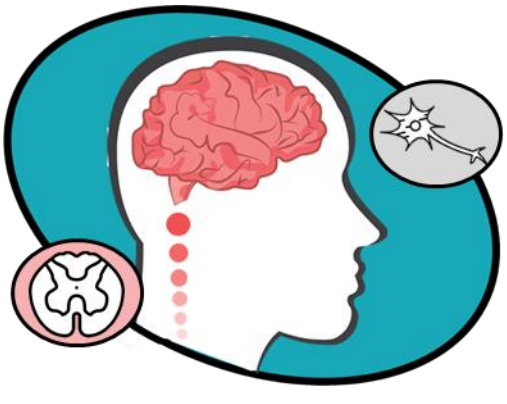

CNS

Microbiology

Sheet Slide

Number

1

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In this lecture we will talk about the microbiology of the central nervous system

The central nervous system is supposedly sterile, so there is no micro flora like that we find on the skin or in the GI tract, but some bacteria, viruses or fungi gain access to the CNS so the immune system responds to their unusual presence in an exaggerated manner which eventually causes damage to the CNS.

We cannot tolerate the damage in the CNS because the neurons cannot regenerate, so if they are damaged we lose them forever.

So, in all the infections that take place in the CNS we always try to minimize the damage that takes place because we want to maintain/keep these precious neurons.

Most common infections in the CNS are:

1. Acute bacterial meningitis.
2. Viral meningitis
3. Encephalitis
4. Focal infections such as brain abscess and subdural empyema.

In this lecture we will be talking about the **bacterial and viral meningitis**.

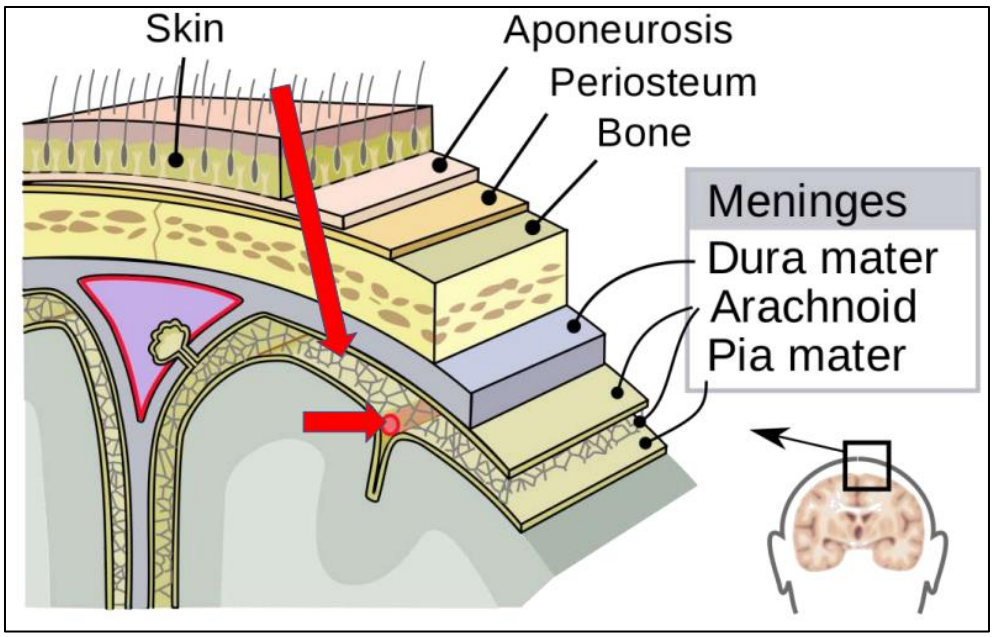
What is meningitis?

- It is basically the inflammation that takes place in the meninges.

- let us revise briefly what we took in the MSS system about the meninges, in this picture below we have a coronal section to the head, we can see the layers of the head which start from the skin, periosteum, bone and then the meninges which are the direct coverings of the brain and the spinal cord, they are divided into:
    1. Dura mater
    2. Arachnoid

3. Pia mater: the closest layer to the brain.

*The space between the arachnoid and pia mater is filled with cerebrospinal fluid (CSF).



