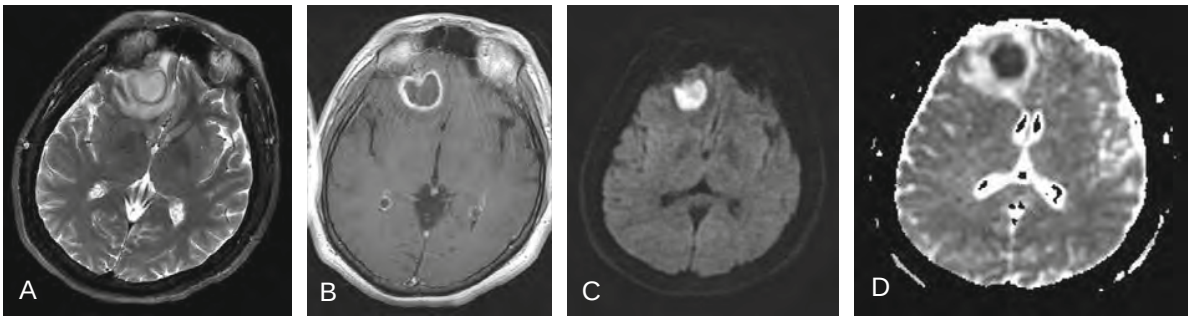

Fig. 15.12. Pyogenic abscess. Cerebral abscess in the right inferior frontal region. (A) T2-weighted image shows patchy T2 hyperintense area representing extensive edema. There is a curvilinear T2 hypointense rim in the center of this large hyperintense area representing capsule. (B) Postcontrast image shows peripherally enhancing centrally necrotic abscess. There is thicker enhancing rim peripherally and a less thick rim at the inner margin of the abscess. (C) Diffusion-weighted image and (D) corresponding apparent diffusion coefficient map show focus of restricted diffusion corresponding to the necrotic center. (Illustration copyright Truwit.)

paramagnetic free radicals within the surrounding macrophages (Zimmermann et al., 1987; Osborn et al., 2004). There is surrounding edema and mass effect associated with the early capsular stage, which may diminish at the late capsular stage. At this point, the cavity collapses and the surrounding capsule thickens. In the past, postcontrast T1-weighted images were accepted as the key image in the diagnosis. However, restricted diffusion on diffusion-weighted imaging has become the hallmark of imaging a pyogenic abscess. T2-weighted images remain helpful to assess the extent of surrounding edema and to identify a T2 hypointense rim (Fig. 15.12). Follow-up imaging of cerebral abscess response to therapy has been shown to correlate better with the evaluation of the T2 hypointense rim than residual capsular enhancement (Whelan and Hilal, 1980; Sze and Zimmermann, 1988; Desprenchins et al., 1999).

Proton MR spectroscopy can also be helpful in the differential diagnosis of a necrotic tumor from brain abscess. Typically, abscess cavities contain amino acids, such as succinate and acetate, generally not present in the spectra of brain tumors.

SPINAL EPIDURAL ABSCESS

Spinal epidural abscess is rare, with an overall frequency of 0.2–1.2 cases per 10 000 (Joshi et al., 2003). Recently, however, there has been an increase in the incidence of spinal epidural abscess mostly secondary to an increased number of spinal surgeries, intravenous drug abuse, and immunodeficiency (Louis and Fernandes, 2005). *Staphylococcus aureus* is by far the most frequent causative organism. A spinal epidural abscess is usually secondary to direct hematogeneous seeding from cutaneous, pulmonary, or urinary tract disease (Osborn, 1994; Louis and Fernandes, 2005).

The classic triad of epidural abscess includes back pain, neurological deficits, and abnormal inflammatory parameters (fever, elevated sedimentation rate). Unfortunately, as with many "classic" descriptions, the triad is seen in only 13% of cases. The typical clinical symptoms are fever and back pain, which are nonspecific and may result in diagnostic delay (Louis and Fernandes, 2005). Such delay may lead to quadriplegia, paraplegia, and even death (Numaguchi et al., 1993; Louis and Fernandes, 2005).

The epidural space is a vertical casing outside the dura mater containing fat, areolar tissue, and a network of veins. It is delimited by the walls of the bony vertebral canal. Notably, the dura is attached to the vertebral body anterior to the spinal cord, limiting the spread of infection. As a result, 80% of epidural abscesses are located posteriorly. Vertical extension of epidural abscess is common with the most common location being thoracic, followed by lumbar and cervical (Louis and Fernandes, 2005). Concomitant discitis and osteomyelitis are seen in 80% of cases (Osborn, 1994). Most epidural abscesses extending from discitis or osteomyelitis are located anterior to the spinal canal, whereas hematogeneous spread of disease more typically results in posterior epidural abscesses (Varma et al., 2001).

Early diagnosis with vigorous management is critical to good outcome. Unfortunately, although plain radiographs may reveal osteomyelitis with associated disc space narrowing, and myelography with CT myelography may show an extradural soft-tissue mass, myelography and CT myelography also carry the risk of seeding the subarachnoid space (Numaguchi et al., 1993).

MRI should be the first diagnostic imaging test for a suspected epidural abscess. MR is 91% sensitive for the detection of epidural abscess (Joshi et al., 2003; Louis and Fernandes, 2005). Epidural abscess on MR has the appearance of an extradural mass, isointense to hypointense compared with the spinal cord on T1-weighted images, and hyperintense on T2-weighted images, although the abscess can demonstrate mixed intensities. There are two basic patterns of enhancement described in spinal epidural abscess (Numaguchi et al., 1993; Osborn, 1994). Diffuse homogeneous or heterogeneous contrast enhancement is seen in 70% of cases and favors the phlegmonous phase (inflammation of the soft tissues with no liquid component or pus). The second finding is a thick enhancing rim surrounding a low signal pus collection, in 40% of cases (Numaguchi et al., 1993; Osborn, 1994).

Spinal epidural abscess often causes significant cord or canal compression necessitating decompression in association with antibiotic therapy (Numaguchi et al., 1993; Louis and Fernandes, 2005). Follow-up postcontrast MRI is important during treatment as it clearly demonstrates change in the size of the abscess and the degree of thecal sac compression. A follow-up study in 7–10 days is appropriate as a decrease in size of most epidural abscesses is observed within 5 days (Numaguchi et al., 1993).

SPINAL SUBDURAL ABSCESS

Spinal subdural abscess is rare compared with intracranial subdural abscess. This probably reflects the absence of venous sinuses in the spine, the wide epidural space acting like a protective coat and the centripedal direction of spinal blood flow (Osborn, 1994).

Like epidural abscess, the clinical presentation is nonspecific. Clinical suspicion should be considered when a febrile patient with a recent history of infection presents with back or neck pain (Levy et al., 1993; Osborn, 1994). The usual clinical triad for subdural abscess is fever, back or neck pain, and signs of spinal cord compression. On imaging studies, an intraspinal space-occupying mass can be seen. Myelography shows the level of CSF block. CT myelography further helps to delineate the extent of the lesion. The myelographic finding of multiple defects involving several levels is more likely to be seen in subdural abscess than epidural abscess, as the subdural abscess can extend longitudinally quite easily (Levy et al., 1993).

MRI allows better delineation of the lesion and its extent, as subdural abscesses are commonly present as multilevel, multiloculated collections. Prompt surgical decompression and drainage and antibiotic therapy are the mainstays of successful therapy (Levy et al., 1993).

SEPTIC DURAL VENOUS SINUS THROMBOSIS (SUPPURATIVE INTRACRANIAL THROMBOPHLEBITIS)

Septic dural venous sinus thrombosis is a potentially fatal condition if unrecognized. With effective use of antibiotic treatment, the incidence has significantly decreased (Ellie et al., 1992; Schuknecht et al., 1998; Kojan and Al-Jumah, 2006). The dural sinuses are vulnerable to septic thrombosis from infection of adjacent foci, as they do not have valves, thus allowing bidirectional blood flow (Kojan and Al-Jumah, 2006). The cavernous sinus is the most commonly affected dural venous sinus followed by the lateral and sagittal sinuses (Southwick et al., 1986; Kojan and Al-Jumah, 2006). Infections of the sphenoid and ethmoid sinuses and mastoid air cells are the most likely sources of infection. Such infection may trigger the thrombosis directly or indirectly, in patients with a prothrombotic illness (Kojan and Al-Jumah, 2006).

