MICROBIOLOGY

Central Nervous System

SHEET NO.2

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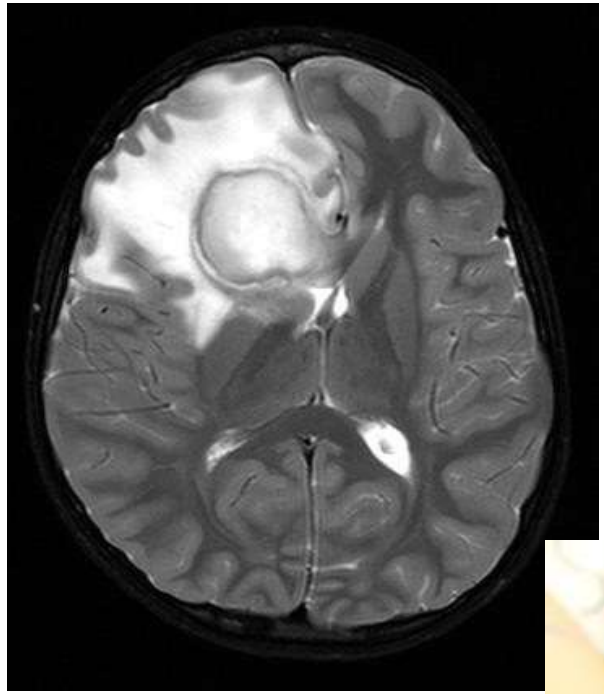
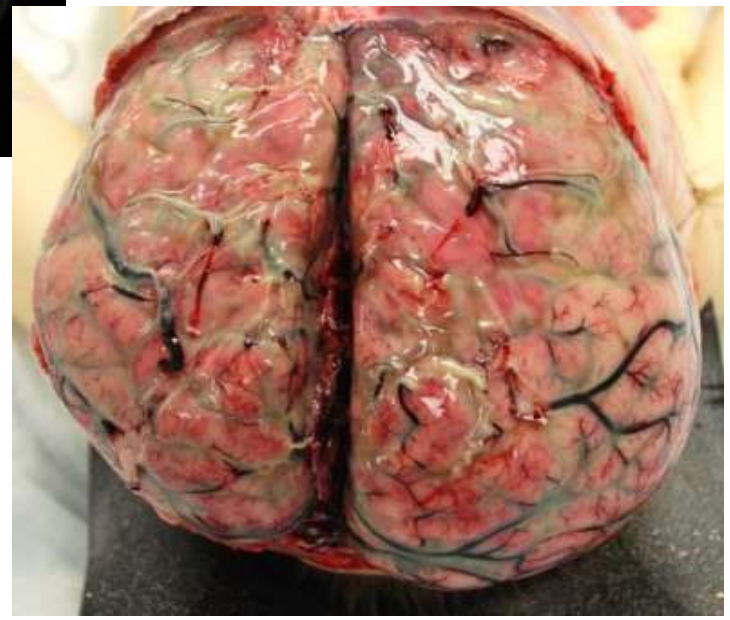
Microbiology of the central nervous system





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Lecture 1

Infections of the central nervous system (CNS)

Although some studies found out that the brain might have some sort of microbiota, other studies could not reproduce the same results. It was concluded that the earlier results were most probably due to contamination, and that there are no microbes residing in the brain.

- The central nervous system is ordinarily **sterile** and has no normal microbiota.
- Bacteria, viruses and other microbes can gain access to the CNS, damage tissue, and importantly, **induce an immune response** that is often **detrimental** to the host.
- Classically , the CNS is described as displaying **immune privilege**, as it shows **attenuated responses** to challenge by alloantigen.

The CNS is described as immune privileged since immune cells do not reach it as easily as they reach other tissues such as the skin, the respiratory, GI and urinary tracts in case of injury. The main reason that there aren't many immune cells in the CNS is that inflammation is accompanied by destruction of nearby tissue and that unlike other cells , neurons cannot regenerate .

- However, the **CNS does show local inflammation in response to infection**. Although pathogen access to the brain parenchyma and retina is generally restricted by **physiological** and **immunological** barriers, certain pathogens may breach these barriers.
- In the CNS, such pathogens may either cause **devastating inflammation** or benefit from immune privilege in the CNS, where they are **largely protected** from the peripheral immune system.

In most CNS diseases, the immune response to the pathogen is the major cause of damage to the CNS rather than the pathogen itself.

Infections of the central nervous system (CNS)

- Distinct clinical syndromes include;

  - **Acute bacterial meningitis**,
  - **Viral meningitis**

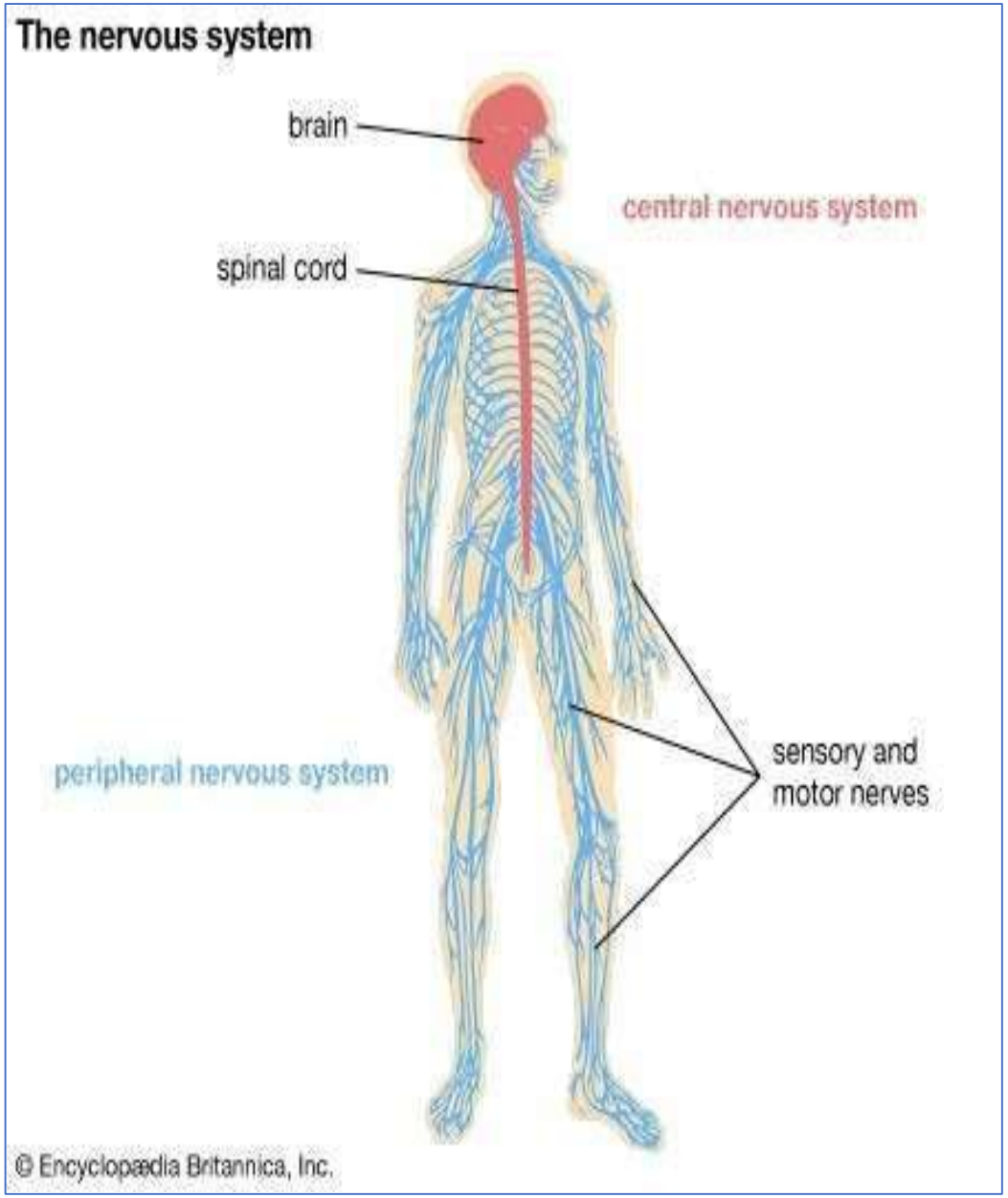
Meningitis is the inflammation of the meninges that surround the brain.

