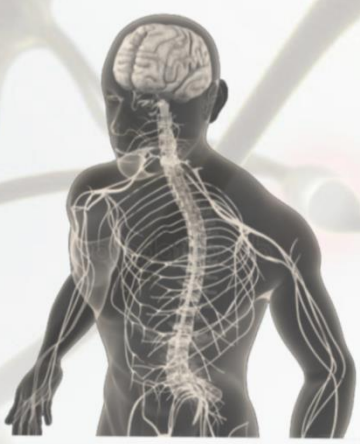
Central Nervous System

Sheet 1



Subject | Microbiology

Done by | Yousef Omar

Correction | ...

Doctor | Anas

-The central nervous system, unlike other systems, is 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.

- Also, CNS is described as displaying **immune privilege**: it's organs of the body that doesn't have high number of immune cells to monitor the invasion of antigens or alloantigen, so immune privileged organs don't mount full immune response, so they show an attenuated response.

- **Note**: Corneal Grafts of the eye, shows no rejections due to immune privilege since there are low number of immune cells.

*Why it's important for the brain to be immune privileged? because normally full immune response might destruct the tissue surrounding it, so we will benefit from attenuated immune response that maintain the surrounding nervous tissue like neurons that if damaged, it would be permanent.

- Pathogens that reach the CNS may cause devastating inflammation, since the brain isn't used to encounter pathogens, so it can mount a severe immune response that can destroy the surrounding tissue, but normally it only mount attenuated immune response.(Remember CNS have low number of immune cells). On the other hand, the pathogens can survive within the CNS, because it doesn't have a strong immune response to eliminate the pathogen.

- CNS have physiological barriers (some are physical like skin/bone) and immunological barrier (like blood brain barrier that limits the passage of pathogen from blood to CNS), to protect itself.

- Nervous system divisions: CNS (brain and spinal cord) and PNS.

*Infections of the CNS:

1. Acute bacterial meningitis – Objective of this lecture -

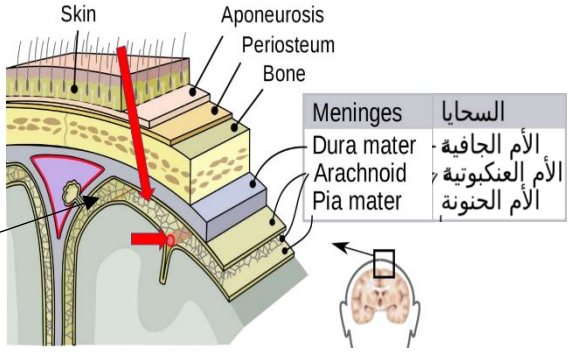
2. Viral meningitis
3. Chronic meningitis
4. Encephalitis
5. Focal infections such as brain abscess a subdural empyema

Note: bacterial and viral meningitis are put in different groups due to different immune response against bacteria and viruses and this disease is mainly dependent on immune response.

*Meninges? three membranous envelopes—pia mater, arachnoid, and dura mater—that surround the brain and spinal cord.

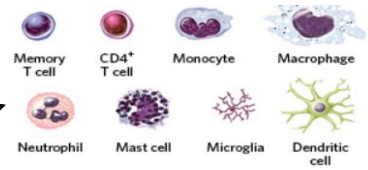
- In this sagittal section, you can see 1st we have skin,…,bone then meninges.

- In subarachnoid space there is Cerebrospinal fluid (CSF) that is secreted by choroid plexus, to provide cushion and nutrition for the brain and spinal cord.



*How can pathogens reach the brain?

- In the case of bacteria: It may occur directly following accidents/traumas/injuries that break all layers covering the brain, but the other more common way is through hematogenous spread of infections from other location that reaches the blood, and then crosses the blood brain barrier to subarachnoid space causing infection.
- In the case of viruses: it may enter the brain by moving along neurons into CNS. (it will be explained in next lectures).



-**Note**: Each bacterium has a different mechanism to pass through the BBB.

-**Note**: BBB is formed of endothelial cells and astrocytes.

-**Note**: Remember that CSF have low number of immune cells, for e.g. CSF lacks neutrophils except in case of injury, at which endothelial cells starts to secrete IL-1, TNF and other cytokines to recruit neutrophil to produce an attenuated immune response. Immune cells are only found in CSF and meninges, so they don't reach the brain parenchyma normally when recruited.

