MICROBIOLOGY

SHEET NO. 2

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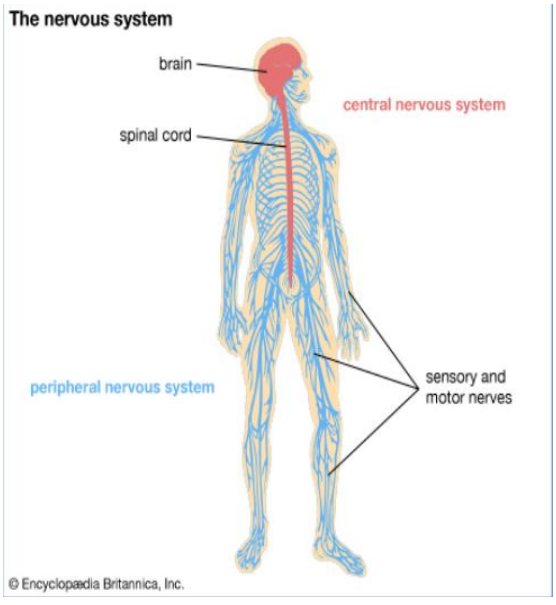
INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

INTRODUCTION

Unlike other systems in the body like the gastrointestinal or respiratory systems, the central nervous system is completely sterile and has no normal microbiota. Therefore, if bacteria, viruses or other microbes gained access to the CNS, they will elicit an immune response and cause tissue damage, which is the biggest problem we might have in CNS infections.

*Usually, it's the intense immune response that results in very severe manifestations rather than damage caused by the microbe or its toxins. And given that the CNS normally has lower numbers of immune and inflammatory cells, it is often described as displaying "**Immune Privilege**" as it shows an attenuated immune response. However, if a pathogen got past the physiological and immunological barriers of the CNS, the system does show an inflammatory response to the infection that may become very severe with time.*

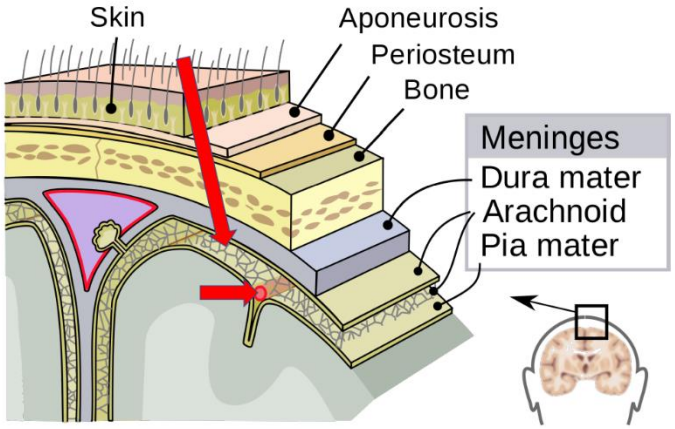
- Why is the immune response "**attenuated**" in the CNS? Only some CD4+ and CD8+ cells with very few, if any, neutrophils circulate the cerebrospinal fluid (CSF) that is contained in the subarachnoid space within the meninges. Within the parenchyma of the brain, we won't find any antigen presenting cells (APCs), only one type of immune cells is present and is responsible for almost all immune functions, that is the **Microglia**. Along with these cells, pattern recognition receptors which sense pattern-associated molecular patterns [PAMPs] and damage-associated molecular patterns [DAMPs]. Together they initiate the inflammatory response within the brain parenchyma.
- What does "**Immune Privilege**" indicate? It means that the immune response to a pathogen or a foreign alloantigen is weaker in the CNS than in any other part of the body. Some pathogens benefit from this phenomenon because they become largely protected from the peripheral *strong* immune response. Not much of a privilege :)).