Patients usually present with acute onset of fever, signs of increased intracranial pressure, and focal signs according to the involved venous sinus. Such signs include cranial nerve palsies in the case of cavernous sinus involvement (Ellie et al., 1992; Schuknecht et al., 1998; Kojan and Al-Jumah, 2006).

CSF cultures, blood cultures, paranasal sinus radiographs, contrast-enhanced CT and MRI are usually obtained initially. Conventional angiography is rarely needed. Recent advances in CT and MRI, with the introduction of MR and CT venography, have allowed for the effective use of these two modalities in diagnosis (Babin et al., 2003; Kojan and Al-Jumah, 2006). The imaging features usually involve enlargement of sinuses with filling defects and heterogeneous enhancement, mostly at the lateral walls. In cavernous sinus thrombosis, there may be associated densification of the retroorbital fat, exophthalmos, and dilatation of the superior ophthalmic vein (Ellie et al., 1992; Schuknecht et al., 1998; Babin et al., 2003; Kojan and Al-Jumah, 2006).

INFECTIONS IN NEUROSURGERY PATIENTS

Neurosurgery-related postoperative infections are of particular significance because of their proximity to the CNS. The reported average rate of postoperative infections after neurosurgical operations is 4% (Hosein et al., 1999; Korinek, 1997; Savitz et al., 1986). Although this rate appears low, the consequences of a neurosurgical site infection can be devastating, and the combined morbidity and mortality approaches 14% (Patir et al., 1992; Hosein et al., 1999). Foreign-body implantations and neural tube defect repair in neonates

carry more risk of infection than do other neurosurgical operations (Hosein et al., 1999).

Superficial surgical site infections may be complicated by bone flap infections, including osteomyelitis of the calvarium. Those that extend deeper may result in meningitis, cerebritis, and abscess (Hosein et al., 1999). Osteomyelitis of the calvarium results in lytic and sclerotic changes of the involved bone on radiographs. CT shows bony defects, calvarial thickening, and new bone formation. MR images usually show an intradiploic mass, heterogeneous in signal intensity on T1- and T2-weighted images. Postcontrast images show strong but inhomogeneous enhancement of osteomyelitis (Klisch et al., 2002). Overall, the accuracy of MRI for the diagnosis of osteomyelitis is 94% (Klisch et al., 2002).

Bacterial meningitis accounted for more than half of all the infections following suboccipital craniotomy and translabyrinthine operations (Blomstedt, 1985). In these patients, bacterial and aseptic meningitis are more common than in patients undergoing supratentorial craniotomies (Blomstedt, 1985). In addition to infection secondary to craniotomy, the introduction of neuroendoscopic procedures and minimally invasive therapies has likewise been accompanied by intracranial infections (Cinalli et al., 2007). Specifically, ventriculoperitoneal shunts are prone to infection. With permament indwelling catheters, there is a risk of ascending infection from colonic perforation, resulting in intracranial abscess (Vougioukas et al., 2003). CSF infection is defined by prolonged fever, nuchal rigidity, elevation of C-reactive protein, CSF pleocytosis, and positive CSF culture. CSF infection may result in ventriculitis (Cinalli et al., 2007). Ventriculitis is an uncommon CNS infection that has been defined in different terms including ependymitis, intraventricular abscess, ventricular empyema, and pyocephalus (Fujikawa et al., 2006). As clinical features of ventriculitis are vague and nonspecific, MR is an important first diagnostic test. MR shows intraventricular debris or pus, abnormal periventricular and subepedymal signal intensity, and enhancement of the ventricular lining (Fujikawa et al., 2006). Recently, FLAIR imaging and diffusion-weighted imaging have been suggested as the most effective MR sequences to detect intraventricular debris (Fujikawa et al., 2006).

NEUROLOGICAL FINDINGS IN INFECTIVE ENDOCARDITIS

CNS involvement is common in patients with infective endocarditis with a reported incidence ranging between 8% and 90% (Chen et al., 2001; Yanagihara et al., 2003). Neurological complications are the result of emboli from cardiac valve vegetations. These vegetations can result in occlusion of cerebral arteries, mycotic aneurysms, meningitis, and abscess. Cerebral septic embolism resulting in infarct is the most frequent neurological complication (Chen et al., 2001; Yanagihara et al., 2003). Unlike usual thromboembolic infarcts, anticoagulation is contraindicated, as it increases the risk of bleeding (Kim et al., 1998). Antibiotic therapy and, if necessary, surgical removal of the valvular vegetations form the mainstay of treatment. Hence, early recognition of septic cerebral embolism is crucial to treatment. Neuroimaging plays an important role at this point and should be performed in infective endocarditis patients with neurological symptoms (Kim et al., 1998). This is particularly important, as the treatment choices for septic embolism are different than for the more common types of thromboembolic stroke (Kim et al., 1998). Multiplicity of lesions is an important imaging finding in the differential diagnosis, whereas solitary lesions are noted in most cases of thromboembolic infarcts (Kim et al., 1998). In addition, the frequency of hemorrhage in septic emboli-related infarcts exceeds that of thromboembolic infarcts (Kim et al., 1998). Noncontrast CT is useful in the initial evaluation and differential diagnosis of hemorrhagic versus nonhemorrhagic infarctions (Tunkel and Pradhan, 2002; Srinivasan et al., 2006). Although cerebral angiography is still considered by many to be the gold standard to establish the diagnosis of intracranial mycotic aneurysm (Tunkel and Pradhan, 2002; Srinivasan et al., 2006), noninvasive CT and MR angiography are now generally accepted, effective primary modalities to identify mycotic aneurysm. Moreover, their counterpart examinations, CT perfusion and MR diffusion/perfusion studies, accurately identify acute stroke and the areas at risk (penumbra) that may progress to infarction. Diffusion-weighted MRI is now incorporated into most of the protocols and is an essential component in the evaluation of stroke.

Brain abscesses are also common in these patients. They tend to be multiple, with microabscesses more common than macroabscesses (Kim et al., 1998). They appear as tiny ring- or nodular-enhancing lesions with a central dot low-signal area and surrounding high signal on T2-weighted images (Fig. 15.13).

Cerebral hemorrhage is the most dramatic, yet fortunately rare, neurological complication of infective endocarditis. It can be caused by rupture of a mycotic aneurysm even years after the infective endocarditis (Heiro et al., 2000). Most of the intracranial hemorrhages are intraparenchymal, and reports of infective endocarditis with subarachnoid or subdural hematoma are rare (Yanagihara et al., 2003).

