Meningitis (s. Arachnoiditis, Leptomeningitis)

ETIOLOGY

- Bacterial (purulent) meningitis
  - Predisposing host factors
  - Additional (herpetic) meningitis
    - Meningitis (pseudomeningitis)

CLASSIFICATION

- Acute meningitis
- Subacute meningitis
- Chronic meningitis
- Recurrent meningitis

PATHOLOGY, PATHOPHYSIOLOGY

- Bacterial meningitis
- Viral meningitis

EPIDEMIOLOGY

- Clinical features
- Acute meningitis
- Subacute/chronic meningitis
- Complications
- Bacterial meningitis
- Diagnosis
- Treatment

Meningitis - inflammation of meninges (inflammatory response is generally confined to arachnoid, subarachnoid space and pia - i.e. leptomeningitis)

ETIOLOGY

BACTERIAL (PURULENT) MENINGITIS

- Almost any pathogenic bacteria (most cases are hematogenous)

In order of frequency:

NEUROBACTERA

1. Listeria monocytogenes (2-10%)
2. Group B streptococci (Streptococcus agalactiae) (50%)
3. Neisseria meningitidis (50%)
4. Group D streptococci (enterococci) (5%)
5. Staphylococcus (rare)

CHILDREN (< 1 month ± 15 yrs):

1. Haemophilus influenzae (40-60%*) - nearly all cases in children < 6 yrs.
2. N. meningitidis (25-40%)
3. Streptococcus pneumoniae (10-20%)

* neonates:

- widespread use of Hib conjugate vaccine

ADULTS:

1. Streptococcus pneumoniae (30-50%): 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%): - major cause of EPIDEMIC* BACTERIAL MENINGITIS (in overcrowded conditions - military barracks, etc); most patients are adolescents and young adults.
3. Haemophilus influenzae (5-15%): - predominant organisms in CSF chills or subcutaneous Ommaya reservoirs.
4. Group B streptococci (1-10%): - most common in elderly.
5. Listeria monocytogenes (5%): - most common in immunocompromised 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.

PREDISPOISING HOST FACTORS

1) Mechanical disturbances (neurosurgical procedures, basal skull fractures).
2) Congenital defects (dermoid sinuses tract, meningomyelocle)
3) Immunologic deficiencies:
   - Allergic immunity (lymphoma, organ transplant recipients, corticosteroid therapy, AIDS) 
   - Intracellular bacteria (esp. TB, L. monocytogenes).
   - Humoral immunity (splenectomy, chronic lymphocytic leukemia, multiple myeloma).
   - Hodgkin's disease after radiotherapy or chemotheraphy 
   - Encapsulated bacteria (S. pneumoniae, H. influenzae type b, N. meningitidis)
   - Neutropenia 

ASEPTIC (SEROUS) MENINGITIS

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

A. Bacterial meningitis:
   - Partially treated
Viral meningitis
Fungal meningitis
Malignant meningitis
Chemical meningitis
Meningitis in other respects
Autonomic dysfunction
Acute febrile illness
Systemic inflammatory response syndrome
Chronic meningitis
Symptoms and signs persist
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

MENINGIS (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 fungus, 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 (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 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-α, IL-1, 8, platelet activating factor:
  1. cytotoxic cerebral edema
  2. increase in BBB permeability → vasogenic edema.

MENINGITIS
Fungal meningitis
- infection of subarachnoid space by *Candida* (MENINGAL CARCINOMATOSIS) or *Typhomyxa* (MENINGAL LYMPHOMATO).
N.B. antileukemic drugs do not induce meningitis! - most common viral meningitis before widespread MMR vaccine use!
- zoster virus

Acute meningitis is disease of young (< 40 yrs)!
- meningitis in immunosuppressed hosts, esp. *lymphoma & leukemia, AIDS*:
  1. *Cryptococcus neoformans* – may also occur in healthy individuals!
  2. *Coccidoides immitis*
  3. *Histoplasma capsulatum*
  4. *Blastomyces dermatitidis*
  5. *Candida albicans* – common in AIDS patients

Bacterial meningitis
- bacterial
  1. *Haemophilus influenzae* (occurs only in immuno suppressed patients), *Streptococcus pneumoniae*, *Moraxella catarrhalis*
  2. *Streptococcus pyogenes*
  3. *Staphylococcus aureus*
  4. *Escherichia coli*
  5. *Salmonella typhosa*
  6. *Pseudomonas aeruginosa*
  7. *Acinetobacter baumannii*
  8. *Klebsiella pneumoniae*

Malignant meningitis
- infiltration of subarachnoid space by *carcinoma* (MENINGAL CARCINOMATOSIS) or *lymphoma* (MENINGAL LYMPHOMATO).