Distinct Clinical Syndromes

1. Acute bacterial meningitis
2. Viral meningitis
3. Chronic meningitis
4. Encephalitis
5. Focal infections

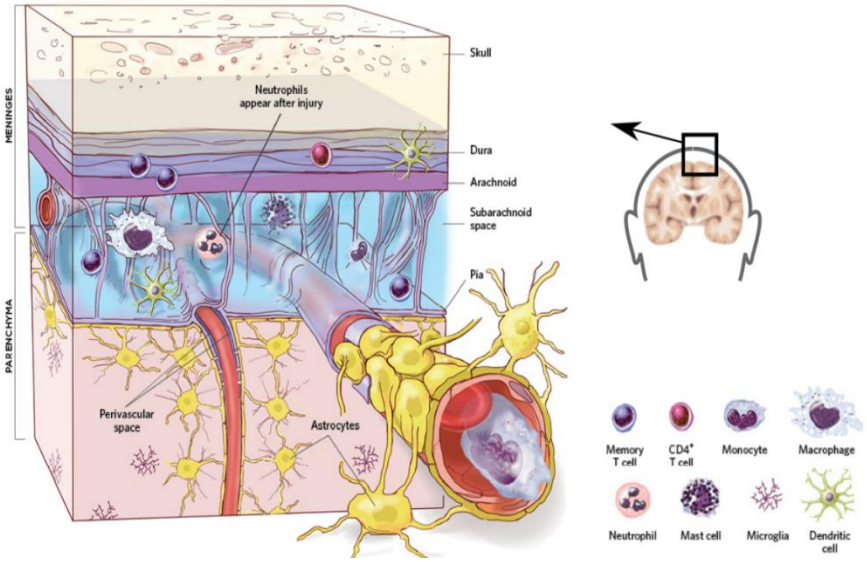
How does the pathogen gain entrance to the CNS?



The brain and spinal cord are heavily protected by multiple physiological barriers that include the skin, aponeurosis, periosteum, bone and the meninges (Dura, Arachnoid and Pia maters), so, how does a pathogen gain access into the CNS past all these barriers?

1. Mainly, by **<u>hematogenous</u>** spread – through the blood.
2. Fractures after trauma -> expose the structures that underlie the bone.

If we look at the adjacent figure, we'll be able to see some **CD4+ and CD8+ T-cells** within the CNS, although in less amounts than in the blood. Neutrophils [PMNs] are *rarely* found except in cases of infection where they travel via the blood and cross the blood-brain barrier (BBB) into the CNS.

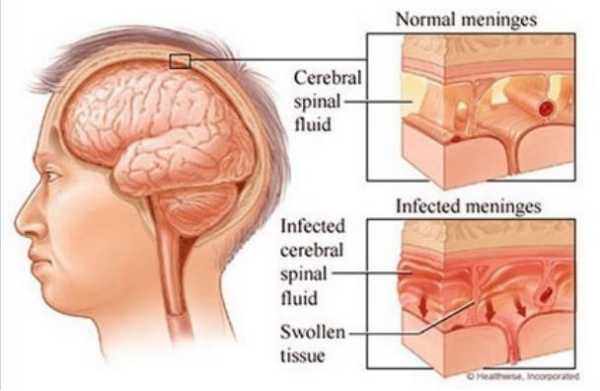


The **microglia and complement proteins** are normally performing homeostatic functions [cleaning cells debris and pruning of neurons, respectively], until PMAPs and DAMPs activate these cells, they enlarge and participate in the immune response and with time some of the other immune cells pass into the parenchyma.

The number of immune cells within the CNS can be used to diagnose infections of the system. So, the immune system is a critical part of a functioning central nervous system even in the absence of injury because it's important for the homeostasis within the brain.

Now into our topic for today …

Meningitis

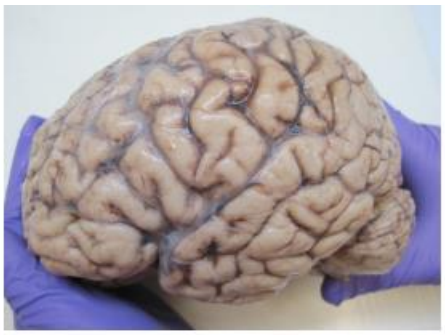


It is inflammation of the **leptomeninges and subarachnoid space** and considered a neurological emergency, so a physician should recognise it early and start the treatment immediately in order to increase the chances of the patient's survival and decrease the morbidity associated with this severe disease.

