2.1. PRELUDE

Bacterial meningitis is a very important and frequent devastating disease. Many bacterial pathogens have been reported to cause meningitis, defined by the onset of symptoms over the cause of several hours unto several days. Despite the large number of bacterial pathogens that have been reported to cause acute meningitis, certain microorganisms are isolated with a higher frequency (Tang et al., 1999).

Bacterial meningitis continues to be an important cause of morbidity and mortality in India and throughout the world despite the availability of effective antimicrobial therapy. Therefore accurate information on the etiologic agents, populations at risk, trends in antimicrobial resistance morbidity and mortality is critical to develop public health measures and ensure appropriate management (Tang et al., 1999). Bacterial meningitis is also a major problem in the developing world. The average incidence of bacterial meningitis is 50 cases per 100,000 population, approximately one in 250 children develops bacterial meningitis during the first 5 years of life, with a mortality rate of greater than 50% children younger than 15 years of age accounted for 74% of cases, 45% of cases were in children younger than 2 years of age, H. influenzae, N. meningitides and S. pneumoniae accounted for 62% of the cases and 70% of death. The case fatality rated for meningitis caused by Enterobacteriaceae was 86%; more than half of these cases in children less than 24 months of age were caused by Salmonella species, an
unusual meningeal pathogen in industrialized nation. The likely etiological agent of bacterial meningitis depends on the age risk factors and underlying disease status of the patient (Tang et al., 1999, Gray et al., 2006).

These data underscore the need for improved therapeutic regimens and vaccine strategies to control bacterial meningitis in developing countries of the world. Following Robert Koch’s pioneering discovery of the cause of anthrax in 1976, the last two decades of the nineteenth century witnessed an explosion of new knowledge on the microbial etiology of disease. As bacteriology evolved from an art into a science, the first report of meningococcal isolation was attributed to Anton Weichselbaum in 1887. He observed Gram-negative diplococci in the CSF of a young patient who had died in Vienna of sporadic meningitis and isolated the organism (which he called Diplococcus intracellularis meningitides) exudates of six of eight patients. As he isolated a pneumococcus from the other two cases, he was therefore cautious in his interpretation of these findings. All three of the major meningeal pathogens (*Neisseria meningitides*, *Streptococcus pneumonia* and *Haemophilus influenzae*) were first isolated and described in a 10 years period at the close of the nineteenth century.

The development and perfection of the technique of lumbar puncture by Heinrich Quince (1842 to 1922) in 1891 facilitated the formal examination of CSF and the diagnosis of meningitis. Heinrich Quince was searching for a safe and simple method to remove CSF from children with hydrocephalus.
Although Quince describe bacteria in the fluid in pathological circumstances, it took nearly 20 years before the first comprehensive description of the chemical composition of CSF was published by William Mestrezat (1883 to 1928) in 1911. The earliest example of the diagnostic value of CSF analysis by biochemical methods was published in 1893 by Ludwig Lichthein (1845 to 1928) when he observed that CSF glucose concentrations were low in the presence of bacterial and tuberculous meningitis. This observation led to the measurement of CSF glucose in the initial diagnostic approach of patients with suspected meningitis over the past century. The other major abnormalities in the CSF found in patients with bacterial meningitis (i.e., the CSF neutrophilic pleocytosis and elevated protein concentration) were well described in the early years of the twentieth century. George Goodwin and Harold Shelley introduced interpretation of the CSF glucose concentration in relation to plasma values as early as 1925. Advances during the twentieth century on these critical analysis were largely methodological in nature, including enzymatic glucose-oxidase and hexokinase methods for determination of CSF glucose and colorimetric methods for determination of CSF protein that supplanted early turbidometric procedures in the early 1950s. The low CSF pH in bacterial meningitis cases was noted as early as 1911, but Nishimura first describes the contribution of elevated lactate concentrations in 1924. While CSF lactate concentrations are not routinely measured in patients with suspected bacterial meningitis, the height of the
CSF lactate correlates directly with prognosis and may be useful in differentiating bacterial meningitis from an abnormal CSF following neurosurgery, based on the neurosurgical procedure itself (Chandramukhi et al., 1989, Donald et al., 1985).

Following the documentation of the primary CSF abnormalities observed in case of bacterial meningitis in the early years of the twentieth century, including CSF pleocytosis, elevated protein and depressed glucose concentrations, many other diagnostic aids were describe in the clinical literature, including detection of bacterial antigens by various techniques, and the polymerase chain reaction for direct identification of microbial DNA in clinical specimens. These advances, as well as their limitations are amply outlined in the pages that follow. Recent contributions to the literature include a suggestion that determination of serum C-reactive protein and procalcitronin may be useful in identification of patient with bacterial meningitis when compared with viral syndromes. These new, inexpensive, and rapid techniques show great promise in the delineation of bacterial from viral meningitis when more established techniques yield equivocal results (Trienekens et al., 1985, Donald et al., 1985, Boving et al., 2009).

Harcharan Singh et al. (1987) showed the importance of immunological Tests (counter immunoelectrophoresis, latex particle agglutination, coagglutination) in diagnosing bacterial meningitis very early (91.7%) conventional techniques gave a precise diagnosis in 21/49 (42.8%)
cases only, whereas counter immunoelectrophoresis, latex particle agglutination, coagglutination were positive in 20/49 (40.8%), 49/49 (100%) and 38/49 (77.5%) cases. *Meningococci, pneumococci, H. influenzae* was the infecting organisms in 49 cases (81.5%) (Dirks Go et al., 1973).

A survey conducted by Indian federation of pediatrics in 1994 all over India reported the isolation of causative organism only in 15.8% cases. In majority of patients the pathogen remains un-notified. Causes being non-availability of culture facility round the clock, delayed and faulty inoculation techniques into culture media, non-availability of rapid diagnostic tests and cases being pretreated with antibiotics before admission.