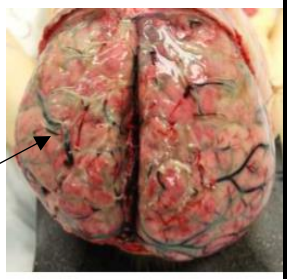
-**Note**: Within brain parenchyma, there is an immune cell which is microglial cell (resident macrophage of the brain that originate from the **yolk sac**, that is different than recruited macrophages after injury that originate from monocytes), which is activated in response to infection or damage in the brain.

*Immune system is critical in the function of the CNS even in the absence of injury, since its necessary for pruning of neurons and getting rid of cell debris. Also, some cells within the brain secrete complement proteins, which work as part of signaling that takes place if a pathogen invades into the brain. So, remember that at homeostatic situations we have a functioning immune system at low grade in the brain.

*Most immune cells are found in CSF, meninges and choroid plexus. Microglia can also be found in brain parenchyma. When the CNS experiences a major insult, however, immune cells join microglia in the parenchyma.

****Now let's start with meningitis:

*__Meningitis__, an inflammation of the leptomeninges and subarachnoid space, is a **neurologic emergency**.


Meningitis

-CSF is important to indicate the causative agent of meningitis.

-A postmortem individual, by looking at his brain, you can see that meninges are inflamed and there is pus formation, so it looks like an acute purulent bacterial meningitis which is the most common form of suppurative CNS infection.

-Meningitis causes:

1. Mostly infectious causes, by bacteria, viruses, fungi, and parasites.
2. Rarely non-infectious, due to drugs (NSAIDS), malignancies (especially in case of metastasis that reach CSF or choroid plexus that can irritate the meninges causing meningitis like-symptoms), or autoimmune diseases (SLE and vasculitis, both form antibodies to irritate the meninges).

***REMEMBER: It's a neurological emergency, that require early recognition, efficient decision making, and rapid institution of therapy that can be lifesaving. So, you must keep in mind how it present and the common causes of it.

*How to identify the common cause of bacterial meningitis? According to age and immune status of the individual (predisposing conditions).

-Now follow me and refer to the figure:

- Very early on, within the 1st 4weeks, patient is affected by the flora of the vaginal canal, while the baby is passing through it during delivery, taking the pathogen with it including GBS (streptococcus agalactia) or E. coli. That's why during pregnancy, they must check if there is colonization of GBS, if found → initiate antibiotic therapy to get rid of it. Also, during this period we have L. monocytogenes.
- E. coli and GBS are the most common causes of meningitis during 1-3months of life.
- 3month to end of life: H. influenza, N. meningitidis, S. pneumonia become predominant causes (Remember all these bacterias have capsules that allow them to survive in blood and reach meninges).

Note: H. Influenza cases declined significantly due to vaccination especially type B. While non-typable H. influenza cause infections that are more localized. So, remember that N. meningitidis and S. pneumonia are the most common cause according to geography. In our region, N. meningitidis is the most common.

- L. monocytogenes can be seen in immunocompromised, very young (0-12weeks), or very old patients (>50).

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

Note: GBS is gram + cocci, E. coli is a gram – rod, L. monocytogenes is a gram + coccobacilli. L. monocytogenes is a facultative intracellular pathogen.

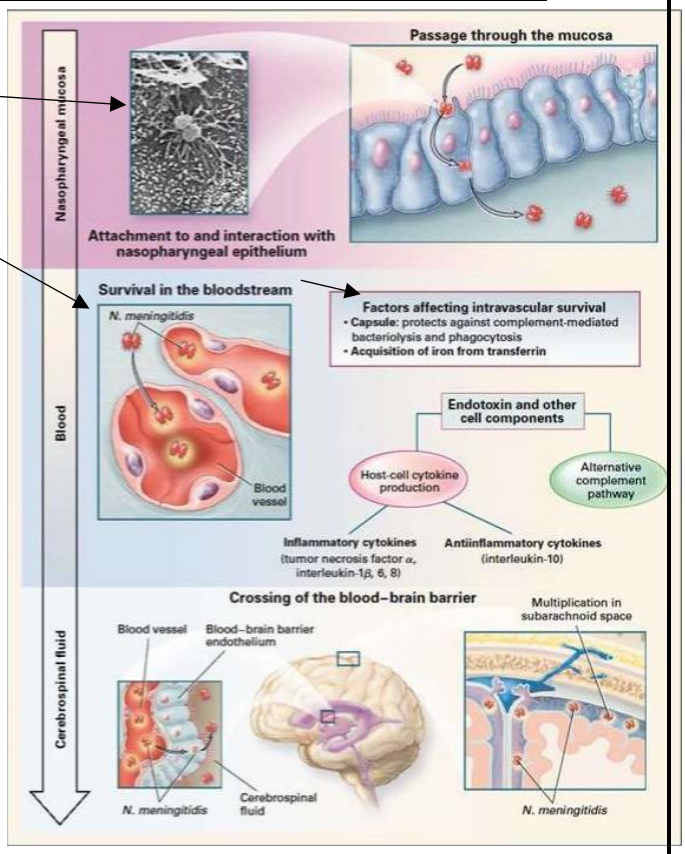
- Head trauma/post-neurosurgery: S. aureus and S. epidermidis from the skin.
- CSF shunts: S. aureus and S. epidermidis since there is involvement of skin.
- Basal skull fracture: may cause formation of a connection between meninges and sinuses/oropharynx/… that can lead to infection similar to otitis and sinusitis for example caused by S. pneumoniae and H. influenza.