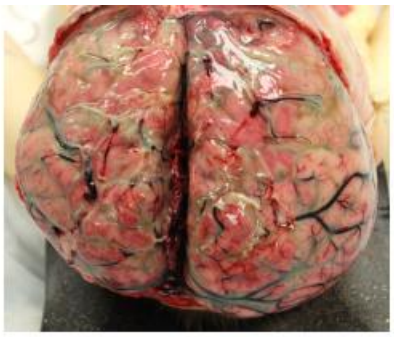
Causes of meningitis (infectious & non-infectious):

1. Infectious [more common] -> bacterial, viral, fungal and parasitic.
2. Non-infectious ->drugs, malignancies and autoimmune diseases (Ads).

These two pictures show the difference between a normal brain and a brain of a patient with meningitis.



Normal



Meningitis

- The CSF becomes **turbid** and **filled with immune cells** in numbers that aren't usually present in the CNS. In addition to **pus formation** associated with bacterial infections [pyogenic].

The common causes of bacterial meningitis

The organisms that cause meningitis usually vary according to **age**, as stated in this table:

For example, within the first month of age, Group B streptococci [strep. Agalactiae], E. coli and Listeria are the most common causes, but in ages 3 months - 18 years it's H. influenzae, N. meningitidis and strep. Pneumoniae. Why?

Table 19.2 Causes of bacterial meningitis

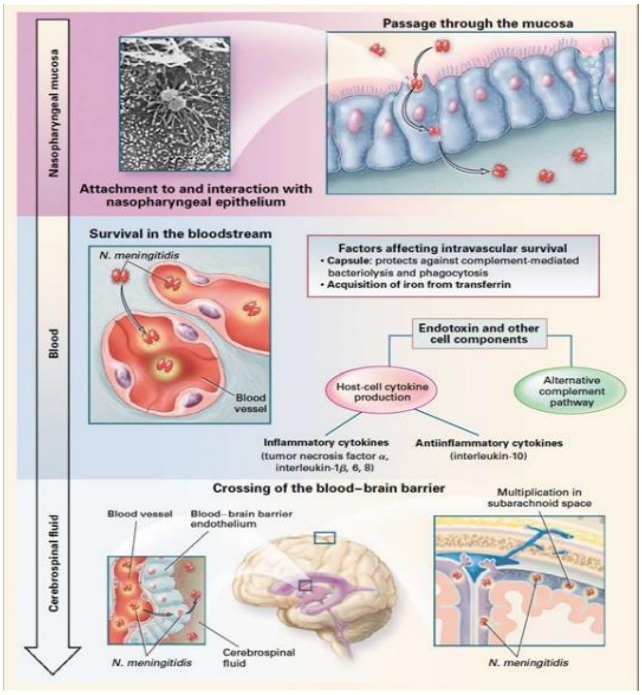
Age/condition	Common organisms
0–4 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *Enterococcus* spp., *Salmonella* spp.
4–12 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *H. influenzae*, *S. pneumoniae*, *N. meningitidis*
3 months to 18 years	*H. influenzae*, *N. meningitidis*, *S. pneumoniae*
18–50 years	*N. meningitidis*, *S. pneumoniae*, *S. suis*
>50 years	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic Gram-negative bacilli, *S. suis*
Immunocompromised	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic Gram-negative bacilli (e.g. *E. coli*, *Klebsiella* spp., *Salmonella* spp., *S. marcescens*, *P. aeruginosa*)
Basal skull fracture	*S. pneumoniae*, *H. influenzae*, GAS
Head trauma, post-neurosurgery	*S. aureus*, *S. epidermidis*, aerobic Gram-negative bacilli
CSF shunt	*S. aureus*, *S. epidermidis*, *P. acnes*, aerobic Gram-negative bacilli

GBS and E. coli are organisms that can ***colonise the birth canal***, so the new-born might catch the organism while passing through it. Nowadays, in some developed countries, pregnant women are screened for these organisms before giving birth and they get prescribed antibiotics to treat the pathogen and prevent transmitting it to the infant.

