Bacterial meningitis in adults: clinical characteristics, risk factors and adjunctive treatment

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Chapter 2

Epidemiology, diagnosis and antimicrobial treatment of acute bacterial meningitis

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Introduction

Given the significant morbidity and mortality associated with acute bacterial meningitis in the United States and throughout the world, accurate information is necessary regarding the important etiological agents and populations at risk to initiate public health measures and ensure appropriate management. In this review, we describe the changing epidemiology of bacterial meningitis in the United States and throughout the world by reviewing the global changes in etiological agents followed by specific microorganism data on the impact of the development and widespread use of conjugate vaccines. We provide recommendations for empirical antimicrobial and adjunctive therapy for clinical subgroups and review available laboratory methods for making the diagnosis of bacterial meningitis. Finally, we summarize risk factors, clinical features, and microbiological diagnostics for the specific bacteria causing this disease.

Epidemiology and vaccination

Studies on the incidence of bacterial meningitis performed in the United States during the 1950s, 1960s, and 1970s found significant attack rates for the common meningeal pathogens at that time (*Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*), although these case-finding efforts were performed with relatively small populations. Despite the retrospective design and relatively small populations in these studies, therapeutic and preventive strategies were targeted toward these microorganisms, given the high frequency of isolation of these specific pathogens (>70% of cases).[1-3]

In 1977, the Centers for Disease Control and Prevention (CDC) established a nationwide surveillance system to gather prospective epidemiological data that would supplant the retrospective and community-based studies of cases of bacterial meningitis in previous reports. In the first published study, 13,974 cases of bacterial meningitis reported to the CDC from 27 states in the United States from 1978 through 1981 were analyzed.[4] The overall attack rate was 3.0 cases per 100,000 population with variability based on age (76.7 cases per 100,000 for children under 1 year of age), race, and sex (males versus females of 3.3 versus 2.6 cases per 100,000, respectively). The three most common pathogens were *H. influenzae*, *N. meningitidis*, and *S. pneumoniae*, accounting for more than 80% of cases. However, there was a significant underreporting in that study because no active effort was taken to detect cases.

In a subsequent study performed in 1986 that was an active, laboratory-based surveillance study for all cases of bacterial meningitis in five states (Missouri, New Jersey, Oklahoma, Tennessee, and Washington) and Los Angeles County, which included a population of almost 34 million, [5] analysis was performed for the five most common etiological agents of bacterial meningitis (*H. influenzae*, *N. meningitidis*, *S. pneumoniae*, *Listeria monocytogenes*, and *Streptococcus agalactiae*). Given the better system of searching for active cases, the overall incidence of bacterial meningitis was two to three times that of the previous report,[4] although *H. influenzae*, *N. meningitidis*, and *S. pneumoniae* continued to account for the

majority of cases (77%). These data confirmed the importance of identifying strategies for the development of effective vaccines against these pathogens.

With the introduction of *H. influenzae* type b conjugate vaccines in the United States and several countries throughout the world, the epidemiology of bacterial meningitis dramatically changed.[6] In a subsequent study conducted by the CDC in 1995 in laboratories serving all of the acute-care hospitals in 22 counties of four states (Georgia, Tennessee, Maryland, and California) that served more than 10 million people, the incidence of bacterial meningitis dramatically declined as a direct result of the vaccine-related decline in cases caused by *H. influenzae* type b;[7] the incidence of the other etiological agents had little or no change compared with the 1986 data. This was accompanied by a change in the mean age of cases of bacterial meningitis, from 15 months of age in 1986 to 25 years of age in 1995, because most cases of *H. influenzae* meningitis reported prior to vaccination occurred in infants and children aged 6 to 12 months. These data highlighted the importance of vaccination and indicated the need for the development of effective conjugate vaccines against the other common meningeal pathogens.

In 2000, a heptavalent pneumococcal conjugate vaccine was introduced and has been associated with a significant decline in the incidence of pneumococcal meningitis. In a CDC surveillance study performed from 1998 to 2003,[8] there was a significant reduction in the incidence of cases of pneumococcal meningitis in patients less than 2 years of age. A tetravalent meningococcal conjugate vaccine was licensed for use in the United States in 2005, although there is currently no epidemiological data for the United States that has examined the impact of this vaccine. More detail on the efficacy of these vaccines is discussed below.

Bacterial meningitis is an even more significant problem in many other areas of the world, especially in developing countries. In Dakar, Senegal, from 1970 through 1979, the average incidence was 50 cases per 100,000 population, with approximately 1 in 250 children developing bacterial meningitis during the first year of life.[9] In African countries with high rates of human immunodeficiency virus (HIV) infection, the majority of meningitis cases are caused by *S. pneumoniae*, and this has been associated with high mortality rates.[10, 11] Sub-Saharan Africa, also referred to as the meningitis belt, is known for epidemics of meningococcal meningitis, with incidence rates of 101 cases per 100,000 in the period of 1981 to 1996 in Niger and up to 40 cases per 100,000 during an outbreak in Burkina Faso.[12, 13]

Studies from Northwest and Southern Europe, Brazil, Israel, and Canada showed epidemiological trends similar to those observed for the United States. The most common agents in adults and children are *S. pneumoniae* and *N. meningitidis* because vaccination has virtually eliminated *H. influenzae* type b meningitis in children.[14-21] In the largest review of 4,100 cases of bacterial meningitis at the Hospital Couta Maia in Salvador, Brazil from 1973 through 1982, the attack rate was 45.8 cases per 100,000 population;[22] *H. influenzae*, *N. meningitidis*, and *S. pneumoniae* accounted for 62% of cases. Other confirmed etiologies were *Enterobacteriaceae* (3.5%), *Staphylococcus* species (1.0%), *Streptococcus* species other than *S. pneumoniae* (0.6%), and *Pseudomonas* species (0.3%). For 33% of cases, no bacteria

could be cultured. Children younger than 15 years of age accounted for 79% of cases and 45% of the cases were children younger than 2 years of age.

The following sections review the epidemiology of the common etiological agents of bacterial meningitis and illustrate how the implementation of the use of conjugate vaccines has dramatically changed the epidemiology of bacterial meningitis.

Haemophilus influenzae

Prior to the availability of *H. influenzae* type b conjugate vaccines in the United States, *H. influenzae* accounted for 45 to 48% of all cases of bacterial meningitis;[4, 5] it now accounts for only 7% of cases.[7, 8] Previously most cases in the US were in infants and children under six years of age (peak incidence 6-12 months), with the majority of cases caused by capsular type b strains.

H. influenzae type b conjugate vaccines have led to a profound reduction in the incidence of *H. influenzae* type b meningitis.[23-25] Each vaccine consists of a carrier protein covalently conjugated to the polyribosylribitol phosphate (PRP), or parts of the PRP, of the outermost layer of the microorganism; the process of conjugation changes the polysaccharide from a T-cell-independent to a T-cell-dependent antigen and greatly improves immunogenicity. The vaccine is recommended for administration to all infants beginning at two months of age with a series of three inoculations, followed by a booster dose at 12 to 15 months of age; if the PRP-OMP (PedVaxHIB) is administered at two and four months, a dose at six months is not required. Since the introduction of vaccination, the number of cases of *H. influenzae* type b meningitis in industrialized nations has decreased more than 90%, with reductions of more the 95% being reported for several series (Table 1). Reductions of 50 to 75% have been seen even in countries where vaccine uptake has been only moderate; this may lie in the ability of conjugate vaccines to reduce the nasopharyngeal carriage of the microorganism and subsequently reduce transmission through herd immunity. Strong evidence of herd immunity was observed when *H. influenzae* type b disease decreased in U.S. children less than 1 year of age before the vaccine was licensed for use in this age group.[26]

H. influenzae type b remains a major cause of pediatric meningitis, with high rates of mortality throughout the world.[27, 28] In 2007, only 42% of children had access to *H. influenzae* type b vaccines, although a further 41% access to vaccines will soon be achieved; for the remainder, vaccination is planned to be initiated in subsequent years (Hib Initiative [www.hibaction.org/]).[29] In developing countries, the use of *H. influenzae* type b conjugate vaccines has not been as extensively studied. One trial with Gambian infants demonstrated that vaccination reduced most cases of meningitis, in which the annual incidence of *H. influenzae* type b meningitis dropped from over 200 cases per 100,000 children younger than 1 year of age from 1990 through 1993 to no cases in 2002.[30] In other developing countries, the overall vaccine efficacy rate has ranged from 88 to 94% (Table 1).[30-33] In a recently published study from Ulaanbaatar, Mongolia, in which all cases of bacterial meningitis from 2002 through 2004 in children 2 months to 5 years of age were analyzed, *H. influenzae* type b was the leading cause and occurred at an incidence rate higher than that for other Asian countries.[28] These data support the decision to introduce the *H. influenzae*

Table 1. Incidence of meningitis caused by *Haemophilus influenzae* type b in children aged 0-5 years in selected areas of the world before and after introduction of the conjugate vaccines.

Geographic area (years of comparison)	Pre-vaccination incidence (per 100,000)	Post-vaccination incidence (per 100,000)
United States (1987 vs 1995)	54	<1
Canada (1985 vs 1994	~44	<1
Brazil (1988-1996 vs 1997	22	10
Chile (1995 vs 1998)	40	<2
Uruguay (1992-1993 vs 1995)	17-22	1
Scandinavia (1970s vs 1995)	31	<1
Austria (1991 vs 1993-1996)	11	<1
The Netherlands (1970s vs 1993-1994)	22-40	0.3
Spain (1993-1995 vs 1997)	14	~0
Switzerland (1976-1990 vs 1991-1993)	25	8
United Kingdom (1991-1992 vs 1993-1994)	15	0.6
Israel (1989-1992 vs 1995)	18	<1
Australia (1991-1992 vs 1993-1994)	21	6
The Gambia (1990-1993 vs 2002)	60	0
Kenya (2000-2001 vs 2004-2005)	66	7.6
Malawi (1997-2002 vs 2005)	20-40	0
Uganda (2001 vs 2003-2006)	42	<3

Data from references 30, 32, 33, 117, 348

type b conjugate vaccine into this region; further surveillance data will measure the impact of the use of this vaccine on the incidence of bacterial meningitis. The *H. influenzae* Type b Initiative website provides a useful overview of the use of vaccination in the developing world (www.hibaction.org/).[29]

Despite reported successes, there has been a report of cases of invasive *H. influenzae* type b disease in children previously vaccinated in Nottingham, United Kingdom,[34] perhaps because in the United Kingdom, children are vaccinated at 2, 3, and 4 months of age without the administration of a booster dose.[35] Subsequently, a booster campaign with *H. influenzae* type b vaccine that offered one dose to all children aged 6 months to 4 years of age was initiated, leading to a dramatic decline in the number of cases in the age groups targeted for the administration of the booster dose;[36] this was followed by a reduction in the number of cases among older children and adults. Even for those children with vaccine failure who developed an episode of invasive *H. influenzae* type b disease, serum antibody concentrations were below those considered to confer long-term protection against invasive disease,[37] suggesting that these children may be at continued risk of *H. influenzae* type b invasive disease and might benefit from an additional dose of *H. influenzae* type b conjugate vaccine. Cases of invasive *H. influenzae* type b disease in vaccinated children in the United States have also been reported.[38]

The benefit of *H. influenzae* type b conjugate vaccine, however, may open up opportunities for non-type-b strains to cause invasive disease. In a surveillance study from Brazil performed before and after the introduction of the *H. influenzae* type b conjugate vaccine, the incidence of *H. influenzae* type b meningitis decreased by 69%, while there was a 9-fold increase in the incidence of meningitis caused by serotype a strains;[39] these data indicate the

importance of maintaining active surveillance for invasive disease caused by non-vaccine-sertype strains.

