Meningitis (s. Arachnoiditis, Leptomeningitis)

ETIOLOGY

1. BACTERIAL (PURULENT) MENINGITIS
2. Predisposing host factors
3. ASDP (HERPES) MENINGITIS
4. MENINGISM (PSEUDOMENINGITIS)
5. CLASSIFICATION
6. ACUTE MENINGITIS
7. SUBACUTE MENINGITIS
8. CHRONIC MENINGITIS
9. RECURRENT MENINGITIS
10. PATHOLOGY, PATOPHYSIOLOGY
11. BACTERIAL MENINGITIS
12. VIRAL MENINGITIS
13. EPIDEMIOLOGY
14. CHILDREN
15. SPECIFIC misnomer (term used just clinically)
16. almost any pathogenic bacteria
17. PVSA
18. PEC
19. PT
20. C

ETIOLOGY

BACTERIAL (PURULENT) MENINGITIS
- Almost any pathogenic bacteria (most cases are hematogenous)
- See infection: p. 225 (12-14) (pneumococci) <<, p. 229 (2-5) (meningococci) >>
- In order of frequency:

NEONATES:
1. Es. coli (predominantly Escherichia coli) with K1 capsular antigen (25-60%)
2. Group B streptococci (Streptococcus agalactiae) (20-50%)
3. Listeria monocytogenes (2-10%)
4. Group D streptococci (enterococci)
5. Staphylococci (rare)

CHILDREN (≤1 month ≤15 yrs):
1. Haemophilus influenzae (40-60%*) — nearly all cases in children ≤ 6 yrs.
2. N. meningitidis (25-40%)
3. St. pneumoniae (10-20%)

*now ↓↓↓ (widespread use of Hib conjugate vaccine)

ADULTS:
1. N. meningitidis (30-50%) (esp. in association with pneumonia, otitis media, skull base fracture with CSF leak) » 50% patients are ≤ 1 or > 50 years of age
2. Neisseria meningitidis (10-35%) - only major cause of EPIDEMICS* of BACTERIAL MENINGITIS (in overcrowded conditions — military barracks, etc); most patients are adolescents and young adults.
3. S. aureus and coagulase-negative staphylococci (5-15%) — predominant organisms in CSF shunts or subcutaneous Ommaya reservoirs.
4. Es. coli (1-10%) — most common in elderly.
5. Listeria monocytogenes (5%) — most common in immunosuppressed patients.
6. Streptococci (5%)
7. Haemophilus influenzae type b (0,5-3%)
8. Anaerobic bacteria (< 1%) — suggest intraventricular rupture of brain abscess.
9. Polymicrobial meningitis (< 18%) - simultaneous infection of two or more bacterial species.

PREDISPOSING HOST FACTORS
1) MECHANICAL disturbances (neurosurgical procedures, basilar skull fractures).
2) CONVICTURAL defects (dermoid sinus tracts, meningomyxalcoelects).
3) IMMUNODEFICIENCIES:
   a) self-mediated immunity (lymphoma, organ transplant recipients, corticosteroid therapy, AIDS) — intracellular bacteria (esp. tuberculosis, σ.- N. meningitidis).
   b) humoral immunity (splenectomy, chronic lymphocytic leukemia, multiple myeloma, Hodgkin’s disease after radiotherapy or chemotherapy) — encapsulated bacteria (S. pneumoniae, H. influenzae type b, N. meningitidis).
   c) neutropenia — P. aeruginosa, Enterobacteriaceae.

ASEPTIC (SEEROUS) MENINGITIS
- misnomer (term used just clinically) — absence of bacteria on microscopic examination & culture:

A. Bacterial meningitis:
   a) partially treated

MENINGIS - inflammation of meninges (inflammatory response is generally confined to arachnoid, subarachnoid space and pia = i.e. LEPTOMENINGITIS)
Viral meningitis
Fungal meningitis

B. Viral meningitis
Precise definition of etiologic agent is often impossible—In order of frequency:
1. Enteroviruses (esp. echovirus, coxsackievirus B) – statistically encountered most commonly (up to 95% of aseptic meningitis cases!)
2. Arboviruses (St. Louis encephalitis virus, California encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Colorado tick fever)
3. HIV
4. Herpes simplex virus – 2 (Mollaret’s meningitis)
5. Mumps (most common viral meningitis before widespread MMR vaccine use!)
6. Lymphocytic choriomeningitis virus (during wintertime when mice migrate indoors)
7. Varicella-zoster virus
8. Epstein-Barr virus
9. Influenza virus types A and B

N.B. Viral meningitis is disease of young (< 40 yrs!)

C. Fungal meningitis (occurs only in immunosuppressed hosts, esp. lymphoma & leukemia, AIDS):
1. Cryptococcus neoformans* – also may occur in healthy individuals!
2. Coccioidoïdes immitis
3. Histoplasma capsulatum* (leakage into CSF of contents from epidermoid tumor, craniopharyngioma, meningioma)
4. Blistomyces dermatitidis
5. Candida albicans

*common in AIDS patients

D. Chemical meningitis – response to nonbacterial irritant introduced into subarachnoid space (air, dyes, drugs, blood, etc)
• drug-induced meningitis (ibuprofen, trimethoprim, isoniazid, IVIG, OKT3, azathioprine).

E. Malignant meningitis – infiltration of subarachnoid space by carcinoma (MENINGEAL CARCINOMATOSIS) or lymphoma (MENINGEAL LYMPHOMATOSIS)
N.B. Antileukemic drugs do not cross BBB!