***So, keep all these points in mind to deal with different scenarios, for example, if a patient had an accident and have symptoms of meningitis, you think of S. aureus. If the patient is a baby and his/her age is less that 4months it might be E. coli/GBS. If the patient is an elderly or immunocompromised, think of the most common which is S. pneumonia and N. meningitides BUT also keep in mind L. monocytogenes.

*** How do bacteria get to the meninges?

1. In the case of N. meningitidis (Gram – diplococci, Fastidious), it can colonize the nasopharyngeal epithelium of normal individual without symptoms. Then it gets internalized into the mucosa and then to the blood. It can survive in the blood due to presence of capsule. Then through the blood, it can cross the BBB and reach into subarachnoid space in the meninges which is lacking in cellular and humoral immunity. so, they start to replicate for some time. Then they are caught by immune cell that are recruited mounting a strong immune response within subarachnoid space. The immune response to the pathogen and its products (e.g. LPS, PGN) further damages the surrounding tissue.

   Note: N. meningitidis when its circulating in the blood, it can also cause meningococcemia, damaging blood vessel in the skin leading to skin lesion like bullae. So, it manifests as bleeding under the skin.



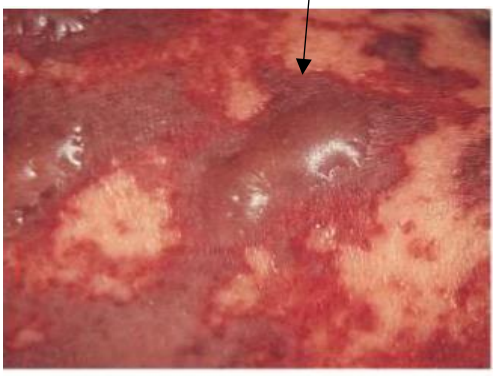
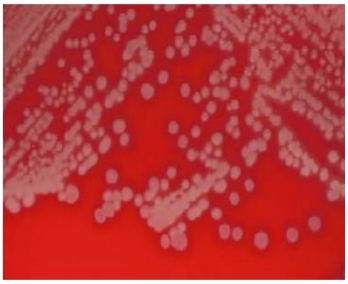
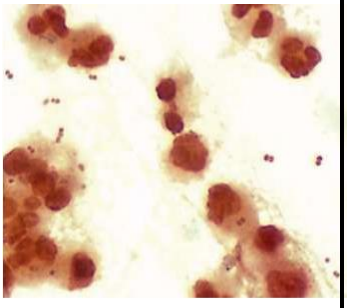


FIGURE 23-5 Skin lesions in a patient with meningococcemia. Note that the petechial lesions have coalesced and formed hemorrhagic bullae.

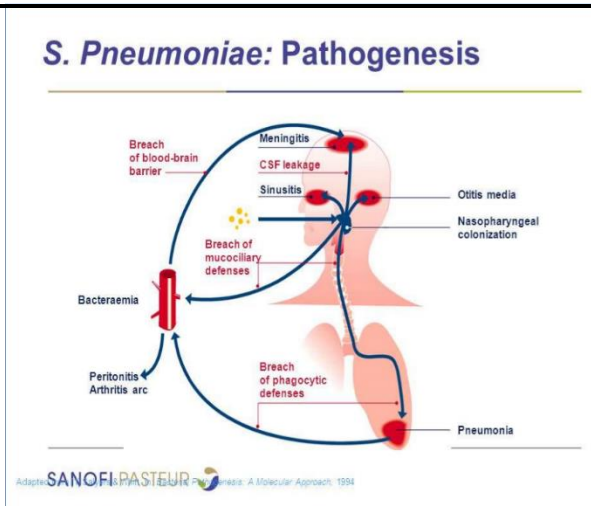


N. meningitidis colonies on blood agar plate



N. meningitidis gram stain

2. In the case of S. pneumonia (gram + cocci), that can also colonize the nasopharynx and from there it can cause otitis media, sinusitis and other infections. Now in case of basal skull fracture which cause CSF leakage, it can lead to meningitis. Or it can reach the blood causing bacteremia, and through the blood it can reach the BBB crossing it and causes meningitis.



