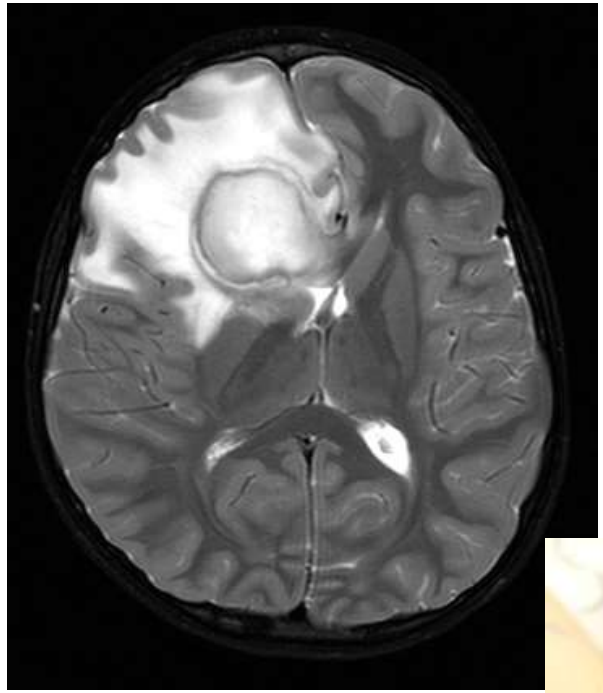
Microbiology of the central nervous system



Anas Abu-Humaidan
M.D. Ph.D.

Lecture 1

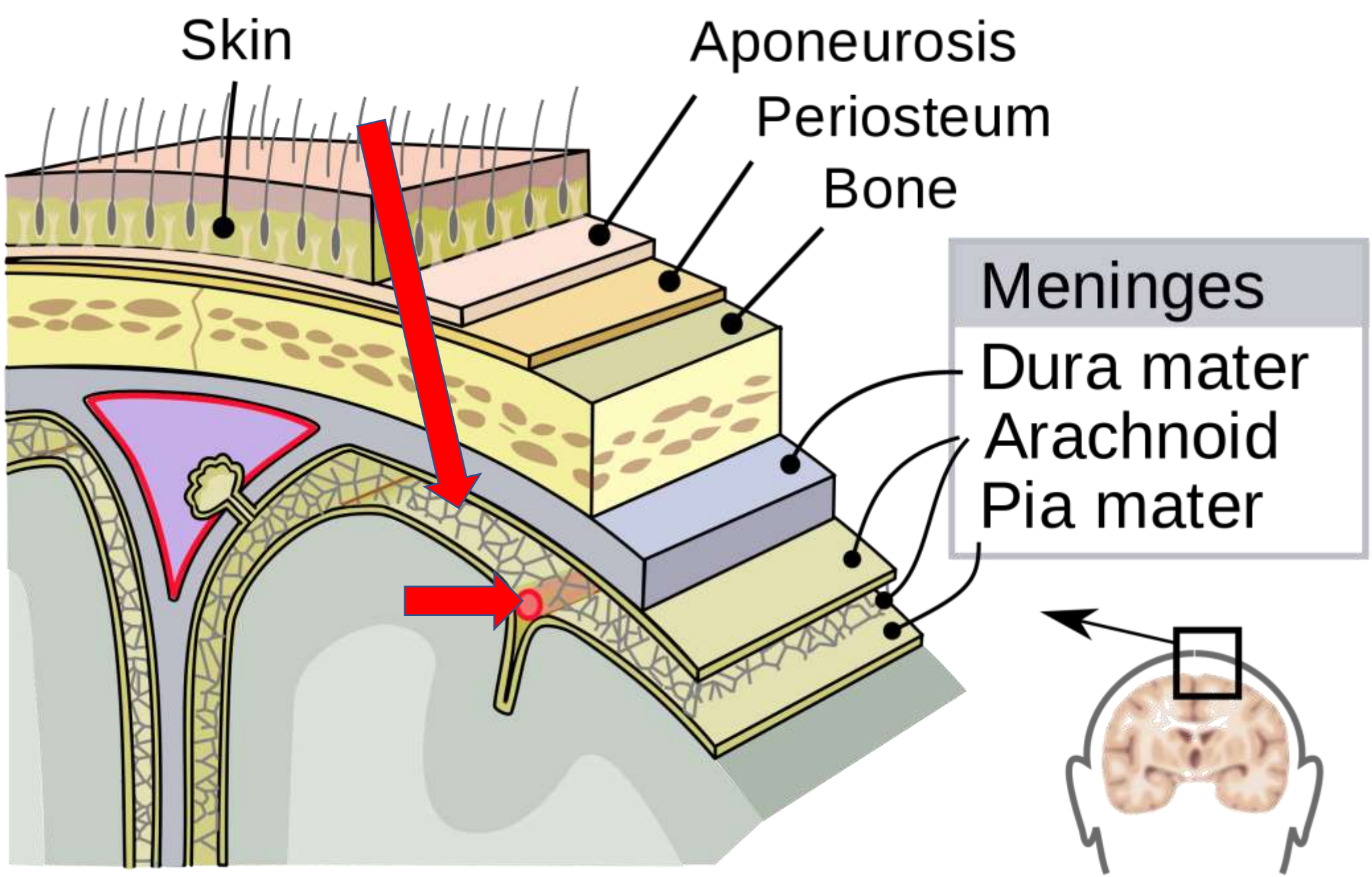
Infections of the central nervous system (CNS)