Gram stain, rapid diagnostic tests plays a vital role in reducing the mortality and morbidity in meningitis cases.

Coral et al. (1999) have reported CRP in CSF as 100% sensitive in differentiating bacterial meningitis from aseptic meningitis. Workers like Mauche et al., do agree with this finding. Kitolainen et al (1998) analyzed the usefulness of CRP in the diagnosis of *Borrelia burgdogferi* infection and stated that CSF and serum CRP are of no value either in diagnosis or in predicting the outcome. They also reported specificity of 100% and positive predictive value of 100% and negative predictive of 89.7%. CRP detection is particularly valuable in partially treated cases Gram stain and culture (James Corral, 1987, Gokul et al., 1989, Feigin et al., 2003, and Rajamani, 2003).
2.2. CEREBROSPINAL FLUID SYSTEM

The entire cerebral cavity enclosing the brain and spinal cord has a capacity of about 1600-1700 ml; about 150 ml of this capacity is occupied by cerebrospinal fluid and the remainder by the brain and cord. This fluid is found in the ventricles of brain, in the cisterns around the outside of brain, and in the subarachnoid space around the brain and the spinal cord. All these chambers are connected with one another and the pressure of the fluid is maintained at a surprisingly constant level.

The major function of the CSF is to cushion within its solid vault. The brain and CSF have about the same specific gravity, so that the brain simply floats in the fluid. CSF is formed at the rate of about 500 ml each day, which is three to four times as much as the volume of fluid in entire cerebrospinal fluid system. About two thirds or more of this fluid originates as a secretion from choroids plexus in the four ventricles, mainly in the two lateral ventricles. Additional small amounts are secreted by all the ependymal surfaces of the ventricles and the arachnoidal membranes and a small amount comes from the brain itself through the per vascular spaces that surround the blood vessels entering the brain. The fluid secreted by the choroids plexus from the lateral ventricles first passes into third ventricle; it flows downward along the aqueduct of sylvius into the fourth ventricle through three small openings, two lateral foramina of Luschka and a midline foramen of Magendie, entering the cisterna, a large fluid space that lies
behind the medulla and beneath the cerebellum. The cisterna magna is continuous with the subarachnoid space that surrounds the entire brain and spinal cord. Almost all the CSF then upward from the cisterna magna through the subarachnoid space surrounding the cerebrum. From here, the fluid flows into multiple arachnoidal villi that project into the large sagittal venous sinus and other venous sinuses of the cerebrum. Finally the fluid empties into the venous blood through the surfaces of these villi.

The normal pressure in the cerebrospinal fluid system when one is lying in a horizontal position averages 130 mm of water (10 mm of Hg), although this may be as low as 65 mm of water or as high as 195 mm of water even in normal healthy individuals. Often a large brain tumor elevates the cerebrospinal fluid pressure by decreasing the rate of absorption of cerebrospinal fluid into the blood. The cerebrospinal fluid pressure also rises considerably when hemorrhage or infection occurs in the cranial vault.

It has been pointed out that the concentrations of several important constituents of cerebrospinal fluid are not the same as in extracellular fluid elsewhere in the body. Further more, many large molecular substances hardly pass at all from the blood into the cerebrospinal fluid or into the interstitial fluids of the brain, even though these same substances pass readily into the usual interstitial fluids of the body. Therefore, it is said that barriers, called the blood-cerebrospinal fluid and brain fluid, respectively. These barriers exists both at the choroids plexus and at the tissue capillary
membranes in essentially all areas of the brain parenchyma except in some areas of the hypothalamus, pineal gland and area postrema, where substances diffuse with ease into the tissue spaces.

In general, blood-cerebrospinal fluid and blood-brain barriers are highly permeable to water, carbon dioxide, oxygen and most lipid soluble substances such as alcohol and anesthetics; slightly permeable to the electrolytes such as sodium, chloride and potassium; and almost totally impermeable to plasma proteins and most non-lipid-soluble large organic molecules.

The cause of the low permeability of blood-cerebrospinal fluid and blood-brain barriers is the manner in which the endothelial cells of the capillaries in the barriers are joined to one another. So-called tight junctions join them. That is, the membranes of the adjacent endothelial cells are tightly fused with one another rather than having extensive slit-pores between them as is the case in most other capillaries of the body (Donald et al., 1985, Kotilainen et al., 1998, Narinder Singh et al., 1995, Boving et al., 2009).

2.3. MENINGITIS

The identity of the causative organism in bacterial meningitis is frequently by epidemiological and clinical clues. The most important clue is the patient’s age; there are striking correlations between the common types of bacterial meningitis and the age groups they afflict (Williams et al., 1988).

Meningitis in the neonate is in most cases (Gokul et al., 1989, Feigin et al., 2003), due to organisms acquired during delivery and to a lesser extent,
organisms acquired in the nursery or in the household group B *Streptococcus* is the most common pathogen, accounting for 40 to 50 percent of cases (Hoban *et al.*, 2001, Hofmann *et al.*, 1995). *Escherichia coli* (predominantly strains possessing the KI antigen is the causative organism in 20 to 30 percent of cases and *Listeria monocytogenes* is the third most common pathogen. These three organisms account for 80 percent of cases of meningitis in the newborn infant (Klare *et al.*, 1977).

Miscellaneous Gram-negative bacilli (such as *Klebsiella*, *Enterobacter*, *Serratia* and *Proteus*) and streptococci other than group B are frequent. *Streptococcus pneumoniae*, *Haemophilus influenzae* type b and *Neisseria meningitides* are rarely encountered in the newborn period; non typable *H. influenzae* is more common (Hussey *et al.*, 1994, Jacoby *et al.*, 1997 and Hoban *et al.*, 2001).

