

## **Bacterial Meningitis**

1- **Definition** - Meningitis - Inflammation of the meninges (due to bacterial infection) - membranes around the brain and CNS - (not parenchymal ) - not to be confused with encephalitis - parenchymal involvement - usually viral - In severe bacterial meningitis there can be parenchymal pathology - and evidence of encephalopathy - due to decreased perfusion, local infarcts - but the organisms do not invade the brain tissue itself.

(See Figure 1 on next page.)

Usually a complication of bacteremia/sepsis - organisms that “seed” the meninges - bind to receptors on meningeal cells - initiate a host inflammatory response - Occasionally due to direct inoculation - following trauma or surgery

Therefore meningitis is usually associated with specific bacteria that are able to achieve high grade bacteremia and have specificity for meningeal receptors. The intensity of the local immune response to the specific organisms often is directly correlated with the amount of pathology and the ultimate outcome. For example, *S. pneumoniae* elicits significant inflammatory responses and is often associated with major neurological sequelae, even if the bacteria are totally susceptible to antibiotics.

## **2. Epidemiology**

### **Age dependent -**

Neonate - Group B streptococci (*Streptococcus agalactiae*)- (GBS)

*E.coli* K1

*Listeria monocytogenes* -

Coagulase negative staphylococci - (premature infants)

*Candida albicans* (Fungus) (premature infants)

Prototype - Group B streptococci are Gram positive, encapsulated organisms, common commensal flora of women of childbearing age. During or immediately prior to birth, the neonate aspirates contaminated amniotic fluid resulting in colonization of the respiratory tract and stomach. In the absence of protective antibody (IgG) - infants (usually following birth complications - prolonged rupture of membranes or associated with prematurity, and/or low birth weight) become bacteremic and occasionally develop meningitis. Thus, organisms that are part of the mother’s vaginal flora AND have the capacity to colonize and cause bacteremia are associated with neonatal meningitis.

*E.coli* capsular type K1 - (Gram negative rod - common commensal flora of the gut) has a capsular antigen that contains sialic acid in a linkage common to human glycosylated proteins. Thus, it is not especially antigenic and many adults lack specific IgG for the K1 capsular antigen. Maternal colonization with K1 *E.coli* is associated with a much higher incidence of bacteremia and meningitis (although it is still rare) than colonization with other strains.