F. Meningitis in connective tissue disorders
1) serum sickness
2) vasculitis, priariartistis nodosa
3) SLE
4) Behçet's disease
5) sarcoidosis.

MENINGISM (PSEUDOMENINGITIS)
- syndrome of headache and signs of meningeal irritation in patients (child or young adult) with acute febrile illness (usually of viral nature) in whom CSF is under increased pressure but normal in other respects
• condition is brief in duration.
• pressure reduction by removal of CSF results in disappearance of symptoms (rarely, more than one puncture is necessary).

CLASSIFICATION

ACUTE MENINGITIS
• patients with obvious meningitis who are evaluated in less than 24 hours after onset.
• most cases are bacterial.

SUBACUTE MENINGITIS
• symptoms and signs causing patient to seek care have developed during period of 1 to 7 days
• includes virtually all cases of viral meningitis, along with some of fungal etiologies.

CHRONIC MENINGITIS
• symptoms and signs persist > 1-28 days
• causes are fungi, tuberculosis, syphilis, malignancy, systemic collagenoses, sarcoidosis, some viruses.

RECURRENT MENINGITIS
• bouts of acute meningitis with complete resolution between episodes.

RECURRENT BACTERIAL MENINGITIS signals host defect in:
A. Immuneologic defenses
B. Local anatomy – usually after trauma.

RECURRENT NON-BACTERIAL MENINGITIS
1) herpes simplex virus type 2
2) chemical meningitis (leakage into CSF of contents from epidermoid tumor, craniopharyngioma, cholestrectoma)
3) primary inflammatory conditions (Vogt-Koyanagi-Harada syndrome, Behçet's syndrome, Mollaret's meningitis, SLE
4) drug hypersensitivity (with repeated administration).

PATHOLOGY, PATHOPHYSIOLOGY

BACTERIAL MENINGITIS
• in CSF, humoral defense mechanisms (Ig and complement activity) are virtually absent; opsonic activity is often undetectable even in infected CSF (phagocytosis of encapsulated bacterial pathogens is inefficient) - bacteria commonly reach very high densities in CSF - use of bacterialidal agent is mandatory part of therapy!
• inflammatory reaction may extend short distance along perivascular spaces into substance of brain and spinal cord, but rarely breaks into parenchyma.
• release of toxic factors from bacteria – activation of neutrophils – release of TNF-α, IL-1, 8, platelet activating factor:
  1) cytotoxic cerebral edema
  2) increase in BBB permeability -> vasogenic edema.
- large numbers of leukocytes in subarachnoid space contribute to purulent exudate and impair CSF absorption by arachnoid villi → **COMMUNICATING HYDRECEPHALUS**.
- pia-arachnoid becomes thickened → adhesions → interfere with CSF flow from 4th ventricle → **OBSTRUCTIVE HYDRECEPHALUS**.
- hydrocephalus causes transendymal movement of fluid from ventricular system into brain parenchyma (**interstitial edema**).
- cerebral edema causes ICPC.
Neutrophilic exudate is seen involving meninges (at left), with prominent dilated vessels; there is edema and focal inflammation (extending down via Virchow-Robin space) in cortex (at right).

Source of picture: “WebPath—The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD)

- meningal and superficial cortical vessels are engorged and stand out prominently.
- since subarachnoid space is continuous over brain, spinal cord, and optic nerves, infection in this space extends throughout cerebrospinal axis unless there is obstruction of subarachnoid space.
- ventriculitis is nearly uniformly present.
- brain parenchyma (cerebritis → abscess), dura (pachymeningitis), subdural and epidural spaces may be secondarily involved.
- when patient recovers, phagocytes completely clear subarachnoid space; if low-grade infection persists, adhesions and leptomeningeal fibrosis develops (see complications).

VIRAL MENINGITIS
- brain swelling, mild to moderate infiltration of leptomeninges with lymphocytes.

EPIDEMIOLOGY

BACTERIAL MENINGITIS
- overall incidence (in USA*) - 3-10 cases (per 100,000 persons per year).
  *bacterial meningitis is much more prevalent in developing countries
- incidence is highest in first month of life.
- incidence increases in late winter's early spring.
- men > women.

VIRAL MENINGITIS
- actual incidence is unknown (most cases are unreported); ≈ 11-27 cases (per 100,000 persons per year).
- prominent increase in summer (seasonal predominance of enteroviruses & arboviruses).

CLINICAL FEATURES

ACUTE MENINGITIS
Patients rapidly deteriorate:
- course is most dramatic in pyogenic meningitis;
- course is much less acute in viral meningitis - patients may be in great discomfort but are not critically ill.

1. Patient looks unusually ill with altered consciousness (up to coma with shock); in viral meningitis - only mild lethargy or drowsiness.

2. Fever
  - temperature is higher in bacterial than viral CNS infection.
  - temperature may be below normal (tuberculosis).

3. Diffuse headache due to displacement & traction of blood vessels traversing through meninges.
  - typically frontal or retroorbital with pain on moving eyes in viral meningitis.
  - pain often causes infant to emit peculiarly shrill cry (meningeal cry).
  - N.B. TRIPTANS can relieve any neurovascular headache (incl. SAH and meningitis) - TRIPTANS should never be used as diagnostic tool.

  - meningeal signs are milder in viral meningitis.
  - meningeal signs may be falsely absent in:
    1) elderly, infants
    2) debilitated, immunosuppressed
    3) receiving anti-inflammatory drugs or antibiotics.

