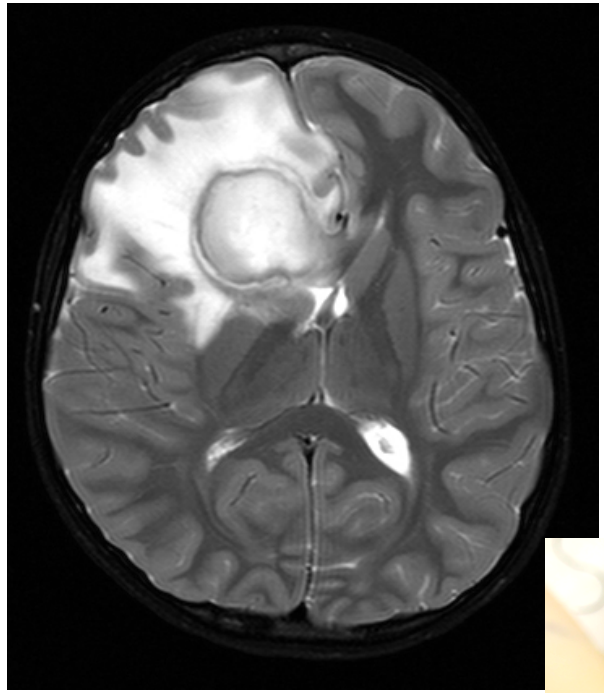
Microbiology of the central nervous system



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M.D. Ph.D.

Lecture 1

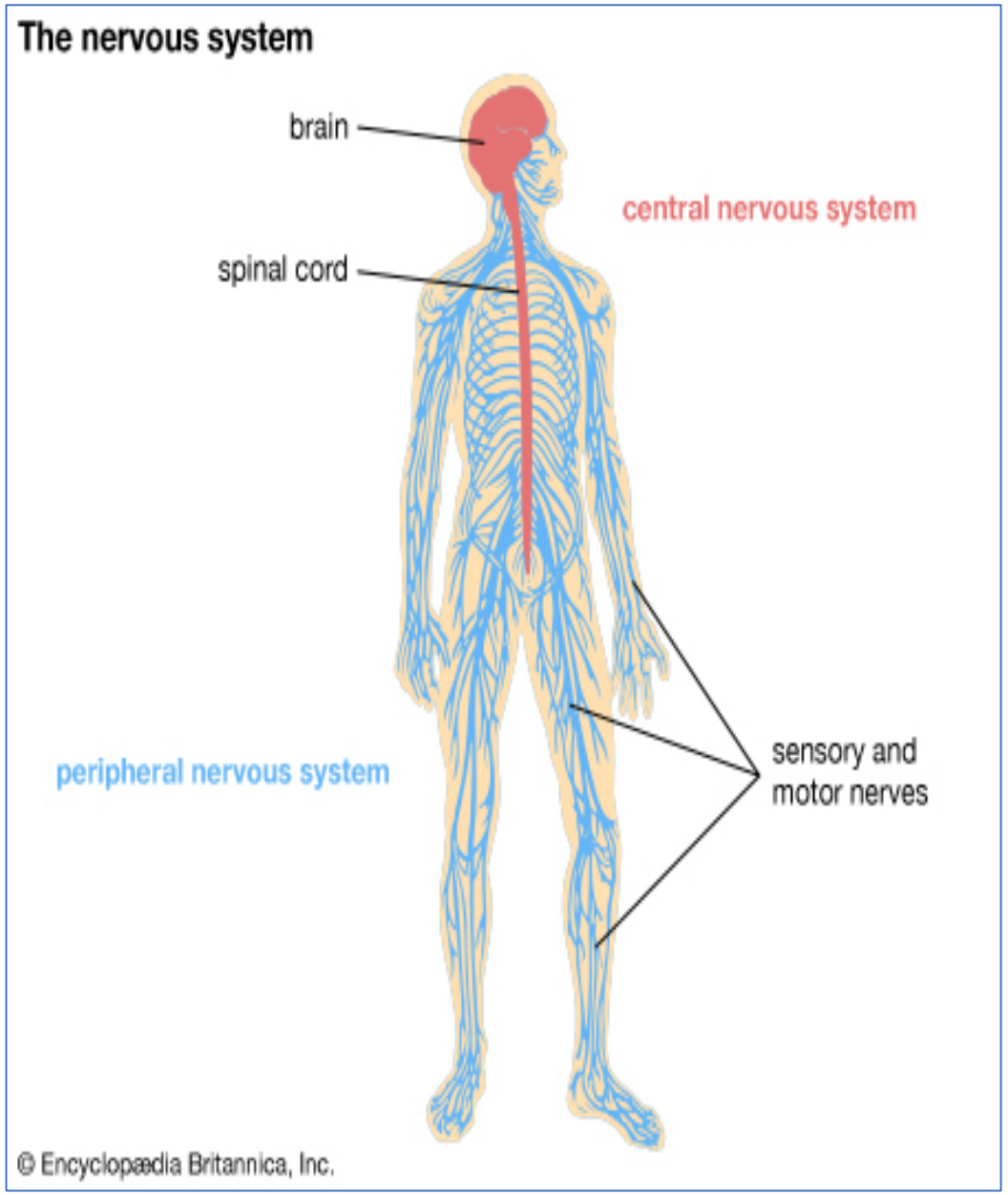
Infections of the central nervous system (CNS)

