Microbiology of the central nervous system

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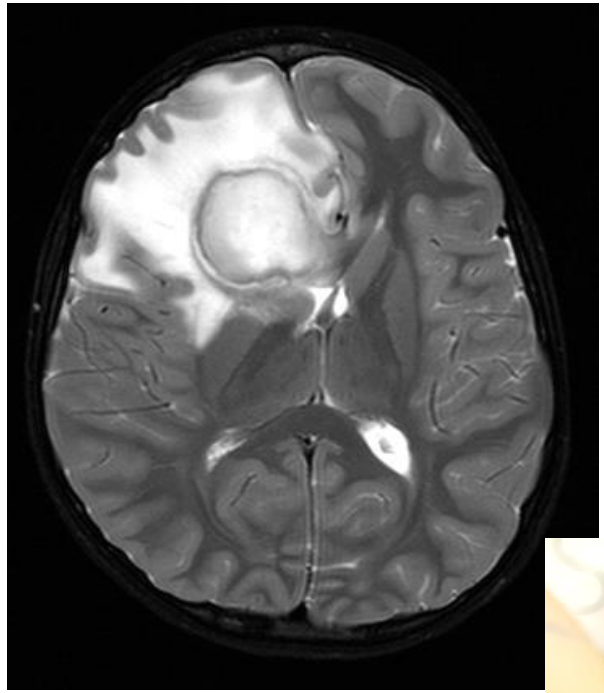


Bacterial and viral meningitis

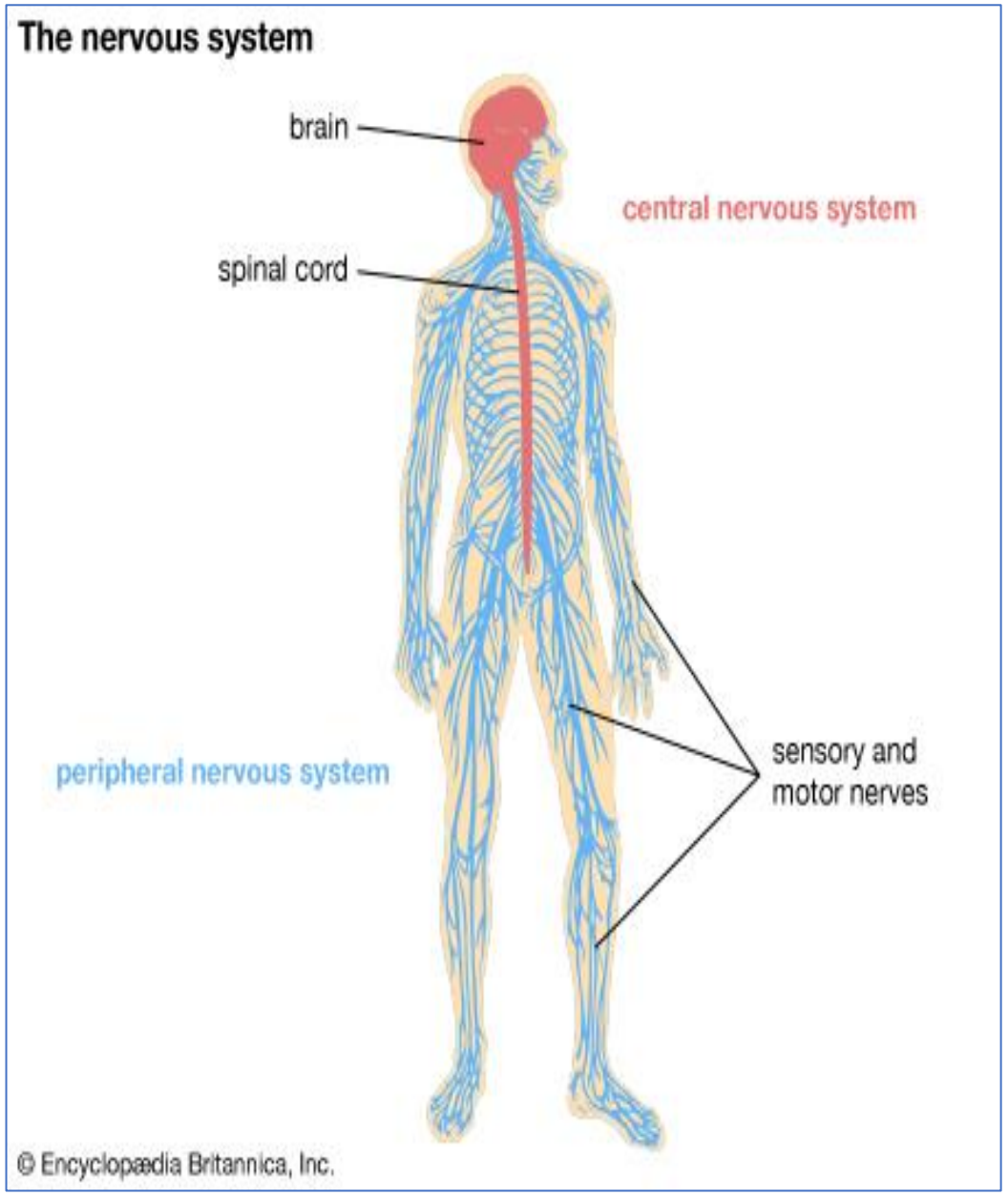
Infections of the central nervous system (CNS)

