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Community-acquired Bacterial Meningitis in Adults

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BACTERIAL MENINGITIS

INTRODUCTION

Bacterial meningitis is an acute purulent infection within the subarachnoid space that is followed by a CNS inflammatory reaction that causes coma, seizure activity, increased intracranial pressure and ischemic infarcts. The meninges, the subarachnoid space and the brain parenchyma are all involved in the inflammatory reaction; hence meningoencephalitis is most appropriate term[1].

It can strike at any age with a predilection for the very young and very old. Meningitis can afflict those with no past medical history or patients with AIDS or cancer.

Meningitis is a devastating neurologic disease of infancy, childhood and adulthood. Despite effective anti-microbial therapy, the morbidity and mortality from this infection remain high. Over the last 10 years our increasing understanding of patho-physiology of the neurologic complications of meningitis has turned our attention not only to treating infection, but also to anticipating and treating the neurologic complications with the hope of eventually preventing them. Despite effective anti-microbial therapy, the care of these patients continues to be difficult, as coma, seizure activity and stroke complicate the course of the disease.

History of Meningitis

Robert Whytt initially described symptoms and signs of tuberculous meningitis in 1768 and called this "dropsy in the brain". He considered the collection of fluid in the ventricles as the disease itself, most likely because at the end of the 18th century the ventricles were regarded as the seat of the soul. Physicians at that time attributed somnolence and coma to a collection of fluid in the "seat of the soul" (i.e. "acute hydrocephalus"). By the end of 18th century, investigators were beginning to shift their attention from the ventricles to the meninges.

Meningococcal meningitis, or as it was previously called, "cerebrospinal fever", was first described by Gaspard Vieusseux on a small outbreak in Geneva in 1805.

The first patient on whom Heinrich Quincke performed a lumbar puncture reportedly had meningococcal meningitis, and Quincke is credited with describing the technique of lumbar puncture (1891), though Heuber was the first to recover "biscuit-shape" meningococci from the spinal fluid. Anton Weichselbaum is credited with identifying the meningococcus in 1887, and describing it as the Diplococcus intracellularis meningitides.

In the late nineteenth century, meningitis was treated by drainage of CSF by repeated lumbar puncture. At the turn of the century, Jochmann in Germany and Flexner in New York began experiments that demonstrated the protective effects of anti-meningococcal serum in experimental meningococcal infections in animals.

The discovery of antibacterial activity of sulfonamides in the early 1930s ushered in the antibiotic era. Francis Schwentker is credited with the first demonstration of a cure of meningococcal meningitis with sulfonamide therapy. In the early part of the twentieth century, the other two major pathogens that cause meningitis today, *Streptococcus pneumoniae* and *H. influenzae*, had not caused epidemics comparable to those

seen with *Neisseria meningitides*[3]. Myco-bacterium tuberculosis and *N. meningitides* were the two most common causative organisms of meningitis. Flemming discovered penicillin in 1931.

Pathogenesis and Pathophysiology

The bacterial meningitis occurs when bacterial virulence factor overcomes host defense mechanisms that normally protect against central nervous system infection in the subarachnoid space[4].

The most common bacteria that cause meningitis, *H. influenzae*, *N. meningitides* and *S. pneumoniae* initially colonize the nasopharynx by attaching to the nasopharyngeal epithelial cells. In order to attach the mucosal epithelial cells, *H. influenzae, N. meningitides* and *S. pneumoniae* secrete IgA proteases that breakdown the mucous barrier allowing bacterial attachment to the epithelium. The organism then attaches to the nasopharyngeal epithelial cells via an interaction between bacterial surface structures, such as finger like projections (pili) and host cell surface receptors. After the bacteria have successfully attached to the nasopharyngeal epithelial cells, they are either carried across the cell in membrane bound vacuoles to the intravascular space or, as in the case of H. influenzae, create separations in the apical tight junctions of columnar epithelial cells and invade primarily by an intercellular route[5].