Listeria monocytogenes is a gram-positive bacillus that resides *inside the cells [**intracellular**]* so, it requires the activation of **cell-mediated immunity** [T-cells]. It usually affects immunocompromised people[elderlies] or infants because their immune system isn't well-developed. Rarely causes disease in immunocompetent.

In older age groups [for example, 3 months – 18 years] more common pathogens like N. meningitidis [gram -ve] or strep. pneumoniae cause the infection.

Streptococcus pneumoniae is part of the normal flora of the upper respiratory tract and normally reside there without causing any harm. But for some reason or another [e.g., weakening of the immune system or if the organism acquired virulent factors], the microbe might *travel to the blood, circulate until it reaches the meninges then penetrate the BBB* causing disease. *The pathogen replicates in the CSF* [which lacks cellular and humoral immunity] *and the immune response for the pathogen and its products [LPS, PGN] further damages the tissues*.



All in all, among all age groups, the most common causes are **N. meningitidis and S. pneumoniae**, both colonise the nasopharynx.

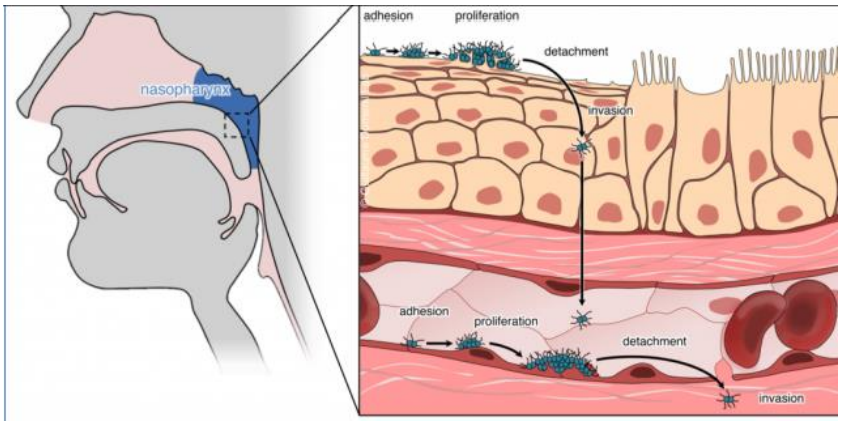
H. influenzae can also cause meningitis, however, the incidence of cases caused by this organism has *declined* due to **vaccination campaigns**.

Any penetrating **trauma** like skull fractures, head injury, neurosurgery or CSF shunts can expose the CNS and CSF to the microbiota of the *skin* like **s. aureus and s. epidermidis**.

> So, ***age and predisposing conditions*** play an important role in identifying the organism that will cause meningitis. And subsequently, that will help to determine the appropriate treatment.

The inflammation and response to the infection are caused by factors from the organism [virulent factors] and factors from the host [the state of the immune system]. Most of these bacteria [s. pneumoniae] are encapsulated and their **capsule** appears to be a very important factor in their pathogenesis, that could be the cause for why people who undergo **splenectomy** are at risk of getting meningitis by these pathogens (remember, the spleen is what gets rid of encapsulated organisms).

It also has been found that patients with **severe complement deficiencies or are on complement inhibition therapy** are more susceptible and have increased risk for developing meningitis.



The pathogens cross the BBB by various mechanisms, either by *the help of other cells* like macrophages or by simply *attaching to the BBB*. Then the pathogen replicates freely until the PAMPs and DAMPs alert the immune system and the inflammatory cells travel to the CNS, which kind of worsens everything :/, because these immune cells are the ones responsible for the damage that occurs in the CNS. And because of this immune response, comorbidities and long-term damage often remain after the resolving of the infection, especially in bacterial meningitis.