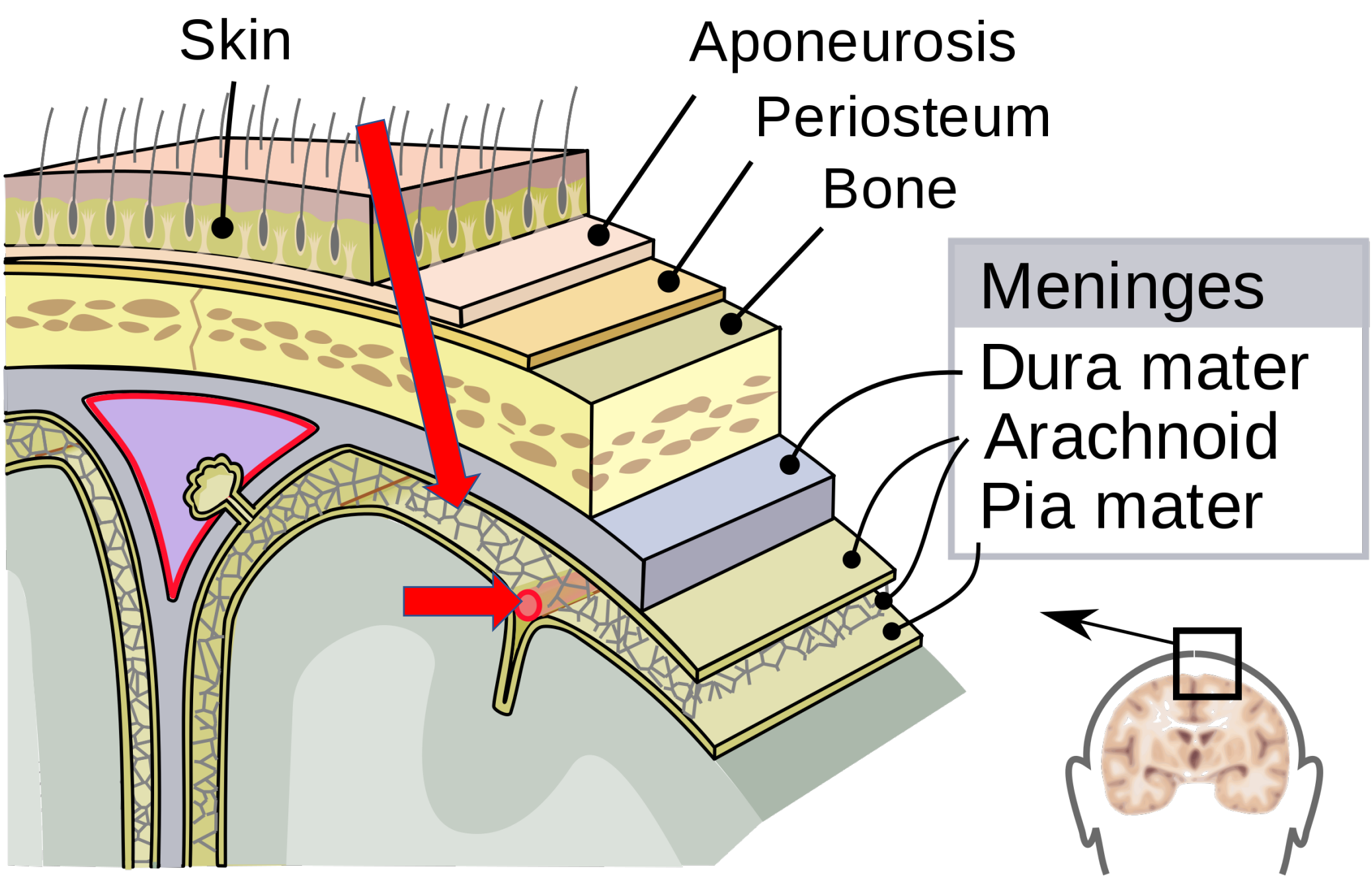
- The central nervous system is ordinarily **sterile** and has no normal microbiota.
- Bacteria, viruses and other microbes can gain access to the CNS, damage tissue, and importantly, **induce an immune response** that is often **detrimental** to the host.
- Classically , the CNS is described as displaying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

