CNS infections 1

Bacterial meningitis

Sources /tables and figures:
Harrisons Infectious diseases 2nd ed Ch 31
Oxford Handbook of Infectious diseases and microbiology 2nd ed Ch 19
Acute meningitis

• Definition:

• Acute meningitis is a syndrome characterized by the onset of meningeal symptoms and cerebral dysfunction.

• 1) meningeal symptoms are: headache, neck stiffness, vomiting, photophobia

• 2) cerebral dysfunction leads to confusion, loss of consciousness.

• Acute means it happens over hours to days.

• It is identified by an abnormal number of white blood cells in the CSF.
• Bacterial meningitis: meningitis caused by an acute purulent infection within the subarachnoid space.
• Bacterial meningitis is associated with Encephalitis, Brain Abscess, and Empyema inflammatory reaction (next lecture)
• All these conditions may result in a collection of similar symptoms such as:
  • - decreased consciousness
  • - seizures
  • - raised intracranial pressure (ICP)
  • - stroke.
• This is due to the meninges and the brain parenchyma through the subarachnoid space, being all frequently involved in the inflammatory reaction (called: meningoencephalitis).
prominent subdural collection especially in the right frontal region
<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td>GBS, <em>E. coli</em>, <em>L. monocytogenes</em>, <em>K. pneumoniae</em>, <em>H. influenzae</em>,</td>
</tr>
<tr>
<td></td>
<td><em>S. pneumoniae</em>, <em>N. meningitidis</em>, <em>Klebsiella</em> spp., <em>Salmonella</em></td>
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<tr>
<td></td>
<td><em>spp.</em>, <em>S. marcescens</em>, <em>P. aeruginosa</em>, <em>Enterobacter</em> spp., <em>S. aureus</em>,</td>
</tr>
<tr>
<td></td>
<td><em>S. epidermidis</em>, <em>Propionibacterium acnes</em></td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>Enteroviruses, mumps virus, measles virus, herpesviruses, influenza</td>
</tr>
<tr>
<td></td>
<td>and parainfluenza viruses, HIV, arboviruses, lymphocytic choriomeningitis</td>
</tr>
<tr>
<td><strong>Rickettsia</strong></td>
<td><em>R. rickettsii</em>, <em>R. conori</em>, <em>R. prowazekii</em>, <em>R. typhi</em>, <em>R. tsutsugamushi</em>,</td>
</tr>
<tr>
<td></td>
<td><em>Ehrlichia</em> spp.</td>
</tr>
<tr>
<td><strong>Protozoa</strong></td>
<td><em>N. fowleri</em>, <em>Acanthamoeba</em> spp., <em>A. cantonensis</em></td>
</tr>
<tr>
<td><strong>Helminths</strong></td>
<td><em>S. stercoralis</em></td>
</tr>
<tr>
<td><strong>Other infectious diseases</strong></td>
<td>IE, parameningeal foci of infection, viral post-infectious syndromes, post-vaccination</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td>Antimicrobials, non-steroidals, azathioprine, OKT-3, cytosine arabinoside, carbamazepine, immune globulin, ranitidine</td>
</tr>
<tr>
<td><strong>Systemic diseases</strong></td>
<td>SLE</td>
</tr>
<tr>
<td><strong>Procedure-related</strong></td>
<td>Post-neurosurgery, spinal anaesthesia, intrathecal injections</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>Seizures, migraine, Mollaret’s meningitis</td>
</tr>
</tbody>
</table>
Epidemiology

• Bacterial meningitis is the most common form of suppurative (pus forming) CNS infection, with an annual incidence in the United States of >2.5 cases/100,000 population.

• The organisms most often seen in community-acquired bacterial meningitis are *Streptococcus pneumoniae* (~50%), *Neisseria meningitidis* (~25%), group B streptococci (~15%), and *Listeria monocytogenes* (~10%).

• *Haemophilus influenzae* type b accounts for < 10% of cases of bacterial meningitis in most series.