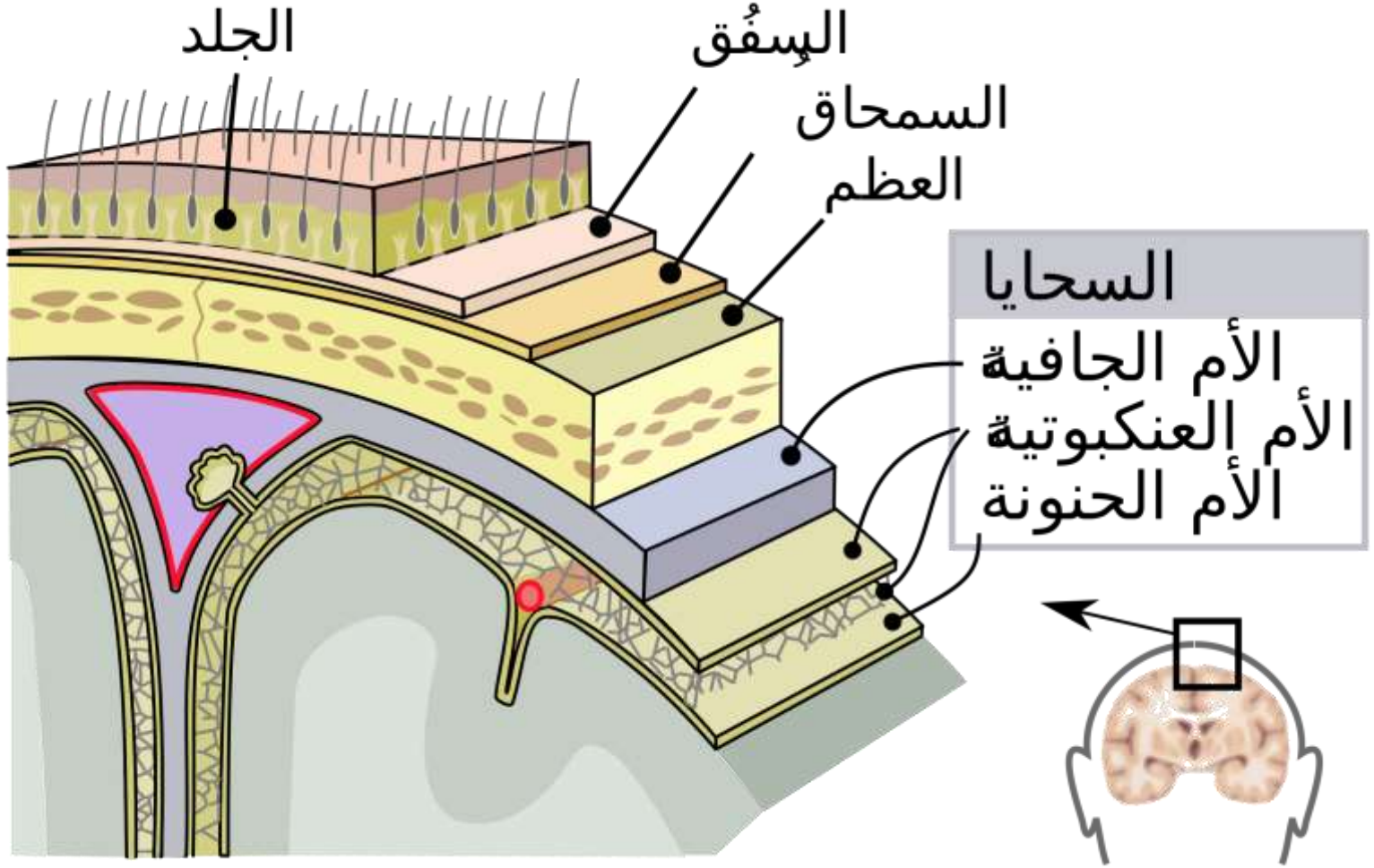
- The central nervous system is ordinarily **sterile** and has no normal microflora.

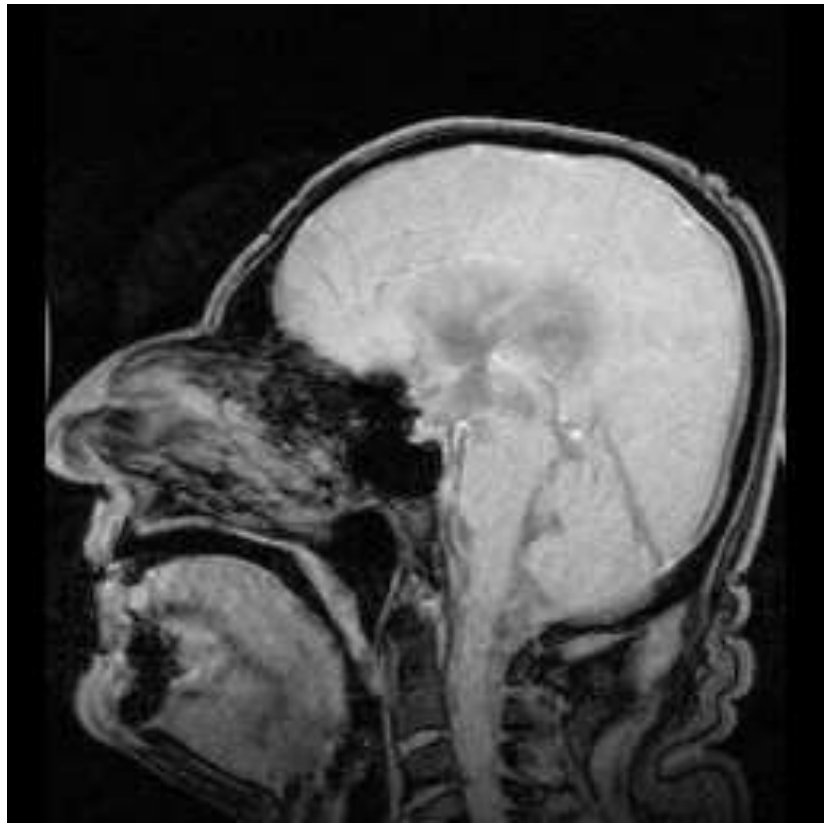
- Bacteria, viruses and other microbes can gain access to the CNS, damage tissue, and importantly, induce an immune response that is often detrimental to the host.

- Distinct clinical syndromes include;

  - **Acute bacterial meningitis**,
  - **Viral meningitis**,
  - **Encephalitis**,
  - **Focal infections** such as brain abscess an subdural empyema.

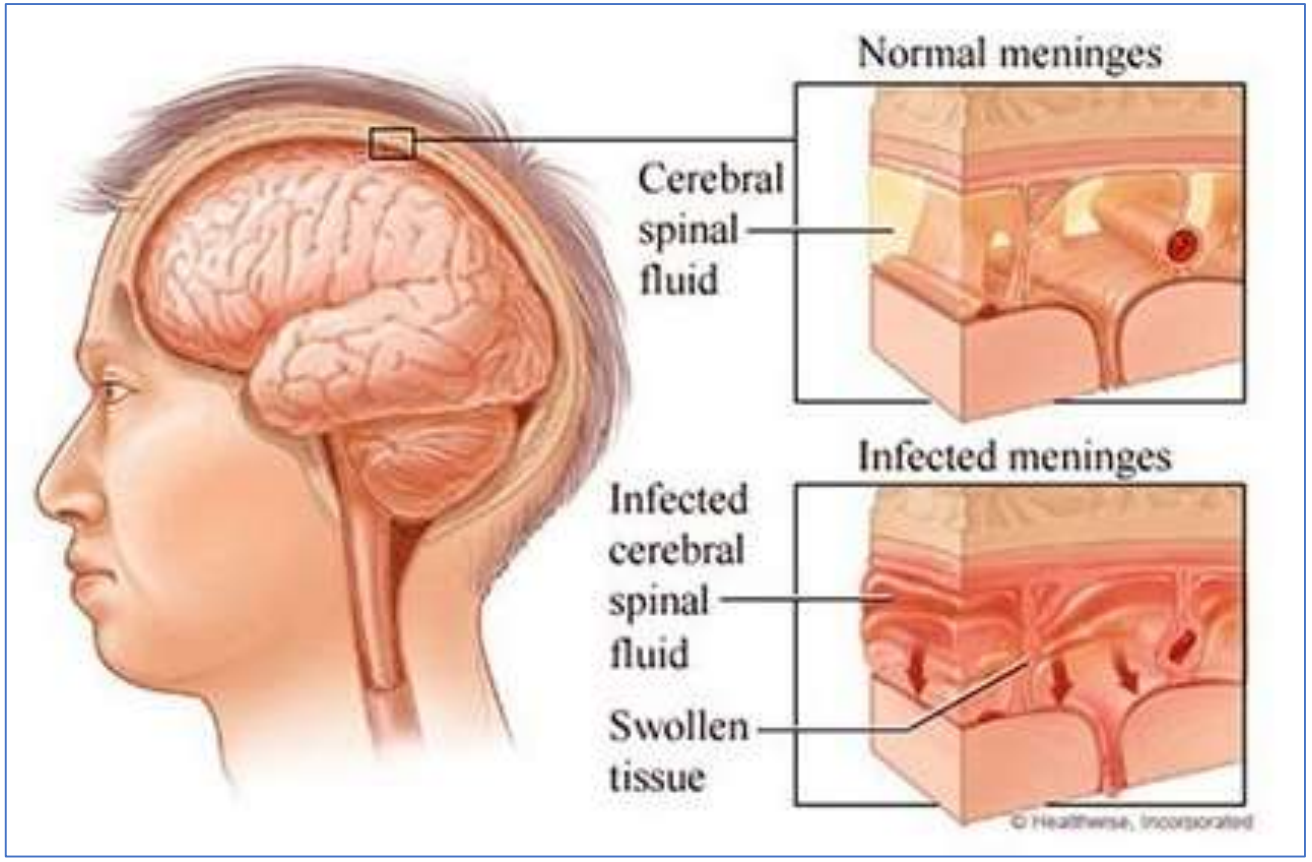

Skin
Aponeurosis
Periosteum
Bone
Meninges
Dura mater
Arachnoid
Pia mater

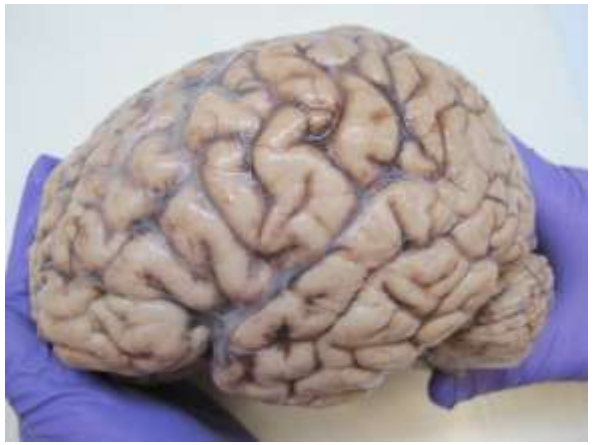

الجلد
السِفُق
السمحاق
العظم
السحايا
الأم الجافية