In the figure, we see skin lesions that might be seen in meningococcal infection caused by the circulating N. meningitides

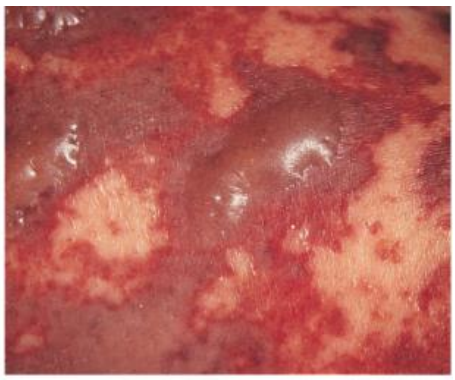
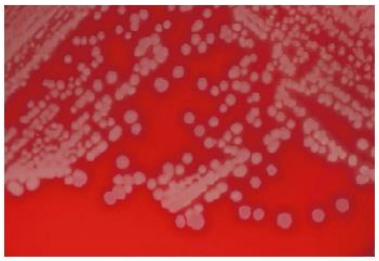
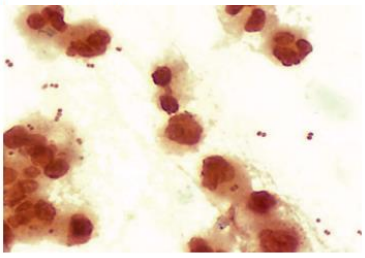


FIGURE 23-5 Skin lesions in a patient with meningococcemia. Note that the petechial lesions have coalesced and formed hemorrhagic bullae.



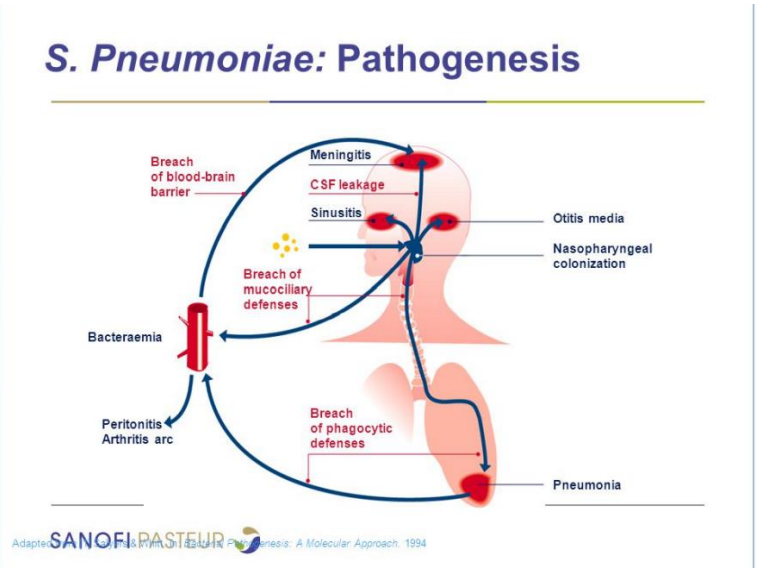
N. meningitidis colonies on blood agar plate