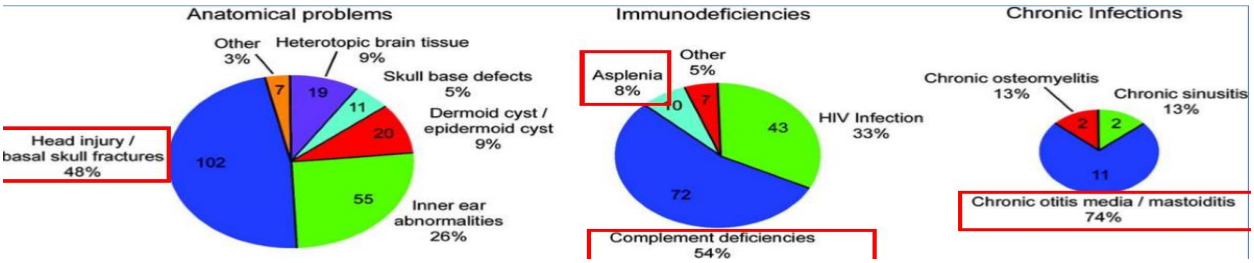
***How common is the bacterial meningitis? In general, it's a very rare disease.

- ✓ In America, the incidence is 2-5 per 100.000.
- ✓ Worldwide it varies a lot, 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.

***What are the predisposing factors of meningitis?

1. Anatomic problems including head injuries/basal skull fractures and inner ear abnormalities (like abnormal ear canals giving access for bacteria to reach meninges)
2. Immunodeficiencies including patients who remove spleen (asplenia) are exposed to meningococcemia, meningitis by N. meningitides and S. pneumonia infections, so you must give these patients vaccine. Also, there are complement deficiencies, especially patients who take complement inhibitors (For example C5 blockers) increase the risk of meningitis 1000-2000times especially by N. meningitidis.
3. Chronic infection within skull area that lead to leakage to meninges including chronic otitis media/mastoiditis.

But remember in general it's a very rare disease, but most of cases are related to accident/trauma, chronic infections or have immunodeficiency patients. ***Doctor hasn't read any numbers in the figure below***



-Note: In north Africa and middle east, N. meningitidis is one of the leading causes of meningitis.

-Note: Hajj and Umrah (حج و عمرة), can increase the risk of meningitis epidemics. That's why in Saudi Arabia there are vaccination policies to limit the spread of meningococcal diseases due to crowdedness.

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*Clinical presentation:

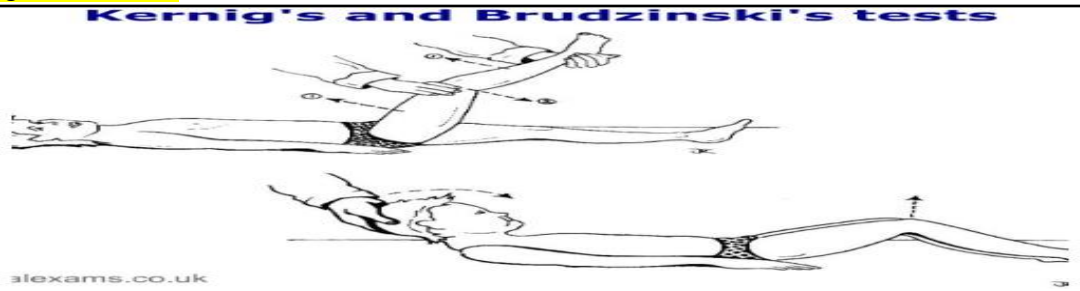
- How do meningitis patients present?

- ❖ Bacterial meningitis mostly present as a fulminant illness progressing within hours. They present with clinical **triad** of fever, headache, and meningism/meningeal signs (include neck stiffness (most imp), photophobia, and positive Kernig's sign and Brudzinski's sign).