5. Vomiting, photophobia, irritability

6. Seizures (30-40% bacterial meningitis) cases, typically during 1st week of illness; focal signs are not typical for uncomplicated viral meningitis; etiology:
  1) fever
  2) focal ischemia, cortical venous thrombosis with hemorrhage
  3) hyponatremia
  4) subdural effusion / empyema (mass effect)
  5) antimicrobial agents (e.g. sepsis, penicillin).

- look for typical petechial-purpuric rash of meningococcemia (esp. in extremities).
1. Low-grade fever
2. Chronic headaches
3. Neck stiffness
4. Subtle personality / mental status change (may be the only sign in elderly!)
5. Cerebral neuropathies, cranial neuropathies, hydrocephalus.

• may be fatal if not successfully treated.

**SUBACUTE / CHRONIC MENINGITIS**

- manifestations are similar to acute meningitis but evolve more slowly:

  1. Low-grade fever
  2. Chronic headaches
  3. Neck stiffness
  4. Subtle personality / mental status change (may be the only sign in elderly!)
  5. Cerebral neuropathies, cranial neuropathies, hydrocephalus.

• may be fatal if not successfully treated.

**COMPLICATIONS**

**BACTERIAL MENINGITIS**

1. Seizures
2. DIC, shock
3. Subdural effusions - usually in infants as self-limited process (as inflammatory process subsides, subdural fluid is reabsorbed).

  Treatment – repeated daily *needle aspirations* through coronal sutures:

  - indications: infected fluid (prolonged fever), increased ICP, rapidly enlarging head circumference in child, focal neurological findings (seizures).
  - no more than 20 mL of CSF should be removed from one side (to prevent sudden shifts in intracranial contents).
  - if effusion persists after 3-4 wk of taps → surgical exploration for possible excision of subdural membrane is indicated.

4. Brain abscess, subdural empyema
5. Cerebral thrombophlebitis
6. Stroke:
   a) vasospasm caused by subarachnoid infection
   b) loss of cerebral autoregulation + hypertension
   c) inflammatory infiltration of arterial wall (vasculitis).
7. Cranial nerve palsies (esp. sensorineural hearing loss; oculomotor paresis)
8. Consequences of ICP* (incl. brain herniation)
9. Chronic adhesive arachnoiditis, hydrocephalus

**DIAGNOSIS**

1. All meningitis suspects must have LUMBAR PUNCTURE **ASAP** - gold standard for diagnosis!

   If mass lesion is consideration (focal neurologic deficit, papilledema, seizures, evidence of head trauma) - contrast-enhanced CT or MRI first.

   nevertheless, two blood samples are drawn for culturing → empirical antimicrobial therapy is started.

   • if ICP is present – administer IV bolus of MANNITOL 1 g/kg (ideally 20 min before LP); use small (but minimum 22G) needle, obtain minimum required sample, in addition, patient can be intubated and hyperventilated.

   • parameters of meningitic CSF:

     - opening pressure moderately↑ (bacterial meningitis) + viral meningitis;
     - cloudy & straw-colored (bacterial meningitis) or clear-cloudy & colorless (viral meningitis);
     - cell count* (esp. in untreated meningitis): 0-1,000/mm³; *PMNs in bacterial meningitis; 5-1,000/mm³ mononuclears (may be PMNs at onset*) in viral meningitis (also in Ibc, fungal**), Lyme, syphilis, toxoplasmosis, or chronic meningitis; (esp. in enteroviral infections)
     - glucose*: most specific (esp. in bacterial, tuberculous, cryptococcal meningitis, normal in viral meningitis*).

     *but ↓ in mumps, lymphocytic choriomeningitis virus

     *protein* (bacterial meningitis > 100 mg/dl; viral meningitis < 100 mg/dl).

     *LDH1* (in bacterial, fungal meningitis).

     *lactate* (>4 mmol/L considered diagnostic; due to PMNs presence, i.e. only in bacterial meningitis).

   • organism detection:

     for more detailed explanations → see p. D40 >>

     - *PMNs with Blastomycosis infection
     - *PMNs with Histoplasmosis infection

   • organism detection:

     for more detailed explanations → see p. D40 >>

     - stains - Gram stain (for all cases with PMNs), India ink stain (in cryptococcal meningitis), Zielh-Neelsen acid-fast stain (Ibc).
     - antigen tests (PCR, latex particle agglutination, counterimmunoelectrophoresis, limulus lysate test*, immunofluorescence, etc).

     *highly sensitive at detecting LPS (Gc- organisms).
Meningitis

**APERT BY VISU** - FDA approved fully automated reverse transcription-PCR test for Enterovirus detection; result in 2.5 hours!

3) **cultures**
   - positive in 70-85% bacterial meningitis cases;
   - gold standard for diagnosis of enteroviral CNS infection, but negative in 25-33% patients, also in mumps.

4) **CSF antibody titers** → CSF/serum antibody index (for viruses, syphilis, Lyme disease); unfortunately, antibodies appear in CSF too late to aid in any therapeutic decisions (used only for retrospective diagnosis).

In 2-3% CSF culture-proven bacterial meningitis cases, CSF profile is normal (incl. Gram stain)! CSF may be normal early in course – do not hesitate to repeat LP if clinical signs persist!

**Antimicrobial therapy**
- will not significantly alter CSF profile (WBC count, glucose & lactate concentration, antigen test results) for at least 2-3 days.
- will decrease sensitivity of Gram’s stain & culture (window of 2-3 hours after giving parenteral antibiotics when CSF cultures are not adversely affected).