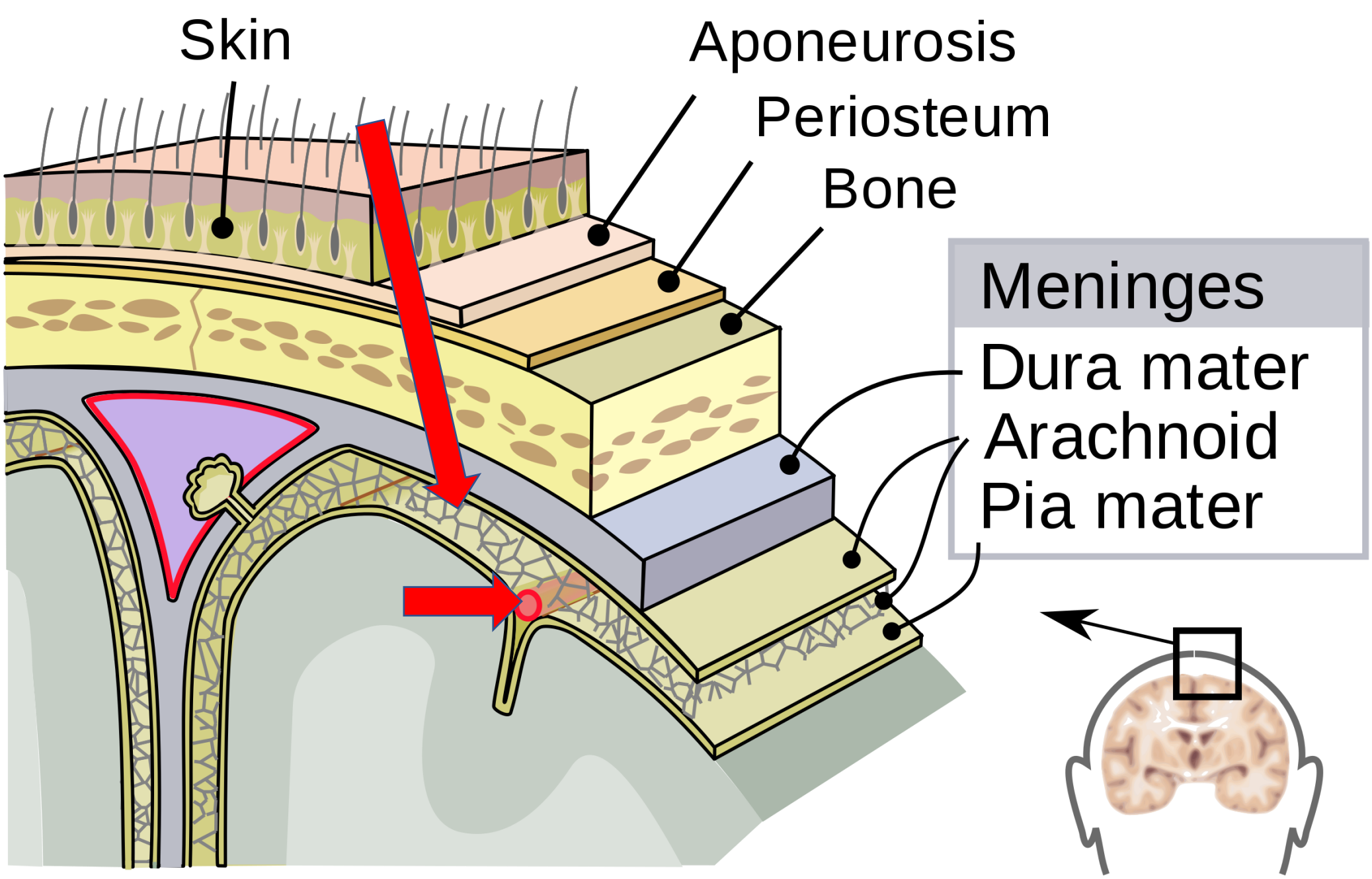
- The central nervous system is ordinarily **sterile** and has no normal microbiota.
- Bacteria, viruses and other microbes can gain access to the CNS, damage tissue, and importantly, **induce an immune response** that is often **detrimental** to the host.
- Classically , the CNS is described as displaying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

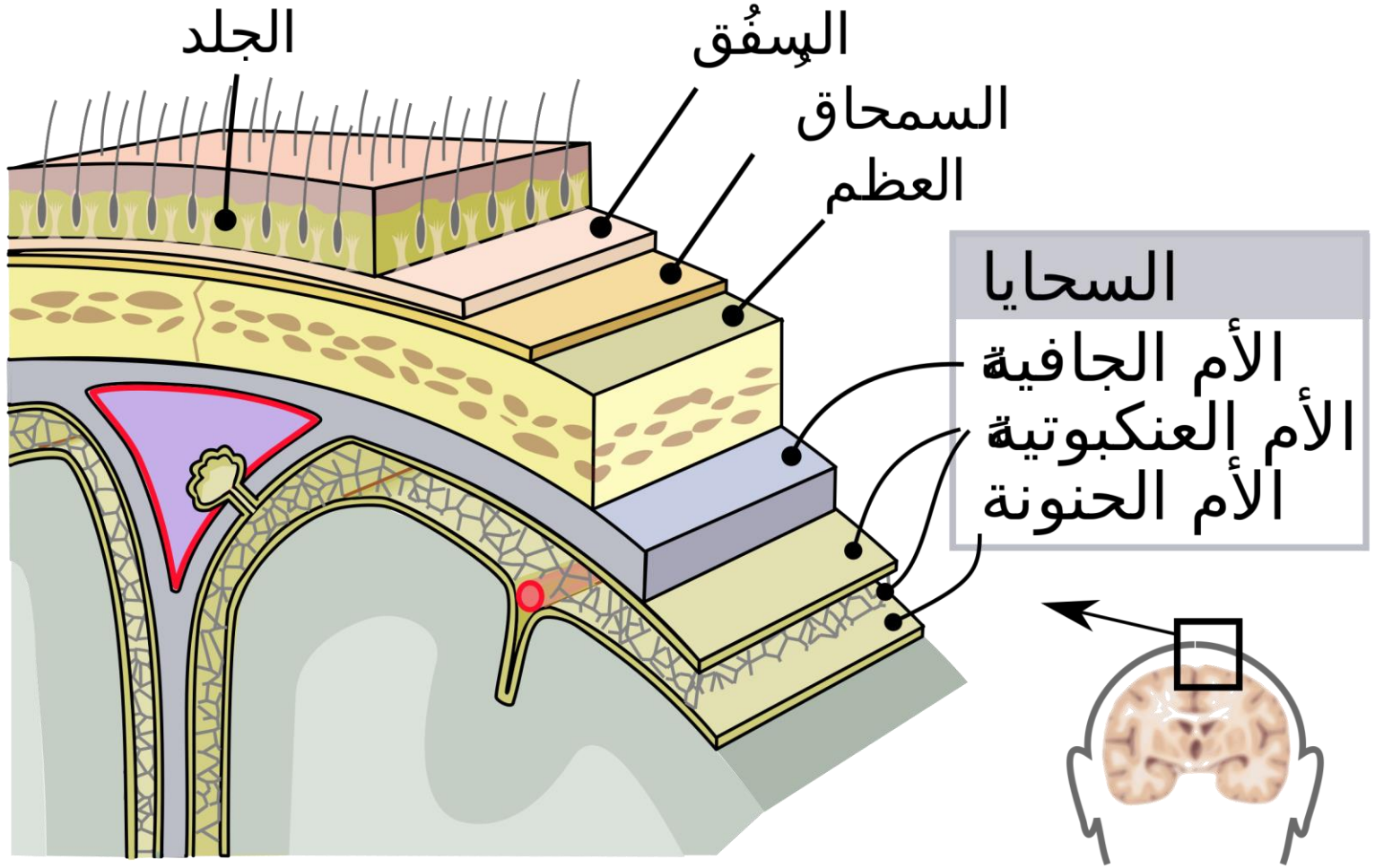
Infections of the central nervous system (CNS)

- Distinct clinical syndromes include;

  - **Acute bacterial meningitis**,
  - **Viral meningitis**,
  - **Chronic meningitis**
  - **Encephalitis**
  - **Focal infections**




