Meningitis (s. Arachnoiditis, Leptomeningitis)

ETIOLOGY

Bacterial (purulent) meningitis

1. Predisposing host factors

2. Aspergillus (serous) meningitis

3. Meningitis (pseudomeningitis)

CLASSIFICATION

1. Acute meningitis

2. Subacute meningitis

3. Chronic meningitis

4. Recurrent meningitis

5. Pathology, Pathophysiology

6. Bacterial meningitis

7. Viral meningitis

8. Epidemiology

9. Clinical features

10. Complications

11. Treatment

12. Hemorrhagic meningitis

13. Prognosis

14. Specific features

15. Immunologic deficiencies

16. Neuropathological findings

17. Surgical complications

18. Chemoprophylaxis

19. Diagnosis

ETIOLOGY

- Bacterial (purulent) meningitis

1. Neisseria meningitidis

2. Streptococcus pneumoniae

3. Hemophilus influenzae

4. Enterobacteriaceae

5. Staphylococci

6. Other organisms

- Viral meningitis

7. Arboviruses

8. Parainfluenza viruses

9. Mycoplasma pneumoniae

10. Enteroviruses

11. Poliovirus

12. Other viruses

- Fungal meningitis

1. Candida

2. Cryptococcus

- Mycobacterial meningitis

1. Mycobacterium tuberculosis

2. Mycobacterium avium, Mycobacterium intracellulare

3. Nocardia

4. Other mycobacteria

- Parasitic meningitis

1. Toxoplasma gondii

2. Cryptococcus neoformans

3. Sarcoidosis

4. Other parasitic infections

- Neoplastic meningitis

1. Primary brain tumors

2. Metastatic tumors

3. Leptomeningeal carcinomatosis

4. Other neoplastic conditions

- Pediatric meningitis

1. Congenital defects (e.g., meningomyelocele)

2. Immunodeficiency

3. Postoperative infections

4. Other causes

- Pregnancy

1. Pre-eclampsia

2. Diabetes mellitus

3. Other conditions

- Endocarditis

1. Infective endocarditis

2. Bacterial endocarditis

3. Other infections

- Trauma

1. Skull fracture

2. Other injuries

- Neonatal meningitis

1. Congenital defects

2. Immunodeficiency

3. Other conditions

- AIDS

1. Opportunistic infections

2. Other conditions

ASEPTIC (SEROUS) MENINGITIS

- Meningitis (s. Arachnoiditis, Leptomeningitis)

A. Bacterial meningitis

1. Partially treated
Viral meningitis
Fungal meningitis
Meningitis in malignancy
Chemical meningitis

B. Viral meningitis (precise definition of etiologic agent is often impossible) — in order of frequency:
1. Enteroviruses (esp. echovirus, coxsackie virus 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. RHD
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* — may also occur in healthy individuals!
2. Coccioidioides immitis
3. Histoplasma capsulatum
4. Blastomyces 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 CARCINOMATOSES) or lymphoma (MENINGEAL LYMPHOMATOSES).
N.B. antileukemic drugs do not cross BBB!

F. Meninitis in connective tissue disorders
1) serum sickness
2) vasculitis, puerperalitis 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 > 7-28 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. Immunologic 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, cholesteatoma)
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 (lg and complement activity) are virtually absent; opsonic activity is often undetectable even in infected CSF (phagocytosis by encapsulated bacterial pathogens is inefficient) — bacteria commonly reach very high densities in CSF - use of bactericidal agents 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-a, IL-1, 8, platelet activating factor:
  1) cytotoxic cerebral edema
  2) increase in BBB permeability — vasogenic edema.
Meningitis

Inf 3

- large numbers of leukocytes in subarachnoid space contribute to purulent exudate and impair CSF absorption by arachnoid villi → COMMUNICATING HYDROCEPHALUS.
- pia-arachnoid becomes thickened → adhesions → interfere with CSF flow from 4th ventricle → OBSTRUCTIVE HYDROCEPHALUS.
- hydrocephalus causes transpendymal movement of fluid from ventricular system into brain parenchyma (interstitial edema).
- cerebral edema causes ICP↑.


Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD)
Neutrophilic exudate is seen involving meninges (at left), with prominent dilated vessels; there is edema and focal inflammation (extending downward via Virchow-Robin space) in cortex (at right).

- meningial 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).
- 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.
4. Meningeal irritation signs – nuchal rigidity, Kernig’s sign, Brudzinski’s sign, tense bulging fontanel.
- 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) hypotension
  4) subdural effusion / empyema (mass effect)
  5) antimicrobial agents (e.g. simupenem, penicillin).
- look for typical petechial-purpuric rash of meningococcemia (esp. in extremities).
similar rash may be seen in other forms of meningitis (e.g. enteroviruses, S. aureus, Acinetobacter sp., and, rarely, S. pneumoniae or H. influenzae). *rash resembling rubella

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, radiculopathies, 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/d 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 + hypotension c) inflammatory infiltration of arterial wall (vasculitis).
7. Cranial nerve palsy (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) - obtain 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:
  - for more detailed explanations → see p. D40 >>
  - opening pressure: moderately* (bacterial meningitis > viral meningitis).
  - cloudy & straw-colored (bacterial meningitis) or clear-cloudy & colorless (viral meningitis).
  - cell count* (esp. in untreated meningitis):
    1. 500-20,000/mm³ PMNs in bacterial meningitis;
    2. 5-1,000/mm³ mononuclears (may be PMNs at onset*) in viral meningitis (also in b/c, fungal**), Lyme, syphilis, toxoplasma, or chronic meningitis.
  - *esp. in enteroviral infections
  - **PMNs with Blastomyces 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).
  - LDH* (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 >>
    - stains - Gram stain (for all cases with PMNs), India ink stain (in cryptococcal meningitis), Zielh-Neelsen acid-fast stain (b/c).
    - antigen tests (PCR, latex particle agglutination, counterimmunoelectrophoresis, limulus lysate test*, immunofluorescence, etc).

*highly sensitive at detecting LPS (Gr. organisms).
MENINGITIS

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 cultures-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:

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) contrast enhancement of meninges is always abnormal except after recent neurosurgical procedure.
3) abnormal signal or density in CSF (high protein content or frank pus)
4) secondary brain edema.
5) 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).

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 pathogen!

7. Etiologic diagnosis in chronic meningitis may require meningeval 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%).
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. Neocortical right-sided periventricular lesion shows central low signal on T1 and high on T2 with peripheral enhancement. Enhancement of periventricular tissues (and 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.

**BACTERIAL MENINGITIS**

- **ANTIMICROBIAL THERAPY** (must be bactericidal in CSF* – i.e. maximum tolerated doses!)
- intravenously (intrathecal / intraventricular therapy is not effective).
- *titers of 10 times minimum bactericidal concentration are required to achieve CSF sterilization
- Crucial step is to initiate **ANTIMICROBIAL THERAPY** immediately!
- If you suspect *meningococcus*, give PENICILLIN before transporting to hospital!

Empiric therapy (all patients must be isolated for first 24 h of therapy):

- **NEONATE** (most likely group B streptococci, *E. coli, L. monocytogenes*) – combination:
  1) **AMPICILLIN**
  2) **GENTAMICIN** or **CEFOTAXIME** or **CEPHALOSPORIN**

- **INFANT 4-12 WEEKS** (*H. influenzae* and *Str. pneumoniae* join neonatal pathogens) – combination:
  1) **AMPICILLIN**
  2) **CEFOTAXIME** or **CEFTRIAXONE** or **CHLORAMPHENICOL**

- **OLDER INFANT < CHILD** (*N. meningitidis* joins pathogens) – combination:
  1) **VANCOMYCIN**
  2) **CEFTRIAXONE**

- **ADULT** (*S. pneumoniae, N. meningitidis* joins pathogens) – combination:
  1) **VANCOMYCIN**
  2) **CEFTRIAXONE** or **CEFOTAXIME**