• *N. meningitidis* is the causative organism of recurring epidemics of meningitis every 8 to 12 years.
Bacterial meningitis: Etiology

- Factors that affect the causative organism of acute bacterial meningitis are:
  - The patient’s age (people are exposed to different bacteria at different ages)
  - Immune status (extremes of age are more susceptible, or perhaps compromised immunity state)
  - Recent head trauma or neurosurgery (direct access for nasopharyngeal flora to meninges).
- The typical story of how meningitis begins, is the introduction of a new pathogen into the nasopharynx followed by nasopharyngeal colonization which would be the stepping stone for this pathogen to gain entry into the blood and cause systemic invasion.

**redisposing Factors: Adults**
- Recent [Otitis Media](#) or [Bacterial Sinusitis](#) (25% of cases)
- [Pneumonia](#) (12% of cases)
- Immunocompromised state (16%)
<table>
<thead>
<tr>
<th>Age</th>
<th>Most common organisms</th>
<th>Empiric therapy</th>
<th>Additional medication considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate (0–30 days)</td>
<td>Group B Streptococcus, <em>Escherichia coli</em>, <em>Listeria monocytogenes</em></td>
<td>Cefotaxime + ampicillin</td>
<td>Add gentamycin if <em>Listeria</em> suspected</td>
</tr>
<tr>
<td>Babies (1–24 months)</td>
<td>Group B Streptococcus, <em>Streptococcus pneumonia</em>, <em>Neisseria meningitides</em>, <em>Haemophilus influenzae</em>, <em>Escherichia coli</em></td>
<td>Cefotaxime + vancomycin</td>
<td>Vancomycin added for resistant <em>S. pneumoniae</em> species</td>
</tr>
<tr>
<td>Child (2–18 years)</td>
<td><em>Neisseria meningitides</em>, <em>Streptococcus pneumoniae</em></td>
<td>Ceftriaxone + vancomycin</td>
<td>Consider vaccination for those at increased risk for meningococcal infections</td>
</tr>
<tr>
<td>Adult (18–65 years)</td>
<td><em>Streptococcus pneumoniae</em>, <em>Neisseria meningitides</em></td>
<td>Ceftriaxone + vancomycin</td>
<td></td>
</tr>
<tr>
<td>Elderly (&gt;65 years)</td>
<td><em>Streptococcus pneumoniae</em>, <em>Listeria monocytogenes</em>, <em>Escherichia coli</em>, + other gram-negative enterics</td>
<td>Ceftriaxone + vancomycin + ampicillin</td>
<td><em>Ampicillin</em> added for <em>Listeria</em> coverage</td>
</tr>
</tbody>
</table>
• In order for this new pathogen to be successful in this story it must have the means (tools/virulence factors) to succeed.

• These factors are:

  1- fimbriae (adhesion)
  2- bacterial capsule to evade phagocytosis once in the blood
  3- production of IgA proteases to break down IgA in mucosal surfaces to be able to successfully colonize these surfaces.

• On the other side of the equation, there are host factors that predispose to meningitis:

  • splenectomy (inability to clear capsulated organisms)
  • complement deficiencies (reduced opsonization).
**S. pneumoniae**

- *S. pneumoniae*: is the most common cause of ALL meningitis cases in adults >20 years of age – this accounts for almost half the reported cases (1.1 per 100,000 persons per year).

- Important Properties:
  - Pneumococci are gram-positive lancet-shaped cocci arranged in pairs (diplococci) or short chains (The term lancet-shaped means that the diplococci are oval with somewhat pointed ends rather than being round.)
  - On blood agar, they produce α-hemolysis, In contrast to viridans streptococci, they are lysed by bile or deoxycholate, and they are sensitive to optochin
Pathogenesis, virulence factors:

• The most important virulence factor is the capsular polysaccharide, and anticapsular antibody is protective.

• Lipoteichoic acid: complement activator, it induces inflammatory cytokine production contributes to the inflammatory response and to the septic shock syndrome that occurs in some immunocompromised patients (a bit similar to protein A in LPS in Gram negatives).

• Pneumolysin, the hemolysin that causes α-hemolysis, may also contribute to pathogenesis.