N. meningitidis gram stain

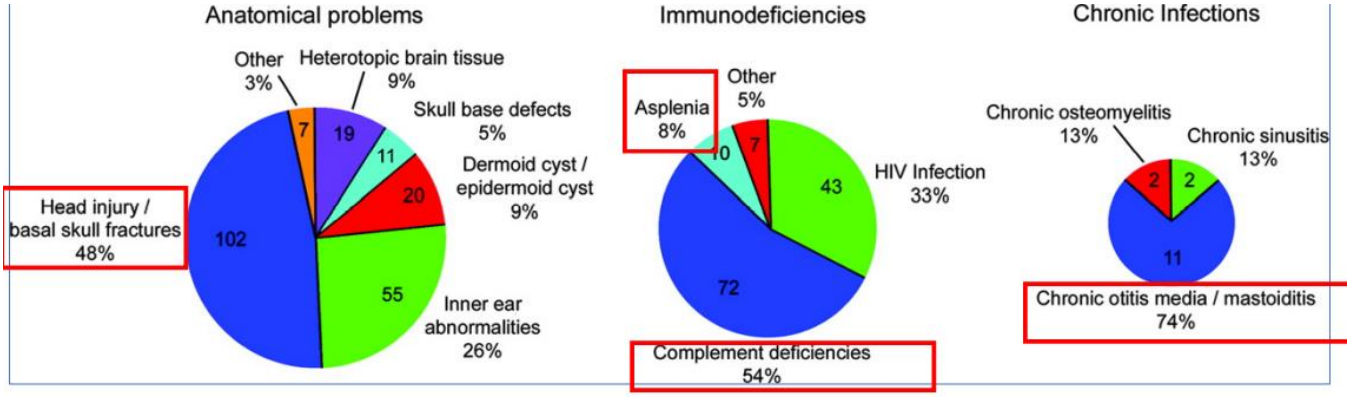
S. Pneumoniae pathogenesis

As we said, these bacteria are part of the nasopharynx' normal flora but it can get detached and caused multiple infections, mainly related to the respiratory system, e.g., pneumonia or otitis media. If the infection become chronic, they can cause infection of the meninges. In some cases, the spread is direct from the nasopharynx to the meninges.



How common is bacterial meningitis?

Bacterial meningitis is still a relatively rare infection by the incidence varies by region [e.g., developed and developing countries] and it should be treated as an emergency. The sub-Saharan Africa is referred to as the **meningitis belt**.



The figure above shows some of the **Predisposing Factors** for meningitis.

With the introduction of H. influenzae type b conjugate vaccines and pneumococcal **conjugate vaccine**, the incidence of meningitis from these causes decreased significantly.

Why "conjugate"? because we want antibodies against the polysaccharides found in the capsules and the immune response against polysaccharides is short-lived and weak. So, we conjugate it to a protein to elicit a response that will produce long-term memory cells.

> Annual Hajj pilgrimages and smaller Umra pilgrimages have historically played a key role in the regional (and to some extent global) spread of meningococcal disease, and have influenced vaccination policies in the region. The mass travel and overcrowded conditions associated with these pilgrimages can facilitate the rapid spread of *N. meningitidis* amongst pilgrims and Saudi nationals.

The Hajj pilgrimage is a key factor influencing outbreaks and transmission, **and the use of vaccines has minimized the effects** on the home countries of the pilgrims and has decreased global dissemination of disease. Wider use of available polyvalent meningococcal conjugate vaccines may provide broader protection against the range of serogroups causing disease or posing a threat in the region.

Neisseria meningitidis is consistently reported to be one of the leading causes of bacterial meningitis in the Middle East and North Africa (MENA) region.

The clinical feature of meningitis

There are three **main** features ->

1. Severe headache
2. Fever
3. Meningism [signs of inflammation of the meninges]: neck stiffness, photophobia, positive Kernig's sign and Brudzinski's sigh.

In severe cases, the infection may reach the brain parenchyma causing ->

1. Cerebral dysfunction: confusion and/or reduced conscious level. **Meningoencephalitis**.
2. Seizures can occur in neonates and adult patients

Accompanying symptoms that help in identifying the causing organism ->

1. Petechial rash in meningococcal septicaemia.
2. Rhinorrhoea in basal skull fractures [CSF leakage].

In chronic meningitis mainly, increased intracranial pressure may happen because the infection might cause **oedema and obstruct the flow of CSF** so it accumulates in the subarachnoid space increasing the pressure.