Once the bacteria gain access to the blood stream, they are successful in avoiding phagocytosis by neutrophils because of the presence of a polysaccharide capsule. In addition, the polysaccharide capsule allows the organism to evade the complement pathway—the chief initial host defense against bacteremia. Bacteria that are able to survive in the circulation then enter the CSF through the choroids plexus of lateral ventricles, and other areas of altered blood brain barrier permeability. Cells in the choroid plexus and cerebral capillaries possess receptors for adherence of specific bacterial cell surface structures that allow for attachment and adherence of meningeal pathogens[5].

Once meningeal pathogens gain access to the CSF, there are insufficient complement components, immunoglobulin concentrations and neutrophils in the subarachnoid space to retard their rapid multiplication. The CSF is an area of impaired host defense. Normal uninfected CSF contains no phagocytic cells, has a low protein concentration, contains no IgM, and has low levels of C_3 and C_4[6]. The opsonization of bacteria by complement and immunoglobulins is an essential step for phagocytosis by neutrophils, however, opsonic activity is virtually undetectable in the CSF of normal subjects, and is insufficient in the CSF of patients with meningitis for bacterial lysis or opsonization. Like complement, immunoglobulin concentrations are low in the CSF of uninfected individuals, and increase only slightly in the course of bacterial meningitis. This typically occurs late in the disease process. As a result of the lack of opsonization of bacteria by complement and immunoglobulins, the phagocytosis of bacteria by leukocytes is inefficient and consequently the multiplication of bacteria in the subarachnoid space rapidly overcomes the clearance mechanisms of the CSF.

The mechanism by which meningeal inflammation develops is now understood. It is not simply the presence of bacteria in the subarachnoid space that induces the inflammatory response, but rather the presence of bacterial cell wall components due to lysis of bacteria that induces the inflammatory response. The lipo-oligosaccharide (LOS) component of the *H. influenzae* type b (Hib) cell wall, and cell wall components of the pneumococcus, specially lipoteichoic acid, have been demonstrated in experimental models of meningitis to induce meningeal inflammation. These are encapsulated pathogens, but the capsular polysaccharide does not appear to contribute to the ability of these organisms to produce meningeal inflammation. Gram-negative bacteria have lipopolysaccharide (LPS) molecules (endotoxin) attached to their outer membranes. The endotoxin of *H. influenzae* has a shorter saccharide chain, thus designation LOS (lipo-oligosaccharide).

The LPS molecule, or endotoxin, also appears to play a significant role in the alteration of the blood-brain barrier permeability.

The effect of antimicrobial therapy on CSF endotoxin levels was measured in children with H. influenzae meningitis. There was a significant increase in levels of free endotoxin in CSF after the institution of therapy with bacteriolytic antibiotics. This increases in CSF free and endotoxin was accompanied by a significant increase in the levels of CSF lactate and LDH white cell origin and decrease in the level of CSF glucose suggesting a shift to anaerobic glycolysis by the brain.

Bacterial cell wall components stimulate the production of the inflammatory cytokines, interleukin-1 and tumor necrosis factor (TNF), which subsequently induce meningeal inflammation. The presence of TNF in CSF appears to be specific for bacterial meningitis. In three large studies, the positivity was 75% in cases of bacterial meningitis, whereas none of the patients with viral meningitis had TNF positivity in CSF[8-9]. Arditi et al[10] found a significant association between admission

CSF TNF concentrations >1000 pg/ml and the development of seizures, and hypothesized that CSF TNF activity may contribute to seizure activity through local metabolic and vascular effects. Waage, et al[11] found a strong correlation between admission serum TNF levels and mortality in patients with meningococcal meningitis; patients with serum TNF concentrations >140 pg/ml died.

Interleukin-1 may have a role in the altered level of consciousness and the production of fever in bacterial meningitis. It has been demonstrated that IL-1 facilitates slow wave sleep and produces fever by its effect on the hypothalamus**.** The infants and children with initial CSF IL-1 beta concentrations ≥ 500 pg/ml were more likely to have neurologic sequelae than the infants and children with lower CSF IL-1 beta concentration. In addition, the CSF IL-1 beta concentration correlated directly with CSF leukocyte count, lactate, protein and TNF concentration, and inversely with the CSF glucose concentration.