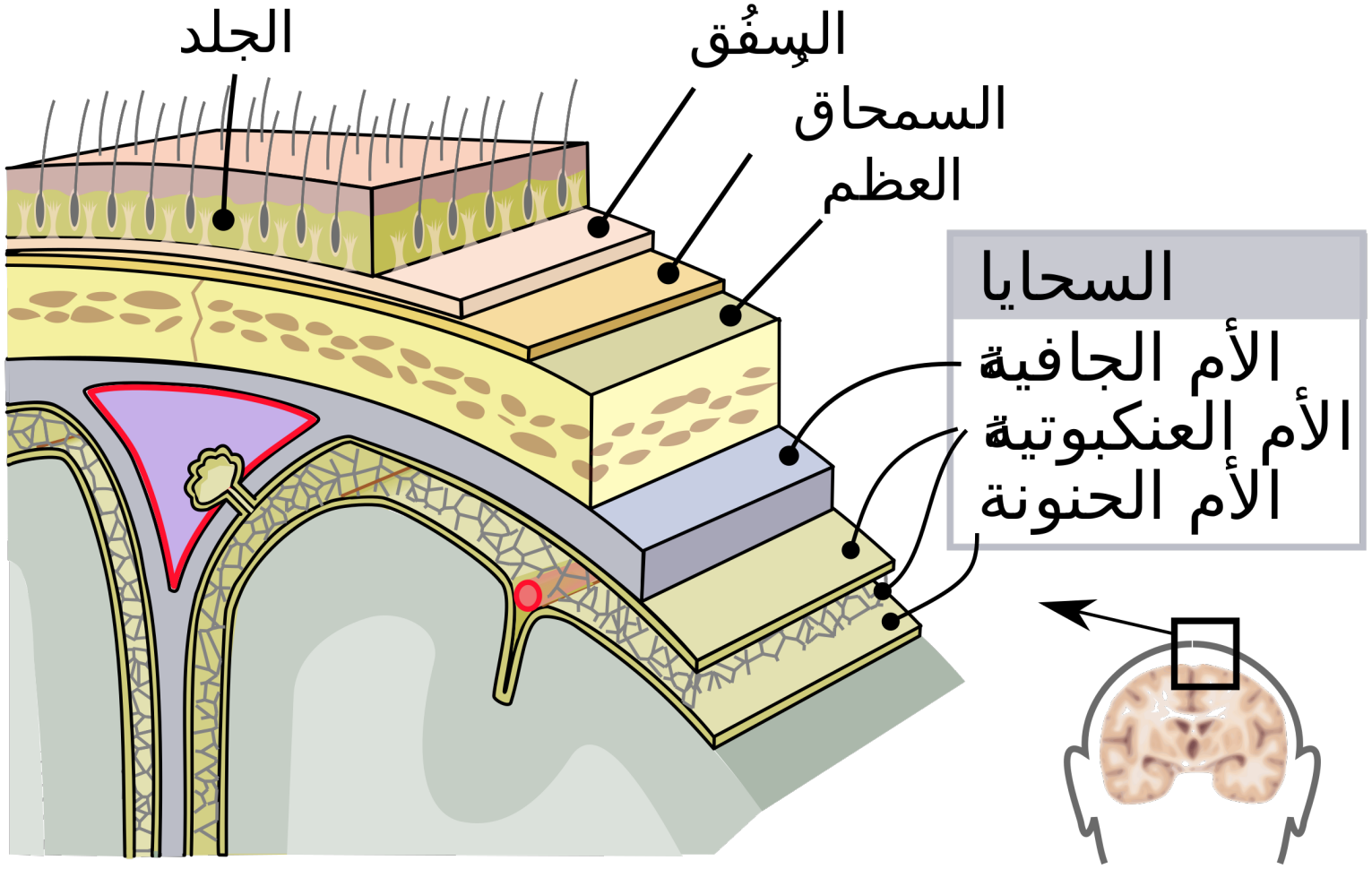
Infections of the central nervous system (CNS)

- Distinct clinical syndromes include;

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




Skin
Aponeurosis
Periosteum
Bone