• Pneumococci produce IgA protease that enhances the organism’s ability to colonize the mucosa of the upper respiratory tract.
Factors that lower resistance and predispose persons to pneumococcal infection include (factors that reduce mucus clearing or factors that decrease immune reaction)

(1) anything that can depress the cough reflux: alcohol or drug intoxication or other cerebral impairment, all contribute to an increase **aspiration** of secretions (and thus pneumoniae)

(2) abnormality of the respiratory tract (e.g., viral infections), pooling of mucus, bronchial obstruction, and respiratory tract injury caused by irritants (which disturb the integrity and movement of the mucociliary blanket) all prevent clearing of mucus and predispose to community acquired pneumonia caused by pneumococcus.

(3) abnormal circulatory dynamics (e.g., pulmonary congestion and heart failure) - will congest the blood in the lung, increase pulmonary secretions → pneumococcus

(4) splenectomy (capsule, reduces immunity) and certain chronic diseases such as sickle cell anemia and nephrosis, patients with sickle cell anemia autoinfarct their spleen, become functionally asplenic, and are predisposed to pneumococcal sepsis.

Trauma to the head that causes leakage of spinal fluid through the nose predisposes to pneumococcal meningitis.
• Being the dominant pathogen, there have been a number of predisposing conditions identified that increase the risk of pneumococcal meningitis:
  • pneumococcal pneumonia (the most important risk factor, how come? BACTEREMIA).
  • coexisting acute or chronic pneumococcal sinusitis or otitis media (close proximity)
  • alcoholism (reduced clearance of bugs in respiratory tract)
  • diabetes (reduced immunity)
  • splenectomy (inability to clear capsulated bacteria)
  • hypogammaglobulinemia
  • complement deficiency
  • head trauma with basilar skull fracture and CSF rhinorrhea.

The mortality rate remains ~20% despite antibiotic therapy (before antibiotics this used to be 100% fatal!!!).
**N. meningitides**: Important Properties

- Neisseriae are Gram-negative cocci that resemble paired kidney beans and are considered STRICT AEROBES.
- (1) *N. meningitidis* (meningococcus) has a prominent polysaccharide capsule that enhances virulence by its antiphagocytic action and induces (adaptive/TIME CONSUMING) protective antibodies— that means if they have meningitis, there is no time to wait for ADAPTIVE immune response and must TREAT. But that also means I can make a VACCINE!
- According to the antigens of their capsule polysaccharide, meningococci are divided into “so far” 13 serologic groups.
- Five of those serotypes cause the most cases of meningitis and meningococcemia (A, B, C, Y, and W-135).
- Serotype A is the leading cause of epidemic meningitis worldwide.
- Serotype B accounts for most disease in the United States.
Those three are colonizers of the URT

TABLE 16–3   Properties of the Polysaccharide Capsule of the Meningococcus

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>(1)</td>
<td>Enhances virulence by its antiphagocytic action</td>
</tr>
<tr>
<td>(2)</td>
<td>Is the antigen that defines the serologic groups</td>
</tr>
<tr>
<td>(3)</td>
<td>Is the antigen detected in the spinal fluid of patients with meningitis</td>
</tr>
<tr>
<td>(4)</td>
<td>Is the antigen in the vaccine</td>
</tr>
</tbody>
</table>

1The same four features apply to the capsule of the pneumococcus and *Haemophilus influenzae.*
• routine immunization of 11- to 18-age group with the tetravalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine has reduced its incidence (this vaccine does not contain serogroup B, which causes about 1/3 of cases).

• Petechial or purpuric skin lesions can provide an important clue to the diagnosis of meningococcal infection.

• In some patients the disease is fulminant, progressing to death within hours of symptom onset.

• Nasopharyngeal colonization can initiate infection, but colonization can result in either an asymptomatic carrier state or invasive meningococcal disease.
• Host and bacterial factors that promote meningococcal disease:
• The host side:
  • The ability to produce anti meningococcal antibodies
  • Competent classic and alternative complement pathways to lyse the pathogenic cells.
• Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infection
Gram negative enterics

• These pathogens cause meningitis in susceptible hosts, particularly in those with chronic illnesses:
  • A) diabetes B) cirrhosis c) alcoholism D) chronic urinary tract infections E) post craniotomy in neurosurgery.

- Infections in the skull such as Otitis, mastoiditis, and sinusitis predispose for all types of meningitis from Streptococcus, gram-negative anaerobes, S. aureus, Haemophilus, and include Enterobacteriaceae (G-ve enterics).