Other inflammatory cytokines have a role in the induction of meningeal inflammation. TNF alpha and IL-1 are potent inducer of the synthesis and release of platelet activating factor (PAF) from various cells including polymorphonuclear leukocytes, macrophages/monocytes, endothelial cells and neuronal cells. Increased intracranial pressure in bacterial meningitis is due to a combination of cerebral edema, an increased volume of CSF, and an increase in cerebral blood volume. The cerebral edema that develops in the course of bacterial meningitis is due to a combination of vasogenic, cytotoxic and interstitial edema. Vasogenic edema is primarily a consequence of the increased blood brain barrier permeability. Interstitial edema is due to diminished resorption of CSF at the level of the arachnoid granulations in the dural sinuses. The fibrinous exudates in the subarachnoid space interferes with the resorptive function of the arachnoid granulations. As resorption is obstructed, CSF dynamics are altered, and there is a trans-ependymal movement of fluid from the ventricular system into the brain parenchyma[12].

An additional contributing factor to interstitial edema is an increased CSF outflow resistance due to the accumulation of a purulent exudates in the basal cisterns. Cytotoxic edema develops secondary to swelling of the cellular elements of the brain as a result of toxic factors released from neutrophils and bacteria. The hyponatremia which occurs secondary to secretion of anti-diuretic hormone also contributes to the pathogenesis of cytotoxic edema, by producing hypotonicity of extracellular fluid and increasing the permeability of the brain to water. Intracranial pressure is maximally elevated within the first 24-48 hours of hospitalization[13].

Abnormalities in cerebral blood flow in bacterial meningitis are due to increased intracranial pressure, loss of auto-regulation, narrowing of large arteries at the base of the brain, vasculitis, and thrombosis of cerebral arteries, veins and major sinuses.

Although there is an early hyperemia in bacterial meningitis, soon thereafter, cerebral blood flow begins to decrease and this contributes significantly to severe neurologic complications.

The most common cerebrovascular complication of bacterial meningitis appears to be narrowing of the large arteries at the base of brain. The arterial narrowing is due to several etiologies, including:

- Encroachment on the vessel by the purulent exudates in the subarachnoid spaces and in the cisterns;
- Infiltration of the arterial wall by inflammatory cells with intimal thickening;
- Subintimal infiltration of the arterial wall (vasculitis);
- Vasospasm[14,15].

Epidemiology

There has been a change in the spectrum bacteria causing community acquired bacterial meningitis in recent years. *H. influenzae*, *N. meningitides* and *S. pneumoniae* form of meningitis having worldwide distribution, occurring mainly during the fall, winter, and spring, and predominating in males. Before 1990, these three most common bacterial pathogens accounted for > 75 percentage of all cases[16]. However, in the past few years, after the introduction of *H. influenzae* vaccine, the incidence of *H. influenzae* meningitis has dropped down dramatically, and today the most common cause of bacterial meningitis in North America is S. pneumoniae. Meningitis in adults is primarily due to meningococcal and pneumococci. *N. meningitides* is the only major cause of epidemics of bacterial meningitis. Recent trends indicate an increase in the proportion of cases due to gram negative bacilli and *Listeria monocytogens*[17].

The yearly incidence rate (per 100,000) of the responsible pathogens now are as follows: *Strep. pneumoniae*, 1.1; *N. meningitides*, 0.6; group *B. streptococcus*, 0.3; *Listeria monocytogens*, 0.2; and *H. influenzae*, 0.2.

Etiologic Organism

Neonates	:	Group B streptococci and gram-negative bacilli, mainly *Escherichia coli*
Children	:	*H. influenzae* type b (Hib), *N. meningitides* and *S. pneumoniae*
Adults	:	*S. pneumoniae* and *N. meningitides*
Older adults (> 50 year)	:	*S. pneumoniae* and enteric gram-negative bacilli
Neurosurgical patients	:	Staphylococci and gram-negative bacilli

Immunocompromised Patients

a. Neutropenia (< 1000/mm^3) (Chemotherapy, radiotherapy and aplastic anaemia): *Pseudomonas aeruginosa, Enterobacter, Listeria monocytogens, E. coli, Klebsiella pneumoniae, S. aureus* and Coagulase negative staphylococci
b. Immunoglobulin deficiency (CLL, multiple myeloma and splenectomy): *S. pneumoniae, H. influenzae* and *N. meningitides*
c. T-lymphocyte and macrophage defects (AIDS and organ transplant recipients): *Listeria monocytogens.*

Clinical Presentation of Bacterial Meningitis

The characteristic symptoms and signs of bacterial meningitis are headache, fever, nuchal rigidity, photophobia, vomiting and lethargy or an altered level of consciousness, but the clinical symptoms and signs may vary depending on the age of the patient and the duration of the illness prior to presentation.