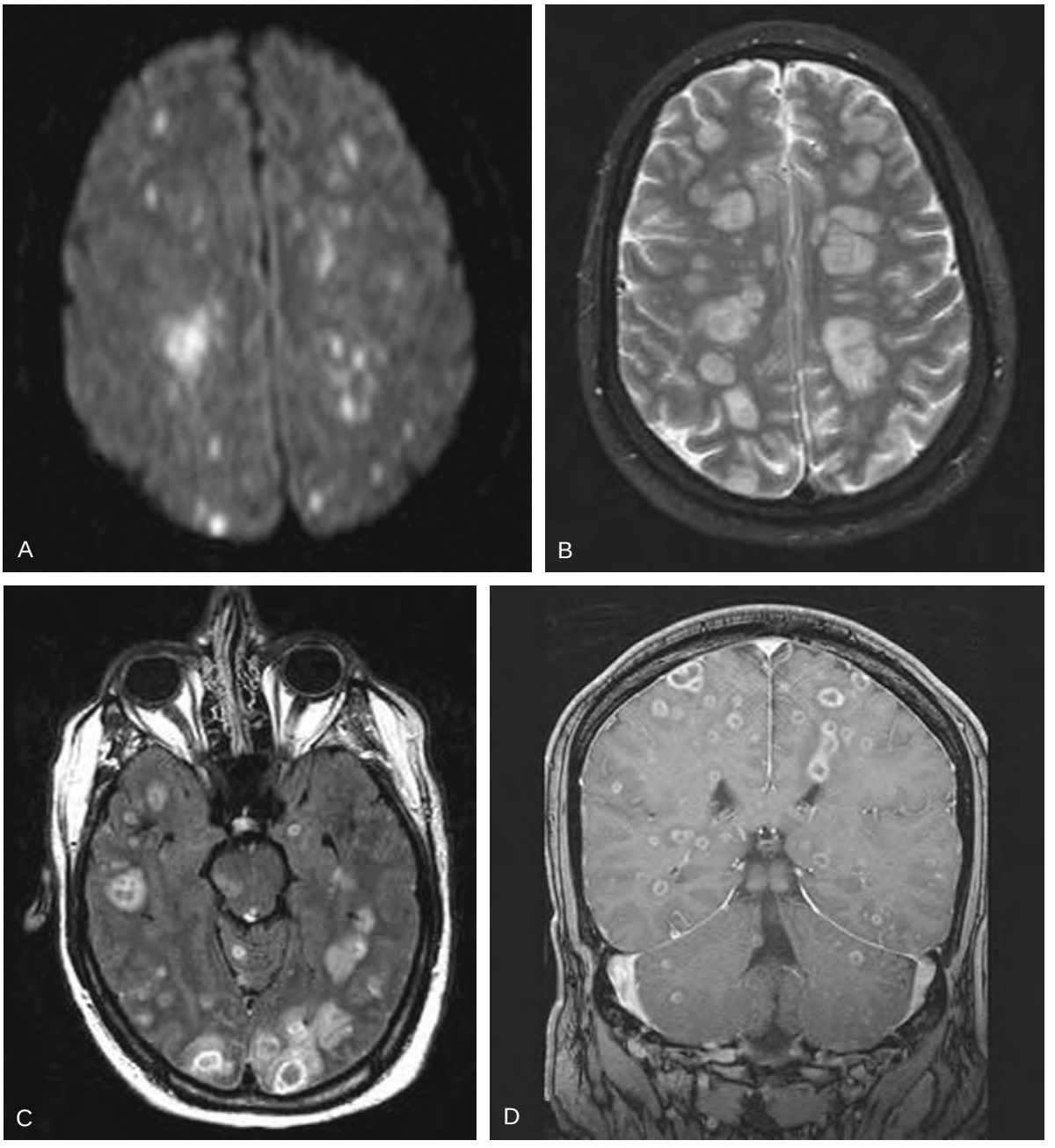

Fig. 15.13. Septic emboli. (A) Diffusion-weighted image shows areas of restricted diffusion corresponding to multiple microabscesses. (B) These areas appear hyperintense on T2-weighted images with central foci of hypointensity. (C) Postcontrast fluid-attenuated inversion recovery and (D) T1-weighted images show multiple peripherally enhancing microabscesses with surrounding edema. (Illustration copyright Truwit.)

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Chapter 16

Toxin-mediated syndromes of the nervous system

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BOTULISM

Background

Botulism is a paralytic illness caused by neurotoxin production by *Clostridium botulinum*. Spores of this ubiquitous, anaerobic bacterium are heat-resistant, leading to germination, reproduction, and toxin production in undercooked food. Toxin ingestion leads to a clinical syndrome characterized by cranial nerve palsies and descending, symmetric flaccid paralysis. Initially recognized as "sausage poisoning" in the 18th and 19th centuries, botulism was first ascribed to *C. botulinum* by Emile van Ermengen in 1897 (Kerner, 1820; van Ermengen, 1897). Prompted by a Belgian epidemic, van Ermengen discovered that *C. botulinum* from contaminated food produced a toxin that could induce weakness after injection into laboratory animals (van Ermengen, 1897). Cases of foodborne illness were soon followed by the discovery of wound botulism in 1943 (Hatheway and Johnson, 1998), infant botulism in 1976 (Midura and Arnon, 1976), and adult intestinal toxemic botulism in 1986 (Chia et al., 1986). In recent years, increased use of botulinum toxin as a therapeutic agent has led to rare cases of inadvertent botulism (Chertow et al., 2006). As the toxin is also considered a weapon of biological warfare, inhalation botulism remains a potential threat.

Etiology

C. botulinum is a large, gram-positive, strictly anaerobic bacillus that forms a subterminal spore under stressful conditions (Cato et al., 1986). The species is divided into four genetically diverse groups that share the common ability to produce botulinum toxin (Smith, 1977; Hatheway and Johnson, 1998). Seven serologically distinct neurotoxins are produced by *C. botulinum*, designated by the letters A-G. Human disease is attributed to toxin types A, B, E, and, less commonly, F. The toxins are zinc-dependent metalloproteinases (Fu et al., 1998), characterized by a heavy chain (100 kDa) and a light chain (50 kDa) that are joined by a single disulfide bond (Lacy et al., 1998).

C. botulinum spores are found throughout the world in soil samples and marine sediments (Hauschild, 1989). These spores are able to tolerate temperatures of 100°C at 1 atmosphere for several hours; because boiling renders solutions more anaerobic, it may actually favor the growth of *C. botulinum* (Tacket and Rogawski, 1989). Proper preparation of food in a pressure cooker will kill spores.

Epidemiology

Distinct syndromes attributed to *C. botulinum* toxin production include the following: foodborne botulism, wound botulism, infant botulism, idiopathic botulism, and iatrogenic botulism.

Foodborne botulism, caused by the ingestion of foods contaminated with A, B, or E toxin, is most frequently reported in the context of an outbreak. In an anaerobic environment with a low pH (<4.5), low salt and sugar content, and favorable temperatures (4–121°C), *C botulinum* grows and elaborates toxin (International Commission on Microbiological Specifications for Foods, 1996). Although commercially canned foods were commonly the source of toxin in the early 1900s, home-canned vegetables, fruits, and fish products are now the most common sources. For example, preferred food preparation practices among

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Alaskan Natives involving fish fermentation has led to botulism (Shaffer et al., 1990). In China, homemade fermented beans are the leading cause (Gao et al., 1990). Commercial foods and restaurants are still occasional sources (Centers for Disease Control and Prevention, 1983; Angulo et al., 1998; Pourshafie et al., 1998). Consumption of peyote for religious reasons has also resulted in botulism (Hashimoto et al., 1998). In the United States, 263 cases occurred due to 163 foodborne botulism events from 1990 to 2000 (17–43 cases per year) (Sobel et al., 2004).

Wound botulism may be caused by either type A or type B organisms, and is the result of wound contamination by *C. botulinum* spores. Subsequent germination and toxin production lead to abscess formation and a clinical syndrome comparable to that seen with foodborne disease. Wound botulism has been associated almost exclusively with injection drug users of "black tar" heroin, first reported in the USA in the 1990s. Contamination of the heroin during preparation led to infection, particularly in patients who injected via "skin-popping" (i.e., drug injection into tissue rather than the vein) (Passaro et al., 1998; Werner et al., 2000). Several similar reports have occurred in Europe since 2000 (Brett et al., 2004; Kalka-Moll et al., 2007), including 12 "black tar" heroin-related cases in Cologne, Germany, in 2005 (Anonymous, 2005).

Infant botulism occurs with toxin types A, B, or F. It is the most common form of the disease, occurring in 80–100 patients in the USA each year (Shapiro et al., 1998). Infection occurs as a consequence of absorption of toxin produced by *C. botulinum in situ*; the organism colonizes the intestine of infants (ages 6 days to 12 months) in the absence of competing normal flora found in children and adults (Arnon, 1998). Infant botulism is often attributed to honey ingestion (Midura et al., 1979), but other sources have emerged since feeding honey to infants has been discouraged (Spika et al., 1983). Two infants without other exposures are believed to have contracted botulism via soil contamination (Hurst and Marsh, 1993). Rare cases of infant botulism have been associated with *C. baratii* (Gimenez et al., 1992) or *C. butyricum* (Suen et al., 1988).

In rare instances, adults become colonized with and subsequently infected by toxin-producing *Clostridium,* leading to gastrointestinal disease. Adults at risk include those with loss of bowel flora due to anatomic abnormalities, functional disorders, or antibiotic use (Chia et al., 1986; McCroskey et al., 1991; Arnon, 1995; Griffin et al., 1997; Fenicia et al., 1999). Most cases of idiopathic botulism are caused by type A toxin and are likely a consequence of this mechanism. Adult botulism of unknown etiology has also been attributed to types B and F (MacDonald et al., 1986). One adult case of type F botulism was caused by *C. baratii* (McCroskey et al., 1991).