Beyond the first month of life and extending through childhood, *H. influenzae*, *N. meningitides* and *S. pneumoniae* are responsible for the vast majority of bacterial meningitides in previously well children (Ramchandra Reddy *et al.*, 1973 Enting *et al.*, 1996). The potential pathogens in infants between 1 and 3 months of age may also include organisms encountered in neonates. *H. influenzae* is the most common pathogen in children under the age of 6 years, accounting for 50 to 60 percent (Thirumoorthi *et al.*, 1995, Srivastave *et al.*, 1968, Saez-Llorens *et al.*, 2003, Ramachandra Reddy *et al.*, 1973 and Curtis, 2010).


2.4. PATHOGENESIS AND PATHOPHYSIOLOGY

CSF is protected from blood-borne pathogen invasion by an effective blood-CSF barrier and is protected externally by the dura and skull. Meningeal infection, therefore, requires either a defect in the external barrier (e.g., congenital ectodermal defects, head trauma, neurosurgery) or possession by the pathogen of virulence factors that facilitate host invasion cases entry into the CSF. Since external barrier defects are relatively uncommon, most cases of bacterial meningitis represent CSF penetration from the bloodstream and involve the following sequence of events: (1) host mucosal colonization, (2) mucosal invasion and bacteremia, (3) penetration of blood-CSF barrier, (4) bacterial replication within the CSF, and (5) production of decease in the meanings and the brain.

The first step in the process of infection is host acquisition of a potential meningeal pathogen by nasopharyngeal mucosal colonization. This initial event is influenced by specialized surface components of the pathogen that interact with receptors on nasopharyngeal epithelial cells. Both \textit{N. meningitides} and \textit{H. influenzae} have pili that facilitate to these cells. The distribution of cell surface receptors for these pili determines the sites of colonization.

After colonization, mucosal invasion is necessary for bacteremic spread. Hosts lacking specific antibody against the colonizing serotype are at greatest risk of systemic invasion. Although colonization may persist for a
variable length of time, recently colonized individuals are at the highest risk for invasive disease.

After entry into the blood, the successful meningeal pathogen must overcome host defenses (i.e., polymorph nuclear leukocytes and the phagocytes of reticulo-endothelial system) to sustain intravascular survival. The major meningeal pathogens (*H. influenzae, N. meningitidis, S. pneumoniae, E. coli K1* and group B *Streptococci*) have polysaccharide capsules that inhibit neutrophil phagocytes and resist classical complement pathway activity (Srivastave *et al.*, 1968 and Thirumoorthi *et al.*, 1995). The alternative complement pathway, however, is directly activated, facilitating phagocytosis. When the alternative pathway is impaired, as in patients with sickle cell disease, opsonization and phagocytosis are deficient, rendering the host more susceptible to pneumococcal meningitis. Similarly, patients with impaired splenic function, either from a hemoglobinopathy or due to splenectomy, have an impaired ability to clear circulating bacteria, rendering them more susceptible to pneumococcal bacteremia (often fulminates) and meningitis.

The mechanism by which meningeal pathogens enter the CSF is not known. Many bacteria, encapsulated and none capsulated, enter the bloodstream and cause bacteremia; however, only a few cross the blood – CSF barrier and produce meningitis. This suggests the presence of specialized receptors on the CSF and in the absence of host defenses (i.e.,
neutrophils, complement, and specific antibody), multiply logarithmically to high concentrations.

The blood-CSF barrier is made up of the choroids plexus and a few other tiny regions around the ventricles. Proliferation of bacteria in the CSF leads to changes in the permeability of this barrier. Breach of the usually highly efficient blood-CSF barrier allows the influx of the serum proteins, including immunoglobulin and complement: Moreover, the presence of bacteria in the CSF generates chemo tactic activity, arachidonic acid metabolites and/or CSF. As a result, polymorph nuclear leukocytes (PMNs) being to enter the CSF through the choroids plexus. The PMNs, however, cannot effectively phagocytize and clear the infecting organisms because the concentrations of complement and specific antibody in the CSF are well below levels optimal for opsonizing activity. Many organisms, therefore, remain extra cellular (as is commonly seen in the Gram-stained smears of purulent CSF before therapy). The CSF, therefore, can be conceptualized as a localized area of impaired host defenses.

The pathologic hallmark of acute bacterial meningitis is inflammatory exudates within the subarachnoid space. This polymorph nuclear response may exert both beneficial and detrimental effects on the host. The exudates may block the normal CSF flow, causing an increase in intracranial pressure (ICP) or causing various forms of hydrocephalus. A decrease in the CSF concentration of glucose is also characteristically observed during bacterial
meningitis, but the precise mechanisms of hypoglycorrhachia remain obscure. Metabolism by PMNs and bacteria within purulent CSF is not sufficient to explain the fall in CSF sugar. Alterations of glucose transport across the blood-brain barrier are largely responsible for hypoglycorrhachia through inhibition of carrier-facilitated diffusion.

The pathologic and physiologic consequences of CSF are attributed to infection, but are not limited to the leptomeninges. The CSF is contiguous with the extra cellular fluid space of the brain parenchyma adjacent microvasculature, thus, bacterial products within CSF could damage the endothelial cells of the microvasculature, which is the site of the blood-brain barrier. This results in increased leaking from capillaries and vasogenic brain edema. Brain edema in bacterial meningitis may have other components: cytotoxic (from inflammatory mediators in cellular exudates) or interstitial (from impaired or CSF resorption). Brain edema leads to increased intra cranial pressure, which can precipitate reversible or irreversible neuronal injury by obstructing CSF flow, compressing cranial nerves or reducing cerebral blood flow.