Gram’s stain and culture should be negative in CSF obtained 24 hours after initiation of IV antimicrobial therapy, if organism is sensitive to that antibiotic.

Neisseria meningitidis (Gr-diplococci) within neutrophile:

![Source of picture: “WebPath - The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD)](https://www.webpath.org/)

India ink stain (budding organisms - cryptococci):

2. **CT** - findings are highly variable (usually normal in uncomplicated meningitis) - vast majority of patients do not require neuroimaging.

*CT should not unnecessarily delay LP or antimicrobial therapy!*

a) **severe acute meningitis**:
   1) striking *pial and ependymal enhancement* (superficially looks like SAH, but seen only in contrast-enhanced CT, vs. SAH)
   2) abnormal signal or density in CSF (high protein content or frank pus)
   3) secondary brain edema.
   4) complications of meningitis (subdural collections, hydrocephalus, cerebral infarction).

b) **chronic meningitis** - may be no imaging findings or merely minimal ventricular enlargement.

3. **EEG** is usually normal or slightly slow.

4. **WBC count** is markedly elevated in bacterial meningitis (mildly in viral meningitis).

5. Serum **antibody titers** - ≥ fourfold rise in paired sera (for viruses).

6. **Organism detection in other fluids**:
   1) **blood cultures** (positive in 80-90% patients with bacterial meningitis; some viruses).
   2) **stool specimen** may be better source of viral isolate (enteroviruses), but is not diagnostic of meningitis.
   3) mumps virus may be isolated from saliva, throat washing.
   4) meningococci may be found in skin lesions, nasopharyngeal secretions.

   In general, cultures of body surfaces and orifices are not helpful in identifying causative pathogens!

7. **Etiologic diagnosis in chronic meningitis** may require **meningial biopsy** (→ histology, electron microscopy, PCR, cultures).
   - target regions that enhance with contrast on MRI or CT.
   - with current microsurgical techniques, most areas of basal meninges can be accessed via limited craniotomy.
   - most common conditions identified - sarcoid (31%), metastatic adenocarcinoma (25%).
Meningitis

Pyogenic meningitis (postcontrast axial CT) - high-attenuation of pial surfaces and filling subarachnoid spaces (it was not present on noncontrast images); patchy diminished density in brain parenchyma may represent encephalitis or ischemic lesions from vasospasm:

Pyogenic meningitis (postcontrast axial CT) - high-attenuation of pial surfaces and filling subarachnoid spaces (it was not present on noncontrast images); patchy diminished density in brain parenchyma may represent encephalitis or ischemic lesions from vasospasm:

Herpes simplex ventriculitis (MRI contrast medium): A) T2-weighted spin-echo; B) T1-weighted spin-echo.

Necrotic right-sided periventricular lesion shows central low signal on T1 and high on T2 with peripheral enhancement. Enhancement of periventricular region (see involvement of corpus callosum) is also present:

TREATMENT

- patients prefer quiet, darkened room.
- ANALGESICS - to relieve headache (often reduced by initial diagnostic lumbar puncture).
- ANTIPYRETICS - to reduce fever.

VIRAL MENINGITIS

- self-limiting - treated symptomatically OUTPATIENTS (with close follow-up within 24 hours).
- indications for hospitalization:
  1) severe cases
  2) deficient humoral immunity (→ trial of IVIG)
  3) herpes meningitis (→ intravenous ACYCLOVIR)
  4) potential nonviral causes.
- PLECONARIL is active against enteroviruses, but FDA has rejected its approval.

BACTERIAL MENINGITIS

1. DEXAMETHASONE

- BACTERIAL MENINGITIS is strongly suspected - prevents neurological disability and death by decreasing meningeal inflammation (due to released bacterial components by bactericidal antibiotics)
- In a 2015 Cochrane meta-analysis of 25 randomized controlled trials including 4121 participants, corticosteroids were found to significantly decrease rates of severe hearing loss, any hearing loss, and neurological complications. Corticosteroids did not significantly impact mortality, although a subgroup analysis demonstrated a reduction in mortality due to meningitis caused by S. pneumoniae
- for adults and children ≥ 2 months of age.
- dosage: 0.15 mg/kg q6h (i.e. 10 mg) IV.
- use H2 antagonist to avoid GI bleeding.
**NEONATE** (most likely group B streptococci, E. coli, L. monocytogenes) – combination:

1. **AMPCILLIN**
2. **GENTAMICIN** or **CEFOXAXIME** or **AMIKACIN** or **TORBAMYCIN**

**INFANT 4-12 WEEKS** (H. influenzae and Str. pneumoniae join neonatal pathogens) – combination:

1. **AMPCILLIN**
2. **CEFOXAXIME** or **CEFOXAXIME** or **CHLORAMPHENICOL**

**OLDER INFANT & CHILD** (N. meningitidis joins pathogens) – combination:

1. **VANCOMYCIN**
2. **CEFOXAXIME** or **CEFTRIAXONE**

**ADULT** (S. pneumoniae, N. meningitidis) – combination:

1. **VANCOMYCIN**
2. **CEFOXAXIME** or **CEFDIXIME**

*for neurosurgical / immunocompromised patient use CEFTAZIDIME (Pseudomonas aeruginosa may be etiologic agent).

