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Review

Bacterial meningitis: An update review

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Bacterial meningitis is still considered serious life-threatening disease in spite of the decline in the morbidity and mortality in the last decade. The expeditious diagnosis of the disease, a prompt empiric antibiotic treatment and the proper adjunctive therapy are corner stones for the successful management of the disease. The objective of this review is to provide the health care professionals with an update of reference for bacterial meningitis diagnosis and treatment. In addition, the various types of vaccines and the empiric chemoprophylaxis treatment are reviewed.

Key words: Neisseria meningitides, cerebrospinal fluid (CSF) examination, polymerase chain reaction, chemoprophylaxis.

INTRODUCTION

Meningitis is an inflammatory disease of the meninges membranes that cover the brain and spinal cord. The inflammation and swelling may extend through the membranes of the pia mater, arachnoid or subarachnoid (Mace, 2008). Meningitis can be classified into infectious and noninfectious disease. Noninfectious meningitis can emerge from administration of certain drugs such as non-steroidal anti-inflammatory drugs, immunoglobulins or some antibiotics. It can also develop from diseases like sarcoidosis and neoplastic meningitis. Infectious meningitis can be further sub-divided to non-bacterial and bacterial (pyogenic) meningitis. Non-bacterial meningitis is typically caused by viral or fungal infections (Mace, 2008). Bacterial meningitis is characterized by the significant polymorph nuclear changes in the cerebrospinal fluid (CSF). This review focuses only on acute bacterial meningitis; the common causes and effective methods of management.

EPIDEMIOLOGY

The introduction of conjugate vaccines and the prophylactic antibiotic treatment during pregnancy caused a change in the epidemiology of bacterial meningitis (Brouwer et al., 2010; World Health Organization (WHO), 2010). In spite of the advances in medical care with the introduction and widespread use of antibiotics, meningitis still has high morbidity and mortality rates. According to WHO, the incidence of bacterial meningitis is exceeding 1.2 million cases each year worldwide (WHO, 1988). In Saudi Arabia, bacterial meningitis epidemics usually occur

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usually occur after Al Hajj and Omrah seasons. Al Mazrou et al. (2004) evaluated the patterns of the disease in a retrospective study (1999 to 2002) and found that 58% of the cases were among local population and 48% of it was reported at the holy areas of Makkah and Al Madinah.

In the United States, the incidence of meningitis was decreased to 1.38 cases in 2006 to 2007 in exchange for two out of every hundred thousand people in 1998 to 1999 (Thigpen et al., 2011). However, the attack rates are very age-specific with a higher extent among newborn infants and elderly. The attack rates for newborn infants are in the range of 400 cases per 100,000 in exchange for 20 per 100,000 in older infants (≤ 2 years) while this reduces to only 1 to 2 per 100,000 in adults (Loring, 2004). Furthermore, males are affected slightly more than females. The incidence and the proportion of deaths among bacterial meningitis diagnosed cases are dependent on area and country, the causative micro-organism and age (Centre for Disease Control (CDC), 2013). The reported mortality rate of meningitis ranges from 3 to 33%. Major of mortality predictors include over-60-age, immunocompromised status, low Glasgow coma scale score and infection with Gram negative bacteria. The common morbidity associated with meningitis typically encompasses neurological sequelae, such as hearing loss, mental disability or weakness of a limb (Tang et al., 1999; Rosenstein et al., 2001).

ETIOLOGY

The causes of acute bacterial meningitis are dependent on age and the clinical setting under which the infection occurs. Infection with *Haemophilus influenzae, Streptococcus pneumoniae*, *Neisseria meningitidis*, group B streptococcus (*Streptococcus agalactiae*) or *Listeria monocytogenes* is considered responsible for more than 80% of cases of bacterial meningitis (Porto, 2012*)*. The existing underlying disease states together with a patient's age highly influence the etiology of the disease. Table 1 shows the common bacterial pathogens according to age and Table 2 shows a list of causative microorganisms and their common host characteristics.

PREDISPOSING FACTORS

Predisposing factors for meningitis include head trauma, immunosuppression, central nervous shunts, cerebrospinal fluid fistula/leak, neurological patients, alcoholism, sinusitis, otitis media, pharyngitis, bacterial pneumonia, splenectomized patients, sickle cell disease and congenital defects. Risk factors for meningitis can be summarized as follows:

1. Age (Geiseler et al., 1980): (extremes of age: elderly (age > 60 years); young children (age < 5 years), especially infants (age < 2years/newborns).
2. Demographic/socioeconomic (Choi, 1992; Chaves-Bueno and McCrcken, 2005): (male gender, African American ethnicity, poor populations, crowding (military recruits and crowded dormitories).
3. Exposure to pathogens (Mace, 2008): recent colonization, (household/close contact with meningitis patient), contiguous infection: sinusitis, mastoiditis, otitis media or bacterial endocarditis, intravenous drug abuse or dural defect: status post neurosurgery, central nervous system (CNS) trauma, congenital defect, ventriculoperitoneal shunt, other CNS devices or cochlear implants).
4. Immuno-compromizing factors (Geiseler et al., 1980; Schutze et al., 2002): Post splenectomy, hematologic disorders such as sickle cell disease or thalassemia major, malignancy, diabetes, alcoholism/cirrhosis or HIV.
5. Drugs (Porto, 2012*)*: Nonsteroidal anti-inflammatory drugs (NSAIDs), trimethoprim-sulfamethoxazole or immunosuppressive drugs.
6. Disease (Porto, 2012*)*: Systemic lupus erythematosus.