Based on the success of *H. influenzae* type b conjugate vaccines, *H. influenzae* meningitis has now become a disease found predominantly in adults in the United States and Europe.[40-42] In a prospective evaluation of adult patients with community-acquired bacterial meningitis in the Netherlands, *H. influenzae* comprised 2% of all cases of culture-proven bacterial meningitis.[40]

Streptococcus pneumoniae

S. pneumoniae is now the most common etiological agent of bacterial meningitis in the United States and Europe, accounting for 61% of total cases in the United States.[8, 19, 43] Vaccination strategies have been employed in attempts to reduce the incidence of pneumococcal meningitis. Initial studies demonstrated that of the serotypes isolated from the cerebrospinal fluid (CSF) of patients with pneumococcal meningitis, 74 to 90% represented serotypes contained in the 23-valent pneumococcal polysaccharide vaccine. Although this vaccine is recommended for the prevention of bacteremic pneumococcal disease in certain high-risk groups, the efficacy of the vaccine in the prevention of pneumococcal meningitis has never been proven. It has been assumed that the overall efficacy against pneumococcal meningitis was about 50%,[44, 45] although there were wide confidence intervals (CIs) in these studies.

Because children less than 2 years of age have the highest rate of invasive pneumococcal disease and the 23-valent vaccine has no proven efficacy in this age group, pneumococcal conjugate vaccines were developed in which capsular polysaccharides were conjugated to carrier proteins from a nontoxic variant of diphtheria toxin (CRM197), tetanus toxoid, or a meningococcal outer membrane protein complex. The heptavalent vaccine (Prevnar) includes the seven common pneumococcal serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F). An initial multicenter, controlled, double-blind study examined the efficacy of the heptavalent pneumococcal conjugate vaccine (coupled to the protein carrier CRM197) administered in 4 doses (2, 4, 6, and 12 to 15 months of age) to 37,868 infants and children.[46] For fully vaccinated children, the overall efficacy was 97.4% for the prevention of invasive pneumococcal disease caused by pneumococcal serotypes in the vaccine. In a study of population-based data from the Active Bacterial Core Surveillance from the CDC after licensure of the heptavalent pneumococcal conjugate vaccine, there was a 59% decline in the rates of pneumococcal meningitis in children younger than 2 years of age.[47] According to Nationwide Inpatient Service data, the incidence rate of pneumococcal meningitis fell 33% (from 0.8 to 0.55 cases per 100,000 population) following the introduction of the heptavalent pneumococcal conjugate vaccine, with the greatest decrease seen for children less than 5 years of age.[48] Another study by the CDC confirmed the lower incidence of pneumococcal meningitis, from 1.13 cases to 0.79 cases per 100,000 between 1998 to 1999 and 2004 to 2005, respectively, although there was an increase in meningitis caused by serotypes (specifically 19A, 22F, and 35B) not included in the vaccine.[49] Declines in the incidence of pneumococcal meningitis have been observed by other studies that did not show evidence of an emergence

of disease caused by serotype replacement.[50] However, multiple other studies did observe an emergence of all-invasive pneumococcal disease caused by serotypes not in the heptavalent vaccine,[38, 51-55] emphasizing the need for continued surveillance and the development of vaccines with efficacy against these other serotypes;[56] 10-valent and 13-valent vaccines have been developed and may prove efficacious against these emerging serotypes. Both the 10- and 13-valent vaccines, however, do not include protection against serotypes 22F and 35B, and only the 13-valent vaccine includes serotype 19A, the major cause of serotype replacement in pneumococcal meningitis. The 13-valent vaccine has recently been licensed by the European Union and other countries. Vaccination with the 7-valent pneumococcal conjugate vaccine initially decreased the amount of multidrug-resistant pneumococcal strains, but this effect was only temporary.[49, 57]

In the developing world, invasive pneumococcal disease (including meningitis) is a leading cause of morbidity and mortality, with an estimated 0.7 to 1.0 million deaths annually among children less than 5 years of age. The World Health Organization has recommended the inclusion of the heptavalent pneumococcal conjugate vaccine in national immunization programs, but only 26 of 193 World Health Organization member states have introduced this vaccine into their national immunization programs for children.[58] Furthermore, the countries that have introduced vaccination are primarily high-income countries with relatively few childhood deaths. These data indicate the need for the development of immunization programs, especially in poor countries, to reduce morbidity and mortality.[59] Surveillance studies of serotypes causing invasive pneumococcal disease in developing countries have also demonstrated that the current 7-valent pneumococcal vaccine would not cover all serotypes causing invasive disease and have suggested that wider coverage would be provided by the 10-valent or 13-valent pneumococcal conjugate vaccines.[59-70] The introduction of these vaccines into these vulnerable populations is a crucial, but expensive, step to control this serious infection. A step forward has recently been made in Rwanda and the Gambia, where the 7-valent pneumococcal vaccine was introduced into the childhood immunization schedule.[71, 72]

Neisseria meningitidis

More than 98% of cases of invasive meningococcal disease in the United States are sporadic. In 2008 in the United States, disease caused by serogroup B (32% of cases), serogroup C (32% of cases), and serogroup Y (24% of cases) accounted for most of the endemic disease, causing meningitis in 53% of cases.[73] For patients with meningococcal meningitis, the relative contributions of each serogroup were not specified. Other predominant serogroups have been found in other countries of the world. Major epidemics of meningococcal meningitis caused primarily by serogroup A have been reported for a number of developing countries (including Brazil, Nepal, China, and several sub-Saharan African nations); attack rates during these epidemics can approach 1% of the population.[74-76] During an outbreak of invasive meningococcal disease coinciding with the Hajj pilgrimage in March 2000, the attack rate of serogroup W-135 disease was 25 cases per 100,000 population.[77] After the Hajj outbreak, serogroup W-135 subsequently

spread worldwide and caused a large epidemic of meningococcal meningitis in Burkina Faso in 2002.[12] A high incidence of serogroup X disease was recently reported for Niger, representing 51% of 1,139 confirmed cases of meningococcal meningitis in 2006.[78]

Previous recommendations for the prevention of invasive meningococcal infection included the administration of a quadrivalent meningococcal polysaccharide vaccine against serogroups A, C, Y, and W-135 in specific populations who were at an increased risk.[79] The vaccine was not recommended for routine use in the United States because of the overall low risk of infection, the inability to protect against serogroup B disease, and the inability to provide long-lasting immunity to young children. As a result of the success of conjugate vaccines against invasive disease caused by *H. influenzae* type b and *S. pneumoniae* (see above), conjugate vaccines against specific serogroups of *N. meningitidis* were developed. These vaccines contain meningococcal polysaccharide conjugated to a protein such as tetanus toxoid, diphtheria toxoid, or CRM197 and are immunogenic and induce immunological memory in young children. The United Kingdom became the world's first country to implement routine immunization with a monovalent serogroup C meningococcal conjugate vaccine in which 3 doses of vaccine were given to children 2, 3, and 4 months of age.[80] After vaccine introduction in a catch-up program in which toddlers and adolescents received a single dose of the CRM197 meningococcal vaccine, short-term vaccine effectivenesses for toddlers and adolescents were 92% and 97%, respectively.[81] In an update of the first 18 months of the meningococcal C conjugate vaccine program in the United Kingdom, the overall reduction of cases of serogroup C invasive disease from 1998 to 1999 to 2000 to 2001 was 81%, with some variability based on age group.[82] In another case-control study of teenagers to assess vaccine efficacy, the protective effectiveness of the vaccine was 93%.[83] Carriage of serogroup C among students aged 15 to 17 years was also reduced by 66%.[84] The reduction in carriage lasted for at least 2 years after vaccine introduction, with no evidence of serogroup replacement.[85]

A quadrivalent meningococcal conjugate vaccine containing serogroups A, C, Y, and W-135 conjugated to diphtheria toxoid was licensed for use in the United States in January 2005 and was initially recommended for routine immunization starting at the age of 11 to 12 years and for catch-up vaccination for 15-year-old adolescents and those entering high school;[86] these recommendations were later changed to include the routine vaccination of all persons aged 11 to 18 years with 1 dose,[87] and revaccination for those at a prolonged, increased risk of meningococcal disease (i.e., persistent complement component deficiencies, anatomical or functional asplenia, and prolonged exposure, such as microbiologists working with *N. meningitidis* or travelers to or residents of countries where meningococcal disease is hyperendemic or epidemic).[88] It is believed that protective antibodies in adolescents will likely persist as long as, and probably longer than, that after the administration of the meningococcal polysaccharide vaccine.[89, 90] A recent trial also demonstrated that another novel tetravalent meningococcal conjugate vaccine, conjugated to CRM197, was well tolerated and immunogenic in infants when vaccination was initiated for those as young as 2 months of age.[91] This vaccine was also well tolerated and generated a strong immune response in adolescents.[92] Licensure of the CRM197 conjugate for adolescents in the United

States is currently pending. Further surveillance data are needed, however, to determine the effectiveness of these vaccines in preventing meningococcal meningitis.

Listeria monocytogenes

L. monocytogenes causes about 2% of cases of bacterial meningitis in the United States.[8] Serotypes 1/2b and 4b have been implicated in up to 80% of meningitis cases. In recent years, the incidence of invasive disease caused by *L. monocytogenes* has been decreasing, likely as a result of a decrease in organism contamination in ready-to-eat food,[93] and is associated with a decrease in non-perinatal Listerial-associated deaths.[94]

Streptococcus agalactiae

The group B streptococcus is a common cause of meningitis in neonates; 66% of all group B streptococcal meningitis cases in the United States have been reported to occur during the first 3 months of life.[95] Given the factors that increase the risk of early-onset group B streptococcal disease, several studies demonstrated that the intravenous or intramuscular injection of antimicrobial agents in colonized women is highly effective in reducing neonatal colonization with group B streptococcus. One meta-analysis of seven trials (including studies of carriers with and without risk factors) estimated a 30-fold reduction of early-onset neonatal group B streptococcal disease with intrapartum antimicrobial chemoprophylaxis,[96] although given the heterogeneity of the therapeutic interventions and flaws in trial methods, the combination of results from those trials may not have been appropriate.[97] During the 1990s, the incidence of disease caused by mother-to-child transmission fell from 1.7 to 0.6 cases per 1,000 live births,[98] likely as a result of the increased use of penicillin during labor for women at high risk of transmitting the infection to their newborns. The CDC and the American College of Obstetricians and Gynecologists have established guidelines for the prevention of early-onset disease that recommend the universal screening of all pregnant women for rectovaginal colonization at 35 to 37 weeks of gestation and the administration of antimicrobial prophylaxis to carriers.[99] If results from rectovaginal cultures are not available at the time of delivery, a risk factor approach is used for prevention.[99] One study demonstrated that the prevalence of early-onset group B streptococcal disease decreased from 2 cases per 1,000 live births in 1990 to 0.3 cases per 1,000 live births in 2004 following the institution of these recommendations.[100] Since screening efforts were instituted in the 1990s, the United States has experienced an 80% reduction in early-onset group B streptococcal disease.[95, 101]

Clinical subgroups and empirical antimicrobial therapy

Clinical subgroups exist for patients with suspected bacterial meningitis. Patients in these subgroups may present with or without the characteristic signs and symptoms of meningeal irritation and brain parenchyma inflammation. The choice of initial antimicrobial therapy for these subgroups is based on the most common bacteria causing the disease according to the patient's age, clinical setting, and patterns of antimicrobial susceptibility (Table 2). After the results of culture and susceptibility testing are available,

Table 2. Empirical antimicrobial therapy for patients with bacterial meningitis based on clinical subgroup.