****Meningeal stretch signs include Kernig's sign and Brudzinski's sign, at which you perform a maneuver on the patient to stretch the meninges, if they are inflamed then with this stretch the patient feels pain.

-In the case of Kernig's sign, you fold the patient leg then hip flexion. The test is positive if there is generalized spinal resistance or involuntary flexion of the opposite hip, because if you move the other hip you try to reduce the stretch occurring on the meninges. So, in this case meninges are inflamed and stretching them causes pain. If this test is negative due to various causes, it doesn't mean that the patient doesn't have meningitis.

-In case of Brudzinski's sign, you raise the patient head stretching the meninges, the test is positive, if there is involuntary flexion at the knee and hip joints to release the stretch/reduce meningeal irritation.



- ❖ In case the infection spreads to brain parenchyma (it often remains in the meninges), then it's called meningoencephalitis (inflammation of meninges and brain parenchyma). This leads to cerebral dysfunction (confusion and/ or reduced conscious level).
- ❖ Seizures can occur in neonatal and adult meningitis patients and varies by the etiological agent.
- ❖ Accompanying symptoms is often present, such as petechial rash (Bleeding under skin) in meningococcal septicemia. Or Rhinorrhea of clear fluid like CSF flowing through the nose, suggesting basal skull fracture.
- ❖ If inflammation takes long time/chronic and is severe enough, it may block the normal cycle of CSF within subarachnoid space around brain and spinal cord, so this inflammation disturb the resorption of this fluid, so the pressure of CSF in subarachnoid space is high, pressing on the brain leading to Increased intracranial pressure secondary

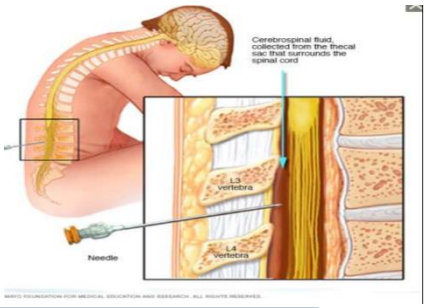
to meningitis can have ocular symptoms like optic disc swelling (papilledema) and cranial nerve palsies.

- ❖ IMPORTANT: Neonates may present with non- specific symptoms, e.g. temperature instability, listlessness, poor feeding, irritability, vomiting, diarrhea, jaundice, respiratory distress.

***How to diagnose bacterial meningitis?

-if there is clinical suspicion, a patient coming to clinic with high fever with neck stiffness and positive sign tests, it indicates meningitis without need of further test, and so on initiate Antibiotic therapy. But if there was enough time to do further tests, before starting empiric antibiotic therapy, you can take lumber puncture taking part of CSF which have information that can direct the therapy. Again, remember it's a neurological emergency that must be treated immediately! But if you have enough time to do more tests by taking CSF then do it.

- As in the figure, we take a lumber puncture using needle, put the CSF in 3tubes(1ml each) each one going to different sections: One to microbiology (to look for bacteria , culture it and do a gram stain), chemistry (to look for protein and glucose) and cytology (to look for WBCs and their types).



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

Note: 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.

Note: In chemistry, we indicate level of protein and glucose which differ according to pathogen.

***Refer to the following table that indicate the difference between normal CSF and infected CSF: (Doctor emphasized bacterial infection only)

- Pressure is increased with bacterial infection (Not imp.)
- Appearance: it's clear normally, but in bacterial infections its turbid.
- Protein(imp): it's elevated in bacterial infection (>1), because there are antibodies being produced, also cytokines, enzymes and destructed bacteria that increase level of protein.
- Glucose level decreases, because during bacterial infection there is increased metabolism by host and bacterial cells that take up glucose found in CSF.
- Gram stain: 60%-90% positive.

	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

- In Cytology, we look at WBC count (WCC), normally there are <3 cells/ml, but in case of bacterial infection, you would have infiltration of WBC of up to 500 cells/ml. Most WBCs in bacterial infection are neutrophils/PMN (90%), but in case of viral infection you would have lymphocytes.
- In conclusion in bacterial infection: High protein, low glucose, gram stain positive, and high number of WBCs mainly neutrophils.

***How to manage suspected bacterial meningitis?

- Prompt empirical antibiotic therapy should be initiated before results of the CSF examination and culture. Empiric therapy indicate 3rd generation cephalosporin (Cefotaxime) along with vancomycin or ampicillin.
- Since inflammation occupy most of pathology in meningitis, Adjunctive therapy with corticosteroid (dexamethasone) to lessen the inflammatory response is sometimes warranted (NOT given in all cases).
- Reduction of raised intracranial pressure if present.
- Chemoprophylaxis (Antibiotics)should be given within 24h to household contacts (any person with contact to respiratory or oral secretions of infected patient). Because after bacteria reach the blood and causes meningitis, it gains virulence factors that makes it dangerous and infectious.
- NOW, after culture tests are released, you direct your therapy against the identified pathogen with specific antibiotics.