Bacteremia is present in 30 to 90 percent of patients admitted to the hospital with bacterial meningitis. Although this bacterial is usually primary and results in seeding of the CSF, studies of experimental meningitis suggest that secondary bacteremia may occur; that is, bacteria in the CSF may enter the blood due to CSF flow from the subarachnoid space to the dural venous sinus through the arachnoids villi.
Due to the effectiveness of the pial barriers, meningeal infection does not extend to the brain parenchyma. Brain abscess, therefore, is not a complication of bacterial meningitis except in neonates with *Citrobacter diversus* meningitis, in which it is a frequent complication. When brain abscess and meningitis coexist, the abscess is usually the primary focus, subsequently leaking into the ventricular system to produce meningitis.

Inflammation of blood vessels (arthritis, phlebitis) that traverse the subarachnoid space is common in bacterial meningitis and particularly severe when *S. pneumonia* is involved. This vasculitis leads to luminal narrowing or thrombus formation and may result in ischemia and occasionally infarction of the cerebral cortex, causing impaired consciousness, focal neurologic deficits, and/or seizures.

Neurologic complications of bacterial meningitis are the consequence of one or more of the following: (1) vasculitis, (2) brain edema, (3) inflammatory exudates within the subarachnoid space (most abundant over basal cisterns) and secondary to meningeal inflammation causing impaired CSF resorption.

### 2.5. CLINICAL MANIFESTATIONS

The symptoms and signs of bacterial meningitis are variable and depend, in part, on the age of the patient and the duration of illness (Arlet, 1990). A history of antecedent upper respiratory infection is
commonly present. The onset is usually acute, fever, headache, vomiting and stiff neck developing over 24 to 36 hours (Kabra, 1991). In some instances, the onset is less acute, extending over 3 to 5 days. The headache is often described generalized, persistent and severe beyond anything previously experienced. The vomiting is more common in children, occurs without abdominal pain or other gastrointestinal symptoms. Evidence of meningeal irritation is almost always present. Myalgia (particularly in meningococcal disease), backache, photophobia, and generalized weakness are common. The illness usually progress rapidly, with the development of confusion, ostentation, and, ultimately, coma and death.

The usual manifestations of meningitis may be absent or partially obscured in elderly patients with severe heart failure or pneumonia. After head or neurosurgical procedures, the signs and symptoms of complicating meningitis are indistinguishable from those related to underlying disease (Short and Tunkel, 2000).

In neonates, the signs of meningeal irritation are usually absent. Lethargy, listlessness, irritability, vomiting, or poor feeding may be the only complaints described by parents. Fever may be absent, especially in premature infants and hypothermia may occur. The only sign of meningitis may be fullness or bulging of the fontanels, and this sign may be obscured by dehydration if the infant has been vomiting. Faun dice is a relatively common finding in premature infants with meningitis (Srivasatave et al., 1968).
Cranial nerve palsies involving primarily the third, fourth, sixth, or seventh nerves occur in 10 to 20 percent of patients with bacterial meningitis. They are usually transient in nature, caused by local effects of the basilar exudates or increased intracranial pressure (sixth nerve). Sensor neural hearing loss, either unilateral or bilateral, may occur and is usually permanent. Ataxia has been a presenting sign in a number of children in whom hearing losses later developed. Presumably insults to the vestibular and auditory system do occur concomitantly in these children.

Seizures (focal or generalized) occur during the first 12 to 48 hours of illness in 20 to 30 percent of patients with bacterial meningitis. These seizures may by focal cerebral injury (secondary to occlusive changes), high fever (in infants), or penicillin neurotoxicity (large doses administered in the presence of renal failure). Seizures caused by cortical vein phlebitis can occur during the first few days of illness or appear late, during the recovery phase.

Focal cerebral signs (hemiparesia, dysphasia and hemianopsia) occur in about 15 percent of patients. They are usually secondary to occlusive inflammation (usually venous) and may develop early or appear late during the recovery phase. Focal signs associated with seizures may be postictal, in which case they are transient and usually persist for no more than a few hours.

Increased intracranial pressure is commonly present. Papilledema, however, is rarely encountered, presumably because of the relatively brief period during which pressure is elevated. The presence of papilledema
should prompt a search for a mass lesion such as brain abscess, subdural collection, or venous sinus thrombosis. Acute brain edema with CSF pressure of over 450 mm H$_2$O is a rare complication of bacterial meningitis. This may produce seizures, third nerve dysfunction, hypertension bradycardia, or coma and may result in a temporal lobe or cerebellar herniation.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is commonly present, causing hyponatremia and water retention. This syndrome places the patient at a greater risk for the development of increased intracranial pressure and seizures.

Subdural effusions occur in 25 to 30 percent of children under 18 months with bacterial meningitis. The incidence appears to be independent of the type of organism producing the disease. Inflammation of the veins that transverse the subdural space and of the dural capillaries may cause an increase in vascular permeability and result in loss of fluid into the subdural space. The effusion may persist sometime after the inflammatory process subsides due to continued transudations through newly formed vessels in the subdural membrane. Subdural effusions are not generally associated with and symptoms. The frequency with which vomiting, seizures, a full fontanel, focal neurologic signs and persistent fever are noted in children with bacterial meningitis without subdural effusions is such that their occurrence can only rarely be attributed to the subdural effusion per se (Williams and Hart, 1988).
Shock may complicate bacterial meningitis. When, it is usually a manifestation of associated bacteremia. Signs of disseminated intravascular coagulation may accompany hypotension in these patients.

2.6. AETIOLOGY OF PYOGENIC MENINGITIS

Age must always be an important parameter when considering specific etiologic agents of bacterial meningitis. Meningitis in this age group, beyond 6 years of age, \textit{H. influenzae} meningitis becomes less common (Hoban \textit{et al.}, 2001).