- Meningitis infections take place in the **subarachnoid space** (it is called arachnoid because it is related in shape to spiders or spider webs)

- How does bacteria gain access to the subarachnoid space which is covered by all the aforementioned layers?

    1. **Directly** through an accident, skull fracture or surgery.
    2. Through **hematogenous spread** (blood vessels).

- So, meningitis is the inflammation of the meninges that most likely happen in the subarachnoid space which is filled with **CSF**.

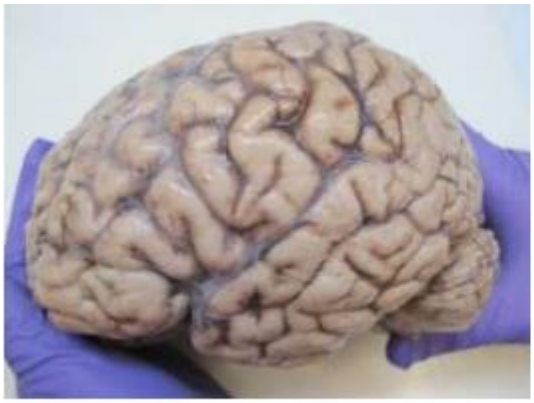
- The **cerebrospinal fluid** helps in protection of the brain, supply nutrients and maintain homeostasis in the CNS, when the microorganisms gain access to the CNS either directly or through hematogenous spread we will see that the CSF

gets infected so we can use it in tests to confirm the infections and to identify its origins whether its bacterial, viral or fungal.

- Besides the microorganisms that change the CSF there will be damage in the meninges which will contribute in the change of the CSF which we examine to confirm meningitis.

- For example, in comparison to a normal brain, in the case of meningitis we will see pus all over the brain and hemorrhages in some places.

- Meningitis is a neurologic emergency, it needs to be dealt with within hours so we have to have an early recognition to start the proper treatment because that can save lives and decrease the consequences of the infection.



Normal

Meningitis

Bacterial meningitis

Bacterial meningitis can have many causes and these causes can vary according to the age of the patient and the predisposing conditions, for example:

1. **In early neonates**, just after birth (less than 4 weeks), common organisms that cause meningitis are **group B streptococci (GBS), E. coli and listeria monocytogenes**. These bacteria are common in this age because the mother is colonized with them so when delivery takes place the baby acquires these bacteria (probably through ingestion) and then this baby will

be infected because the immune system isn't well developed so meningitis can happen.

2. **In adults**, other common organisms can cause meningitis like: **Hemophilus influenzae, Neisseria meningitides and streptococcus pneumoniae**. But nowadays the most common cause in adults is S. pneumoniae because H. influenzae has decreased significantly although it was an important cause because of vaccination.

3. In the cases of **head trauma or CSF shunts** the most common causes of meningitis are **S. aureus and S. epidermidis** because they are on the skin as a part of the normal flora.

Pathophysiology of bacterial meningitis

N. meningitides

- N. meningitides is gram negative diplococci which can be found in the **nasopharynx** as a part of the normal flora, in certain cases N. meningitides can cross the epithelium in the nasopharynx and goes to the blood vessels which considered as a new environment for N. meningitides, as we know the blood contains a lot of immune cells and other humoral immune mechanisms such as immunoglobulins and complement system so **how does N. meningitides survive (virulence factors)?**