The symptoms and signs of bacterial meningitis in the neonate are often subtle and typically non-specific and include fever (50%), lethargy, poor feeding, respiratory distress, irritability, vomiting and diarrhoea, seizures (40%) and bulging fontanel (30%)[18]. Very low birth weight and premature infants are at risk for late onset sepsis and meningitis and, in the infants, the initial clinical presentation of meningitis is non-specific and typical of sepsis. The predominant findings are apnoea, bradycardia, abdominal distention and seizures[19]. Fever is present at sometime during the illness in most infants with meningitis, but may not be present in the neonate and premature infant. The temperature response to invasive bacterial infection in the premature infant is often that of hypothermia rather than fever.

In children and adults, the typical symptoms and signs of bacterial meningitis are fever, headache, vomiting, photophobia, nuchal rigidity and lethargy, confusion or coma.

Meningitis in children typically presents as either a subacute infection that gets progressively worse over several days and was preceded by a URI or otitis media, or as an acute fulminent illness that develops rapidly in few hours. The clinical presentation of bacterial meningitis may be altered slightly by prior antibiotic therapy in the pediatric age group. Children who have been treated with oral antibiotics prior to the diagnosis of meningitis may have a longer duration of symptoms, more physical findings of ENT infections and less of a temperature elevation than children who have not had prior oral antibiotic therapy. In adults, a URI frequently precedes the developments of meningeal symptoms and should be sought after in the history. The clinical presentation of meningitis in an older adult consists of fever and either confusion, stupor or coma. The presentation of bacterial meningitis in immuno-compromised patients may be either suggestive of a mild infectious illness with headache and fever, or that of a fulminant illness presenting with coma and nuchal rigidity. Neck stiffness is sometimes difficult to interpret in the elderly individual.

Seizures occur in 40% of patients with bacterial meningitis and typically occur in the first week of illness. The majority of seizures have a focal onset, suggesting that focal ischemia from cerebrovascular disease is a major cause of seizure activity in bacterial meningitis. Generalized seizure activity and status epilepticus are due to fever, hyponatremia, anoxia from decrease cerebral perfusion due to increased intracranial pressure, spread from a focal onset to a generalized tonic clonic convulsion or toxicity from antimicrobial agents (imipenem, penicillin). Various presenting symptoms and signs are appended in Table 1.

Table 1: Presenting symptoms and signs in patients with bacterial meningitis[4]

Symptoms and Signs	*Relative Frequency (%)*
Headache	>90
Fever	>90
Meningismus	>85
Altered sensorium	>80
Kernig's sign	>50
Vomiting	35
Seizures	30
Focal neurologic findings	10-20
Papilledema	<1

Differential Diagnosis

The differential diagnosis of headache, fever, focal neurologic symptoms and/or an altered level of consciousness is as under (Table 2).

Investigations

The lumber puncture is an indispensable part of the examination of patients with the signs and symptoms of meningitis or of any patient in whom this diagnosis is suspected. If there is focal deficit with evidence of raised intracranial pressure, then CT scan or MRI brain, looking for mass lesion, is a prudent first step, but in most cases it is not necessary and should not delay the administration of antibiotics. Lumbar puncture should be included in the diagnostic evaluation of infants with possible sepsis. Approximately 20-30 percentages of cases of neonatal sepsis are complicated by bacterial meningitis**.** The risk of iatrogenic meningeal infection due to lumbar puncture in a bacteremic infant is extremely small.