Figure 1

MICROBIOLOGY/INFECTIOUS DISEASES

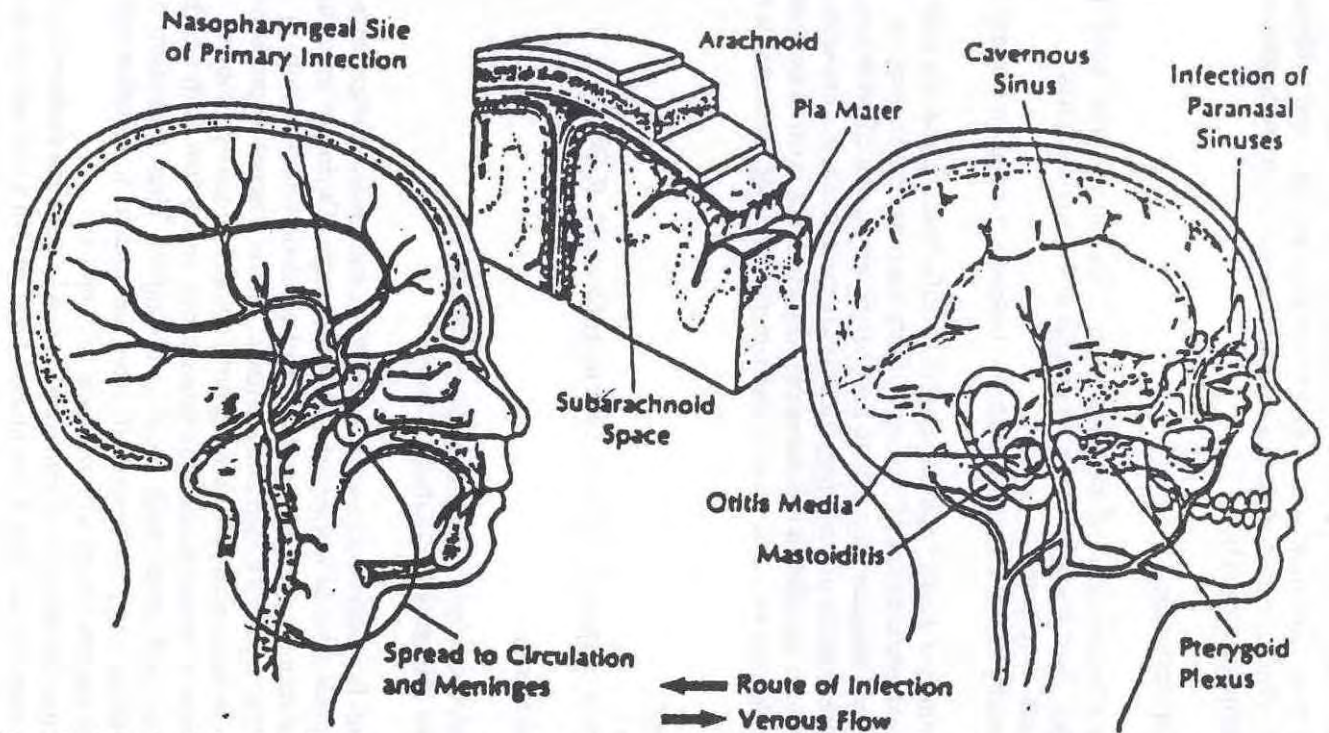


Fig. 1. Bacterial meningitis may develop following nasopharyngeal infection when organisms enter general circulation and spread to brain (*left*). Less often, organisms spread directly through bone to leptomeninges from in-

fecting sinuses and mastoid, or from middle ear via inner ear. Sluggish circulation in venous channels draining infected sites can also carry organisms to the leptomeninges (*right*).

*Listeria monocytogenes* is a Gram positive rod, that is catalase positive and has a characteristic tumbling motility. These organisms are widespread in nature and frequently contaminate food that has been fertilized with manure. Food born transmission is extremely common and outbreaks of *L. monocytogenes* infection have been associated with contaminated Mexican style soft cheeses and other dairy and poultry products.

Very small premature infants are at risk for bacteremia due to normal commensal skin flora - coagulase-negative staphylococci. High grade bacteremia can also be associated with meningitis.

Infants - children - *S. pneumoniae*  
*N. meningitidis*  
*H. influenzae* type B (unvaccinated populations)

These are all encapsulated organisms that require specific IgG for efficient phagocytosis. Infants acquire maternal IgG passively and lose it over the first 6 months - 1 year of age. They then acquire their own IgG repertoire over the next few years, leaving a window (approximately 6 months- 2 years or longer) when they are at increased risk for both bacteremia and meningitis due to these common encapsulated bacteria. Organisms are acquired by direct contact (droplets).

Adults - *N. meningitidis*  
*S. pneumoniae*

Those at risk lack specific IgG to facilitate phagocytosis, or lack splenic function which is important in clearing encapsulated organisms from the blood. Patients with anatomical defects enabling organisms in the respiratory tract to gain access to the CNS are also at higher risk for pneumococcal meningitis. These would include fractures of the cribriform plate and other basilar skull fractures. In the absence of specific IgG, complement is an alternate means of opsonizing these organisms. Patients with complement deficiency are at increased risk of meningococcal disease.

### 3. Pathogenesis and host immune response -

Organisms can reach the central nervous system by two major routes: the most common is hematogenous route and the other is by extension from infection adjacent to the nervous system. Figure 1 illustrates the anatomy of the nervous system with reference to meningitis.

#### **Colonization**

Bacteria adhere to nasopharyngeal cells with specific surface structures—e.g., *Neisseria meningitidis* organisms bind to nasopharyngeal cells and are transported across the non-ciliated columnar cells within a vacuole and gain access to the blood stream.

*S. pneumoniae* and *H. influenzae* type B similarly attach to specific glycoconjugate receptors on the epithelial surface. Natural antibodies of the IgA type in mucosal secretions may inhibit adhesion of microorganisms. Such antibody is due to cross-reactive antigens of nonpathogenic strains and pathogens. Many pathogenic bacteria, however, produce **IgA proteases** which cleave IgA in the hinge region of the molecule. These bacteria reach the bloodstream and overcome host defense mechanisms. Their polysaccharide capsules are a major virulence factor, allowing the organisms to resist classical complement bactericidal activity and neutrophil phagocytosis.

The factors which cause bacterial invasion of the subarachnoid space are not fully understood. Cells in the choroid plexus and cerebral capillaries express receptors for bacteria and allow transport of bacteria into CSF. Outer membrane proteins of bacteria as well as lipopolysaccharide (Gram negative organisms) and teichoic acid (Gram positive organisms) also are important in evoking a host inflammatory response. Group B streptococci (cause meningitis in infants) have been shown to recognize specific meningeal receptors and are internalized in glial endothelial cells, where they are relatively protected from the host immune response (and many antibiotics).