Local anatomy
Immunologic defenses
- antibody response to *Treponema pallidum* is mandatory part of therapy!

Toxic shock syndrome
- *E. coli* 

Meningitis in other respects
- rupture of the wall of the dura mater

Meningitis in connective tissue disorders
- serum sickness
- vasculitis, priaparietritis nodosa
- SLE
- Behçet’s disease
- sarcoidosis.

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Arboviruses
- commonly encountered are: *yellow fever virus*, *Japanese encephalitis virus*, *West Nile virus*, *st. Louis encephalitis virus*, *encephalitis virus, Venezuelan equine encephalitis virus* (dengue, wintertine when mice migrate indoors)

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  8. *Klebsiella pneumoniae*
  9. *Morganella morganii*

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MENINGITIS

- 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↑.
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).

VIRAL MENINGITIS

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

EPIEDEMOLOGY

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).

4. Meningeal irritation signs - nuchal rigidity, Kerning'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% of 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) hypothermia
  4) subdural effusion / empyema (mass effect)
  5) antimicrobial agents (e.g. snipem, 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).
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 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!

   \[ \text{If mass lesion is consideration (local neurologic deficit, papilledema, seizures, evidence of head trauma) - contrast-enhanced CT or MRI first.} \]

   - 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 \( \rightarrow \) see p. D40 >>
   1) opening pressure (moderately! bacterial meningitis > viral meningitis).
   2) cloudy & straw-colored (bacterial meningitis) or clear-cloudy & colorless (viral meningitis).
   3) cell count (esp. in untreated meningitis):
      - 500-20,000/mm² PMNs in bacterial meningitis;
      - 5-1,000/mm² mononuclears (may be PMNs at onset*) in viral meningitis (also in tuberculous meningitis).
   - glucose:
     - most specific (esp. in bacterial, tuberculous, cryptococcal meningitis, normal in viral meningitis*).
     - *but I in mumps, lymphohypocytic choromeningitis virus meningitis;
   - 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 \( \rightarrow \) see p. D40 >>
   - (1) stains - Gram stain (for all cases with PMNs), India ink stain (in cryptococcal meningitis), Ziehl-Neelsen acid-fast stain (bc).
   - antigen tests (PCR, latex particle agglutination, counterimmunoelectrophoresis, limulus lysate test*, immunofluorescence, etc).
   - *highly sensitive at detecting LPS (Grs. 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 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.**

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**Neisseria meningitidis (Gr-diplococci) within neutrophils:**

India ink stain (budding organisms - cryptococci):
**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.

Neurotic right-sided periventricular lesion shows central low signal on T1 and high on T2 with peripheral enhancement. Enhancement of periventricular lesions (that mimics periventricular DQ) 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-limited - 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**

1. **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 G before transporting to hospital!

   Empiric therapy (all patients must be isolated for first 24 h of therapy): dosages → see p. Inf1

   NEONATE (most likely group B streptococci, E. coli, L. monocytogenes) – combination:
   1) AMPICILLIN
   2) CEPHALOSPORIN + AMICIN or TORMAMICIN

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

   OLDER INFANT + CHILD (N. meningitidis joins pathogens) – combination:
   1) VANCAMICIN
   2) CEPHALOSPORIN

   ADULT (S. pneumoniae, N. meningitidis) – combination:
   1) VANCAMICIN
   2) CEPHALOSPORIN

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

   3) for adult > 50 yrs / immunocompromised / pregnant - add AMPICILLIN (Gr- aerobic bacilli; L. monocytogenes – resistant to cephalosporins): if severe penicillin allergy – TROMSINX
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>Neisseria meningitidis</td>
<td>PENICILLIN G or AMPICILLIN + AMIKacin or GENTAMICIN</td>
<td>PENICILLIN G or AMPICILLIN or CEFOTAXIME or CEFTRIAXONE or CHLORAMPHENICOL. * (at end of therapy) oral RIFAMPIN for 2 d. *</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>CEFOTAXIME or CEFTRIAXONE</td>
<td>VANCOMYCIN ** + CEFOTAXIME or CEFTRIAXONE</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>CEFOTAXIME or AMIKacin or GENTAMICIN</td>
<td>CEFOTAXIME or CEFTRIAXONE or AMIKacin or GENTAMICIN</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>CEFAZIDIME or CIPROFLOXACIN or TICARICILLIN ± GENTAMICIN</td>
<td></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>AMPICILLIN + AMIKacin or GENTAMICIN</td>
<td>AMPICILLIN or TMD-SSMX</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>CEFOTAXIME</td>
<td>CEFOTAXIME or CEFTRIAXONE or CHLORAMPHENICOL (with AMPICILLIN)</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin-sensitive)</td>
<td>METHICILLIN</td>
<td>OXAICILLIN</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin-resistant)</td>
<td>VANCOMYCIN</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>VANCOMYCIN ± RIFAMPIN</td>
<td></td>
</tr>
</tbody>
</table>