The most serious complication of lumbar puncture is uncal or cerebellar herniation. When the presence of raised intra-cranial pressure is suspected, a bolus dose of mannitol 1 gram per kg of body weight can be given intravenously and lumbar puncture performed 20 minutes later. Approximately 10-12 ml of CSF should be withdrawn from the adult for analysis and the withdrawal of 3-5 ml is recommended in the neonate & child[20].

A pleocytosis is diagnostic. The CSF WBC count ranges from 250 to 100,000 cells per mm^3, but it is usually1000 to 10,000 cells/mm^3. Neutrophils predominate (85 to 95 % of total), but an increasing proportion of mononuclear cells is found as the infection continues, especially in partially treated meningitis. Cell count of > 50,000 cells/mm^3 raise the possibility of brain abscess having ruptured into a ventricle. There may be an increase in CSF total WBC count within 18-36 hours of the initiation of antibiotic therapy.

Table 2: Differential diagnosis

Diseases	*Clinical Presentation*	*Diagnosis*
1. Herpes simplex virus encephalitis	Fever, confusion, change in behavior, headache, new onset focal or generalized seizure, focal neurologic deficits	*CSF:* Lymph. Pleocytosis, RBCs *CT/MRI:* Signal intensity on T2 wt. images in temporal lobe(s) - *EEG*-periodic spike & slow waves in temporal lobe(s)
2. Mass lesion-brain abscess, sub-dural empyema/epidural abscess	Hemicranial / generalized headache, focal deficits, seizure (focal or gen.) +/– fever	*CSF*- Contraindicated *CECT / CEMR* - mass lesion
3. Sub-arachnoid hemorrhage	Explosive severe headache, vomiting, syncope, nuchal rigidity, ophthalmoplegia, focal deficit, altered sensorium	*CSF*: RBCs, xanthochromia *CT* (*non-contrast*): blood in basal cisterns
4. Fungal meningitis	Fever, headache, skin lesions, cranial nerve palsies.	*CSF:* lymphocytic pleomorphosis, Positive cryptococcal antigen.Biopsy skin lesion.
5. Neuroleptic malignant syndrome	History of taking anti-psychotic medicines, fever, rigidity, fluctuating sensorium, autonomic instability	*CSF:* normal *Serum CPK:* markedly elevated *TLC*: 15,000-30,000 cells / mm^3
6. Lyme disease	History of tick bite &/ or erythema chronicum migrans, facial nerve palsy	*CSF:* mononuclear pleocytosis & intra-thecal. anti-borrelia burgdorferi antibody productionSerum: Lyme serology
7. Rickettsial infection	Headache, fever, petechial rash, altered mental status	Biopsy of skin lesions
8. Tuberculous. meningitis	Headache, meningisums, confusion, seizures & coma	*CSF:* lymphocytic pleocytosis, *AFB*, polymerase chain reaction *(PCR)* Chest X-ray: infiltration / military mottling.

The CSF glucose concentration is normally lower than that of serum. The normal CSF glucose concentration is between 45 to 80 mg/dl in patients with a serum glucose of 70 to 120 mg/dl or approximately 65 percentage of serum glucose. CSF glucose concentration below 40 mg/dl is abnormal. Hyperglycemia increases the CSF glucose concentration and its presence may mask a decreased CSF glucose concentration[21]. The CSF glucose concentration is therefore best determined by the CSF : serum glucose ratio. The normal CSF: serum glucose ratio is 0.6. A CSF: serum glucose ratio less than or equal to 0.40 is highly predictive of bacterial meningitis. This value has been shown to be 80 percentage sensitive and 98 percentage specific for bacterial meningitis in children older than 2 months of age[22].

The upper range of normal for the lumbar CSF protein concentration in the adult is 50 mg/dl, and may be as high as 150 mg/dl in the neonate. The normal value for protein concentration in cisternal and ventricular CSF ranges from 13 to 30 mg/dl in adults and from 20 to 170 mg/dl in neonates. An increased CSF protein concentration is typically seen in bacterial meningitis.