Clinical subgroup	Initial therapy (daily dose [dosing interval])[a]	Predominant bacteria	References
Neonates – early onset[b]	Ampicillin (150 mg/kg/day [8 h]), plus gentamicin (5 mg/kg/day [12 h]) or cefotaxime (100–150 mg/kg/day [8-12 h])	*S. agalactiae, E. coli, L. monocytogenes*	105-109
Neonates – late onset[c]	Ampicillin (200 mg/kg/day [6-8 h]), plus an aminoglycoside[d] or cefotaxime (150–200 mg/kg/day [6-8 h])	*L. monocytogenes, S. agalactiae,* gram-negative bacilli	105, 107, 109
Infants and Children	Expanded-spectrum cephalosporin[e] plus vancomycin (60 mg/kg/day [6 h])[f,g]	*S. pneumoniae, N. meningitidis*	27, 116, 118, 119
Adults[h]	Expanded-spectrum cephalosporin[g] plus vancomycin 30-60 mg/kg/day [8-12 h])[f,g]	*S. pneumoniae, N. meningitidis*	19, 21, 113, 137 ,139
Elderly	Expanded-spectrum cephalosporin[i] plus ampicillin (12 g/day [4 h]) plus vancomycin (30-60 mg/kg/day [8-12 h])[f,g]	*S. pneumoniae, N. meningitidis, L. monocytogenes*	113, 137, 148, 149
Immunocompromised	Expanded-spectrum cephalosporin[i] plus ampicillin (12 g/day [4 h]) plus vancomycin (30-60 mg/kg/day [8-12 h])[f,g]	*S. pneumoniae, N. meningitidis, L. monocytogenes*	10, 113, 137, 167, 168
Community-acquired recurrent meningitis	Expanded-spectrum cephalosporin[i] plus vancomycin (30-60 mg/kg/day [8-12 h])[f,g]	*S. pneumoniae, N. meningitidis, H. influenzae*	137, 155, 156, 349
Nosocomial meningitis	Vancomycin (30-45 mg/kg/day [8-12 h])[f] plus either ceftazidime (6 g/day [8 h]), cefepime (6 g/day [8 h]), or meropenem (6 g/day [8 h]	*S. aureus, S. epidermidis,* aerobic gram-negative bacilli	113, 174, 181
Basilar skull fracture	Expanded-spectrum cephalosporin[i] plus vancomycin (30-60 mg/kg/day [8-12 h])f,g	*S. pneumoniae*	178-181, 183

[a] Dosages recommended in patients with normal renal function. [b] Within first week of life. [c] Between first and sixth week of life. [d] Gentamicin 7.5 mg/kg/day administered every 8 h, tobramycin 7.5 mg/kg/day administered every 8 h, or amikacin 30 mg/kg/day administered every 8 hours. [e] Cefotaxime 225–300 mg/kg/day administered every 6-8 h, or ceftriaxone 80–100 mg/kg/day administered every 12-24 h. [f] Vancomycin should be added in regions with cephalosporin resistance to pneumococci. [g] Maintain vancomycin trough levels of 15-20 mg/mL. [h] In areas with very low penicillin-resistance rates (<1%), monotherapy with penicillin 24 million units/day administered every 4 hours may be considered, although many experts recommend combination therapy for all patients until results of in vitro susceptibility testing are known. [i] Cefotaxime 8-12 g/day administered every 4-6 hours, or ceftriaxone 4 g/day administered every 12 hours.

antimicrobial therapy can be modified for optimal treatment. The following sections review clinical presentations, results of CSF examination, and most common bacteria in subgroups of patients presenting with bacterial meningitis.

Neonates

Neonates with bacterial meningitis often present with nonspecific signs and symptoms.[102, 103] CSF examination cannot rule out the possibility of meningitis in these patients, so empirical antimicrobial therapy should be initiated based on low clinical suspicion

and should be continued until CSF culture results are negative.[103, 104] However, this approach must be individualized, and some patients, especially those who have received prior or concurrent antimicrobial therapy, may require treatment with an appropriate antimicrobial course despite negative culture results.

A cohort study of 150 neonatal intensive care units in the United States evaluated lumbar puncture results for 9,111 neonates at an estimated gestational age of 34 weeks or older.[103] Of the 95 neonates with culture-proven meningitis included in this study, 10% had fewer than 3 leukocytes per mm3 in the CSF. The median CSF leukocyte count was low (6 cells per mm3; range, 0 to 90,000). For culture-proven meningitis, CSF white blood cell (WBC) counts of more than 21 cells per mm3 had a sensitivity of 79% and a specificity of 81%. CSF glucose concentrations varied from 0 to 11 mmol/liter or 0 to 198 mg/dl (median, 1.1 mmol/liter or 20 mg/dl), and protein concentrations varied from 0.4 to 19.6 g/liter (median, 2.7 g/liter); culture-proven meningitis was not diagnosed accurately by CSF glucose or by protein.[103] Gram staining of CSF can be helpful in the diagnosis of neonatal meningitis, but a negative CSF Gram stain does not rule out the disease. One review reported a sensitivity of 60% for Gram staining for showing bacteria in the CSF of neonates.[105]

Common causative microorganisms of neonatal meningitis during the first week of life are *S. agalactiae*, *Escherichia coli*, and *L. monocytogenes*;[106-110] *L. monocytogenes* has been reported to be spread by nursery personnel.[111, 112] Late-onset neonatal meningitis occurs between the first week of life and 2 to 3 months of age and may be caused by a wide variety of species, including staphylococci, *L. monocytogenes*, and Gram-negative bacilli.[105, 107, 109] Empirical therapy for neonatal meningitis should consist of ampicillin, gentamicin, and cefotaxime. The use of gentamicin to cover neonatal meningitis due to Gram-negative bacteria has been debated, as CSF concentrations are usually only minimally above the MIC.[105, 107] The general recommendation for the addition of gentamicin has been based on data from *in vitro* studies, which showed synergistic activity in antimicrobial killing.[105, 107, 113]

The role of adjunctive dexamethasone in neonatal meningitis is unclear.[114] One clinical trial that alternately assigned 52 neonates to dexamethasone therapy or no dexamethasone reported no effect of this adjunctive therapy on outcome or sequelae.[115] However, that study was not a randomized clinical trial and had insufficient statistical power. At present, there are insufficient data to make a recommendation on the use of adjunctive dexamethasone for neonates with bacterial meningitis.

Children

Clinical characteristics of childhood bacterial meningitis have remained similar over time despite the changing epidemiology of the common causative bacteria.[49, 116-120] Infants may present with nonspecific signs and symptoms such as fever, poor feeding, vomiting, lethargy, and irritability.[116, 119, 121] Older children are more likely to present with symptoms and signs of meningeal irritability, with vomiting, photophobia, headache, and neck stiffness.[116, 119] Lumbar puncture results are essential for establishing a diagnosis.

In a cohort of 231 children aged 1 month to 19 years, relatively small proportions of children presented with neck stiffness (40%) and altered mental status (13%).[118] A retrospective

cohort study used to create a prediction model to differentiate between bacterial and aseptic meningitis showed that CSF examination was normal for 2 of 125 patients (2%).[122] Normal CSF examinations have been reported, particularly for children with bacterial meningitis with prominent signs of sepsis.[119] The sensitivity of CSF Gram staining for identifying the causative organism has been reported to be 50 to 65%.[116, 118]

A retrospective cohort study conducted in emergency departments of 20 academic medical centers in the United States evaluated the sensitivity and negative predictive value of the bacterial meningitis score for the diagnosis of bacterial meningitis.[123] This score classifies patients at very low risk of bacterial meningitis if they lack all of the following criteria: positive CSF Gram stain, CSF leukocyte count of at least 1,000 cells per mm3, CSF protein level of at least 0.8 g per liter, peripheral blood leukocyte count of at least 10,000 cells per mm3, and a history of seizure before or at the time of presentation.[122] Among 3,295 patients with CSF pleocytosis, 121 (3.7%; 95% CI, 3.1 to 4.4%) had bacterial meningitis. Of the 1,714 patients categorized as very low risk for bacterial meningitis by the bacterial meningitis score, only 2 had bacterial meningitis (sensitivity, 98.3% [95% confidence interval, 94.2 to 99.8%]; negative predictive value, 99.9% [95% confidence interval, 99.6 to 100%]), and both were younger than 2 months of age. Although these data are suggestive that this score is an accurate decision support tool, practice guidelines from the Infectious Diseases Society of America recommend that these prediction rules should not be used for clinical decisions for individual patients.[113] One additional aspect of particular importance to physicians working in emergency medicine and other urgent outpatient settings is that all of the studies were performed with hospitalized patients.[124-128] Therefore, in all of the studies evaluating the potential to differentiate bacterial from viral meningitis, every patient was admitted to the hospital for observation regardless of whether or not they received antibiotics.[129] One should use appropriate caution when attempting to apply these kinds of decision rules to the diagnosis of patients with viral meningitis, thereby withholding antibiotic treatment and perhaps outpatient monitoring.

The most common causative bacteria of community-acquired bacterial meningitis in children aged 3 months and older are *S. pneumoniae* and *N. meningitidis*, causing 80% of cases in the United States.[27, 116, 118, 119]. The remainder of cases is caused by group B streptococcus, *Escherichia coli*, nontypeable *H. influenzae*, other gram-negative bacilli, *L. monocytogenes* and group A streptococci.[118] Empirical coverage with an expanded-spectrum cephalosporin (cefotaxime or ceftriaxone) at appropriate doses for meningitis is recommended based on a broad spectrum of activity and excellent penetration into the CSF under inflammatory conditions. Due to the worldwide emergence of multidrug-resistant strains of *S. pneumoniae*, most experts recommend the addition of vancomycin to the initial empirical antimicrobial regimen.[119]

A Cochrane meta-analysis of randomized trials showed that adjunctive dexamethasone treatment decreases hearing loss in children with bacterial meningitis in high-income countries.[114, 130-133] In low-income countries, no benefit was established.[114, 134] The advised dexamethasone regimen is 0.6 mg/kg daily, with the first dose given before or with the first dose of antibiotics, for four days.[114] A recent trial from South America showed a decrease of

severe neurological sequelae in dexamethasone treated children;[135] this trial had a factorial design and also evaluated the use of adjuvant glycerol 1.5 g (1.5 mL) per kg every 6 h for 48 hours.[135] However, several concerns were raised about the allocation concealment and blinding in the trial.[136] New well-designed studies are therefore needed before glycerol can be advised as adjunctive treatment in children with bacterial meningitis.