CLINICAL PRESENTATION

Clinical manifestations are nonspecific and vary depending upon the patient's age. The classic triad of symptoms in meningitis in adults includes fever, stiff neck and altered mental status. Approximately 44% of cases present with this classic triad. The majority of patients show at least two of the following four symptoms: fever, headache, neck stiffness and altered mental status (Tunkel et al., 2009; van de Beek et al., 2004). Positive Kernig's and Brudzinski's signs of meningeal irritation may be also seen in a number of patients. Other symptoms such as nausea, vomiting, cardiorespiratory arrest, focal CNS signs, photalgia and seizures may frequently occur (Tunkel et al., 2009; Bamberger, 2010). In newborns and infants, the common symptoms include fever, poor feeding, vomiting, lethargy, diarrhea and sometimes apnea. They can be limited to temperature instability and the presence of bulging fontanel in newborns (Tunkel et al., 2009). In older children, in addition, photalgia and mental disorder may occur. Sometimes the symptoms may be limited to only seizures especially in pediatric patients with pneumococcal meningitis. In Neisseria-caused-meningitis, rash and petechiae are common in more than half of the cases (Tunkel et al., 2009). For elderly and immunocompromised patients, signs may be masked with the common age- or immunodeficiency-related symptoms. Such groups of patients can present with lethargy and mental disorder as the common early signs (Tunkel et al., 2009). Other symptoms such as headaches, photalgia, seizures, rash, nausea and vomiting

Table 1. Common bacterial meningitis pathogens in different age groups.

Age/predisposing factor	Pathogens	Less common organisms
Newborns (<1 month)	*Group B streptococcus (S. agalactie), E. coli, L. monocytogenes*	*L. monocytogenes*, *Herpes simplex*, type 2
1-3 months	*Group B streptococcus (S. agalactie), E. coli, L. monocytogenes, S. pneumonia, N. meningitides, H. influenza*	Viruses
3 months-50 years	*Pneumonia, N. meningitides*	*E. coli* , Viruses
More than 50 years	*Pneumonia, N. meningitides, L. monocytogenes, gram-negative bacilli*	*L. monocytogenes*; aerobic, Gram-negative bacilli, viruses

Source: Mace (2008).

are also seen. Physical examination may reveal signs of meningeal irritation, stiff neck and positive Kernig and Brudzinski signs.

DIAGNOSIS

Combining the laboratory tests together with the investigational local meningeal irritation signs, confirmed by physical examination and the patient's medical history can confirm the diagnosis of acute bacterial meningitis; however, the key factor remains the CSF examination. When meningitis is suspected, patients' CSF should be examined after collection by a lumbar puncture (LP) unless uncorrected coagulopathy or cases known to cause elevated intracranial pressure are present. The high intracranial cases include seizure, focal neurologic deficits and/or head trauma. The presence of cardiopulmonary instability is considered another contraindication for LP, and in such cases brain imaging is often recommended (Tunkel et al., 2004; Chavez-Bueno and McCracken Jr., 2005). CSF analysis should highlight differential white blood cell counts and the level of protein and glucose. Gram stain and culture should be performed to confirm the presence and to deter-mine the type of bacterial infection. In bacterial meningitis, CSF analysis findings include: high white blood cell (WBC) with values exceeding 1,000 cells/mm^3 with predominance of neutrophils, high CSF protein (> 100 mg/dl) and low CSF glucose (usually < 40 mg/dl) due to the inflammatory process. Table 3 provides a summary of the findings. Normal or near normal findings may be seen in young children, immunocompromized and partially treated patients (Fraser et al., 1947). Determination of the causative microorganism allows for the selection of the most effective treatment. Gram staining of CSF is recommended as a fast, inexpensive and accurate tool to determine the bacterial etiology since CSF cultures can take up to 48 h. Positive gram stain is reported in 60 to 80% of untreated cases of bacterial meningitis and in 40 to 60% of partially treated cases. The sensitivity according to the causative organism varies from 90% for pneumococcal- or staphylococcal caused meningitis to less than 50% in Listeria-caused meningitis (Seehusen et al., 2003).

Polymerase chain reaction (PCR) and latex agglutination test may be applied to confirm a diagnosis of bacterial meningitis when negative culture results are obtained in patients with prior antibiotic treatment as it does not depend on the presence of viable bacteria.