3. for adult > 50 yrs / immunocompromised / pregnant - add AMPICILLIN (Gr. aerobic bacilli; L. monocytogenes – resistant to cephalosporins); if severe penicillin allergy –

TMP/SMX

**Therapy according to Gram stain:**

Gr+ organisms – **CEFOXAXIME** or **CEFTRIAXONE** + **VANCOMYCIN**.

- if organisms are pleomorphic (Listeria spp.) – add AMPICILLIN.

Gr- bacilli – **TICARCILLIN** or **CEFTRIAXONE** + aminoglycoside.

Once causative organism has been identified:

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Infants (&lt; 2000 g)</th>
<th>Children &amp; Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B streptococcus</td>
<td>PENICILLIN G or AMPICILLIN + AMIKACIN or GENTAMICIN</td>
<td></td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>PENICILLIN G or AMPICILLIN or CEFOTAXIME or CEFTRIAXONE or CHLORAMPHENICOL + (at end of therapy) oral RIFAMPIN for 2 d. *</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td><strong>VANCOMYCIN</strong> * or CEFOTAXIME</td>
<td></td>
</tr>
<tr>
<td>Enteric Gr- bacilli (except Ps. aeruginosa)</td>
<td>CEFOTAXIME or AMIKACIN or GENTAMICIN</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>CEFTAZIDIME or CIPROFLOXACIN or TICARCELLIN + GENTAMICIN</td>
<td></td>
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<tr>
<td>Listeria monocytogenes</td>
<td>AMPICILLIN + AMIKACIN or GENTAMICIN</td>
<td>AMPICILLIN or TMP/SMX</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>CEFOTAXIME or CEFTRIAXONE or CHLORAMPHENICOL (with AMPICILLIN)</td>
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</tr>
<tr>
<td>Staphylococcus aureus (methicillin-sensitive)</td>
<td>METHICILLIN</td>
<td>OXACILLIN</td>
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<tr>
<td>Staphylococcus aureus (methicillin-resistant)</td>
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</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>VANCOMYCIN</td>
<td>RIFAMPEN</td>
</tr>
</tbody>
</table>

*to eradicate nasopharyngeal carriage

*some pneumococci are resistant to penicillins, cephalosporins, chloramphenicol!

**PRIMARY FOCUS OF INFECTION** should be eradicated (by surgery if necessary; e.g. persistent CSF fistulas must be closed by suturing of dura – unless dramatic response to therapy occurs, fistulas must be closed by suturing of dura – otherwise meningitis will almost certainly recur).

- unless dramatic response to therapy occurs, CSF should be re-examined 24-48 hrs after initiation of treatment (to assess effectiveness of medication – CSF sterility + conversion to lymphocytic predominance).

- drug dosages should not be reduced when clinical improvement occurs (drug generation decreases as meningitis become less inflamed).

- duration of therapy (based largely on tradition; should be individualized and based on clinical response): neonates – 3 weeks; H. influenzae, S. pneumoniae – 10-14 days; N. meningitidis – 7 days. Gr- aerobic bacilli – 3 weeks.

- post-treatment CSF examination is not meaningful criterion of recovery (i.e. CSF need not be re-examined if patient is clinically well!).

**3. OTHER MEASURES** (treatment of dehydration, coagulopathy, seizures, raised ICP & cerebral edema)

Hypothermia

**N.B. VANCOMYCIN** effect may be adversely affected (since meningeal inflammation improves VANCOMYCIN penetration into CSF); H. use higher doses of VANCOMYCIN (15 mg/kg q8h) or intrathecal VANCOMYCIN.

- **course – first 4 days of antimicrobial therapy**
- **First dose of antimicrobial should be administered 20 min before first antimicrobial dose**
- if no bacteria grows in culture or is otherwise identified after 24-48 h, corticosteroids should be stopped, and antibiotic coverage reassessed (corticosteroids for 1 day should not be detrimental even if cause is virus, fungus, or TB).

**2. ANTIMICROBIAL THERAPY** (must be bacterial in CSF* – i.e. maximum tolerated doses)! intravenously (intrathecal / intraventricular therapy is not effective).

*If you suspect meningococcus, give PENICILLIN G before transporting to hospital!

Empire therapy (all patients must be isolated for first 24 h of therapy): dosages → see Inf! >

CEFTRIAXONE 2 g q8h + VANCOMYCIN 15mg/kg q12h (goal trough: 15 – 20 mg/L)

*for type I penicillin hypersensitivity (i.e. anaphylaxis) substitute with ATROPINE + 2 g or CIPROFLOXACIN 400 mg q8h

**CRUCIAL step is to initlate ANTIMICROBIAL THERAPY immediately!!!!!!!!!!**

- if organisms are pleomorphic (Microbe +) – add AMKANIC.

- if no bacteria grows in culture or is otherwise identified after 24 hrs, initiation of treatment is not warranted unless meningitis is confirmed (by CSF analysis if patient is clinically well).

- if no bacteria grows in culture or is otherwise identified after 24 hrs, meningitis is confirmed (by CSF analysis if patient is clinically well).

- if no bacteria grows in culture or is otherwise identified after 24hrs, meningitis is confirmed (by CSF analysis if patient is clinically well).
EMPIRICAL THERAPY for CHRONIC MENINGITIS

- when all attempts at diagnosis fail:
  1) antitylarchical agents
  2) AMPHOTERICIN B
  3) glucocorticoids (for noninflammatory causes).