Adults

Adults with bacterial meningitis typically present with symptoms and signs of meningeal irritation and brain parenchyma inflammation. Nevertheless, only a minority presents with the classical clinical triad of fever, altered mental status, and neck stiffness.[19] In a prospective study including 696 adults with bacterial meningitis, almost all patients presented with at least two of the four signs and symptoms of headache, fever, neck stiffness, and altered mental status.[19, 137] In this study, one-third of the patients presented with focal neurological deficits and 14% were comatose on admission.[19] Individual CSF findings predictive of bacterial meningitis (a glucose concentration of less than 34 mg/dL [1.9 mmol per liter], a ratio of CSF glucose to blood glucose of less than 0.23, a protein concentration of more than 2.2 g per liter, or a white-cell count of more than 2000 per mm^3) were found in 88% of 696 patients.[19, 138] Positive Gram stain results of CSF were reported in 60 to 80% of adults with bacterial meningitis.[19, 139]

The most common causative bacteria of community-acquired bacterial meningitis in adults are *S. pneumoniae* and *N. meningitidis*, causing 75 to 90% of cases.[19, 21, 139] Empirical coverage with an expanded-spectrum cephalosporin (cefotaxime or ceftriaxone) is recommended in combination with vancomycin, depending on local *S. pneumoniae* sensitivity patterns (see below). Monotherapy with penicillin may be considered only in areas with very low penicillin resistance rates (<1%), although many experts recommend combination therapy for all patients until results of *in vitro* susceptibility testing are known.[137] Empirical treatment for patients aged 50 years or older should also include ampicillin for additional coverage of *L. monocytogenes*, which is more prevalent among this age group. No clinical data on the efficacy of the addition of rifampin in patients with pneumococcal meningitis are available. However, based on *S. pneumoniae* susceptibility, some experts recommend the use of rifampin in combination with an expanded-spectrum cephalosporin and vancomycin for patients with pneumococcal meningitis caused by bacterial strains that are likely to be highly resistant to penicillin or cephalosporins based on local resistance profiles.[113, 137]

Since 2002, three large trials have been performed to evaluate the role of adjunctive dexamethasone therapy for adults with community-acquired bacterial meningitis.[11, 140, 141] A European trial showed a clear reduction in mortality for all suspected bacterial meningitis patients, while trials in Malawi and Vietnam did not. The Vietnam trial, however, did show a decreased rate of mortality for patients with confirmed bacterial meningitis.[141] Currently, adjunctive dexamethasone is advised for patients with suspected bacterial meningitis in high-income countries.[113]

Activated protein C has been shown to decrease mortality for patients with severe sepsis but cannot be advised for those with a low risk of death due to increased bleeding complications.[142, 143] A retrospective analysis of 4,096 patients included in activated protein C trials showed a high rate (6%) of intracranial hemorrhage for the 128 adults with meningitis.[144] Therefore, activated protein C cannot be recommended for patients with bacterial meningitis.[145]

Elderly

Elderly patients with bacterial meningitis more often present with an altered mental status and focal neurological deficits than younger patients, while neck stiffness and headache are notably less frequent.[146-148] CSF Gram staining identifies bacteria in high proportions of patients (85 to 90%).[146, 148, 149] *S. pneumoniae* and *L. monocytogenes* cause most episodes; however, a wide variety of other pathogens can be found, depending on coexisting conditions and associated immunocompromise.[146, 148, 149] In a prospective case series including 257 patients aged 60 years or older, *S. pneumoniae* was cultured in 176 episodes (68%), *N. meningitidis* was cultured in 36 episodes (14%), *L. monocytogenes* was cultured in 18 episodes (7%), and other bacteria were cultured in 27 episodes (11%).[146] Therefore, empirical therapy should include vancomycin, an expanded-spectrum cephalosporin, and ampicillin.[113, 137] Vancomycin is added because of concerns of local rates of resistance of *S. peumoniae* to cephalosporins.

Immunocompromised State

Alcoholism, human immunodeficiency virus (HIV) infection, diabetes mellitus, the use of immunosuppressive drugs, asplenia, and cancer may cause dysfunction of the immune system and thereby increase the risk of invasive infections, including meningitis.[150-152] A physiological immunodeficiency is present in young children, in whom protective antibodies are not yet produced, and the elderly, whose humoral and cellular immunity functions diminish.[149, 153, 154] As a general rule, a recurrence of meningitis without anatomical defects warrants further investigation to detect an immunodeficiency.[155, 156]

HIV-infected individuals have a 6- to 324-fold-higer risk of invasive pneumococcal infections.[157-159] Highly active antiretroviral therapy (HAART) reduces this risk but leaves it 35 times higher than that for individuals without HIV infection.[157, 160, 161] The increased risk of pneumococcal infections of HIV-infected patients has a profound impact in low-resource countries, where up to 95% of patients with pneumococcal meningitis have been reported to be HIV positive.[162-166] The clinical presentations of HIV-positive and HIV-negative patients with bacterial meningitis are similar,[165, 166] although one study reported a higher seizure rate among HIV-positive patients.[167]

The most common pathogen in immunocompromised patients with bacterial meningitis is *S. pneumoniae*, but other pathogens such as *L. monocytogenes*, *E. coli*, *Salmonella* species, and *S. aureus* are also frequently encountered.[10, 11, 19, 168, 169] For immunocompromised patients, the recommended empirical antimicrobial regimen is the combination of vancomycin, an expanded-spectrum cephalosporin (cefotaxime or ceftriaxone), and

ampicillin.[113, 137] However, the availability of these usually expensive drugs in resource-poor areas with high HIV prevalences and devastating attack rates is low.[10]

Recurrent bacterial meningitis

Recurrent bacterial meningitis accounts for 1 to 6% of meningitis cases acquired in the community.[139, 155, 156, 170] Conditions associated with recurrent meningitis are age dependent. For children, the most common conditions are congenital anatomical defects; for adults, the most common conditions are remote head trauma or CSF leakage.[155, 156, 171] Immunodeficiencies may also predispose a patient to recurrent meningitis; most commonly, there are complement component deficiencies, asplenism, and HIV infection.[155, 156, 162] The clinical presentation of recurrent bacterial meningitis is similar to that seen for patients with a first episode.[155, 156]

The most common causative bacterium of recurrent bacterial meningitis in the community setting is *S. pneumoniae*. In a recent review, *S. pneumoniae* was found to be responsible for 57% of cases, and the majority were associated with compromised meningeal integrity.[155] Recurrent meningitis due to *N. meningitidis* has been associated with complement deficiencies.[153, 155, 172] *H. influenzae*, particularly of non-b serotypes, is the third most common causative agent and is found in patients with anatomical defects.[153, 156] Empirical antimicrobial coverage in recurrent meningitis consists of an expanded spectrum cephalosporin and vancomycin.[137, 156]

The recurrence of community-acquired meningitis should prompt an evaluation aimed at the detection and surgical repair of anatomical defects in patients with meningitis due to *S. pneumoniae* or *H. influenzae* and analysis of the complement system for those with meningitis due to *N. meningitidis*.[155, 156] Patients with recurrent meningitis due to complement component deficiency or splenectomy should be vaccinated.[152, 173]

Nosocomial meningitis

Adults with nosocomial meningitis are a distinct patient group, with infection caused by specific bacterial pathogens compared to those of community-acquired bacterial meningitis. Underlying conditions, especially a history of neurosurgery or a distant focus of infection, are present for a large majority of patients.[174-181] Clinical features of nosocomial bacterial meningitis are variable but most frequently include fever and an altered level of consciousness.[175, 179, 180, 182] CSF analysis has been reported to be normal for 20% of patients with culture-proven nosocomial meningitis.[175]

Meningitis after neurosurgery, following penetrating trauma, or after basilar skull fracture in patients with prolonged hospitalization can be caused by staphylococci and aerobic Gram-negative bacilli (including *Pseudomonas aeruginosa*).[174, 175, 177, 181] Therefore, vancomycin plus either cefepime, ceftazidime, or meropenem are recommended as empirical antimicrobial therapy for adult patients with bacterial meningitis postneurosurgery.[113, 174, 181] The majority of cases of bacterial meningitis after basilar skull fracture, or early after otorhinologic surgery, are caused by microorganisms that colonize the nasopharynx

(especially *S. pneumoniae*) such that empirical therapy with vancomycin plus an expanded-spectrum cephalosporin (either cefotaxime or ceftriaxone) should be utilized.[178-181, 183]

Laboratory diagnosis

To diagnosis bacterial meningitis, CSF examination is mandatory.[137] CSF culture is the "gold standard" for diagnosis, and it is obligatory to obtain the *in vitro* susceptibility of the causative microorganism and to rationalize treatment. CSF Gram staining, latex agglutination testing, and PCR are additional diagnostic tools that might aid in etiological diagnoses, especially for patients with negative CSF cultures (i.e., after antibiotic pretreatment). However, the incremental yield of these techniques is sometimes limited. If lumbar puncture cannot be performed, serum inflammatory marker, blood culture, skin biopsy, and urine antigen testing may provide supportive evidence to diagnose bacterial meningitis. In the following sections, the use of different laboratory diagnostic methods for bacterial meningitis will be discussed.

CSF cell count, glucose and protein

Characteristic CSF findings for bacterial meningitis consist of polymorphonuclear pleocytosis, hypoglycorrhachia, and raised CSF protein levels.[137] A prediction model based on 422 patients with bacterial or viral meningitis showed that individual predictors of bacterial meningitis consisted of a glucose concentration of less than 0.34 g/liter (1.9 mmol per liter), a ratio of CSF glucose to blood glucose of less than 0.23, a protein concentration of more than 2.2 g per liter, or a white cell count of more than 2,000 cells per mm^3.[138] However, CSF protein (<0.5g/liter) and neutrophil count (≥100) thresholds are also indicative of bacterial meningitis, with odds ratios (ORs) of 14 and 12, respectively.[184]

Table 3. Sensitivity of various diagnostic tests to determine the microbial etiology in patients with community-acquired bacterial meningitis.

Pathogen	Blood culture	CSF Gram stain	Latex agglutination test[a]	PCR	References
Haemophilus influenzae	25-90%	25-65%	78-100%	72-92%	40, 113, 118, 201, 202, 226
Streptococcus pneumoniae	60-90%	69-93%	59-100%	61-100%	3, 21, 139, 186, 203, 204-206, 208, 209, 216, 220, 250
Neisseria meningitidis	40-60%	30-89%	22-93%	88-94%	113, 197, 188, 210, 211, 234, 350, 351
Listeria monocytogenes	10-75%	10-35%	N/A	N/A	110, 168, 190, 191, 212- 215
Streptococcus agalactiae	80-85%	80-90%	N/A	N/A	192-194
Streptococcus pyogenes	60-65%	66-73%	N/A	N/A	312, 313
Streptococcus suis	50%	50%	N/A	99%	166, 236, 237
Staphylococcus aureus	75-100%	20-44%	N/A	N/A	330, 331, 352

N/A, not applicable; PCR, polymerase chain reaction; CSF, cerebrospinal fluid. [a] No longer routinely recommended to determine the etiologic diagnosis of bacterial meningitis; see text for details.

The majority of patients presenting with community-acquired bacterial meningitis have CSF parameters characteristic of bacterial meningitis (Table 3).[40, 185, 186] However, low CSF white blood cell counts do occur, especially in patients with septic shock and systemic complications.[187, 188] Experimental pneumococcal meningitis studies also showed a relationship between a large bacterial CSF load, a lack of response of CSF leukocytes, and intracranial complications,[189] probably indicating excessive bacterial growth and a lack of a CSF leukocyte response.

In a prospective cohort study of 258 adults with culture proven meningococcal meningitis, CSF leukocyte counts of less than 1,000 leukocytes per mm3 were found for 19% of patients.[188] CSF examination was reported to be normal for five (1.7%) of these patients.[188] For three of five patients, the CSF Gram stain showed bacteria.