Agglutination test should not be used alone as it is not sensitive to *N. meningitidis* (Hall et al., 1995). Serum procalcitonin and C-reactive protein can be useful to give a primary indication of bacterial infection though they lack bacterial species specificity. They are beneficial for differential diagnosis of bacterial and viral meningitis (Brouwer et al., 2010).

MANAGEMENT

Patients suspected of having meningitis must be diligently cared for. Meningitis management involves fast and appropriate diagnosis, antimicrobial therapy, adjunctive and supportive therapy, chemoprophylaxis for contacts and vaccination for prevention. Table 4 represents the recommendations for empirical therapy by age group and specific risk factor. In addition, a list of common bacterial meningitis organisms is presented in Table 5.

ANTIMICROBIAL THERAPY

Often, the selection of antimicrobial agents is based on a variety of factors which include: (a) patients age; (b) clinical setting; (c) presumed immune status; (d) CSF count; (e) ability to achieve concentration in the CSF above the minimum inhibitory concentration; (f) gram stain; (g) culture and sensitivity of CSF and blood isolate. The choice of the antimicrobial agent should be made

Table 2. Microorganisms and common host characteristics.

Organism	Common host characteristic
Streptococcus pneumoniae	Normal; could be impaired
Neisseria meningitides	Normal
Hemophillusinfluenzae	Normal
Listeria monocytogenes	Normal (infants), often immunocompromised in older adults
Streptococcus agalactiae	Colonization during delivery (infants). Gastrointestinal source of bacteremia (older adults)

Source: Bleck, (2013).

Table 3. Common CSF findings in acute meningitis.

Finding	Viral	Bacterial
WBC (Cells/mm^3)	100-1,000	>1,000
Neutrophils (%)	20-40	≥80
Glucose (mg/dl)	Normal	≤40
Blood/CSF ratio	Normal	≤0.4
Protein (mg/dl)	Normal	>100
Positive Gram stain	NA	60%-95%
Positive culture	NA	>95%
Lymphocyte predominance	Yes	NA
Polymerase chain reaction	Enterovirus, Herpesvirus	Under investigation for *pneumonia, N. meningitides and H. influenza*

Source: Porto (2012).

with as much information as possible but treatment should not be delayed while waiting for test results (Brouwer et al., 2012; van de Beek et al., 2012). As soon as the microorganism has been identified, and its *in vitro* susceptibilities known, a modification of therapy may be applied if necessary. Table 6 summarizes the recommended antimicrobial therapy for each pathogen-specific acute meningitis. The blood brain barrier (BBB) characteristics and the physicochemical properties of the antimicrobial agent such as logP and pKa are considered the most critical factors affecting adequate CSF concentrations (Sinner and Tunkel, 2004; Nau et al., 2010).

CSF penetration

The first determinant in the ability of the drug to treat bacterial meningitis effectively is its ability to cross BBB. The CSF has a unique environment and as a result has different pharmacokinetic parameters than in other areas of the body. Generally, antimicrobial agents are not significantly metabolized in the CSF and because of that, concentrations of most drugs primarily depend on penetration and elimination through the BBB that is affected by the following factors (Andes and Craig, 1999):

Lipid solubility: Lipophilic agents, such as the fluoroquinolones, chloramphenicol, rifampin and sulfonamides are able to enter the CSF via passive diffusion which allows them to reach peak CSF concentrations more rapidly, maintain adequate CSF concentrations and reach CSF half-lives similar to those in serum, regardless of the presence or absence of meningeal inflammation. In contrast to hydrophilic agents, such as β-lactams and vancomycin, these depend on the opening of tight junctions for entry and as a result have poor penetration and delayed onset of peak CSF concentrations (Lutsar et al., 1998; Chowdhury and Tunkel, 2000; Sinner and Tunkel, 2004).

Molecular weight: Fluoroquinolones and rifampin have low molecular weights and simple structures, which result in a better CSF penetration compared with larger compounds with more complex structures, such as vancomycin (Lutsar et al., 1998; Chowdhury and Tunkel, 2000; Sinner and Tunkel, 2004).

Ionization: Drugs with high ionization have poor CSF penetration. In bacterial meningitis, the pH of CSF is lower than that of plasma, so drugs such as β-lactam antibiotics which are weak acids and highly ionized in the physiologic pH of plasma have poor penetration into the CSF and tend to pass from the CSF into the plasma instead of in the reverse direction (Lutsar et al., 1998; Chowdhury and Tunkel, 2000; Sinner and Tunkel, 2004).

Protein binding: Only unbound fractions of antimicrobials enter the CSF; a high degree of protein binding in the

Table 4. Recommendations for empiric therapy by age group and specific risk factors.