* for neurosurgical / immunocompromised patient use **CEFTAZIDIME**
(Pseudomonas aeruginosa may be etiological agent).
- for adult > 50 yrs / immunocompromised / pregnant - add **AMPICILLIN** (Gr. aerobic bacilli; *L. monocytogenes* – resistant to cephalosporins); if severe penicillin allergy – **TMPSMX**
Therapy according to Gram stain:
Gr+ organisms → CEFTAXIME or CEFTRIAZOLE + VANCOMYCIN.
- If organisms are pleomorphic (Listeria sp.) add AMPICILLIN.
Gr- bacilli → TICARCEILLIN or CEFTAXIME + 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></td>
<td></td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>PENICILLIN G or AMPICILLIN + AMIKACIN or GENTAMICIN</td>
<td>PENICILLIN G or AMPICILLIN or CEFOTAXIME or CEFTRIAZOLE or CHLORAMPHENICOL + (at end of therapy) oral Rifampin for 2 d.*</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteric G+ bacilli (except Ps. aeruginosa)</td>
<td>CEFOTAXIME + AMIKACIN or GENTAMICIN</td>
<td>CEFOTAXIME or CEFTRIAZOLE + AMIKACIN or GENTAMICIN + VANCOMYCIN** + CEFTAXIME or CEFTRIAZOLE</td>
</tr>
<tr>
<td>Pneumococcus aeruginosus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>AMPICILLIN + AMIKACIN or GENTAMICIN</td>
<td>AMPICILLIN or TIP-SMX</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>CEFOTAXIME</td>
<td>CEFOTAXIME or CEFTRIAZOLE or CHLORAMPHENICOL (with AMPICILLIN)</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin-sensitive)</td>
<td>METHICILLIN</td>
<td>OXACILLIN</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin-resistant)</td>
<td>AMIKACIN</td>
<td>VANCOMYCIN</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>VANCOMYCIN ± RIFAMPIN</td>
<td></td>
</tr>
</tbody>
</table>

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

- ** PRIMARY FOCUS OF INFECTION ** should be eradicated (by surgery if necessary; e.g. persistent CSF fistulae 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 hours 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 penetration decreases by decreasing meningeal inflammation due to released bacterial components by bactericidal antibiotics).
- N. B. VANCYMYCIN's effect may be adversely affected (since meningeal inflammation improves VANCYMYCIN penetration into CSF). H. influenza's higher doses of VANCYMYCIN (15 mg/kg q6h) or intrathecal VANCYMYCIN.
- Course: then 4 days of antimicrobial therapy.
- First dose of DEXAMETHASONE 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. DEXAMETHASONE
- Of BACTERIAL MENINGITIS is strongly suspected - prevents neurological disability and death by decreasing meningeal inflammation (due to released bacterial components by bactericidal antibiotics).
- In adults with community-acquired bacterial meningitis, survival benefit from dexamethasone is obtained in acute phase of disease and remittes for as long as 20 years!
- For adults and children ≥ 2 months of age.
- Dose: 0.15 mg/kg q6h IV or 0.4–0.6 mg/kg q12h IV.
- Use H. Antagonist to avoid GI bleeding.
- 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).

3. OTHER MEASURES
- Treatment of dehydration, coagulopathy, seizures, raised ICP & cerebral edema.

Hyponatremia
- Majority of children are hyponatremic serum [Na⁺] < 135 mEq/L due to syndrome of inappropriate antidiuretic hormone secretion (SIADH).
- Time-honored treatment of SIADH was fluid restriction (but autoregulation of cerebral blood flow is lost - decrease in mean systemic arterial pressure = decrease in cerebral blood flow). X.
- Present recommendations - limit initial IV rate to 3/4 of normal maintenance requirements; IV fluid should be multielectrolyte solution containing 20 to 40 mEq/kg/day.
- If child has seizures as result of low serum sodium, infuse 3% NaCl (5 mEq/L per 1 hour).
- Once serum [Na⁺] > 135–140 mEq/L, fluids can be gradually increased.

EMPIRICAL THERAPY for CHRONIC MENINGITIS
- When all attempts at diagnosis fail:
  1. anti-mycobacterial agents
  2. AMPROMYCIN B
  3. GLOUCESTERTHELIS (for noninfectious inflammatory causes).