Patients with listerial meningitis often do not have characteristic CSF findings, with relatively low CSF leukocyte counts and high CSF protein concentrations.[168] A mononuclear cell predominance in the CSF is found more frequently than for other types of bacterial meningitis.[190] For patients with listerial brainstem encephalitis, the CSF typically shows low-grade pleocytosis, with a lymphocytic predominance and slightly elevated protein levels. Hypoglycorrhachia is found in only 21% of cases.[191] CSF white blood cell counts are inconclusive for many neonates with meningitis due to *S. agalactiae*. In a study including 276 children with meningitis due to *S. agalactiae* (83% neonates), a normal CSF examination was found for 6% of patients.[192] Adults with *S. agalactiae* meningitis have typical CSF findings.[193, 194]

CSF cultures

CSF culture remains the gold standard for the diagnosis of bacterial meningitis; aerobic culturing techniques are obligatory for community-acquired bacterial meningitis. Anaerobic culture may be important for postneurosurgical meningitis or for the investigation of CSF shunt meningitis. In a retrospective series of 875 meningitis patients for whom the diagnosis was defined by a CSF white blood cell count of over 1,000 cells per mm^3 and/or more than 80% polymorphonuclear cells, the CSF culture was positive for 85% of cases in the absence of prior antibiotic treatment.[195] CSF cultures were positive for 96% of patients if meningitis was due to *H. influenzae*, 87% of patients with pneumococcal meningitis, and 80% of patients with meningococcal meningitis.[195] A study of 231 children showed positive CSF cultures for 82% of patients.[196] However, lower yields of CSF cultures were reported. For 3,973 meningitis cases from Brazil, cultures were positive for 67% of cases when culture-negative cases were defined by the CSF profile.[22] In a study from the United Kingdom including 103 patients with clinically defined meningococcal meningitis, only 13% had positive CSF cultures.[197]

The yield of CSF culture is lower for patients who have received antibiotic pretreatment before lumbar puncture. Two large case series reported decreases in yield from 66 to 62% and 88 to 70% if patients were pretreated with antibiotics.[195, 196] In one of those studies, pretreatment for more than 24 h was associated with a further decrease of positive CSF cultures to 59%.[196] A decrease in culture positivity from 19 to 11% was seen for pretreated

patients with clinically defined meningococcal meningitis in a study from the United Kingdom.[197] Another study of 21 patients with meningococcal meningitis diagnosed either by culture or by PCR showed positive CSF cultures for 9% of patients receiving pretreatment and 50% for those who did not.[198]

CSF Gram stain

CSF Gram staining may swiftly identify the causative microorganism for patients with suspected bacterial meningitis.[19, 137, 169] It is a cheap and well-validated diagnostic tool. Several studies have shown the additional value of Gram staining for CSF culture-negative patients. For 3,973 patients with bacterial meningitis defined by CSF parameters, 1,314 (31%) had negative CSF cultures; 581 (45%) of the CSF culture-negative patients had a positive Gram stain.[22] Forty-four percent of patients in this cohort were pretreated with antibiotics. In an Indian study of 535 suspected meningitis cases, CSF Gram staining identified the causative organisms for 36 (65%) of 55 pretreated patients, while CSF culture was positive for only 5 (9%) patients.[199] In a large study from Denmark, CSF Gram staining was the only positive laboratory finding for 4% of 875 patients with bacterial meningitis.[195] In a recent French study, 24 (6%) of 363 CSF culture-negative children with meningococcal meningitis were diagnosed by CSF pleocytosis and a positive Gram stain.[200]

The yield of CSF Gram staining may be decreased in antibiotic pretreated patients compared with antibiotic-naïve patients. Pretreatment with antibiotics decreased the yield of CSF Gram staining only slightly, from 56 to 52% for 481 Danish patients.[195] A study of U.S. children showed similar yields of CSF Gram staining for pretreated patients.[196] For 73 meningococcal meningitis patients, the reported yield of Gram staining decreased slightly, from 34 to 27% for pretreated patients.[197]

The reported sensitivities of CSF Gram staining vary considerably for different microorganisms (Table 3). CSF Gram staining correctly identifies the organism in 50 to 65% of children and in 25 to 33% in adults with *H. influenzae* meningitis.[40, 118, 201, 202] Gram staining correctly identifies the pathogen in 69 to 93% of patients with pneumococcal meningitis.[3, 21, 139, 186, 203-209] The reported yield for meningococcal meningitis is highly variable and ranged from 89% for untreated adult patients in the Netherlands to 73% for U.S. children, 62% for Greek children, 49% for Spanish children, and 30% for patients of all ages in the United Kingdom.[118, 188, 197, 210, 211] The yield of Gram staining for *Listeria* meningitis is low, ranging from 23 to 36% for both children and adults,[168, 212-214] and even lower (14%) for patients with *Listeria* rhombencephalitis.[215]

Latex agglutinations tests

Latex agglutination is a diagnostic test that has been utilized for the etiological diagnosis of bacterial meningitis, providing results in less than 15 min.[113] These tests utilize serum containing bacterial antibodies or commercially available antisera directed against the capsular polysaccharides of meningeal pathogens and have been recommended for patients with suspected bacterial meningitis with no bacteria seen upon CSF Gram staining and negative CSF cultures.[113] The reported sensitivities of latex agglutination

testing of CSF samples from patients with bacterial meningitis ranged from 78 to 100% for *H. influenzae* type b meningitis, 59 to 100% for pneumococcal meningitis, and 22 to 93% for meningococcal meningitis.[198, 216-220] However, in a 10-year retrospective study of 176 children with culture-negative meningitis who were pretreated with antibiotics before lumbar puncture, none had a positive CSF latex agglutination result (95% confidence interval, 0 to 2%).[217] In another study of 28 patients with negative CSF cultures who had clinical presentation and CSF parameters compatible with bacterial meningitis, CSF latex agglutination had a sensitivity of only 7% for detecting bacteria.[221] A third study showed only 7 positive agglutination tests out of 478 CSF samples tested; all 7 patients had a CSF Gram stain showing the causative microorganism.[219] A study of meningococcal meningitis patients showed a strong decline in the sensitivity of latex agglutination, from 60% for patients without antibiotic pretreatment prior to lumbar puncture to 9% for antibiotic-pretreated patients.[198] The limited additional value of latex agglutination testing was also shown by several other studies, and its use is therefore limited.[217, 218, 221-223]

Meningococcal antigens may also be detected in urine by these techniques. However, the diagnostic accuracy of this test is limited since false-positive results are common; it had no additional diagnostic value above that of CSF Gram staining.[218, 224, 225]

Polymerase chain reaction

Nucleic acid amplification tests such as PCR assays have been evaluated for their effectiveness in detecting the presence of bacterial DNA in CSF from patients with suspected and proven bacterial meningitis. One study including 65 patients with culture-confirmed community-acquired bacterial meningitis evaluated the diagnostic accuracy of a broad-range PCR including primers for *H. influenzae*, *S. pneumoniae*, and *N. meningitidis*. The sensitivity for *H. influenzae* was 92%, that for *S. pneumoniae* was 100%, and that for *N. meningitidis* was 88%; the specificity was 100% for all organisms (Table 3).[226] In another study of 139 bacterial meningitis patients defined by positive CSF culture in 94 cases and positive CSF Gram stain in 12 cases and based on clinical suspicion with negative cultures in 31 cases found sensitivities for *H. influenzae* (88%), *S. pneumoniae* (92%), and *N. meningitidis* (94%) using a multiplex PCR assay, with a specificity of 100% for all three microorganisms.[227] The sensitivities of multiplex PCR for CSF from 409 bacterial meningitis patients in Burkina Faso (diagnosed by either CSF culture, latex agglutination test, PCR, or Gram stain) were considerably lower: 72% for *H. influenzae*, 61% for *S. pneumoniae*, and 88% for *N. meningitidis*, with specificities of 95%, 95%, and 97%, respectively (244). In that study, the incremental value of PCR next to culture, Gram stain, and latex agglutination was high: 29 (43%) of 68 patients with *H. influenzae* meningitis, 43 (27%) of 162 with pneumococcal meningitis, and 66 (37%) of 179 with meningococcal meningitis were diagnosed with only PCR.[228]

Meningococcal DNA detection by PCR has been used widely and is performed routinely for patients with suspected meningococcal meningitis and negative CSF cultures in many parts of the world. In the United Kingdom, a large proportion of meningococcal disease cases are now diagnosed by PCR without culture.[229] PCR detection of meningococcal

DNA requires special techniques and is expensive and, therefore, not widely available. A prospective French study including 363 children with clinically defined meningococcal meningitis and negative CSF cultures showed that PCR for meningococcal DNA was positive for 205 children (57%); for 169 (47%) children, meningococci were identified by PCR only.[200] Pretreatment with antibiotics may decrease the sensitivity of PCR of CSF samples. In a prospective study including 28 patients with clinically defined meningococcal meningitis, PCR of meningococcal DNA was positive for 13 (81%) of 16 patients who were treated with antibiotics prior to lumbar puncture, compared to all 21 patients without pretreatment.[198] PCR can also be a useful tool for the swift typing of meningococcal strains in an evolving epidemic.[230,231]

An initial study of the PCR detection of *L. monocytogenes* in patients with bacterial meningitis showed that a high concentration of bacteria in the CSF is needed for PCR detection.[232] Recent studies of multiplex PCRs including *L. monocytogenes* showed lower detection thresholds.[233-235] The sensitivity, specificity, and incremental value of PCR in *L. monocytogenes* meningitis are unclear, as only one patient was included in each of these studies.[233-235] Data on PCR detection of group B streptococci in CSF are limited, and group B streptococci have been tested only with multiplex PCR detection assays.[233] *Streptococcus suis* DNA was detected by PCR in CSF samples from 149 of 151 patients (sensitivity, 99%) in a cohort study, with unknown specificity.[166,236]

A high bacterial load determined by quantitative PCR has been associated with unfavorable outcomes of both pneumococcal and meningococcal disease,[237,238] but it remains unclear whether this information has any additional value for clinical prognosis.[239]

sTREM-1

Soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) in CSF was found to be a biomarker for the presence of bacterial meningitis in a retrospective study of 85 bacterial meningitis patients, 8 viral meningitis patients, and 9 healthy controls.[240] At a cutoff level of 20 pg/ml, the sensitivity of sTREM-1 in CSF was 73% (95% confidence interval, 0.65 to 0.80), the specificity was 77% (95% confidence interval, 0.57 to 0.89), the positive predictive value was 0.94 (95% confidence interval, 0.88 to 0.98), and the negative predictive value was 0.34 (95% confidence interval, 0.23 to 0.48). High levels of sTREM-1 were associated with unfavorable outcomes. A second study found immeasurably low sTREM-1 levels for 12 viral meningitis patients and an increased level for 7 of 9 patients.[241] The incremental yield compared to those of other CSF diagnostic tests must be determined before the test can be recommended in clinical practice.