Age-Group	Therapy
Neonate<1 month	Ampicillin plus aminoglycoside or ampicillin plus cefotaxime
Infant (1-23 months)	Third-generation cephalosporin (cefotaxime or ceftriaxone) plus vancomycin
Pediatric and adult (2 to 50 years)	Third-generation cephalosporin (cefotaxime or ceftriaxone) plus vancomycin
Elderly (>50 years)	Third –generation cephalosporin (cefotaxime or ceftriaxone) plus ampicillin plus vancomycin
Penetrating head trauma, post neurosurgery or cerebrospinal fluid shunt	Vancomycin plus cefepime or ceftazidime or meropenem
Skull Fracture	Vancomycin+ ceftriaxone or cefotaxime

Table 5. Common bacterial meningitis organisms.

Organism	Age	Risk factors	Proportion of cases	Case fatality
S. pneumoniae	All ages	Immunoglobulin alternative complement deficiency, asplenia, alcoholism	57%	17.9%; higher if immunocompromised
N. meningitidis	Aged 11 to 17 years and younger adults	Multiperson dwellings, travel to Sub Saharan Africa	17%	10%
L. monocytogenes	Neonates and adults	Cell-mediated immunodeficiencies (e.g. steroids, HIV, alcoholism), newborns	4%	18%
H. influenzae	Children and adults	Newborns	6%	7%
Group B streptococcus	Neonates	86% of cases are in patients aged G2 months	17%	11%
Gram-negative rods (*E. coli,* K. *pneumoniae*)	Adults	Nosocomial infection; only 3% from community	33% of all nosocomial meningitis	35% nosocomial; 25% community acquired

Source: Bartt (2012).

binding in the serum (for example, with ceftriaxone) limits the degree of CSF penetration (Lutsar et al., 1998; Chowdhury and Tunkel, 2000; Sinner and Tunkel, 2004).

Mode of administration

Mode of administration of the drug can be by intermittent or continuous intravenous administration. The standard clinical practice of intermittent administration usually leads to higher peak CSF concentrations but may not maintain concentrations above the minimal bactericidal concentration (MBC) for the entire dosing interval. In contrast, continuous infusion administration maintains concentrations above the MBC during nearly 100% of the dosing interval, although a lower peak CSF concentration is attained (Sinner and Tunkel, 2004). The mode of administration has been a concept of considerable debate but fewer clinical failures were seen in infections treated with continuous intravenous infusion of antibiotics that act by time-dependent killing (for example, β-lactams) and even with aminoglycosides that exhibit concentration-dependent killing (Kasiakou et al., 2005).

Table 6. Recommendations for antimicrobial therapy for pathogen-specific acute meningitis.

Microorganism	First choice	Alternative agents
S. pneumonia	Vancomycin plus ceftriaxone or cefotaxime	Meropenem, fluoroquinolone
Neisseria meningitides	Ceftriaxone or cefotaxime	Penicillin G, ampicillin, fluoroquinolones, aztreonam
GBS (*S. agalactiae*)	Ampicillin or penicillin G+/-aminoglycoside	Cefotaxime or ceftriaxone
Listeria monocytogenes	Ampicillin or penicillin G+/-aminoglycoside	meropenem
Haemophilusinfluenzae	Ceftiaxone or cefotaxime	Chloramphenicol, cefipime, meropenem, fluoroquinolone
S. aurues		
Methicillin-sensitive	Ampicillin+gentamicin	NA
Ampicillin-resistant	Vancomycin+/-rifampin	NA
Vancomycin resistant	linezolid	NA
P. aeruginosa	Ceftazidime or cefepime +/- aminoglycoside	Azteronam, fluoroquinolone, meropenem+/-aminoglycoside

Source: Bartt (2012).

Table 7. Recommended doses for certain antibiotics.

Antibiotic	IV Dosage (children)	IV Dosage (adult)
Amikacin	20-30 mg/kg/day ÷ every 8 h	15 mg/kg/day ÷ every 8 h
Ampicillin	200-400 mg/kg/day ÷ every 6 h	12 g ÷ every 4 h
Cefepime	150 mg/kg/day ÷ every 8 h.	6 g ÷ every 8 h
Cefotaxime	225-300 mg/kg/day ÷ every 6-8 h	8-12 ÷ g every 4-6 h
Ceftazidime	150 mg/kg/day ÷ every 8 h	6 g ÷ every 8 h
Ceftriaxone	100 mg/kg/day ÷ every 12 h	4 g ÷ every 12-24 h
Ciprofloxacin	NA	800 - 1200 mg ÷ every 8-12 h
Gentamicin	7.5 mg/kg/day ÷ every 8 h	5 mg/kg/day ÷ every 8 h
Meropenem	120 mg/kg/day ÷ every 8 h	6 g ÷ every 8 h
Nafcillin	200mg/kg/day ÷ every 6 h	9-120 g-every 4 h NOT sure of dosing here
Penicillin G	300,000 million unit/kg/day ÷ q 4-6 h	24 million units every 4 h
Rifampin	10-20 mg/kg/day ÷ q 12-24 h	600 mg q 24 h
Tobramycin	7.5 mg/kg/day ÷ every 8 h	5 mg/kg/day ÷ every 8 h
Trimethoprim-Sulfamethoxazole	10-20 mg/kg/day ÷ q 6-12 h	10-20 mg/kg/day q 6-12 h
Vancomycin	60 mg/kg/day ÷ q 6 h	30-60 mg/kg/day q 8-12 h

