serum, and then combining them through two formulas to obtain the ***Tibbling Link*** **and** ***Tourtelotte*** **values**.
In Fig.13 there is a depiction of what might be seen. According to the position of the dots, different scenarios might be recognised.
The orange line provides an index of **BBB impairment**. A high albumin ratio *(seen by moving along the orange arrow towards the top-right portion of the graph, ed.)* reflects an increased concentration of albumin, which is a big molecule, in the CSF, indicating a leakage through the BBB and therefore an impairment of the barrier.
On top of the orange arrow, the purple line represents the **production of IgG in the CNS**. So, after correcting this value for albumin concentration, the amount of IgGs produced in the CNS - related to those in the periphery - can be checked. It is a measure of **intrathecal inflammation**, hence it indicates whether there is an ongoing inflammatory process and how many of these immunoglobulins are being produced locally.

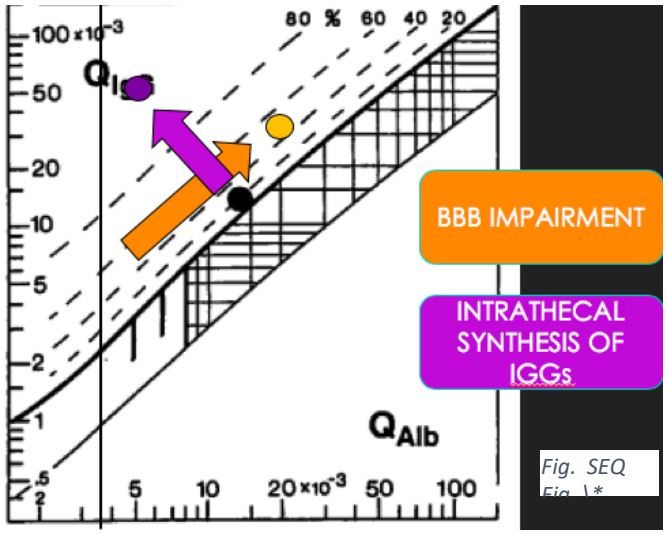


Fig. SEQ Fig. *

Overall, it's very cheap and can help to get an idea of the situation.
Subsequent tests define if the **IgGs** are **monoclonal, polyclonal or oligoclonal**. Oligoclonal IgGs in the CSF is one of the criteria for the diagnosis of multiple sclerosis, a disease characterized by an autoimmune process in the brain.

MENINGITIS

Meningitis is an inflammation of the meninges and/or of the CSF, i.e. the liquid within the meninges. The onset of meningeal symptoms is usually **acute**, over a matter of hours or at most a few days. There are also some forms of **chronic** meningitis in which symptoms appear over a time span of a few weeks or months (usually > 4 weeks), but they are very uncommon.

PRIMARY CLASSIFICATION

Meningitis can be divided into bacterial and aseptic**.**

- **Bacterial meningitis** usually presents an unclear purulent CSF, which might appear yellowish or whitish. The CSF contains an elevated number of cells, up to thousands, mostly granulocytes and neutrophils. At the beginning of this process there might be a predominant increase of lymphocytes. Other findings in the CSF include elevated levels of proteins and low glucose concentration[18]. It's mainly due to bacteria, whereas other causes (such as Amoeba or Cerebral abscesses) are less common. It is important to remember that since some of these bacteria are transmittable person-to-person, the patient should be isolated.

- **Aseptic meningitis**: CSF is clear and colorless, with sometimes "dust-like" particles. The number of cells, usually lympho-monocytes, is elevated but usually to a lower extent compared to bacterial meningitis. Protein concentration is also elevated but again, not as much as for BM. Glucose concentration is normal, because viruses do not use glucose (the same is true for intracellular bacteria). Etiological agents may be viruses, intracellular bacteria (Leptospira, Brucella, Borrelia...), or partially treated bacterial meningitis. In fact, a patient at home with bacterial meningitis who has

[18] Glucose concentration is low because it is consumed by the bacteria.

been treated with antibiotics, might present with difficult-to-recognize symptoms and a CSF resembling aseptic meningitis. *Always ask patients if they have been taking antibiotics.*

The orange line (last row) in Fig.14 represents an **exception of aseptic meningitis** in which the CSF appears clear, the cell count remains in the same range as before, maybe consisting of lymphomonocytes and neutrophils at the beginning, but there is very high level of proteins and low glucose levels. In this case, the main suspicion is **Mycobacterium Tuberculosis**; to sum up, TB meningitis has very clear CSF presentation, resembling aseptic meningitis, but glucose is heavily consumed. Fungi could also be a possible cause but a

	Cells/ul	Proteins (mg/dl)	Glucose (mg/dl)	Aetiologies
Bacterial Meningitis	200-20000 (N) (10% with L predominance)	⇧⇧ > 100	⇩ < 45	*Bacteria, Amoeba, Cerebral abscess*
Aseptic Meningitis	100-1000 (LMs)	⇧(50-100)	N	*Viruses Intracellular bacteria (Leptospira, Brucella, Borrelia…) Fungi Protozoa Partially treated BM*
Aseptic meningitis*	100-1000 (LMs, initially N)	⇧⇧ > 100	⇩	*Mycobacterium tuberculosis Fungi*

pretty rare one.

EPIDEMIOLOGY

- **Bacterial Meningitis**

The two most common causes are ***Streptococcus pneumoniae*** **and** ***Neisseria meningitidis***, but it may also be due to *Haemophilus influenzae*.
In general, Bacterial Meningitis is not common, but the situation changes from country to country. In **western countries** (Finland, Netherlands, and the United States) the incidence is **0.7-0.9 per 100,000 people/year**, and over time in the last 30 years the prevalence has reduced thanks to vaccination. In some **African countries** like Burkina Faso and Malawi the incidence is still very high, **10-40 per 100,000 people/year**.

- **Aseptic meningitis**:
  - Predominantly caused by ***Enteroviruses***
  - In the US **30-75,000 cases/year**
  - Predominance of infection during **summer and fall** in areas with a temperate climate because people spend more time outdoor, while in areas with tropical climates the infection is present all year round
  - It's spread from person-to-person mainly through **fecal-oral transmission**, although houseflies, wastewater and sewage may contribute to the spread
  - It may affect both **children and adults**
  - Risk factors such as **rituximab**, a monoclonal antibody, have been associated with a higher chance of presenting aseptic meningitis

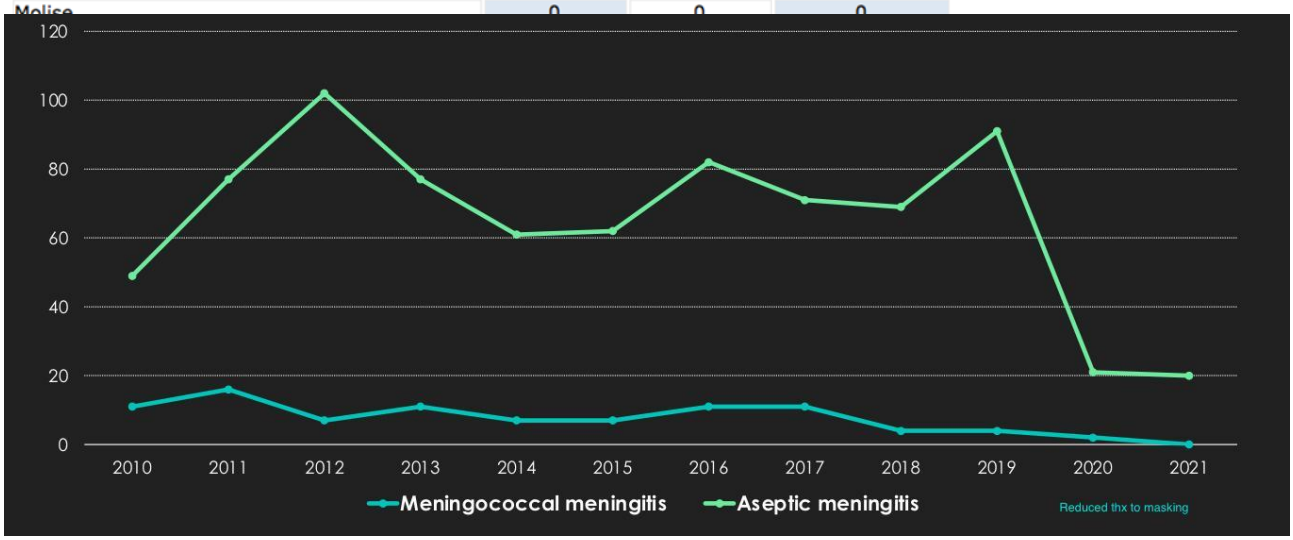
THE "MENINGITIS BELT"

The area in Sub-Saharan Africa was named this way due to the recurrent epidemics that occur every year due to **Neisseria meningitidis**. They are usually due to non-B serotypes, mostly **serogroup A**, although **after the MenA[19] vaccination (2010) C, Y, W135 and X** have also been more common[20].
There is a higher risk during **dry season** (December-June); the suspicion is that the dust particles may carry the meningococci leading to a larger spread which may cause several epidemics. **Every 5-10 years**[21] there is a **large-scale epidemic** in the area. Pilgrims to Saudi Arabia are requested a certification of vaccination in order to the avoid spread.