Meninges
Dura mater
Arachnoid
Pia mater


الجلد
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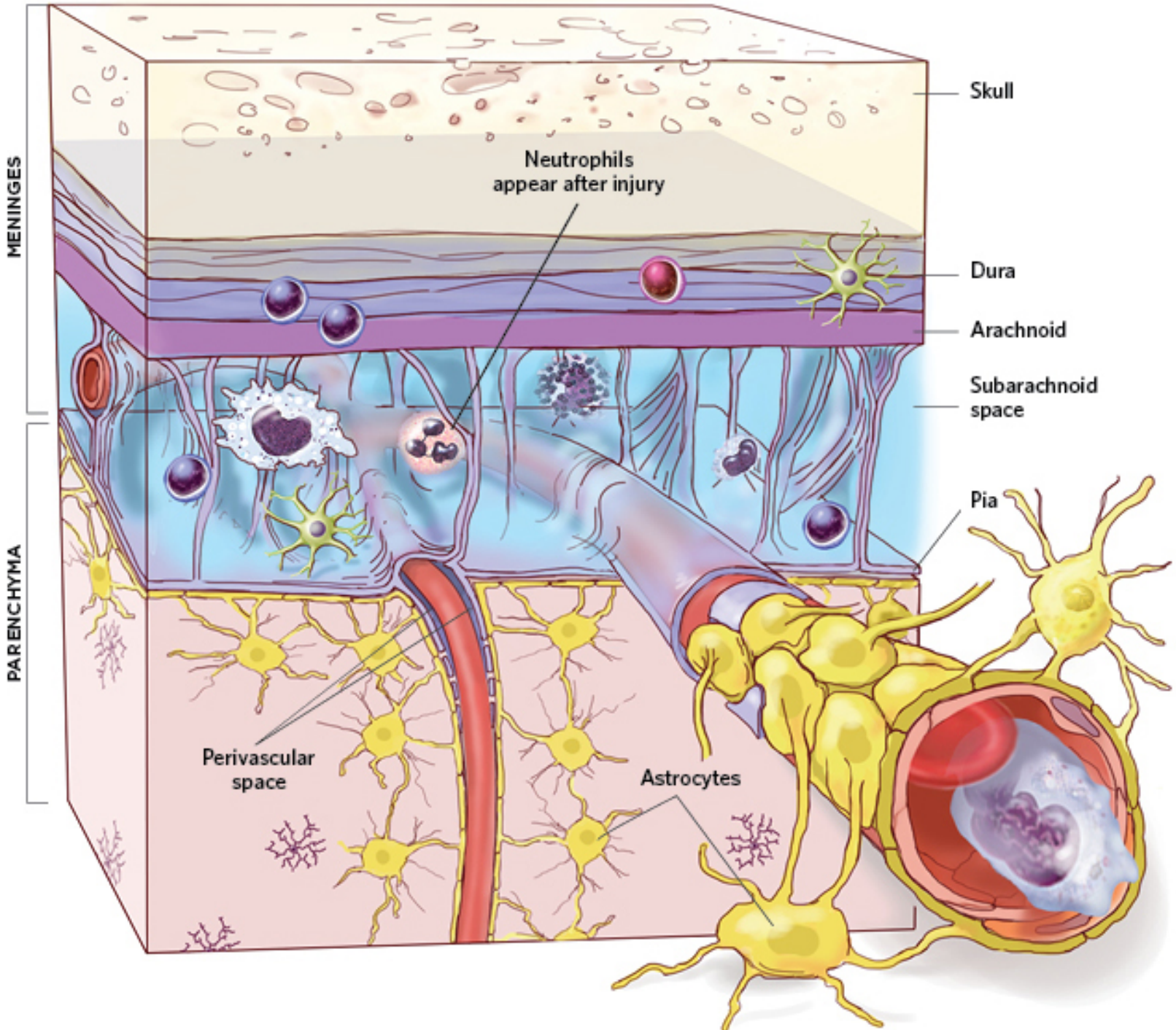
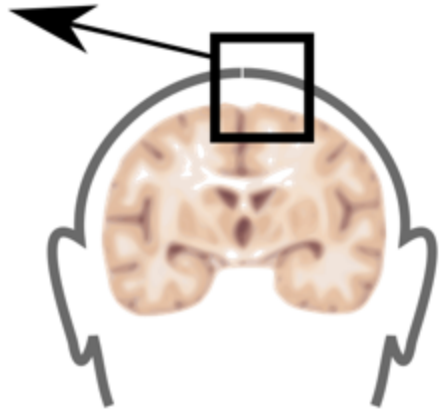
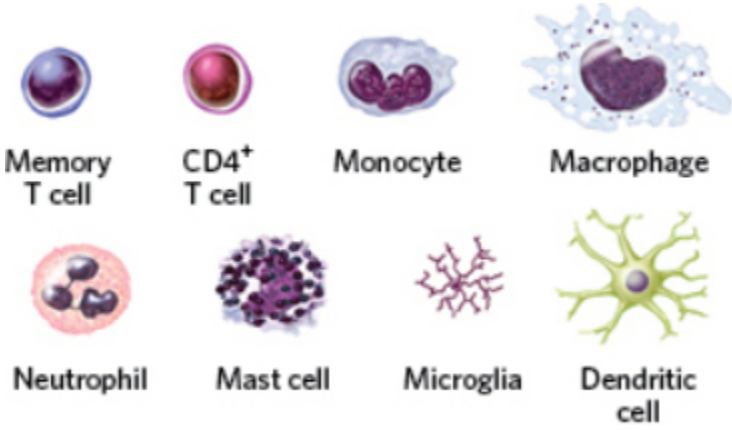