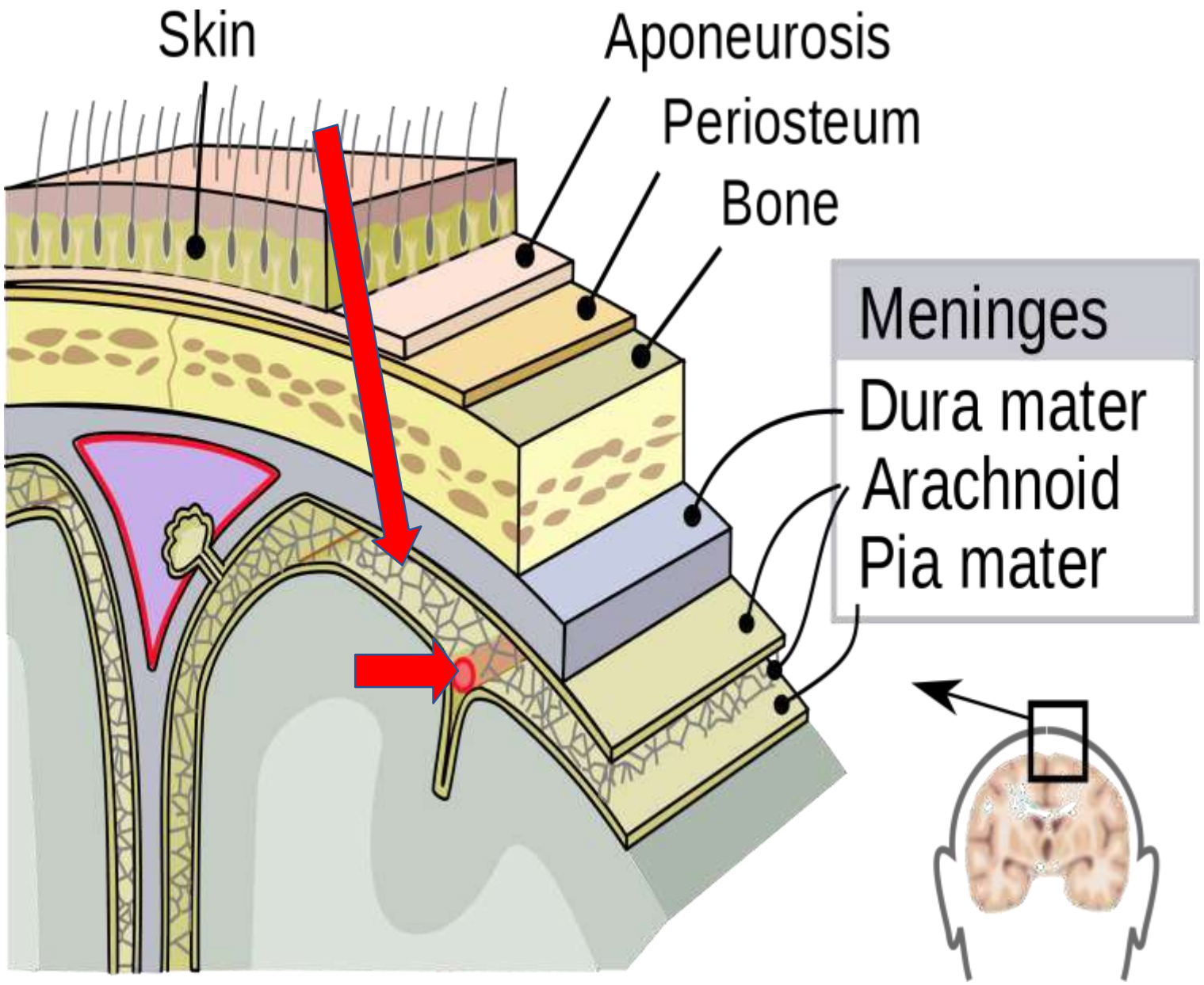
Both bacterial and viral meningitis present acutely.

But they differ in :