The US Food and Drug Administration (FDA) approved the use of botulinum toxin types A and B for cosmetic and therapeutic purposes (e.g., blepharospasm, strabismus, cervical dystonia). As a result, expanding on- and off-label applications of these toxins have led to widespread use. Iatrogenic botulism cases have been reported with the unlicensed use of botulinum toxin A and the therapeutic use of toxin B (Chertow et al., 2006; Souayah et al., 2006). Patients have developed symptoms indistinguishable from foodborne illness after a supratherapeutic injection. No fatalities have been reported.

Inhalational botulism does not occur in nature, but is one of the potential routes of a bioterrorist attack with botulinum toxin. A deliberate release of botulinum toxin should be suspected if patients with acute flaccid paralysis and prominent bulbar palsies present in large numbers. An unusual toxin type (such as C, D, F, or G) or symptoms among patients with a common geographic factor (e.g., work location, airport) may suggest an act of bioterrorism.

Pathogenesis

Clinical botulism results from the entry of botulinum toxin into the systemic circulation and subsequent inhibition of acetylcholine release from the presynaptic nerve terminals. Toxin enters the circulation through a mucosal surface (e.g., foodborne, infant, inhalational botulism) or via a break in the skin (e.g., wound and iatrogenic botulism).

Once absorbed into the bloodstream, the toxin is carried to the synapses of peripheral and cranial nerves. The heavy chain mediates binding of the toxin to presynaptic receptors, allowing for receptor-mediated endocytosis (Black and Dolly, 1986).

Acetylcholine release at the neuromuscular junction is mediated by a synaptic fusion complex. This complex consists of three soluble, *N*-ethylmaleimide-sensitive fusion attachment protein receptors (SNARE proteins): synaptosomal-associated protein of 25 kDa (SNAP-25), syntaxin, and synaptobrevin. Synapatobrevin, a surface protein of the synaptic vesicle, binds to SNAP-25 and syntaxin, docking the vesicle on the membrane (Fig. 16.1) (Trimble et al., 1988). A fourth protein, synaptophysin, likely forms the fusion pore that allows release of the vesicle contents into the synaptic cleft (Buckley et al., 1987).

Each botulinum toxin (A–G) inhibits vesicle release by a different mechanism, cleaving peptide bonds of these SNARE proteins (Simpson, 1989; Blasi et al., 1994). Botulinum neurotoxins B, D, F, and G cleave

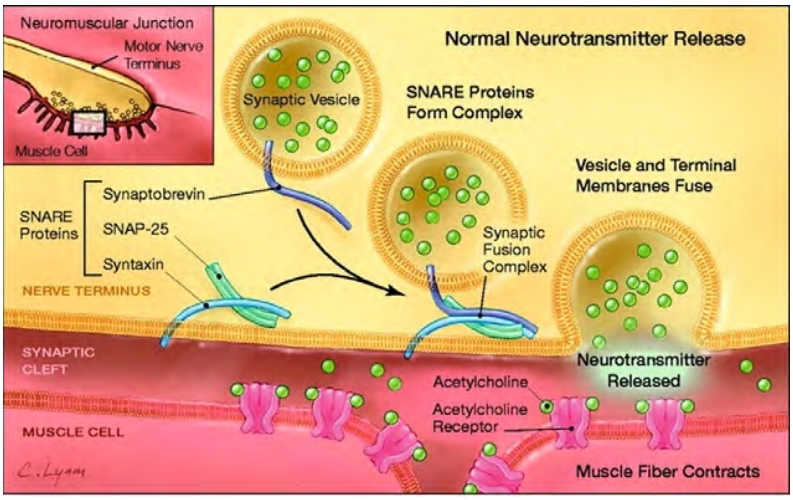


Fig. 16.1. Mechanism of action of botulinum toxin.

synaptobrevin (Schiavo et al., 1992; Nowakowski et al., 1998); toxins A, C (Lacy et al., 1998), and E cleave SNAP-25 (Sciavo et al., 1993); and toxin C affects syntaxin. As a result, stimulation of the presynaptic cell (e.g., the alpha motor neuron) fails to result in transmitter release, thus producing paralysis in the motor system, or autonomic dysfunction when parasympathetic nerve terminals or autonomic ganglia are involved. Botulinum toxin is transported within nerves in a manner analogous to tetanospasmin, and can thereby gain access to the central nervous system (CNS). However, symptomatic CNS involvement due to botulism is rare.

Clinical manifestations

The clinical presentation of foodborne botulism is distinct, characterized by bilateral cranial nerve palsies within 2–36 hours of ingestion of contaminated food, followed by symmetric, descending flaccid paralysis (Hughes et al., 1981). Abdominal cramps, nausea, vomiting, and diarrhea may also occur early in the illness (Cherington, 2004). Affected patients are not febrile, confused, or obtunded. In addition, the sensory system is spared (McCroskey et al., 1991).

Oculobulbar weakness is an early feature of botulism; its absence indicates an alternative diagnosis. Blurred vision, diplopia, impaired accommodation, and ptosis occur due to paralysis of cranial nerves III, IV, and VI (Terranova et al., 1979). Additional symptoms arise with involvement of cranial nerves IX, X, and XII, including dysarthria, dysphagia, and hypoglossal weakness.

Cranial nerve palsies are followed by descending symmetric paralysis affecting the voluntary muscles of the neck, shoulders, and upper extremities, followed by the proximal and distal lower extremities. Deep tendon

reflexes, initially present, diminish or disappear within a few days of illness. Respiratory dysfunction may result from either upper-airway obstruction (pharyngeal collapse due to cranial nerve involvement) or diaphragmatic and accessory muscle weakness. Patients needing mechanical ventilation require mean periods of 58 days (type A) and 26 days (type B) for ventilatory weaning (Hughes et al., 1981). Recovery may not begin for up to 100 days (Colerbatch et al., 1989).

Autonomic dysfunction may manifest as hypothermia, urinary retention, dry mouth and throat, postural hypotension, and constipation (Vita et al., 1987). Pupillary dilatation occurs in less than 50% of cases (Cherington, 2004); although these are very useful signs when present, their absence does not diminish the likelihood of botulism. Pupillary responses may remain abnormal for months after motor recovery (Friedman et al., 1990).

Hughes summarized published reports to analyze differences in the clinical findings of intoxication with different toxin types (Table 16.1) (Hughes, 1991). Type A is more commonly associated with dysarthria, blurred

Table 16.1

Symptoms and signs in patients with the common types of human botulism

	Type A (%)	Type B (%)	Type E (%)
Neurologic signs and symptoms			
Dysphagia	96	97	82
Dry mouth	83	100	93
Diplopia	90	92	39
Dysarthria	100	69	50
Upper-extremity weakness	86	64	NA
Lower-extremity weakness	76	64	NA
Blurred vision	100	42	91
Dyspnea	91	34	88
Paresthesias	20	12	NA
Gastrointestinal signs and symptoms			
Constipation	73	73	52
Nausea	73	57	84
Vomiting	70	50	96
Abdominal cramps	33	46	NA
Diarrhea	35	8	39
Miscellaneous symptoms			
Fatigue	92	69	84
Sore throat	75	39	38
Dizziness	86	30	63
Neurologic findings			
Ptosis	96	55	46
Diminished gag reflex	81	54	NA
Ophthalmoparesis	87	46	NA
Facial paresis	84	48	NA
Tongue weakness	91	31	66
Pupils fixed or dilated	33	56	75
Nystagmus	44	4	NA
Upper-extremity weakness	91	62	NA
Lower-extremity weakness	82	59	NA
Ataxia	24	13	NA
DTRs diminished or absent	54	29	NA
DTRs hyperactive	12	0	NA
Initial mental status			
Alert	88	93	27
Lethargic	4	4	73
Obtunded	8	4	0

Adapted from Bleck TP (2005). Botulism. In: Mandell, Douglas, and Bennett's Principles and Practices of Infectious Diseases (6th edn.). Elsevier Inc., Philadelphia, pp. 2822–2826.
DTR, deep tendon reflex; NA, not available.

vision, dyspnea, diarrhea, sore throat, dizziness, ptosis, ophthalmoplegia, facial paresis, and upper-extremity weakness. Types B and E appear to produce more autonomic dysfunction. Nystagmus is occasionally noted, usually in type A disease. None of these differences is diagnostic of the toxin type, however.