Blood culture

Blood cultures are valuable to detect the causative organism and establish susceptibility patterns if CSF cultures are negative or unavailable. Blood culture positivity differs for each causative organism: 50 to 90% of *H. influenzae* meningitis patients,[118,202] 75% of pneumococcal meningitis patients,[3, 21, 139, 186, 203-209] and in 40% of children and 60%

of adult patients with meningococcal meningitis.[188,242] The yield of blood cultures was decreased by 20% for pretreated patients in two studies.[196,198]

Skin biopsy

Gram staining and culturing of skin lesions can be of additional diagnostic value for patients with suspected meningococcal meningitis. In a prospective analysis of 31 patients with meningococcal disease, Gram stains of skin lesions were positive for 5 (36%) of 14 patients with a clinical diagnosis of meningitis.[243] For one of these patients, Gram stain and culture of the skin lesions were the only microbiological confirmations of meningococcal disease. For three patients, lumbar puncture was contraindicated, and Gram staining of the skin lesion provided the diagnosis. A retrospective analysis of 51 meningococcal disease patients did not show an additional value of Gram staining of the skin lesion for patients for whom CSF Gram staining was performed, although the test did provide an early diagnosis for patients for whom lumbar puncture could not be performed.[244] In a French study of 1,344 children with meningococcal meningitis, Gram staining of the skin lesion provided the diagnosis in 7 cases (0.5%).[200] Microbiological examination of skin lesions is not affected by previous antibiotic therapy.[243, 244]

Serum inflammatory markers

In the distinction between viral and bacterial meningitis, serum inflammatory markers may suggest the diagnosis.[245] A recent retrospective study of 96 children with bacterial meningitis defined by documented bacterial infection in CSF (Gram stain, culture, latex agglutination, or PCR) or blood culture, compared to 102 with aseptic meningitis, showed that increased serum procalcitonin levels (≥0.5 ng/ml) and C-reactive protein levels (≥20 mg/liter) were associated with bacterial meningitis.[184] In that study, the odds ratio for bacterial meningitis with increased procalcitonin levels was 434 (95% confidence interval, 57.0 to >1,000.0), and that with increased C-reactive protein levels was 9.9 (95% confidence interval, 4.8 to 20.8). A Finnish study showed a specificity of C-reactive protein of 100% (95% confidence interval, 0.97 to 1.00) for patients with a C-reactive protein level below 40 mg/liter and a sensitivity of 93% (95% confidence interval, 0.90 to 0.96) in a study of 325 children with bacterial meningitis and 182 children with viral meningitis.[246] In conclusion, concentrations of C-reactive protein and procalcitonin in serum have been evaluated for their usefulness in determining the diagnosis of bacterial meningitis; although elevated concentrations can be suggestive of bacterial infection, they do not establish the diagnosis of bacterial meningitis.

Bacterial subgroups

Patients with meningitis caused by specific bacterial subgroups may present with specific associated conditions, clinical features, or complications. In the following sections, we

summarize risk factors, clinical features, and the diagnostic value of microbiological tests for the specific bacteria causing meningitis.

Haemophilus influenzae

Predisposing conditions for *H. influenzae* meningitis include diabetes mellitus, alcoholism, splenectomy or asplenic states, head trauma with CSF leakage, multiple myeloma, and immune deficiency such as hypogammaglobulinemia.[40]

The majority of patients have a focus of infection such as sinusitis, otitis media, epiglottitis, and pneumonia, suggesting that both the contiguous and hematogenous spreads of infection are important pathogenic routes to the central nervous system.[247-249] Fever, neck stiffness, and altered mental status are important clinical features.[7, 40, 201, 202, 247, 249, 250] For children with *H. influenzae* type b meningitis, seizures have been reported for 60% of cases.[250, 251]

Expanded-spectrum cephalosporins have become standard therapy for meningitis due to *H. influenzae* since the emergence of chloramphenicol-resistant and β-lactamase-producing *H. influenzae* strains (Table 4).[113] The rate of β-lactamase producing *H. influenzae* strains has steadily increased over the last decades and has not decreased since the introduction of conjugate vaccines. The rates of isolation of β-lactamase-producing strains vary worldwide and are 4% in Russia, 15% in the United Kingdom, 26% in the United States, 31% in France, and 42% in Spain.[252-254] For nontypeable strains, this rate is substantially higher at 42% in the USA.[255] In Japan, the rate of β-lactamase-negative ampicillin-resistant (BLNAR) *H. influenzae* meningitis has rapidly increased from 6% in 2000 to 35% in 2004.[353] Due to this increase, antibiotic therapy has changed to cefotaxime or ceftriaxone combined with meropenem for meningitis patients in regions with BLNAR *H. influenzae*.[353] Levofloxacin was effective in eradicating BLNAR *H. influenzae* in a mouse model.[354]

In 1988, two studies from the United States including a total of 137 children with *H. influenzae* meningitis showed a decrease in hearing loss from 17% for untreated children to 3% for dexamethasone-treated children (OR, 0.14; 95% confidence interval, 0.02 to 0.68; $P<0.01$).[130] Other trials of childhood bacterial meningitis showed a beneficial effect of dexamethasone on hearing loss; the majority of these patients had meningitis caused by *H. influenzae*.[133, 135, 256] A subsequent meta-analysis of nine trials showed a combined odds ratio of 0.31 (95% confidence interval, 0.14 to 0.69) for the reduction of severe hearing loss in dexamethasone-treated *H. influenzae* meningitis patients.[131] More comprehensive meta-analyses confirmed the beneficial effect of dexamethasone on hearing loss in children with *H. influenzae* meningitis.[114,132]

Reported mortality rates for *H. influenzae* meningitis range from 3 to 42%.[27, 202, 250] A meta-analysis of pediatric patients with bacterial meningitis showed a mortality rate of 4% among 1,085 patients with *H. influenzae* meningitis.[257] In adults, mortality rates vary from 6 to 14%.[7, 40, 201, 202] Hearing loss is the most common sequela after *H. influenzae* meningitis, occurring in up to 16% of children and 10 to 25% of adult patients.[40, 202]

Table 4. Specific antimicrobial therapy for bacterial meningitis based on causative microorganism.

Micro-organism	Standard Therapy	Alternative Therapies
Haemophilus influenzae		
β-Lactamase negative	Ampicillin	Expanded-spectrum cephalosporin[a]; cefepime; chloramphenicol; aztreonam; fluoroquinolone
β-Lactamase positive	Expanded-spectrum cephalosporin[a]	Cefepime; chloramphenicol; aztreonam; fluoroquinolone
β-Lactamase negative amoxicillin resistant (BLNAR)	Expanded-spectrum	Expanded-spectrum cephalosporin[a] plus
	cephalosporin[a] plus	fluoroquinolone
	meropenem	
Neisseria meningitidis		
Penicillin MIC <0.1 mg/mL	Penicillin G or ampicillin	Expanded-spectrum cephalosporin[a]; chloramphenicol
Penicillin MIC 0.1-1.0 mg/mL	Expanded-spectrum cephalosporin[a]	Chloramphenicol; fluoroquinolone; meropenem
Streptococcus pneumoniae		
Penicillin MIC <0.1 mg/mL	Penicillin G or ampicillin	Expanded-spectrum cephalosporin[a]; chloramphenicol
Penicillin MIC 0.1-1.0 mg/mL	Expanded-spectrum cephalosporin[a]	Meropenem; cefepime
Penicillin MIC ≥2.0 mg/mL; or cefotaxime or ceftriaxone MIC >1.0 mg/mL	Vancomycin plus a expanded-spectrum cephalosporin[a,b]	Expanded-spectrum cephalosporin[a] plus moxifloxacin
Listeria monocytogenes	Ampicillin or penicillin G[c]	Trimethoprim-sulfamethoxazole
Streptococcus agalactiae	Ampicillin or penicillin G[c]	Expanded-spectrum cephalosporin[a]
Staphylococcus aureus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin; meropenem; linezolid; daptomycin
Methicillin-resistant	Vancomycin[b]	Trimethoprim-sulfamethoxazole; linezolid; daptomycin
Staphylococcus epidermidis	Vancomycin[b]	Linezolid
Streptococcus pyogenes	Penicillin	Expanded-spectrum cephalosporin[a]

[a] Cefotaxime or ceftriaxone. [b] Addition of rifampin may be considered; see text for indications. [c] Addition of an aminoglycoside should be considered. Adapted from Tunkel AR, et al.113

Streptococcus pneumoniae

Invasive disease caused by *S. pneumoniae* (including meningitis) is seen during the extremes of age (less than 2 or greater than 50 years of age); in patients with underlying conditions such as splenectomy or asplenic states, multiple myeloma, hypogammaglobulinemia, alcoholism, chronic liver or kidney disease, malignancy, Wiskott-Aldrich syndrome, thalassemia major, diabetes mellitus, and basilar skull fracture with leakage of CSF; and in children with cochlear implants with positioners.[156, 186, 205, 209, 258-261] The use of immunosuppressive drugs, a history of splenectomy, the presence of diabetes mellitus, alcoholism, or infection with HIV is found for 20% of adults with pneumococcal meningitis.[186, 205] HIV infection is an important factor that affects the etiology of acute meningitis, especially in lower-income countries.[10]

Defects in innate immunity have been described to be associated with susceptibility to pneumococcal infections within families.[262, 263] Several studies of extreme phenotypes have identified genetic defects in the complement system and intracellular signaling proteins to be associated with increased susceptibility.[264] A meta-analysis of case-control studies of genetic factors in susceptibility to pneumococcal disease showed associations between invasive pneumococcal disease and several genetic polymorphisms.[264] The strongest association was found for complement component mannose-binding lectin.

Contiguous or distant foci of infection, including pneumonia, otitis media, mastoiditis, sinusitis, and endocarditis, have been described for up to 60% of patients with pneumococcal meningitis.[186, 205] Therefore, consultation with an otorhinolaryngologist should be routine for patients with pneumococcal meningitis. The classical triad of fever, nuchal rigidity, and altered mental status is found for 60% of patients.[185] *S. pneumoniae* meningitis is a severe disease, which is reflected by the high rate of patients presenting with focal neurological abnormalities (40%) and seizures (25%).[186, 205, 209, 265, 266] One of five patients is admitted to the hospital in a comatose state.[186]

The increase of drug-resistant pneumococci has become an emerging problem worldwide,[45, 137, 267] with a reported prevalence of penicillin-resistant strains of up to 35% in some regions of the US.[45] Penicillin resistance in pneumococci often coincides with a decreased susceptibility to other antimicrobial agents, and multidrug-resistant bacteria have been reported to result in treatment failures for patients with pneumococcal meningitis.[267] Although pneumococci with low to intermediate susceptibility to penicillin may respond well to monotherapy with penicillin in adequate dosages, levels in CSF are expected to be insufficient to kill highly resistant organisms.[268] Therefore, empirical therapy for pneumococcal meningitis should consist of vancomycin and an expanded-spectrum cephalosporin (cefotaxime or ceftriaxone) until *in vitro* susceptibility is known.[113, 137]

The roles of newer β-lactam antibiotics (cefepime, meropenem, and ertapenem), quinolones (garenoxacin, gemifloxacin, gatifloxacin, and moxifloxacin), and lipopeptides (daptomycin) are being explored in experimental meningitis studies, with a special emphasis on the treatment of infection with highly resistant pneumococcal strains.[269,270] The efficacy of antibiotics could be enhanced by combining synergistically acting agents (e.g., cephalosporins, vancomycin, and rifampin).[137, 271] Decreasing the antibiotic-induced release of immunostimulatory cell wall components might also prove to be an efficient new strategy.[270, 272] Pretreatment with rifampin was shown to decrease the inflammatory response and improve survival in a rabbit meningitis model, but the clinical applicability of this finding is limited.[272] This strategy could affect the efficacy of adjunctive treatments that aim to attenuate the host inflammatory response to immunostimulatory bacterial products.[273] Animal experiments were not performed with adjunctive dexamethasone therapy, further limiting the clinical applicability of these studies.