CHEMOPROPHYLAXIS

- for family members and other intimate contacts of child with meningocecal or H. influenzae infection.
  *only of there are children < 4 years between contacts (then administer chemoprophylaxis to all contacts [except pregnant women], independent to their Hb vaccination status, because vaccination does not prevent nasopharyngeal colonization)
  *not routinely warranted for medical personnel (except those who have had direct mucosal contact with patient's secretions - mouth-to-mouth resuscitation, intubation, suctioning, etc.)

RIFAMPIN (started within 24 hours of diagnosis of contact case) meningocecal - 10 mg/kg (5 mg/kg for newbons; 600 mg for adults) q12h for 2 d. H. influenzae type B - 20 mg/kg (10 mg/kg for newbons, 600 mg for adults) x 11d for 4 d.

N.B. rifampin prophylaxis eradicates organisms only from nasopharynx!

PROGNOSIS

BACTERIAL MENINGITIS

- MORTALITY ≤ 10-20% (many deaths occur during first 48 hours of hospitalization); 50-90%* in untreated cases.
  *almost 100% in pneumococcal meningitis!
- PERMANENT MENTAL INTELLIGENCE DEFICIENCY occurs in 20-50% survivors: permanent hearing loss (10%), mental retardation*, cerebral palsy, permanent seizure disorders, behavioral problems.
  *bacterial meningitis is one of most preventable causes of mental retardation!

VIRAL MENINGITIS

Death is exceptional!
- adults - prognosis for full recovery is excellent (rarely - persisting headache, mild mental impairment, incoordination, generalized asthenia for weeks to months).
- infants / neonates – prognosis is less certain (intellectual impairment, learning disabilities, hearing loss have been reported).

SPECIFIC FEATURES

MYCOBACTERIUM TUBERCULOSIS

- INCUENCE is slowly increasing (HIV-infected individuals + immigration from Asian, Latin American, and African countries).
- most common in childhood (in 3rd countries) and early adult life (in Western countries).

Immunopathology

- tuberculous meningitis is always secondary to tuberculosis elsewhere in body (usually in lungs, but may be in any organ).
- progression of primary infection (children) / reactivation (adults) -→ bacteria & miliary dissemination -→ CNS entrance -→ miliary tuberculides (sharply outlined round white nodules) in brain parenchyma and/or meningeal tissue.
Corticosteroids from vascular abnormalities (perivascular demyelination) or Tuberculous meningitis, usually asymptomatic; infection) Intracerebral Prognosis

- **Clinical Features**
  - insidious onset, vague nonspecific protracted progressive course*: moderate constitutional symptoms (low-grade fever, anorexia, weight loss, night sweats, malaise), unremitting headache, ± meningismus.

  *some patients present with acute meningeal symptoms (coma, ICP↑, seizures, focal neurological deficits)

- **Diagnosis** - CSF examination:
  1. pressure?, CSF clear or cloudy (straw-colored) with fibrin web formation on standing. 10-50 lymphocytes (in early stages may be > 80% PMN), protein 7-100-500, glucose, |↓|<45.
  2. Ziehl-Neelsen acid-fast stain - usually negative (small numbers of organisms in CSF)
  3. **CSF cultures** onto Lowenstein-Jensen medium (wait at least for 8 weeks – will be positive in 90% cases); if negative, (10-20 samples) is required for adequate culture?
  4. **PCR tests** (likely will replace many of current tests for mycobacteria)!

N.B. CSF-chloride as diagnostic aid for the meningitis is no longer clinically relevant!

- **MRI after gadolinium enhancement** - florid contrast enhancement within basal cisterns; hydrocephalus, areas of infarction, tuberculomas.

- **additional diagnostic data**
  1. positive tuberculin skin test
  2. chest X-ray evidence of tuberculous lesion (most children, 50% adults)
  3. evidence of active infection elsewhere (20-30% patients).

- **history of contact with case of tuberculosis.**
  - If suspicion is high, treatment should begin before bacteriologic proof:
    - **isoniazid + rifampin + pyrazinamide + ethambutol** → **isoniazid + rifampin** for at least 7-10 months (i.e. 9-12 months*; up to 24 months)

      *longer than for pulmonary tuberculosis

  - **Curative treatment** indicated for all patients (esp. with ICP↑, cerebral edema, mental status↓, focal signs, spinal block, hydrocephalus) - for first 3 weeks (then gradually decreased during next 3 weeks).

- **Shunting for hydrocephalus.**

**Drug** | **Children** | **Adults**
--- | --- | ---
ISONIAZID | 10 mg/kg/d* since daily | 300 mg/d + 30 mg/d pyridoxine
RIFAMPIN | 600 mg/d | 600 mg/d
PYRAZINAMIDE | 30 mg/kg | 30 mg/kg
ETHAMBUTOL | 15-25 mg/kg | 200-40 mg/kg
STREPTOMYCIN | | |
rifabutin | 300 mg/d | |

*up to 15 mg/kg/I in HIV-infected patients

**Progression** - treatment is less effective - mortality is higher (than in bacterial meningitis).

- **sequelae** occur in ~25% patients who recover (facial weakness, intellectual disorganization, deafness, seizures, blindness, plegias).

- **intracranial calcifications** may appear after 2-3 years.

**Intracerebral tuberculosis** - rounded tuberculoid intraparenchymal mass (localized tuberculous infection); always secondary to tuberculomas elsewhere in body (e.g. frequent finding in tuberculous meningitis, usually asymptomatic).