Infant botulism is characterized by constipation in 95% of cases (Long, 1984; Istre et al., 1986). Bulbar and extremity weakness follow as affected infants develop feeding difficulties, a weakened cry, ptosis, and hypotonia (Cornblath et al., 1983). Upper-airway obstruction (Oken et al., 1992) may be an indication for early intubation (Schreiner et al., 1991), as pharyngeal hypotonia can occur rapidly in this age group. Symptoms may progress for 1–2 weeks, stabilizing for 2–3 weeks before resolving (Angulo et al., 1998). Autonomic abnormalities often persist beyond motor recovery. Relapses of infant botulism may occur (Glauser et al., 1990).

Patients with wound botulism present with neurological findings identical to those of foodborne illness in the absence of a gastrointestinal prodrome. Notably, the reported incubation period is longer, varying from 4 to 14 days (Hatheway, 1995). Fever is unusual and may reflect bacterial superinfection of the original wound. In rare instances, *C. botulinum* may produce local skin and soft-tissue abscesses (Elston et al., 1991).

The signs and symptoms exhibited by victims of inhalational botulism are the same as those seen with ingestion. The latency between exposure and clinical disease after inhalation appears to be between 12 hours and 3 days, with maximal disease by about 5 days (Arnon et al., 2001).

Botulinum toxin has achieved widespread notoriety for its use in cosmetic procedures. It has also been used to treat a variety of chronic pain syndromes, achalasia, and anal fissures (Schantz and Johnson, 1997). Dysphagia and other symptoms of neuromuscular impairment have been reported rarely after the therapeutic use of botulinum A toxin (Comella et al., 1992).

Diagnosis

The diagnosis of botulism is most often made after a careful assessment of historical and clinical data. If more than one patient is affected, as in an outbreak setting, the condition is easily recognized. However, due to the rarity of the disease, botulism cases in isolation are frequently misdiagnosed.

The differential diagnosis of botulism is limited. The most common considerations include Guillain–Barré syndrome (GBS), myasthenia gravis, stroke, tick paralysis and the Lambert–Eaton myasthenic syndrome (LEMS). In contrast to the descending symptoms seen in botulism, GBS presents with ascending paralysis in 95% of cases (Pascuzzi and Fleck, 1997). A history of preceding respiratory or gastrointestinal illness (*Campylobacter jejuni* in one-third of cases) also suggests GBS. The Miller Fisher variant of GBS, characterized by ophthalmoplegia, ataxia, and early areflexia, may be mistaken for descending paralysis. Following lumbar puncture, GBS patients display an increased cerebrospinal fluid (CSF) protein concentration. Tick paralysis is excluded by a careful physical examination as the *Dermacentor* tick will still be attached to the scalp in symptomatic patients. Myasthenia gravis may be distinguished by a sustained response to anticholinesterase therapy (Tensilon test); however, an improvement in strength has been reported in cases of botulism (Edell et al., 1983), and electromyography may be required for differentiation. LEMS is differentiated by increased strength with sustained contraction in affected patients.

In polio, patients are febrile, demonstrate a CSF pleocytosis, and have asymmetrical weakness. Magnesium intoxication may mimic botulism and must be distinguished by the clinical history and appropriate body fluid analysis (Cherington, 2004). Rarely, botulism may be confused with diphtheria, organophosphate poisoning, or brainstem infarction (Dunbar, 1990).

Conventional diagnosis of botulism relies on the demonstration of toxin in serum, gastric secretions, stool, or food samples (Centers for Disease Control and Prevention, 1998). The most sensitive means of botulism toxin detection is the mouse bioassay (Notermans and Nagel, 1989). Samples are diluted in phosphate buffer and injected into the peritoneum of laboratory mice. The mice are then followed for the development of botulism-like symptoms: fuzzy hair, muscle weakness, and respiratory failure. Unfortunately, depending on toxin concentration in the sample, symptoms may not be evident for 24–48 hours. Toxin type may be determined by injecting infected mice with type-specific botulism antitoxin. Botulism symptoms are absent from infected mice that receive the appropriate antitoxin (Hatheway, 1988). Confirmation and toxin typing are obtained in almost 75% of cases (Dowell et al., 1977). The mouse bioassay is labor- and resource-intensive, and therefore the testing is performed in only a limited number of public health laboratories.

Cultures of fecal material or gastric aspirates in affected patients may reveal *C. botulinum*. However, strict anaerobic conditions are required for growth, and competing fecal flora or nontoxigenic *C. botulinum* strains may make isolation difficult.

Though mouse bioassay remains the gold standard, several alternative methods of botulism diagnosis are under investigation. Most promising is the application

of enzyme-linked immunosorbent assay (ELISA), which has demonstrated botulinum toxin in contaminated food samples such as fish fillets, canned salmon and corned beef, pasta products, and canned vegetables (Shone et al., 1985; Roman et al., 1994; Rodriguez and Dezfulian, 1997; Del Torre et al., 1998). However, the utility of ELISA has been limited in food substances with endogenous proteinases (e.g., egg yolk, milk) and clinical specimens such as serum or feces (Dezfulian et al., 1984; Doellgast et al., 1993; Poli et al., 2002; Sharma and Whiting, 2005).

In patients with a clinical syndrome suggestive of botulism, yet negative toxin assay and stool culture results, electrophysiological testing can provide a presumptive diagnosis. Cases are commonly characterized by a small, evoked muscle action potential in response to supramaximal nerve stimulus of a clinically affected muscle. Sensory nerve studies are normal. Motor conduction velocities are normal, while the amplitude of compound muscle action potentials is reduced in 85% of cases (Gutmann et al., 1992). Repetitive nerve stimulation at high rates (20 Hz or greater) may reveal a small increment in the motor response. Posttetanic facilitation (PTF) is 30–100% in botulism and may last for several minutes while, in cases of LEMS, PTF is 200% or more but lasts only 30–60 seconds (Gutmann and Pratt, 1976; Fakadej and Gutmann, 1982; Gutmann et al., 1992). This test is very uncomfortable, and should not be requested unless botulism or LEMS is a serious consideration. The therapeutic use of botulinum A toxin for dystonic disorders can produce electrophysiological evidence of toxin dissemination to distant sites (Buchman et al., 1993).

Treatment

Supportive therapy is still the mainstay of botulism treatment. With the advent of modern mechanical ventilation in the 1940s, mortality rates have dropped from 60–70% in the early 20th century to the current rate of 3–5% (Gangarosa, 1971). Patients with suspected or proven infection should undergo serial vital capacity assessment in the intensive care unit early in the hospital course. Mechanical ventilation is a consideration in any patient with upper-airway compromise (due to pharyngeal muscle paralysis) or a decline in vital capacity. Gastric lavage may be attempted if the food exposure was relatively recent. In addition, in the absence of an ileus, enemas or cathartic agents may prove useful in eliminating unabsorbed toxin from the gastrointestinal tract.

Early antitoxin therapy consisted of a trivalent (types A, B, and E) equine serum. However, its use was complicated by a hypersensitivity reaction in 9–20% of cases (Black and Gunn, 1980). In 2006, a randomized, controlled trial demonstrated the safety and efficacy of a human botulism immunoglobulin (BabyBIG) in infected infants (Arnon et al., 2006). Treatment with intravenous BabyBIG (50 mg/kg or 1 ml/kg) was associated with reduction in the mean length of hospital stay, duration of mechanical ventilation, and associated costs when compared with treatment with intravenous immunoglobulin. BabyBIG contains 15 IU antitoxin A and 4 IU antitoxin B per 50 mg and has a half-life of 28 days; a single dose is used in suspected or proven cases. Information on BabyBIG may be obtained from the California Department of Health Services by telephone at +1-510-231-7600 or at www.infantbotulism.org.