MENINGITIS VALUES IN ITALY

In **2015 and 2016** there has been a rise in **meningitis C** cases in Italy, for which **Tuscany** was the epicenter and actually the only region involved. In Piedmont there were around 10-15 cases every year, but in Tuscany the number of cases was its double in 2015 and triple in 2016. It was mostly due to meningococci C, even in vaccinated patients. It therefore raised questions about its virulence and about the effectiveness of the vaccination.

	2014	2015	2016*
Abruzzo	1	4	3
Basilicata	1	1	2
Calabria	1	1	3
Campania	15	10	16
Emilia-Romagna	16	14	17
Friuli Venezia Giulia	0	2	2
Lazio	13	24	18
Liguria	1	2	4
Lombardia	45	34	30
Marche	0	2	6
Molise	0	0	0



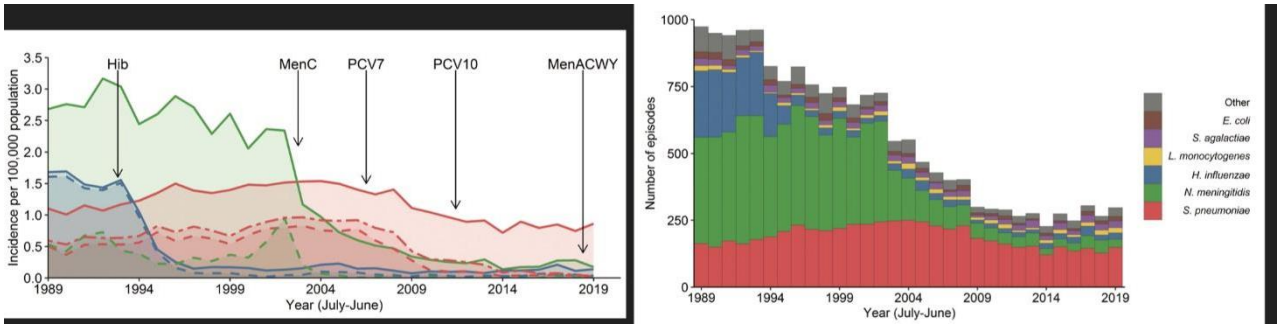
[19] Meningococcal A vaccine

[20] From the slides: *1000 per 100k pop*

[21] In the slides it's *5-12 years*

Fig.17 shows the most recent data from **Piedmont**. Aseptic meningitis is the most common form, with an incidence of 50-100 cases every year, while the incidence of bacterial meningitis (mostly meningococcal meningitis) is around 10-15 cases every year. In both cases the trend has remained quite stable over the last 7 years. However, in the last years, the incidence has reduced to almost zero, because of mask usage but also because Piedmont started to have vaccination for the Meningococcus B strand.

This (fig.18) is a graph showing the effect of vaccination on the etiology. You can see that overtime, when the



vaccine was introduced, for example H. influenzae vaccine, N. meningitis vaccine, there has been a steep reduction of the strains. The one that is still present is S. pneumoniae, because the vaccination is reserved for people over 65 and those with chronic lungs problems, and is not that effective. The primary cycle of the vaccine is administered very young, and it protects from pneumonia below the age of five. When people are older they get revaccinated.

From fig. 19, it is possible to see that there is a very strong age determinant. For example, some of these affects only newborns, like S. agalactiae. N. menigitis as well is mostly see in the young ones, below the age of 20. S. pneumoniae is more common below the age of 5 (that's why we vaccinate children) but then is again present below the age of 65.

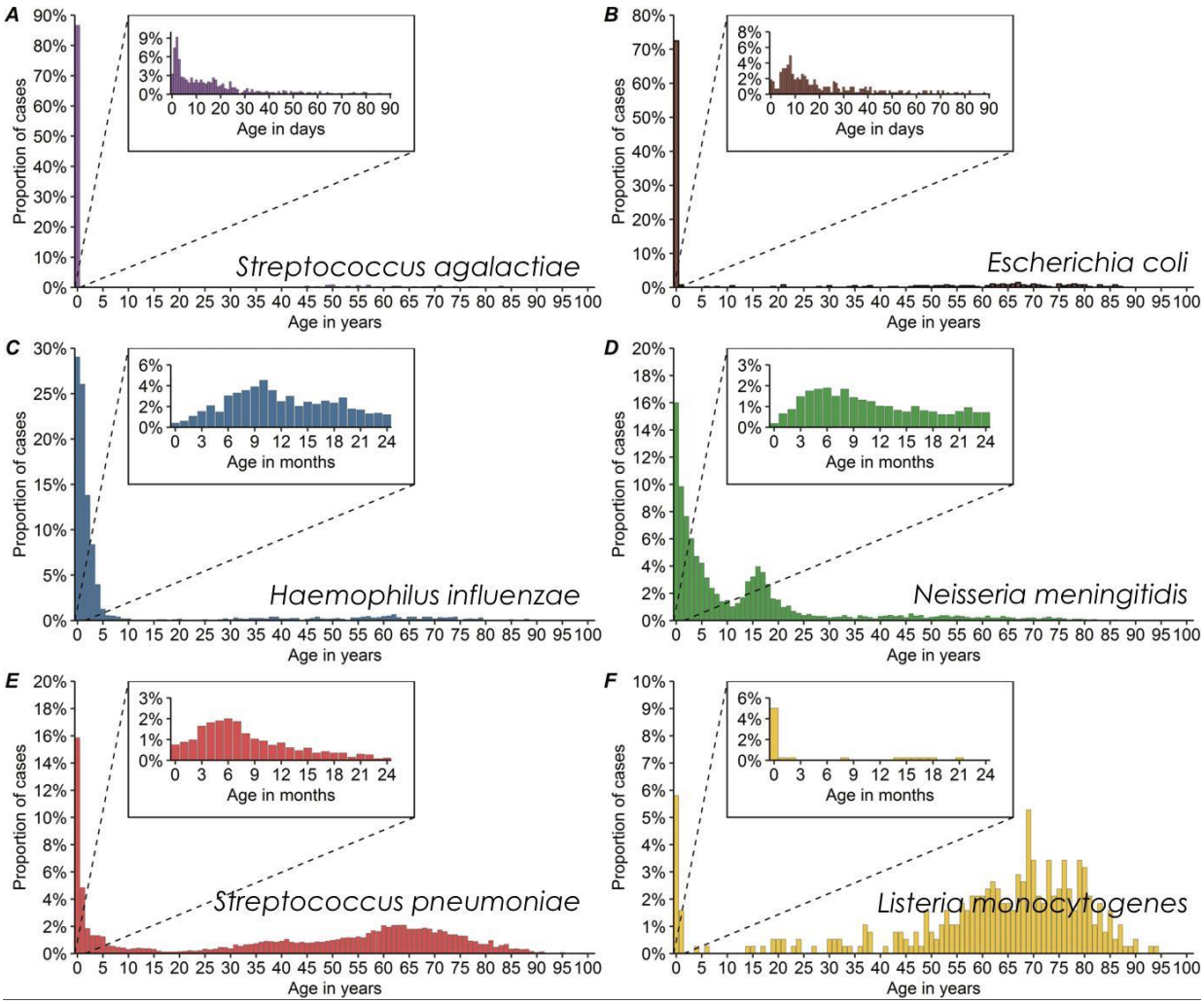


Fig. 19

CAUSATIVE AGENTS OF MENINGITIS

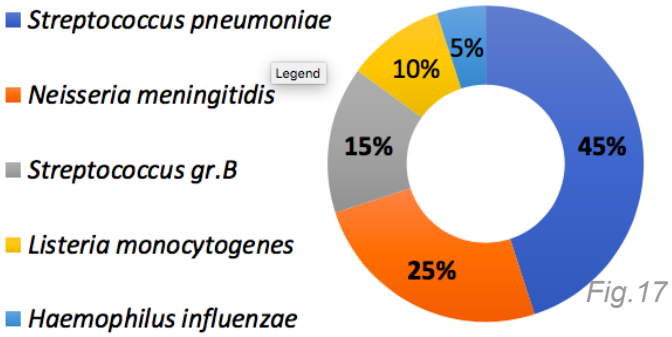


Fig.17

As anticipated, the most common causative agents of meningitis nowadays is *Streptococcus pneumoniae*[22] (45%), followed by *Neisseria meningitidis* (25%), then by *group B Streptococcus*[23] (15%), *Listeria monocytogenes* (10%), and a very small number due to *Haemophilus influenzae* (5%).