- Similarly meningitis can be a complication of endocarditis (seeding from the heart) due to viridans streptococci, S. aureus, S. bovis, the HACEK group (Haemophilus spp., Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae), or enterococci.
Group B Streptococcus (S. agalactiae) previously responsible for meningitis predominantly in neonates

• This was usually due to colonization by the this bug of the birth canal
• Neonatal sepsis and meningitis and usual consequences
• It has been reported with increasing frequency in individuals >50 years of age, particularly those with underlying diseases.
Listeria monocytogenes is an increasingly important cause of meningitis in two age groups:

- neonates and >60 years old and in the immunocompromised of all ages.

Infection is acquired by ingesting foods contaminated by Listeria (so not colonization).

Foodborne human listerial infection has been reported from contaminated coleslaw (cabbage), milk, soft cheeses, and several types of “ready-to-eat” foods, including delicatessen meat and uncooked hotdogs.
**H. influenzae**

- The frequency of type b meningitis in children has declined dramatically since the Hib conjugate vaccine.
- *H. influenzae* causes meningitis in unvaccinated children and older adults, and non-b *H. influenzae* is an emerging pathogen.
Important Properties

- *H. influenzae* G-ve ROD encapsulated with a polysaccharide capsule
- one of the three important encapsulated pyogens (pneumococcus and the meningococcus).
- Using serologic methods against the antigen of the polysaccharide capsule, six serotypes are detected, with serotype B (group B) being the most significant one.
- Serotype B is the one most responsible for the more serious illnesses (meningitis, epiglottitis, sepsis)
- The type B capsule is composed of polyribitol phosphate, promotes anti-phagocytosis and invasiveness.
- Unencapsulated strains are less invasive but can cause disease usually limited to the upper respiratory tract (sinusitis and otitis media).
- Growth of the organism on laboratory media requires the addition of two components, heme (factor X) and NAD (factor V), for adequate energy production.
Pathogenesis & Epidemiology

- *H. influenzae* infects only humans with no animal reservoir.
- Similar to other respiratory pathogens, it is transmitted by the inhalation of airborne droplets into the respiratory tract, this can result in asymptomatic colonization or infection (otitis media, sinusitis, pneumonia).
- Also like all respiratory pathogens, to be able to survive in this environment, the organism produces an IgA protease that degrades secretory IgA which would otherwise inhibit its attachment to the mucosa.
- After becoming established in the upper respiratory tract, the organism can enter the bloodstream (bacteremia) and spread to the meninges.
- As mentioned, capsulated strains cause meningitis (they have to have antiphagocytic capability to survive the trip through the blood to reach the meninges, this is true for Pneumococcus and Meningococcus)
- meningitis caused by capsular type b has been greatly reduced by vaccine contains the type b polysaccharide as the immunogen.
- Similar to pneumococcus and meningococcus, the pathogenesis of *H. influenzae* is pyogenic with no exotoxin production (capsule and endotoxin based)
Staphylococcus aureus

- Infection with S.A. occurs following introduction of foreign material into the CNS by invasive neurosurgical procedures such as:
  - shunt introduction for hydrocephalus
  - Introduction of a subcutaneous Ommaya reservoirs for administration of intrathecal chemotherapy.