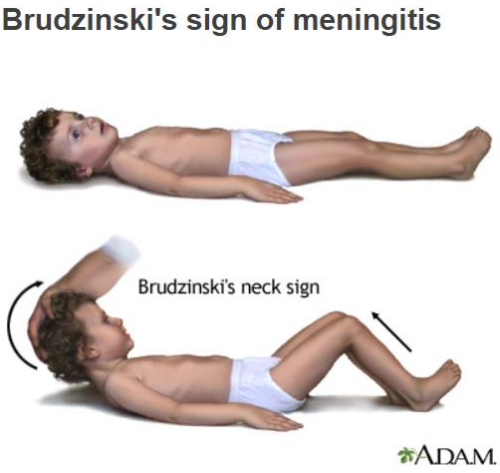
Neonates may present with **nonspecific symptoms** -> temperature instability, listlessness, poor feeding, irritability, vomiting, diarrhoea, jaundice and respiratory distress.

Kernig's sign ->

The physician flexes the hip joint then extends the knee joint; the presence of resistance could be an indicator of meningitis. Because these movements *stretch the meninges* and if they were inflamed the patient will feel pain and **resist the movement**.

Brudzinski's sign ->

The physician flexes the neck, and that will stretch the meninges. If the meninges were inflamed, the patient would **flex their knee** to relieve the stretch on the meninges [a positive sign].

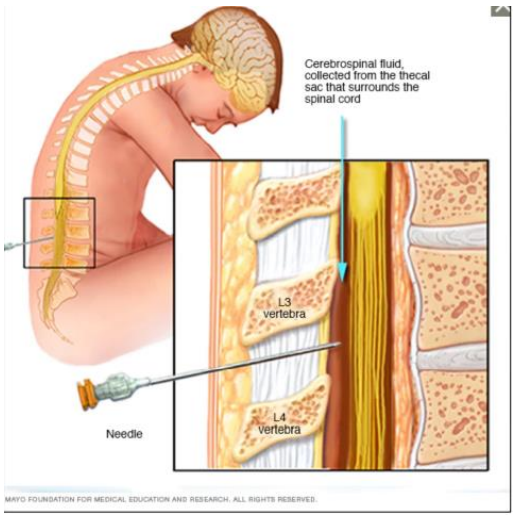


These tests are confirmatory but not all patients will have positive signs.

How do we confirm meningitis?

Test the CSF and culture. We perform a lumbar puncture by inserting a needle into the subarachnoid space and draw samples of the CSF and send these samples to the microbiology, chemistry and cytology lab.

1. Microbiology -> culture to identify the causing pathogen
2. Chemistry -> levels of glucose and proteins
3. Cytology -> inflammatory and immune cells levels



If there's an increase in ICP we cannot take a CSF sample because that will cause **disturbance of the equilibrium and herniation of parts of the brain**.

TEST	BACTERIAL	VIRAL	FUNGAL	TB
Pressure(70-180mm H2O)	+	Normal	Variable	Variable
WBC(0-5 cells)	>1,000	<100	Variable	Variable
Cells	PMNs	Lymphocytes	Lymphocytes	Lymphocytes
Protein(<40mg/dL)	++	+	+	+++
Glucose(40-70mg/dL)	- - -	Normal	-	-

These values can help in the diagnosis of meningitis and tell is a lot about the causative agent. For example, high levels of PMNs indicate a bacterial infection, while in viral infections we expect hight levels of lymphocytes.

Management of meningitis

Starting empirical treatment is necessary as soon as we suspect meningitis before results of CSF examination and culture. Just like the causative pathogen, the indicated therapy varies with age.

Some guidelines warrant the use of corticosteroids [dexamethasone] to lessen the inflammation.

We should also try to reduce the high ICP if present.

Table 19.3 Empirical antibiotic therapy

Age/condition	Empiric therapy
Age 0–4 weeks	Ampicillin + cefotaxime or aminoglycoside
Age 4–12 weeks	Ampicillin + cefotaxime or ceftriaxone
Age 3 months to 18 years	Cefotaxime or ceftriaxone
Age 18–50 years	Ceftriaxone or cefotaxime ± vancomycin
Age >50 years	Ceftriaxone or cefotaxime + ampicillin
Immunocompromised	Vancomycin + ampicillin + ceftazidime or meropenem
Health care-associated meningitis	Vancomycin + ceftazidime or meropenem
Basal skull fracture	Cefotaxime or ceftriaxone
Head trauma/ neurosurgery	Vancomycin + ceftazidime
CSF shunt	Vancomycin + ceftazidime
β-lactam allergy	Vancomycin + moxifloxacin ± co-trimoxazole (if *Listeria* suspected)

Anyone who came in contact with a patient with meningitis should be give prophylactic therapy [because it's transmitted orally and by respiratory droplets].