### ***Inflammation in the CNS***

Once inside the subarachnoid space, bacterial proliferation is unopposed: there is virtually no complement, immunoglobulin levels are very low and there are no resident macrophages for surveillance. Bacteria elicit a profound inflammatory response, which causes most of the pathology found in meningitis.

The response to cell wall fragments, peptidoglycan, and teichoic acid triggers an inflammatory cascade. In response to the bacterial products endothelial expression of selectins (ELAM-1, endothelial leukocyte adhesion molecule) is up-regulated, followed by an increase in the expression of the integrin ICAM-1 and CD14. Thus, leukocytes are attracted to the area and migration of PMN's across the endothelium is stimulated. For Gram negative organisms, such as *Haemophilus* or *Neisseria*, LPS triggers TNF- $\alpha$  and IL-1 expression, which serves to activate several classes of inflammatory cells and further increases leukocyte binding to the endothelium via LAM-1.

Activated leukocytes within the CSF secrete a number of products which are either directly toxic to the surrounding tissue themselves (elastase, reactive oxygen intermediates) or promote pathological changes in the CSF (leukotrienes, vasoactive lipid autocoids [arachidonates]). The endothelial barrier is perturbed, causing interstitial edema, impaired resorption of CSF, and loss of the usual autoregulation of CNS blood flow (Fig. 2). The amount of inflammation is directly related to the clinical presentation. The severity of bacterial meningitis due to *H. influenzae* type B, for example, can be correlated with the levels of TNF found in the CSF.

These derangements in the blood-brain barrier result in changes in the usual components of the CSF. The intracranial pressure is increased as a result of both vasogenic edema, from increased vascular permeability (due to the effects of arachidonic acid metabolites which affect the membranes of the neuronal cells), and cytotoxic cerebral edema. CNS metabolism of glucose is increased with increased production of lactate.

Bacterial meningitis also produces effects on blood vessels in the subarachnoid space with resulting vasculitis, vessel narrowing, thrombosis, and ischemia or infarction of the brain. CSF outflow resistance is elevated and inhibits CSF flow from the subarachnoid space to the dural sinuses.

Much of our understanding of the pathophysiology of meningitis has been obtained using animal models of *S. pneumoniae* meningitis and from clinical studies of children with *H. influenzae* type B meningitis which was extremely common until the introduction of the vaccine directed against the type B capsular antigen in 1992. It was recognized that the presence of anti-capsular antibody would prevent the high grade bacteremia necessary to enable infection of the meninges. Thus, the virtual eradication of *H. flu* type B meningitis has been achievable based on the development of an effective vaccine, which was possible by understanding the pathogenesis of this once very common infection.

(See Figure 2 on next page.)

**Specific pathogens -**

***NEISSERIA MENINGITIDIS***

*N. meningitidis* is a human pathogen which can cause sporadic disease (type B) or epidemics (types A and C). Strains of types D, X, Y, W135, 129E also cause meningitis. Disease due to *N. meningitidis* occurs in two peaks; infants less than 1 year of age and in the elderly.

Organisms attach to the epithelial cells of the nasopharynx in patients with and without pre-existing antibody. The bacteria are taken up by receptor-mediated endocytosis and delivered to the basolateral side of the epithelial cell, where they enter the bloodstream. Immune individuals who have specific anticapsular antibody, usually from colonization by *N. lactamica* strains (commensal flora which elicit a protective antibody response), do not become ill. Non-immune individuals can develop bacteremia and meningitis. An adult who is immune can be colonized with meningococci without becoming infected, since he has antibody. He introduces the organisms into the household, exposing non-immune children, usually in the winter months, when ventilation is poor and individuals crowd together. The military setting is similar: a seasoned soldier who has antibody becomes a carrier and transmits the organism to recruits in his barracks. When the carrier state exceeds 30 percent, occasional cases occur in individuals without natural immunity. Since the *Neisseria* organisms will be present in aerosols formed by coughing and individuals are in close contact with each other, colonization will occur.

Bacterial factors which aid in invasion include an IgA protease and the expression of sialylated glyco-conjugates which mimic neuronal adhesion molecules and thus do not trigger an appropriate protective antibody response. This is particularly true for the type B capsule, which fails to elicit a protective antibody response.