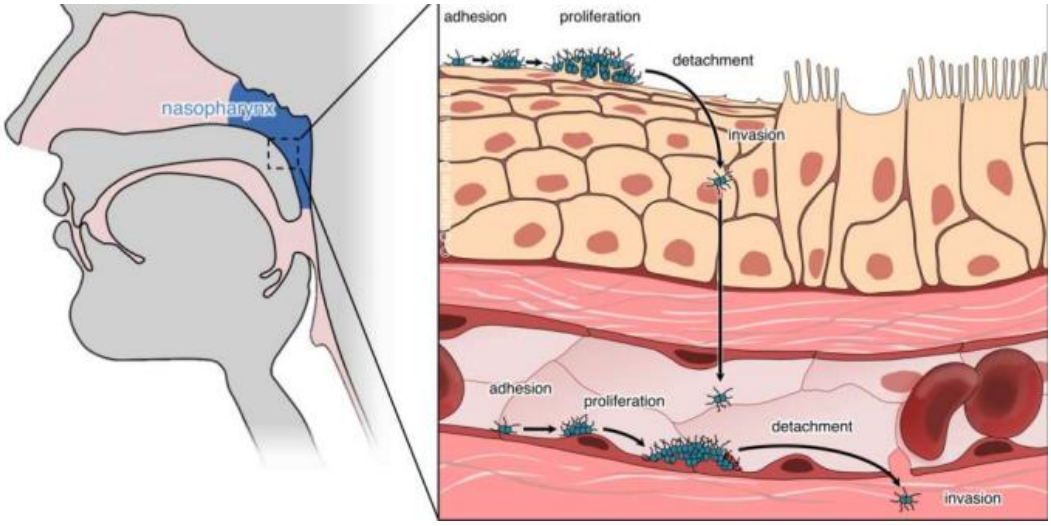
    1. It has a **capsule**, which prevents phagocytosis because antibodies and other opsonizing agents are less efficient in attaching to the capsule.

    2. It expresses some types of proteins that help in surviving such as **complement inhibitors**, because complement system is important in opsonization of N. meningitides, so complement inhibitors prevent the deposition of complement proteins on the bacteria which will make it harder to be phagocytosed.

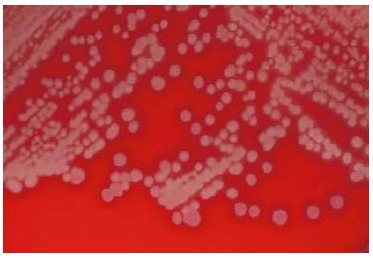
3. Some bacteria produce immunoglobulin degrading enzymes like **IgA protease** which protects the bacteria from opsonization and phagocytosis because IgA will be degraded.

- So different bacteria have different ways of surviving within the blood stream, because it needs to survive for a certain time until it reaches the blood brain barrier, when the immune system fails to clear the bacteria within the blood it can cross to the CSF which will be found in the subarachnoid space, the CSF is different from the blood because It lacks immune cells (less than 3 WBCs per microliter), also it has very little amounts of immunoglobulins and complement proteins, so the CSF is a good environment for the bacteria to replicate.

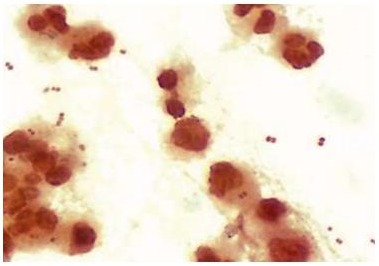
- As the bacteria replicates the immune system is initiated against it mostly in the form of **neutrophils**, neutrophils will start going to the site of infection and start releasing cytokines, granules and ROSs in order to kill the bacteria but at the same time they damage the surrounding tissue and also they form blocks within the CSF which will cause the CSF not to flow normally, the flow of the CSF will be disturbed and will lead to an **increased intracranial pressure**.



- When N. meningitides goes to the blood stream we call it meningococcal septicemia, meningococcemia or bacteremia which can cause in this form skin manifestations like **petechial lesions** (small blood under the skin) which can coalesce and form **hemorrhagic bullae**.