- tend to lie superficially in brain (most characteristically adjacent to Sylvian fissure; brain stem and cerebellum are other favorite rostral sites)
- central core of caseous necrosis surrounded by typically tuberculous granulomatous reaction.
- up to several centimeters in diameter → mass effect (minims tumor).
- CT density as brain (or slightly denser) + little or no surrounding edema → tuberculoma is one of few supratentorial masses which might be overlooked on CT without IV contrast.
- on CT with IV contrast, tuberculomas enhance strongly (solid or thick-walled mass).
- calcification may occur in inactive lesions.
- treatment is based on chemotherapy; large accessible lesion → surgical excision.

**Tuberculous encephalopathy** - purely allergic phenomenon - cerebral edema (occasionally with periocular demyelination) or homologous leukocoelephathy deep in white matter at distance from vascular abnormalities and purulent exudate.
**MENINGITIS**

**CRYPTOCOCCUS neoformans**

- **Meningitis** is caused by Cryptococcus neoformans, a fungus that can be found in soil and bird droppings.
- **Pathogenesis**: Inhalation of the fungus spores can lead to meningitis.
- **Clinical presentation**: Subacute to chronic meningitis with symptoms such as headache, low-grade fever, lassitude, and weight loss.
- **Imaging**: May show no enhancement in neuroimaging. 10% of cases develop cryptococcomas, which are rounded lesions on T2-weighted MRI, low intensity on T1-weighted MRI, and high intensity on T2-weighted MRI. They are most common in basal ganglia (distribution of lenticulostriate arteries) but may occur elsewhere. Minimal or absent inflammation and edema.
- **Treatment**: Antifungal therapy such as itraconazole or amphotericin B.

**MYCOBACTERIUM AVIUM, MYCOBACTERIUM INTRACELLULARE**

- **Pott's disease** is due to hematogenous dissemination from respiratory or GI source.
- **Pathogenesis**: Mycobacterium avium and Mycobacterium intracellulare cause similar clinical presentations.
- **Clinical presentation**: CNS disease is a result of hematogenous dissemination from respiratory or GI source of infection.
- **Immunocompromised patients**: Primarily affects patients with advanced HIV disease (< 50 CD4+ cells/µl).
- **Clinical features**: Meningitis, meningoencephalitis, rhombencephalitis, brain abscess, or cranial neuropathies.
- **Treatment**: At least a four-drug regimen:
  1. **CLARITHROMYCIN** (500 mg ×2/day)
  2. **RIFAMPIN** (600 mg/day)
  3. **ETHAMBUTOL** (25 mg/kg/day for 2 months then 15 mg/kg/day)
  4. **STREPTOMYCIN** (0.75-1.0 g at least three times per week).
- **Alternative regimens**: CLARITHROMYCIN and AZITHROMYCIN have excellent activity. **AZITHROMYCIN** (250 mg/day), **RIFABUTIN** (300 mg/day), **ETHAMBUTOL**, **STREPTOMYCIN**.
- **Treatment duration**: Until cultures are negative for at least 12 months (will likely need to be continued for life of patient).

**FUNGAL MENINGITIS**

**Cryptococcal meningitis**

- **Pathogenesis**: Inhalation of Cryptococcus neoformans spores can lead to meningitis.
- **Clinical presentation**: Subacute to chronic meningitis resembling tuberculous meningitis.
- **Imaging**: May show no enhancement. 10% of cases develop cryptococcomas, which are rounded lesions on T2-weighted MRI, low intensity on T1-weighted MRI, and high intensity on T2-weighted MRI. They are most common in basal ganglia but may occur elsewhere. Minimal or absent inflammation and edema.

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Cryptococcal meningitis

Cryptococcus neoformans is an agent that is common in AIDS patients. (GMS stain - organisms didn't even bother to make capsule; budding Cryptococcus cells have narrow bases.

**Treatment of**

**AMPHOTERICIN B** (drug of choice for all fungi and yeasts): adults – 1 mg test dose (by slow IV infusion) → gradually increase as tolerated to maximum 1 mg/kg/d; total of 2-6 g is usually given. children – test dose 0.25 mg/kg IV in 6-h infusion → daily dosage is increased by 0.25 mg/kg to no more than 1 mg/kg/d.

- **AMPHOTERICIN B** need not be continued for > 10 wk if its blood level can be maintained at concentration at least twice that needed to inhibit fungal growth in culture.

- **intravenousida** (via Ommaya reservoir) **AMPHOTERICIN B** is sometimes necessary to eradicate infection (e.g. coccidioidal meningitis).

**Treatment of**

**CRYPTOCOCCAL Meningitis** - dual-agent induction: **AMPHOTERICIN B** + **FLUCYTOSINE** 25-35 mg/kg q8h for 2 weeks → consolidation: **FLUCONAZOLE** 400 mg/d for 8 weeks or until CSF is sterilized; in HIV-positive patients: lifelong suppressive therapy 200 mg/d. see p. 269

- *the only “azole” that crosses BBB*
- less effective alternatives: **ITRACONAZOLE**

- **often develop symptomatic intracranial hypertension.**
- – ventriculomegaly (hydrocephalus) is not always present
- – most patients do well with serial lumbar punctures combined with antifungal therapy.
- – in one case series (50 patients), only 20% patients needed permanent shunting.

- Jacobs-Cherian et al. Shunting in cryptococcal meningitis: DOI: https://doi.org/10.1177/0300067215581255
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- when required, shunting provides sustained relief from intracranial hypertension symptoms.

- authors favor shunt placement over trials of external lumbar or ventricular drains (external drains require immobilization and demand a higher level of nursing care, high rate of eventual progression to shunting).