In adults \textit{Streptococcus pneumonia} and \textit{N. meningitidis} are responsible for the majority of cases. Primary \textit{H. influenzae} meningitis in adults is so unusual that its presence suggests predisposing anatomic or immunologic defects. In the elderly, \textit{S. pneumoniae} is the most frequent cause of bacterial meningitis’s. \textit{N. Meningitidis} is uncommon in the elderly, but other organisms, including Gram-negative bacilli and \textit{L. monocytogenes}, may be involved (Gazouli \textit{et al.}, 1997).

Isolation of an anaerobic organism from cerebrospinal fluid (CSF) is rare; it usually suggests intraventricular leakage of a brain abscess or the presence of a parameningeal focus of infection. Mixed bacterial meningitis is also uncommon; it occurs more frequently in adults than in children. Predisposing factors include infection at contiguous foci and fistulous communications with the central nervous system (Table-2.1)
2.6.1. *Haemophilus influenzae* meningitis

*H. influenzae* is a polymorphic Gram negative coccobacillus. It is the leading cause of bacterial meningitis worldwide, accounting for about half of all reported cases. Although there are six antigenically different types of encapsulated *H. influenzae*, type b is the major pathogen causing meningitis and accounts for more than 95 percent of cases.

*H. influenzae* type b meningitis occur primary in children under 6 years of age, with 90 percent of cases occurring between the ages of 1 month and 3 years. The highest incidence occurs in infants 6 to 12 months old. *H. influenzae* meningitis is uncommon in children older than 6 years and rare in adults, due to acquisition of antibody to capsular polysaccharide in other bacteria. The occurrence of *H. influenzae* meningitis in adults should prompt search for the presence of an otitis media, a sinusitis, a CSF leak, or an immunodeficiency disease.

*H. influenzae* meningitis is usually a complication of otitis media, sinusitis, pneumonia, or previous head trauma. The clinical features are not distinctive. In contrast to meningococcal meningitis, petechiae rarely occur in *H. influenzae* meningitis. Owing to the young age of affected children, subdural effusions are a commonly recognized complication. Monoarticular or polyarticular arthritis may rarely occur during the recovery phase of *H. influenzae* meningitis. The arthritis is usually reactive due to immunologic mechanisms.
<table>
<thead>
<tr>
<th>Predisposing factor</th>
<th>Common bacterial pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td><em>Streptococcus agalactiae</em>, <em>Escherichia coli</em>, <em>Listeria monocytogenes</em>, <em>Klebsiella species</em></td>
</tr>
<tr>
<td>1-23 month</td>
<td><em>Streptococcus pneumoniae</em>, <em>Neisseria meningitides</em>, <em>Streptococcus agalactiae</em>, <em>Haemophilus influenzae</em>, <em>Escherichia coli</em>.</td>
</tr>
<tr>
<td>2-50 years</td>
<td><em>Neisseria meningitides</em>, <em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>&gt;50 years</td>
<td><em>Streptococcus pneumoniae</em>, <em>Neisseria meningitides</em>, <em>Listeria monocytogenes</em>, <em>Aerobic Gram-negative bacilli</em></td>
</tr>
<tr>
<td>Nosocomial acquisition</td>
<td>Aerobic Gram-negative bacilli (including <em>Pseudomonas aeruginosa</em>), <em>Staphylococci</em> (Staphylococcus aureus and coagulase-negative Staphylococci)</td>
</tr>
<tr>
<td>Head trauma basilar skull fracture</td>
<td><em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, group A-hemolytic Streptococci</td>
</tr>
<tr>
<td>penetrating trauma</td>
<td></td>
</tr>
<tr>
<td>Post neurosurgery</td>
<td><em>Staphylococcus aureus</em>, <em>Staphylococcus epidermidis</em>, aerobic Gram negative bacilli (including <em>Pseudomonas aeruginosa</em>), <em>Propionibacterium acnes</em></td>
</tr>
<tr>
<td>Cerebrospinal fluid shunt</td>
<td><em>Staphylococcus aureus</em>, <em>Staphylococcus epidermidis</em>, aerobic Gram negative bacilli (including <em>Pseudomonas aeruginosa</em>), <em>Propionibacterium acnes</em></td>
</tr>
<tr>
<td>Immunocompromised state cellular immunodeficiency</td>
<td>Listeria monocytogenes, Nocardia species</td>
</tr>
<tr>
<td>Humoral immunodeficiency</td>
<td><em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, <em>Neisseria meningitides</em>, <em>Staphylococcus aureus</em>, other <em>Streptococci</em></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Aerobic Gram-negative bacilli (including <em>Pseudomonas aeruginosa</em>), <em>Staphylococcus aureus</em></td>
</tr>
</tbody>
</table>
2.6.2. Meningococcal Meningitis:

Meningococcal meningitis is the only bacterial meningitis that occurs in outbreaks, usually in susceptible populations subjected to close living quarters. It accounts for 15 to 30 percent of all reported cases of bacterial meningitis worldwide. Its relative frequency among the meningitis will depend on whether statistics have been gathered during an epidemic period. The highest attack rates are in children under 1 year of age. Attack rates decline steadily with increasing age, presumably due to acquisition of protective antibodies, so that less than 10 percent of cases occur in persons over age 45. Most of these antibodies develop in response to intestinal or pharyngeal colonization with organisms that are antigenically cross-reactive with the capsular polysaccharide of *N. meningitides*. Deficiencies of late complement factors (C6, C7 and C8) and selective IgG subclass 2 deficiencies are associated with a high incidence of meningococcal disease. Most cases of meningitis occur in the winter and early spring.

