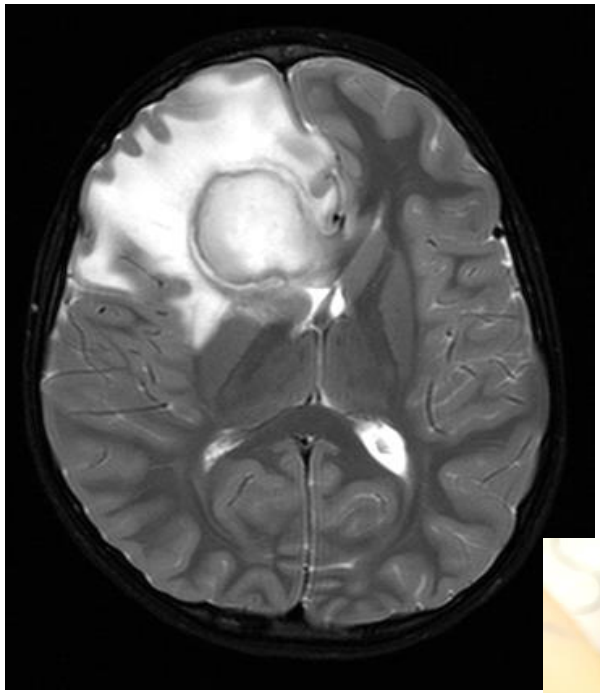
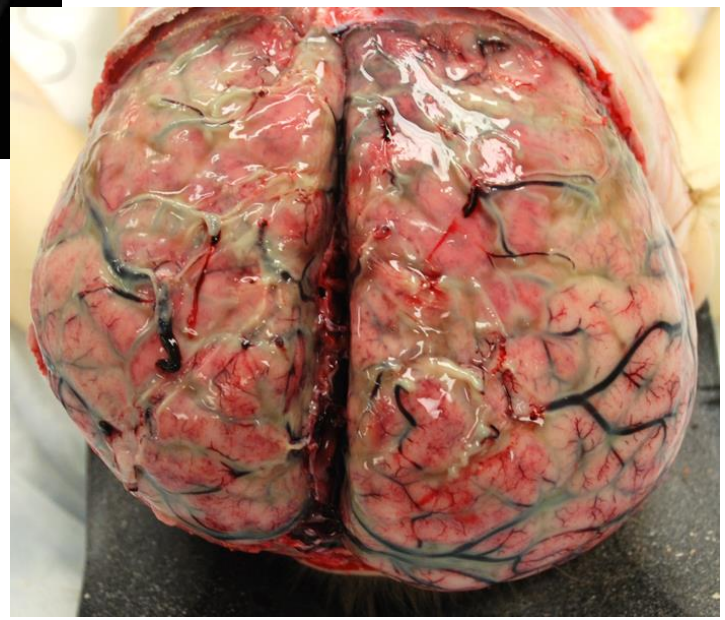
Microbiology of the central nervous system





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

Lecture 3

ESCMID guideline: diagnosis and treatment of acute bacterial meningitis

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

1) Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands, 2) Department of Infectious Diseases, Hospital Universitari de Bellvitge, Barcelona, Spain, 3) Department of Infectious Diseases, Charles University, Third Faculty of Medicine, Prague, Czech Republic, 4) Pediatric Highly Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy, 5) Department of Neurology, Klinikum Großhadern, Munich, Germany, 6) Institute for Infectious Diseases, University of Bern, Bern, Switzerland, 7) Department of Intensive Care Medicine, Groupe Hospitalier Bichat-Claude Bernard, Paris, France, 8) Department of Clinical Microbiology, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark, 9) Department of Infectious Diseases, "D. Cotugno" Hospital, Naples, Italy, 10) Department of Infectious Diseases, Southampton General Hospital, Southampton, United Kingdom and 11) Department of Infectious Diseases and Clinical Microbiology, Ege University, Izmir, Turkey

TABLE 1.1. Quality of evidence

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

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

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

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

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

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

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

Level 2	Neonates with bacterial meningitis often present with nonspecific symptoms.