In cases of foodborne botulism, antimicrobial therapy is not indicated and has not been shown to eradicate *C. botulinum* or its toxin from the intestine (Arnon et al., 1977; Smith, 1978). Lysis of *C. botulinum* in the gut by antimicrobial agents may also increase the toxin available in infant botulism (Centers for Disease Control and Prevention, 1998). In addition, aminoglycosides and tetracyclines, which can impair neuron calcium entry, worsen infant botulism (Wilson et al., 1982). Patients with wound botulism should undergo careful debridement. *C. botulinum* abscess formation may be treated with penicillin G or metronidazole.

Although the greatest improvement in muscle strength occurs in the first 3 months of recovery from botulism, patients still show improvements in strength and endurance for up to 1 year after disease onset (Wilcox et al., 1990). Recovery from botulism may also be followed by persistent psychological dysfunction, which may require mental health intervention (Cohen et al., 1988).

Prevention

The most important aspect of botulism prevention is proper food handling and preparation. Because the toxin is heat-labile, terminal boiling, or similarly intense heating of contaminated food, will inactivate it. Food containers that appear to bulge may contain gas produced by *C. botulinum,* and should not be opened.

Immunity to botulinum toxin does not develop even with severe disease, and the repeated occurrence of botulism has been reported (Beller and Middaugh, 1990). A pentavalent toxoid (ABCDE) vaccine is used among high-risk laboratory workers and military personnel in the USA (Siegel, 1988). A recombinant vaccine, expressing the type A binding domain (Byrne et al., 1998), or vaccination with the carboxy-terminal fragment (Oshima et al., 1997), promises to make vaccination less expensive and less painful.

TETANUS

Background

Tetanus is a spastic illness caused by neurotoxin production by the spore-forming, anaerobic bacillus *Clostridium tetani*. Persistent, tonic spasms accompanied by muscle rigidity of the neck and jaw (trismus or lockjaw) characterize early infection, later followed by autonomic instability. The clinical manifestations of tetanus were first described by Hippocrates in the fifth century BCE (Gowers, 1888), but the mechanism of infection would remain unknown for centuries. In 1884, Arthur Nicolaier produced a syndrome resembling tetanus by inoculating laboratory animals with contaminated soil (Nicolaier, 1884). A few years later, Shibasaburo Kitasato and Emil von Behring isolated *C. tetani* in culture and identified its neurotoxin (Behring and Kitasato, 1890). Soon thereafter, tetanus toxoid (TT) was developed in 1924 (McGrew and McGrew, 1985; Pascual et al., 2003). TT achieved success in protecting military personnel from tetanus in World War II (United States Army, 1955). However, despite the widespread availability of tetanus–diphtheria toxoid (Td) vaccine today, clinical cases still occur due to lapses in immunization practices worldwide (Centers for Disease Control and Prevention, 2003).

Etiology

C. tetani is a gram-positive, spore-forming, obligate anaerobic bacillus. Two toxins, tetanospasmin (or tetanus toxin) and tetanolysin, are produced during the growth phase. Mature organisms subsequently develop a terminal spore (Hoeniger and Tauschel, 1974). Tetanospasmin is a zinc-dependent metalloproteinase (Geisler et al., 1997) synthesized as a single, 151-kDa chain. It is characterized by a heavy chain (100 kDa) and a light chain (50 kDa) connected by a disulfide bridge (Matsuda, 1989). Tetanospasmin is encoded on a plasmid that is present in all toxigenic strains (Eisel et al., 1986). The role of tetanolysin in pathogenicity is not well understood (von Behring and Kitasato, 1991).

C. tetani and its spores are ubiquitous, found in soil and in the gastrointestinal tract of animals and humans worldwide. Hardy spores are resistant to environmental challenges; spore destruction requires autoclaving at 121°C and 103 kPa (15 psi) for 15 minutes or prolonged exposure to iodine, hydrogen peroxide, formalin, or gluteraldehyde (Feingold, 1998; Wassilak et al., 2004).

Epidemiology

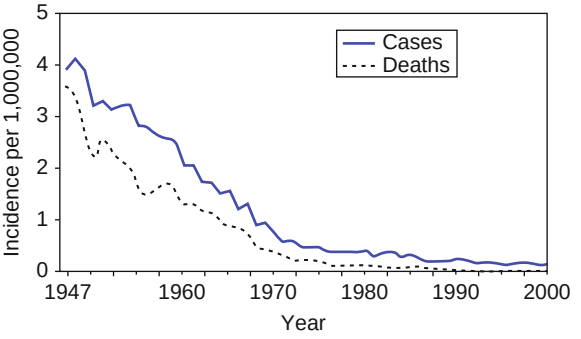
Until recently, primary tetanus immunization programs in developing countries were ineffective. As a result, 800 000–1 000 000 annual deaths were attributed to tetanus during the 1980s (Dietz et al., 1996). Two-thirds of cases worldwide occurred in sub-Saharan Africa, where over 40% of tetanus is a result of neonatal infection (Dietz et al., 1996; UNICEF, 2000); nearly one-third of affected infants were born to mothers of a previously afflicted child, highlighting a failure to immunize (Traverso et al., 1991).

A worldwide commitment to the elimination of neonatal tetanus by the World Health Assembly was established in 1989 (WHO, 1989, 1993). As a result, cases of neonatal tetanus declined by over 50% over the next 10 years (Galazka et al., 2004). A resurgent effort in 1999, renamed the Maternal and Neonatal Tetanus Elimination Program (WHO, UNICEF, and UNFPA, 2000), met with additional success. Current estimates suggest that worldwide neonatal tetanus now accounts for fewer than 200 000 deaths annually (Roper et al., 2007). The Global Immunization Vision and Strategy, launched by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) in 2005, continues to target tetanus as a preventable cause of neonatal death by promoting routine tetanus toxoid administration in hard-to-reach, previously underserved areas (WHO and UNICEF, 2005).

In the USA, tetanus is a rare occurrence. The disease became reportable in 1947, when 3.9 cases per million residents were noted. Current estimates suggest that as few as 0.15–0.16 cases per million occur annually (Pascual et al., 2003) – a 96% decline (Fig. 16.2).

Among 130 US tetanus cases from 1998 to 2000, 9% were aged <9 years (including one neonate), 55% were aged 22–59 years, and 36% were aged ≥ 60 years. However, 15 of the 20 deaths (75%) occurred in patients who were ≥ 60 years of age. Populations at risk of infection included persons of Hispanic ethnicity, elderly patients with diabetes, and injection drug users (Pascual et al., 2003).

Centers for Disease Control and Prevention surveillance data suggest that tetanus most often followed



Source: Data from the National Notifiable Disease Surveillance System, CDC, Atlanta, GA.

Fig. 16.2. Reported cases and deaths from tetanus in the USA, 1947–2000. (Data from Pascual et al., 2003.)

acute injury (73%). Sustained injuries included acute trauma (50%), lacerations (33%), and abrasions (9%). Tetanus also occurred among those without an acute injury (26%). Neonatal tetanus was uncommon, accounting for only one case during this time period (Barlow et al., 2001).

Pathogenesis

Clinical manifestations of tetanus are a consequence of tetanospasmin activity; the role of the toxin tetanolysin is unclear (von Behring and Kitasato, 1991). Spore inoculation occurs via a disrupted skin barrier, most often after a penetrating injury (Ernst et al., 1997). *C. tetani* subsequently transforms into a vegetative state, allowing for neurotoxin production.

Tetanospasmin accesses the nervous system via the presynaptic terminals of lower motor neurons. It is then carried by retrograde axonal transport to its main sites of action in the brainstem and spinal cord (Bleck and Brauner, 1997). Once the toxin enters the CNS, it diffuses to the terminals of inhibitory cells. A bacterial protease cleaves the disulfide bond between the toxin's heavy (100 kDa) and light (50 kDa) chains. The heavy chain, further divided into fragments B and C by pepsin, mediates binding of the toxin to presynaptic receptors and allows for receptor-mediated endocytosis (Farrar et al., 2000; Caccin et al., 2003; Rummel et al., 2003). The light chain prevents the presynaptic release of γ-aminobutyric acid (GABA), an inhibitor of sustained, excitatory nervous impulses. The clinical signs and symptoms of tetanus (muscle rigidity and spasm) result. Tetanospasmin also affects the autonomic neurons, allowing for disinhibition of adrenal cathecholamine release and a hypersympathetic state.