- P.s. Ommaya is a Pakistani neurosurgeon, he invented a reservoir that provides entry into the CSF to give chemotherapy with
• So now we have a representative of each Gram reaction and shape that cause Meningitis:
  • G+ve coccus : *S. pneumoniae* (less so *S. aureus*)
  • G+ve rod : *Listeria monocytogenes*
  • G-ve coccus : *Neisseria*
  • G-ve rod : *Haemophilus influenzae* (Less *E.coli*)
<table>
<thead>
<tr>
<th>Age/condition</th>
<th>Common organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4 weeks</td>
<td>GBS, <em>E. coli</em>, <em>L. monocytogenes</em>, <em>K. pneumoniae</em>, Enterococcus spp., <em>Salmonella</em> spp.</td>
</tr>
<tr>
<td>4–12 weeks</td>
<td>GBS, <em>E. coli</em>, <em>L. monocytogenes</em>, <em>K. pneumoniae</em>, <em>H. influenzae</em>, <em>S. pneumoniae</em>, <em>N. meningitidis</em></td>
</tr>
<tr>
<td>3 months to 18 years</td>
<td><em>H. influenzae</em>, <em>N. meningitidis</em>, <em>S. pneumoniae</em></td>
</tr>
<tr>
<td>18–50 years</td>
<td><em>N. meningitidis</em>, <em>S. pneumoniae</em>, <em>S. suis</em></td>
</tr>
<tr>
<td>&gt;50 years</td>
<td><em>S. pneumoniae</em>, <em>N. meningitidis</em>, <em>L. monocytogenes</em>, aerobic Gram-negative bacilli, <em>S. suis</em></td>
</tr>
<tr>
<td>Immunocompromised</td>
<td><em>S. pneumoniae</em>, <em>N. meningitidis</em>, <em>L. monocytogenes</em>, aerobic Gram-negative bacilli (e.g. <em>E. coli</em>, Klebsiella spp., <em>Salmonella</em> spp., <em>S. marcescens</em>, <em>P. aeruginosa</em>)</td>
</tr>
<tr>
<td>Basal skull fracture</td>
<td><em>S. pneumoniae</em>, <em>H. influenzae</em>, GAS</td>
</tr>
<tr>
<td>Head trauma, post-neurosurgery</td>
<td><em>S. aureus</em>, <em>S. epidermidis</em>, aerobic Gram-negative bacilli</td>
</tr>
<tr>
<td>CSF shunt</td>
<td><em>S. aureus</em>, <em>S. epidermidis</em>, <em>P. acnes</em>, aerobic Gram-negative bacilli</td>
</tr>
</tbody>
</table>
Pathophysiology

- *S. pneumoniae* and *N. meningitidis*, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells.
- Once colonized. Bacteria borough through the vascular layers into the blood stream.
- Once in the bloodstream, bacteria are able to avoid phagocytosis by neutrophils and classic complement-mediated bactericidal activity because of the presence of a polysaccharide capsule.
- Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid plexus epithelial cells, and gain access to the CSF.
- Some bacteria, such as *S. pneumoniae*, can adhere to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF.
• Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses (it is a sterile area!).

• Normal CSF has few white blood cells (WBCs) small quantity of complement proteins and immunoglobulins.

• Since there is little WBC, and little immunoglobulins and complement proteins, effective opsonization is hindered (which is essential for clearing these capsulated organisms).

• Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate.

• Reduced phagocytosis and opsonization makes the CSF a vulnerable environment = bacteria gain entry, infection is most likely immanent.
• Neurologic manifestations and complications of bacterial meningitis result from the immune response to the invading pathogen and not due to direct injury by the pathogen.

• This means even after clearing the pathogen (by Abx) neurologic injury can continue (Abx do not work on the immune system).

• After lysis of bacteria, there will be a release of highly immunogenic cell-wall components (lipopolysaccharide (LPS) G-ve bacteria and teichoic acid and peptidoglycans of G+ve) into the subarachnoid space which is the first step into the inflammatory response and the formation of a purulent exudat.
Invasion of SAS by meningeal pathogens

- Multiplication of organisms and lysis of organisms by bactericidal antibiotics
- Release of bacterial cell-wall components (endotoxin, teichoic acid)
- Production of inflammatory cytokines

- Altered blood-brain barrier permeability
- Adherence of leukocytes to cerebral capillary endothelial cells
- Alterations in cerebral blood flow
- Production of excitatory amino acids and reactive oxygen and nitrogen species

- Permeability of blood vessels with leakage of plasma proteins into CSF
- Leukocytes migrate into CSF, degranulate, and release toxic metabolites
- Exudate in SAS obstructs outflow and resorption of CSF and surrounds and infiltrates cerebral vasculature
- Cytotoxic edema, stroke, seizures

- Vasogenic edema
- Obstructive and communicating hydrocephalus and interstitial edema
- Cerebral ischemia
- Intracranial pressure

- Coma

Cell injury and death
Clinical features

• Classical symptoms and signs are: fever, headache, meningism (neck stiffness, photophobia, positive Kernig’s sign and Brudzinski’s sign), and cerebral dysfunction (confusion and/or reduced conscious level).