Skin
Aponeurosis
Periosteum
Bone
Meninges
Dura mater
Arachnoid
Pia mater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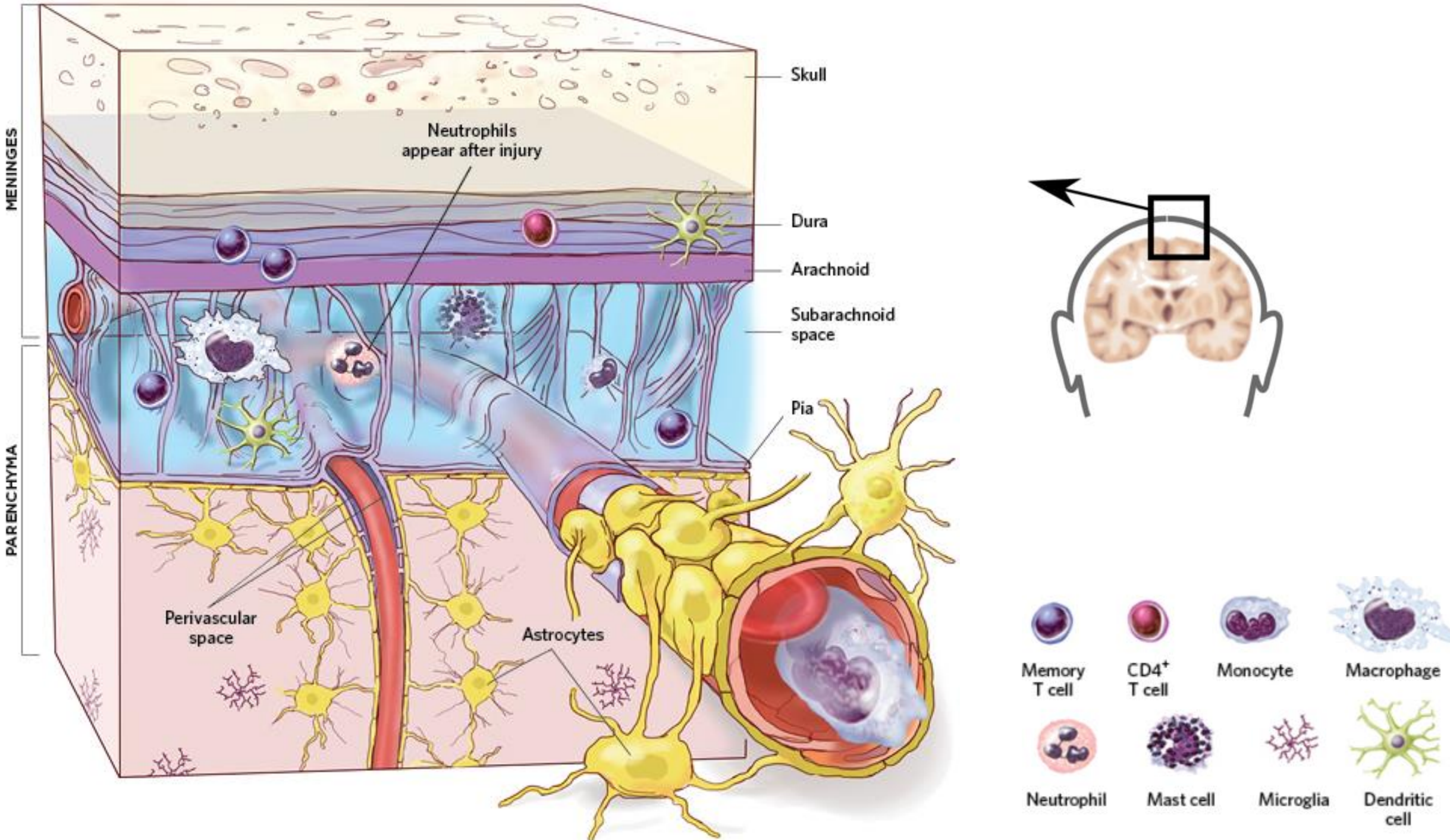
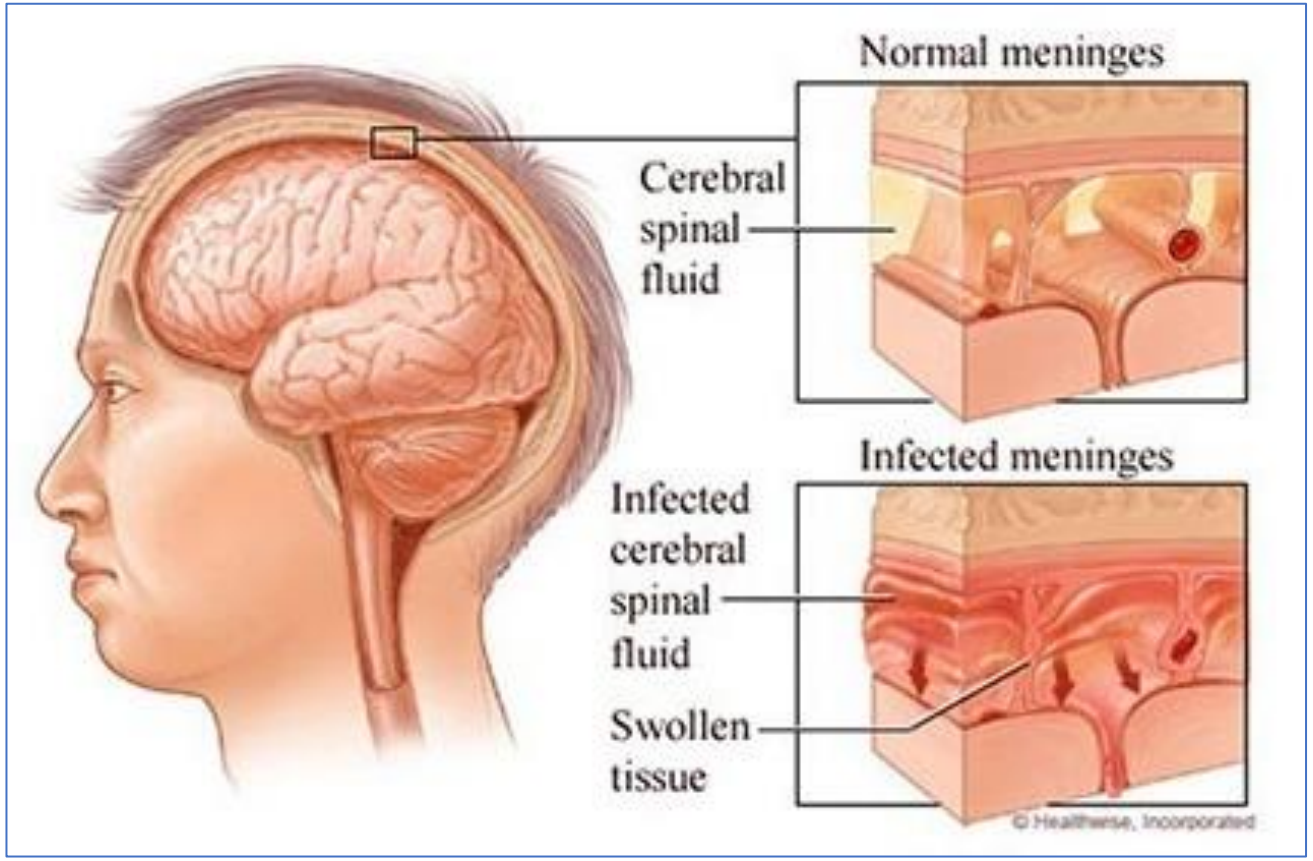

MENINGES
PARENCHYMA
Skull
Neutrophils
appear after injury
Dura
Arachnoid
Subarachnoid
space
Pia
Perivascular
space
Astrocytes
Memory
T cell
CD4+
T cell
Monocyte
Macrophage
Neutrophil
Mast cell
Microglia
Dendritic
cell

- 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**.