Host factors which predispose toward meningococcal disease include factors which promote bacterial colonization, such as antecedent viral infections, poor living conditions, facilitating the spread of organisms to non-immune individuals such as young children, or the military setting. In addition, *N. meningitidis* infection is more common in patients who lack the higher components of complement, (C5-9) which are critically important in clearing the organism from the blood.

Figure 2

MICROBIOLOGY/INFECTIOUS DISEASES

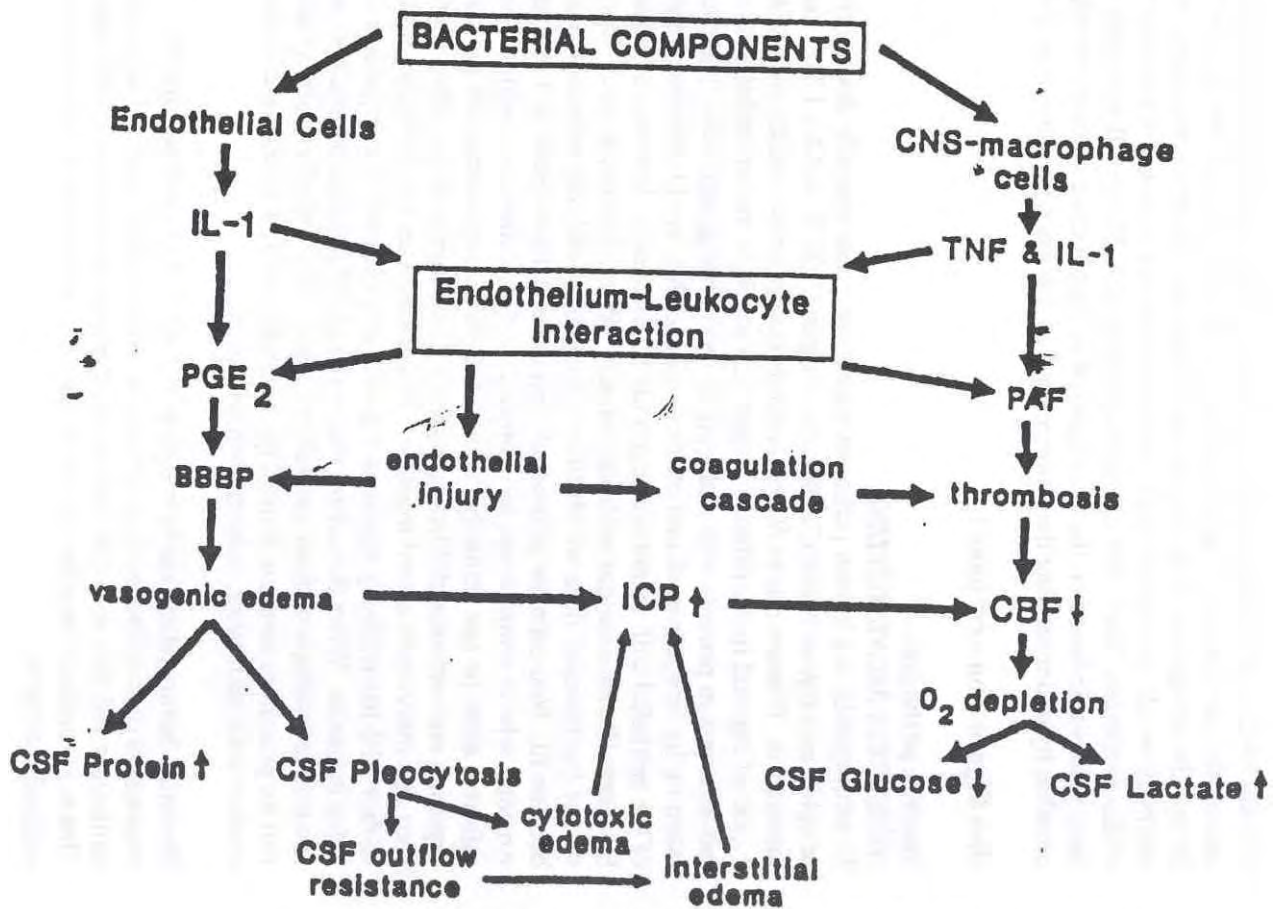


Fig. 2. Hypothetical schema of pathophysiologic events that occur during bacterial meningitis. CBF, cerebral blood flow.

### **Vaccines**

*N. meningitidis* vaccine contains types A, C, Y, and W135. This vaccine is recommended for individuals at high risk of disease, such as asplenic individuals or those with deficiencies of terminal components of complement, travelers to endemic areas, military recruits, and those exposed to certain types of outbreaks, e.g., those in schools (college freshmen). There is currently no effective vaccine against type B - which has an antigenic structure much like host neuronal tissue and hence, is not especially antigenic.