Over time, there has been a **steep decrease of Neisseria and Haemophilus infections** due to the widespread vaccination, and therefore the incidence is actually lower than the values previously mentioned, so although it varies depending on the country, it may even be as low as 0.1cases/100K people/year[24]. There is a lot of risk factors for the development of meningitis, for example immunodepression and splenectomy, because people without

[22] a.k.a. *Pneumococcus*

[23] Recall that the only member of GBS (Group B Streptococci) is *Streptococcus agalactiae*, as explained by prof. Lembo, ed.

[24] From the slides: *0.12-3 cases/100k persons/year*

spleen have a higher risk of capsulated bacterial infection.

- **Streptococcus pneumoniae**

Streptococcus Pneumoniae is the **main cause of meningitis in patients above the age of 20**, so it has to be suspected in adults.
The most important **risk factors** are **sinusitis** and **otitis media**. Most of the patients have a history of sinusitis or ear pain that has not been treated. This is because the bacteria colonize the sinuses or the ear and after that they can create a contact and get directly into the meninges. Performing a CT scan, it is possible to notice bone involvement and perforation, which allows bacteria to cross and enter into the CNS.
CT scans are essential: *first, because they detect the presence of masses. Among the numerous bacteria, there is one able to relocate from the throat to the circulation and then to reach the brain, where it replicates leading to a very high bacterial load, which results in severe clinical manifestations.*[25] The second reason is that entry points to the brain should be repaired. If a patient has a damaged bone wall, this must be repaired immediately to prevent recurrent meningitis by pneumococci. The professor had a patient who had meningitis from streptococcus seven times, because he had rhino-liquorrhea due to a small damage in the skull bone. They saw the damage with a CT scan and repaired it. Moreover, people who had traumatic damages to their skull, for example after a motorcycle accident, have a higher risk of developing meningitis in their life.
There are other **less common risk factors** such as pneumonia, alcohol abuse, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, fracture of the skull base, and rhino-liquorrhea (more due to damage in the bone structure).
Mortality is still quite high, around 18-26%, and in older adults it rises to 30-35%.

- **Neisseria meningitidis**

Neisseria meningitis is most common in **children and young adults** (2-20 years of age). **Epidemics** of Neisseria meningitidis occur only in 2% of cases, while the remaining 98% of cases are **sporadic**. There are differences in different strains in terms of **virulence**. Some deficiencies in humoral immunity or complement (C6 to C9) might explain the difference in vulnerability in different individuals.
However, usually the first step consists of a transient **nasopharyngeal colonization**, which can be observed in 5-10% of the normal population. Then the bacteria might outgrow and give rise to an **invasive disease** with a mortality of around 10%[26] (much lower than Pneumococcus but still quite relevant).
One of the warning/alert signs that should be explained to the children's mothers is the presence of **petechiae**, which are usually very relevant in the course of the infection and can be the first step of a **fulminant disease**, leading to death within few hours after the onset of the petechiae. So, a child with very

[25] This is my best interpretation of what the professor says in slide 36 (00:47): *"First, because it tells you something about (body/bony?) mass. There is a lot of bacteria; there is just one bacterium that was in the throat, gets in the circulation and went to the brain. Here there is a very high bacterial load and for this reason the severity of the disease is very high."*
A better explanation may be found from the article "Pathogenesis and Pathophysiology of Pneumococcal Meningitis": *The most common route of infection starts by nasopharyngeal colonization by Streptococcus pneumoniae, which must avoid mucosal entrapment and evade the host immune system after local activation. During invasive disease, pneumococcal epithelial adhesion is followed by bloodstream invasion and activation of the complement and coagulation systems. The release of inflammatory mediators facilitates pneumococcal crossing of the blood-brain barrier into the brain, where the bacteria multiply freely and trigger activation of circulating antigen-presenting cells and resident microglial cells. The resulting massive inflammation leads to further neutrophil recruitment and inflammation, resulting in the well-known features of bacterial meningitis*

[26] From the slides: ***Mortality 3-13%***

high fever, uncommon behavior and petechiae should be taken to the emergency room as soon as possible.

Fig.21 reports a list of all the major infectious (viruses, rickettsiae, bacteria, spirochetes, protozoa and helminths, and other infectious syndromes) and non-infectious causes (intracranial tumors and cysts, drugs,

TABLE 89-1 Differential Diagnosis of Acute Meningitis

Major Infectious Causes	Protozoa and Helminths
Viruses	*Naegleria fowleri*
Nonpolio enteroviruses[a]	*Angiostrongylus cantonensis*
Arboviruses[b]	*Baylisascaris procyonis*
Herpesviruses[c]	*Taenia solium*
Lymphocytic choriomeningitis virus	*Toxocara* spp.
Human immunodeficiency virus	*Strongyloides stercoralis* (hyperinfection syndrome)
Adenovirus	***Other Infectious Syndromes***
Parainfluenza virus types 2 and 3	Parameningeal foci of infection[d]
Rickettsiae	Infective endocarditis
Rickettsia rickettsii	Viral postinfectious syndromes
Rickettsia conorii	Postvaccination[e]
Rickettsia prowazekii	**Noninfectious Causes and Diseases of Unknown Etiology**
Rickettsia typhi	***Intracranial Tumors and Cysts***
Orientia tsutsugamushi	Craniopharyngioma
Ehrlichia and *Anaplasma* spp.	Dermoid/epidermoid cyst
Bacteria	Teratoma
Haemophilus influenzae	***Medications***
Neisseria meningitidis	Antimicrobial agents[f]
Streptococcus pneumoniae	Nonsteroidal anti-inflammatory agents[g]
Listeria monocytogenes	Muromonab-CD3 (OKT3)
Escherichia coli	Azathioprine
Streptococcus agalactiae	Cytarabine (high dose)
Propionibacterium acnes	Carbamazepine[h]
Staphylococcus aureus	Immune globulin
Staphylococcus epidermidis	Ranitidine
Enterococcus spp.	Phenazopyridine
Klebsiella pneumoniae	***Systemic Illnesses***
Pseudomonas aeruginosa	Systemic lupus erythematosus
Salmonella spp.	Behçet's disease
Acinetobacter spp.	Sarcoidosis
Viridans streptococci (e.g., *S. salivarius*)	Vogt-Koyanagi-Harada syndrome
Streptococcus gallolyticus	***Procedure-Related***
Fusobacterium necrophorum	After neurosurgery
Stenotrophomonas maltophilia	Spinal anesthesia
Streptococcus pyogenes	Intrathecal injections[i]
Streptococcus suis	Chymopapain injection
Pasteurella multocida	***Miscellaneous***
Capnocytophaga canimorsus	Seizures
Nocardia spp.	Migraine or migraine-like syndromes
Mycobacterium tuberculosis	
Spirochetes	
Treponema pallidum (syphilis)	
Borrelia burgdorferi (Lyme disease)	
Borrelia miyamotoi	
Leptospira spp.	

Fig.

systemic illnesses, procedure-related and some miscellaneous causes) of symptoms that are similar to acute meningitis. This gives an idea of the complexity of the **differential diagnosis** of meningitis.

ASEPTIC MENINGITIS – ETIOLOGY

Enteroviruses are a large group of viruses, there is cocksackievirus, echovirus, poliovirus. They are neurotrophic, that is why they can infect the brain. Another important group is the **arboviruses**. *A common question the professor asks to students at the exam is: "when you think about meningitis, when you perform a lumbar puncture and you can see a clear CSF, so an aseptic meningitis, which are the viruses you think first?" and the answer is enteroviruses and arboviruses.*

OTHER CAUSATIVE AGENTS OF MENINGITIS

Some **risk factors** of the other causative agents of meningitis are listed in fig.22.

Listeria monocytogenes	Newborns Pregnant patients Elderly (>60 years) Immune-deficient	Food-borne (soft cheeses, cabbage saladeuncooked meat, hot dog, milk…)
***Streptococcus agalactiae* (group B)**	Newborns Elderly (>50 years)	Co-morbidities
Haemophilus influenzae type b	Children	Unvaccinated (or poor response to vaccination)
Gram – Enterobacteriaceae	Hospitalized adults	Co-morbidities (Diabetes, cirrhosis, alcohol abuse, chronic UTIs) Neurosurgery
***Staphylococcus aureus* CONs**	Hospitalized adults	Neurosurgery

For example, ***Staphylococcus aureus*** infection is sometimes observed in hospitalized patients and after neurosurgery.
Gram negative *Enterobacteriaceae* may also be present in patients that have been hospitalized with severe co-morbidities and after neurosurgery.
Haemophilus Influenzae Type B is sometimes observed in children, more commonly in the USA than in Europe, but unvaccinated children are more prone to this infection.
***Streptococcus agalactiae* (group B)** is usually observed in elderly but also in newborns, so mothers are screened for the presence of *GBS* in the vagina.