N. meningitidis colonies on blood agar plate



N. meningitidis gram stain

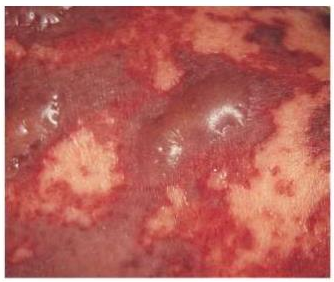
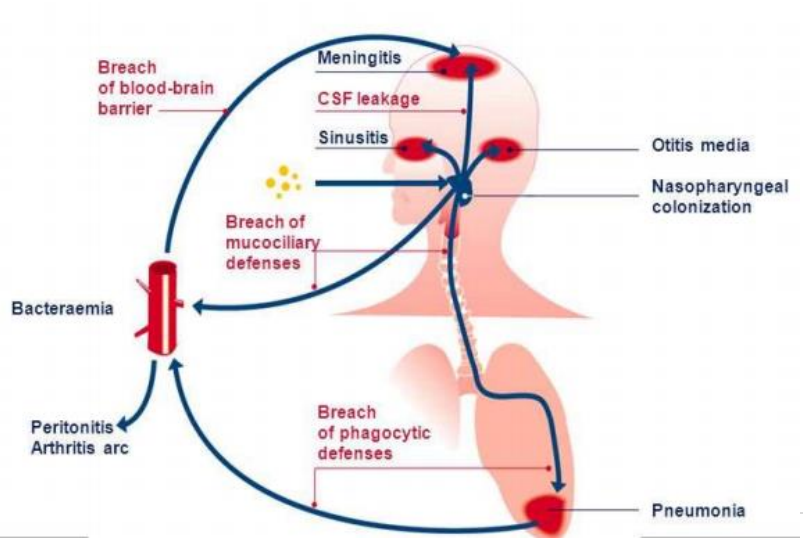


FIGURE 23-5 Skin lesions in a patient with meningococcemia. Note that the petechial lesions have coalesced and formed hemorrhagic bullae.

S. pneumoniae

- In adults, usually there is an associated pneumonia with meningitis so S. pneumoniae establishes its infection within the **lungs** and from there it spreads into the blood stream through the blood vessels causing bacteremia which then reaches the blood brain barrier and causes meningitis.

- Other associated causes include chronic ear infection (otitis media) and chronic sinus infection (sinusitis) which can spread from them into the meninges.



- Those are the two most common examples of the pathophysiology of meningitis (N. meningitides and S. pneumoniae) but other causes have the same pathophysiology which is basically the spread of the bacteria from the site of infection to the blood stream then to the CSF after overcoming the blood brain barrier causing meningitis.

How common is bacterial meningitis?

- Meningitis is rare in general, it is less than 5 cases per 100,000 but incidence varies by region. For example, **Sub-Saharan Africa is called meningitis belt** which is due to the very high incidence of meningitis that can reach to 100 cases per 100,000.

- With the introduction of H. influenzae type b conjugate vaccines and pneumococcal conjugate vaccine, the incidence of meningitis from these causes decreased significantly. But still they remain among the major causes of meningitis.

- Certain Factors can increase the risk of meningitis like:

    - **Anatomical problems:**

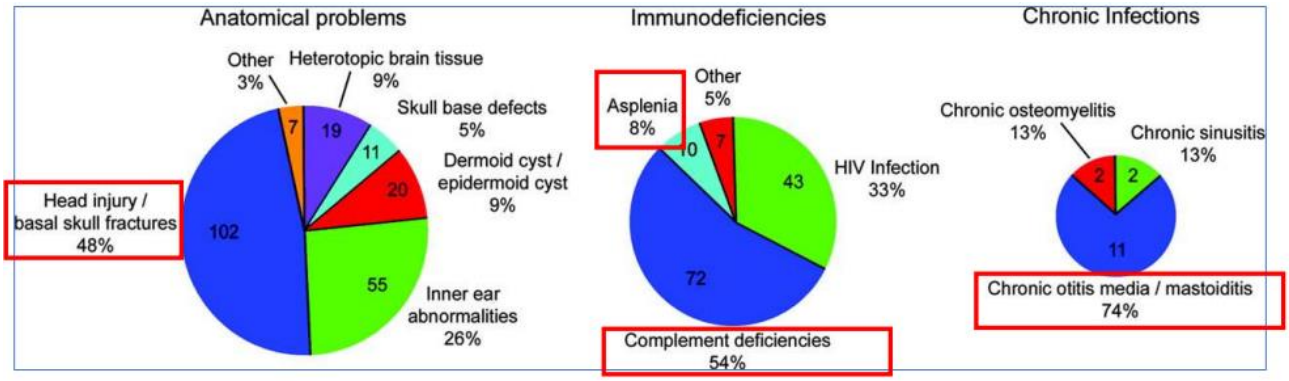
        1. **Head injury or basal skull fracture**: the most common anatomical problem which will cause the bacteria to spread directly into the meninges.
        2. **Congenital anomalies** such as dermoid or epidermoid cyst.