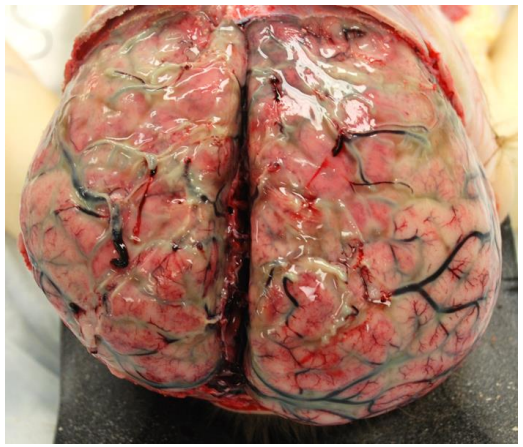
- The brain is rich in **resident macrophages**, called **microglia**, which become activated in response to tissue damage or infections in the brain. The threshold for their activation, however, may be higher than that of macrophages in other tissues.

What is meningitis ?

- Meningitis, an inflammation of the meninges 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).



Normal



Meningitis

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**.

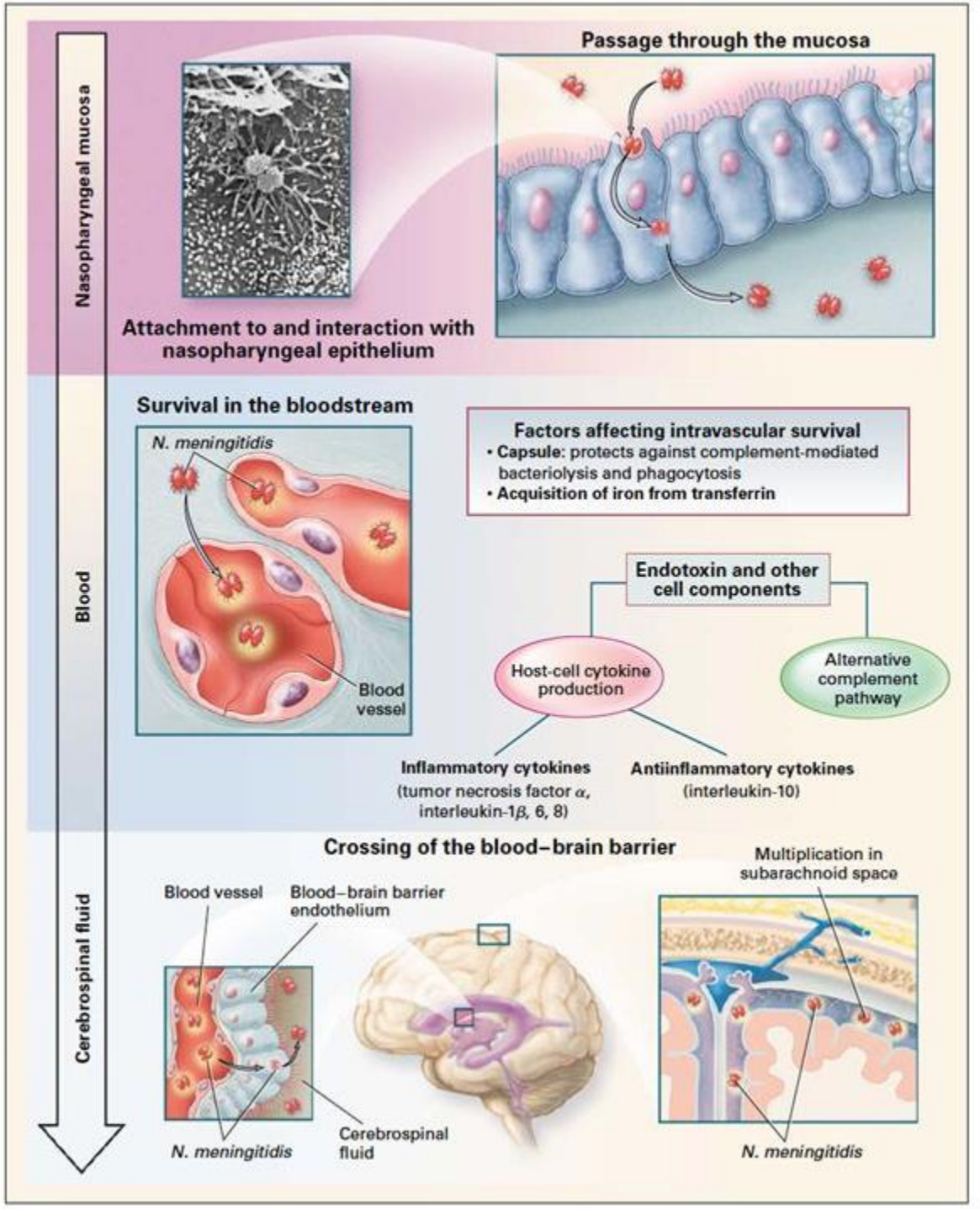
- Bacterial meningitis mostly presents as a fulminant illness progressing within **hours**.