- **Listeria monocytogenes**

One important causative agent of meningitis is *Listeria monocytogenes*, which usually causes an **aseptic meningitis**[27], but sometimes the CSF is not clear. It might be observed in **newborns**, **pregnant women**, **elderly** and **immune deficient patients** including homeless people, cirrhotic patients, end-stage kidney-diseased patients and alcohol abusers.[28]
The epidemics in the last years have involved foie gras, watermelons from Australia, and carne mechada from Spain. So, there are different **foods** that can carry Listeria bacterium, although in the beginning only cheese was thought to be involved, mostly soft cheeses. That is why pregnant women are suggested to not eat them, because listeria infection in pregnancy can be dangerous both for the mother and the fetus.
Listeria infection is therefore a **foodborne disease** and quite **uncommon**, affecting 3-6 people/1 million/year in Italy.
A French study conducted by MONALISA[29] collected all the cases with a 2 year follow up and reported the different presentations associated with Listeria infection.

[27] This is what the professor says. However, several sources on the Internet claim that it's a ***bacterial*** meningitis, not aseptic (e.g. the article "Aseptic and Bacterial Meningitis: Evaluation, Treatment, and Prevention" by H. R. Mount et al.).
[28] From the slides: *Older age, innate and cellular immune defects, malignances, HIV infection, cirrhosis, diabetes mellitus, alcoholism, and immunosuppressive therapies*.
[29] *"Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study"* by Chralier C. et al.

	Maternal (n=107)	Bacteraemia (n=427)	Neurolisteriosis (n=252)	Difference in means or proportions between bacteraemia and neurolisteriosis (95% CI)	p value for bacteraemia vs neurolisteriosis
Age (years)	30 (5)	73 (14)	67 (16)	6 (4 to 8)	<0·0001*
Male	..	246/427 (58%)	152/252 (60%)	−3 (−10 to 5)	0·489†
Female	107/107 (100%)	181/427 (42%)	100/252 (40%)	3 (−5 to 10)	0·489†
Associated comorbidities					
Median number of comorbidities	0 (0–1)	3 (2–5)	3 (1–4)	0·7 (0·4 to 1·0)	<0·0001*
Median number of immunosuppressive comorbidities‡	0 (0–0)	2 (1–4)	2 (1–3)	0·5 (0·3 to 0·8)	<0·0001*
At least one immunosuppressive comorbidity‡	7/107 (7%)	416/427 (97%)	216/252 (86%)	12 (7 to 16)	<0·0001†
Median time interval from first symptom to diagnosis (days)	1 (0–3); n=98	2 (0–6); n=369	2 (1–4); n=243	1·6 (0·3 to 3·0)	0·684*
Temperature >37·7°C	83/107 (78%)	370/427 (87%)	244/252 (97%)	−10 (−14 to −6)	<0·0001†
Mean maximal body temperature (°C)	39 (1); n=100	39 (1); n=389	40 (1); n=246	−0·5 (−0·6 to −0·3)	<0·0001*
Influenza-like symptoms (muscle and joint pains, chills)	35/107 (33%)	87/427 (20%)	69/252 (27%)	−7·0 (−13·7 to −0·3)	0·036†
Systolic blood pressure <90 mm Hg	1/93 (1%)	27/390 (7%)	8/247 (3%)	3·7 (0·3 to 7·0)	0·047†
Diarrhoea (>3 stools per day)	8/107 (8%)	92/427 (22%)	38/252 (15%)	6 (1 to 12)	0·039†
Septic shock	0	5/427 (1%)	5/252 (2%)	−1 (−3 to 1)	0·512§
Score on Glasgow Coma Scale					
Mean score	15 (0); n=107	14 (2); n=420	12 (3); n=244	2·1 (1·7 to 2·4)	<0·0001*
<14 (change in mental status)	1/107 (1%)	57/420 (14%)	121/244 (50%)	−36 (−43 to −29)	<0·0001†
<8 (coma)	0	12/420 (3%)	24/244 (10%)	−7 (−11 to −3)	0·0001†
Blood cultures					
Performed	85/107 (79%)	427/427 (100%)	252/252 (100%)	..	..
Positive	47/85 (55%)	427/427 (100%)	158/252 (63%)	37 (31 to 43)	<0·0001†

Fig. 23

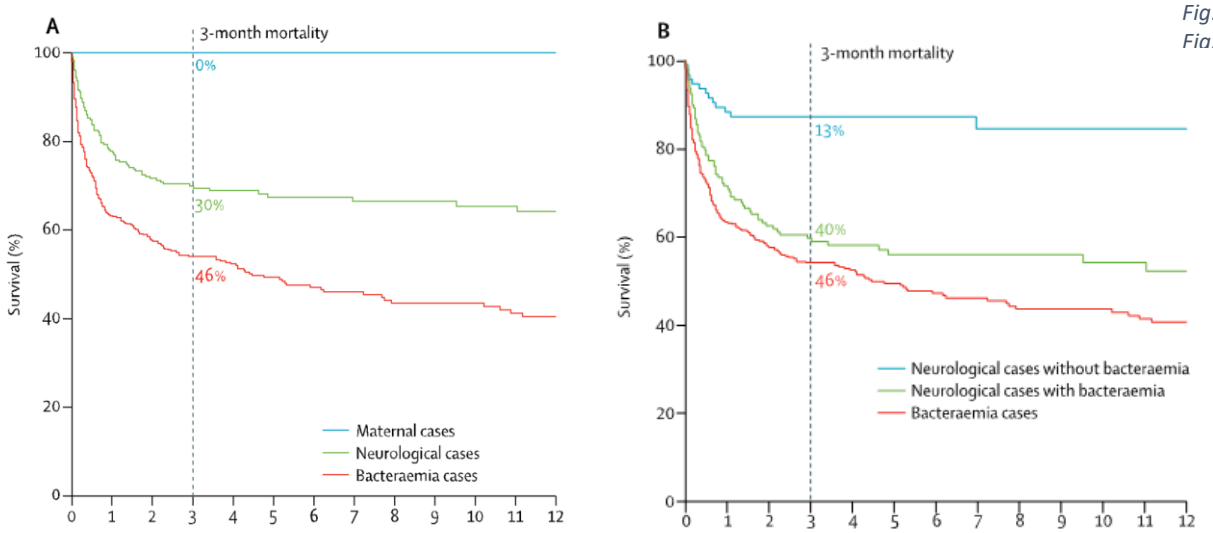
Fig.23 shows the results collected from over 700 cases during the study. The cases were divided into maternal cases (i.e. during pregnancy), bacteremia (i.e. patients in which Listeria was isolated in blood cultures) and neurolisteriosis (in which there was CNS involvement). As shown, patients with **neurolisteriosis** were older, with an average age of 67, and they had some comorbidities (around 3 per patient). 97% of patients presented fever, whereas diarrhea and septic shock were not so common. The Glasgow Coma Scale was 12, which is a relevant value. 2/3 of the patients had positive blood cultures for Listeria once the CNS was involved.

In fig.24, the **mortality rates** recorded by the study are shown. In the graph on the left (A), the red line (lower) indicates bacteremia cases (46%), whereas the green (middle) represents neurological cases (30%). It is possible to see that the mortality in bacterial cases (blue line) is very low, 0%. Mortality was “intermediate” in patients with neurological symptoms. This may be due to the fact that neurological cases allowed a rapid recognition of the problem, while bacteremia was more difficult to recognize because the symptoms were pretty a-specific. However, in graph on the right (B) it can be noticed that the neurological cases that had

bacteremia (green line in the middle) had a higher mortality rate (40%).
Neurolisteriosis patients receiving adjunctive dexamethasone also displayed an increased mortality.[30]
For both bacteremia and neurolisteriosis, the **strongest mortality predictors/risk factors** are:

- **Ongoing cancer**
- **Multiple Organ Failure**
- **Aggravation/worsening of any preexisting organ dysfunction**
- **Lymphomonocytopenia**[31]

*Fig. SEQ Fig. **



Therapy for listeria is ampicillin, pretty common and can be used for many infections, and all patients above the age of 60 or immunocompromised with a suspicion of listeriosis should receive the antibiotic.

PATHOPHYSIOLOGY

[30] From the slides.