• Seizures can occur in 1/3 of patients. Cranial nerve palsies and focal signs are seen in 10–20% of cases. Hemiparesis may be due to a subdural effusion.

• Skin rash (initially macular, then petechial) occurs in patients with meningococcal septicaemia but can occur in pneumococcal, H. influenzae.

• Leaking of fluid from nose or ear (Rhinorrhea or otorrhoea) suggests basal skull fracture- port of entry-.
• L. monocytogenes meningitis has more risk of seizures and focal signs; ataxia, cranial nerve palsies, and nystagmus

• Neonates and elderly may present with non-specific symptoms,

• Neonates temperature instability, listlessness (uninterested), poor feeding, irritability, vomiting (may indicate high ICP), diarrhoea, jaundice, respiratory distress.

• Seizures occur in 40%, and a bulging fontanelle is a late sign.

• In elderly confusion, lethargy, no fever, and variable signs of meningeal inflammation.
Dx

• When bacterial meningitis is suspected, blood cultures should be immediately obtained and empirical antimicrobial and adjunctive dexamethasone therapy initiated without delay

• The diagnosis is confirmed by examination and culture of the CSF.

• In bacterial meningitis, the following are typically seen:
- opening pressure >18mm of CSF;
- CSF WCC 1000–5000 cells/mm³ (range 100–10 000);
- CSF neutrophils ≥80%;
- CSF protein 0.1–0.5g/dL;
- CSF glucose ≤40mg/dL or ≤2.2mmol/L;
- CSF lactate ≥35mg/dL or ≥1.9mmol/L;
- Gram stain positive in 60–90%;
- culture positive in 70–85%;
- bacterial antigen detection positive in 50–100%;
- bacterial PCR positive in 90%.
Management

• The following algorithm from Oxford is extremely important, learn it well, keep it with you
Consider meningitis or meningococcal sepsis if any of the following are present:
Headache, fever, neck stiffness, rash, seizures, altered conscious level, shock

Immediate action
- Check airway, breathing, circulation
- Check GCS, focal neurology, papilloedema, capillary glucose
- Senior review and critical care if warning signs present (rapidly progressive rash, poor perfusion, BP <90 mmHg, resp rate <8 or >30/min, pulse <40 or >140/min, ABG pH<7.3 or base excess worse than −5, WCC<4, lactate >4mmol/L, GCS<12 or drops 2, poor response to fluid resuscitation)

Suspected meningitis
in the absence of shock, severe sepsis or signs of raised ICP
- Blood cultures, LP
- Dexamethasone 10mg IV
- Appropriate antibiotics (Table 19.3)
- CT scan not normally indicated
- Careful fluid resus (avoid overload)
  If LP cannot be done in the first hour, give antibiotic immediately after taking blood cultures

Suspected meningitis with signs of raised ICP
- Critical care review
- Secure airway, give oxygen
- Blood cultures
- Dexamethasone 10 mg IV
- Appropriate antibiotics (Table 19.3)
- Delay LP
- Arrange head imaging once stable

Sepsis or rapidly evolving rash
with or without signs of meningitis
- Critical care review
- Secure airway, give oxygen
- Fluid resus
- Blood cultures
- Appropriate antibiotics (Table 19.3)
- Delay LP
- Manage according to sepsis protocols

Careful monitoring and repeated review
Empirical antimicrobial therapy should be commenced immediately, pending investigations.