Antimicrobial pharmacodynamics in CSF

Knowledge of the pharmacodynamic properties of antimicrobials allows for appropriate optimization of bactericidal drug concentrations (Lutsar et al., 1998; Aronin, 2000). Bacterial killing is particularly important in the CSF in which there is a decreased immune response from relatively lower concentrations of antibody and complement and inefficient phagocytosis. The recommended doses for commonly used antibiotics are included in Table 7. Antibiotics may exhibit either time-dependent or concentration-dependent killing activities. Time-dependent antimicrobial activity (demonstrated by the β-lactam antibiotics and vancomycin) depends on the time that the drug concentration in CSF is above the MBC (T > MBC). An experimental study of cephalosporin-resistant pneumococcal meningitis showed that the T > MBC was the most important single determinant of ceftriaxone efficacy and correlated best with the bacterial kill rate supported by the direct linear relationship that was found between T > MBC and the bacterial killing rate (Lutsar et al., 1997). Aminoglycosides and fluoroquinolones exhibit concentration-dependent killing (Ahmed et al., 1997; Rodriguez-Cerrato et al., 2001), although fluoroquinolones, particularly trovafloxacin and gatifloxacin have been shown to have features of time-dependent killing in which the T > MBC was also considered a factor in bacterial killing (Kim et al., 1997; McCracken, 2000). The efficacy of concentration-dependent killing depends on attaining high peak CSF meningitis

Table 8. Therapy of common pathogen and duration of therapy.

Organism	Recommended therapy	Alternative therapy	Duration of therapy (days)
Streptococcus pneumoniae	MIC< 0.1 mcg/ml: (a) Penicillin G 4 Million Units IV q4h; (b) Ampicillin 2 g IVq4h	MIC< 0.1 mcg/ml: (a) Third –generation cephalosporin or chloramphenicol MIC 0.1-1 mcg/ml; (b) Cefepime or meropenem	10-14
	MIC 0.1-1 mcg/ml: (a) Third-generation cephalosporin		
	MIC>2 mcg/ml: (a) Vancomycin plus third-generation cephalosporin	MIC > 2 MCG/ml: Fluoroquinolone	
Neisseria meningitidis	MIC 0.1-1 mcg/ml: (a) Penicillin G 4 Million Units IV q4h; (b) Ampicillin 2 g IVq4h	MIC 0.1-1 mcg/ml: Third –generation cephalosporin or chloramphenicol	7
	MIC 0.1-1 mcg/ml: Third-generation cephalosporin	MIC 0.1-1 mcg/ml: Chloramphenicol, fluroquinolone, or meropenem	
H. Influenzae	Beta lactamase negative: Ampicillin 2 g IV q4h	Beta lactamase negative: Third –generation cephalosporin , cefepime, chloramphenicol or Fluoroquinolone	10-14
	Beta lactamase positive: Third-generation cephalosporin	Beta lactamase positive: Cefepime, chloramphenicol or fluoroquinolone	
Streptococcus agalactiae	Penicillin G 4 Million units IV q4h; Ampicillin 2 gm IVq4h	Third –generation cephalosporin	14-21
Listeria monocytogenes	Penicillin G 4 million Units IV q4h; Ampicillin 2 g IVq4h	Trimethoprim- sulfamethoxazole or meropenem	>21

syndrome.

ADJUNCTIVE TREATMENT

As with any severe infection, physiological support is paramount while one is awaiting the effect of the definitive therapy. Fluid and oxygenation are keystones of supportive therapy and must be augmented by pressors and ventilation as required. Convulsions must be treated appropriately. Fluid management must be adequately addressed. Careful monitoring of the hydration status of the patient is critical as over hydration can result in the possibility of associated cerebral edema and increased intracranial pressure. As improvement is noted (after 24 to 48 h), liberalization of fluid intake may be allowed but intake and output as well as serum electrolytes should be continuously monitored (van de Beek et al., 2012).

Dexamethasone has been found to prevent sensorineural hearing loss after *H. influenzae* and pneumococcal meningitis without interfering with antimicrobial therapy. It is recommended on individual basis for children greater than 2 months of age, with consideration of the benefit and possible risk when the diagnosis of bacterial meningitis

Table 9. Empiric therapy for acute meningitis syndrome.