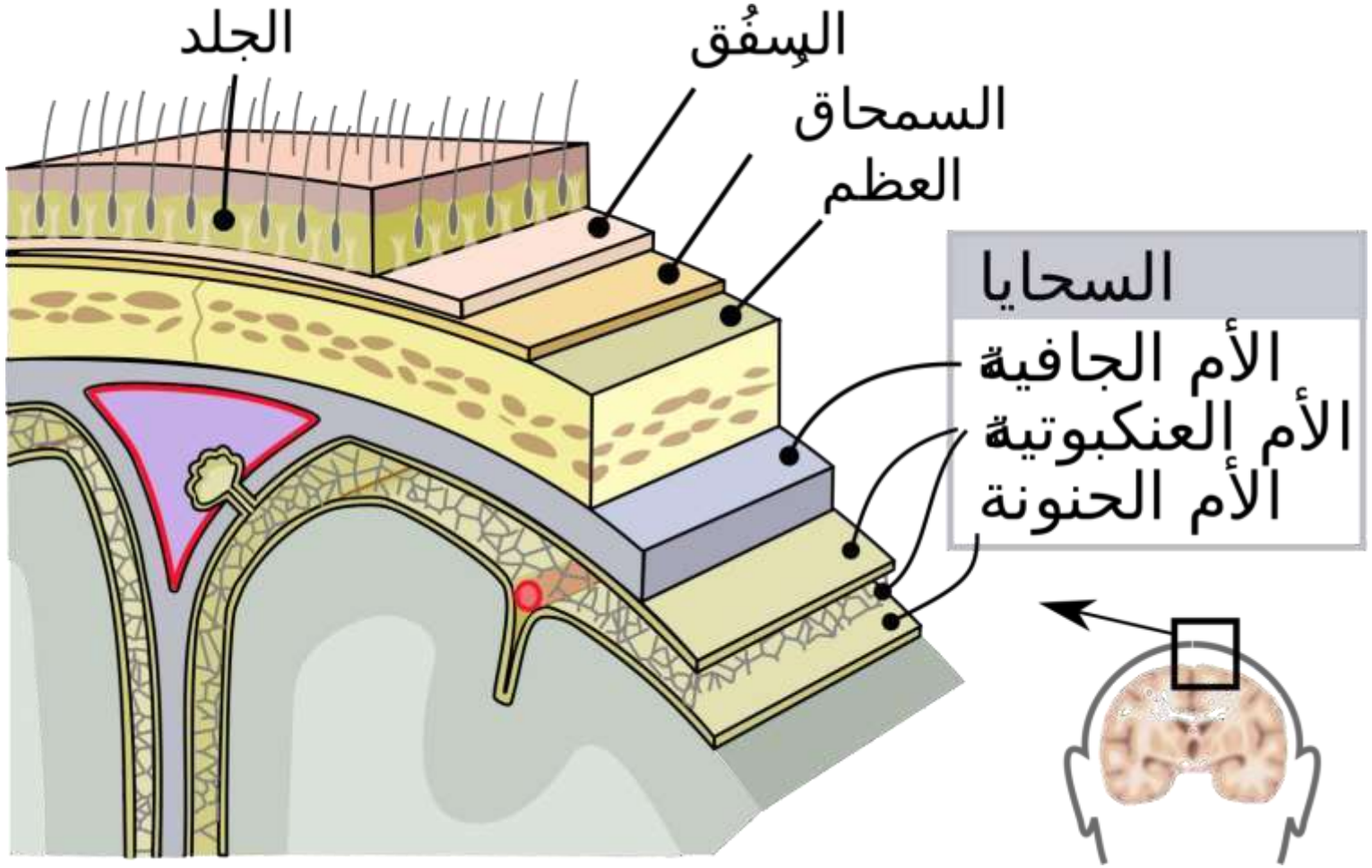
1. Labs results
2. Symptoms
3. Sequelae

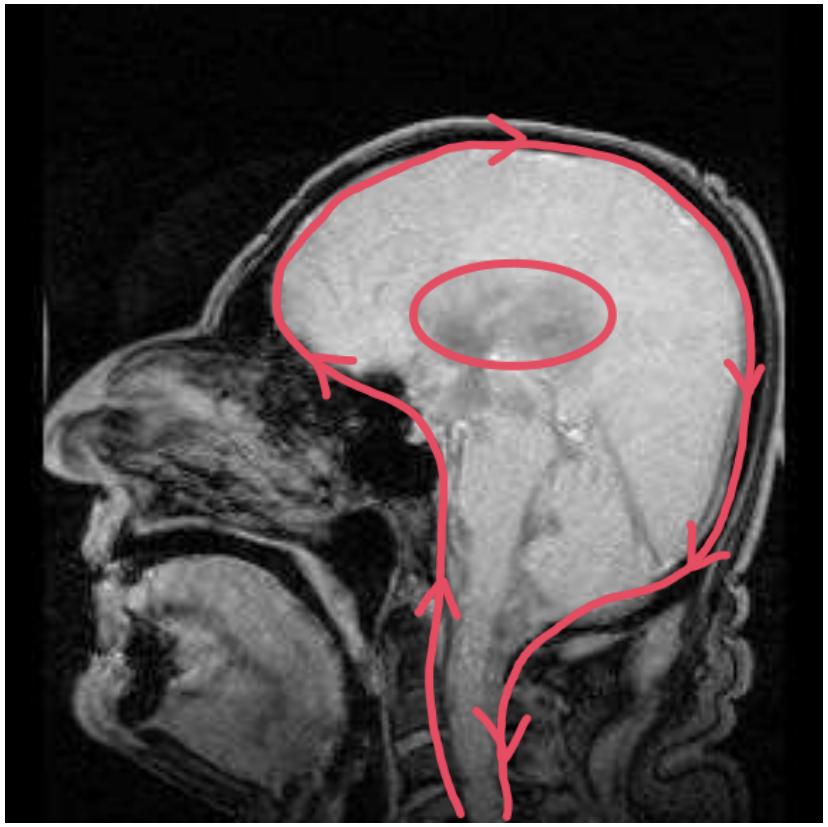
  - **Chronic meningitis**
  - **Encephalitis** is when the brain parenchyma becomes inflamed.
  - **Focal infections** that cause space occupying lesions in the brain



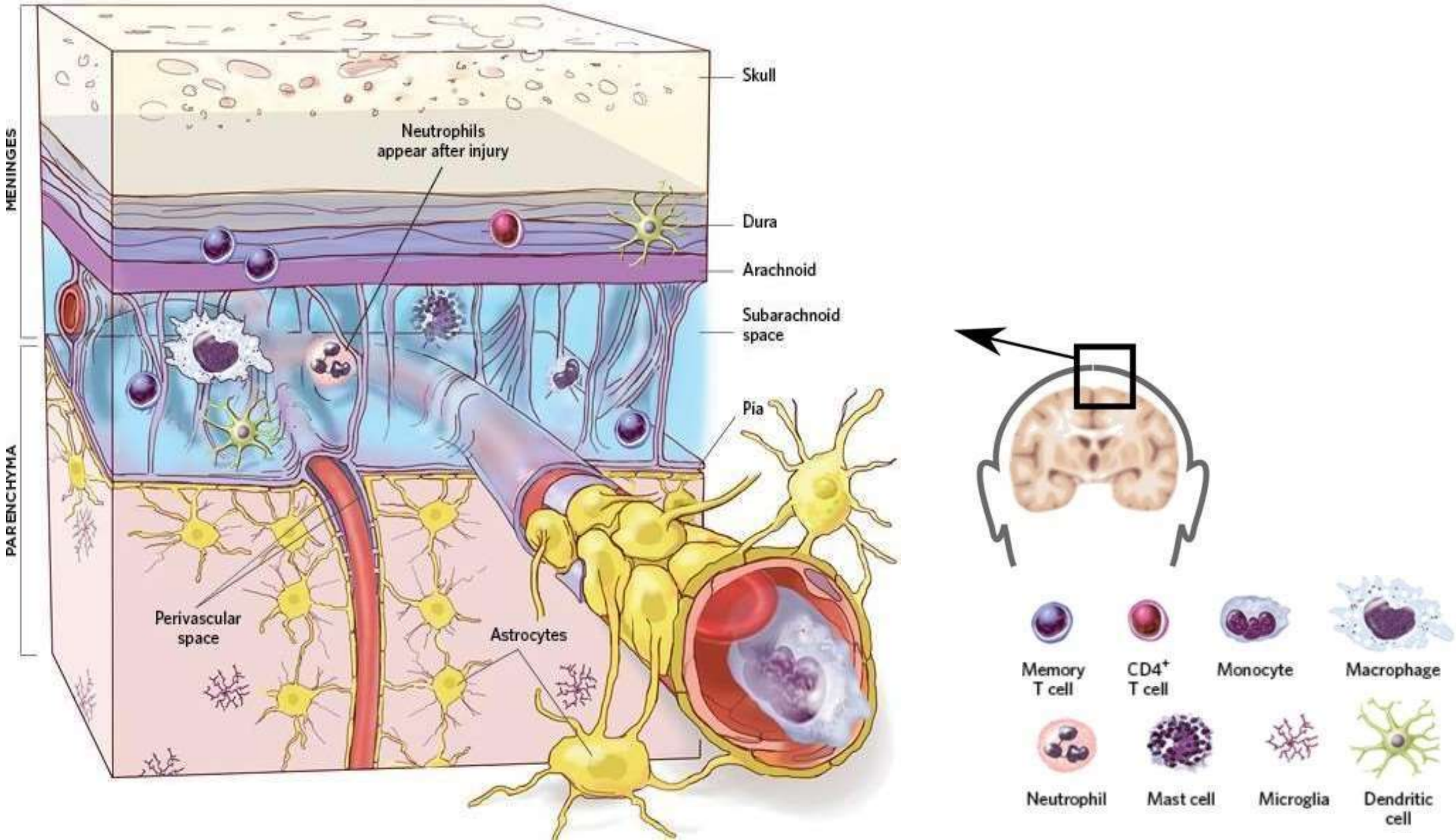


Bacteria can reach the meninges either:
1)Hematogenously (through the blood) which is the most common way. The pathogen circulates in the blood, then crosses the blood brain barrier ending up in the CSF where it starts replicating.
2)After injury and trauma that breaks all the barriers (skin, bone, and meninges), so the pathogen can reach the CSF directly.





The CSF is present in the areas indicated in red and it keeps on circulating around the brain and the spinal cord. The CSF is continuously being formed and resorbed (500 ml formed everyday, 125 ml at any one time). In case of infections, there is swelling in the subarachnoid space that prevents the continuous flow of the CSF, resulting in its accumulation and increased intracranial pressure.


MENINGES
PARENCHYMA
Skull
Neutrophils appear after injury
Dura
Arachnoid
Subarachnoid space
Pia
Perivascular space
Astrocytes
Memory T cell
CD4+ T cell
Monocyte
Macrophage
Neutrophil
Mast cell
Microglia
Dendritic cell

- The **immune system** is **a critical part of a functioning central nervous system (CNS)**, even in the absence of injury. But most immune cells are largely relegated to the cerebral spinal fluid (**CSF**), the brain's **meninges**, and the epithelium of the **choroid plexus**. When the CNS experiences a major insult, however, immune cells join **microglia** in the **parenchyma**.