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)

The doctor hasn't read anything in this table.

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

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*** What is the outcome of bacterial meningitis?

- It's a malignant disease, mortality rate is high even with prompt antibiotic therapy, and varies with etiological agent (e.g. 5% for N. meningitidis, 20% for S. pneumoniae) -(Each 5 individual with meningitis, 1 will die). So it must be recognized very early to initiate therapy to reduce mortality.
- Damage caused by meningitis is lifelong damage, and this damage is increased with delayed treatment and comorbid conditions (e.g. elderly, diabetes, immunocompromised, cancer, etc.), which affect survival and sequalae.
- Decreased level of consciousness on admission, onset of seizures within 24 h of admission which indicate spread of infection to brain, and signs of increased ICP all increase mortality.
- **Neurological sequelae** occur in a substantial number of patients following bacterial meningitis. Most frequently reported sequelae are focal neurological deficits, hearing loss, cognitive impairment and epilepsy.

Note: Focal neurological deficits indicate damaged part of the brain, that is manifested in the form of paralysis for example. Children with bacterial meningitis, usually manifest with cognitive impairment (Retardation), deafness or with epilepsy.

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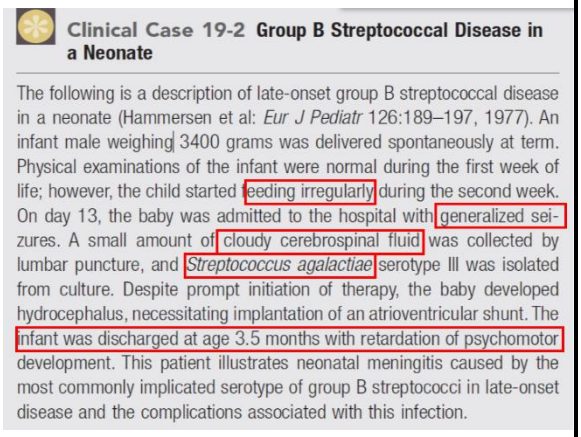
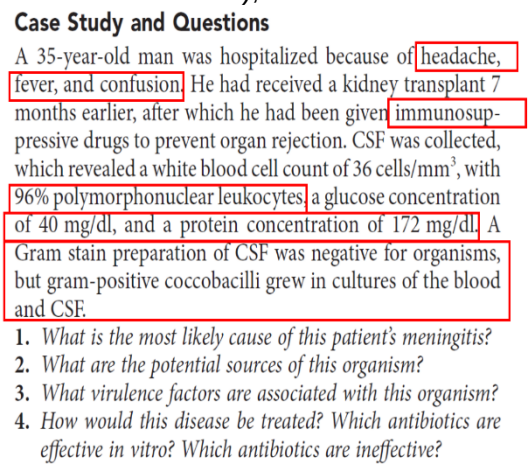
*2 cases mentioned by the doctor: (don't memorize them, just understand how to diagnose meningitis)



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.

1) as the case indicate, a neonate was found with GBS infection (refer to figure page 3), and he was found with non-specific symptoms (Point page 7). So, this baby was normal during the 1st week of life, but then he started feeding irregularly during 2nd week. In day 13, he had generalized seizures and fever with admission to hospital. So, his doctor decided to take CSF, which appeared to be cloudy, which normally should be a clear fluid. One of tubes with CSF was given to microbiologists, to culture it, and apply gram stain. test results have shown Gram + streptococci and found out that its GBS with further testing. Despite prompt initiation of therapy, the baby developed hydrocephalus (increased intracranial pressure), so a shunt implantation was performed. And the infant was discharged at age of 3.5months with retardation of psychomotor development (check note written above), so this indicate having neurological sequalae.



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?*

2) Read this case:

- Headache and fever, which is part of triad. Confusion indicate meningoencephalitis. High WBCs with 96% PMNs indicate bacterial infection. Decreased glucose concentration and raised protein concentration. Culture from CSF results revealed gram positive coccobacilli which is L. monocytogenes. Sources of this organism is cold cuts. Virulence factors make it a facultative intracellular pathogen. *doctor hasn't read Q4*