- ventriculoperitoneal shunts are the favored method of diversion (via Ommaya reservoir).

- no cases of shunt infection reported, improvement in children dependence on intravenousidation.

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only presenting sign may be alteration of mental status.
elderly patient is at high risk for meningitis - identification of infection outside CNS (in patient with mental status change) is clear indication for LP (because of risk of bacteremic seeding).

**POSTTRAUMATIC MENINGITIS**

Trauma (bassilar fractures with CSF leak, penetrating head injuries, linear fractures through nasal sinuses or middle ear) → host defect in local anatomy → RECURRENT BACTERIAL MENINGITIS

- meningitis develops 2-8 days after injury but several years may pass between trauma and first bout of meningitis (esp. with fractures through mastoid or nasal sinuses).

- etiology:
  a) early meningitis (within 3 days of injury) - usually Str. pneumoniae → PENCILLIN G or CEFOXITAXIME
  b) meningitis more than 3 days after trauma - often Ge. organisms → CEFOXITAXIME or CEFTHAZON + NAFICILLIN (coverage of S. aureus).
  c) in children, posttraumatic meningitis may be due to Haemophilus influenzae.
  d) CSF rhinorhhea/or theotrauma (detected by significant concentration of glucose in nasal or aural secretions) may be transient (H: monitoring course of radioisotope-labeled albumin instilled instilled intrathecally or CT after intrathecal injection of metrizamide).

- prophylaxis: pneumococcal vaccine + long-term prophylactic penicillin (***) → surgical closure of CSF fistulas.

  - prophylactic antibiotics are not recommended in acute setting in CSF leaks caused by bassilar skull fractures

**HAEMOCOGEN MENINGITIS**

- temperature may be elevated for first few days after most cranioanatomies.
  - if fever continues > 72 hours (in setting of good pulmonary toilet), asptic or bacterial meningitis should be suspected.

- diagnosis - sterile xanthochromic CSF under pressure with several hundred leukocytes / mm³.

- treatment - antipyretics and DEXAMETHASONE.

-Basal meningitis - around brainstem and cranial nerves, along undersurface of frontal and temporal lobes.

- multiple cranial neuropathies (CNI-XII).

**SNAPE MENINGITIS (ARACHNOIDITIS)**

- injury to rootlets (as they traverse subarachnoid space and penetrate meninges; permanent intradural adhesions) → multiple radiculopathies: radicular pain, sensory loss, motor weakness, sphincter dysfunction.

- usually begins as intracranial meningitis.

- etiology:
  a) most commonly - iatrogenic (myelography performed with iophendylate (Myodil)) - involves caudal sac (rarely ascending above L5/S4 discs); lumbar disc surgery itself is rarely cause.
  b) trauma.
  c) intradural infections - tuberculosis, fungal and parasitic (esp. cysticercosis)
  d) spinal SAH
  e) intraspinal tumors (rarely)
  f) spinal spondylosis.

- inflammation can encircle cord → myelopathy.

- myelomalacia and syringomyelia often develop in extensive cases.

- on rare occasions, organized exudates become calcified and even ossified (ARACHNOIDITIS OSSIFICANS).

- MRI with IV gadolinium (modality of choice): N.B. myelography should be avoided when arachnoiditis is suspected!

**Acute meningitis**: variable patterns of surface enhancement of nerve roots and meninges (linear, nodular, plaque-like, etc.)

**Chronic meningitis**: - localization & deformity of subarachnoid spaces, tapering / obstruction of lower end of subarachnoid space, central clumping / peripheral adhesion of roots of cauda equina (empty thecal sac with thickened sac walls), irregular deformity of spinal cord (with central signal change in severe cases).

Patients with slowly progressive involvement of multiple cranial nerves and/or spinal roots are likely to have chronic meningitis.

Spinal adhesive arachnoiditis (high resolution T2: MRIs of lumbar spine) - three main diagnostic features:

- A) central clumping of nerve roots (CSF is white).
- B) peripheral adhesion of roots leaving clear central subarachnoid space.
- C) adhesion of margins of thecal sac near point of exit of root sheaths (arrows).
- D) norma - roots lie clearly seen as they enter spinal root sheaths on each side.

Spinal meningitis due to Lyme disease (TI-MRI of lumbar spine after IV gadolinipate - diffuse enhancement of outer surface of cord and spinal roots.

**MOLLARE MENINGITIS (S. lentum recurrent lymphocytic meningitis)**
Meningitis

- recurrent spontaneous, short-lived, benign aseptic meningitis.
- proposed etiology - herpes simplex type 2: primary infection / reactivation in sacral dorsal root ganglion → seeding of subarachnoid space.
- first attack may appear at any age (childhood = late adult years).
- mild meningitis without associated neurologic abnormalities: temperature, signs of meningeal irritation.
- there may also be symptoms of sacral radiculitis.
- meningitis episodes last 2-5 days.
- CSF: pleocytosis (200 to several thousand mononuclears/mm^3), slight protein elevation, normal sugar, large fragile endothelial cells (in early phases of disease; their presence is variable and is not considered essential for diagnosis); positive PCR for HSV-2 DNA.
- rapid spontaneous recovery without specific therapy (no effective therapy for shortening attack or preventing fresh attacks; may benefit from prophylactic ACYCLOVIR?).
- between attacks, patient enjoys good health.
- episodes last for 3-5 years.

BIBLIOGRAPHY for ch. “Infections of Nervous System” → follow this LINK >>