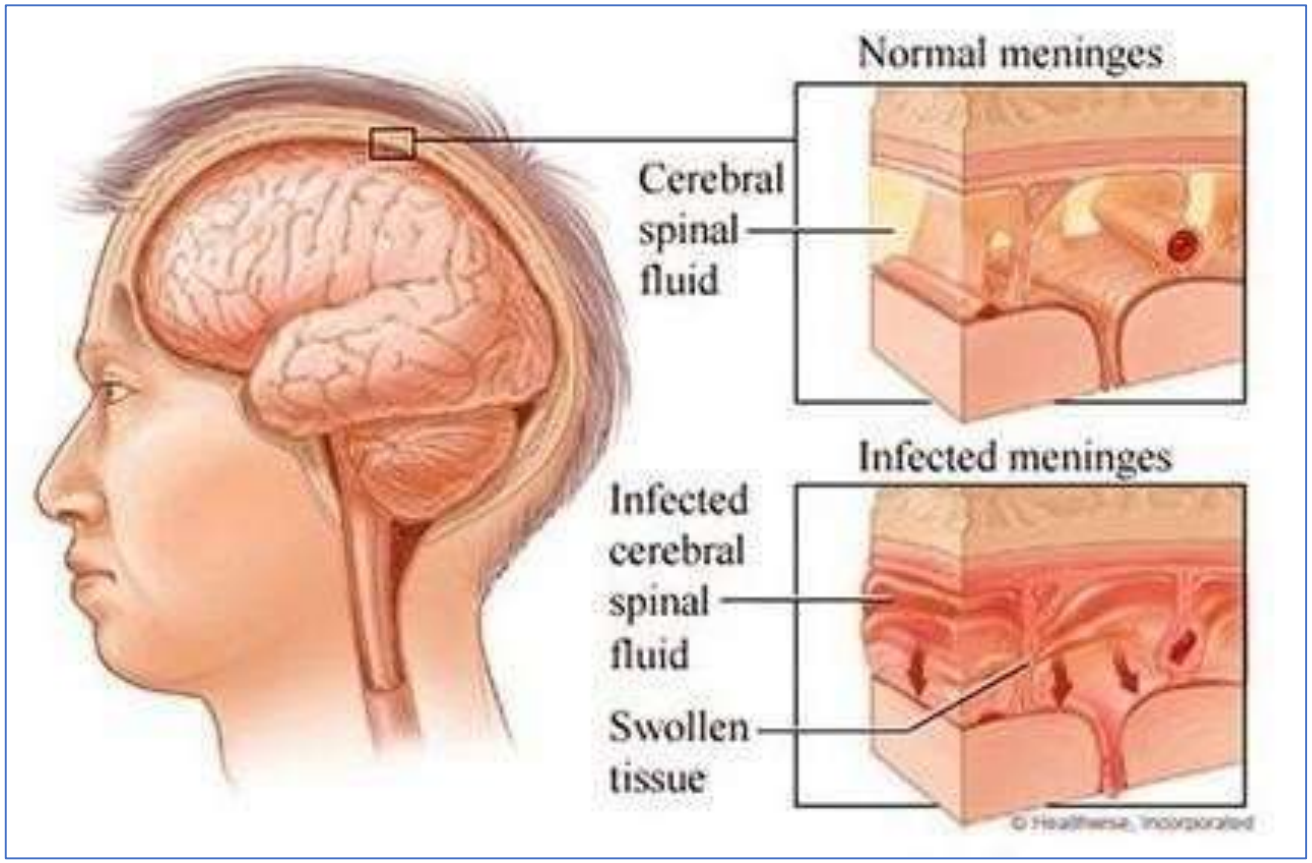
- The brain is rich in **resident macrophages**, called **microglia**, which become activated in response to tissue damage or infections in the brain. The threshold for their activation, however, may be higher than that of macrophages in other tissues.

- Most of the WBCs in the CNS can be found in the CSF. Even though the CSF contains WBCs, their concentration is significantly lower than that of the blood (CSF may contain up to 5 WBCs per mm^3). Most of these WBCs are lymphocytes with some monocytes. Neutrophils are only seen in case of injury. Increase in the WBCs in the CSF is an indicator of meningitis.
- Immune cells are also present in the brain parenchyma but to a lesser extent. The brain parenchyma may contain microglia, which are macrophages with unique properties. Microglia are not only concerned with immune responses, rather they have some physiological functions such as neuron pruning and phagocytosis of dead cells.
- In addition, there are some complement proteins that are synthesized in the brain parenchyma. For example, C1q has been shown to target neuronal axons for degradation and engulfment. This helps in the rewiring of the CNS during development.

What is meningitis ?

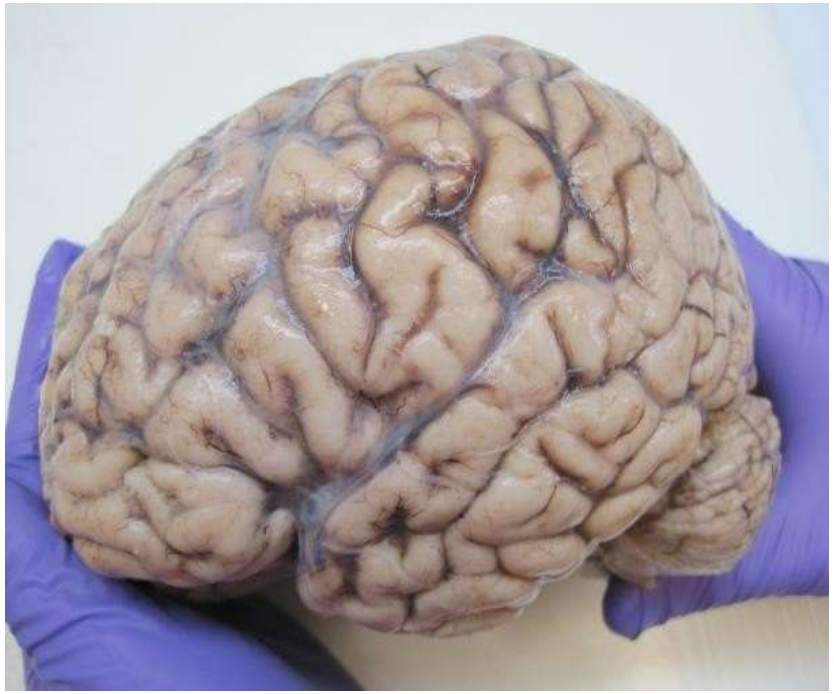
- Meningitis, an inflammation of the leptomeninges and subarachnoid space, is a **neurologic emergency**.
- **Early recognition**, efficient decision making, and **rapid institution of therapy** can be life saving.
- Meningitis commonly has **Infectious causes** (bacterial, viral, fungal and parasitic), but can also be non-infectious (drugs, malignancies, autoimmune diseases).

In case of meningitis, infectious causes are more common than non-infectious ones. While in PNS disturbances, infectious causes are less common.

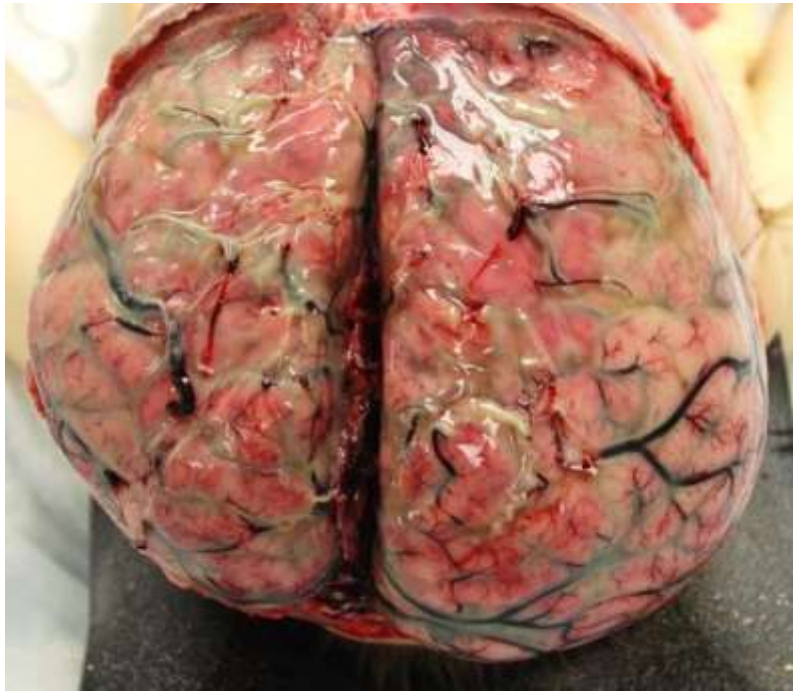


Normally, the CSF should be clear. When infection occurs, there the CSF will become turbud and adjacent tissue will swell. Turbidity is caused by bacterial growth similar to that seen when growing bacteria in broth.

Post-mortem



Normal



Meningitis

Pus and hemorrhage can be seen in different areas of the brain.
Since the CSF circulates around the brain, infection will spread throughout the subarachnoid space.

What is bacterial meningitis ?