    - **Immunodeficiencies:**

        1. **Complement deficiencies**: which increases the risk of meningitis up to a thousand times, also complement inhibiting drugs cause the same risk as the deficiencies.
        2. **Asplenia:** when the spleen is removed following trauma for example, the patient is always at risk of getting infected with

an encapsulated bacterium like N. meningitides, S. pneumoniae or H. influenzae.

- **Chronic infections** in the ear (**otitis media**) or sinuses (**sinusitis**).



How do bacterial meningitis patients present to the clinic?

- We have a **triad** of features that are very common in meningitis patients which are fever, headache and meningism. **Meningism** means meningeal signs that indicate an irritation or inflammation within the meninges, these signs are **neck stiffness, photophobia, positive Kernig's sign and Brudzinski's sign**.

- So, fever, headache and neck stiffness are direct signs for meningitis which as we said is a **neurological emergency** and should be dealt with within hours.

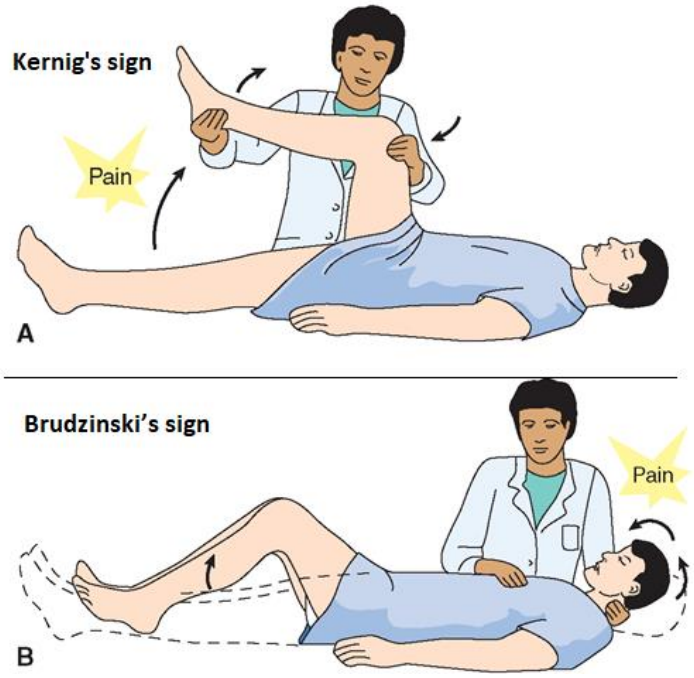
- In order for us to assure that the patient has meningitis, he has to have neck stiffness, Kernig's sign and Brudzinski's sign, these signs appear because the patient **cannot stretch his meninges**. To make this concept easier to understand, remember when we took in the respiratory system that if the patient has pleuritis (inflammation in the pleura) he will not be able to stretch his lungs to take a deep breath because he will feel pain so he will have shortness of breath, the same concept applies here. So, the

patient of meningitis will have stiffed neck, Kernig's sign and Brudzinski's sign because if he stretched his meninges he will feel pain.

- **What are Kernig's sign and Brudzinski's sign?**

  In **Kernig's test**, the patient is supine, in order to stretch the meninges, you flex the hip and the knee and then you start extending the knee, when you start extending the knee the patient will show pain and we conclude that he has meningitis (the patient has positive Kernig's sign so he has meningitis).