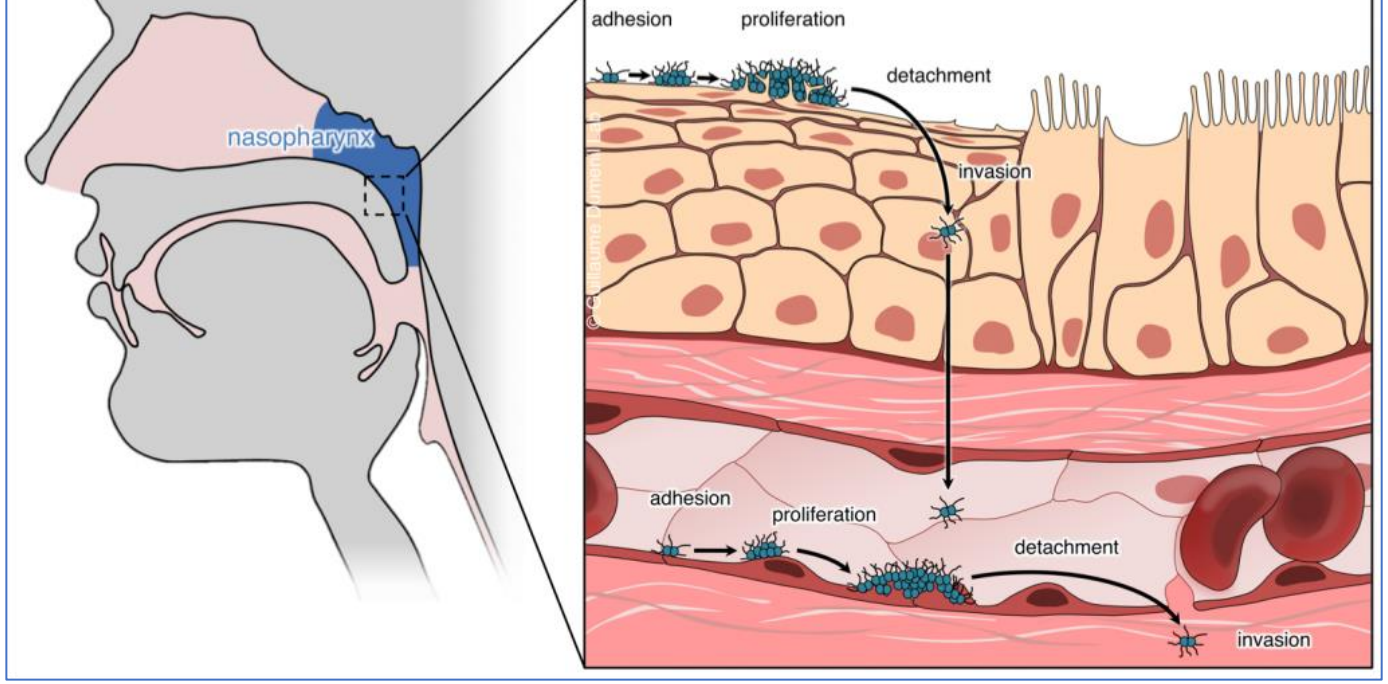
Table 19.2 Causes of bacterial meningitis

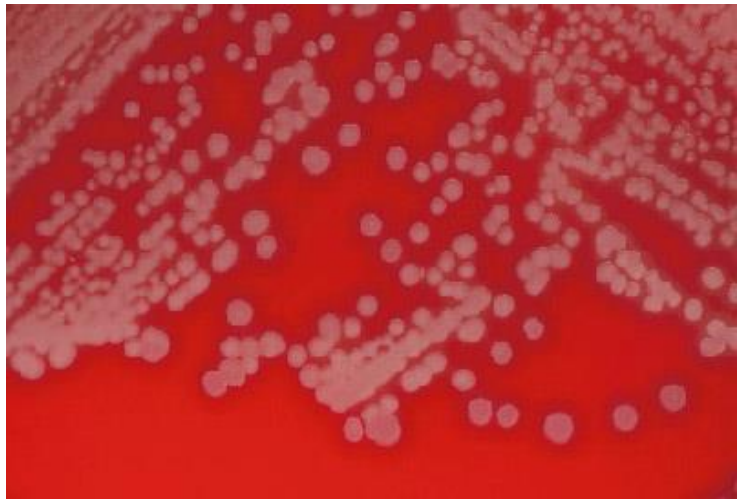
Age/condition	Common organisms
0–4 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *Enterococcus* spp., *Salmonella* spp.
4–12 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *H. influenzae*, *S. pneumoniae*, *N. meningitidis*
3 months to 18 years	*H. influenzae*, *N. meningitidis*, *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

How do bacteria get to the meninges?

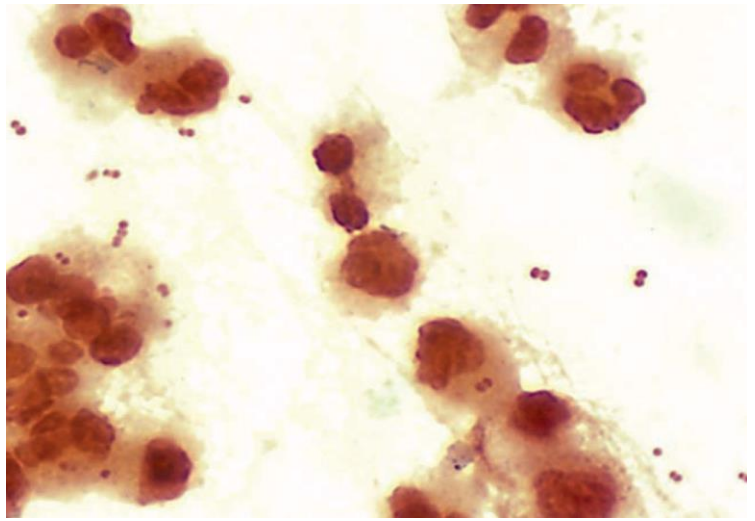
- Attachment and **colonization of the nasopharyngeal epithelium** is followed by crossing the mucosa and **entering the blood**.
- The bacteria then **crosses the blood brain barrier** and gain access to the cerebrospinal fluid, which is **lacking in cellular and humoral immunity**.
- The pathogen replicates in the CSF and an immune response is initiated against it.
- The **immune response** to the pathogen and its products (e.g. LPS, PGN) further **damages** the surrounding tissue.







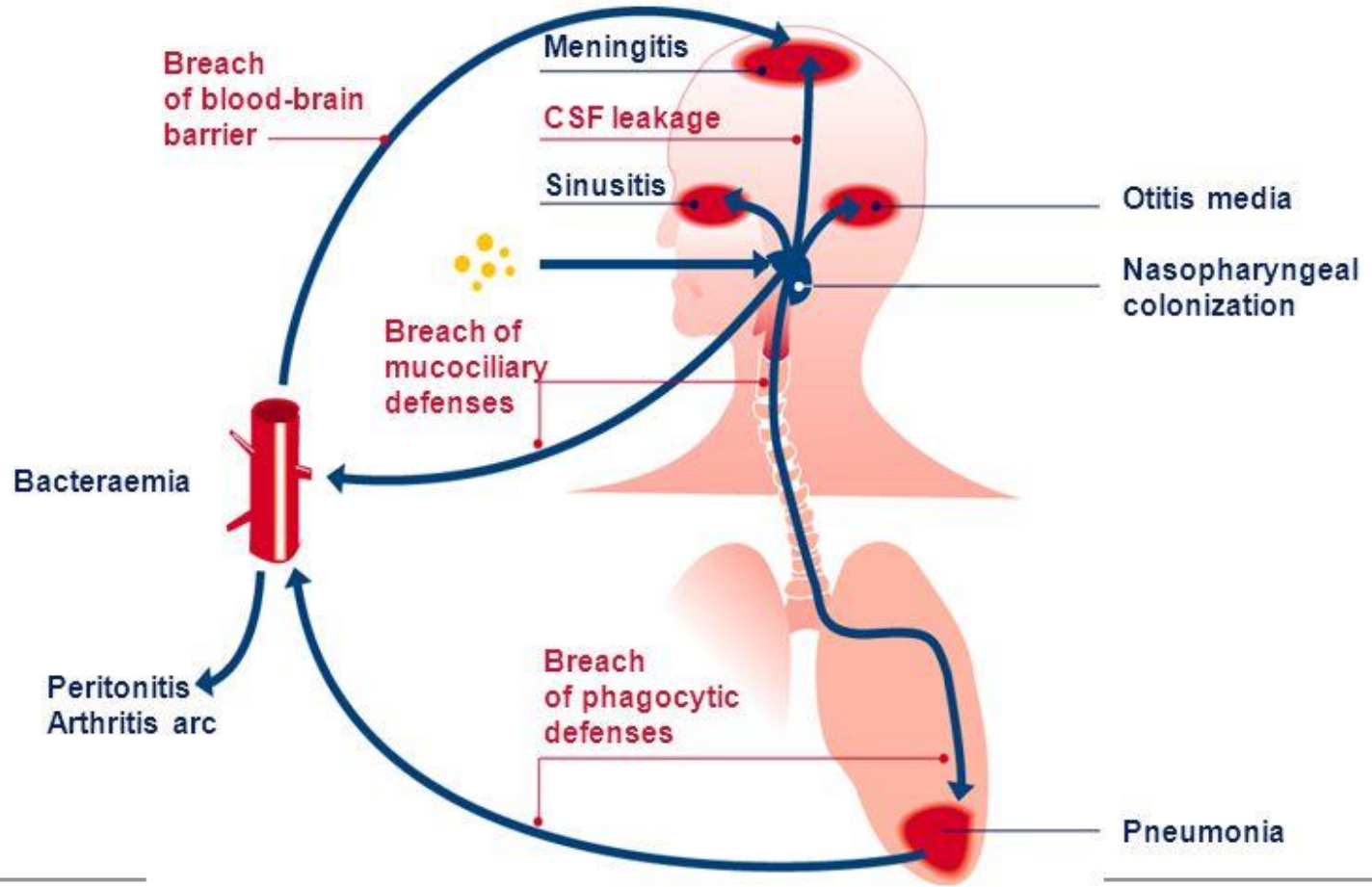
N. meningitidis colonies on blood agar plate