After the lab identifies the exact pathogen and then you can treat it with the suitable drug.

Table 19.4 Specific antibiotic therapy

Organism	Antimicrobial therapy
S. pneumoniae	Penicillin MIC <0.06 micrograms/mL: benzylpenicillin Penicillin MIC ≥0.12 and <1 microgram/mL: ceftriaxone Penicillin MIC ≥1 microgram/mL: ceftriaxone plus vancomycin
N. meningitidis	Penicillin MIC <0.1 microgram/mL: benzylpenicillin or ampicillin Penicillin MIC 0.1–1 microgram/mL: ceftriaxone
L. monocytogenes	Ampicillin or benzylpenicillin
GBS	Ampicillin or benzylpenicillin
E. coli	Ceftriaxone or cefotaxime
P. aeruginosa	Ceftazidime or meropenem
H. influenzae	β-lactamase-negative: ampicillin β-lactamase-positive: ceftriaxone
S. aureus	Meticillin-susceptible: flucloxacillin Meticillin-resistant: vancomycin
Enterococcus spp.	Ampicillin-susceptible: ampicillin + gentamicin Ampicillin-resistant: vancomycin + gentamicin Ampicillin- and vancomycin-resistant: linezolid

The outcome of meningitis

Even with the best treatment, mortality of meningitis is still high and varies with etiological agent. And the **delay in treatment with the presence of comorbidities** like cancer or diabetes affects survival and sequalae of the disease.

Decrease level of consciousness on admission, onset of seizures within 24 h of admission, signs of increased ICP all increase mortality.

Neurological sequelae occur in a substantial number of patients following bacterial meningitis. Most frequently reported sequelae are focal neurological deficits, hearing loss, cognitive impairment and epilepsy.

Clinical cases

Case Study and Questions

A 35-year-old man was hospitalized because of headache, fever, and confusion. He had received a kidney transplant 7 months earlier, after which he had been given immunosuppressive drugs to prevent organ rejection. CSF was collected, which revealed a white blood cell count of 36 cells/mm^3, with 96% polymorphonuclear leukocytes, a glucose concentration of 40 mg/dl, and a protein concentration of 172 mg/dl. A Gram stain preparation of CSF was negative for organisms, but gram-positive coccobacilli grew in cultures of the blood and CSF.

1. *What is the most likely cause of this patient's meningitis?*
2. *What are the potential sources of this organism?*
3. *What virulence factors are associated with this organism?*
4. *How would this disease be treated? Which antibiotics are effective in vitro? Which antibiotics are ineffective?*

Clinical Case 19-2 Group B Streptococcal Disease in a Neonate

The following is a description of late-onset group B streptococcal disease in a neonate (Hammersen et al: *Eur J Pediatr* 126:189–197, 1977). An infant male weighing 3400 grams was delivered spontaneously at term. Physical examinations of the infant were normal during the first week of life; however, the child started feeding irregularly during the second week. On day 13, the baby was admitted to the hospital with generalized seizures. A small amount of cloudy cerebrospinal fluid was collected by lumbar puncture, and *Streptococcus agalactiae* serotype III was isolated from culture. Despite prompt initiation of therapy, the baby developed hydrocephalus, necessitating implantation of an atrioventricular shunt. The infant was discharged at age 3.5 months with retardation of psychomotor development. This patient illustrates neonatal meningitis caused by the most commonly implicated serotype of group B streptococci in late-onset disease and the complications associated with this infection.

1. Listeria
2. Cold cuts & dairy products
3. It's and intracellular organism that requires cell-mediated immunity and the patient is on immunosuppressants
4. Empirical treatment with ceftriaxone then ampicillin.