Source or syndrome	Common pathogens	Suggested empiric therapy
Community acquired		
Adult or child	*S. pneumonia, N. meningitides, L. monocytogenes, H. influenzae*	Vancomycin + ceftriaxone
Neonate	Group B streptococcus: *L. monocytogenes and S. pneumoniae*	Ampicillin +cefotaxime or aminoglycoside
Immunocompromised e.g. patients with HIV, asplenia, alcoholism, cancer, or patients older than 60 years)	*S. pneumonia, L. monocytogenes* Aerobic gram-negative bacilli (eg, Enterobacteriaceae family)	Vancomycin + ampicillin +extended-spectrum cephalosporin
Adjunctive therapy (community-acquired disease unless contraindicated)	-	Dexamethasone (before or with first dose of antibiotics)
Identified focus of infection		
Maxillary sinusitis or otitis	Streptococcus species, Gram-negative bacilli, Staphylococcus aureus, Haemophilus species	Vancomycin +metronidazole + extended-spectrum cephalosporin
Endocarditis	*Viridians streptococcus; S. aureus Streptococcus;* bovis HACEK group, Enterococci	Vancomycin + extended-spectrum cephalosporin
Nosocomial	Gram-negative bacilli, Staphylococci species	Vancomycin +extended-spectrum cephalosporin
Penetrating trauma or recent neurosurgical procedure (eg, shunt)	S. aureus and other species (especially MRSA),Enterobacteriaceae family Pseudomonas species	Vancomycin + metronidazole + extended-spectrum; Cephalosporinor Vancomycin + meropenem
Encephalitis (e.g., seizures, obtundation)	Herpes family (especially herpesvirus type 1)	Acyclovir

Source: Bartt (2012).

is proven or highly suspected on the basis of CSF analysis report, Gram stain or positive agglutination test results. It is preferable to start steroid therapy as soon as diagnosis is made or at least at the start of antimicrobial administration.

The practice guidelines of the Infectious Diseases Society of America include the recommendation of adjunctive use of dexamethasone with the start of antibiotic treatment in patients with suspected pneumococcal meningitis (Tunkel et al., 2004). The mode of administration is 10 to 20 min before or concomitantly with the first dose of an antibiotic. For children, a dose of dexamethasone 0.6 mg/kg/day intravenously divided into four doses is recommended for four days while 10 mg IV every 6 h is recommended for adults (van de Beek et al., 2012).

PROPHYLAXIS

Chemoprophylaxis

In the case of *H. influenzae* or *N. meningitidis*, people in close contact including family, health care professionals or school settings are considered at high risk of contracting the disease. Other types of bacterial meningitis including cases

caused by *S. pneumoniae* are considered to be less transmissible to close contacts. A two-day rifampin course of therapy is proved as the first-line regimen for chemoprophylaxis (Lieberman et al., 1990). The recommended dosage is 10 mg/kg every 12 h for children older than 1 month or 600 mg every 12 h for adults. Other option includes the use of single dose 500 to 750 mg ciprofloxacin or a single dose of ceftriaxone at a dose of 125 mg in children or 250 mg in adults given intramuscular (Darouiche et al., 1990; Schaad et al., 1995).

Vaccines

There are currently three vaccines available that target the most common bacterial causes of meningitis: *S. pneumoniae*, *H. influenzae*. These microorganisms are largely human pathogens, contain a polysaccharide capsule as the main virulence determinant of and that capsular types associated with meningitis are only a small subset of those that colonize the nasopharynx, these similarities are important for vaccine development (Mcintyre et al., 2012). *H. influenzae* vaccine is available as a single antigen conjugate vaccine and in combination with other vaccines. Despite the type of vaccine, the recommended dose is to be given at 2, 4 and 6 months or at 2 and 4 months. Pneumococcal vaccine can be classified as a pneumococcal conjugate vaccine (PCV) or a pneumococcal polysaccharide vaccine (PPSV). Approved PCV include: the 7-valent (PCV-7), the 10-valent (PCV-10) and the 13-valent (PCV-13). PCV is recommended for all children with ages younger than 5 years. PCV-7 was approved by Food and Drug Administration (FDA) in 2000 for use in infants and young children. It consists of seven serotypes conjugated to a carrier protein. These serotypes (which include 4, 6B, 9V, 18C, 19F, and 23F) have been found to be responsible for about 82% of meningitis cases caused by pneumococci and effective in reducing invasive infection by 79% (Seppa, 2011). However, an increase in the incidence of infection caused by other serotypes was observed (for example, 19A), that led to the development of the 10-valent and 13-valent pneumococcal conjugate vaccine. In 2009, the European Commission gave authorization for marketing of 10-valent PCV containing serotypes 1, 5 and 7F in addition to all serotypes of PCV-7. Shortly after that, the 13-valent was also introduced in 2010 (European Medicines Agency, 2013). This vaccine covers an additional three serotypes (which are 3, 6A and 19A). These 13 serotypes are responsible for 63% of invasive pneumococcal cases in children less than 5 years and 5 to 6 years with underlying medical conditions such as chronic lung disease, diabetes or heart disease. The main disadvantages of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) are the inability to induce immunologic memory and effect on nasopharyngeal carriage.

The CDC Advisory Committee on Immunization Practices (ACIP) recommends the PPSV23 for children aged ≥ 2 years that have underlying medical conditions after completing all recommended doses of PCV13. A poster dose of PPSV23 given 5 years after the first dose is recommended for children with anatomic or functional asplenia. PPSV23 is also recommended for elderly subjects only if it is proved that they did not receive pneumococcal vaccination at least in the last five years. High risk populations such as subjects with chronic pulmonary or cardiovascular diseases, diabetes and/or immunodeficiency, in addition to nursing home residents and smokers, should be considered for PPSV23 vaccine.

Meningococcal vaccines are active against many strains of *N. meningitidis*. Immunization against meningococcal is not warranted as post exposure prophylaxis unless the strain is documented to have a capsular serotype represented in the vaccines (type A, B, C, Y or W-135). A marked reduction in *H. influenzae* meningitis has been associated with the use of *H. influenzae* vaccine directed against the type b capsular polysaccharide of this organism in children in developed countries since 1987.

Conclusion

Bacterial meningitis continues to carry high morbidity and mortality rates. Awareness of appropriate empiric and directed antimicrobial therapy regimens may help to lower the morbidity and mortality rates. Vaccinations, dexamethasone and chemoprophylaxis should be used judiciously in the appropriate patient population to provide the best patient care.

Conflict of interest

Authors reported none.

REFERENCES

Ahmed A, Paris MM, Trujillo M, Hickey SM, Wubbel L, Shelton SL, McCracken GH Jr (1997). Once-daily gentamicin therapy for experimental *Escherichia coli* meningitis. Antimicrob. Agents Chemother. 7(41):49–53.

Al-Mazrou YY, Al-Jeffri MH, Abdalla MN, Elgizouli SA, Mishskas AA (2004). Changes in epidemiological pattern of Meningococcal disease in Saudi Arabia. Does it constitute a new challenge for prevention and control? Saudi Med. J. 25(10):1410-1413.

Andes DR, Craig WA (1999). Pharmacokinetics and pharmacodynamics of antibiotics in meningitis. Infect. Dis. Clin. North Am. 13:595–618.

Aronin SI (2000). Bacterial meningitis: principles and practical aspects of therapy. Curr. Infect. Dis. Rep. 2:337–344.

Bamberger DM (2010). Diagnosis, initial management, and prevention of meningitis. Am. Fam. Physician 82:1491-1498.

Bartt R (2012). Acute bacterial and viral meningitis. Infect. Dis. 18(6):1255-1270.

Bleck TP (2013). Bacterial meningitis and other nonviral infections of the nervous system. Crit. Care Clin. 29:975-987.
Brouwer MC, Thwaites GE, Tunkel AR, van de Beek D (2012). Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. Lancet 380:1684.
Brouwer MC, Tunkel AR, van de Beek D (2010). Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin. Microbiol. Rev. 23:467-942.
CDC, Centers for Diseases Control and Prevention (2011). Epidemiology of Meningitis Caused by *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenza*. Available at: http://www.cdc.gov/meningitis/lab-manual/chpt02-epi.html Accessed December, 2013.
Chavez-Bueno S, McCracken GH Jr (2005). Bacterial meningitis in children. Pediatr. Clin. North Am. 52:795–810.
Choi C (1992). Bacterial meningitis. Clin. Geriatric Med. 8(4):889–902.
Chowdhury MH, Tunkel AR (2000). Antibacterial agents in infections of the central nervous system. Infect. Dis. Clin. North Am. 14:391–408.
Darouiche R, Perkins B, Musher D, Hamill R, Tsai S (1990). Levels of rifampin and ciprofloxacin in nasal secretions: correlation with MIC90 and eradication of nasopharyngeal carriage of bacteria. J. Infect. Dis. 162:1124-1127.
European Medicines Agency (2012). Prevenar: pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/001104/WC500057248.pdf Date accessed 23 of March, 2014.
Fraser DW, Geil CC, Feldman RA (1947). Bacterial meningitis in Bernailillo County, New Mexico: a comparison with three other American populations. Am. J. Epidemiol. 100(1):29–34.
Geiseler PJ, Nelson KE, Levin S, Reddi KT, Moses VK (1980). Community-acquired purulent meningitis: a review of 1316 cases during the antibiotic era 1954–1976. Rev. Infect. Dis. 2(5):725–745.
Hall LMC, Duke B, Urwin G (1995). An approach to the identification of the pathogens of bacterial meningitis by the polymerase chain reaction. Eur. J. Clin. Infect. Dis. 14(12):1090-1094.
Kasiakou SK, Sermaides GJ, Michalopoulos A, Soteriades ES, Falagas ME (2005). Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomized controlled trials. Lancet Infect. Dis. 5:581–589.
Kim YS, Liu Q, Chow LL, Tüuber MG (1997). Trovafloxacin in treatment of rabbits with experimental meningitis caused by high-level penicillin-resistant Streptococcus pneumoniae. Antimicrob. Agents Chemother. 41:1186–1189.
Lieberman JM, Greenberg DP, Ward JI (1990). Prevention of bacterial meningitis. Vaccines and chemoprophylaxis. Infect. Dis. Clin. North Am. 4:703-729.
Loring KE (2004). CNS infections. In: Tintinalli JE, Kelen GD, Stapczynski JS (Eds.), Emergency medicine: a comprehensive study guide, 6th edition. McGraw-Hill, New York. pp. 1431–1437.
Lutsar I, Ahmed A, Friedland IR, Trujillo M, Wubbel L, Olsen K, McCracken GH Jr (1997). Pharmacodynamics and bactericidal activity of ceftriaxone therapy in experimental cephalosporin-resistant pneumococca meningitis. Antimicrob. Agents Chemother. 41:2414–2417.
Lutsar I, McCracken GH Jr, Friedland IR (1998). Antibiotic pharmacodynamics in cerebrospinal fluid. Clin Infect Dis. 27:1117–1129.
Mace SE (2008). Acute Bacterial Meningitis. Emerg. Med. Clin. N. Am. 38:281–317.
McCracken G (2000). Pharmacodynamics of gatifloxacin in experimental models of pneumococcal meningitis. Clin. Infect. Dis. 31(Suppl 2):S45–50.
McIntyre PB, O'Brien KL, Greenwood B, van de Beek D (2012) .Effect of vaccines on bacterial meningitis worldwide. Lancet 380:1703–1711.
Seppa N (2011). Vaccinations cut cases nearly one-third over past decade. Science News. Bacterial Meningitis Rates Fall http://www.usnews.com/science/articles/2011/05/26/bacterial-meningitis-rates-fall
Nau R, Srgel F, Eiffert H (2010). Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin. Microbiol. Rev. 223:858.
Porto I (2012). Acute Bacterial Meningitis.US Pharmacist. Accessed Feb.2013, http://www.uspharmacist.com/continuing_education/ceviewtest/lessonid/108112/]
Rodriguez-Cerrato V, McCoid CC, Michelow IC, Ghaffar F, Jafri HS, Hardy RD, Patel C, Olsen K, McCracken GH Jr (2001). Pharmacodynamics and bactericidal activity of moxifloxacin in experimental *Escherichia coli* meningitis. Antimicrob. Agents Chemother. 45:3092–3097.
Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM (2001). Meningococcal Disease. N. Engl. J. Med. 344:1378-1388.
Schaad UB, Abdus Salam M, Aujard Y, Dagan R, Green SD, Peltola H, Rubio TT, Smith AL, Adam D (1995). Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. Pediatr. Infect. Dis. J. 14:1-9.
Schutze GE, Mason EO Jr, Barson WJ, Kim KS, Wald ER, Givner LB, Tan TQ, Bradley JS, Yogev R, Kaplan SL (2002). Invasive pneumococcal infections in children with asplenia. Pediatr. Infect. Dis. J. 21:278–282.
Seehusen DA, Reeves MM, Fomin DA (2003). Cerebrospinal fluid analysis "and remove "15:" and replace 1109 by "1108". Am. Fam. Physician 15:68(6):1103-1109.
Sinner SW, Tunkel AR (2004). Antimicrobial agents in the treatment of bacterial meningitis. Infect. Dis. Clin. North Am. 1:581–602.
Tang LM, Chen ST, HSU WC, LYU RK (1999). Acute bacterial meningitis in adults: a hospital-based epidemiology study. Q. J. Med. 92:719-725.
Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Stat M, Lynfield R, Hadler JL, Harrison LH, Farley MM, Arthur Reingold A, Nancy M, Bennett NM, Craig AS, Schaffner W, Thomas A, Melissa M, Lewis MM, Elaine Scallan E, Schuchat A (2011). Bacterial meningitis in the United States, 1998-2007. N. Engl. J. Med. 364:2016-2025.
Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Karen L, Roos KL, Scheld WM, Whitley RJ (2004). Practice guidelines for the management of bacterial meningitis. Clin. Infect. Dis. 39:1267-1284.
Tunkel AR, van de Beek D, Scheld MW (2009). Acute meningitis. In: Mandell GL, Bennett JE, Dolin R (Eds.), Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases, 7th ed., Churchill Livingstone Elsevier, Philadelphia. pp. 1189-1229.
Van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR (2012). Advances in treatment of bacterial meningitis. Lancet 380:1693-1702.
Van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen MD (2004). Clinical features and prognostic factors in adults with bacterial meningitis. N. Engl. J. Med. 351:1849-1859.
World Health Organization (WHO). 2010. Changing epidemiology of pneumococcal serotypes after introduction of conjugate vaccine: July 2010 report. Wkly Epidemiol. Rec. 85:425–436.