Meningococcal can be segregated into 13 serogroups on the basis of capsular polysaccharide antigens. Five serogroups (A, B, C, Y, and W 135) are responsible for most cases of meningitis. Serogroups A and C are most often associated with epidemics; serogroups B is the primary cause of sporadic cases; and serogroup Y causes sporadic cases of pneumonia, sometimes associated with meningitis. The source of organisms is most often an asymptomatic carrier. Occasionally the source may be a person with a primary
infection of the pharynx and a sore throat. In virtually all cases, the organisms reach the meninges hematogenously. The bacteremia, however, may be transient and not demonstrable when the patient is admitted to the hospital.

About half the patients with meningococcal meningitis have petechiae, purpuric lesions, or both. The early rash in some cases may be morbilliform and may resemble viral exanthema; however, it rapidly becomes petechial. The presence of petechiae in a patient with meningitis is highly suggestive of meningococcal etiology. Petechiae may also occur in asplenic patients with pneumococcal meningitis, in concomitant meningitis and endocarditic caused by \textit{S. pneumonias} or \textit{S. aureus}, in meningitis caused by echovirus type 9, and rarely in \textit{H. influenzae} meningitis.

Unlike other bacterial meningitides, metastatic infection is a relatively common event in meningococcal meningitis. It can be postulated that, bacteremia is an essential event in the pathogenesis; the meninges represent the most common site of metastatic infection. There may be concomitant infection of the eyes, joints, pericardium, endocardium, testes and lungs. Disseminated intravascular coagulation may occur and progress to hemorrhagic infection of the adrenals, renal cortical necrosis, shock and death.

A distinctive clinical feature of meningococcal meningitis is the development of manifestations induced by immunologic reactions. These usually appear 3 to 7 days after the onset of the disease, when the patient appears to be improving on therapy. The characteristic features
include varying degrees of fever, arthritis (monoarticular or oligoarticular, usually involving the large joints) and percarditis. The synovial fluid contains large numbers of PNMs and increased concentrations of protein, but normal levels of glucose. Cultures are sterile. Signs and symptoms may persist for a week or longer. Additional antimicrobial therapy is not required. Treatment with salicylates or other no steroidal anti-inflammatory agents is usually effective.

2.6.3. Pneumococcal Meningitis

*S. pneumoniae* accounts for 20 to 30 percent of all reported cases of bacterial meningitis worldwide. Pneumococcal meningitis occurs in all age groups; it is particularly common in children under 2 years of age. In adults, especially those over age 60, *S. pneumoniae* is the most frequent cause of bacterial meningitis.

*S. pneumoniae* is divided into 83 serotypes on the basis capsular polysaccharide antigens However, 15 serotypes are responsible for over 80 percent of cases of pneumococcal meningitis in the United States.

No predisposing focus of infection can be identified in about 50 percent of cases of pneumococcal meningitis, which are classified as primary. In some instances, bacteremia may originate from asymptomatic colonization of the pharynx by *S. pneumoniae*. Over 50 percent of cases are secondary to infection of the ear, paranasal sinuses, or lungs. When pneumococcal pneumonia is complicated by meningitis, there may be
an initial bacteremia causing endocarditic (usually involving the aortic value), which then leads to persistent bacteremia and deposition of organisms or infected emboli in the meninges. Old or recent head trauma, a CSF leak, spleenectomy, sickle hemoglobinopathy, multiple my Loma, bone marrow transplantation, alcoholism, and cirrhosis predispose to or accompany pneumococcal meningitis in children with sickle cell disease are caused by *S. pneumoniae*; the risk of pneumococcal meningitis for these children is increased in these patients.

Patients with pneumococcal meningitis are more likely to have alterations of consciousness’ (particularly coma), seizure, or focal neurology defects than are patients with meningococcal or *H. influenzae* meningitis. Rarely, the disease may start abruptly with severe headache, come, or seizure in a healthy person.

A distinctive feature of pneumococcal meningitis is its tendency to recur in some patients. factors associated with recurrence include (1) tears in the dura due to fracture of the cribriform plate or par nasal sinuses and nasal meningocele-lesions that produce connection between the external environment and the subarachnoid space; and (2) repeated episodes of acute otitis media, especially when complicated by involvement of the bony walls of the middle ear. A person with pneumococcal meningitis who has of these predisposing conditions is at risk repeated attacks.
2.6.4. Gram-negative bacillary meningitis:

The incidence of meningitis caused by Gram-negative bacilli (excluding H. influenzae) has increased significantly in the past two decades. These organisms are currently the fourth most common cause of bacterial meningitis, following H. influenzae, S. pneumoniae and N. meningitides.

Beyond the neonatal period, Gram-negative bacillary meningitis occurs primarily in patients whose anatomic defenses against central nervous system (CNS) infection have been compromised. Nearly 60 percent of the antibiotics directed primarily against Gram-positive pathogens may account; to some degree, for the predominance of Gram-negative bacilli (60 to 70 percent) in post neurosurgical meningitides. Approximately 20 percent of the cases occur in conjunction with head trauma, usually after penetrating skull or spine wounds. The remaining 20 percent of the cases occur mostly as a complication of bacteremia, diseases. Whenever an elderly patient with significant underlying disease acquires meningitis in the hospital, a Gram-negative bacillary etiology should be considered. Rarely, Gram-negative bacillary meningitis may be secondary to a ruptured brain abscess, strongly oxidases, spinal anesthesia, or chronic otitis media. When a chronic communication from the subarachnoid bacilli (S. aureus) are the usual causes of complicating meningitis.
The most common Gram-negative bacilli causing meningitis after the neonatal period are *Klebsiella pneumoniae* (30 to 40 percent of the cases) and *E. coli* (15 to 30 percent). Others including *Pseudomonas aeruginosa* marcescens, *Enterobacter* spp, *Providencia* spp, *Acinetobacter* spp and *Citrobacter* spp, may also cause meningeal infection. Meningitis secondary to introduction of bacteria during spinal anesthesia is most often due to *Pseudomonas aeruginosa*.