Level 2	In children beyond the neonatal age the most common clinical characteristics of bacterial meningitis are fever, headache, neck stiffness and vomiting. There is no clinical sign of bacterial meningitis that is present in all patients.

Level 2	In adults the most common clinical characteristics of bacterial meningitis are fever, headache, neck stiffness and altered mental status. Characteristic clinical signs and symptoms such as fever, neck stiffness, headache and altered mental status can be absent.

Diagnostic accuracy of laboratory techniques in bacterial meningitis

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

Diagnostic accuracy of laboratory techniques in bacterial meningitis

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

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

Recommendation

Grade A

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

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

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

Grade A

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

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

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

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

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

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

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

Level 3

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

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

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

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

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

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

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

What is chronic meningitis?

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

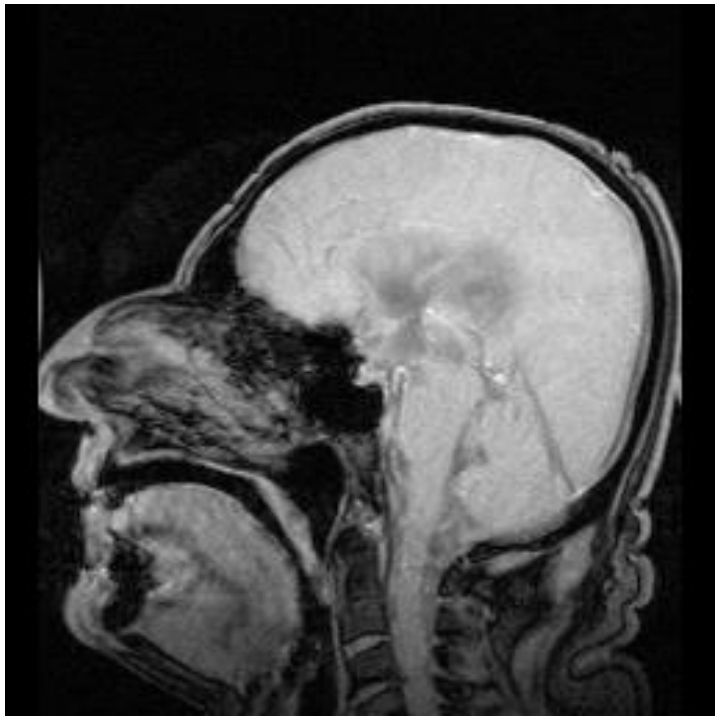
- **Subacute meningitis** develops over days to a few weeks.

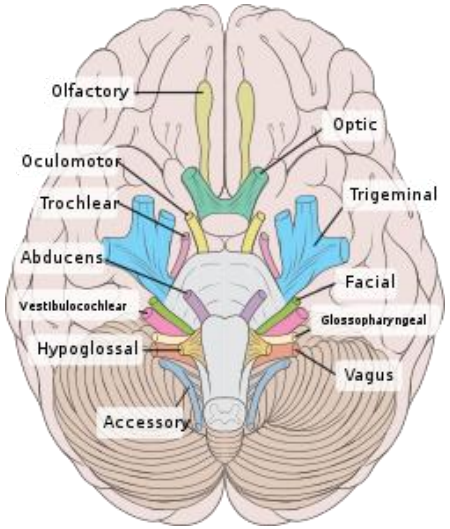
TABLE 37-1

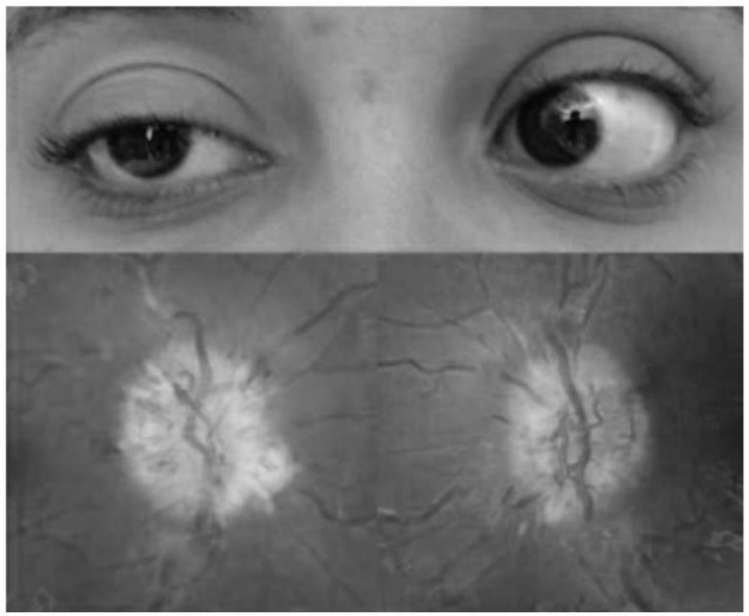
SYMPTOMS AND SIGNS OF CHRONIC MENINGITIS