In cases of tetanus, toxin binding appears to be an irreversible event. As a result, initial recovery requires the growth of a new axon terminal. Later, the new synapses are removed when the original ones re-establish their connections (Meunier et al., 2002).

Clinical manifestations

Tetanus is classically divided into four clinical types: (1) generalized; (2) localized; (3) cephalic; and (4) neonatal. These are valuable diagnostic and prognostic distinctions, but reflect host factors and the site of inoculation rather than differences in pathogenesis and pathophysiology.

The incubation period of tetanus (i.e., time from inoculation to the onset of symptoms) is usually 3–21 days (Weinstein, 1973; Patel and Mehta, 1999), though symptoms have been reported as early as 1 day and as late as 2 months after injury (LaForce et al., 1969; Farrar et al., 2000). An incubation period of <48 hours is associated with severe disease (Veronesi and Focaccia, 1981; Bleck, 1991; Kefer, 1992).

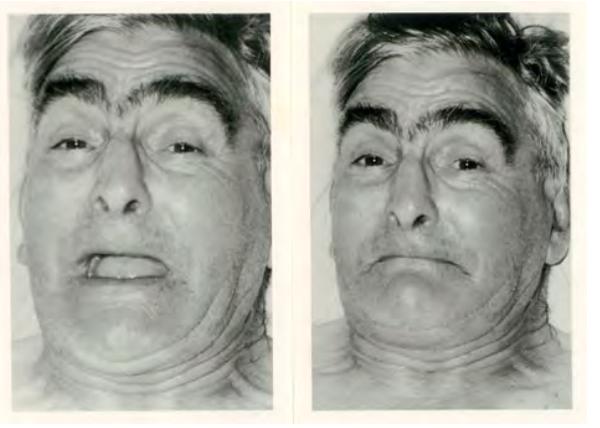


Fig. 16.3. Left: trismus. The patient is opening his mouth as fully as possible. Right: risus sardonicus. Note the straightened upper lip at rest. (Reproduced from Parsons, 1983.)

Early generalized tetanus is most often characterized by muscle rigidity of the masseter muscles (trismus or lockjaw), occurring in 80% of cases (Bunch et al., 2002). Dysphagia, and neck, shoulder, back, and abdominal stiffness, may also be present. A subtle, yet pathognomonic, finding of tetanus is risus sardonicus, a flat-lipped grimace as a consequence of tightened facial muscles (Fig. 16.3).

The onset period of tetanus (i.e., time from first symptoms to first spasm) is typically 1–3 days, ranging from several hours to 5 days (Patel and Mehta, 1999; Brauner et al., 2002; Thwaites et al., 2004). Initially occurring in response to sensory stimuli, spasms quickly progress to spontaneous, painful involvement of several muscle groups. The generalized spasm of tetanus results in opisthotonus, posturing with clenched fists, adduction of the shoulders, flexion of the elbows and wrists, and extension of the legs (Fig. 16.4). Of note, patients remain conscious in tetanus and experience severe pain with each spasm. Subsequent contractions of the pharyngeal and thoracic muscles may cause respiratory failure, accounting for the majority of tetanus deaths worldwide (Farrar et al., 2000). Generalized tetanus is further complicated by autonomic instability. Signs and symptoms

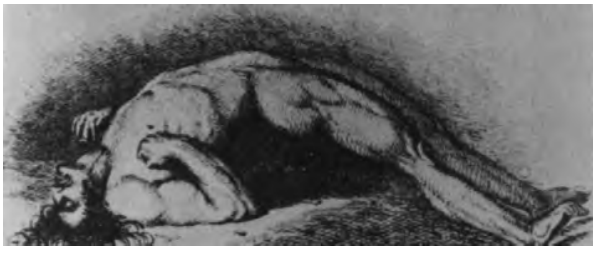


Fig. 16.4. Opisthotonus. (Reproduced from Bell, 1824.)

include hypertension or hypotension, diaphoresis, cardiac arrhythmias, and hypermetabolism.

Spasms and autonomic instability peak within 2 weeks, but muscle rigidity may persist for several months (Kefer, 1992; Ernst et al., 1997; Farrar et al., 2000). The severity of clinical manifestations may be decreased by partial immunity (Luisto and Iivanainen, 1993). Lower motor neuron dysfunction may not be apparent until spasms remit, and recovery from this deficit in neuromuscular transmission may take weeks (Bleck and Calderelli, 1983).

Localized tetanus refers to the limited symptoms that occur in association with spore inoculation. Localized symptoms may be mild and persistent, often resolving spontaneously. Lower motor neuron dysfunction (weakness and diminished muscle tone) is often present in the most involved muscle. Localized disease often precedes generalized tetanus; systemic symptoms may occur after the toxin gains access to the CNS.

Cephalic tetanus is localized disease involving the cranial nerves due to head trauma or contamination of a cranial wound. Classic clinical symptoms include dysphagia, trismus, and focal cranial neuropathies. The facial nerve is most commonly affected (Weinstein, 1973), but involvement of cranial nerves III, IV, VI, and XII may also occur.

Neonatal tetanus results from contamination of the umbilical stump, most often due to aseptic surgical technique or inadequate immunization of the mother (Schofield et al., 1961). Ninety percent of affected infants demonstrate symptoms in the first 3–14 days of life (Salimpour, 1978; WHO, 1993; Patel and Mehta, 1999). An early sign of infection is an inability to nurse, as trismus and lip muscle rigidity interfere with normal feeding (Salimpour, 1978). As in adults, apnea is a leading cause of death among neonates; mortality rates approach 60%, even in areas with adequate medical support (Saltigeral Simental et al., 1993; Ertem et al., 2004; Omoigberale and Abiodun, 2005). Complications of neonatal tetanus include bacterial superinfection of the umbilical stump, nosocomial pneumonia as a result of mechanical ventilation, and severe malnutrition (Egri-Okwaji et al., 1998). Several case series suggest that survivors may have neurological damage after infection, including psychomotor retardation, cognitive deficits, and behavioral abnormalities (Teknetzi et al., 1983; Khanna et al., 1985; Anlar et al., 1989; Tutuncuoglu et al., 1994; Okan et al., 1997; Barlow et al., 2001).

Diagnosis

The diagnosis of tetanus is based on the signs and symptoms outlined above, especially in the presence of a recent tetanus-prone injury or in the absence of adequate immunization. Serological tests are not helpful as most affected patients do not have detectable antitetanus antibodies. In addition, tetanus has been reported in patients with antibody concentrations above the protective concentration of 0.01 IU/l (Goulon et al., 1972).

Wound cultures are also of limited utility, yielding *C. tetani* in fewer than 30% of cases (Kefer, 1992). The growth of *C. tetani* in culture is also nonspecific for infection as the organism may not contain the toxin-producing plasmid. *C. tetani* may also be present without causing disease in patients with adequate immunity (Bleck, 1989).

The differential diagnosis of tetanus is limited. Drug-induced dystonia may cause neck stiffness, involuntary movement of the head and neck, and pronounced eye deviation. However, patients with dystonia will not have tonic contractions between spasms. In addition, a dystonic reaction can be alleviated with an anticholinergic agent. Neuroleptic malignant syndrome (NMS) may manifest with autonomic instability and muscle rigidity, but symptoms inconsistent with tetanus, such as fever and altered mental status, are also present. An offending drug in cases of NMS is often identified. Trismus may occur with a dental abscess, but affected patients lack the progressive spasms seen with tetanus. Finally, accidental or intentional strychnine poisoning may produce a clinical syndrome resembling tetanus. As the initial treatment of tetanus and strychnine intoxication is similar, supportive care should be instituted before the results of serum and urine toxicology assays are available.

Treatment

Tetanus management demands a multifaceted approach aimed at preventing neurotoxin absorption, treating symptoms, administering antimicrobial agents, stabilizing autonomic aberrations, and controlling the airway with mechanical ventilation. To avoid provoked muscle spasms, the patient should be placed in a quiet, darkened area.