[31] Lymphomonocytopenia is seen in several infections. The pathogenesis is unknown. It is a prognostic factor in viral pneumonia, such as Covid-19 disease, which will be dealt with later during the course.

- **Bacterial meningitis**

Nasopharyngeal colonization is usually the first step. It is then followed by local invasion, often bacteremia, invasion of the meninges, then a process of microvascular invasion starts, with macrophages, neutrophils and other CNS cells releasing cytokines, leading to subarachnoid space inflammation and possibly cerebral vasculitis and cerebral infarction. Remember that most of these infections are associated with **secondary vasculitis and vascular problems in the CNS**.

In Fig.26, some of the **bacterial and host features that might favor each of these steps** are depicted. Some of these may favors mucosal colonization, intravascular survival, meningeal invasion or survival in the subarachnoid space – all of these may increase persistence, invasiveness and pathogenicity of this bacteria.

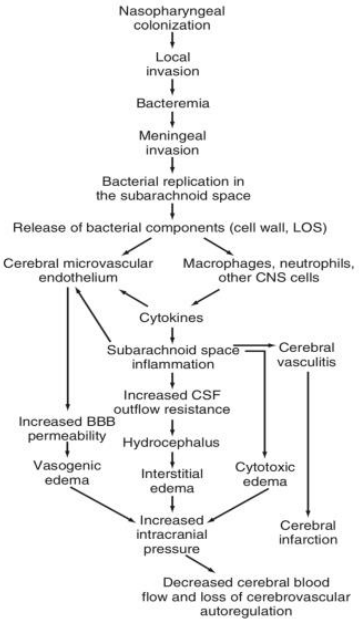


Fig. 25

Event	Bacterial	Host
Mucosal colonization	Fimbriae, polysaccharide capsule, IgA protease production, bacteriocins	Mucosal epithelium, secretory IgA, ciliary activity, anticapsular antibodies, pilin phosphotransferase
Intravascular survival	Polysaccharide capsule	Complement activation, organism-specific antibodies, TLR-9 single nucleotide polymorphisms, migration inhibitory factor single nucleotide polymorphisms
Meningeal invasion	Fimbriae, association with monocytes, *ibe10*, OmpA, extracellular loops of OmpA, platelet-activating factor receptor, pneumococcal choline-binding protein A, lipoteichoic acid, listeriolysin O	Blood-brain barrier, cytotoxic necrotizing factor-1, cysteinyl leukotrienes, biopterin, cytosolic phospholipase A2α, β2-adrenoceptor
Survival in the subarachnoid space	Polysaccharide capsule	Poor opsonic ctivity

- **Aseptic meningitis**

There are different **ways for viruses to reach the CNS**[32].

1. **Mucosal colonization** involving either the peri-tonsillar lymphatics or Peyer's patches in the gut, leading then to viremia and finally to the crossing of the BBB by the viral particles
2. Some viruses are **carried by leukocytes** (e.g. Measles, Mumps, Herpes)
3. Directly enter the CNS by **crossing the choroid plexus**
4. **Olfactory nerves** may also be a way of entry (e.g. influenza)
5. **Peripheral nerves** may also be a route entry into the CNS (e.g. Herpes virus).

CLINICAL MANIFESTATIONS

[32] This topic will be discussed in more detail when dealing with the pathogenesis of encephalitis.

- **Bacterial meningitis**

Headache, fever and **meningismus**[33] are the most common symptoms of bacterial meningitis, followed by altered sensorium[34]. Others signs and symptoms like vomiting, seizures, focal neurological findings and papilledema may vary.

Symptom/sign	frequency
Headache	≥85
Fever	≥80
Meningismus	≥80
Altered sensorium	≥75
Vomiting	~35
Seizures	~30
Focal neurological findings	0-35
Papilledema	<5

- In **neonates**, however, the clinical manifestations are different. Meningismus is usually absent, and newborns may present instead temperature instability (hypo- or hyperthermia), listlessness[35], high-pitched crying, fretfulness, lethargy, refusal to feed, weak suction, irritability, jaundice, vomiting, diarrhea, or respiratory distress.
- In very young **children**, bulging fontanelle[36] may be observed. Neck stiffness, seizures *(outside the febrile-convulsion age range), and reduced food intake*[37] are also typically found in children.
- In **adults**, fever, nuchal rigidity and altered mental status are seen only in 2/3 of the patients. The classical case is very easy to recognize, but in 1/3 of cases there are uncommon symptoms that might render the diagnosis more difficult. Also, depending on whether patients took antibiotics, there could be the presentation of different or less common signs.

Fig.28 depicts a patient intubated because of a pneumococcal meningitis. Notice how his body is covered by numerous petechiae. The **intubation** is required in order to protect the airways since the value of the Glasgow Coma Scale is so low that the patient is unable to breathe autonomously.

In order to provide clear advice to families, the **meningitis glass test** may be employed (fig.29). The presence

[33] **Meningismus** = A state of meningeal irritation with symptoms suggesting meningitis.

[34] From Wikipedia: *A clouded sensorium, also known as an **altered sensorium**, is a medical condition characterized by the inability to think clearly or concentrate.*

[35] From Dictionary.com: ***Listlessness** = having or showing little or no interest in anything; languid; spiritless; indifferent: a listless mood.*

[36] The presence of bulging fontanelle usually worries the mothers. Once, the professor has seen such a big bulging fontanelle that it has very hard and impossible to be pressed back into the skull. The following information was provided by the sbobinatore: *A **fontanel**, also called fontanelle, is more commonly known as a soft spot. When a baby's born, they typically have several fontanels where bones of their skull haven't fused yet. A newborn has fontanels on the top, back, and sides of their head. Changes in texture or appearance can be a sign of serious health issues. Parents should watch for soft spots that are curved outward on their baby's head and feel very firm. This is known as a **bulging fontanel** and may be a sign of brain swelling or fluid buildup in the brain. A bulging fontanel is an emergency. It can be a sign of pressure rising inside the skull which may result in damage to the baby's developing brain.*

[37] From the slides.

of fever with spots/rash/petechiae that do not fade after pressing the side of a clear glass firmly against the skin, indicates a medical emergency.

- **Aseptic Meningitis**
  - **Neonates** usually present fever and gastrointestinal discomfort such as vomiting and anorexia. They may also present a rash and upper respiratory tract symptoms such as cough. Sometimes also nuchal rigidity and bulging fontanelle are present. In newborns, outcomes may be very severe when infection occurs early on, i.e. through transplacental transmission, which may lead to Multiple Organ Failure.
  - In **children and adults**, fever is usually present and it may be biphasic – an acute early fever followed by a later second rise in temperature. 50% of the patients present nuchal rigidity, usually with headache and photophobia[38], often accompanied by non-specific symptoms including:
    - pleurodynia[39], herpangina[40], and hand-foot-and-mouth disease[41] caused by *Coxsackievirus*, which are a subfamily of *Enteroviruses*
    - scattered maculopapular rash caused by *Echovirus 9*
    - pleural and pericardial effusion caused by *Coxsackievirus B*[42]
    - enteroviruses, typically *Enterovirus 71*, can lead to some severe syndromes in older children (mortality up to 14%).

Fig. 30

Fig.30 shows a patient with **herpangina**, a typical symptom associated with aseptic meningitis. It is one of the oral manifestations of enterovirus infection, and it is characterized by ulcers on the back of the throat which cluster together in the same area.

SIGNS OF MENINGITIS

There are several signs that a neurologist should look for in a patient with meningitis. The most important two according to the professor's opinion are the **neck rigidity (Brudzinski sign)** and the **Kernig sign.**
In meningitis, the neck is stiff making the patient unable to bend the neck over the chest, and its passive flexion by the physician causes flexion of both legs and thighs (Brudzinski sign).
The Kernig sign is positive when a patient lying down with the hip flexed at 90° cannot fully extend the knee.
All these signs are **signs of inflammation of the meninges and of the spinal nerves**, and are due to the involuntary attempt of the patient to reduce the pain caused by these maneuvers. The position of meningitis patients is the lateral position, with the head extended and the eyes closed, and they do not move. This is very typical of meningitis, as every movement is painful.

[38] **Photophobia** = extreme sensitivity to light

[39] **Pleurodynia** = severe pain in the muscles between the ribs or in the diaphragm, caused typically by Coxsackie B

[40] **Herpangina**, also called mouth blisters, is a painful mouth infection caused by coxsackieviruses, usually coxsackievirus A

[41] **Hand, foot, and mouth disease**: A common illness of infants and children under 10 years old characterized by fever, sores in the mouth, and a rash with blisters due to infection most commonly with coxsackievirus A16 or less often enterovirus 71 or another enterovirus.