N. meningitidis gram stain

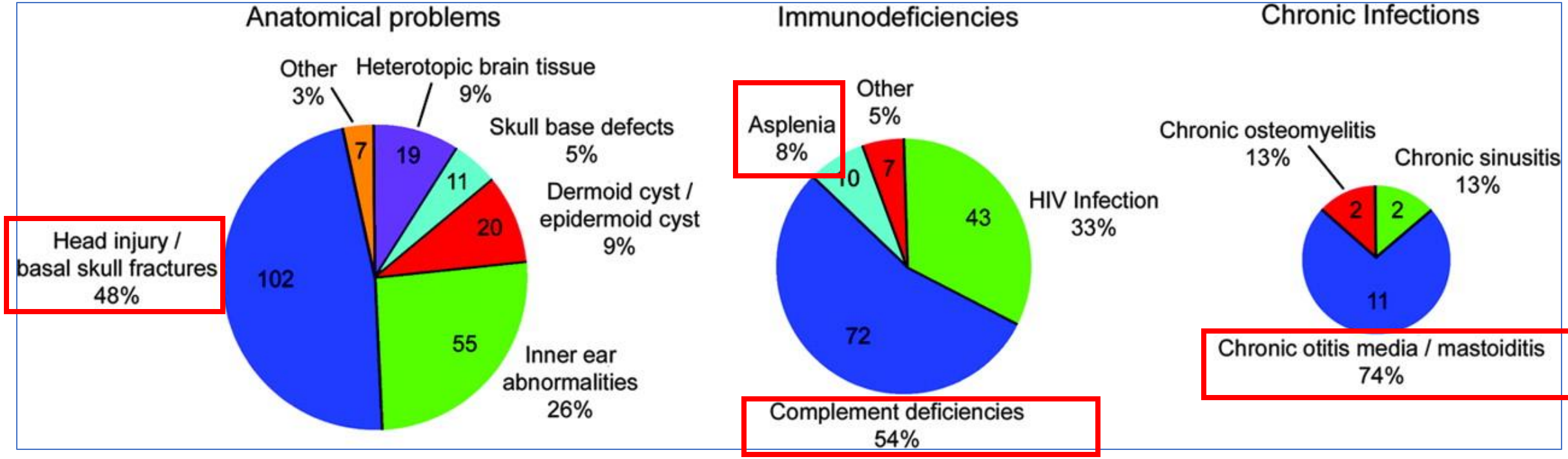
FIGURE 23-5 Skin lesions in a patient with meningococcemia. Note that the petechial lesions have coalesced and formed hemorrhagic bullae.

S. Pneumoniae: Pathogenesis



Adapted from: Salyers & Whitt. In: *Bacterial Pathogenesis: A Molecular Approach*. 1994

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.

- 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?

- Classical features include **fever**, **headache**, **meningism** (neck stiffness, photophobia, positive Kernig's sign and Brudzinski's sign).

- **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.

- 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

How do meningitis patients present?