### ***STREPTOCOCCUS PNEUMONIAE***

Pneumococcal infections such as pneumonia, otitis, and sinusitis are very common but only rarely give rise to pneumococcal meningitis. Instead, pneumococcal bacteremia is usually the antecedent infection and may be coincident with the clinical symptoms associated with bacterial meningitis. Specific antibody directed to the capsular carbohydrate is critical in the host response. Patients with impaired splenic function (SS disease for example) or defects in polymorphonuclear leukocytes are at increased risk for pneumococcal meningitis. As detailed above, organisms recognize receptors on the meninges and trigger inflammation. Cell wall peptidoglycan fragments are highly immunostimulatory and several bacterial components or virulence factors all contribute to the pathophysiology of this disease.

Pneumococcal Vaccines - There is a 23-valent pneumococcal vaccine - based on the carbohydrate antigens of the capsule, that is relatively effective in adults and older children. In infants and young children, there is a relatively new **conjugate vaccine**, in which seven common pneumococcal antigens are linked to protein carriers to elicit a T cell dependent Ab response. This is expected to decrease the incidence of pneumococcal meningitis in the vaccinated population.

### **Clinical Presentations of Meningitis**

**Neonates** - Neonates and young infants lack Ab, and have defects in PMN chemotaxis and perhaps bacterial killing. They do not have a highly developed blood-brain barrier, hence infections that are associated with high grade bacteremia can cause meningitis. The clinical presentation of bacterial meningitis, in an infant with an open fontanelle and sutures, may be entirely non-specific. Fever is often but not always present; lethargy, irritability and eventually vomiting and seizures are common presenting signs.

### **Children and adults -**

Fever, headache, lethargy, vomiting, and seizures are frequent findings in children with meningitis. Stiff neck and back pain are also common. Some patients will look flushed but have no neurological signs and only minimal neck stiffness. Others will have altered consciousness, stiff neck, and Kernig and Brudzinski signs indicating meningeal irritation. In adults, severe headache is common as well as altered mental status. As bacterial meningitis is associated with very significant morbidity and mortality, and can be readily treated, the astute clinician should try to make a diagnosis promptly.

### **Laboratory Diagnosis of Meningitis**

The peripheral WBC count is usually elevated in bacterial meningitis. The diagnosis of meningitis ultimately rests on CSF findings. In classic bacterial meningitis, the CSF is cloudy, due to neutrophils, the protein is elevated, and the glucose is low.

Normal CSF is colorless and clear. A yellowish color (xanthochromic) is due to breakdown of red cells or an increased amount of protein. CSF is grossly turbid if there are  $\geq 200$  WBC.

Cerebrospinal fluid of normal children and adults contains fewer than 5 cells/mm<sup>3</sup> and some clinicians consider even a single PMN abnormal. Monocytes and lymphocytes may be present, particularly in treated bacterial meningitis, and are more commonly associated with mycobacterial and viral infections.

The ratio of glucose in CSF to that in blood is normally 0.6 (if the blood glucose is between 70 and 120 mg/dl). In general, CSF glucose levels  $\leq$  half the serum glucose levels are consistent with bacterial meningitis, due to a general disturbance of the blood brain barrier (NOT BACTERIAL CONSUMPTION OF GLUCOSE).

CSF protein levels are normally < 50 mg/dl but are higher in some very elderly individuals. Elevations of CSF protein concentrations occur in many conditions and do not represent a specific diagnostic clue to meningitis. The presence of bacteria in the CSF will establish a diagnosis, but in many instances they are present in numbers too small to be seen readily since more than 10<sup>4</sup>CFU/ml must be present to be visible after Gram staining.

The CSF cell count is usually helpful, and chemistries (protein and glucose) should be determined. A morphologic study which includes total cell count and differential count is performed, and sugar concentration (with a simultaneous blood sugar) and protein content are determined.

Latex agglutination tests, by detecting the capsular antigen present in the CSF, are available for the encapsulated organisms. However, the sensitivity of these tests has been disappointing.

**Sequelae of meningitis** - While some individuals may recover completely from bacterial meningitis, the amount of inflammation, vascular insults and parenchymal damage will all contribute to long term sequelae. Infants and children with bacterial meningitis are at significantly increased risk for developmental, hearing and learning disorders as well as more severe sequelae such as hemiplegias, deafness and blindness.