  In **Brudzinski's test**, again the patient is supine, in order to stretch the meninges, you flex the neck of the patient, if the patient has a positive Brudzinski's sign he will flex his knees as a sign of pain and may scream a little bit.



- The patient of meningitis sometimes shows other symptoms accompanying the disease such as:

1. **Cerebral dysfunction** (confusion and/ or reduced conscious level) can be present if the brain parenchyma is involved in the inflammatory reaction (**meningoencephalitis**).
2. **Seizures** can occur in neonatal and adult meningitis patients (30% of meningitis patients).
3. Accompanying symptoms is often present, such as **petechial rash** in meningococcal septicemia. Or **rhinorrhea** (the CSF may find its way through the nasal secretions in this case) suggesting basal skull fracture.
4. Increased intracranial pressure secondary to meningitis can have ocular symptoms like **optic disc swelling (papilledema) and cranial nerve palsies**.

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

- Now we know how the patient of bacterial meningitis will be presented to the clinic. So, if we suspected that the patient has meningitis we start directly **empirical antibiotic therapy** even without confirming that it is bacterial meningitis.

How to confirm a diagnosis of bacterial meningitis?

- **CSF examination**: our biggest clue is found in the CSF where the infection is taking place, so by a procedure called lumber puncture we take a sample from the CSF.

- The CSF is around 125ml and 500ml is produced every day, so we take a sample from the CSF and put it in three tubes to be tested in three major fields which are **microbiology, chemistry, and cytology**.

- **In microbiology**, the microbiologist will take the sample and culture it, stain it and look under the microscope to confirm which type of pathogen is causing the disease.

- **In cytology** we will look for WBCs and their count in the sample.
- **In chemistry**, because the constituent of glucose and proteins in the CSF will change in the infectious state, we send a sample to the chemistry lab to look for these changes.

- So, if there was a bacterial meningitis patient the tests from the 3 fields will be in comparison to a normal person as showed in the table below:

	Normal	**Bacterial meningitis**
Appearance of CSF	Normal	Turbid
Protein level	Normal	Increased*
Glucose level	Normal	Decreased**
Gram stain	Normal	Positive in many cases (Not G+ve bacteria, but a bacteria that reacts with G stain. Either G+ve or –ve)
WBC count	< 3 (normal)	> 500 (increased)
other		90% PMN (mostly neutrophils)

*because the WBCs are secreting cytokines, immunoglobulins and granules that contain proteins.
**because there is more consumption of glucose by the bacteria and other cells.

- Beside the CSF examination we should do **blood tests** because the bacteria usually spread through the hematogenous route.

How to manage suspected bacterial meningitis?

- As we said even before confirming with the CSF examination that the patient has bacterial meningitis, when we see the aforementioned clinical signs and symptoms we start **empirical antibiotic therapy** (means it is not a specific therapy).

- Patients **less than 3 months** of age we give them ampicillin and cefotaxime, patients with ages **more than 3 months** we give them ampicillin, cefotaxime and ceftriaxone.

- Patient with **head trauma or CSF shunts** where we suspect S. aureus we change the empirical therapy to **vancomycin**.
- Some people say that in addition to antibiotics there is a place for **corticosteroids** in the therapy of bacterial meningitis, because corticosteroids will dampen the inflammatory response which is the major destroyer of the CNS tissue (the main damage isn't from the toxins of the bacteria, it is from the immune response), so we use **dexamethasone** to lessen the inflammatory response.

- **Reduction of raised intracranial pressure if present**. Also, we shouldn't take lumber puncture if there is increased intracranial pressure.

- **Chemoprophylaxis** should be given within 24h to **household contacts** (any person with contact to respiratory or oral secretions of meningitis patient).

What is the outcome of bacterial meningitis?

- **Mortality is high** even with antibiotic therapy, and varies with etiological agent (5% for N. meningitidis, 20% for S. pneumoniae).