[42] From the slides: *Coxsackievirus A -> herpangina while B -> pleural and pericardial effusion*

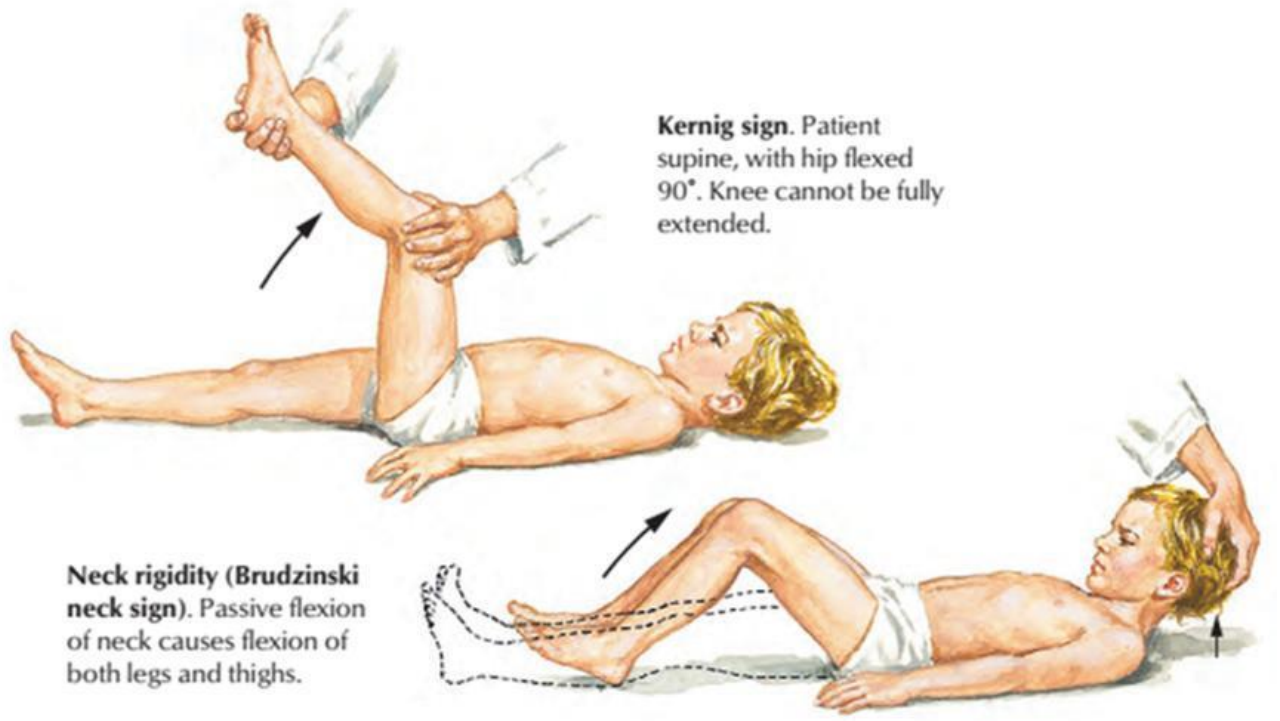


Fig. 31

Another sign of meningitis that has been recently introduced is the **jolt accentuation of headache**. It is performed by rotating 1-2 times the head of a patient with headache, resulting in a steep accentuation of the pain. The professor doesn't consider this test to be very specific for meningitis, as no one would be very happy to have their head rotated if they had a headache, which would probably worsen after this maneuver.

DIAGNOSIS

CSF	Bacterial Meningitis	Aseptic Meningitis
Gram stain	60-90% 25% for *Listeria*	-
Culture	70-90%	-
Bacterial antigens	Sens 70% Spec 99.4%	-
PCR	Sens 100% Spec 98.2%	76-99%
Stool and throat swab	-	96% (Kupila L. et al. CID 2005)

The diagnosis is based on the **CSF analysis**. In bacterial meningitis, gram staining (often positive) and culture exam (positive in 70-90% of the cases) are needed. Bacterial antigens may be obtained quickly (usually within one hour), and even though their sensitivity is not very high (70%), specificity is approximately 100%.
PCR is the most sensitive and specific technique both for bacterial and aseptic meningitis.
Bear in mind that stool or throat swabs for enteroviruses have a specificity for 96%, so they might be useful.

There are also some scores that might be helpful. For example, the **Bacterial Meningitis Score** suggests that

there is **low risk (NPV 99.7%)** of bacterial meningitis when:

- CSF gram stain is negative
- CSF absolute neutrophil count < 1,000
- CSF protein < 80 mg/dL
- peripheral absolute neutrophil count < 10,000.

Bacterial meningitis score (BMS)

Predictor	Points: Present	Points: Absent
CSF Gram stain	2	0
CSF protein > 80mg/dl	1	0
CSF ANC>1000/cc	1	0
Peripheral blood ANC > 10,000/cc	1	0
Seizures at or before presentation	1	0

Lactate can also be used for the differential diagnosis between bacterial and aseptic meningitis. Elevated CSF lactate concentration suggests bacterial meningitis, *for which it shows a sensitivity of 93-97% and a specificity of 94-96%, better than some other CSF parameters.*[43]

FILM ARRAY

It is possible to perform **multiple PCRs**, i.e. PCRs that are carried out at the same time for two different targets. This technique is called **film array**, and it covers the most important bacteria (*Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes, Haemophilus influenzae, Streptococcus B, Escherichia coli*), yeasts like *Cryptococcus neoformans/gattii* and the most important viruses[44] (*Enterovirus, Herpes 1 to 6, Human parechovirus, Varicella Zoster Virus* and *Cytomegalovirus*).

Bacteria	Viruses
Escherichia coli K1	Cytomegalovirus (CMV)
Haemophilus influenzae	Enterovirus
Listeria monocytogenes	Herpes simplex virus 1 (HSV-1)
Neisseria meningitidis	Herpes simplex virus 2 (HSV-2)
Streptococcus agalactiae	Human herpes virus 6 (HHV-6)
Streptococcus pneumoniae	Human parechovirus
	Varicella zoster virus (VZV)
Yeast	
Cryptococcus neoformans/gattii	

Fig. 34

The results can be available in 2-6 hours, which can be very helpful in targeting treatment.

COMPLICATIONS

There are many. In the case of bacterial: DIC, sepsis and shock. There are several neurological complications, including cranial nerve palsies, that can be examined by pressing the cranial nerves inducing palsies. Other complications include seizures, focal signs, hydrocephalus. The latter is caused by CSF cannot flow, so the ventricles enlarge and this can induce coma. There are also several sub-acute and chronic complication. A complication very important in children is neurodevelopmental delay.

MANAGEMENT

- **Rapid initiation of antimicrobial treatment** is fundamental and it's the first thing to do. It should be initiated within hours even if the lumbar puncture is delayed.[45]
- **Management of elevated intracranial pressure**: it includes procedures like the specific position of the **head at 30°**, **CSF drainage** (suggested in certain situations), **osmotic dehydration** by using 0.25-0.5 g/kg of mannitol (advised in cases of edema or brain masses). **Mass removal or decompression** may also be necessary, for example in case of a very big brain abscess. Also **hypothermia** and **hyperventilation** can be employed to treat ICU[46] patients with elevated intracranial pressure.

[43] From the slides.

[44] Not all the viruses, but the majority of them.

[45] Recall the study reported in Fig.9, which suggested that within 2 hours all patients were started on antibiotic treatment.

[46] ICU: intensive care unit

- **Management of seizures**: seizures should be managed with **anticonvulsants**, usually after consulting a neurologist.
- **Fluid management**: administration and replacement of fluids is necessary to maintain a **normovolemic state**. Fluids may be lost due to sweating in case of fever, tachypnea in case of sepsis, or simply because patients do not eat or hydrate properly. The balance of volemia is important in critical care patients with severe CNS infections.

ANTIMICROBIAL TREATMENT – BACTERIAL MENINGITIS

Professor says he usually does not ask this at the exam.

- **Ceftriaxone [2g x 2/day]:** The standard treatment for bacterial meningitis is Ceftriaxone at double dose because it has to cross the BBB.[47]
- **Vancomycin [15-20 mg/Kg x 2/day]:** if in the last 6 months the patient has had a recent trip to a country or has been living in a country with penicillin-Resistant-pneumococci, vancomycin is suggested as an additional agent (so, ceftriaxone plus vancomycin).
- **Ampicillin (amoxicillin) [2g x 6/day]:** in newborns, patients above the age of 60 and immunocompromised subjects (including diabetics and alcohol abusers), the addition of ampicillin or amoxicillin is suggested in case of *Listeria* and mostly when the CSF appears clear.
- **Chloramphenicol [25 mg/Kg x 4/day]:** in case of a history of severe allergies or anaphylaxis to penicillin and cephalosporins, chloramphenicol may be used instead with or without the addition of **Cotrimoxazole [2.5-5 mg/kg x 4/day]**.