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

Abbreviation: CN, cranial nerve.

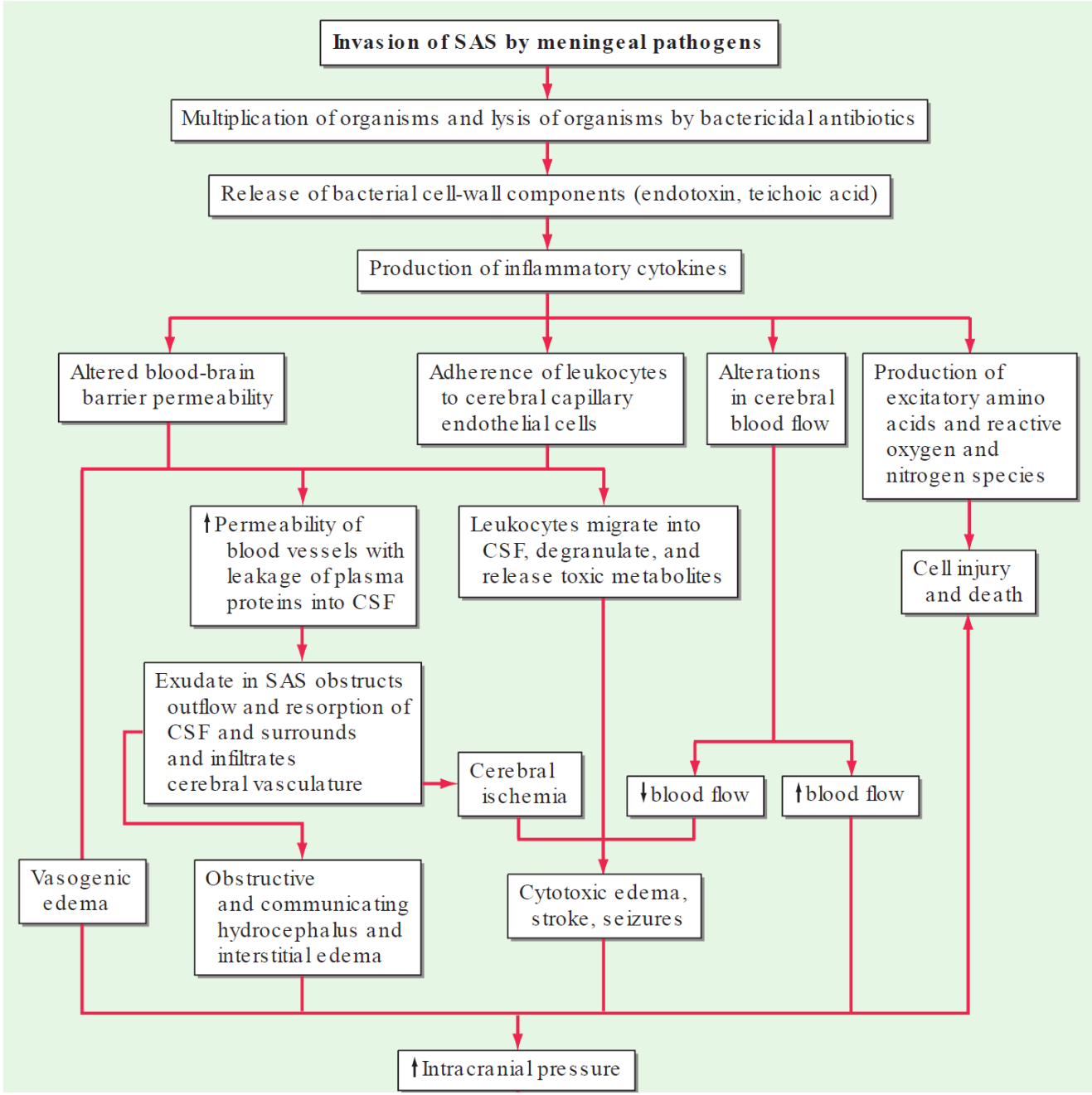






(A) Ptosis and an abduction deficit in the right eye of the patient.

(B) Bilateral papilloedema



What is chronic meningitis?

- Most common etiologies of chronic meningitis:

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

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Abbreviation: CN, cranial nerve.

Common causes of infectious chronic meningitis?

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

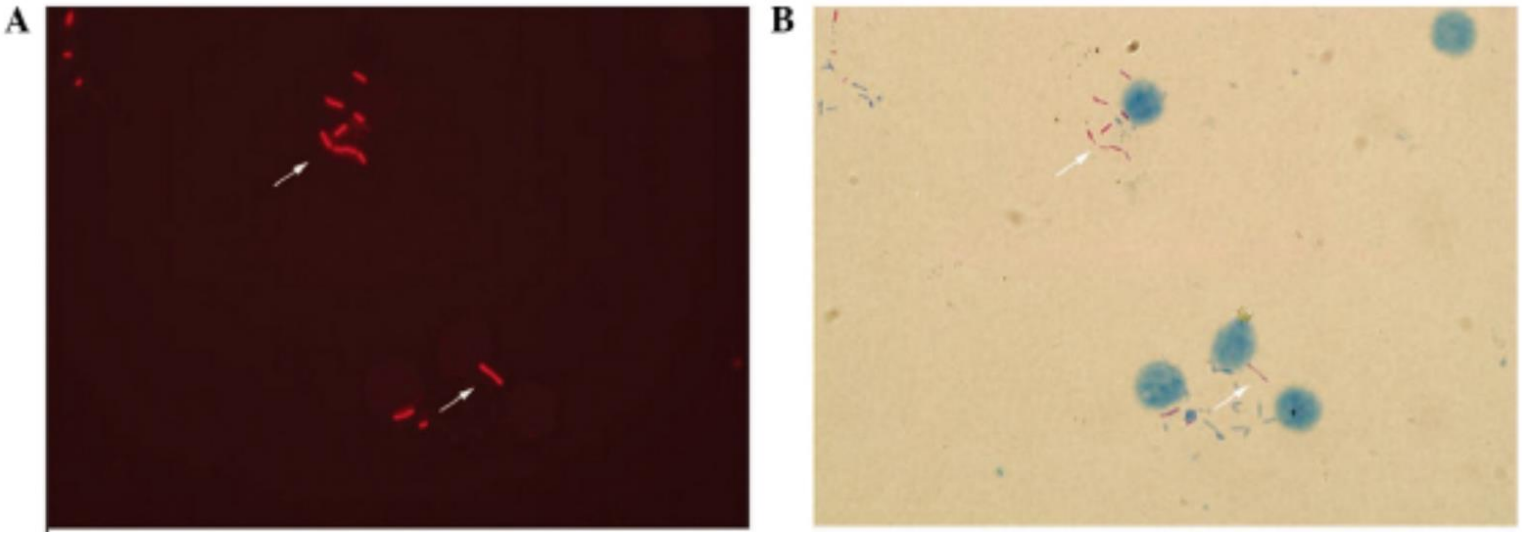
- History is important in identifying risk factors. (e.g. Exposure to TB cases, tick bites, Syphilis)

Table 19.5 Causes of chronic meningitis/meningoencephalitis

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

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

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



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

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

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

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

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

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

How to approach a patient with chronic meningitis?

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

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

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

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

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

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

Further reading:

- Oxford handbook of infectious diseases and microbiology-

Part4: Clinical syndroms

Chapter 19: Neurological infections

- Harrison's Infectious Diseases 3rd Edition

SECTION III Infections in organ systems

Chapter 36