*to eradicate nasopharyngeal carriage
**some pneumococci are resistant to penicillin, 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 – 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 unless dramatic response to therapy occurs, treatment should be stopped, and antibiotic coverage reassessed (corticosteroids for 1 day should be administered 20 min before first dose of antimicrobial; 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**
  - **CHRONIC MENINGITIS** is strongly suspected - prevents neurological disability and death by decreasing meningeval 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 remains 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: antagonists to avoid GI bleeding.
  - use IV: higher doses of dexamethasone (15 mg/kg q8h) or intrathecal VANCOMYCIN.
  - 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).

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

- **Hypotension**
  - majority of children are hypotensive (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). **present recommendations** - limit initial IVI rate to 3/4 of normal maintenance requirements; IV fluid should be multielectrolyte solution containing ½% normal saline and 20 to 40 mEq/L potassium in 5% dextrose.
    - if child has seizures as result of low serum sodium, infuse 3% NaCl (5 mEq/L over 1 hour).
    - once serum [Na+] increases > 135 to 140 mEq/L, fluids can be gradually increased.

- **CHEMOPROPHYLAXIS** - for family members and other intimate contacts of child with meningococcal or **H influenzae** infection.
  *only if there are children ≤ 4 years between contacts (then administer chemoprophylaxis to all contacts [except pregnant women], independent to their Hib vaccination status, because vaccination does not prevent nasopharyngeal colonization)
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 neurologic sequelae:** occur in 20-50% survivors: permanent hearing loss (10%), mental retardation*, cerebral palsy, permanent seizure disorders, behavioral problems.

*bacterial meningitis is one of the 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

**MYCOBACTERIAL TUBERCULOSIS**

**Epidemiology:**
- **Incidence:** 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).

**Etiopathophysiology:**
- Tuberculous meningitis is always secondary to tuberculosis elsewhere in body (usually in lungs, but may be in any organ).
- Progression of primary infection (children) or reactivation (adults) → bacilluria & miliary dissemination → CNS entrance → miliary tubercles (sharply outlined round white nodules) in brain parenchyma and/or meningeal tissue.
- Cerebral foci (subependymal and/or near subarachnoid space) may rupture and discharge (esp. in presence of impaired host immunity) bacilli and tuberculous antigens into subarachnoid space → subarachnoid/chronic granulomatous meningitis (most common form of the infection in nervous system).
- Gelatinous gray-white exudate tends to pool in basal cisterns - surrounds cranial nerves (CN lesions), major blood vessels (vasculitis & ischemia); obstructive hydrocephalus may develop.
- Ependymal lining is covered with exudate or appears roughened (GRANULAR EPENDYMITIS).
- Thick collar of fibrosis (rubious adhesive arachnoiditis) may form around optic nerves, cerebral peduncles, and basilar surface of pons and midbrain.
- Complications are initiated by hypersensitivity reaction (to tubercles proteins) in subarachnoid space.
- Proliferative changes in inflamed vessels of meninges (OLIGERATIVE ENDARTERITIS) → thrombosis → infarcts (most frequently in basal ganglia).

**Clinical Features:**
- Insidious onset, vague nonspecific protracted progressive course*; moderate constitutional symptoms (low-grade fever, anorexia, weight loss, night sweats, malaise), unrelenting headache, ± meningeal signs.
- *some patients present with acute meningococcal meningitis (coma, ICP)*, seizures, focal neurological deficits.
- Later – CN palsies (esp. CN6, CN3), seizures, plegias, alteration of mental status.
- Frequently, hydrocephalus develops.