- Bacterial meningitis is an acute purulent infection within the subarachnoid space and is the **most common form of suppurative CNS infection.**
- A few bacterial species are often involved in meningitis, they vary by **age** and **predisposing conditions**.
- Bacterial meningitis mostly presents as a fulminant illness progressing within **hours**.

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

- In infants less than 3 months of age , GBS, E.coli , and Listeria monocytogenes are common causes of meningitis.
- GBS : group B streptococcus / streptococcus agalactiae
- GBS and E.coli can colonize the birth canal and cause meningitis . Pregnant women are usually screened for GBS, and if GBS was present , antiobiotics should be given .
- L. Monocytogenes are motile , gram positive rods that grow intracellular. People with deficient cell mediated immunity are more susceptible to L. Monocytogenes. This includes:

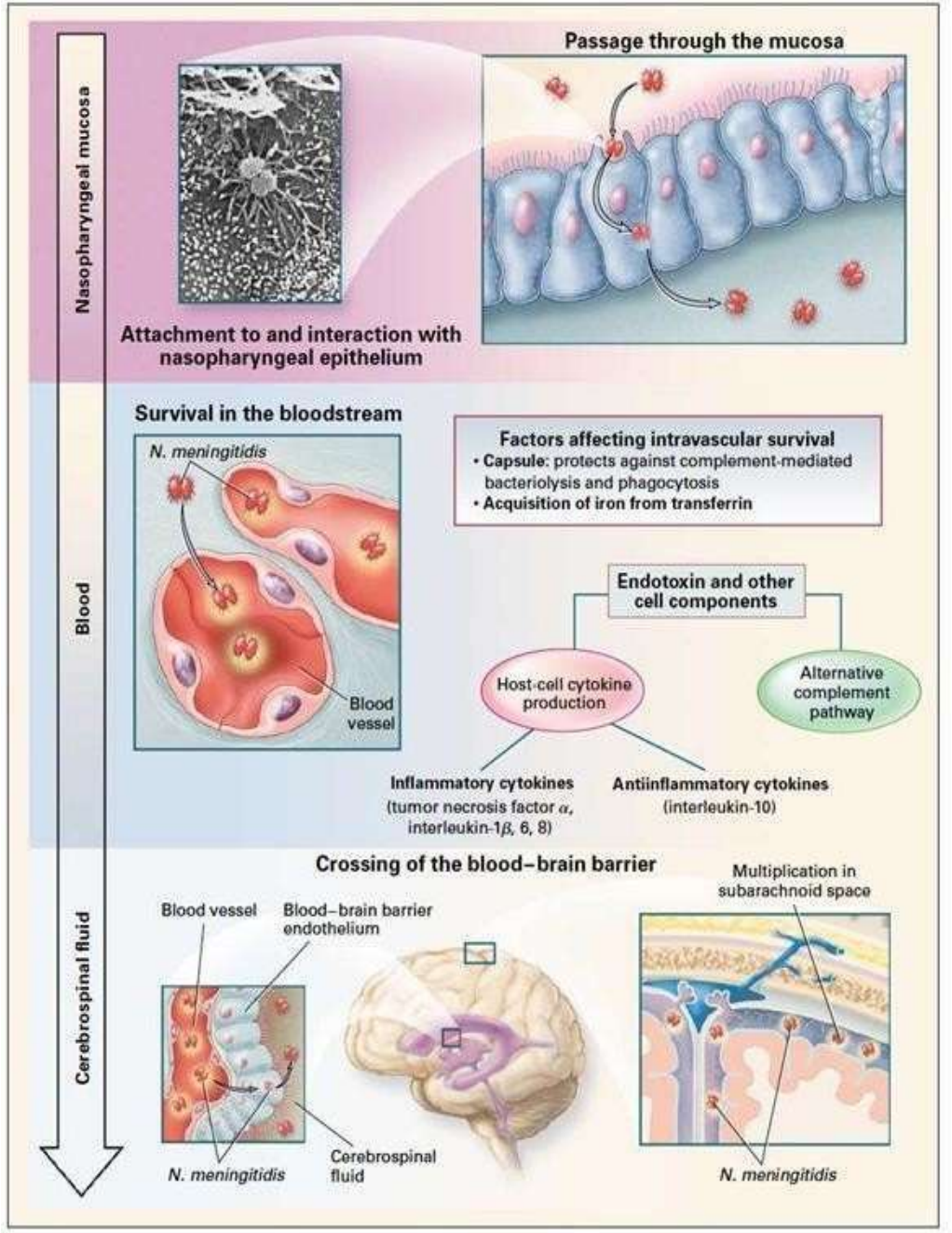
☆infants >>>> lymphocytes are not fully developed
☆elderly >>>> lymphocytes lack diversity
☆HIV patients
☆Organ transplant patients that receive immunosuppressive therapy

- In infants older than 3 months and months , Neiserria meningitides and Streptococcus pneumoniae are the most common causes of meningitis. Both of these bacteria are diplococci, with streptococcus pneumoniae being gram positive while N.mengitides is gram negative. Hemophilus infuenzae has become a less common cause of meningitis after the introduction of vaccines, but still infants after 3 months of age and before getting vaccinated are susceptible to H.influenzae, because maternal antibodies have disappeared and the infant’s immunity hasn’t developed yet .
- Staphylococcus aureus and epidermidis are the main suspects in case of head trauma and VP shunts (used to drain excess CSF in increased intracranial pressure).
- Bacterial meningitis is a medical emergency with most of the damage occurring the first hours. Therefore, it must be diagnosed and treated as early as possible.

How do bacteria get to the meninges?

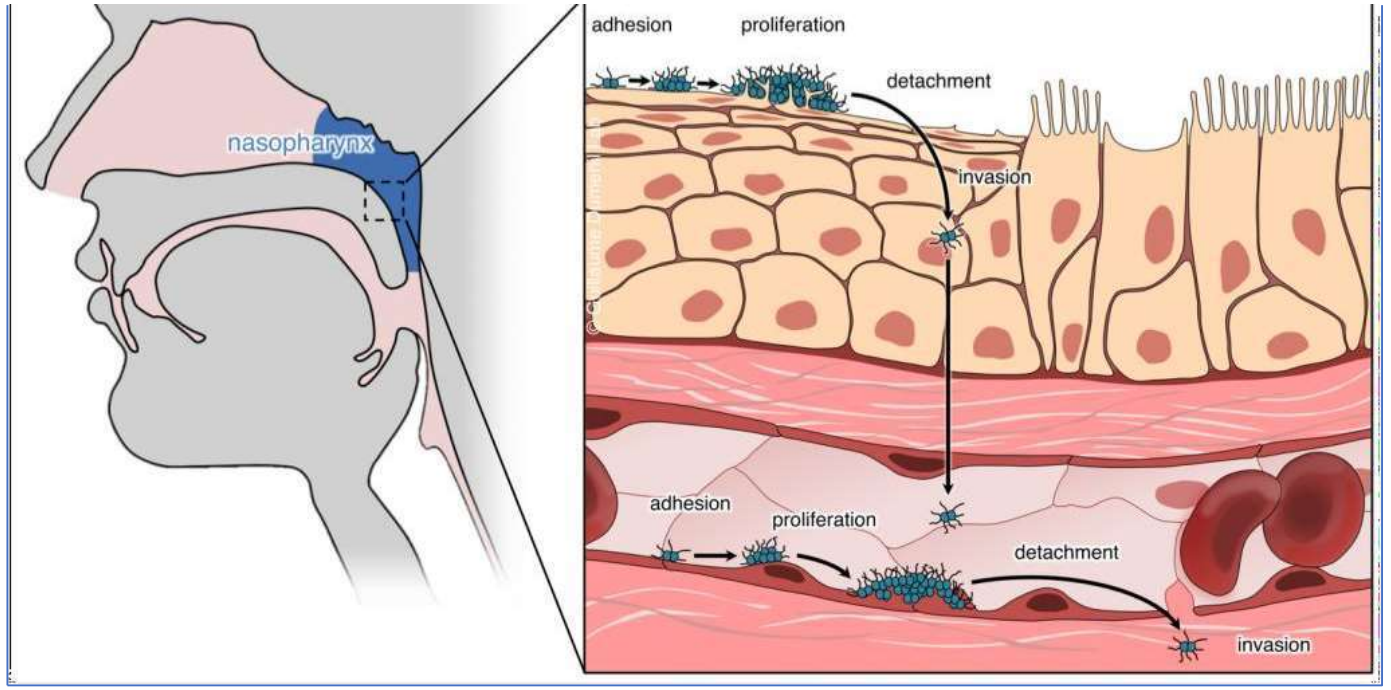
- Attachment and **colonization of the nasopharyngeal epithelium** (by Streptococcus pneumoniae and Neiserria meningitides)is followed by crossing the mucosa and **entering the blood**, if the appropriate virulence factors are present such as:
  A) a capsule that prevents phagocytosis
  B) complement inhibitors especially against C5.
  ** The risk of meningitis increases 1000-2000 fold in PNH patients taking anti-C5 antibodies.