<table>
<thead>
<tr>
<th>Age/condition</th>
<th>Empiric therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0–4 weeks</td>
<td>Ampicillin + cefotaxime or aminoglycoside</td>
</tr>
<tr>
<td>Age 4–12 weeks</td>
<td>Ampicillin + cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td>Age 3 months to 18 years</td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td>Age 18–50 years</td>
<td>Ceftriaxone or cefotaxime ± vancomycin</td>
</tr>
<tr>
<td>Age &gt;50 years</td>
<td>Ceftriaxone or cefotaxime + ampicillin</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>Vancomycin + ampicillin + ceftazidime or meropenem</td>
</tr>
<tr>
<td>Health care-associated meningitis</td>
<td>Vancomycin + ceftazidime or meropenem</td>
</tr>
<tr>
<td>Basal skull fracture</td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td>Head trauma/neurosurgery</td>
<td>Vancomycin + ceftazidime</td>
</tr>
<tr>
<td>CSF shunt</td>
<td>Vancomycin + ceftazidime</td>
</tr>
<tr>
<td>β-lactam allergy</td>
<td>Vancomycin + moxifloxacin ± co-trimoxazole (if Listeria suspected)</td>
</tr>
</tbody>
</table>
If the CSF Gram stain or culture is positive, treatment should be tailored to the infecting organism.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antimicrobial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>Penicillin MIC $&lt; 0.06$ micrograms/mL: benzylpenicillin</td>
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<tr>
<td></td>
<td>Penicillin MIC $\geq 0.12$ and $&lt; 1$ microgram/mL: ceftriaxone</td>
</tr>
<tr>
<td></td>
<td>Penicillin MIC $\geq 1$ microgram/mL: ceftriaxone plus vancomycin</td>
</tr>
<tr>
<td><em>N. meningitidis</em></td>
<td>Penicillin MIC $&lt; 0.1$ microgram/mL: benzylpenicillin or ampicillin</td>
</tr>
<tr>
<td></td>
<td>Penicillin MIC $0.1–1$ microgram/mL: ceftriaxone</td>
</tr>
<tr>
<td><em>L. monocytogenes</em></td>
<td>Ampicillin or benzylpenicillin</td>
</tr>
<tr>
<td>GBS</td>
<td>Ampicillin or benzylpenicillin</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Ceftriaxone or cefotaxime</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Ceftazidime or meropenem</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>$\beta$-lactamase-negative: ampicillin</td>
</tr>
<tr>
<td></td>
<td>$\beta$-lactamase-positive: ceftriaxone</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>Meticillin-susceptible: flucloxacillin</td>
</tr>
<tr>
<td></td>
<td>Meticillin-resistant: vancomycin</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>Ampicillin-susceptible: ampicillin + gentamicin</td>
</tr>
<tr>
<td></td>
<td>Ampicillin-resistant: vancomycin + gentamicin</td>
</tr>
<tr>
<td></td>
<td>Ampicillin- and vancomycin-resistant: linezolid</td>
</tr>
</tbody>
</table>
• As for steroid adjunctive therapy:
• The recommended regimen was dexamethasone 10mg qds (4 times daily) for 4 days (4x4) given before or with the first dose of antibiotic.
• Recent data suggest their value is more in developed countries and less so in developing world (AMR?)
• Reduction of high ICP must be done if present
• Fractures need to be corrected, neurosurgery may be required
Prevention

- Vaccination—Hib and meningitis C as part of scheduled vaccines.
- The quadrivalent meningitis vaccine (ACYW135) is recommended for patients with complement or properdin deficiency, asplenic patients, travellers to endemic areas, and medical or laboratory personnel routinely exposed to *N. meningitidis*.* S. pneumoniae*
- Vaccination is recommended in certain high-risk patients (chronic illnesses)
- Chemoprophylaxis for exposed people:
  - Rifampicin for *H. influenzae* type B meningitis.
  - *N. meningitidis*, the agents used are rifampicin (600mg bd for 2 days), ciprofloxacin (500mg stat), or ceftriaxone (250mg IM).
  - Penicillins for pregnant women colonized with GBS
PROGNOSIS

• Mortality rates are high:
  • 3–7% for meningitis by *H. influenzae, N. meningitidis, group B streptococci*
  • 15% for *L. Monocytogenes*
  • 20% for *S. pneumoniae.*
Signs that point to higher risk of mortality

• (1) decreased level of consciousness on admission. (this hints at level and degree of involvement of brain parenchyma)
• (2) onset of seizures w/in 24 h of admission (also hints at serious focal structural damage, or severe alteration of the supply for the brain)
• (3) increased ICP (high BP, headache, vomiting, less responsive pupillary light reflex)
• (4) extremes of age (infant or >50 y/o)
• (5) the presence shock and/or the need for mechanical ventilation
• (6) delay in the initiation of treatment. (this one is on you)
• Decreased CSF glucose concentration [3 g/L (>300 mg/dL)] have been predictive of increased mortality and poorer outcomes in some series.
• Moderate or severe sequelae occur in ~25% of survivors, although the exact incidence varies with the infecting organism. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances