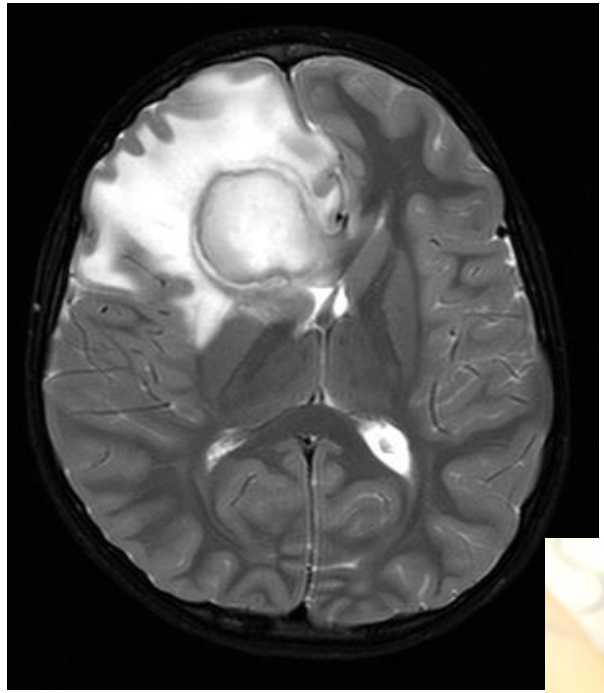
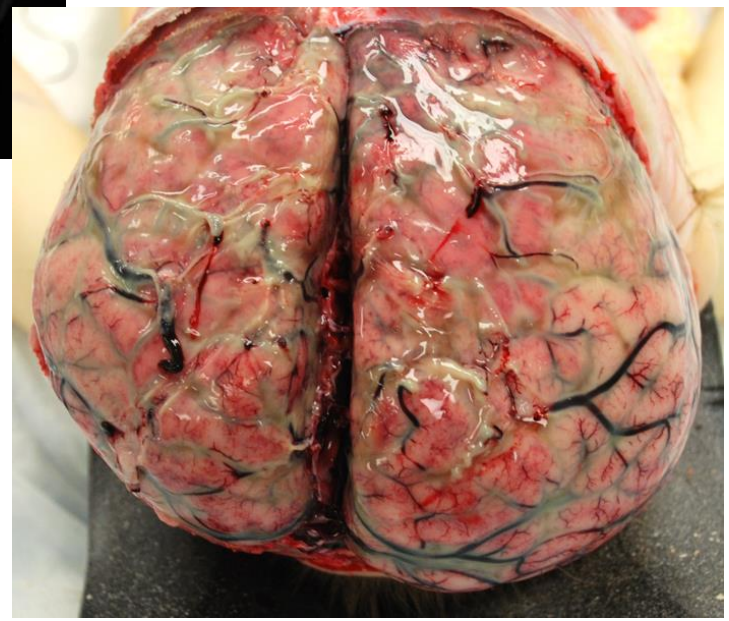
Microbiology of the central nervous system





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

Lecture 1

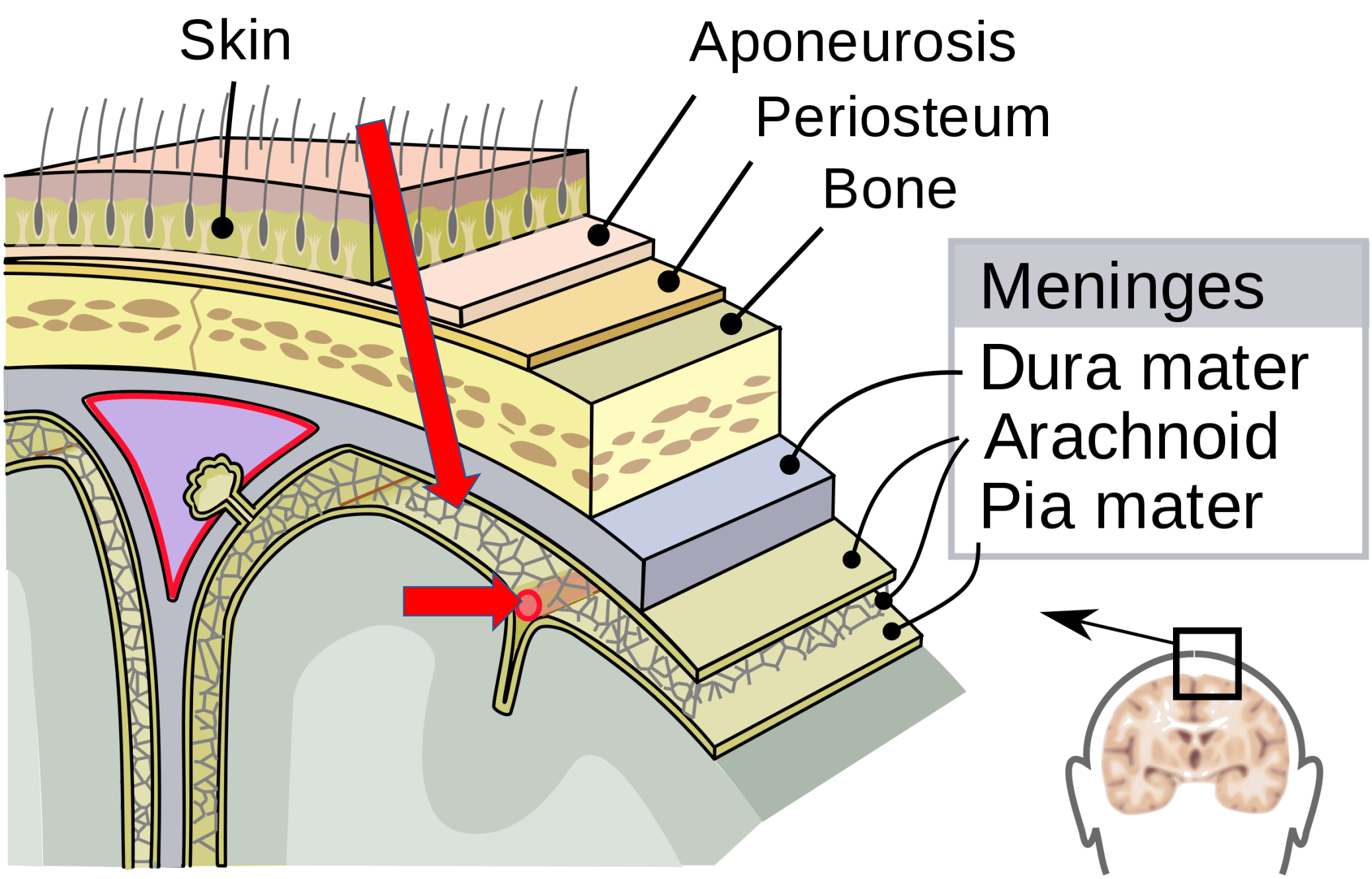
Infections of the central nervous system (CNS)

- 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
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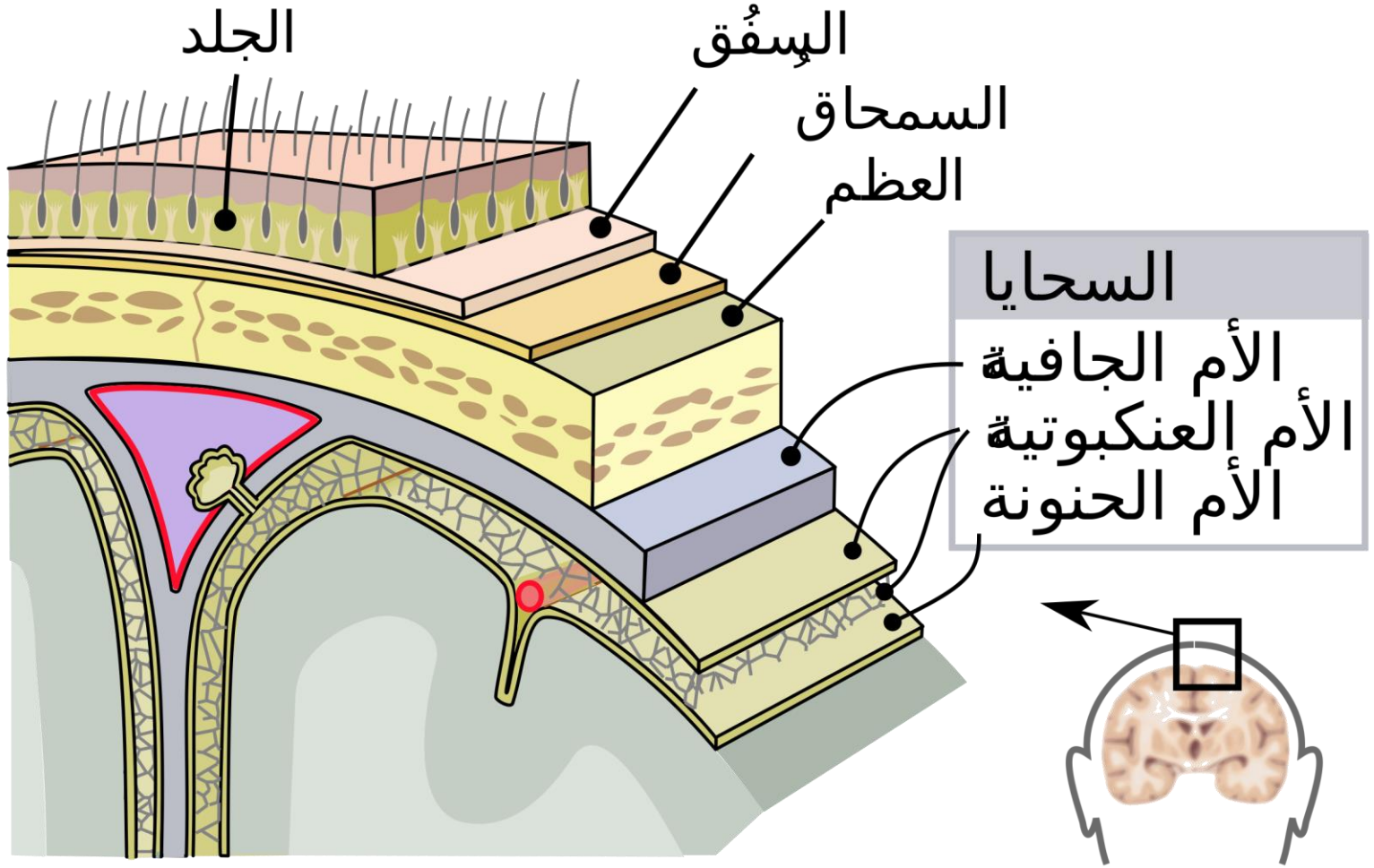
Periosteum
Bone
Meninges
Dura mater
Arachnoid
Pia mater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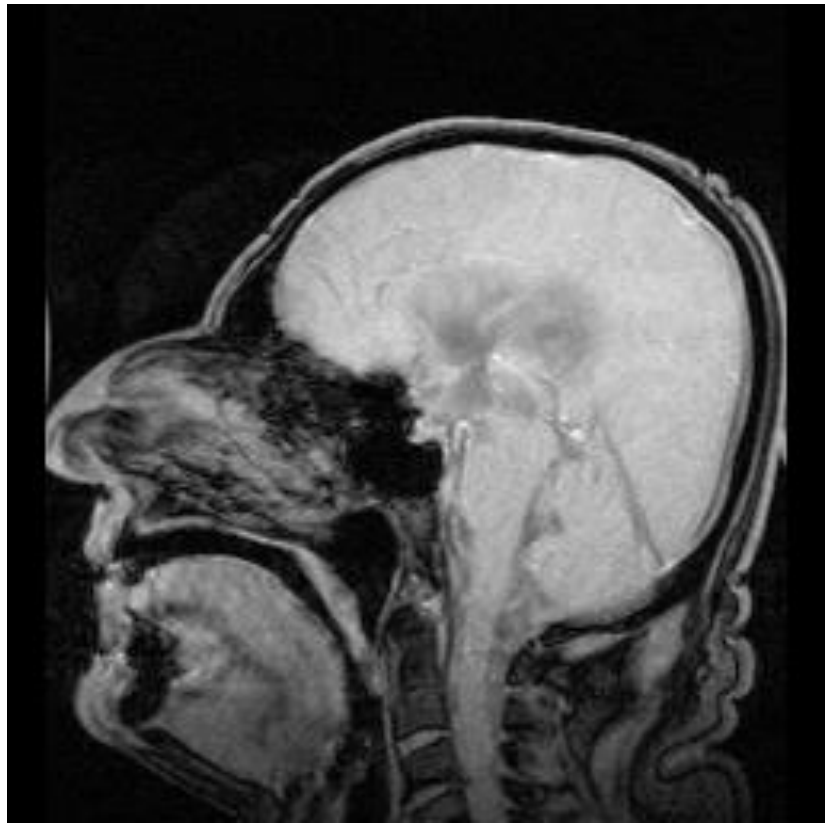
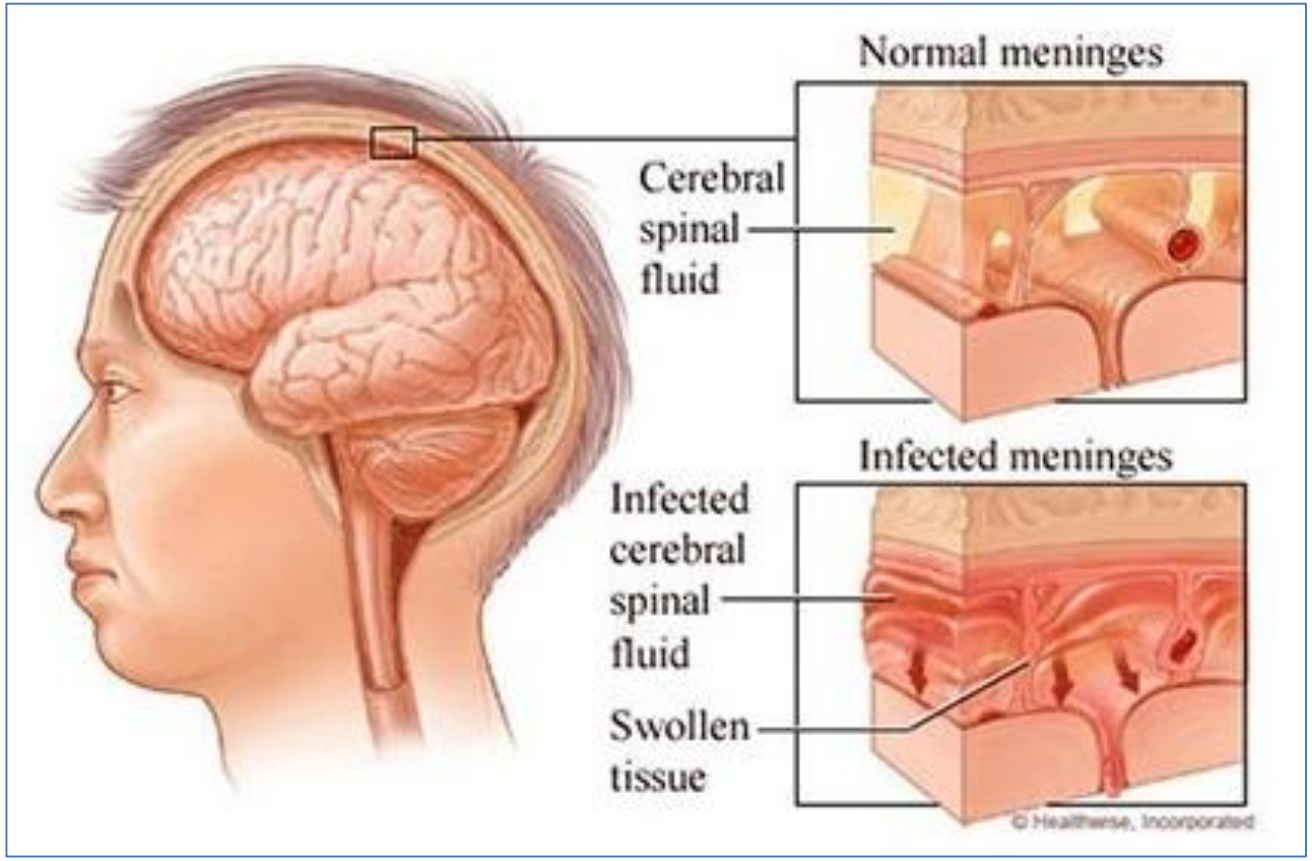
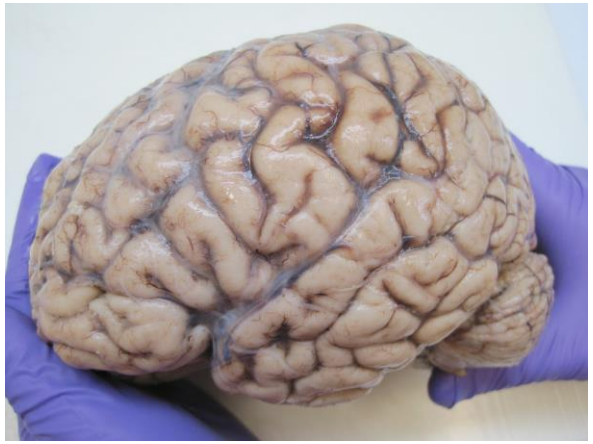


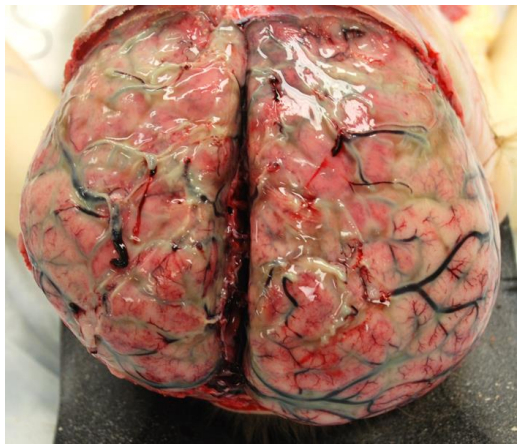
What is meningitis ?

- 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**.

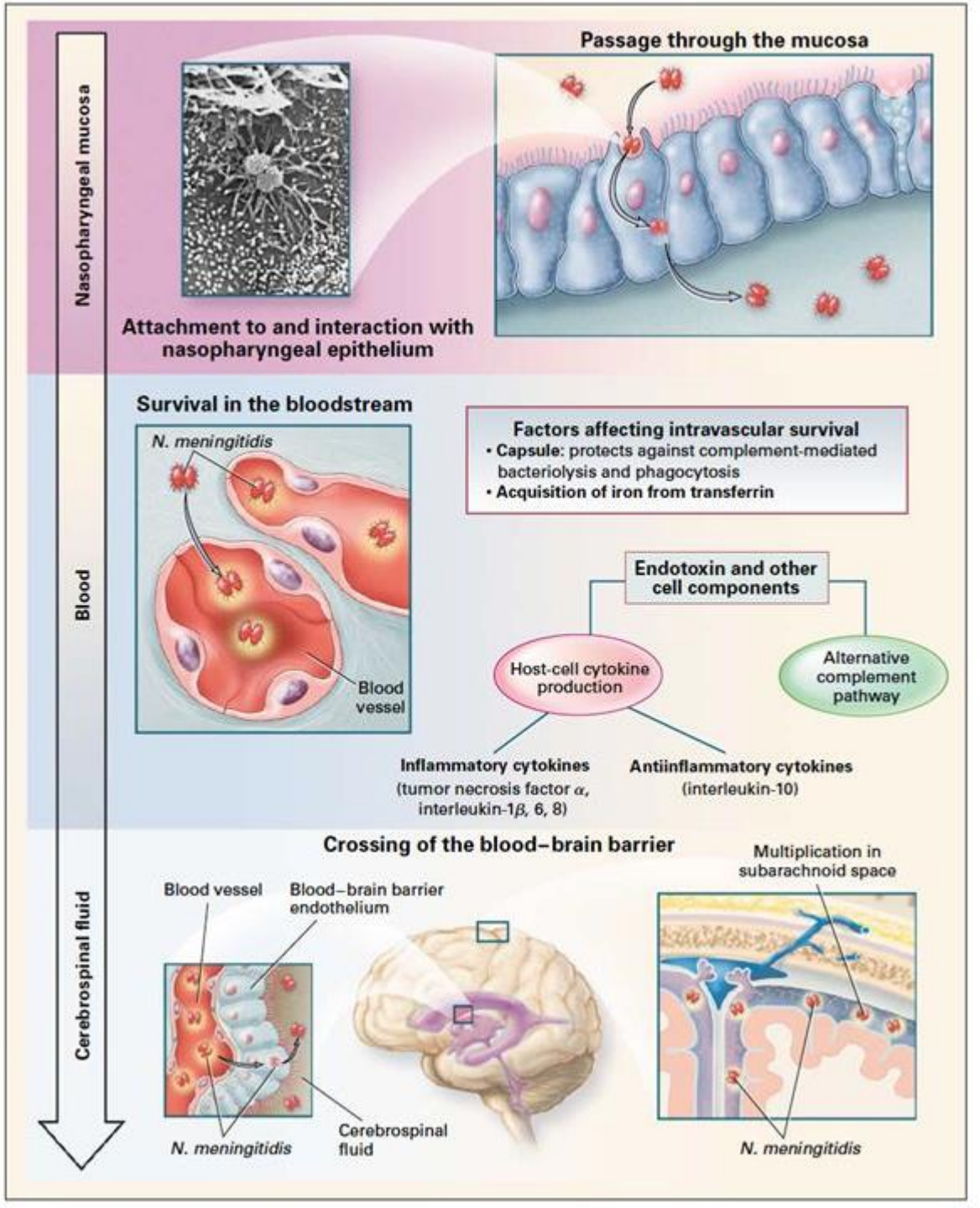
- Bacterial meningitis mostly presents as a fulminant illness progressing within **hours**.

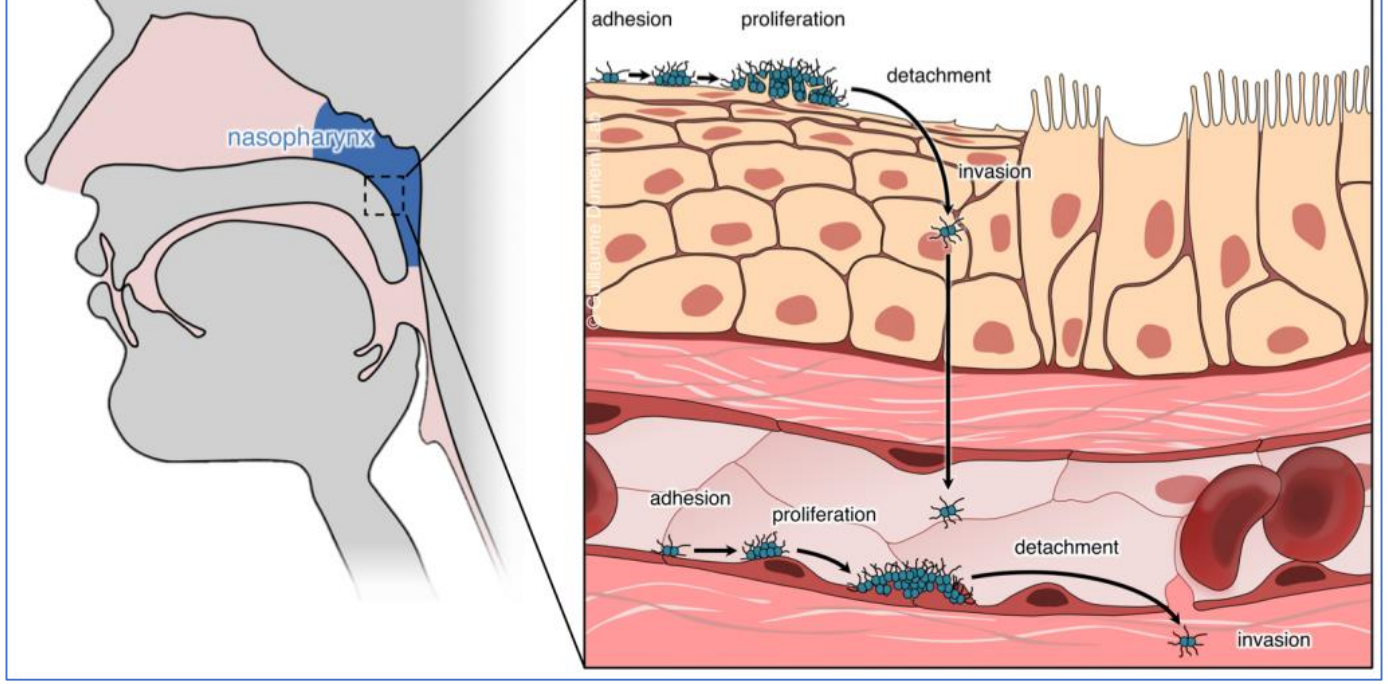
Table 19.2 Causes of bacterial meningitis

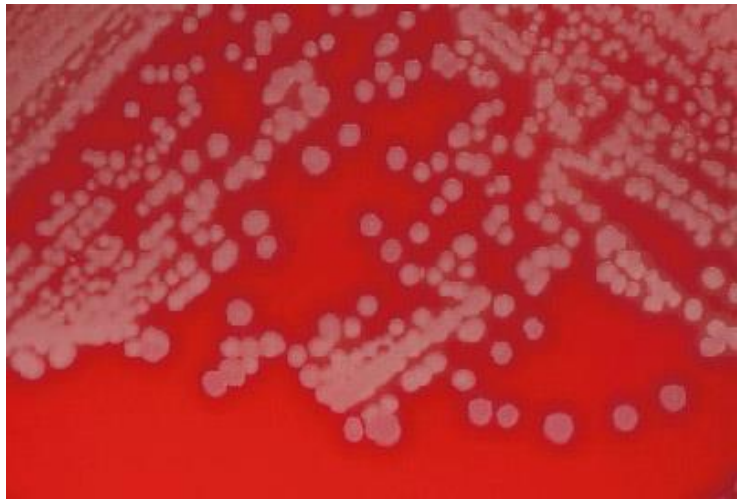
Age/condition	Common organisms
0–4 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *Enterococcus* spp., *Salmonella* spp.
4–12 weeks	GBS, *E. coli*, *L. monocytogenes*, *K. pneumoniae*, *H. influenzae*, *S. pneumoniae*, *N. meningitidis*
3 months to 18 years	*H. influenzae*, *N. meningitidis*,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

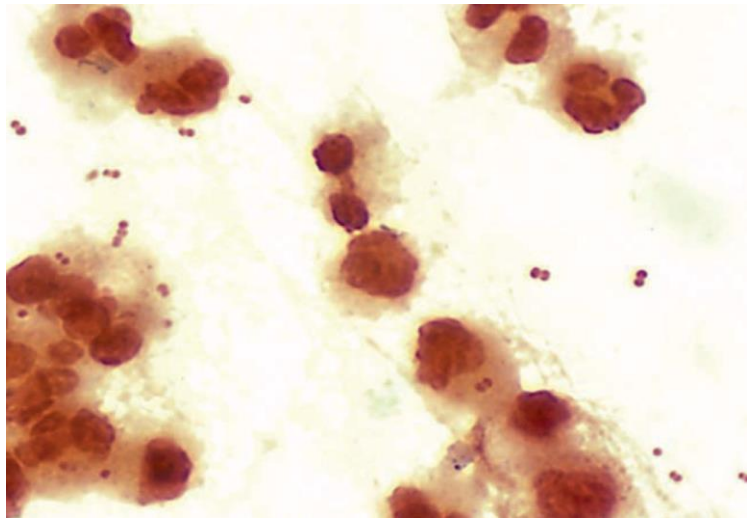
- Attachment and **colonization of the nasopharyngeal epithelium** is followed by crossing the mucosa and **entering the blood**.
- The bacteria then **crosses the blood brain barrier** and gain access to the cerebrospinal fluid, which is **lacking in cellular and humoral immunity**.
- The pathogen replicates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

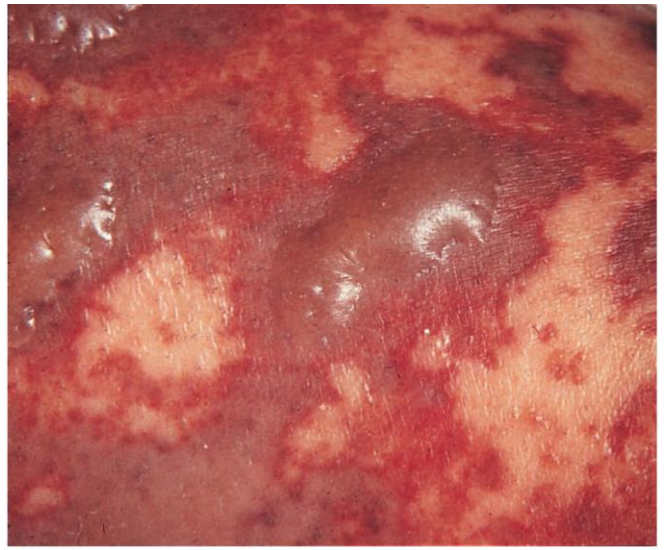
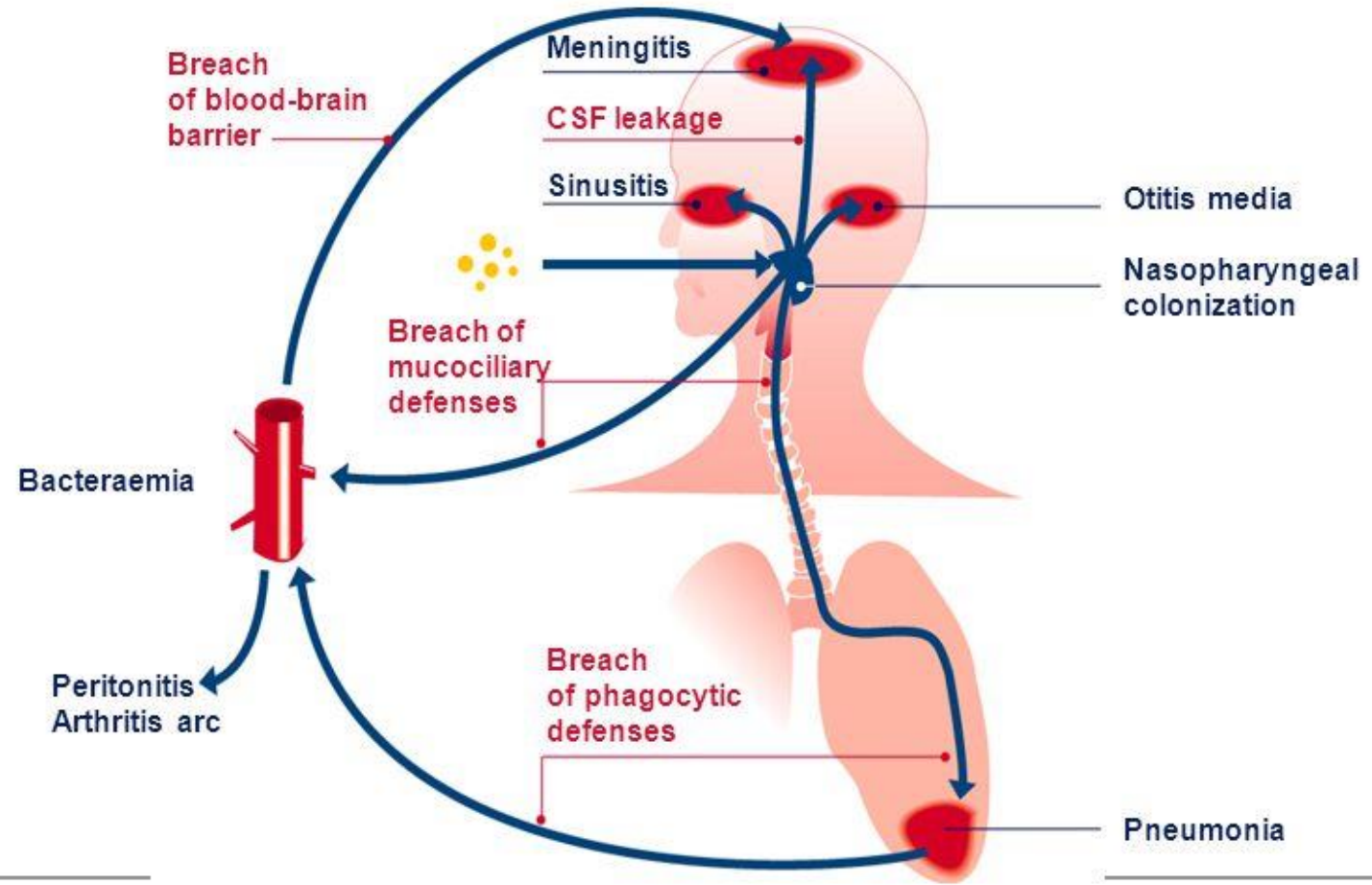


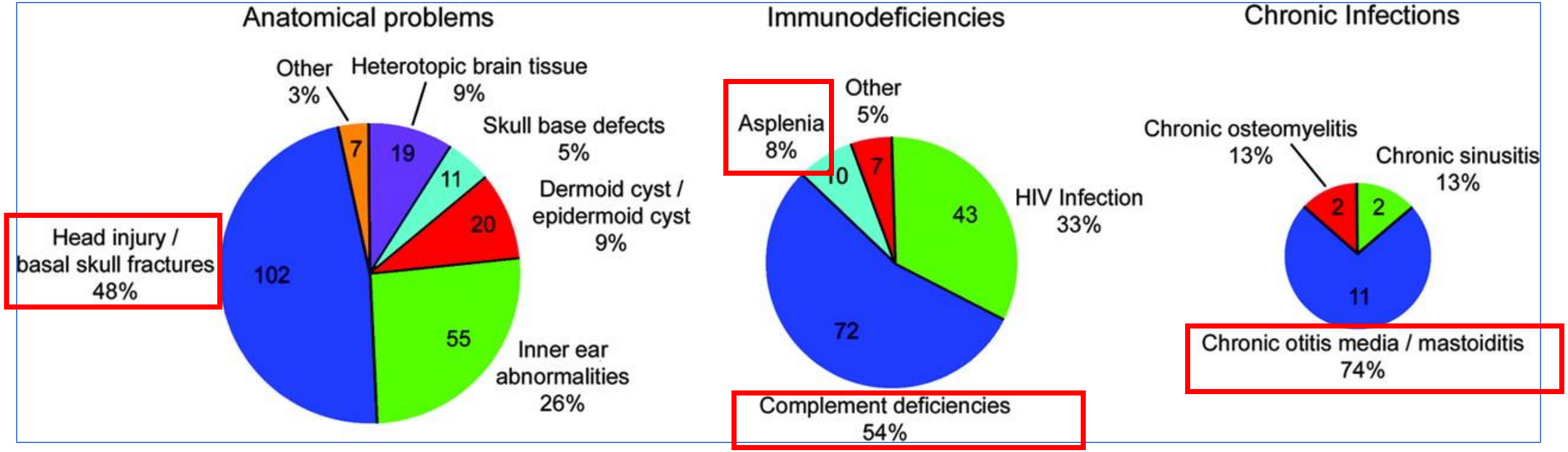
FIGURE 23-5 Skin lesions in a patient with meningococcemia. Note that the petechial lesions have coalesced and formed hemorrhagic bullae.

S. Pneumoniae: Pathogenesis



Adapted from: Tuomanen & Wilkinson. *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?

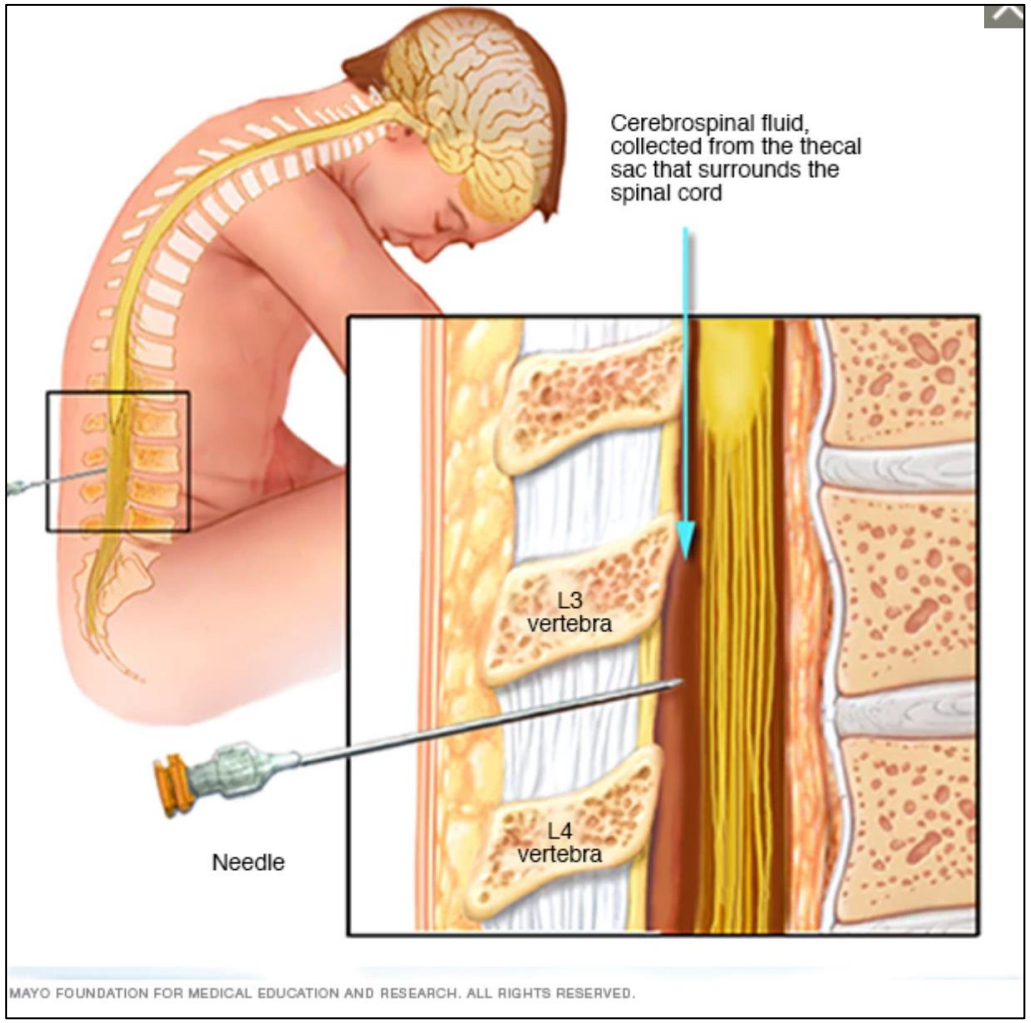
Kernig’s Sign

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 (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?

- 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.

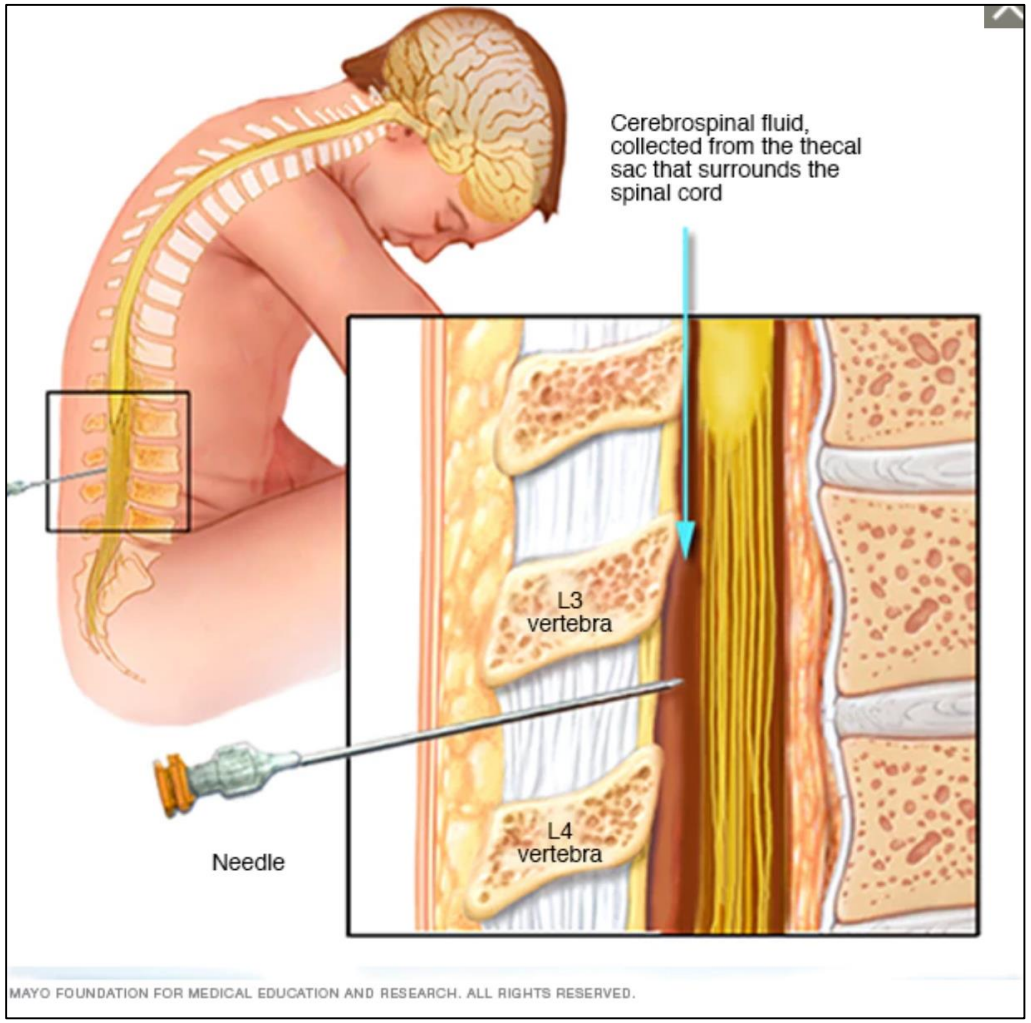
- **VZV meningitis** is associated with a characteristic, diffuse vesicular rash.

- **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.



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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?*

ESCMID guideline: diagnosis and treatment of acute bacterial meningitis

D. van de Beek[1], C. Cabellos[2], O. Dzupova[3], S. Esposito[4], M. Klein[5], A. T. Kloek[1], S. L. Leib[6], B. Mourvillier[7], C. Ostergaard[8], P. Pagliano[9], H. W. Pfister[5], R. C. Read[10], O. Resat Sipahi[11] and M. C. Brouwer[1], for the ESCMID Study Group for Infections of the Brain (ESGIB)

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TABLE 1.1. Quality of evidence

Class	Conclusions based on:
1	Evidence from at least one properly designed randomized controlled trial.
2	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–control analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments.
3	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies.

European Society for Clinical Microbiology and Infectious Diseases **(ESCMID)**

Key Question 1. What are the causative microorganisms of community-acquired bacterial meningitis in specific groups (neonates, children, adults and immunocompromised patients)?

Level 2	Most common causative pathogens in neonatal meningitis are *Streptococcus agalactiae* and *Escherichia coli*.

Level 2	Most common causative pathogens in children beyond the neonatal age are *Neisseria meningitidis* and *Streptococcus pneumoniae*.

Level 2	Most common causative pathogens in adults are *Streptococcus pneumoniae* and *Neisseria meningitidis*. Another important causative microorganism in adults is *Listeria monocytogenes*.

Key Question 2. What are the clinical characteristics of community-acquired bacterial meningitis, and what is their diagnostic accuracy?

Level 2	Neonates with bacterial meningitis often present with nonspecific symptoms.
Level 2	In children beyond the neonatal age the most common clinical characteristics of bacterial meningitis are fever, headache, neck stiffness and vomiting. There is no clinical sign of bacterial meningitis that is present in all patients.
Level 2	In adults the most common clinical characteristics of bacterial meningitis are fever, headache, neck stiffness and altered mental status. Characteristic clinical signs and symptoms such as fever, neck stiffness, headache and altered mental status can be absent.

Diagnostic accuracy of laboratory techniques in bacterial meningitis

Level 2	It has been shown that in both children and adults, classic characteristics (elevated protein levels, lowered glucose levels, CSF pleocytosis) of bacterial meningitis are present in $\geq$90% of patients. A completely normal CSF occurs but is very rare.
Level 2	In neonatal meningitis, CSF leukocyte count, glucose and total protein levels are frequently within normal range or only slightly elevated.
Level 2	CSF culture is positive in 60–90% of bacterial meningitis patients depending on the definition of bacterial meningitis. Pretreatment with antibiotics decreases the yield of CSF culture by 10–20%.

Diagnostic accuracy of laboratory techniques in bacterial meningitis

Level 2	CSF Gram stain has an excellent specificity and varying sensitivity, depending on the microorganism. The yield decreases slightly if the patient has been treated with antibiotics before lumbar puncture is performed.
Level 2	In patients with a negative CSF culture and CSF Gram stain, PCR has additive value in the identification of the pathogen.
Level 2	In adults and children with bacterial meningitis, blood cultures are useful to isolate the causative microorganism. The yield of blood cultures decreases if the patient is pretreated with antibiotics.

Subquestion 4.1. If lumbar puncture is delayed, should we start treatment?

Recommendation

Grade A

It is strongly recommended to perform cranial imaging before lumbar puncture in patients with:

- Focal neurologic deficits (excluding cranial nerve palsies).
- New-onset seizures.
- Severely altered mental status (Glasgow Coma Scale score <10).
- Severely immunocompromised state.

In patients lacking these characteristics, cranial imaging before lumbar puncture is not recommended.

Grade A

It is strongly recommended to start antibiotic therapy as soon as possible in acute bacterial meningitis patients. The time period until antibiotics are administered should not exceed 1 hour. Whenever lumbar puncture is delayed, e.g. due to cranial CT, empiric treatment must be started immediately on clinical suspicion, even if the diagnosis has not been established.

Key Question 5. What is the optimal type, duration and method of administration of antibiotic treatment when started empirically, after the pathogen has been identified or in culture-negative patients?

Level 2	A delay in antibiotic treatment administration is associated with poor outcome and should therefore be avoided.
Level 3	The empiric antibiotic treatment in bacterial meningitis patients is based on expert opinion and differentiated for demographic/ epidemiologic factors (age and rate of reduced antibiotic susceptibility).
Level 3	The specific antibiotic treatment in bacterial meningitis patients is based on antimicrobial susceptibility testing.

Key Question 6. Does dexamethasone have a beneficial effect on death, functional outcome and hearing loss in adults and children with bacterial meningitis?

Level 1	Corticosteroids significantly reduced hearing loss and neurologic sequelae but did not reduce overall mortality. Data support the use of corticosteroids in patients with bacterial meningitis beyond the neonatal age in countries with a high level of medical care. No beneficial effects of adjunctive corticosteroids have been identified in studies performed in low-income countries. The use of dexamethasone for neonates is currently not recommended.
Level 3	In the absence of scientific evidence, the committee has reached consensus that when antibiotic treatment has already been started, adjunctive dexamethasone treatment can still be started up to 4 hours after initiation of antibiotic treatment.

Key Question 8. Does the use of prophylactic treatment of household contacts decrease carriage or secondary cases?

Level 1	Prophylactic antibiotic treatment of household contacts of meningococcal meningitis patients prevents secondary cases and eradicates meningococcal carriage.

Level 3

- Based on the recurrence risk of 1–5% of pneumococcal meningitis, the committee sees substantial benefits in vaccination with pneumococcal vaccines after an episode of pneumococcal meningitis.
- Vaccination with pneumococcal vaccines is deemed beneficial in bacterial meningitis patients with CSF leakage to reduce recurrences.

Key Question 9. What complications occur during community-acquired bacterial meningitis, what ancillary investigations are warranted when complications occur and how should they be treated?

Level 2	Neurologic and systemic complications occur in a large proportion of children and adults with bacterial meningitis. In patients with neurologic deterioration, cranial imaging (MRI or CT) is often indicated, and repeated lumbar puncture and EEG may be indicated in selected cases.

Level 3	Bacterial meningitis complicated by hydrocephalus, subdural empyema and brain abscess may require neurosurgical intervention.

Key Question 10. What follow-up of community-acquired bacterial meningitis patients should be provided (e.g. testing for hearing loss, neuropsychological evaluation)?

Level 2	Sequelae occur in a substantial proportion of children and adults with bacterial meningitis and most frequently consist of hearing loss, neuropsychologic defects and focal neurologic deficits.

Level 2	Hearing loss needs to be detected early during the disease course to facilitate effective cochlear implantation in the case of severe hearing loss.

What is chronic meningitis?

- **Chronic meningitis** is diagnosed when a characteristic **neurologic syndrome** exists for **>4 weeks** and is associated with a **persistent inflammatory response in the cerebrospinal fluid** (CSF) (white blood cell count >5/µL).

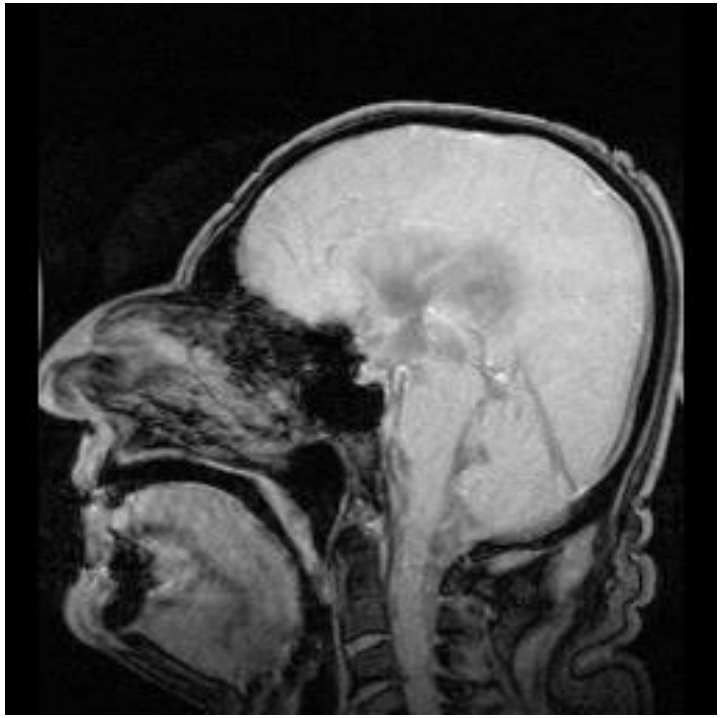
- **Subacute meningitis** develops over days to a few weeks.

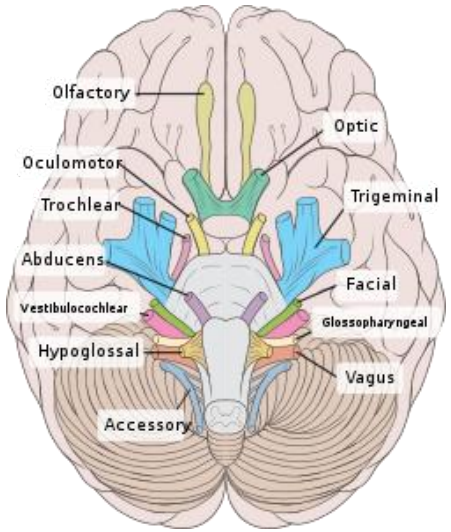
TABLE 37-1

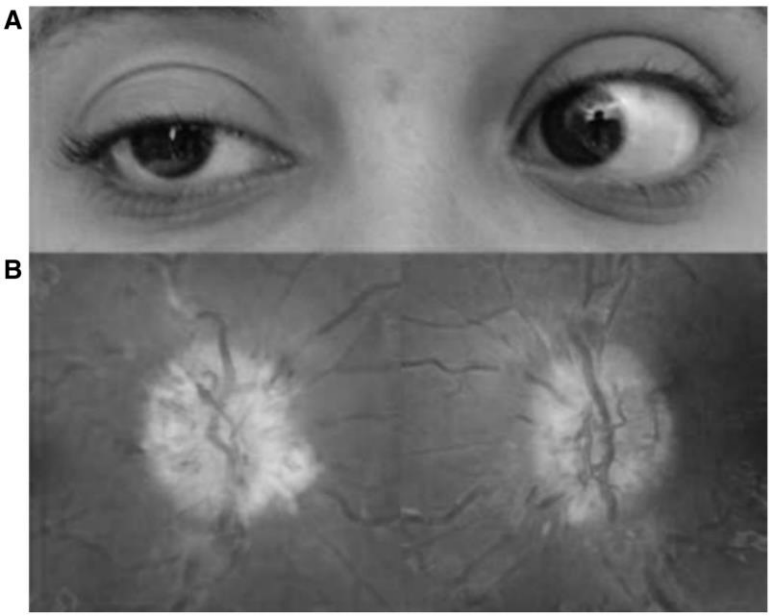
SYMPTOMS AND SIGNS OF CHRONIC MENINGITIS

SYMPTOM	SIGN
Chronic headache	± Papilledema
Neck or back pain/stiffness	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN paresis
Double vision	Paresis of CNs III, IV, VI
Diminished vision	Papilledema, optic atrophy
Hearing loss	Eighth CN paresis
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Urinary retention/ incontinence	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Abbreviation: CN, cranial nerve.

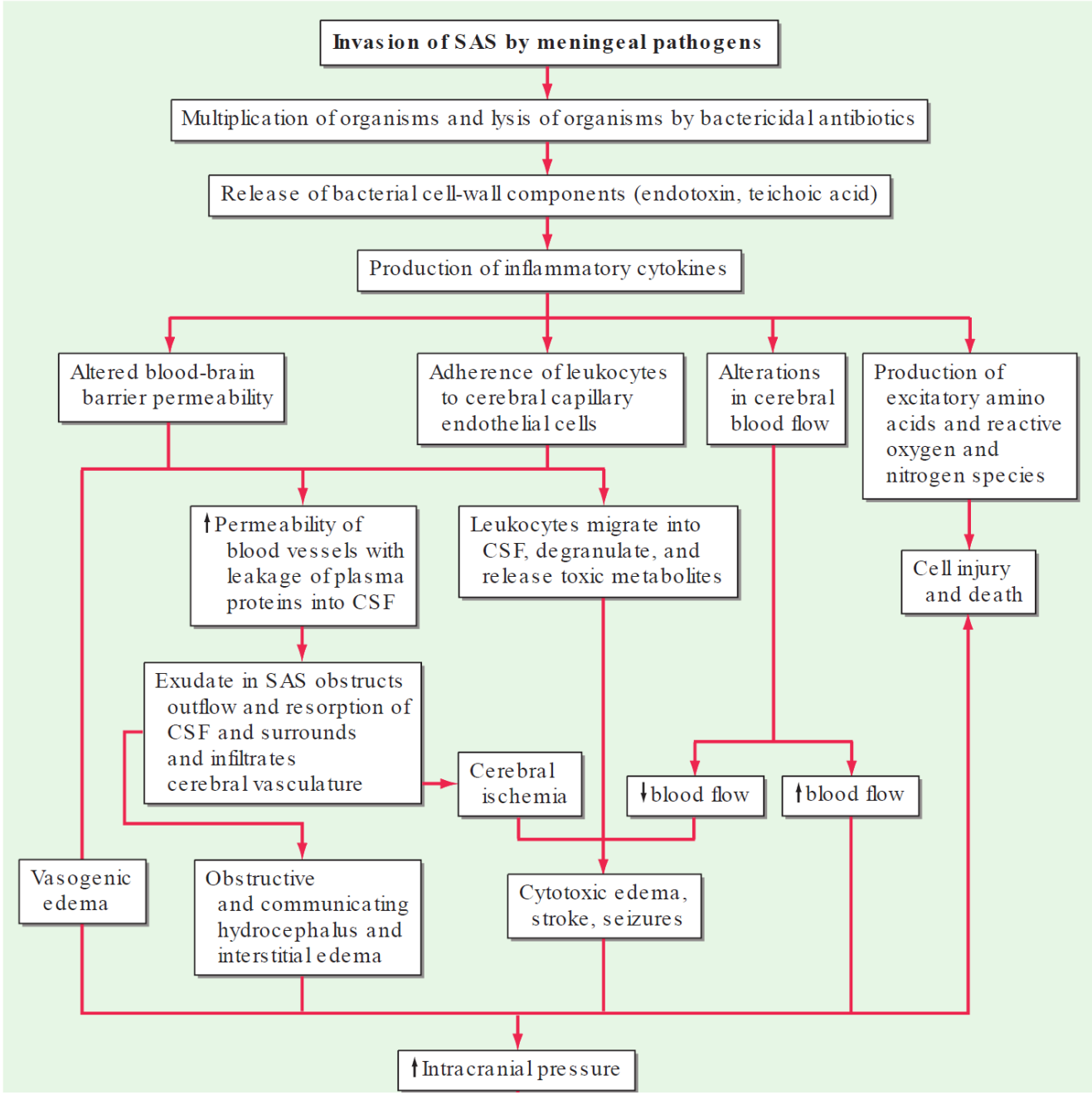






(A) Ptosis and an abduction deficit in the right eye of the patient.

(B) Bilateral papilloedema



What is chronic meningitis?

- Most common etiologies of chronic meningitis:

(1) meningeal infections,
(2) malignancy,
(3) autoimmune inflammatory disorders,
(4) Para-meningeal infections.

TABLE 37-1

SYMPTOMS AND SIGNS OF CHRONIC MENINGITIS

SYMPTOM	SIGN
Chronic headache	± Papilledema
Neck or back pain/stiffness	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN paresis
Double vision	Paresis of CNs III, IV, VI
Diminished vision	Papilledema, optic atrophy
Hearing loss	Eighth CN paresis
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Urinary retention/ incontinence	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Abbreviation: CN, cranial nerve.

Common causes of infectious chronic meningitis?

- Possible causes include fungi, Mycobacterium tuberculosis, spirochetes, Toxoplasma gondii, HIV, enteroviruses

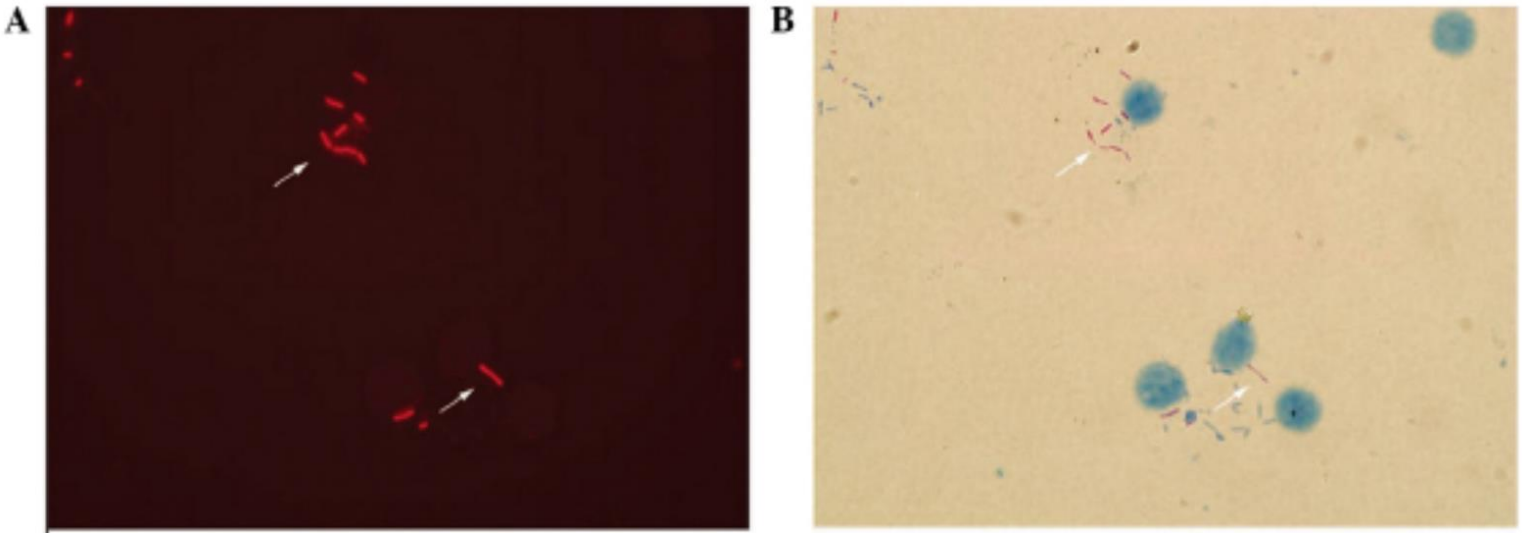
- History is important in identifying risk factors. (e.g. Exposure to TB cases, tick bites, Syphilis)

Table 19.5 Causes of chronic meningitis/meningoencephalitis

	Syndrome	Causes
Infectious	Meningitis	*Acanthamoeba* spp., *A. cantonensis*, brucellosis, candidiasis, coccidioidomycosis, cryptococcosis, *Ehrlichia chaffeensis, F. tularensis*, histoplasmosis, *Leptospira* spp., *Listeria* spp., Lyme disease, sporotrichosis, syphilis, TB, Whipple's disease
	Focal lesions	Actinomycosis, blastomycosis, cysticercosis, aspergillosis, nocardiosis, schistosomiasis, toxoplasmosis, TB
	Encephalitis	African trypanosomiasis, CMV, enterovirus (hypogammaglobulinaemia), EBV, HIV, HTLV, HSV, measles, SSPE, rabies, VZV
Non-infectious	Meningitis	Drugs (NSAIDs, IVIG, intrathecal agents), Behçet's disease, benign lymphocytic meningitis, CNS vasculitis, Fabry's disease, granulomatous angiitis, malignancy, sarcoidosis, SLE, Wegener's granulomatosis, Vogt–Koyanagi–Harada disease

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Common Bacterial Causes			
Mycobacterium tuberculosis	Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBCs/μL); low CSF glucose, high protein	Tuberculin skin test may be negative; AFB culture of CSF (sputum, urine, gastric contents if indicated); tuberculostearic acid detection in CSF; identify tubercle bacillus on acid-fast stain of CSF or protein pellicle; PCR	Exposure history; previous tuberculous illness; immunosuppressed, anti-TNF therapy or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis
Lyme disease (Bannwarth's syndrome): Borrelia burgdorferi	Mononuclear cells; elevated protein	Serum Lyme antibody titer; western blot confirmation (patients with syphilis may have false-positive Lyme titer)	History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy, meningoencephalitis–multiple sclerosis-like syndrome
Syphilis (secondary, tertiary): Treponema pallidum	Mononuclear cells; elevated protein	CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody–absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis	Appropriate exposure history; HIV-seropositive individuals at increased risk of aggressive infection; "dementia"; cerebral infarction due to endarteritis
Partially treated suppurative meningitis	Mononuclear or mixed mononuclear-polymorphonuclear cells	CSF culture and Gram's stain	History consistent with acute bacterial meningitis and incomplete treatment



Micrographs of acid-fast bacilli obtained with fluorescence microscopy and transmitted light microscopy (modified Z-N staining)

Because tuberculous meningitis has a rapid and destructive course and because diagnostic tests are limited, this infection should be **treated based on clinical suspicion**. Currently, the WHO recommends treatment with the **anti-TB drugs** isoniazid, rifampin, pyrazinamide, and ethambutol for 2 mo followed by isoniazid and rifampin for 6 to 7 mo. **Corticosteroids** (prednisone or dexamethasone) may be added if patients present with stupor, coma, or neurologic deficits.

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Fungal Causes			
Cryptococcus neoformans	Mononuclear cells; count not elevated in some patients with AIDS	India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF	AIDS and immune suppression; pigeon exposure; skin and other organ involvement due to disseminated infection
Coccidioides immitis	Mononuclear cells (sometimes 10–20% eosinophils); often low glucose	Antibody detection in CSF and serum	Exposure history—southwestern U.S.; increased virulence in dark-skinned races
Candida spp.	Polymorphonuclear or mononuclear	Fungal stain and culture of CSF	IV drug abuse; post surgery; prolonged IV therapy; disseminated candidiasis
Histoplasma capsulatum	Mononuclear cells; low glucose	Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF	Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions
Blastomyces dermatitidis	Mononuclear cells	Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum	Midwestern and southeastern U.S.; usually systemic infection; abscesses, draining sinus, ulcers
Aspergillus spp.	Mononuclear or polymorphonuclear	CSF culture	Sinusitis; granulocytopenia or immunosuppression

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Helminthic Causes			
Cysticercosis (infection with cysts of Taenia solium)	Mononuclear cells; may have eosinophils; glucose level may be low	Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum	Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification
Protozoal Causes			
Toxoplasma gondii	Mononuclear cells	Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum)	Usually with intracerebral abscesses; common in HIV-seropositive patients
Viral Causes			
Mumps	Mononuclear cells	Antibody in serum	No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks
Herpes simplex (HSV)	Mononuclear cells	PCR for HSV, CMV DNA; CSF antibody for HSV, EBV	Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy

How to approach a patient with chronic meningitis?

- The occurrence of **chronic headache**, **hydrocephalus**, **cranial neuropathy**, and/or **cognitive decline** in a patient should prompt consideration of a lumbar puncture for evidence of meningeal inflammation.

- If the possibility of **raised ICP** exists, a **brain imaging study (CT scan, MRI) should be performed before lumbar puncture**. If ICP is elevated because o a mass lesion, lumbar puncture carries the potential **risk of brain herniation**.

- Once chronic meningitis is confirmed by CSF examination, effort is focused on **identifying the cause**.

- The **epidemiologic history** is of considerable importance and may provide hints to the causative agent as well as selection of laboratory studies.

- **CSF samples** sent or bacterial, fungal, and tuberculous **culture**; Venereal Disease Research Laboratories (**VDRL**) test; **cell count and differential**; **Gram's stain**; and measurement of **glucose** and **protein**. **Wet mount** for fungus and parasites, Rapid diagnosis may be facilitated by **serologic tests** and polymerase chain reaction (**PCR**) testing to identify DNA sequences in the CSF that are specific for the suspected pathogen.

- In addition to the CSF examination, an attempt should be made to uncover pertinent **underlying illnesses**. (e.g. Tuberculin skin test, chest radiograph, urine analysis and culture, blood count and differential).

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