In 1997, a meta-analysis of 10 trials of adjunctive dexamethasone therapy in bacterial meningitis evaluated the efficacy of dexamethasone in 197 patients with pneumococcal meningitis.[131] That study was the first to show a borderline significant association of dexamethasone with a decrease in neurological or hearing deficits in patients with

pneumococcal meningitis (odds ratio, 0.23; 95% confidence interval, 0.04 to 1.05). In 2002, a European multicenter, randomized, placebo-controlled trial including 301 adults with community-acquired bacterial meningitis comparing 10 mg dexamethasone given every 6 h for 4 days started before or with the first dose of antibiotics, showed a beneficial effect on unfavorable outcomes 6 weeks after randomization (relative risk, 0.48; 95% confidence interval, 0.24 to 0.96).[140] The beneficial effect was most prominent in the pneumococcal meningitis subgroup, showing a reduction in the mortality rate from 34 to 14% (relative risk, 0.41; 95% confidence interval, 0.19 to 0.86). Two large randomized clinical trials of adjunctive dexamethasone in bacterial meningitis from Malawi were reported in 2002 and 2007.[11, 134] The first trial included 598 children, 338 (40%) of whom had meningitis caused by *S. pneumoniae*.[134] No effect of dexamethasone on mortality (relative risk, 0.89; 95% confidence interval, 0.66 to 1.21) or hearing loss (relative risk, 0.98; 95% confidence interval, 0.67 to 1.44) was found. The second study was performed with 465 adults with bacterial meningitis; 272 (58%) were cases of pneumococcal meningitis.[11] That study also showed no benefit of dexamethasone in patients with pneumococcal meningitis (odds ratio, 1.10; 95% confidence interval, 0.68 to 1.77). Simultaneously with the latter trial, a randomized controlled trial with adults from Vietnam was reported, in which 55 (13%) of 535 included cases were due to *S. pneumoniae*;[141] no deaths occurred in the dexamethasone treated patients with pneumococcal meningitis, while 5 patients died in the placebo group (*P* value for difference between groups of 0.03). A Cochrane meta-analysis of trials showed that the beneficial effects of adjunctive dexamethasone were found in high-income countries and suggested that differences in baseline characteristics explained the variable results of the performed trials.[114] Guidelines from the Infectious Diseases Society of America, the European Federation of Neurological Sciences, and the British Infection Society recommended adjunctive dexamethasone as a standard treatment for patients with suspected or proven pneumococcal meningitis.[113, 274, 275]

The associated rate of mortality of pneumococcal meningitis is high. For children, a review of outcomes showed an overall mortality rate of 15%.[209,265] Recent case series of childhood pneumococcal meningitis reported rates of 8%.[209, 256] A study including children with pneumococcal meningitis in a resource-poor setting reported a mortality rate of 37%.[27] For adults with pneumococcal meningitis, reported case-fatality rates vary between 20 and 37% in high-income countries and up to 51% in resource-poor areas (e.g., Malawi).[11, 186, 206, 265, 276, 277] Most common causes of death among patients with pneumococcal meningitis are cardiorespiratory failure, stroke, status epilepticus, and brain herniation. A low Glasgow coma score upon admission, cranial nerve palsies upon admission, a raised erythrocyte sedimentation rate, a high CSF protein concentration, and a CSF leukocyte count of less than 1,000 leukocytes per mm^3 have been identified as independent predictors of an unfavorable outcome for adults with pneumococcal meningitis.[186]

Neurological sequelae, including deafness, focal neurological deficits, epilepsy, and cognitive impairment, have been found for up to 50% of surviving patients after pneumococcal meningitis.[186, 205, 257] Cognitive impairment is found for up to 27% of patients, even those with apparent good recovery, and consists mainly of cognitive slowness.[186, 278] The loss of

cognitive speed is stable over time after bacterial meningitis; however, there is a significant improvement in subjective physical impairment in the years after bacterial meningitis.[279]

Neisseria meningitidis

The meningococcus is the leading pathogen of meningitis in young children beyond the neonatal period and in young adults.[137, 242] Meningococcal disease has been associated with smoking, living in the same household as a patient (including students), and meningococcal disease in proxies.[79, 280]

An increased incidence of invasive meningococcal disease has been observed for patients with deficiencies in the terminal complement components (C5, C6, C7, C8, and, perhaps, C9) and dysfunctional properdin,[281-284] suggesting that screening tests for complement function should be performed for patients with recurrent disease.[154] Multiple genetic defects that lead to these complement component deficiencies have been identified.[264] Other genetic determinants of susceptibility to meningococcal disease are found in the interleukin-1 receptor antagonists, nasopharyngeal adhesion molecules, and surfactant proteins.[264]

The clinical manifestations of meningococcal disease vary considerably, ranging from transient fever and bacteremia to fulminant disease. Wolf and Birbara described four major clinical syndromes: (i) bacteremia without sepsis, (ii) meningococcemia without meningitis, (iii) meningitis with or without meningococcemia, and (iv) meningoencephalitis.[285] Variations of these scenarios have also been reported, and the patient may progress from one to another during the course of disease. Even for patients with culture-proven meningococcal meningitis, the classical triad of neck stiffness, fever, and altered consciousness is found for only 27% of patients.[188, 211, 242] For patients with meningococcal meningitis, skin lesions typical of meningococcal disease (petechiae, purpura, and ecchymoses) are found upon presentation for 60% of adults and 60 to 90% of children.[188, 197, 210, 211, 242]

Current treatment guidelines for proven meningococcal meningitis recommend the use of penicillin or ampicillin.[113] Although meningococcal strains with reduced susceptibility to penicillin have been described, the clinical significance remains unclear.[211, 286-288] Treatment failures with penicillin have been described in isolated case reports.[289, 290] A Spanish study of the evolution of penicillin resistance in a children's hospital described a rise in rates of penicillin resistance in strains of *N. meningitidis* from 9.1% in 1986 to 71.4% in 1997.[291] Although the majority of patients with *N. meningitidis* strains of intermediate susceptibility to penicillin described in the literature have responded well to penicillin therapy, another Spanish study described an association between reduced susceptibility to penicillin and an increased risk of death or neurological sequelae for children with meningococcal meningitis.[211] Based on these data, for patients with suspected meningococcal meningitis caused by bacterial strains that, on basis of the local epidemiology, are likely to be resistant to penicillin, an expanded-spectrum cephalosporin (cefotaxime or ceftriaxone) should be given until *in vitro* susceptibility testing is performed.[113]

A meta-analysis of trials of adjunctive dexamethasone therapy in bacterial meningitis showed that 517 adults and children (25%) with meningococcal meningitis were included out of a total 2,074 patients.[114] The mortality rate for the subgroup of patients with meningococcal meningitis was low: 9 patients (3.5%) treated with dexamethasone out of 258 died, compared to 13 (5%) in the placebo group (relative risk 0.71, confidence interval 0.31 to 1.62).[114] A 2004 meta-analysis of adjunctive dexamethasone trials with adults also showed no decrease in mortality for dexamethasone-treated patients (relative risk, 0.9; 95% confidence interval, 0.3 to 2.1).[132]

Other adjunctive therapies tested for meningococcal disease include bactericidal/permeability-increasing protein (BPI), a natural neutralizing protein of endotoxin, and HA-1A, a human monoclonal antibody to endotoxin.[292, 293] A study including 393 children with severe meningococcal disease, 37 of whom had confirmed meningococcal meningitis, evaluated the effect of recombinant BPI and showed no beneficial effect on rates of mortality (odds ratio, 0.76; 95% confidence interval, 0.36 to 1.61).[293] The effect of HA-1A was evaluated in a trial including 269 children with meningococcal septic shock; a nonsignificant trend toward a benefit was found (odds ratio, 0.59; 95% confidence interval, 0.31 to 1.05).[292]

The mortality of meningococcal meningitis has been reported to be 4 to 8% for children and up to 7% for adults.[27, 188, 257] Most patients die of systemic complications, mostly sepsis.[188, 211, 294] Signs of sepsis, advanced age, and infection due to meningococci of clonal complex 11 are all associated with unfavorable outcomes.[188] Bacterial load detection by quantitative PCR has also been associated with unfavorable outcomes,[238] but it remains unclear whether this information has any additional value for clinical prognoses.[239] Meningococcal meningitis is frequently complicated by arthritis (10%) and hearing loss (10%).[188, 295] Arthritis is caused either by hematogenous bacterial seeding of joints (septic arthritis) or by immune complex deposition in joints (immune-mediated arthritis). A patient with immune-mediated arthritis during meningococcal infection typically develops symptoms from day 5 of the illness or during recovery from the infection, generally involving the large joints.[295]

Listeria monocytogenes

L. monocytogenes is spread by contaminated food, which was discovered after outbreaks of listeriosis in the 1980s, but is also found in soil, water, and sewage.[296-298] Risk factors for listerial infection include the extremes of age (infants less than 1 month of age and adults older than 50 years of age), alcoholism, malignancy, the use of corticosteroid therapy, immunosuppression, diabetes mellitus, liver disease, chronic kidney disease, collagen-vascular diseases, and conditions associated with iron overload.[168, 190, 212, 213] *Listeria* meningitis has also been reported after administration of anti-tumor necrosis factor alpha (TNF-α) agents, such as infliximab and etanercept.[299, 300] However, *Listeria* meningitis can occur throughout life and in patients without predisposing conditions.[168, 213] A large review showed that 6 percent of cases of CNS disease in adults occur in young, previously healthy persons.[212] However, that study did not distinguish between patients with meningitis and those with brainstem encephalitis in this subgroup; brainstem

encephalitis is known to occur in young healthy patients. In a prospective cases series, no cases of young patients with no predisposing conditions were found.[168]

Listeria meningitis in children predominantly presents in the first month of life and symptoms consist of fever, irritability and meningeal signs in almost all patients.[110, 214] The clinical presentation for adults is similar to that for patients with pneumococcal and meningococcal meningitis, although the duration of symptoms before presentation is longer.[168] In a prospective case series of 30 patients with meningitis due to *L. monocytogenes*, symptoms were present for longer than 24 h in 63% of patients; for 8 patients (27%), symptoms were present for 4 days. The classical triad of fever, neck stiffness, and change in mental status was present in 13 (43%) of 30 patients.[168]

Brainstem encephalitis accounts for approximately 10% of listerial central nervous system infections and is observed mainly for middle-aged, previously healthy adults (71% of cases).[191, 301] Listerial brainstem encephalitis has been described to be a biphasic illness, in which a prodromal phase, consisting of malaise, headache, nausea or vomiting, fever, and prelusions of neurological impairment, is followed by the development of a neurological syndrome consisting of single or multiple asymmetric cranial nerve deficits in association with ipsilateral or contralateral sensory-motor long-tract and/or cerebellar signs in 82% of cases.[191]

Ampicillin and penicillin are highly effective against *L. monocytogenes*, and one of these antibiotics should therefore be included in empirical therapy for immunocompromised and elderly patients with suspected or proven bacterial meningitis.[137, 168, 190, 212] Expanded-spectrum cephalosporins are not effective against this organism. Although aminoglycosides have proven enhanced killing *in vitro*, retrospective clinical data on its use showed no benefit.[190, 302] In a cohort of 118 patients with listeriosis, renal failure was more commonly found in the aminoglycoside-treated group, and after correction for other risk factors for death, aminoglycoside treatment even seemed to increase the mortality rate;[302] naturally, results of this retrospective study may be confounded by indication. Chloramphenicol and vancomycin are also bactericidal *in vitro* but were associated with treatment failures in patients. Trimethoprim-sulfamethoxazole is recommended as an alternative for patients who are allergic to penicillin.[190]