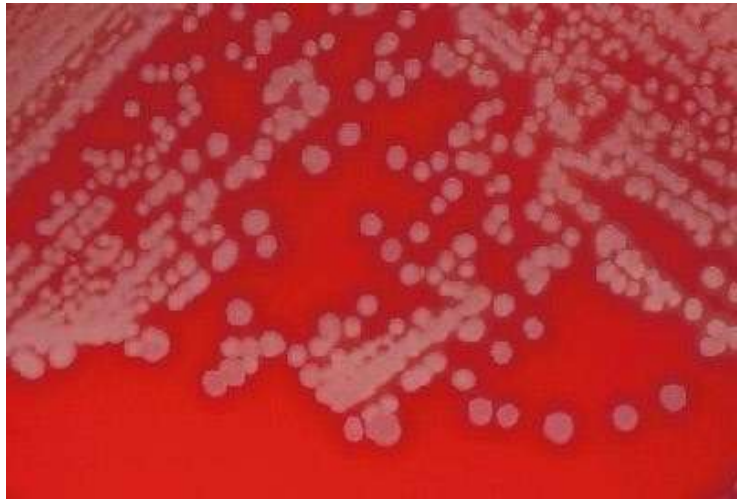
- The bacteria then **crosses the blood brain barrier** and gain access to the cerebrospinal fluid, which is **lacking in cellular and humoral immunity,** a less hostile environment than the blood.



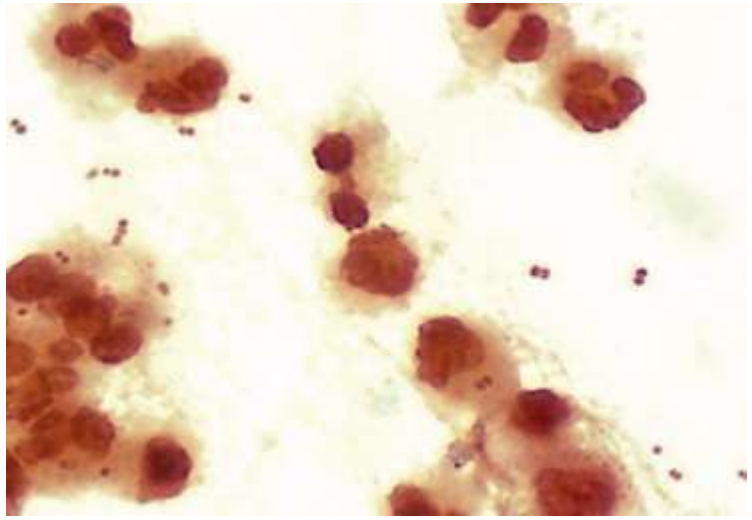
- The pathogen replicates in the CSF and an immune response is initiated against it. The immune cells will travel in the blood and cross the BBB, as it becomes more permeable with the ongoing infection. In the CSF, neutrophils start releasing elastases, collagenases, and other degrading enzymes, leading to tissue damage.

- The **immune response** to the pathogen and its products (e.g. LPS, PGN) further **damages** the surrounding tissue.





N. meningitidis colonies on blood agar plate



N. meningitidis gram stain

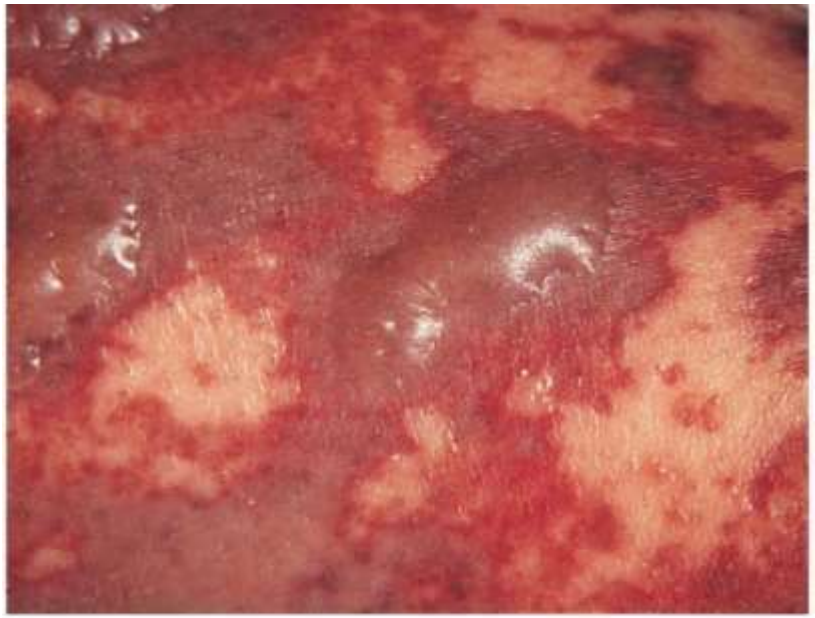
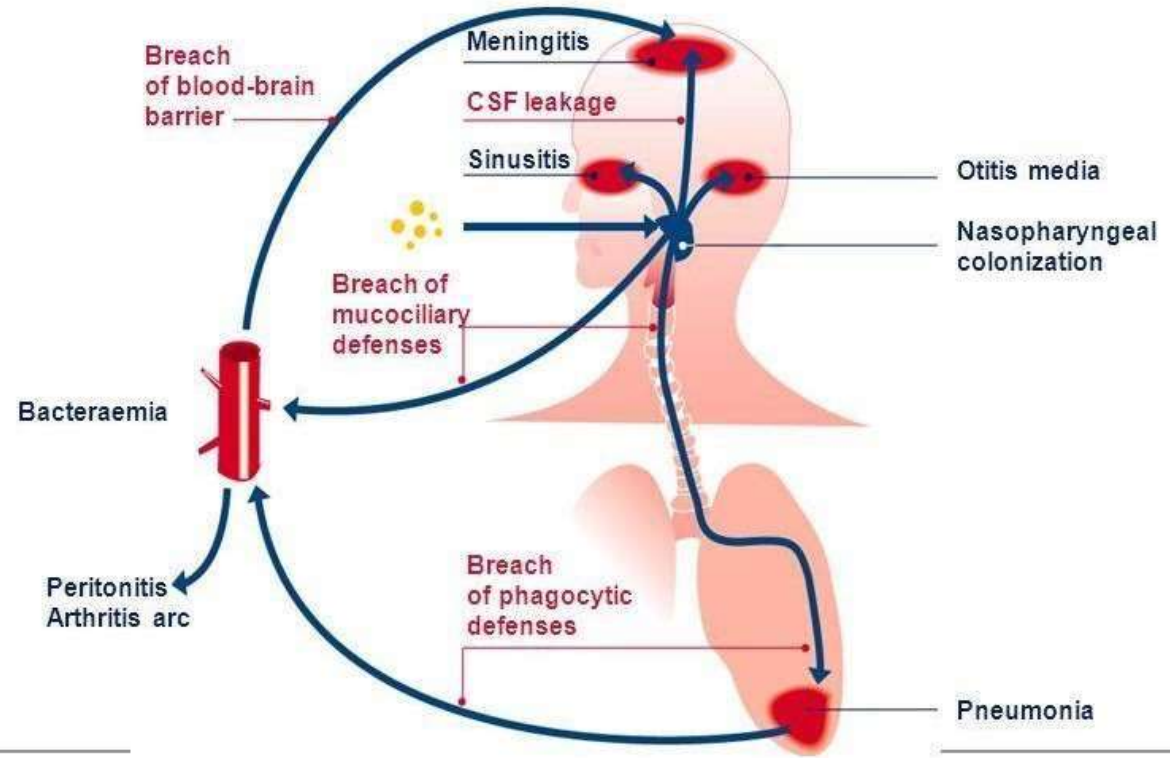


FIGURE 23-5 Skin lesions in a patient with meningococcemia. Note that the petechial lesions have coalesced and formed hemorrhagic bullae.