**Diagnostics:**
- **CSF examination:**
  1) pressure
  2) clarity
  3) color
  4) pH
  5) protein
  6) glucose
  7) cell count
  8) culture
  9) latex test
  10) PCR
  11) ESR
  12) CT
  13) MRI
- **Blood cultures:**
  1) blood cultures
  2) bone marrow cultures
  3) CSF cultures
- **Radiologic examination:**
  1) plain x-ray
  2) CT
  3) MRI
- **Additional diagnostic tests:**
  1) tuberculin skin test
  2) focal neurological examination
  3) electroencephalography
  4) evoked potentials

**Treatment:**
- **Empirical antimicrobial therapy:**
  1) cephalosporins
  2) aminoglycosides
  3) fluoroquinolones
  4) clindamycin
  5) rifampin
- **Adjunctive therapy:**
  1) corticosteroids
  2) anticonvulsants
  3) antihypertensive agents
  4) CSF diversion

**Prognosis:**

- **Overall mortality:** ≤ 10%
- **Relapse rate:** 50% of treated cases
- **Favorable outcome:** in children under 5 years old
- **Unfavorable outcome:** in adults, immunocompromised patients, infants, and children over 5 years old

- **Incidence in different age groups:**
  1) neonates
  2) children
  3) adults

**Mortality:**

- **Neonates**
  1) perinatal
  2) nosocomial

- **Children**
  1) primary infection
  2) reactivation

- **Adults**
  1) primary infection
  2) reactivation

**Epidemiology:**

- **Incidence:** 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).

**Etiopathophysiology:**

- Tuberculous meningitis is always secondary to tuberculosis elsewhere in body (usually in lungs, but may be in any organ).
- Progression of primary infection (children) or reactivation (adults) → bacilluria & miliary dissemination → CNS entrance → miliary tubercles (sharply outlined round white nodules) in brain parenchyma and/or meningeal tissue.
- Cerebral foci (subependymal and/or near subarachnoid space) may rupture and discharge (esp. in presence of impaired host immunity) bacilli and tuberculous antigens into subarachnoid space → subarachnoid/chronic granulomatous meningitis (most common form of the infection in nervous system).
- Gelatinous gray-white exudate tends to pool in basal cisterns - surrounds cranial nerves (CN lesions), major blood vessels (vasculitis & ischemia); obstructive hydrocephalus may develop.
- Ependymal lining is covered with exudate or appears roughened (GRANULAR EPENDYMITIS).
- Thick collar of fibrosis (rubious adhesive arachnoiditis) may form around optic nerves, cerebral peduncles, and basilar surface of pons and midbrain.
- Complications are initiated by hypersensitivity reaction (to tubercles proteins) in subarachnoid space.
- Proliferative changes in inflamed vessels of meninges (OLIGERATIVE ENDARTERITIS) → thrombosis → infarcts (most frequently in basal ganglia).

**Clinical Features:**

- Insidious onset, vague nonspecific protracted progressive course*; moderate constitutional symptoms (low-grade fever, anorexia, weight loss, night sweats, malaise), unrelenting headache, ± meningeal signs.
- *some patients present with acute meningococcal meningitis (coma, ICP)*, seizures, focal neurological deficits.
- Later – CN palsies (esp. CN6, CN3), seizures, plegias, alteration of mental status.
- Frequently, hydrocephalus develops.

**Diagnostics:**

- **Empirical antimicrobial therapy:**
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- **Adults**
  1) primary infection
  2) reactivation
If suspicion is high, treatment should begin before bacteriologic proof: see p. 237 >>

1. 4 agents for first 2 months (ISONIAZID + RIFAMPIN + PYRIMETHAMINE + ETHAMBUTOL) → ISONIAZID + RIFAMPIN for at least 7-10 months (i.e. 9-12 months*; up to 24 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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Children</th>
<th>Adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISONIAZID</td>
<td>10 mg/kg/d* once daily</td>
<td>300 mg/d + 50 mg/d pyrazinamide</td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td>10 mg/kg/d*</td>
<td>600 mg/d</td>
</tr>
<tr>
<td>PYRIMETHAMINE</td>
<td>30 mg/kg/d</td>
<td></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></td>
<td>500 mg/d</td>
</tr>
</tbody>
</table>

Up to 15 mg/kg/d in HIV-infected patients

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

sequela occur in ≥ 25% patients who recover (facial weakness, intellectual disorganization, deafness, seizures, blindness, pleocytosis)

intracranial calcifications may appear after 2-3 years.

Intracerebral TUBERCULOMA - rounded, nodule-like intraparenchymal mass (localized tuberculous infection; always secondary to tuberculomas elsewhere in body (e.g. frequent hydrocephalus).