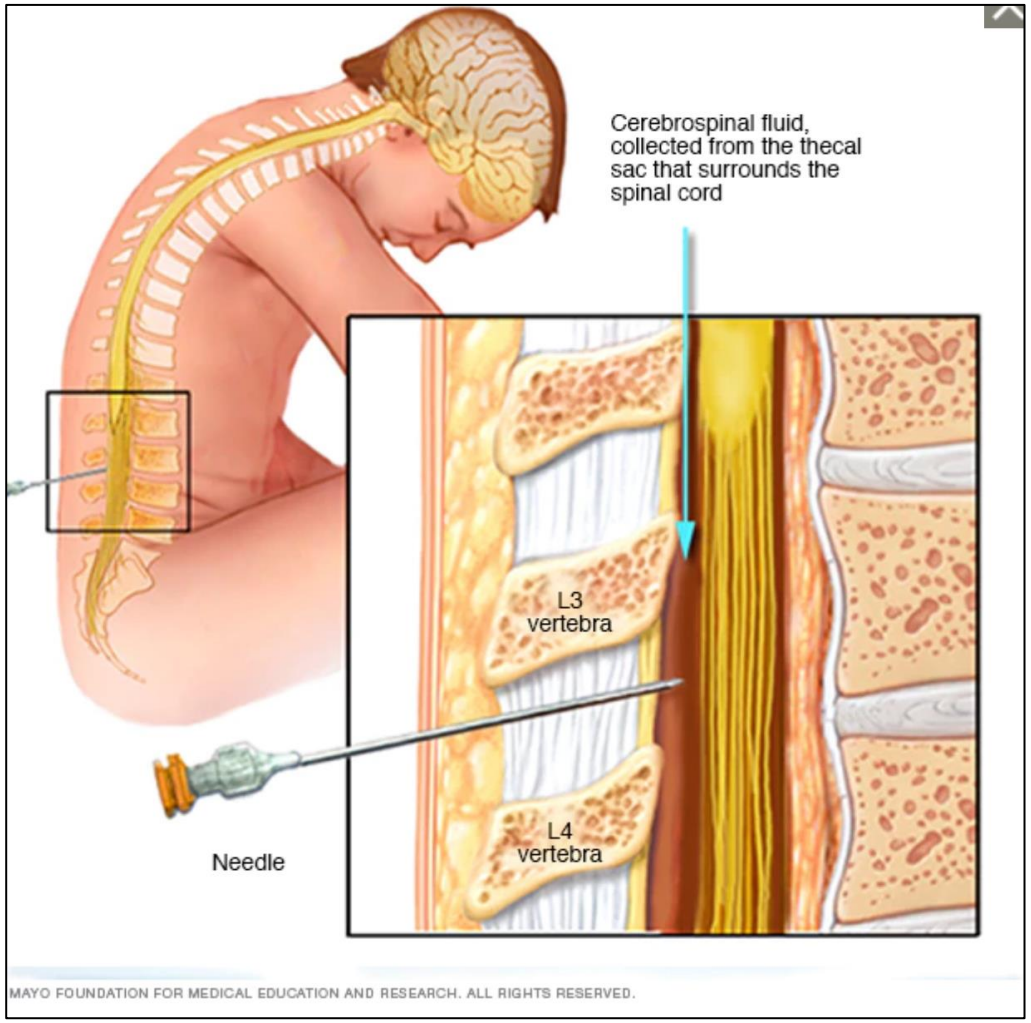
Kernig’s Sign

Brudzinski’s 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.
- 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 for **microbiology**, **chemistry**, and **cytology**.
- Blood should be collected when a spinal tap is contraindicated, or bacteremia suspected.



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	-	-

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.
- **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)

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

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**.

How is viral meningitis different from bacterial meningitis?

- The term **aseptic meningitis** encompasses broad differential diagnoses related to inflammation of the meninges not due to pyogenic bacteria. Although viral pathogens are the most common etiology, many different causes – both infective and non-infective – can be responsible for aseptic meningitis.

- The spectrum of non-infectious causes may include druginduced (e.g. amoxicillin, nonsteroidal anti-inflammatory medications or trimethoprimsulfamethoxazole), neoplastic, neurosarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, or vasculitis (e.g. Kawasaki disease) (during the nonwinter months).

How is viral meningitis different from bacterial meningitis?

- Viral meningitis (aseptic meningitis) has **similar symptoms to bacterial meningitis** (headache, fever, and signs of meningeal irritation), but **rarely** produces **focal neurological defects** and profound alterations in conciousness.

- **Enteroviruses** are the **leading cause** of viral meningitis, e.g. echoviruses, Coxsackie viruses, enteroviruses 70 and 71.

- Incidence is not clear but **seasonal variations** are found. (In temperate climates, there is a substantial increase in cases during the nonwinter months).

Acute Meningitis	
Common	Less Common
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71) Varicella-zoster virus Herpes simplex virus 2 Epstein-Barr virus Arthropod-borne viruses HIV	Herpes simplex virus 1 Human herpesvirus 6 Cytomegalovirus Lymphocytic choriomeningitis virus Mumps

Specific viral presentations

- **Enterovirus**— in neonates, fever is accompanied by vomiting, anorexia, rash, and upper respiratory tract symptoms. In older children and adults, symptoms are milder with fever, headache, neck stiffness, and photophobia

- **Mumps virus**— CNS symptoms usually occur 5 days after the onset of parotitis.

- **VZV meningitis** is associated with a characteristic, diffuse vesicular rash.

- **Herpesviruses**— HSV- 2 meningitis presents with classical symptoms.

Acute Meningitis	
Common	Less Common
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71) Varicella-zoster virus Herpes simplex virus 2 Epstein-Barr virus Arthropod-borne viruses HIV	Herpes simplex virus 1 Human herpesvirus 6 Cytomegalovirus Lymphocytic choriomeningitis virus Mumps

Enteroviral meningitis in Northern Jordan: prevalence and association with clinical findings