Patients with suspected or known tetanus should receive human tetanus immunoglobulin (HTIG) to prevent further toxin activity. Passive immunization with HTIG, 500 units intramuscularly, shortens the course of tetanus and may lessen its severity (Blake et al., 1976). Pooled intravenous immune globulin has been proposed as an alternative to HTIG (Lee and Lederman, 1992). A meta-analysis of the benefits of intrathecal HTIG therapy was inconclusive (Abrutyn and Berlin, 1991). However, in a recent randomized trial, the administration of intrathecal HTIG with intramuscular HTIG resulted in shorter duration of spasms, shorter hospital

stay, and decreased respiratory assistance demands when compared with intramuscular HTIG alone (Miranda-Filho et al., 2004).

Active immunization is indicated in all cases of tetanus, as prior infection does not confer immunity. A single dose of tetanus–diphtheria–acellular pertussis vaccine (Tdap) (Pichichero et al., 2005) should be administered to any affected adult who has not received Tdap in the past. Those who have received Tdap once during adulthood should receive Td instead. TT alone should be given only to those patients with a documented allergy or reaction to diphtheria toxoid. Active immunization should also be administered to affected children: children <7 years of age should receive diphtheria–tetanus–acellular pertussis (DTaP) vaccine, those 7–11 years of age should receive Td, and those 11–18 years of age should receive Tdap. In a 1998–2000 tetanus surveillance report, only 63% of patients eligible for prophylaxis received vaccination (Pascual et al., 2003).

In most cases of tetanus, an inoculation site or a source injury can be identified. The course of tetanus is not affected by wound debridement; surgical management of the wound should be pursued only after the patient has been stabilized.

The cornerstone of tetanus symptom management is benzodiazepine therapy. As GABA agonists, benzodiazepines allow for muscle relaxation and sedation in affected patients (Ernst et al., 1997). Caution should be exercised with higher doses of benzodiazepines as the vehicle, propylene glycol, may produce lactic acidosis (Kapoor et al., 1981); this effect can be avoided with enteral administration. Alternatively, intravenous midazolam (5–15 mg/h or more) is effective and does not contain propylene glycol, but must be given as a continuous infusion because of its brief half-life (Orko et al., 1988). As high doses of benzodiazepines must be administered to control initial spasms, patients often require a taper of therapy to avoid withdrawal during recovery. Extended, high-dose benzodiazepine therapy may result in airway compromise, necessitating mechanical ventilation.

Neuromuscular blocking agents such as vecuronium or pancuronium may be warranted when benzodiazepines alone fail to alleviate symptoms; these have replaced the use of phenothiazines and barbiturates as adjunctive therapy (Fassoulaki and Eforakopoulou, 1988). Dantrolene, a direct skeletal muscle relaxant, may also prove useful in alleviating symptoms of muscle rigidity and spasticity (Tidyman et al., 1985; Farquhar et al., 1988; Sternlo and Andersen, 1990). In a retrospective study, intrathecal baclofen controlled muscle spasticity and rigidity associated with tetanus (Santos et al., 2004). However, the efficacy and ease of intravenous benzodiazepine therapy have precluded its use.

The administration of metronidazole in cases of tetanus has been shown to reduce patient mortality (Ahmadsyah and Salim, 1985). As penicillin is a GABA antagonist and may be associated with increased spasticity, metronidazole is the preferred agent in tetanus. Therapy with oral metronidazole resulted in lower mortality, shorter hospitalization, and less progression of disease than intramuscular penicillin (Ahmadsyah and Salim, 1985).

Autonomic dysfunction is a consequence of excessive catecholamine release. Intravenous labetalol may be used as it offers combined α- and β-adrenergic blockade (Domenghetti et al., 1984). Beta-blockers should not be used in isolation, as unopposed α-adrenergic effects may be life-threatening (Buchanan et al., 1978). A continuous morphine sulfate infusion (0.5–1.0 mg/kg/h) may also alleviate hypertension (Rocke et al., 1986) with the added benefit of sedation.

Magnesium sulfate, a presynaptic neuromuscular inhibitor, blocks catecholamine release and reduces receptor response to catecholamines (Lipman et al., 1987). In a randomized trial, magnesium sulfate infusion reduced medication requirements in the control of autonomic instability among tetanus patients when compared with placebo (Thwaites et al., 2006).

Supportive therapy is essential for the treatment of tetanus. As the endotracheal tube may stimulate spasms and if prolonged ventilation is anticipated, an early tracheostomy may be beneficial (Mukherjee, 1977). Early nutritional support via enteral feeding is critical, as the caloric requirements of affected patients are extremely high. Patients may also suffer from complications of a prolonged intensive care unit stay, such as deep-vein thrombosis, skin breakdown, or stress ulcers; preventive measures (e.g., prophylactic heparin, flotation beds, H_2-blockers) should be employed as indicated.

The mortality rate for severe tetanus may reach 60%, even in expert centers (Nolla-Salas and Garcés-Brusés, 1993). A well-designed protocol can substantially reduce morbidity and mortality in such cases (Brauner et al., 2002). Tetanus survivors often have serious psychological problems related to the disease and its treatment that persist after recovery; such patients may require psychotherapy (Edwards and James, 1979).

Prevention

TT, a heat-inactivated toxin, was developed in 1924 (Behring and Kitasato, 1890).

The vaccine was initially used among military personnel in World War II. As a result, tetanus accounted for only 12 of nearly 3 million hospitalizations during the war; five cases were fatal (Glenn, 1946; United States Army, 1955).

The Advisory Committee on Immunization Practices (ACIP) recommends a primary tetanus vaccination in combination with diphtheria and pertussis (DTaP) in the first year of life, followed by a dose at age 15–18 months and again at age 4–6 years. An adult formulation booster (Td) should be administered at age 11–12 years and again 10 years later (Kretsinger et al., 2006).

In 2005, the US FDA approved the use of an adult formulation of tetanus, diphtheria, and acellular pertussis (Tdap) in lieu of the Td booster (Pichichero et al., 2005). At this point, a single dose of Tdap should be given to adults aged 19–64 years if they received their last dose of Td $\geq$10 years ago and have never received Tdap. For adults who require tetanus toxoid-containing vaccine as part of wound management, a single dose of Tdap is preferred if they have not received it previously and have not received Td in $\geq$5 years (Kretsinger et al., 2006).

A dose of Tdap may also be given as soon as 2 years after the last Td dose if a booster for pertussis is desired. Settings in which a pertussis booster is indicated include the following: adults who anticipate close contact with an infant $<$12 months of age, women who are considering pregnancy or who are in the immediate postpartum period, and all health care personnel (Kretsinger et al., 2006). Tdap is not licensed for multiple administrations; after an initial dose of Tdap, adults should receive a Td booster every 10 years.

Serological analysis of the US population suggests that tetanus immunity wanes with age (Murphy et al., 1995; McQuillan et al., 2002). While 80% of patients aged 6–39 years were noted to have protective antibodies to tetanus, only 28% of patients over 70 years of age were seropositive (McQuillan et al., 2002).

Neonatal tetanus may occur due to inadequate immunization of the mother. Although a full series of maternal immunizations is ideal, even one or two doses of tetanus toxoid confer substantial protection against neonatal tetanus (Koenig et al., 1998). Application of topical antimicrobial agents to the umbilical cord stump markedly decreases the incidence of neonatal tetanus when maternal immunization is insufficient (Parashar et al., 1998).

Mild reactions to tetanus toxoid (e.g., local tenderness, edema, low-grade fever) are common. More severe reactions are rare, likely due to a hypersensitivity response to the preservative thiomersal (Jacobs et al., 1982). Although there have been reports suggesting a connection between tetanus immunization and GBS, a careful epidemiological analysis did not confirm an association (Tuttle et al., 1997).

HTIG binds directly to toxin, providing temporary immunity. Current guidelines suggest that patients with suspected tetanus or a tetanus-prone wound should receive HTIG in conjunction with vaccination if they did not complete a primary immunization series or if their immunization status is unknown (Kretsinger et al., 2006). Tetanus-prone wounds are characterized by devitalized tissue such as a crush injury, or those with potential contamination with dirt or rust.

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