An increase CSF lactate concentration in bacterial meningitis was first recognized in 1925[23]. CSF lactic acid concentration has been suggested for clinical use as a aid in differentiating bacterial and tubercular meningitis from viral meningitis. A lactic acid concentration of ≥ to 35 mg/dl has been suggested to be highly predictive of the presence of meningitis of bacterial or tubercular origin[24].

The initial CSF lactic acid concentration has also been demonstrated to have prognostic significance in patient with bacterial meningitis. Patients with the highest initial CSF lactic acid levels were more likely to die or recover with a neurologic deficit than those with lower initial CSF lactic acid levels[25].

In the presence of CSF pleocytosis, a CSF C-reactive protein concentration >100 ng/ml is useful in identifying bacterial meningitis. The CRP has been reported to have a 100 percentage sensitivity and 94 percentage specificity in differentiating bacterial from non-bacterial meningitis in infants (4 weeks & older) and children[26].

Several techniques are available to detect bacterial antigens in CSF including the Phadebact coagglutination (CoA) test, the Directigen latex agglutination (LA) test, counter-immunoelectrophoresis (CIE) and the Limulus amebocyte lysate (LAL) test.

The LA test has a specificity of 100 percentage for Hib and *N. meningitides* and 96 percentage for *S. pneumoniae*. The LAL test is very sensitive in detecting gram-negative bacterial meningitis. The test is reported to have a sensitivity of 99.5% and a specificity of 86-99.8 percentage[27].

Meningococcal Meningitis

Meningitis due to *N. meningitides* is most common in children and young adults. *N. meningitides* meningitis may occur in epidemics (usually due to serogroup A & C). congenital (late component) complement deficiency (C5, 6, 7, 8 & C9) are risk factors for meningococcemia[28]. The typical symptoms of meningococcal meningitis are fever, vomiting, lethargy, neck stiffness and headache. The presence of diffuse erythematous maculo-papular rash resembling a viral exanthem may be an early manifestation of meningococcemia, though these lesions rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes, conjunctiva and occasionally on the palms and soles. A few differences in the clinical presentation of *H. influenzae* and *N. meningitides* meningitis should be emphasized. The presence of petechial rash is highly suggestive of meningococcemia, however, petechae are rarely seen in *H. influenzae*, pneumococcal and staphylococcal meningitis. Other infectious disease that may manifest with a petechial, purpuric or erythematous maculo-papular rash like that of meningococcemia are as follows:

1. *H. influenzae meningitis*
2. *Pneumococcal meningitis*
3. *Enteroviral meningitis*
4. Rocky mountain spotted fever
5. Echo virus type 9
6. *N. gonorrheae* sepsis
7. *Staphylococcus aureus endocarditis*

The term Waterhouse—Friderichsen syndrome historically has referred to an acute fulminating infectious disease with wide spread petechial or purpuric skin lesions, septic shock and death. Meningococci were first isolated from the blood of a man who died of adrenal hemorrhage in 1906. Bilateral massive adrenal hemorrhage was the pathologic hallmark sign of this condition. This syndrome is attributed to fulminating meningococcal septicemia and is reported in 10-20 percentage of the children with meningococcal infection[29].

Therapy of Bacterial Meningitis

Bacterial meningitis is a medical emergency. The first therapeutic measures are directed to sustaining blood pressure and treating septic shock and choosing an antibiotic that is known to be bactericidal for the

established or suspected organism. The choice of the antibiotic depends on the age group of the patient and the ability of the drug to enter the CSF in effective amounts. Treatment should begin while awaiting the results of diagnostic tests and should be changed later according to the findings. The problem arises while differentiating a life threatening illness from self-limiting viral infections. Significantly, a delay in therapy of even a few hours affects the prognosis adversely, and is thus a common reason for malpractice litigation. Outcome analysis of 269 patients with bacterial meningitis found that patients whose prognostic stage did not advance (no development of hypotension, seizures or altered mental status) from initial assessment to the time of antibiotic administration, did not have a worse out come. Conversely, if the clinical stage did advance during that time, adverse outcome was directly correlated with delay in antibiotic administration.

In bacterial meningitis, the permeability of the BBB is increased leading to a high degree of penetrability to many antibiotics like a lactams. The highly lipid soluble antibiotics, like chloramphenicol and rifampicin, have a higher penetration into the CSF even when the meninges are not inflamed.