الأم العنكبوتية
الأم الحنونة



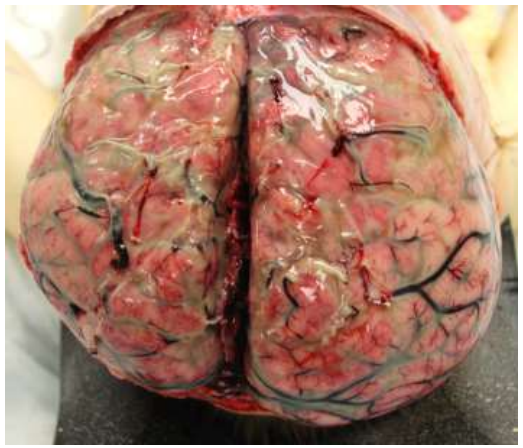
What is meningitis ?

- 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.





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, and vary by **age** and **predisposing conditions**.

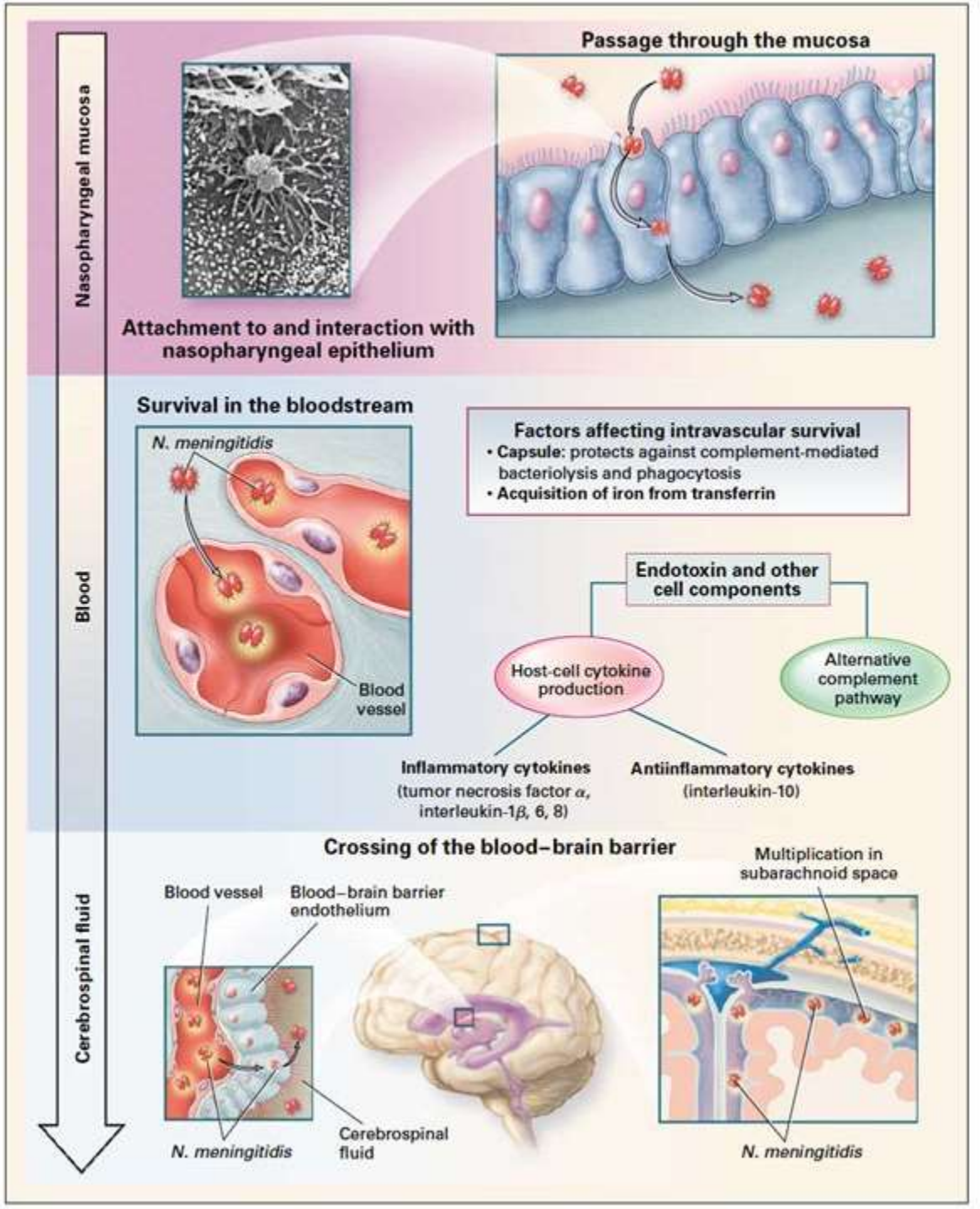
- Bacterial meningitis mostly presents as a fulminant illness progressing within **hours**.

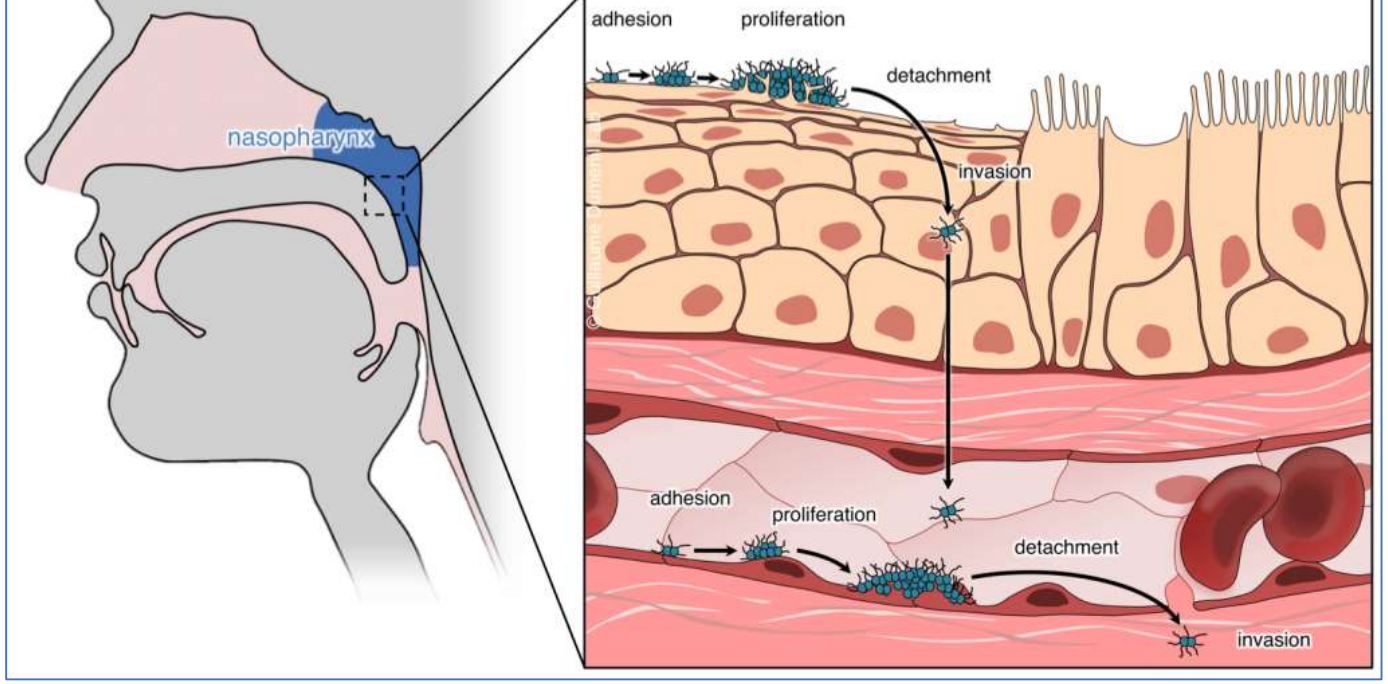
Table 19.2 Causes of bacterial meningitis

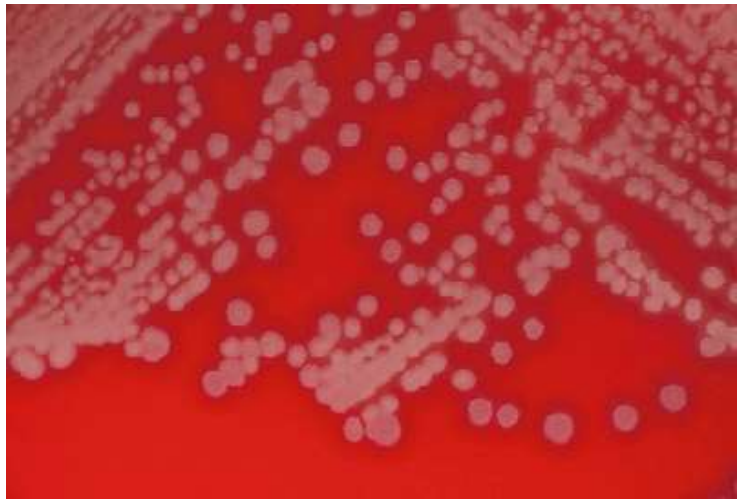
Age/condition	Common organisms
0–4 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *Enterococcus* spp., *Salmonella* spp.
4–12 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *H. influenzae*, *S. pneumoniae*, *N. meningitidis*
3 months to 18 years	*H. influenzae*, *N. meningitidis*,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

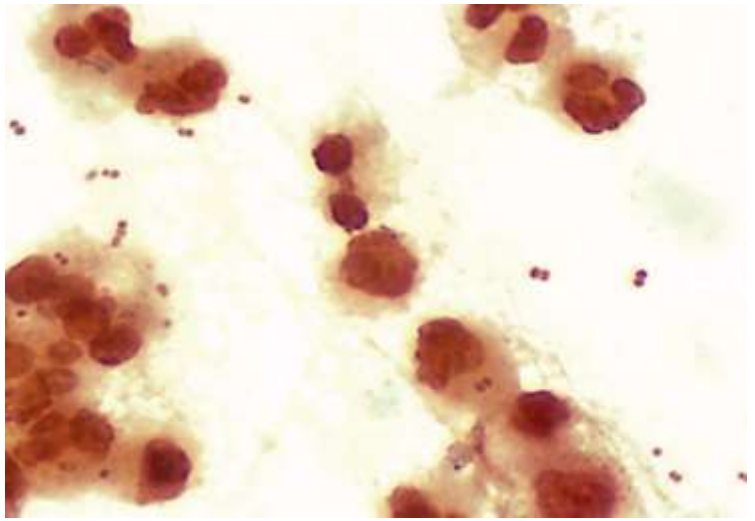
- Attachment and **colonization of the nasopharyngeal epithelium** is followed by crossing the mucosa and **entering the blood**.
- The bacteria then **crosses the blood brain barrier** and gain access to the cerebrospinal fluid, which is **lacking in cellular and humoral immunity**.
- The pathogen replicates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

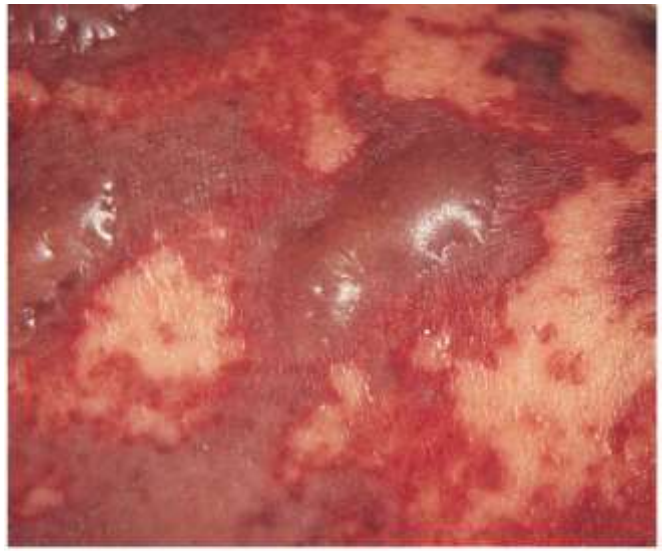
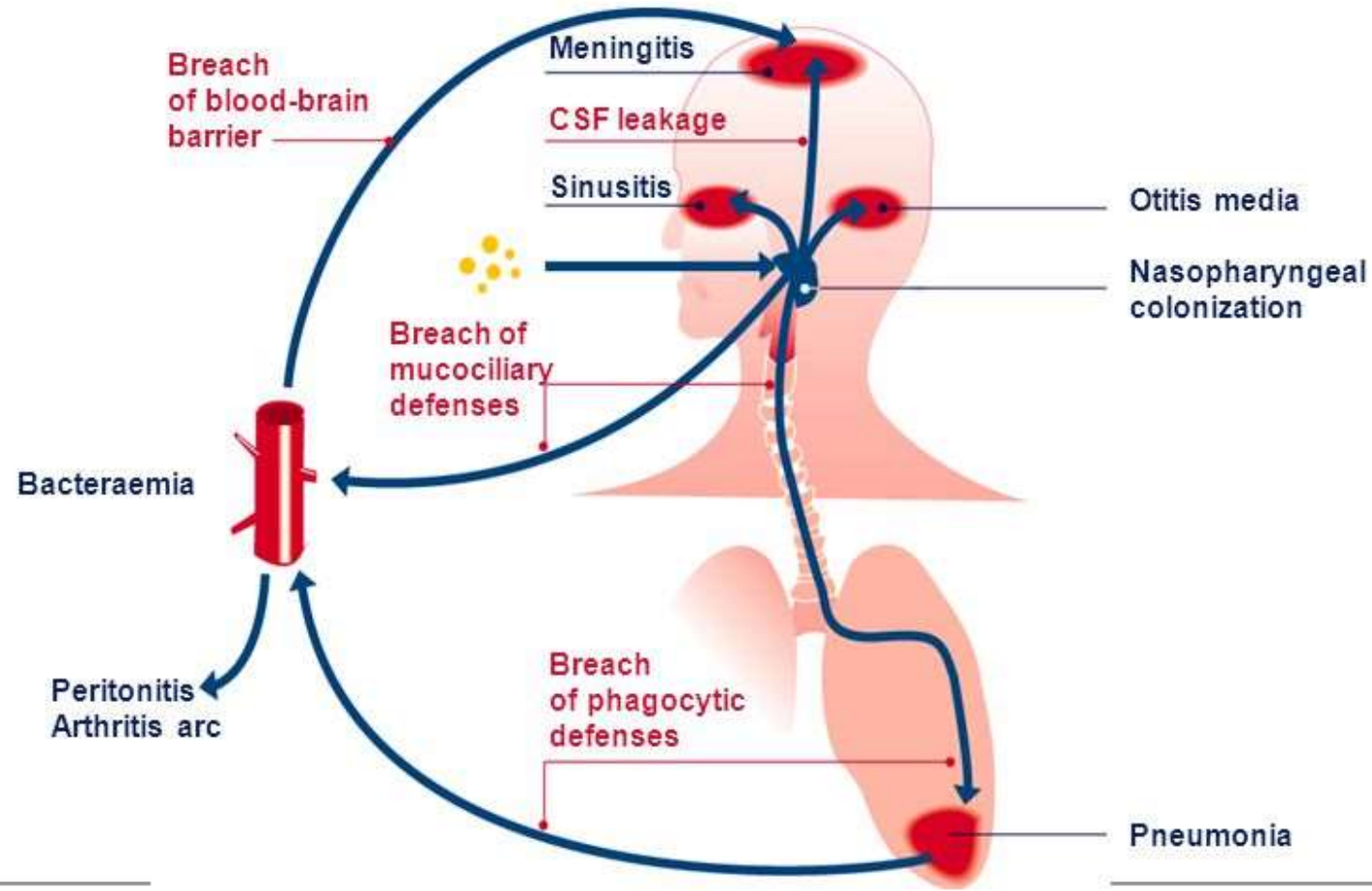


FIGURE 23-5 Skin lesions in a patient with meningococcemia. Note that the petechial lesions have coalesced and formed hemorrhagic bullae.

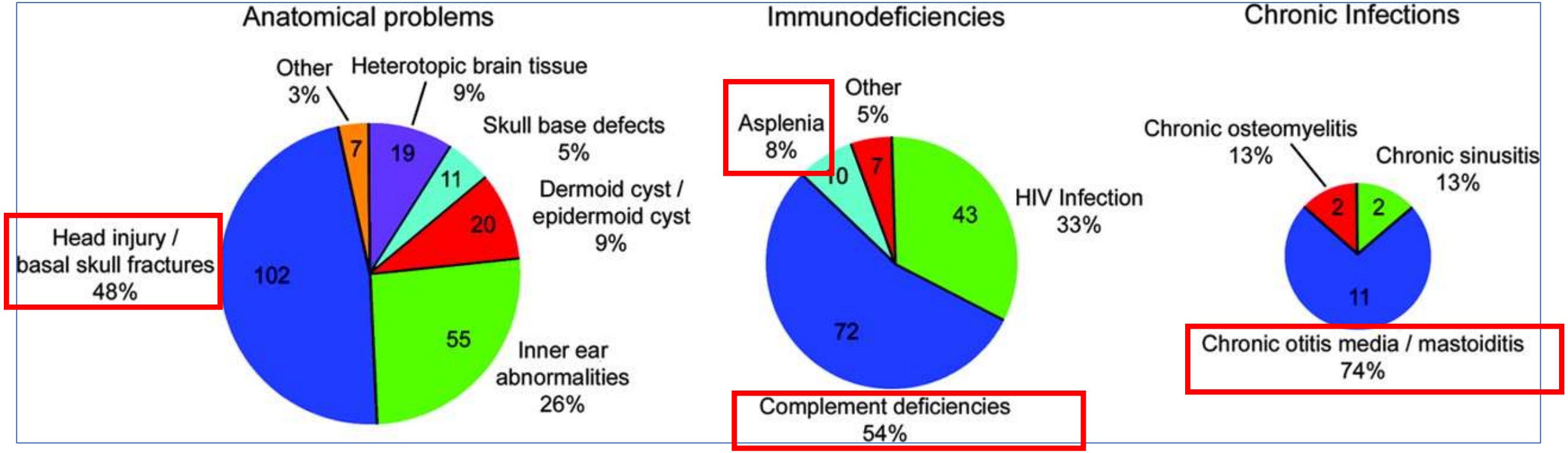
S. Pneumoniae: Pathogenesis



SANOFI PASTEUR

Adapted from Scaylers & 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)

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?

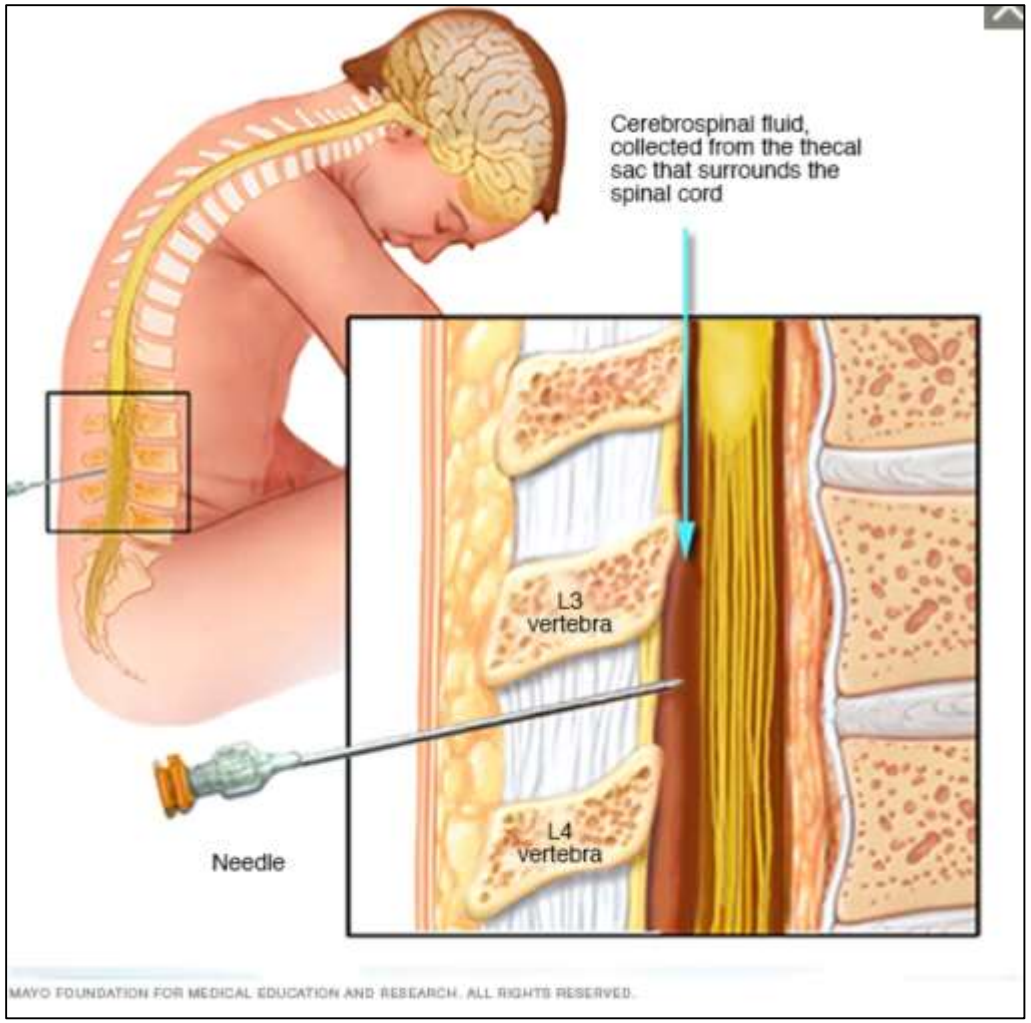
Kernig’s Sign

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.
- 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.



	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

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 (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.

How is viral meningitis different?

- Viral meningitis has **similar symptoms to bacterial meningitis** (head ache, 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.

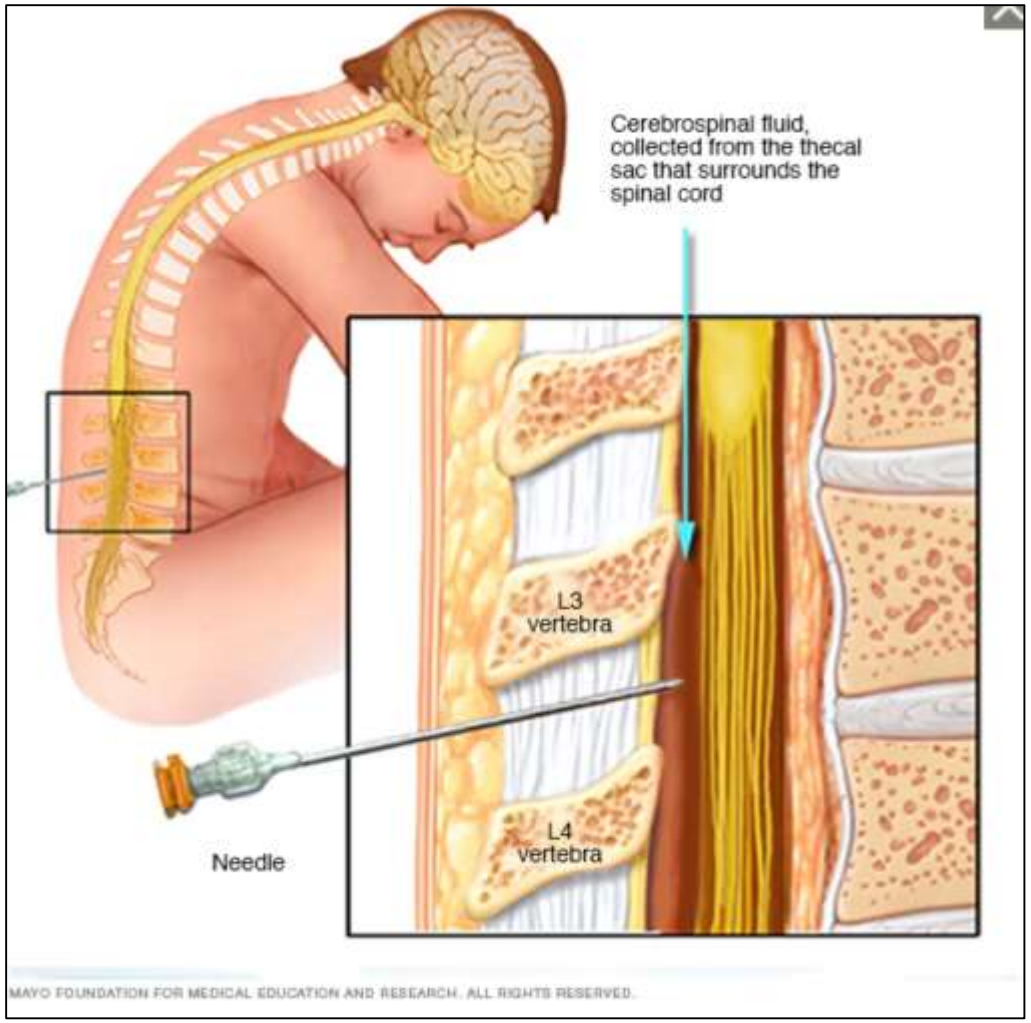
- **VZV meningitis** is associated with a characteristic, diffuse vesicular rash.

- **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

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.



	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

Neutrophiles predominate

Lymphocytes predominate

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.

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