MENINGES
PARENCHYMA
Skull
Neutrophils
appear after injury
Dura
Arachnoid
Subarachnoid
space
Pia
Perivascular
space
Astrocytes



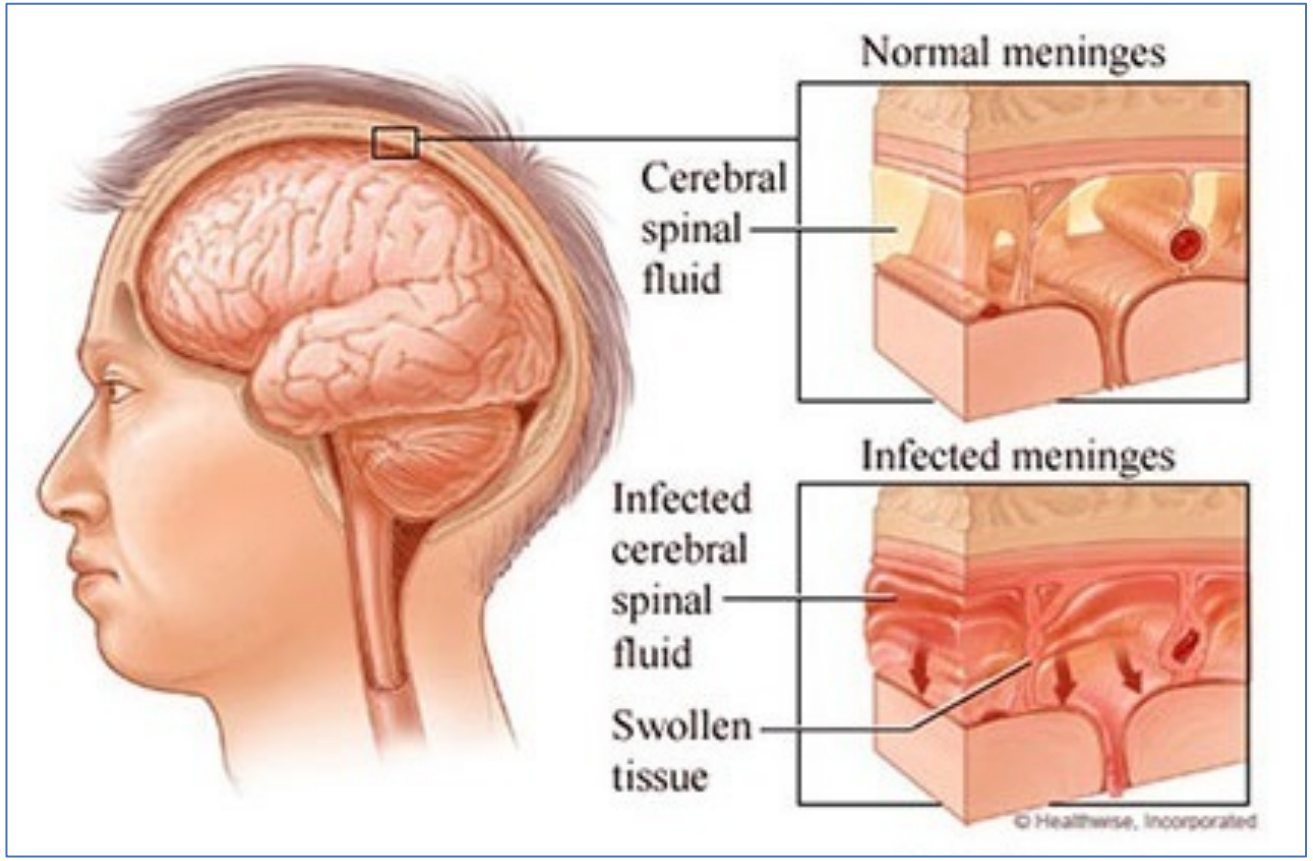

Memory
T cell
CD4+
T cell
Monocyte
Macrophage
Neutrophil
Mast cell
Microglia
Dendritic
cell

- 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 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).



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**.

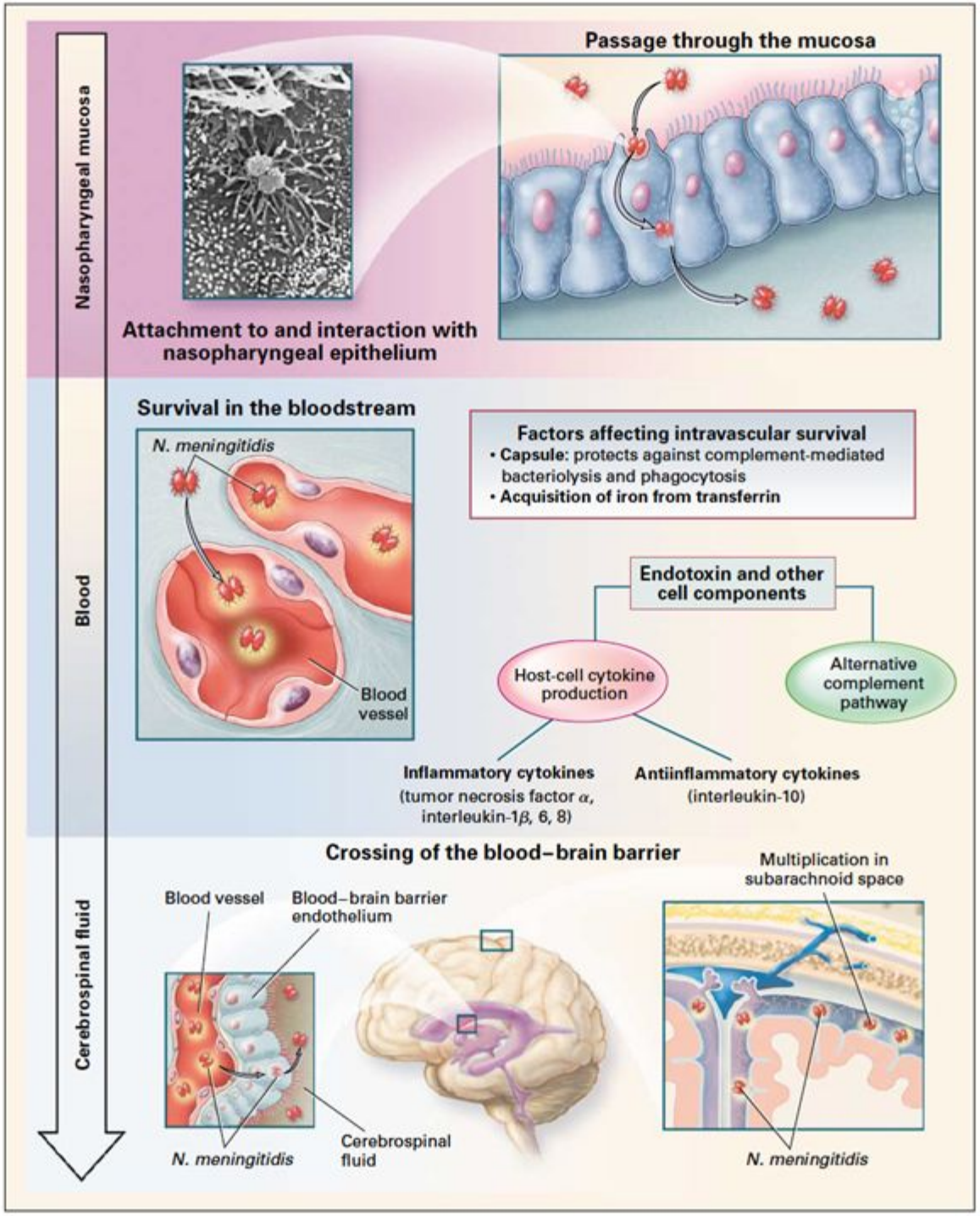
- Bacterial meningitis mostly presents as a fulminant illness progressing within **hours**.