Urgent hospital admission is mandatory if there is a strong suspicion of meningitis. The indications for admission are—sign of meningeal irritation, impaired conscious level, petechieal rash, febrile or unwell with recent fit, any illness specially headache and recent history of close contact with a patient of meningococcal infection. Worldwide, there is an increasing rate of susceptibility to penicillin and third generation cephalosporins among pneumococci. Vancomycin has been recommended for inclusion in all suspected cases of bacterial meningitics in United States[30].

Antibiotic Therapy

The choice of the antibiotic depends on the age group of the patient (Tables 3, 4 and 5) and the ability of the drug to enter the CSF in effective amounts[31].

Table 3: Empirical therapy before pathogens are identified

Patient group	*Antibiotics*
A) *Immuno-competent*	Ampicillin + cephalosporin/
• Neonates	aminoglycoside Third generation
• Infants and children	cephalosporin + vancomycin Third
• Adults	generation cephalosporin + vancomycin
• Elderly	Ampicillin + third generation cephalosporin
B) *Immuno-compromised*	Ampicillin + Ceftazidine
C) *Head trauma, CSF shunt or nosocomial*	Vancomycin + Ceftazidine

Table 4: Empiric therapy of bacterial meningitis in immunocompromised patients

Type of immune abnormality	*Antibiotics*
A. *Neutropenia (< 1000/cmm) due to*	
• Chemotherapy	Ceftriaxone or
• Radiotherapy	Cefotaxim or
• Leukemia	Ceftazidine Plus
• Aplastic anemia	Vancomycin
B. *T-lymphocyte & Macrophage Defects due to:*	Ampicillin
• AIDS	
• Organ transplantation	
• Lymphoma	
• Adenocorticosteroid therapy	
C. *Immunoglobulin Deficiency due to:*	Ceftriaxone or
• Chronic lymphocytic leukemia	Cefotaxim
• Multiple myeloma	
• Splenectomy	

Dosage:	Ampicillin	100 mg/kg every 8 hours
	Cefotaxime	2 grams IV every 6 hours or 50 mg/kg IV every 6 hours for children < 18 years.
	Ceftriaxone	2 grams IV every 12 hours Or 50-100 mg/kg IV every 12 hours.
	Ceftazidin	2 grams IV every 8 hours
	Vancomycin	500 mg every 6 hours
	Penicillin G	20-24 million U/day IV (divided doses every 4 hours).

The duration of antibiotic therapy (Table 5) depends on type of organism isolated[32].

Table 5: Duration of antibiotic therapy

Pathogen	*Suggested Duration (in days)*
H. influenzae	7
N. meningitides	7
S. pneumoniae	10-14
L. monocytogens,	14-21
Group B streptococci	14-21
Gram-negative bacilli (other than *H. influenzae*)	21

Majority of children with bacterial meningitis are hyponatremic with serum sodium concentrations less than 135 mEq/L at the time of admission. The degree and duration of hyponatremia in children with bacterial meningitis correlate significantly with the complications and neurologic sequelae of this disease[33]. Hyponatremia is due to the syndrome of inappropriate ADH secretion (SIADH) which result in free water retention and delusional hyponatremia. The incidence of this complication in childhood bacterial meningitis ranges from 28-88 percentage[34,35].

The diagnostic criteria for SIADH are:

a) Hyponatremia with hypo-osmolol serum;
b) Inappropriately concentrated urine;
c) Urinary sodium of > 25 mEq /L;
d) Absence of renal or endocrine disease.

The primary treatment of SIADH is fluid restriction. The initial rate of IV fluid administration is limited to approximately one half of normal maintenance requirements or 800-1000 ml/m^2/24 hours.