The above picture depicts bleeding and hemorrhage into the skin, that occurs in patients with meningococcemia, which is the presence Neisseria in the blood. This can happen after infection with either Neisseria gonorrhea or meningitides. As these bacteria circulate the blood, they might reach vessels near the skin, leading to their destruction with subsequent bleeding and bullae formation. The presence of these lesions along with the symptoms of meningitis highly indicates infection with Neiserria meningitides.

S. Pneumoniae: Pathogenesis

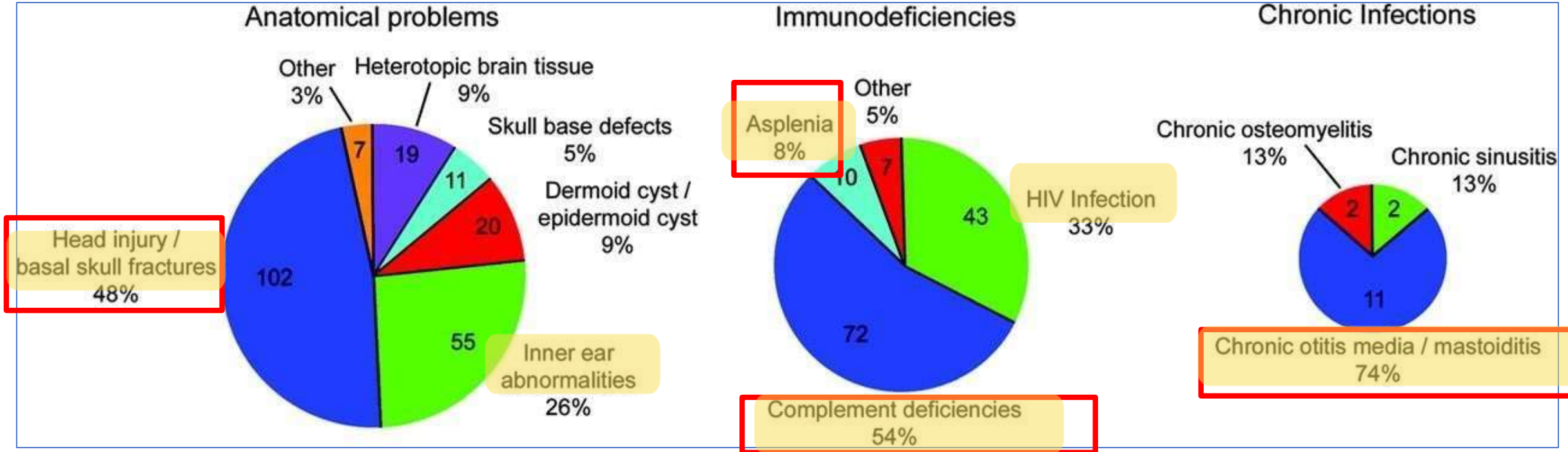


SANOFI PASTEUR

Adapted from Sanders & Wilson, Int Bacterial Pathogenesis: A Molecular Approach, 1994

Another common cause of meningitis is Streptococcus pneumoniae, which usually colonizes the nasopharynx. S. Pneumoniae might infect nearby structures such as the middle ear leading to otitis media and the sinuses leading to sinusitis, or they can directly migrate to the meninges causing meningitis, although this is less likely to happen. The common route to reach the meninges is through the circulation until they reach the meninges. In other cases, it can reach the lung, leading to lobar pneumonia (it is the most common cause of pneumonia).

How common is bacterial meningitis?



- Meningitis is **rare** in general, but incidence varies by region (2-40 per 100,000). For example Sub-Saharan Africa, also referred to as the **meningitis belt**, is known for epidemics of meningococcal meningitis, with incidence rates of 101 cases per 100,000 population.
- With the introduction of ***H. influenzae* type b conjugate vaccines** and **pneumococcal conjugate vaccine**, the incidence of meningitis from these causes decreased significantly.

There is also a conjugate vaccine for Neisseria meningitides. Conjugate vaccines are made by attaching a polysaccharide to a protein, to elicit a T cell dependent B cell response. This type of vaccine is used because the capsule, which is the main virulence factor, is made up of polysaccharides.

- Certain Factors can **increase the risk of meningitis** (listed above)

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.

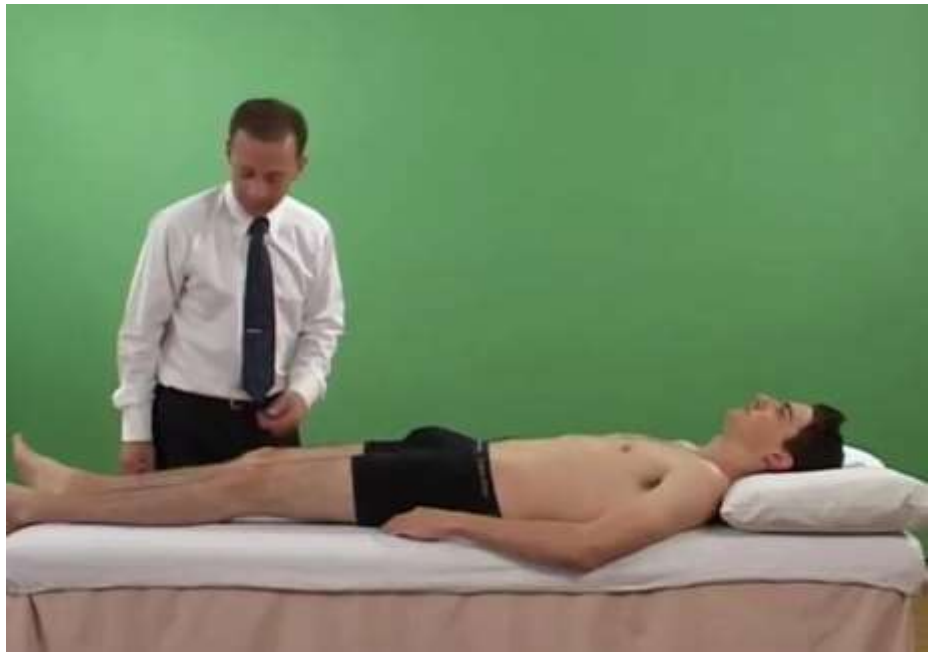
Neisseria meningitidis is consistently reported to be one of the leading causes of bacterial meningitis in the Middle East and North Africa (MENA) region.

How do meningitis patients present?

Fever and headache are present in most infections. Meningitis is accompanied with high grade fever and headache that is out of proportion and described as the worst that the patient has ever felt . Other symptoms are more specific for meningitis such as neck stiffness. It is thought that when the meninges are inflamed , any movement that stretches the meninges (e.g. moving one's neck) will cause pain. As a result , patient will avoid moving their neck rendering it stiff.