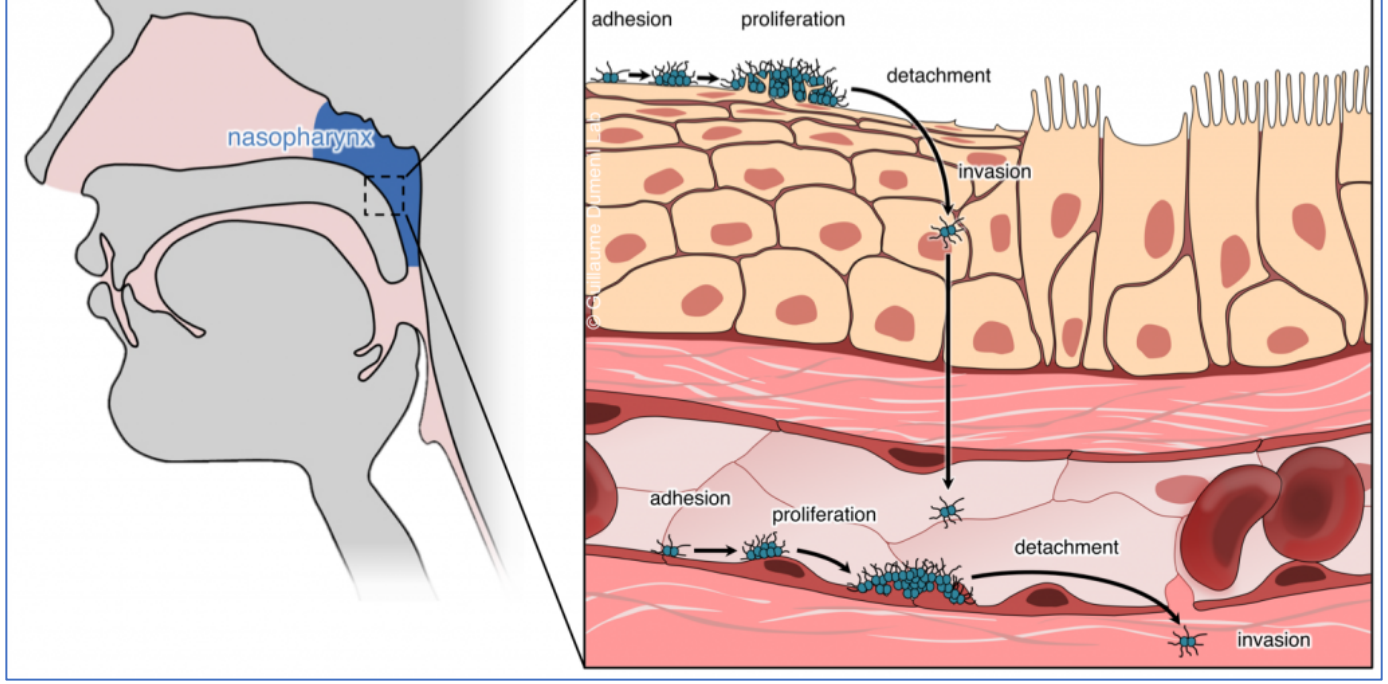
Table 19.2 Causes of bacterial meningitis

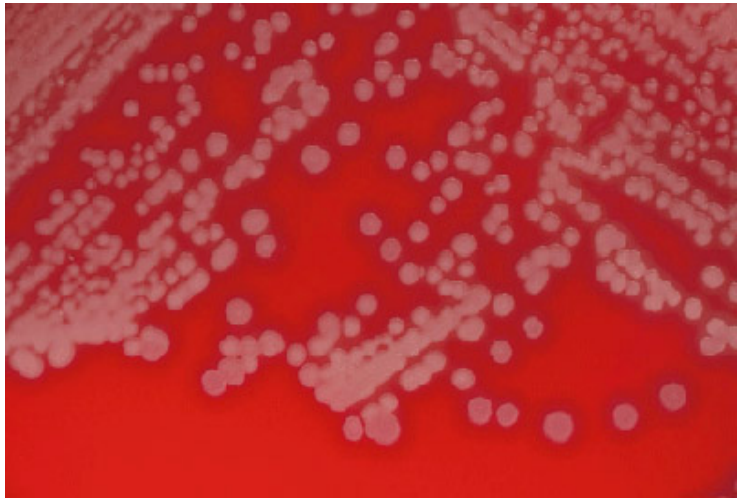
Age/condition	Common organisms
0–4 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *Enterococcus* spp., *Salmonella* spp.
4–12 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *H. influenzae*, *S. pneumoniae*, *N. meningitidis*
3 months to 18 years	*H. influenzae*, *N. meningitidis*,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

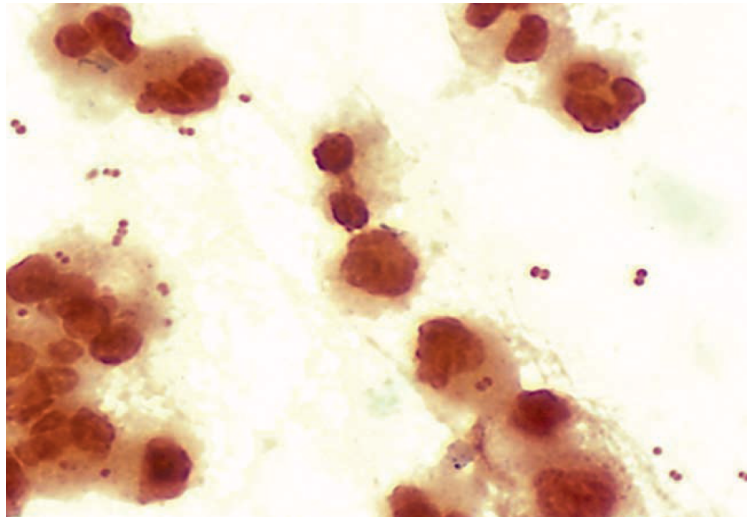
- Attachment and **colonization of the nasopharyngeal epithelium** is followed by crossing the mucosa and **entering the blood**.
- The bacteria then **crosses the blood brain barrier** and gain access to the cerebrospinal fluid, which is **lacking in cellular and humoral immunity**.
- The pathogen replicates 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.