Role of Steroids

Inflammatory cytokines like interleukin-1, 6 and tumor necrosis factor-alpha increase in the CSF in response to release of biologically active bacterial cell wall products. These can exacerbate inflammation and further damage BBB. On the basis of above evidence, adjunctive glucocorticoid therapy has been tried. In four prospective, placebo controlled trials in children more than 2 months old, adjunctive dexamethasone therapy resulted in reduce audiologic and neurologic sequelae.[36] However, most of the children were infected with *H. influenzae* and the benefits of glucocorticoid therapy may not apply to children infected with other organisms especially *S. pneumoniae*. The benefit of adjunctive glucocorticoid therapy in adults is even less clear[33]. It may decrease the CSF penetration of some antibiotics like vancomycin. Therefore dexamethasome therapy is recommended in children more than 2 months of age who have bacterial meningitis, presumably *H. influenzae*, i.e. children not vaccinated against *H. influenzae* or those with gram-negative cocco-bacilli on gram's stain of CSF. Dexamethasone is given in a dose of 0.15 mg/kg given IV, every 6 hrs. for 4 days. In adults use of glucocorticoid is limited to those with a high concentration of bacteria in CSF (those with a positive gram's stain of CSF) and evidence of increased intracranial pressure. A dose of 0.15 mg/kg IV every 6 hrs. for 4 days is recommended[33].

Prophylaxis

Chemoprophylaxis

The occurrence of meningitis in a given patient always raises concern about the spread of meningitis in the family members or other close contacts. Out breaks of meningitis within families are uncommon although nasal carriage occurs frequently with *S. pneumoniae*, *N. meningitides* and *H. influenzae*. Antimicrobial chemoprophylaxis is considered in cases of *N. meningitides* and *H. influenzae* for eliminating nasal carriage[37].

Chemoprophylaxis should be considered in medical and paramedical staff treating such patients and also in the individuals staying in same dwelling as index case of close family members and close associates (Table 6). Chemoprophylaxis should be initiated as soon as possible within 24 hours of identification of the index case. Prophylactic treatment beyond 14 days after the case is identified is of little or no value.

The most employed regimen for prophylaxis is rifampin, ceftriaxone or ciprofloxacin. Rifampin in a dose of 600 mg 12 hourly for two days for adults and 10 mg/kg 12 hourly for two days in children more than one month old. For infants (less than one month old) the recommended dose is 5 mg/kg 12 hourly for two

Table 6: Chemoprophylaxis for meningococcal meningitis

Drug	*Doses Adult*	*Children*	*Pregnant Women*
A. Rifampin	600 mg BID for 2 days	*Infants:* 5 mg / kg BID for 2 days > *one month:* 10 mg / kg BID for 2 days	Contraindicated
B. Ciprofloxacin	500 mg single dose	Relative contraindication	Contraindicated
C. Ceftriaxone	250 mg IM, single dose	125 mg IM, single dose	Indicated

days. Rifampin is contraindicated in pregnancy because of teratigenicity. Ceftriaxone is given in the dose of 250 mg IM (one dose) for adults and 125 mg IM (one dose) for children. Ciprofloxacin can be given as a single oral dose of 500 mg. It is contraindicated in children below 18 years of age and pregnant or lactating mothers because of the increased risk of cartilage damage.

The WHO states that minocycline and spiramycin are also acceptable alternatives for chemoprophylaxis.

Immunoprophylaxis

The polysaccharide vaccines for meningococcal meningitis have been available for more than 30 years. The vaccine covers serogroups A, C, Y, and W- 135 in variety of combinations. A vaccine against serogroup B has been difficult to produce because of its poor immunogenicity. This is probable because of the likeness serogroup *B. antigens* share with fetal neurocrest cells.

Overseas travellers that may be visiting areas with periodic epidemics or areas that are hyperendemic are recommended to receive the vaccine at least 10 days prior to departure.

The polysaccharide vaccine used in adults and children is given as a single 0.5 ml dose. After 7 to 10 days, protective levels of serum antibodies are observed. Adverse effects are low, with the most common being pain and redness at the site of the injection which lasts one to two days. Some patients may experience transient fever. Contraindication to the vaccine are previous anaphylactic reaction to the vaccine or its components. Revaccination after 3 to 5 years is recommended if the indication persists. The Centers for Disease Control and Prevention (CDC) does not advise altering the recommendations of vaccinations in cases of pregnancy. The vaccine has been found to be safe and efficacious in pregnant women, with antibody level in the baby falling after birth within first few months[38].

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