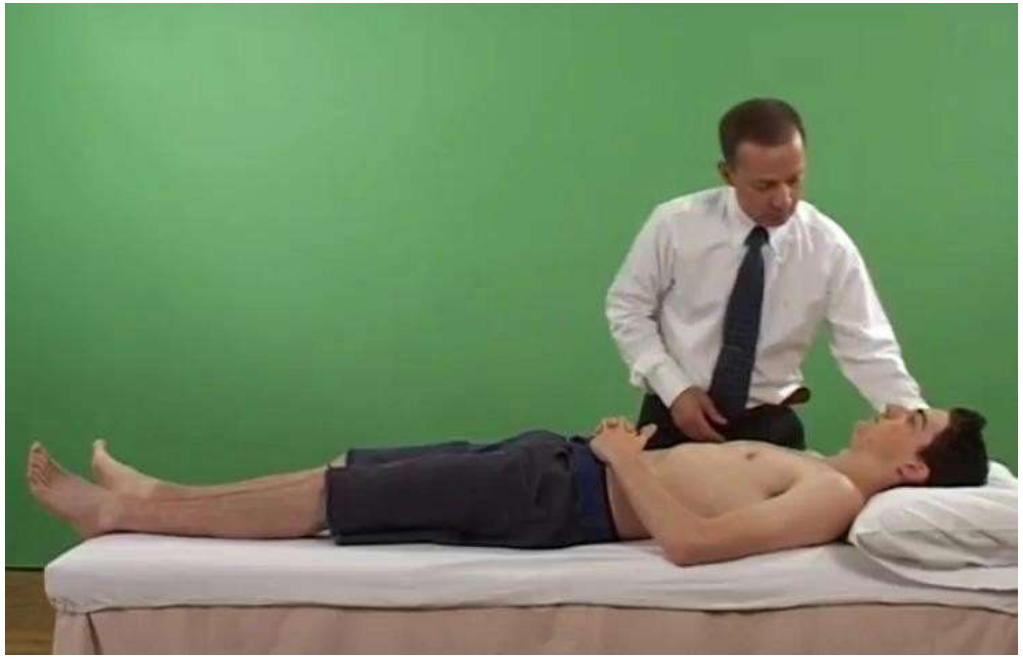
- Classical features include **fever**, **headache**, **meningism** (neck stiffness, photophobia, positive Kernig's sign and Brudzinski's sign). A positive Kernig's sign and Brudzinski's sign are not necessary for the diagnosis of meningitis. Fever, headache, and neck stiffness are the three main symptoms .
- **Cerebral dysfunction** (confusion and/ or reduced conscious level) can be present if the brain parenchyma is involved in the inflammatory reaction. (**meningoencephalitis**).
- **Seizures** can occur in neonatal and adult meningitis patients and varies by the etiological agent. Seizures occur in case the inflammation reached the brain parenchyma .
- Accompanying symptoms is often present, such as **petechial rash** in meningococcal septicaemia. Or **rhinorrhoea** suggesting basal skull fracture.
- **Increased intracranial pressure** secondary to meningitis can have ocular symptoms like optic disc swelling (**papilledema**) and cranial nerve palsies Usually seen in chronic meningitis

How do meningitis patients present?



Kernig's Sign

This manoeuvre can be done by flexing the hip joint and extending the knee. This will elicit pain if the patient has meningitis.



Brudzinski's sign

This test involves passive flexion of the neck (although it is stiff). The patient will try to relieve the pain by flexing the hip joint and knee. This unconscious flexion is considered a positive sign.

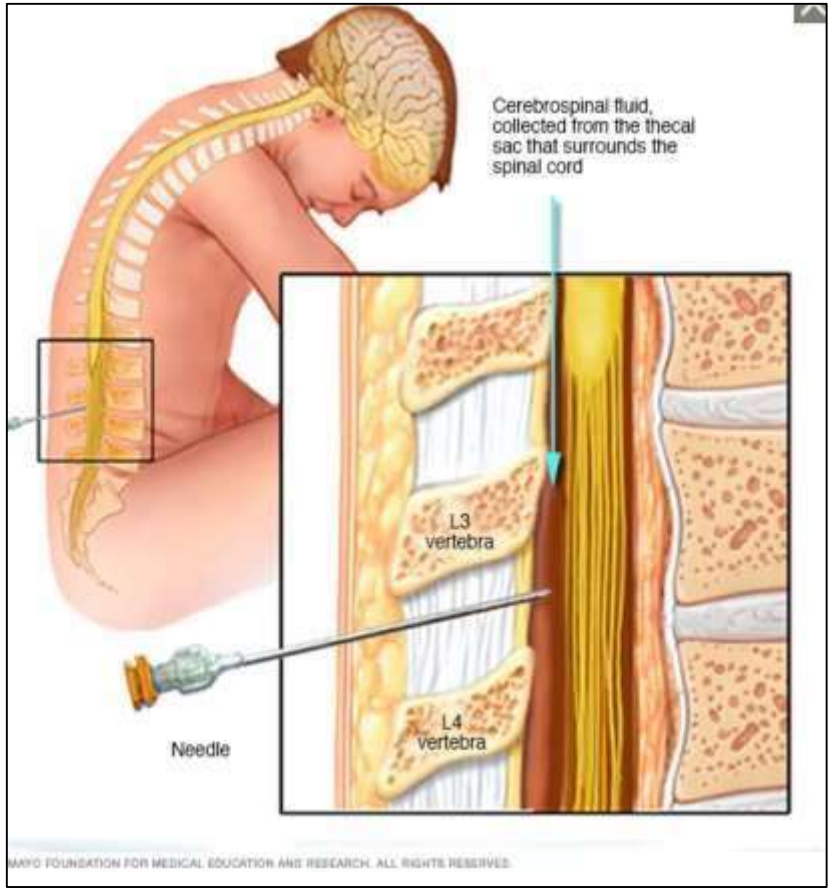
Remember! **Neonates** may present with **non- specific symptoms**, e.g. temperature instability, listlessness, poor feeding, irritability, vomiting, diarrhoea, jaundice, respiratory distress.

How to confirm a diagnosis of bacterial meningitis?

- **CSF examination** and **culture** are important to confirm the diagnosis, but this should be preceded by the administration of empirical antibiotics.
- There is about 125mL of CSF at any one time, and about 500 mL is generated every day. CSF acts as a cushion or buffer, providing basic mechanical and immunological protection to the brain inside the skull.
- If possible, three tubes (1 ml each) of CSF should be collected by a lumbar puncture between L3 and L4 for

1. **Microbiology:** gram stain , culture, and antibiotics susceptibility tests .
2. **Chemistry :**to measure sugar and protein levels (refer to the table in the following slide)
3. **Cytology :**to look for WBCs and determine their type (neutrophils vs lymphocytes)

- Blood should be collected when a spinal tap is contraindicated, or bacteremia suspected.



Spinal tab is contraindicated in case of increased intracranial pressure, because collecting the sample will decrease the pressure at the site of the puncture creating a difference in pressure that pushes the brain across the foramen leading to brain herniation and death.

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	-	-

- Bacterial meningitis
  *Bacteria consume all the glucose, so the levels of glucose decrease significantly in the CSF. While the concentration of proteins increase, because of the cytokines and antibodies that are present.
  *The CSF looks turbid.
  *The bacteria are usually gram positive. The culture might be positive or negative , but a negative culture doesn't rule out meningitis, escpecially if antiobiotics were given prior to the spinal tab .
- WBCs are increased in all types of infections, but the type of the dominant WBC differs. Neutrophils are usually seen in bacterial meningitis, while lymphocytes are seen in viral, fungal and TB infections.
- Proteins are increased in all infections because of the inflammatory mediators. While glucose levels are decreased.

How to manage suspected bacterial meningitis?

- **Prompt empirical antibiotic therapy should be initiated** before results of the CSF examination and culture.
- Adjunctive therapy with corticosteroids (**dexamethasone**) to lessen the inflammatory response is sometimes warranted.
- **Reduction** of raised intracranial pressure if present. Using a shunt
- **Chemoprophylaxis** should be given within 24h to **household contacts** (any person with contact to respiratory or oral secretions)

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)

- Third generation cephalosporins and ampicillin are given to children younger than three months.
- Third generation cephalosporins (cefotaxime / ceftriaxone) are given to adults. Vancomycin is added in case of head trauma because of the presence of Staphylococci

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

This table is
Not important. In general, ampicillin, cefotaxime and ceftriaxone are used to treat meningitis.

What is the outcome of bacterial meningitis?

- **Mortality is high** even with promt antibiotic therapy**,** and varies with etiological agent (e.g. 5% for N. meningitidis, 20% for S. pneumoniae)
- **Delay in treatment** and **comorbid conditions** affect survival and sequalea.
- 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 amount** of patients following bacterial meningitis. Most frequently reported sequelae are **focal neurological deficits**, **hearing loss**, **cognitive impairment** and **epilepsy**.

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.

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?*

Further reading:

- Oxford handbook of infectious diseases and microbiology-
Part4: Clinical syndroms
Chapter 19: Neurological infections

- Harrison's Infectious Diseases 3rd Edition
SECTION III Infections in organ systems
Chapter 36