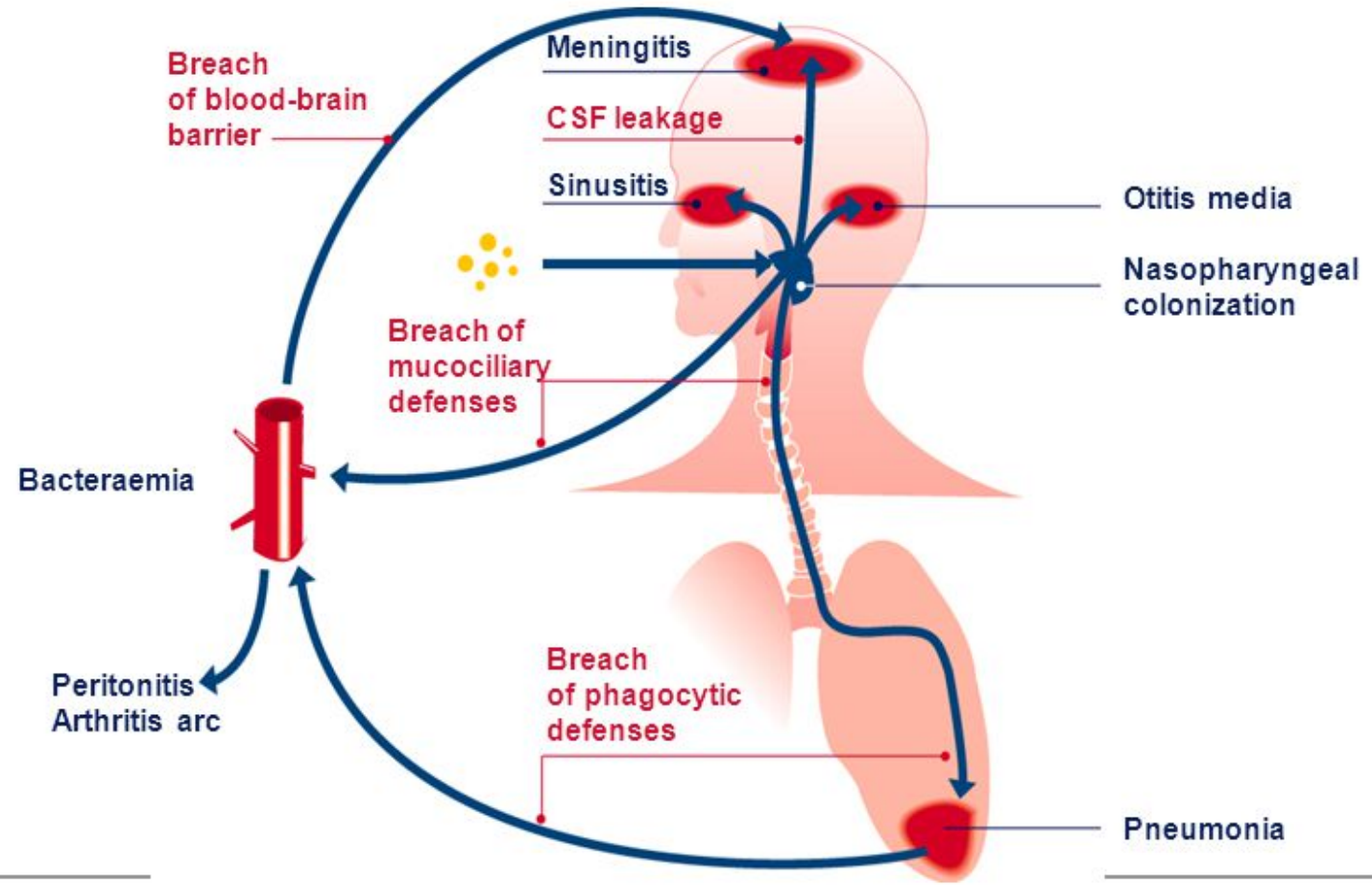
N. meningitidis colonies on blood agar plate



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.