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Affiliations + expand

PMID: 11782931 DOI: 10.1002/jmv.2133

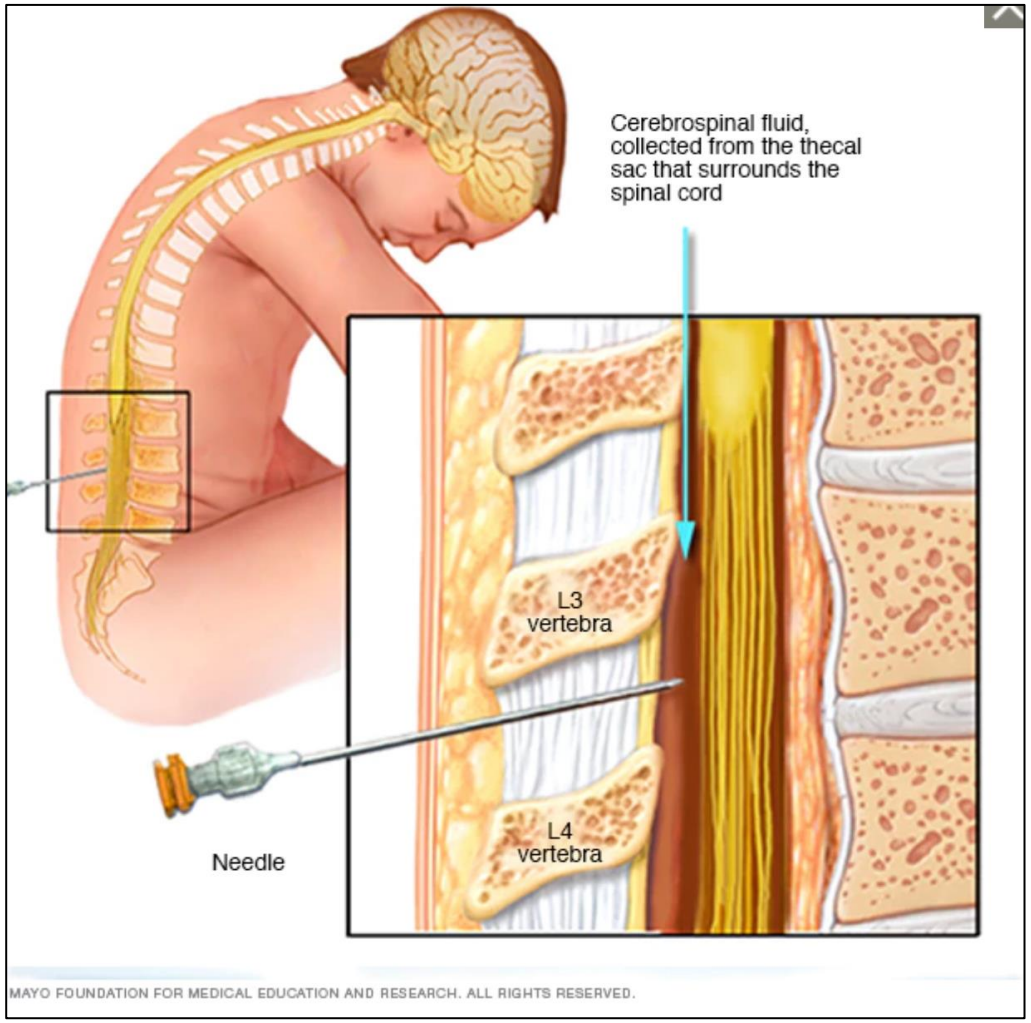
Abstract

During the summer-autumn of 1999, 390 specimens of cerebrospinal fluid were taken from infants and children younger than 15 years of age. They were suspected of having meningitis and were admitted to Princess Rahma Hospital, Northern Jordan. They were investigated for the presence of enteroviruses using shell vial culture and indirect immunofluorescence assays. Most cases (46.9%) occurred in children younger than 1 year of age in which males represented 71.9%. The common symptoms were fever, vomiting, and headache. Enteroviruses were isolated from 32 (8.2%) cases, coxsackievirus B types 2, 4, and 5 from 15 (46.9%) cases, and echovirus 9 (31.3%) was the most common identified serotype. The virus isolation rate was directly proportional to the number of leukocytes in the cerebrospinal fluid. However, enteroviral isolation was demonstrated in 4 (12.5%) of 32 cerebrospinal fluid specimens without pleocytosis. Leukocyte differential count revealed a predominance of polymorphonuclear cells in 71.4% of the cases. Hospitalization ranged from 1 day to 25 days with a mean of 7 days. The majority of enterovirus-infected patients (88.9%) were treated with at least one type of antibiotic. These results emphasize the importance of shell vial culture assay for diagnosing enteroviruses, especially in laboratories that do not have access to advanced techniques such as polymerase chain reaction.

https://pubmed.ncbi.nlm.nih.gov/11782931/

How to confirm a diagnosis of viral meningitis?

- **CSF examination** and **viral culture** are important.
- **Serology** for enteroviral infections is possible by detection of enteroviral IgM antibodies.
- Amplification o viral-specifc DNA or RNA rom CSF using **Polymerase chain reaction** (PCR) has become the **single most important method** for diagnosing CNS viral infections.



Test	*Bacterial*	*Viral*	*Fungal*	*Tubercular*
Opening pressure	Elevated	Usually normal	Variable	Variable
White blood cell count	≥1,000 per mm^3	<100 per mm^3	Variable	Variable
Cell differential	Predominance of PMNs*	Predominance of lymphocytes†	Predominance of lymphocytes	Predominance of lymphocytes
Protein	Mild to marked elevation	Normal to elevated	Elevated	Elevated
CSF-to-serum glucose ratio	Normal to marked decrease	Usually normal	Low	Low

CSF = cerebrospinal fluid; PMNs = polymorphonucleocytes.

**—Lymphocytosis present 10 percent of the time.*
†*—PMNs may predominate early in the course.*

How to manage viral meningitis?

- Based upon the history, physical examination, and cerebrospinal fluid (CSF) findings, patients can be classified as having **probable bacterial meningitis**, **probable viral meningitis**, or **indeterminant**.

- For patients with suspected bacterial meningitis (eg, WBC count >1000/microL, glucose concentration <40 mg/dL [2.2 mmol/L], protein concentration >100 mg/dL), antibiotics should be initiated promptly.

- Patients with probable viral meningitis include those with CSF findings of cell count <500/microL, >50 percent CSF lymphocytes, protein concentration less than 80 to 100 mg/dL, normal glucose concentration, and negative Gram stain. Patients who are elderly, immunocompromised, or have received antibiotics prior to presentation should be given antibiotics even if viral meningitis is the suspected diagnosis. Otherwise, the clinician can consider observing the patient without antibiotic therapy.

How to manage viral meningitis?

- When it is not clear whether the patient has a viral or bacterial process, the treating physician **can choose empiric antibiotics after obtaining blood and CSF cultures or observation with repeat lumbar puncture (LP) in 6 to 24 hours**. The majority of clinicians opt for empiric antibiotics until culture results are available in 24 to 48 hours.

- If the patient is symptomatically improved and culture results are negative, then antibiotics can generally be stopped without a repeat LP if the suspicion for bacterial meningitis is unlikely. However, repeat LP may be indicated in patients with persistent symptoms who do not have a clear diagnosis.

How to manage viral meningitis?

- Treatment of almost all cases of viral meningitis is primarily symptomatic and includes use of **analgesics**, **antipyretics**, an **antiemetics**. Fluid an electrolyte status should be monitored .

- In adults, the prognosis for **full recovery** from viral meningitis is **excellent**.

- The outcome in **infants and neonates** (<1 year) is less certain; **intellectual impairment**, **learning disabilities**, **hearing loss**, and other lasting sequelae have been reported in some studies.

How to manage viral meningitis?

Answers

1. The key signs and symptoms were sore throat, fever, faint rash, excessive napping, lethargy, headache, and pain upon turning head (stiff neck). The presence of lymphocytes in the CSF and normal glucose and protein levels minimizes the diagnosis of a bacterial infection.
2. The differential diagnosis is aseptic meningitis that is likely caused by a virus such as an enterovirus, HSV, or lymphocytochoriomeningitis virus, or by an arboencephalitis virus from the Togaviridae, Flaviviridae, or Bunyaviridae families. *Cryptococcus neoformans* (fungus), *Mycobacterium tuberculosis,* and *Borrelia burgdorferi* are also possible. However, the presence of a rash and sore throat before signs of meningitis strengthen the likelihood of an enterovirus infection, such as coxsackievirus A or echovirus. At an earlier time (30 years ago), polio would also be in the differential diagnosis.
3. The rash and sore throat in the prodrome period and the presence of lymphocytes in the CSF distinguish an enterovirus meningitis from other microbial causes.
4. An RT-PCR analysis would identify the enterovirus in the CSF and confirm the diagnosis.
5. Enteroviruses are spread by the fecal-oral and aerosol routes.
6. The initial target tissues for enteroviruses are the mucoepithelium, lymphoid tissue of the tonsils and pharynx, and Peyer patches of the intestinal mucosa. The virus is cytolytic.

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?*

How to manage viral meningitis?

Case Study and Questions

A 6-year-old girl was brought to the doctor's office at 4:30 PM because she had a sore throat, had been unusually tired, and was napping excessively. Her temperature was 39° C. She had a sore throat, enlarged tonsils, and a faint rash on her back. At 10:30 PM, the patient's mother reported that the child had vomited three times, continued to nap excessively, and complained of a headache when awake. The doctor examined the child at 11:30 PM and noted that she was lethargic and aroused only when her head was turned, complaining that her back hurt. Her CSF contained no red blood cells, but there were 28 white blood cells/mm^3—half polymorphonuclear neutrophils and half lymphocytes. The glucose and protein levels in the CSF were normal, and Gram stain of a specimen of CSF showed no bacteria.

1. *What were the key signs and symptoms in this case?*
2. *What was the differential diagnosis?*
3. *What signs and symptoms suggested an enterovirus infection?*
4. *How would the diagnosis be confirmed?*
5. *What were the most likely sources and means of infection?*
6. *What were the target tissue and mechanism of pathogenesis?*

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