The clinical manifestations of meningitis caused by Gram-negative bacilli are often obscured by the underlying predisposing conditions. Altered consciousness, signs of meningeal irritation and abnormal CSF (elevated protein and/or white blood cell count) are not uncommon after craniotomy or head trauma. Complicating meningitis, therefore, is less likely to be suspected. The CSF Gram stain reveals the pathogen in 50 to 70 percent of cases and a low CSF sugar may be the only clue to the diagnosis. In the elderly and debilitated hosts with Gram-negative bacteremia and meningitis, the classic signs and symptoms of meningeal infection may not be present; low-grade and changes in mental status may occur without headache.

2.6.5. **Listeria meningitis:**

*L. monocytogenes* is being recognized with increasing frequency as a cause of meningitis. Most cases occur in the neonate and in persons with impaired cell-mediated immunity, such as organ transplant recipients,
patients with lymphoma and patients receiving corticosteroid or immunosuppressive therapy. Normal adults, particularly the elderly, may occasionally develop Listeria meningitis. Unlike the three common forms of acute bacterial meningitis, the clinical presentation of Listeria meningitis may be subtle and the course more indolent. The organism may appear coccid on a Gram stained smear and may be mistaken for pneumococci. It may be misidentified as diphtheroids and regarded as contaminant by the laboratory.

Although listeria meningitis may be associated with a mononuclear CSF response, this finding is unusual. The majority of patients with listeria meningitis have CSF findings typical of purulent bacterial meningitis.

2.6.6. *Staphylococcus aureus* meningitis:

*S. aureus* accounts for 2 to 6 percent of all bacterial meningitis. Most cases occur in association with neurosurgical procedures, penetrating cranial trauma, ventricular CSF shunts, endocarditic (predominantly in intravenous drug abusers), other extra-CNS foci of infection, and prematurely (in neonates). Bacteremia may be percent in 50 percent and disseminated intravascular coagulation in few percent of cases.

2.7. POST-TRAUMATIC MENINGITIS

Bacterial meningitis may complicate head trauma associated with a basilar skull fracture, creating a communication (dural fistula) between the subarachnoid space and the nasal cavity, the Para nasal sinuses, or the ear.
These disruptions occur most commonly in the frontal fosse, especially the cribriform plate and allow CSF to escape through the torn arachnoids and dura. If the leak is large, CSF rhinorrhea is evident; if small, nasal cilia sweep the fluid posterior, where temporary plugs the laceration, resulting in delayed or intermittent drainage. Less frequently dural fistulas occur in the middle criminal fossa, secondary or petrous bone fracture and result in CSF otorrhea, if there is an associated rupture of the tympanic membrane. Repeated attacks of bacterial meningitis are sometimes the only indication that an exterior communication with the subarachnoid space exists. CSF leaks usually close and stop draining during periods of inflammation due to meningitis.

*S. pneumoniae* is the most common cause of meningitis in patients dural fistulas in the cribriform plate or Para nasal sinuses; accounting for up to 90 percent of cases *H. influenzae* and various non pneumococcal *Streptococci* account for most of the remainder; Gram-negative bacilli and *S. aureus*, however, more commonly cause meningitis associated with CSF otorrhea.

The interval between head trauma and meningitis is usually less than 1 month; however, in some patients, many years may elapse before infection occurs. This fact emphasizes the importance of eliciting any history of head trauma, even if remote, in-patients with bacterial meningitis, especially if caused by *S. pneumoniae*. 
In all patients with post traumatic or recurrent meningitis, the presence of a basilar skull fracture should be investigated by conventional radiography and computed tomography to localize the associated dural tear. If demonstrated, it should be repaired to prevent recurrence of meningitis.

In-patients with suspected CSF rhinorrhea, the presence of glucose in the secretions suggests CSF origin. The most reliable method for confirming CSF leak and demonstrating its location is the intrathecal injection of radio-labeled albumin and examination of cotton pledgets placed in nasal cavities. CSF rhinorrhea occurring after head trauma ceases spontaneously within 1 to 2 weeks cases. Operative repair of dural tear is usually reserved for cases complicated by meningitis, for leaking persisting beyond 4 to 6 weeks (2 weeks for high-volume leakage) and for late-onset, post-traumatic leaks. The administration of prophylactics in patients with a CSF occurring after head trauma is not successful in preventing recurrent of the meningitis.

Meningitis associated with open and penetrating head wounds is usually due to enteric Gram-negative bacilli, *Pseudomonas* spp., *Streptococcal* species other than *Pneumococcus* and *S. aureus*. The sources of these organisms are usually wound infections.

### 2.8. LABORATORY DIAGNOSIS

To diagnosis bacterial meningitis, CSF examination is mandatory (Van de Beek, 2006; Boving et al., 2009) 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 (Coonrod et al., 1976, Lalitha et al., 1989; Deivananyagam N 1993, Drieer et al., 2004, Boving et al., 2009 and Bamberger 2010) that might aid in etiological diagnoses, especially for patients with negative CSF cultures (i.e., after antibiotic pre-treatment). 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.

2.8.1. CSF cell count, glucose and protein

Characteristic CSF findings for bacterial meningitis consist of polymorphonuclear pleocytosis, hypoglycorrhachia and raised CSF protein levels (Van de Beek, 2006; Boving et al., 2009). 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 µmol 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. However, CSF protein (<0.5 g/liter) and neutrophil count (=100) thresholds are also indicative of bacterial meningitis, with odds ratios (ORs) of 14 and 12, respectively.
The majority of patients presenting with community-acquired bacterial meningitis have CSF parameters characteristic of bacterial meningitis. However, low CSF white blood cell counts do occur, especially in patients with septic shock and systemic complications.