- If the patient is immunocompromised or has meningoencephalitis, decreased consciousness, seizures and increased intracranial pressure, all of these **comorbid conditions** will worsen our prognosis for bacterial meningitis patients.

Viral meningitis

- Viral meningitis has similar symptoms to bacterial meningitis (head ache, fever, and signs of meningeal irritation), but **rarely produces focal neurological defects** because the inflammatory response to viral infections is **less severe and more selective** toward the pathogen.

- This selectivity towards the pathogen is caused by **the predomination of lymphocytes in viral meningitis** in comparison to bacterial meningitis in which neutrophils predominate, lymphocytes are more selective in killing the pathogen (part of adaptive immunity), while neutrophils which are part of the innate immunity are not selective so they release granules, cytokines and NETs which are not selective and clog the CSF.

- **Enteroviruses** are the leading cause of viral meningitis, but we have other common causes including **varicella-zoster virus** and **herpes simplex virus**.

- According to the associated symptoms we can tell which virus is causing meningitis for example:

    1. If there is an infection in the parotid gland (**parotitis**) the cause will be **Mumps virus**.
    2. If the patient has rash similar to **shingles** the **varicella-zoster virus** is the cause.
    3. If the patient has **anorexia, vomiting and some rash** the case will be **enteroviruses**.

- These symptoms are not definitive for the cause, so we have to confirm diagnosis by CSF examination just like in bacterial meningitis (microbiology, cytology and chemistry).

	Normal	**viral meningitis**
Appearance of CSF	Normal	Clear
Protein level	Normal	Normal
Glucose level	Normal	Normal
Gram stain	Normal	Normal (no bacteria)
WBC count	< 3 (normal)	> 1000 (increased)
Other		Lymphocytes predominate

- The golden standard for diagnosing viral infection within the CSF is the **polymerase chain reaction (PCR)**, in PCR we look for viral DNA or RNA in the CSF to confirm viral meningitis.

- Serology and viral culture also play a role in diagnosing viral meningitis.

How to manage viral meningitis?

- The management of viral meningitis is different than bacterial meningitis, in bacterial meningitis after we know the type of bacteria causing meningitis, we stop the empirical therapy and start using specific antibiotics for the pathogen which we use sensitivity testing to see which is the most suitable antibiotic against this specific bacteria, while in the case of viral meningitis we just give the patient **analgesics** for the pain, **antipyretics** for the fever and **antiemetics** if there is vomiting.

- The outcome of viral meningitis in infants and neonates could be problematic, so it could cause **intellectual impairment, learning disabilities and hearing loss** depending on the etiology of the virus. While in older patients or adults we will have better prognosis and even **sometimes full recovery**.

Clinical case 1

the following is a description of late-onset group B streptococcal disease, an infant male weighing 3400 grams (normal weight) was delivered spontaneously at term (normal delivery). Physical examinations of the infant were normal during the first week of life; however, the child started **feeding irregularly during the second week** (as we said this is non-specific symptom appears in neonates). On day 13, the baby was admitted to the hospital with **seizures**. A small amount of **cloudy cerebrospinal fluid** (turbid) was collected by lumbar puncture, and Streptococcus agalactiae serotype Ill was isolated from culture. Despite prompt

initiation of therapy (empirical then specific antibiotic therapy), the baby developed hydrocephalus (because of increased intracranial pressure), 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.

Clinical case 2

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/mm3, with 96% polymorphonuclear leukocytes**, a **glucose concentration of 40 mg/dl (decreased), and a protein concentration of 172 mg/dl** (elevated) . 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?
   listeria monocytogenes because gram positive coccobacilli.
2. What are the potential sources of this organism?
   Food
3. What virulence factors are associated with this organism?
   Going intracellularly to evade the humoral immunity, that's why they couldn't stain it or see it by the microscope in the CSF.
4. How would this disease be treated? Which antibiotics are effective in vitro? Which antibiotics are ineffective?
   We start with empirical therapy first and then specific antibiotics for listeria monocytogenes.