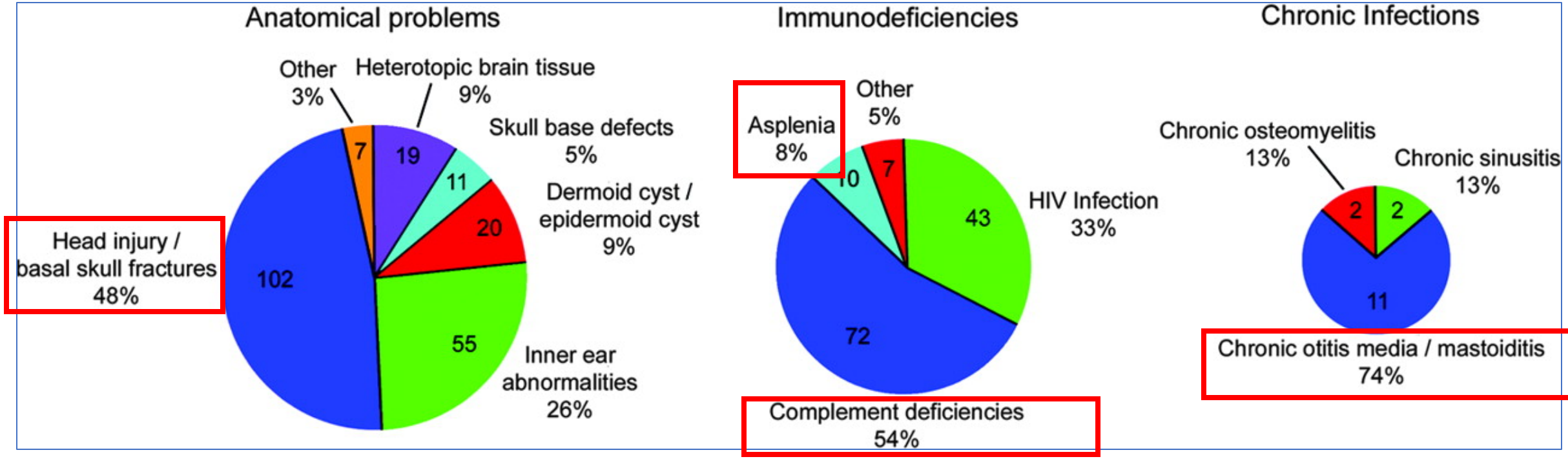
S. Pneumoniae: Pathogenesis



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

SANOFI PASTEUR

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?

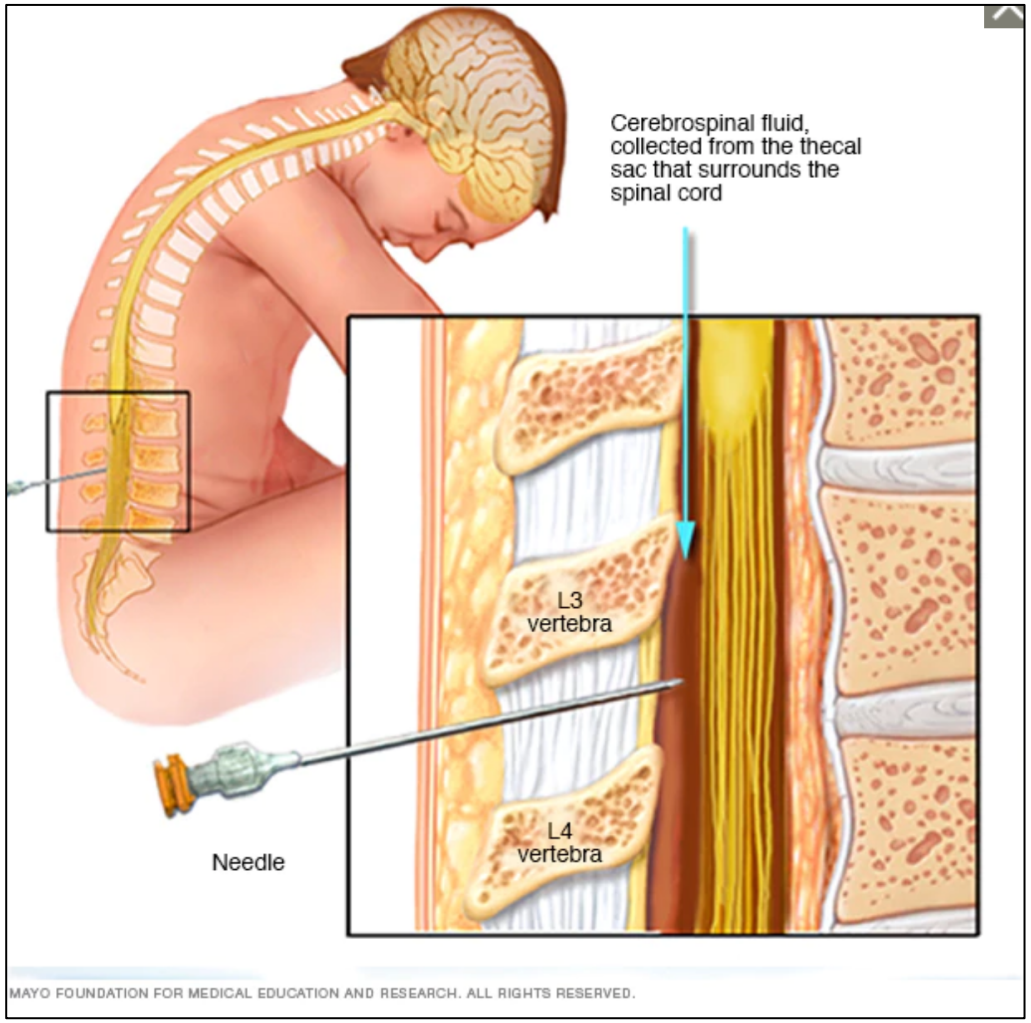
Kernig’s Sign

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.



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	Normal	Bacterial	Viral	Fungal/TB
Pressure (cmH20)	5-20	> 30	Normal or mildly increased	
Appearance	Normal	Turbid	Clear	Fibrin web
Protein (g/L)	0.18-0.45	> 1	< 1	0.1-0.5
Glucose (mmol/L)	2.5-3.5	<2.2	Normal	1.6-2.5
Gram stain	Normal	60-90% Positive	Normal	
Glucose - CSF:Serum Ratio	0.6	< 0.4	> 0.6	< 0.4
WCC	< 3	> 500	< 1000	100-500
Other		90% PMN	Monocytes 10% have >90% PMN 30% have >50% PMN	Monocytes

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**.

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