CHEMOPROPHYLAXIS
- For family members and other intacts of child with meningococcal or H influenza* infection.
  *only if there are children < 4 years between contacts when administer chemoprophylaxis to all contacts (except pregnant women), independent to their Hib vaccination status, because vaccination does not prevent nasopharyngeal colonization.
**Clinical Features:**
- insidious onset, vague nonspecific protracted progressive course*: moderate constitutional symptoms (low-grade fever, anorexia, weight loss, night sweats, malaise), unrelenting headache, \( \pm \) meningeal signs.
- *some patients present with acute meningeovasculitis (coma, ICP\(^+\)), seizures, focal neurological deficits
- later – CN palsies (esp. CN6, CN3), seizures, pleigias, alteration of mental status.
  - frequently, hydrocephalus develops.

**Differential:**
- CSF examination:
  1) pressure, CSF clear or cloudy (taurous-colored) with fibrin web formation on standing, 10-500 lymphocytes (in early stages may be > 80% PMN), protein \( \approx 100–500 \), glucose \( \approx 45 \).
  2) Ziehl-Neelsen acid-fast stain - usually negative (small numbers of organisms in CSF) – ependymal lining is covered with exudate or appears roughened (granular ependymitis).
  3) thick collar of fibrosis (thickened subependymal membranes) may form around optic nerves, cerebral peduncles, and basal surface of pons and midbrain.
- complications are initiated by hypersensitivity reaction (to tuberculosapon proteins) in subarachnoid space.
- proliferative changes in inflamed vessels of meninges (obliterative endarteritis) – thrombosis – infants (most frequently in basal ganglia).

**Specifc Features:**
- tuberculosis 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) – bacteremia & miliary dissemination – CNS entrance – miliary tubercles (sharply outlined round white nodules) in brain parenchyma and/or meningeal tissue.
- caseous foci (subependymal or near subarachnoid space) may rupture and discharge (esp. in presence of impaired host immunity) bacilli and tuberculous antigens into subarachnoid space → subacute/subacute/a chronic granulomatous meningitis (must common form of the infection in nervous system).
- gelatinous gray-white exudate tends to pool in basilar cisterns - surrounds cranial nerves (CN lesions), major blood vessels (vasculitis & ischemia); obstructive hydrocephalus may develop.
- CNS involvement is one of most preventable causes of mental retardation!
If suspicion is high, treatment should begin before bacteriologic proof:

1. 4 agents for first 2 months
   - rifampin + isoniazid + ethambutol + pyrazinamide
   - oral for at least 12 months
   - *longer than for pulmonary tuberculosis*

2. Corticosteroids indicated for all patients (esp. with ICP; cerebral edema, mental status, focal signs, spinal block, hydrocephalus) - for at least 3 weeks (then gradually decreased during next 3 weeks).

3. Shunting for hydrocephalus.

### Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Children (mg/kg/d)</th>
<th>Adult (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISONIAZID</td>
<td>10 mg/kg/d, up to 300 mg/d + 50 mg/d pyrazinamide</td>
<td></td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td>15 mg/kg/d</td>
<td>600 mg</td>
</tr>
<tr>
<td>PYRAZINAMIDE</td>
<td></td>
<td>30 mg/kg/d</td>
</tr>
<tr>
<td>ETHAMBUTOL</td>
<td>15-25 mg/kg/d</td>
<td></td>
</tr>
<tr>
<td>STREPTOMYCIN</td>
<td>20-40 mg/kg/d</td>
<td></td>
</tr>
<tr>
<td>RIFABUTIN</td>
<td>500 mg/d</td>
<td></td>
</tr>
</tbody>
</table>

### Tuberculosis Therapy

- Up to 15 mg/kg/d in HIV-infected patients
- *penetrate CNS with or without meningeval inflammation

- 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 or oval mass (localized tuberculous infection); always secondary to tuberculomas elsewhere in body (e.g. frequent finding in tuberculous meningitis, usually asymptomatic).
- May be no enhancement in MRI (A, B) and coronal T1 images (C), but may occur elsewhere (e.g. brain stem; mimics tumor).
- Calcification may occur in inactive lesions.
- Tuberculous meningitis - purulent meningitis, cerebral edema (occasionally with perivascular demyelination) or hemorrhagic leukoencephalopathy deep in white matter at distance from vascular abnormalities and puerulent exudate.

### Pott's Disease

- Vertebral tuberculosis (compression fractures, etc).

### Mycobacterium Avium, Mycobacterium Intra cellularare

- Clinically identical.
- CNS disease is result of hematogenous dissemination from respiratory or GI source of infection.
- Occurs primarily in patients with advanced HIV disease (< 50 CD4 cells/µl).
- Meningitis, meningeal or perineural, rhinencephalitis, brain abscess, or cranial neuropathies.

### Treatment

- At least four drug regimen:
  - clarithromycin and azithromycin have excellent activity!
  - rifampin + isoniazid + ethambutol + pyrazinamide

### Clinical presentation

- Subacute/chronic meningitis
- *history of exposure to agent is important

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- Fever, headache, mental status changes, mental status↓, focal signs, paralysis, seizures, blindness.

- Treatment is continued until cultures are negative for at least 12 months (will likely need to be continued for life of patient).

### Fungal Meningitis (General)

- cryptococcal meningitis
- Meningococcal meningitis
- Haemophilus influenzae meningitis

### Pathogenesis

- Hematogenous:
  - *history of exposure to agent is important

### Clinical presentation

- Subacute/chronic meningitis (resembles the meningitis) can be obscure even in healthy adult population (headache, low-grade fever, lassitude, weight loss).

### May be no enhancement in imaging

- Cryptococcus (spherule) in brain stem and basal ganglia - *tubular on coronal or sagittal imaging.

### Cryptococcosis (Coccidioides immitis)

- *tubular on coronal or sagittal imaging.

- May be no enhancement in imaging

- 10% cryptococcal meningitis cases develop cryptococcosis - dural Virchow-Robin spaces filled with cryptococcus organisms - rounded lesions (low intensity on T1-MRI and high intensity on T2-MRI; most commonly in basal ganglia (distribution of lenticulostriate arteries) but may occur elsewhere (e.g. brain stem); minimal or absent inflammation (non-enhancing, no edema).

- Tubular or coronal or sagittal imaging.

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- Tubular or coronal or sagittal imaging.
Cryptococcus neoformans – polysaccharide capsule visible by India ink preparation in CSF:

Treatment is complex (prolonged, often with multiple agents):

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

**Flucytosine** (azole that crosses BBB; less effective alternatives - **itraconazole, voriconazole**)

Treatement of **CRYPTOCOCCAL meningitis** – induction: **AMPHOTERICIN B + FLUCYTOSINE 25-35 mg/kg/d 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;
Spinal adhesive arachnoiditis. Dysfunction.

- handling is painful and child cannot be comforted.
- temperature instability (may be normal or even subnormal, esp. in preterms).
- in children, posttraumatic meningitis may be due to Haemophilus influenzae.
- meningitis rhinorrhea / otorrhea (detected by significant concentration of glucose in nasal or aural secretions) may be transient (H: monitoring course of radiodense-labeled albumin instilled nasally or CT after intrathecal injection of metrizamide).
- prophylactic: pneumococcal vaccine + l.

- usually begins as intracranial meningitis.
- meningitis involves caudal sac (rarely ascending above L3/4 disc)
- posttraumatic or obstetric meningitis s.
- CSF leaks caused by basilar skull fractures

- N.B. a) early meningitis (within 3 days of injury) - usually Str. pneumoniae → PENCILLIN G. or CEFOTAXIME.
- b) meningitis more than 3 days after trauma - often G. organisms → CEFOTAXIME or CEFTRIAXONE + NAPCILLIN (coverage of S. aureus).
- c) in children, posttraumatic meningitis may be due to Haemophilus influenzae.
- meningitis usually begins as intracranial meningitis.
- meningitis involves caudal sac (rarely ascending above L3/4 disc).
- lumbar disc surgery itself is commonly associated with meningitis.
- in the acute setting in neonates, meningitis is often caused by particular organisms (e.g., Haemophilus influenzae).
Meningitis

Spinal meningitis due to Lyme disease (T1 MRI of lumbar spine after IV gadolinium) - diffuse enhancement of outer surface of cord and spinal roots.

MOLLARET MENINGITIS (s. benign recurrent lymphocytic 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 /mm³), 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 >>