Complications occur for a large proportion of patients with listeriosis, including hyponatremia in 80% of patients.[168] For children, reported mortality rates vary from 15 to 17%.[303, 304] Higher mortality rates have been reported for adults, ranging from 17 to 27%.[168, 190, 212] Overall, neurologic sequelae are described in 25% patients surviving listerial meningitis.[168, 190, 212] For patients with brainstem encephalitis, the risk of poor outcome is even higher, with 35% dying and neurological sequelae described for 55% of surviving patients.[191]

Streptococcus agalactiae

Risk factors for *S. agalactiae* meningitis in neonates consist of premature rupture of membranes, maternal fever, positive vaginal group B streptococcus culture, prematurity, clinical asphyxia in the neonate, and an Apgar score of less than 3 at 1 min.[106] Infection

occurs after perinatal vertical transmission or horizontal transmission from caregivers in the first weeks.[107, 108, 119, 194, 305, 306] *S. agalactiae* can also cause meningitis in adults, most often in association with severe underlying conditions.[193, 194, 307, 308] Risk factors include age over 60 years, diabetes mellitus, pregnancy or the postpartum state, cardiac disease, collagen-vascular disorders, malignancy, alcoholism, hepatic failure, kidney failure, previous stroke, neurogenic bladder, decubitus ulcers, and corticosteroid therapy; disease may also occur in patients without underlying conditions.[169, 194, 306]

Neonates with *S. agalactiae* meningitis often present with nonspecific symptoms, and usually, a mixed clinical picture of sepsis and meningitis is seen.[106, 306] Symptoms consist of irritability, tonus change (both hypotonia and hypertonia), and respiratory symptoms. Fever is found for a minority of patients.[106] A retrospective cohort study and literature review of *S. agalactiae* meningitis in adults showed that there is a slight female predominance, with 63% of cases occurring in women.[194] Predisposing factors have been reported for 80% of patients, and distant foci of infection were found for 50% of patients, which consisted mostly of endocarditis, endometritis, and sinusitis.[193, 194] Clinical presentation for adults consists of fever for 90%, neck stiffness for 62%, and an altered level of conscious for 67% of patients.[193]

S. agalactiae is susceptible to penicillin, ampicillin, and cephalosporins. Resistance to macrolide antibiotics and aminoglycosides occurs frequently.[107, 309] Despite the resistance to aminoglycosides, the combination of penicillin and an aminoglycoside has been standard therapy for group B streptococcal meningitis in neonates.[107, 119, 306] This choice is based on animal experiments, which showed improved outcomes with combination therapy compared to penicillin monotherapy.[310] Alternatives are expanded-spectrum cephalosporins and vancomycin.

Reported mortality rates for neonates vary between 7 and 27%, and a recent large study of 276 cases showed a mortality rate of 14%.[7, 192, 194, 305, 306] For adults, the mortality rate is considerably higher, at 25 to 30%.[193, 194] Long-term outcomes for children showed sequelae for one-third of survivors, consisting of spastic quadriplegia, profound mental retardation, hemiparesis, deafness, or blindness.[311] For adults, sequelae (mostly hearing loss) were reported for 7% of patients in one review.[194]

Streptococcus pyogenes

S. pyogenes (group A streptococcus) accounts for 0.2 to 1.2% of all cases of bacterial meningitis in adults and children and is community acquired in the majority of cases.[4, 19, 312] Predisposing conditions are present for 78 to 96% of patients and consist of otitis, sinusitis, pneumonia, recent head injury, recent neurosurgery, the presence of a neurosurgical device, altered immune status, alcoholism, or CSF leakage.[312, 313] For children, the most common predisposing factor is otitis.[314]

The clinical presentation is similar to that of meningitis caused by more common microorganisms, with headache, fever, and neck stiffness found for large proportions of patients with meningitis due to *S. pyogenes*.[312]

In vitro resistance of *S. pyogenes* to macrolide antibiotics and tetracyclines has been reported.[315-317] Reported resistance rates to tetracyclines range from 4 to 42% and varies geographically.[312] Cefotaxime was reported to fail to prevent and treat *S. pyogenes* meningitis in one case, despite in vitro susceptibility of the isolate.[318] No resistance of group A streptococci to β-lactam antibiotics has been reported and, therefore, penicillin remains the first choice antibiotic.[312, 319, 320] Cephalosporin therapy should be used either cautiously or not at all in view of the reported treatment failure.[318]

The reported mortality rates in case series and reviews of the literature vary from 4 to 27%.[312-314, 319] Neurological sequelae have been reported for 28% of children and consisted of learning difficulties, visual-field defects, and hearing defects.[314] For adults, neurological sequelae were present in 43% of patients in a large case series.[312] A large proportion of patients (58%) in this series developed hyponatremia during hospitalization.

Streptococcus suis

S. suis is an important pathogen of pigs and can be transmitted to humans by close contact with pigs.[321, 322] *S. suis* meningitis occurs sporadically in adults in European countries and America, while large outbreaks in Vietnam and China have been described.[166, 322-324] *S. suis* meningitis in children is unusual and only one case has been reported.[166, 325] Risk factors for contracting *S. suis* meningitis include professional exposure to pigs and pig meat, such as butchers and farmers.[166, 322]

In a cohort of 151 Vietnamese patients with *S. suis* meningitis, there was a strong male predominance.[166] Headache, neck stiffness, and fever were present in virtually all patients (>90%). Widespread subcutaneous hemorrhages were seen for 6% of patients.[166, 321, 322]

Antibiotic treatment of *S. suis* meningitis commonly consists of penicillin G or ceftriaxone.[321] In a large cohort of patients with *S. suis* meningitis, all strains were susceptible to penicillin, ceftriaxone, and vancomycin, but resistance to tetracycline (83%), erythromycin (20%), and chloramphenicol (3%) occurred.[166] Resistance to cephalosporins has also been described and was related to genetic variation in the bacteria.[326]

In a randomized clinical trial of adjunctive dexamethasone in Vietnam, a decrease in rates of severe hearing loss from 33 to 16% was observed for patients with *S. suis* meningitis treated with adjunctive dexamethasone (odds ratio, 0.23; 95% confidence interval, 0.06 to 0.78).[141, 166] In regions where *S. suis* meningitis is endemic and for patients at high risk for *S.suis* meningitis, adjunctive dexamethasone is warranted.[141, 166]

Reported mortality rates vary depending on geographic location, with rates of 3% in Vietnam and 18% in China.[166, 321, 322] Hearing loss at discharge has been reported for 40 to 66% of patients.[166, 327]

Staphylococcus aureus

S. aureus meningitis is acquired mainly nosocomially and occurs predominantly after neurosurgical procedures or following the placement of CSF shunts.[176, 328, 329] *S. aureus* meningitis may be acquired in the community setting, where it is associated with predisposing conditions such as endocarditis, immunocompromised state, and injection

drug use.[330, 331] Concomitant infections have been found for most patients and consist of endocarditis, pneumonia and osteomyelitis.[328-333]

S. aureus meningitis should be treated with vancomycin until susceptibility testing is performed due to the increase of disease caused by methicillin-resistant strains.[334] For treatment failures, linezolid and daptomycin can be considered, although the success of these agents has been described only in case reports.[335, 336]

The mortality rate in nosocomial *S. aureus* meningitis has been reported to be 14%.[331, 337] Community-acquired *S. aureus* meningitis is associated with high mortality (50 to 67%) due to associated underlying diseases.[330]

Aerobic gram-negative bacteria

Klebsiella species, *Acinetobacter baumannii*, *Escherichia coli*, *Pseudomonas aeruginosa*, and other aerobic gram-negative bacteria can cause bacterial meningitis after head trauma or neurosurgical procedures.[338-341] Postneurosurgical meningitis caused by aerobic Gram-negative bacteria can occur late after surgery; the median time to the development of *Acinetobacter* meningitis after a neurosurgical procedure was found to be 12 days (range, 1 to 40 days).[342] Community-acquired meningitis due to aerobic Gram-negative bacteria is uncommon but can be found for immunocompromised patients, such as HIV-infected patients, but also neonates and the elderly.[165,167,343] Clinical findings consist mostly of fever and altered consciousness.[344]

After the introduction of expanded-spectrum cephalosporins, the prognosis for bacterial meningitis due to Gram-negative bacteria has substantially improved.[113, 169] However, multidrug resistance of *A. baumannii* and other Gram-negative bacteria poses an increasing threat to postneurosurgery patients.[338, 345] A surveillance study from the United States showed increased resistances of *A. baumannii* to ceftazidime, from 30% in 1999 to 68% in 2008, and to cefepime, from 20% to 62% during this period.[346] Rates of resistance to meropenem and imipenem have also risen sharply during this period; strains were slightly less resistant to imipenem (47%) than to meropenem (59%).[346] The rates of resistance of *Pseudomonas aeruginosa* to ceftazidime (10%), cefepime (6%), ciprofloxacin (20%), imipenem (15%), and meropenem (8%) remained relatively stable from 1999 to 2008.[346] Resistance to ceftazidime, cefepime, ciprofloxacin, and gentamicin was also found for 6 to 17% of *Klebsiella* species isolates. Since 2003, resistance of *Klebsiella* species to imipenem and meropenem has emerged and now occurs in 5% of strains.[346] Global data showed similar trends in antibiotic resistance rates.[345] Empirical antimicrobial therapy of meningitis after neurosurgical procedures includes vancomycin and ceftazidime, cefepime, or meropenem to cover aerobic Gram-negative bacteria.[113, 174] Meropenem is the carbapenem of choice, as it is 8- to 16-times-more potent in the treatment of infections caused by *Enterobacteriaceae* than imipenem and 2-times-more potent than ertapenem.[346] However, meropenem-resistant strains may be imipenem susceptible, requiring the performance of susceptibility testing of the specific carbapenem being used. In addition, carbapenem heteroresistance appears to be more of a problem with meropenem than with imipenem, suggesting that imipenem is the preferred therapy for *Acinetobacter* meningitis.[355] Alternatives for patients with

carbapenem-resistant Gram-negative meningitis (especially that caused by *A. baumannii*) consist of colistin (usually formulated as colistimethate sodium) or polymyxin B, which may also need to be administered by the intrathecal or intraventricular route.[338,347]

Conclusions

The introduction of conjugate vaccines and preventive treatment of colonized pregnant women have had a major impact on the epidemiology and characteristics of bacterial meningitis. However, these successes are limited mainly to high- and median-income countries. Worldwide, bacterial meningitis remains a disease with devastating attack rates and growing drug resistance among causative bacteria, leading to treatment failures. Empirical antibiotic therapy should be adjusted to local drug resistance patterns and clinical subgroups. Currently, the majority of bacterial meningitis episodes occur in adults and are caused by *S. pneumoniae* and *N. meningitidis*. CSF examination remains crucial for diagnosis; it is required to confirm the diagnosis, identify the causative microorganism, and allow testing for antibiotic sensitivities to help rationalize treatment. CSF Gram staining is an important and rapid diagnostic tool. PCR is increasingly being used to determine the etiological diagnosis. As PCR techniques evolve and become more readily available, it will likely become a standard method, but studies are needed to validate its diagnostic accuracy. However, PCR, even multiplex PCR, will detect only the pathogens that are already suspected and included in the primer mix. In a world of increasing resistance to antibiotics and emerging pathogens, culture combined with susceptibility testing remains the gold standard for diagnosis. Progression in prevention, diagnostic methods, and treatment has benefited patients primarily in high-income countries, while the main burden of disease lies in resource-poor countries. The worldwide availability of effective vaccines remains the best option for the control of this devastating disease.

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