Experimental pneumococcal meningitis studies also showed a relationship between a large bacterial CSF load, a lack of response of CSF leukocytes and intracranial complications. In a prospective cohort study of 258 adults with culture proven meningococcal meningitis, CSF leukocyte counts of less than 1,000 leukocytes per mm$^3$ were found for 19% of patients (Boving, 2009; Van de Beek, 2006). CSF examination was reported to be normal for five (1.7%) of these patients.

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. A mononuclear cell predominance in the CSF is found more frequently than for other types of bacterial meningitis. 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. 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
Adults with *S. agalactiae* meningitis have typical CSF findings (Donald, 1985; Van de Beek, 2004).

### 2.8.2. 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 post-neurosurgical 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 (Donald, 1985).

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 (A study of 231 children showed positive CSF cultures for 82% of patients) (Donald, 1985).

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 (Kotilainen, 1998). In a study from the United Kingdom including 103 patients with clinically defined meningococcal meningitis, only 13% had positive CSF cultures (Van de Beek, 2004).
The yield of CSF culture is lower for patients who have received antibiotic pre-treatment before lumbar puncture. Two large case series reported decreases in yield from 66 to 62% and 88 to 70% if patients were pre-treated with antibiotics (Kotilainen, 1998; Donald, 1985).

In one of those studies, pre-treatment for more than 24 h was associated with a further decrease of positive CSF cultures to 59%. A decrease in culture positivity from 19 to 11% was seen for pre-treated patients with clinically defined meningococcal meningitis in a study from the United Kingdom (Kotilainen, 1998). Another study of 21 patients with meningococcal meningitis diagnosed either by culture or by PCR showed positive CSF cultures for 9% of patients receiving pre-treatment and 50% for those who did not.

2.8.3. CSF Gram stain

CSF Gram staining may swiftly identify the causative microorganism for patients with suspected bacterial meningitis (Van de Beek, 2004, Van de Beek, 2006). 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 (Kotilainen, 1998).

Forty-four percent of patients in this cohort were pre-treated with antibiotics. In an Indian study of 535 suspected meningitis cases, CSF Gram
staining identified the causative organisms for 36 (65%) of 55 pre-treated patients, while CSF culture was positive for only 5 (9%) patients (Shameem et al., 2008).

In a large study from Denmark, CSF Gram staining was the only positive laboratory finding for 4% of 875 patients with bacterial meningitis. 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.

The yield of CSF Gram staining may be decreased in antibiotic pre-treated patients compared with antibiotic-naïve patients. Pre-treatment with antibiotics decreased the yield of CSF Gram staining only slightly, from 56 to 52% for 481 Danish patients.

A study of U.S. children showed similar yields of CSF Gram staining for pre-treated patients. For 73 meningococcal meningitis patients, the reported yield of Gram staining decreased slightly, from 34 to 27% for pre-treated patients (Kotilainen, 1998; Schuurman, 2004).

The reported sensitivities of CSF Gram staining vary considerably for different microorganisms. CSF Gram staining correctly identifies the organism in 50 to 5% of children and in 25 to 33% in adults with H. influenzae meningitis. Gram staining correctly identifies the pathogen in 69 to 93% of patients with pneumococcal meningitis (Durand et al., 1993).
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. The yield of Gram staining for *Listeria meningitis* is low, ranging from 23 to 36% for both children and adults (Brouwer and Beek, 2009) and even lower (14%) or patients with *Listeria rhombencephalitis*.

### 2.8.4. 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 (Pedersen, 2009).

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 (Chinchankar *et al.*, 2002; Brouwer and Beek, 2009; Pedersen, 2009). 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 (Gray *et al.*, 1992). However, in a 10-year retrospective study of 176 children with culture-negative meningitis who were pre-treated with antibiotics
before lumbar puncture, none had a positive CSF latex agglutination result (95% confidence interval, 0 to 2%) (Gray et al., 1992).

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 (Gray et al., 1992).

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 (Perkins, 1995). A study of meningococcal meningitis patients showed a strong decline in the sensitivity of latex agglutination, from 60% for patients without antibiotic pre-treatment prior to lumbar puncture to 9% for antibiotic pre-treated patients (Rao et al., 1995).

The limited additional value of latex agglutination testing was also shown by several other studies, and its use is therefore limited (Perkins, 1995).

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.

2.8.5. 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
(Schuurman, 2004; Nolte, 2011). 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 (Corless et al., 2001).

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 (Tzanakaki et al., 2009).

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. 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 (Parent et al., 2005).
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 (Gray et al., 2006).

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. Pre-treatment 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 pre-treatment.

PCR can also be a useful tool for the swift typing of meningococcal strains in an evolving epidemic (Parent et al., 2005). 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 (Hedberg et al., 2009). Recent studies of multiplex PCRs including
*L. monocytogenes* showed lower detection thresholds (Chiba, 2009; Boving *et al.*, 2009, Hedberg *et al.*, 2009).

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 (Chiba, 2009; Boving *et al.*, 2009; Hedberg *et al.*, 2009). 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. *Streptococcus aureus* DNA was detected by PCR in CSF samples from 149 of 151 patients (sensitivity, 99%) in a cohort study, with unknown specificity (Mai NTH A high, 2008) bacterial load determined by quantitative PCR has been associated with unfavorable outcomes of both pneumococcal and meningococcal disease (Carrol *et al.*, 2007; Darton *et al.*, 2009) but it remains unclear whether this information has any additional value for clinical prognosis (Chiba, 2009; Brouwer *et al.*, 2009).