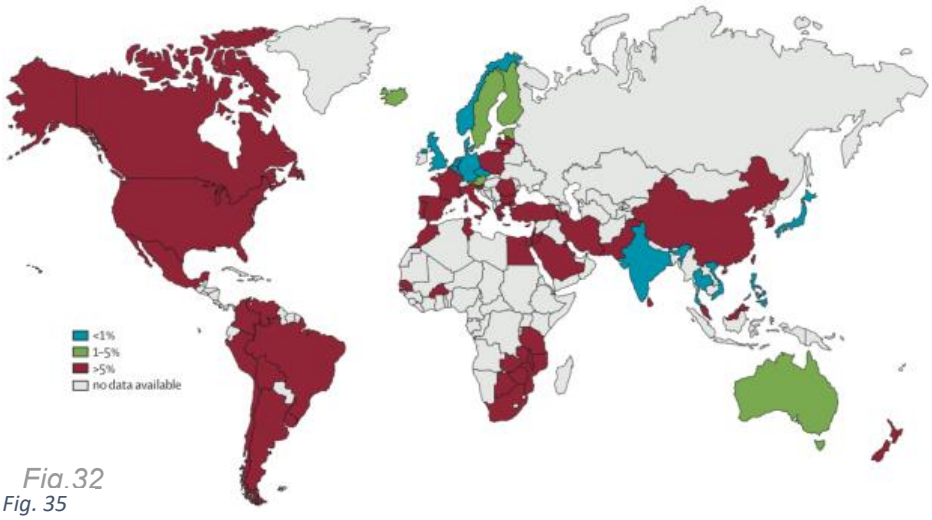


Fig.32
Fig. 35

Fig.35 shows in red the countries that are suggested to have a significant prevalence (> 5%) of **penicillin-resistant pneumococci**. Italy[48] is one of these nations[49]. This means that in these areas, in order to protect the patient against penicillin-resistant pneumococci, vancomycin should be administered in addition to ceftriaxone in most of the cases. Then, after the results of the culture and the antibiogram are out, ceftriaxone may be given by itself, without a second antibiotic.

The **duration** of the antibiotic treatment is indicated as follows:

- ***S. pneumoniae***: treatment should last 10-14 days (14 days if there is a slow recovery or the if the culture reveals a penicillin-resistant strain)
- ***Neisseria meningitidis***: British guidelines suggest 5 days, whereas in Italy treatment usually last 5 to 7 days
- ***Listeria monocytogenes***: the therapy is longer, around 21 days (3 weeks)
- **Other bacteria**: the duration ranges from 10 days to 3 weeks according to clinical conditions.

[47] From the slides: *Cefotaxime (2g x 4/day) may also be used*

[48] "We will see in our discussion that Italy is always red on the maps, so it's bad" cit.

[49] From the slides: *The other countries are Canada, China, Croatia, Greece, Mexico, Pakistan, Poland, Spain, Turkay, and USA.*

Organism	Duration of treatment
Streptococcus pneumoniae	10 days
	14 days if slow recovery or penicillin-resistant
Neisseria meningitidis	5 days
Listeria monocytogenes	21 days
Haemophilus influenzae	10 days
Enterobacteriaceae	10 (if recovered) to 21 days

Other compounds can be used too. In Fig.37, the **CPR** (CSF to plasma ratio) of the drugs is shown, both in normal conditions (3rd column) or in case of inflamed meninges (4th column), so in the first days of treatment. Most drugs reach very low concentrations (2-5%) with just a few exceptions. Most of the medications reported can be safely used and in some cases the dose may be increased. For instance, ***Linezolid*** is one of the oxazolidinone antibiotics used for treating resistant gram-positive infections and it can also be employed effectively against various CNS infections thanks to its good pharmacokinetics in the CSF.

		CPR	CPR (inflam)	
β-lactams	Benzylpenicillin	0·02	0·1	Poor CSF penetration, but high systemic doses are well tolerated and attain CSF concentrations that greatly exceed the MIC of susceptible bacteria. 40% of cefotaxime vs 90% of ceftriaxone is protein bound. Avoid imipenem because it could lower the seizure threshold. Continuous infusions could enhance bacterial killing
	Amoxicillin/ampicillin	0·01	0·05	
	Cefotaxime	0·1	0·2	
	Ceftriaxone	0·007	0·1	
	Meropenem	0·1	0·3	
Aminoglycosides	Gentamicin	0·01	0·1	Poor CSF penetration and toxicity limits increases in systemic doses. Consider intraventricular/intrathecal delivery if needed
	Amikacin	No data	0·1	
Glycopeptides	Vancomycin	0·01	0·2	Poor CSF penetration and toxicity limits increases in systemic doses. Continuous infusions could enhance bacterial killing. Limited data for intraventricular/intrathecal delivery
	Teicoplanin	0·01	0·1	
Fluoroquinolones	Ciprofloxacin	0·3	0·4	Good CSF penetration. Moxifloxacin is an alternative agent for the treatment of penicillin-resistant pneumococcal meningitis
	Moxifloxacin	0·5	0·8	
	Levofloxacin	0·7	0·8	
Others and New	Chloramphenicol	0·6	0·7	Excellent CSF penetration, although toxicity concerns limit its use
	Rifampicin	0·2	0·3	80% protein bound; CSF concentrations greatly exceed MIC of susceptible bacteria
	Cefepime	0·1	0·2	Effective against penicillin-resistant pneumococcal meningitis
	Linezolid	0·5	0·7	Case report/series suggest effectiveness for pneumococcal, staphylococcal, and enterococcal meningitis, although high interindividual variability in CSF pharmacokinetics suggests therapeutic drug measurements could be needed
	Daptomycin	No data	0·05	Poor penetration, but CSF concentrations exceed MIC of susceptible bacteria; case reports/series suggest efficacy in staphylococcal and enterococcal meningitis
	Tigecycline	No data	0·5	Good CSF penetration, but concentrations achieved at current standard doses could be insufficient to ensure bacterial killing

Fig. 37

In some cases, an **intraventricular antibiotic therapy** may be employed. It is usually performed in neurosurgery wards after a neurosurgical intervention. In fact, it can be difficult to treat ventriculitis (i.e. infection of the ventriculi) with normal antibiotics, so in some cases the antibiotics are instead directly injected inside the ventricles for a few days in order to increase the amount of drugs reaching the target and to reduce the bacterial load. Afterwards, systemic therapy is continued.

Risk factors for a fatal outcome in meningococcal disease[50]

There are some risk factors that should be considered when dealing with a patient with meningococcal disease are:[51]

[50] From Wikipedia: ***Meningococcal disease*** *describes infections caused by the bacterium Neisseria meningitidis (also termed meningococcus).*

[51] In bold are the most important ones.

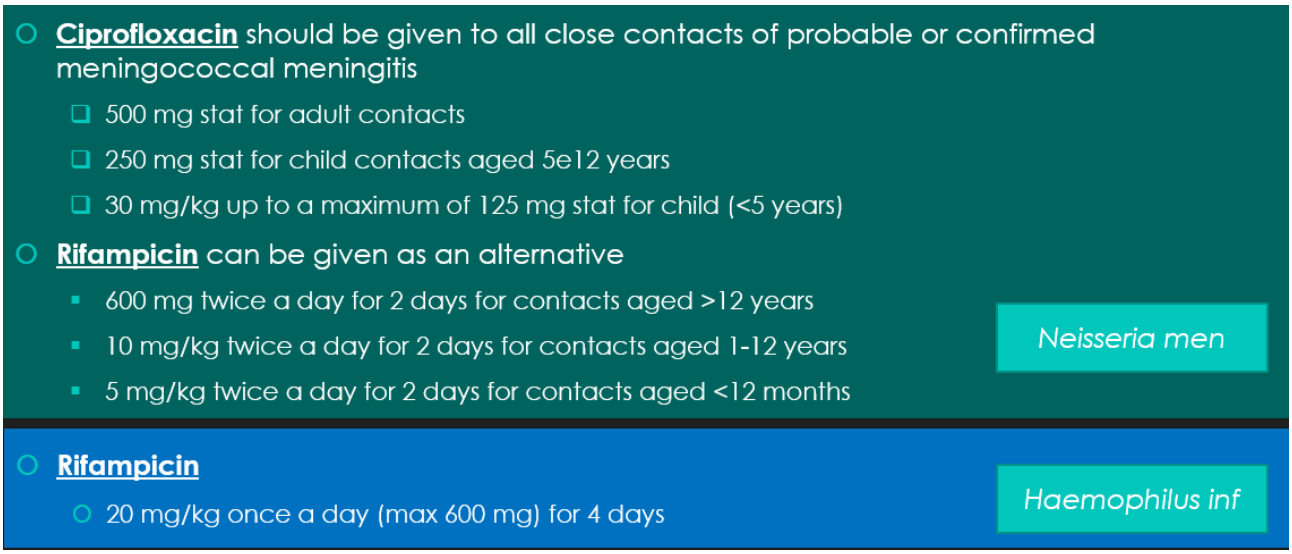
- **Low or normal peripheral WBC count**: it means no response from the immune system
- **Low acute phase reactants** such as PCR and ESR
- **Low platelets**: it implies blood vessels involvement
- Coagulopathy: it implies liver involvement
- **Absence of meningitis**
- Hypotension and shock: the progression of meningococcal sepsis can be very rapid, and in some cases it can progress within few hours into MOF and death
- *Rapidly progressing rash*
- *Coma*
- *Lactate > 4 mmol/L*[52]

PROPHYLAXIS

- **Neisseria meningitidis***:* it is the *only bacterium that can be spread from person-to-person*.[53] As transmission is mediated by droplets, anyone who has come into close contact (roughly within a 1-meter distance) with an infected patient displaying fever, without protection, is considered to be at risk of infection. This includes family members, doctors, nurses, paramedics, etc. All these people should therefore be treated prophylactically with Ciprofloxacin or Rifampicin.

- **Haemophilus influenzae**: despite being uncommon, it is also easily transmissible by close contact, therefore it's suggested to receive prophylaxis with Rifampicin because of the high degree of colonization and chance of infection.

It is very important to isolate the patient with active meningitis.



CORTICOSTEROIDS

A review from the Cochrane library[54] reports the updated version of *"Corticosteroids for acute bacterial meningitis"*. The professor highlighted three sentences in purple and one in yellow (here reported), which

[52] From the slides.

[53] This is what the professor says, although to me it seems incorrect since many other bacteria causing meningitis have person-to-person transmission, such as *S. pneumoniae* (from Wikipedia: *It spreads by direct person-to-person contact via respiratory droplets and by autoinoculation*). Maybe he meant that *Neisseria meningitidis* is the only bacterium responsible for meningococcal meningitis and it is spread from person-to-person, or that the bacterium only infects humans since there is no animal reservoir.

[54] "Cochrane reviews are a bit boring to read, I think everyone - well, epidemiologists - just read the main results" cit.

are the main concepts that must remembered[55]:

1. *"There was insufficient evidence that corticosteroids caused a reduction in mortality overall. However, they caused lower rates of severe hearing loss, any hearing loss, and neurological sequelae".*
2. *"Corticosteroids reduced mortality in Streptococcus pneumoniae meningitis"*
3. *"Corticosteroids reduced severe hearing loss in children with H. Influenzae meningitis, but not in children with meningitis due to non-Haemophilus species"*
4. *"In high-income countries, corticosteroids reduced severe hearing loss, any hearing loss and short-term neurological sequelae. There was no beneficial effect of corticosteroid therapy in low-income countries"*

There is evidence suggesting that in children the use of corticosteroids was associated with **lower rates of severe hearing loss and neurological sequelae**, mainly in cases of *Haemophilus influenzae* infection.
Corticosteroids also reduce **mortality in *Streptococcus Pneumoniae* meningitis** and, despite the differences between high- and low-income countries, globally the suggestion is to use **short-term corticosteroids for the first days** of bacterial meningitis. It is important to administer these drugs as soon as possible, therefore right before giving antibiotics or together with antibiotics.

TREATMENT FOR ENTEROVIRUSES

While most cases of aseptic meningitis are mild and last for just a few days with no sequelae, there are also some severe forms in immunocompromised patients and newborns which might benefit from treatment. One of the potential drugs that may be used in these settings is ***Pleconaril***, but it is still under development (phase 3), so it is not available on the market yet.

MOLLARET'S MENINGITIS

Mollaret's meningitis is a syndrome that may be diagnosed simply by listening to the patient's **medical history**[56]. It's characterized by:

- Repeated episodes of **meningitis**, typically lasting 2-5 days, occurring weeks to years apart;
- Usually **mild symptoms**, including headache and photophobia; it may also be associated with disorientation and dizziness;
- Almost 50% of patients over time develop **long-term neurological impairment**, such as problems with memory, balance, coordination and/or hearing;
- 25% of cases are caused by **HSV-2** (but also HSV-1 and EBV have been detected in some cases), even in patients without a history of recurrent genital herpes;
- Treatment of acute episodes with **acyclovir or valacyclovir**, and, potentially, prophylaxis with **valacyclovir** (1000 mg/day).

Prophylaxis with valacyclovir is effective. The professor followed 2 patients who displayed a decreased number of episodes (only one over 2 years instead of one every 6 months) during the prophylaxis. Therefore, it may provide some benefits although there are no randomized clinical trials to actually support this hypothesis.

CHRONIC MENINGITIS

Chronic meningitis is characterized by an **indolent onset**, a **duration > 4 weeks** and **signs of inflammation in the CSF**. Differently from recurrent aseptic meningitis (Mollaret's syndrome), it does not present with several

[55] The complete results are reported on slide 72.

[56] Once a patient stopped the professor on the stairs and started telling him his medical history, and after roughly 5 minutes the professor was able to tell him that he had Mollaret's syndrome.

acute episodes, instead it develops indolently and chronically over time. *It is also different from sequelae*.[57] In order to make a diagnosis, it is necessary to obtain an **accurate history** (travel, exposure to animals or foods), perform a **neurological examination** (which is usually abnormal), carry on with **further tests** according to the hypothesis and examination, such as skin biopsy, lymph nodes, eye examination, etc., and ask for a **brain contrast-enhanced MRI**. Sometimes even a **brain biopsy** has to be employed, giving an idea of how difficult it is to reach the diagnosis.

Mycoses
Cryptococcus (cryptococcosis)
Coccidioides (coccidioidomycosis)
Histoplasma (histoplasmosis)
Candida (candidiasis)
Sporothrix (sporotrichosis [rare])
Blastomyces (blastomycosis [rare])
Other molds (rare): *Scedosporium, Aspergillus, Cladophialophora* and other dark-walled molds
Bacteria
Mycobacterium tuberculosis (tuberculosis)
Treponema pallidum (syphilis)
Borrelia burgdorferi (Lyme disease)
Tropheryma whipplei (Whipple's disease)
Actinomyces (actinomycosis [parameningeal, rare])
Nocardia (nocardiosis [with brain abscess])
Brucella (brucellosis [rare])
Parasites
Acanthamoeba (acanthamebiasis)
Taenia solium (cysticercosis)
Angiostrongylus cantonensis (angiostrongyliasis)
Viruses
Echovirus (meningoencephalitis)
Postneurosurgical Causes
Infected cerebrospinal fluid shunt
Infected prosthetic material
Tumors
Diffuse gliomatosis
Metastatic meningeal malignancy, including lymphomatous meningitis
Other Causes
Sarcoidosis
Vogt-Koyanagi-Harada syndrome
Behçet's syndrome

Fig.39 reports the **infectious and non-infectious causes** of chronic meningitis. One of them is **chronic enteroviral meningoencephalitis in patients with agammaglobulinemia**, a chronic viral meningoencephalitis by enteroviruses. Another possible cause is **Vogt-Koyanagi-Harada syndrome**, an autoimmune disease associated with choroiditis, chronic iridocyclitis, and alopecia. Some of these conditions are very rare, so a complete workout with the neurologist is necessary to get the diagnosis.

[From the slides: *In persons who are agammaglobulinemic, a chronic enteroviral meningitis or meningoencephalitis may develop and last several years, often with a fatal outcome; this syndrome has been designated* ***chronic enteroviral meningoencephalitis in agammaglobulinemia (CEMA)*** *CEMA is a constellation of neurologic symptoms that include headache, seizures, hearing loss, lethargy/coma, weakness, ataxia, paresthesias, and loss of cognitive skills. In about half of these patients, a rheumatologic syndrome, usually dermatomyositis, also develops, probably as a direct result of enteroviral invasion of affected tissues.*

Vogt-Koyanagi-Harada syndrome *is presumably an autoimmune disease consisting of bilateral eye disease, chronic meningitis, and, later in the course, skin findings. Ocular findings are* ***diffuse choroiditis or chronic iridocyclitis****. CNS findings include headache, nausea, neck stiffness, tinnitus, and CSF pleocytosis.* ***Alopecia****,* ***vitiligo****, or poliosis occur later in the disease.*]

[57] From the slides.