- tend to be superficially in brain (most characteristically adjacent to Sylvian fissure; brain stem and cerebellum are other favoured sites)
- central core of caseous necrosis surrounded by typically tuberculous granulomatous reaction.
- up to several centimeters in diameter → mass effect (mimics tumor).
- CT density as brain (or slightly denser) + little or no surrounding edema ← tuberculoma
- MRI: transverse T2-weighted (A, B) and coronal T1-weighted (C); minimal or absent inflammation (mimics tumor).
- treatment is less effective - mortality is higher (than in bacterial meningitis).

Tuberculomas are well-demarcated rounded lesions (up to several centimeters in diameter → mass effect) that enhance strongly on contrast-enhanced imaging (CT, MRI).

Intraventricular TUBERCULOMA - meningitis - intraparenchymal mass (localized tuberculous infection; always secondary to tuberculomas elsewhere in body (e.g. frequent hydrocephalus).

- occurs primarily in patients with advanced HIV disease (< 50 CD4⁺ cells/µl)
- meningitis, meningoencephalitis, rhombencephalitis, brain abscesses, or cranial neuropathies.

Treatment: at least four drug regimen:

1) CLARITHROMYCIN and AZITHROMYCIN have excellent activity!
2) ISONIAZID (600 mg/d) + PYRIMETHAMINE (25 mg/kg/d for 2 months then 15 mg/kg/d)
3) ETHAMBUTOL (0.75-1.0 g at least three times per week).
4) STREPTOMYCIN (300 mg/d) + AZITHROMYCIN (250 mg/d) + RIFABUTIN (300 mg/d).

alternatives regimen: AZITHROMYCIN (250 mg/d) + ETHAMBUTOL + STREPTOMYCIN

- 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

- Cryptococcus neoformans in brain stem and basal ganglia - associated with T2-MRI (A, B) and coronal T1-MRI (C); ganglia took like "fried brains"

Pathogenesis: inhalation* → hematogenous spread to CNS.

*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)
- reflects immune status of host (more severe immunological compromise - more rapid clinical onset)
- frequent hydrocephalus.

May be no enhancement in imaging.

- 10% Cryptococcal meningitis cases develop Cryptococcosis - dural, Virchow-Robin spaces filled with cryptococcos organisms - 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).
Cryptococcus neoformans – polysaccharide capsule visible by India ink preparation in CSF:

- Cryptococcus neoformans meningitis in AIDS patient (GMS stain) - organisms didn't even bother to make capsule; budding Cryptococcus cells have narrow base.
- Cryptococcus neoformans in lung – numerous organisms with large mucoid capsule (clear zone around faint round nucleus).

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).

Tentative treatment for **CRYPTOCOCCAL meningitis** – induction: **AMPHOTERICIN B** + **FLUCYTOSINE** 25-35 mg/kg q6h for 2 weeks → consolidation: **FLUCONAZOLE*** 400 mg/d for 8 weeks or until CSF is sterilized; in HIV-positive patients → lifelong suppressive therapy **FLUCONAZOLE** 200 mg/d.  

*the only “azole” that crosses BBB; less effective alternatives - **ITRACONAZOLE**, **VORICONAZOLE**

See p. 269 >>

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

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CANDIDA MENINGITIS
- see p. 311

NEONATAL MENINGITIS
- sterile
- risk factors: maternal infections (esp. urinary tract and uterus), obstetrical risk factors (prolonged rupture of membranes, birth trauma, prematurity, low birth weight, congenital anomalies, perinatal hypoxia / asphyxia, cardiorespiratory resuscitation).
- meningitis occurs in 25-50% neonatal sepsis cases!
- symptoms and signs are often subtle and nonspecific (e.g. in sepsis) - lethargy, seizures, irritability, poor feeding, vomiting, high-pitched crying, respiratory alterations, most appear toxic or moribund
- handling is painful and child cannot be comforted.
- temperature instability (may be normal or even subnormal, in pts. in pretrom)
- CSF: 25-75% will not have bacterial Buddin
- tense bulging fontanel is more reliable sign (but may be absent in dehydration).
- see p. 315

GERIATRIC MENINGITIS
- only pitying sign may be alteration of mental status.
- elderly patients 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 bactereemic seeding).

POSTTRAUMATIC MENINGITIS
Trauma (basilar fractures with CSF leak, penetrating head injuries, linear fractures through nasal sinuses or middle ear) → host defect in local anatomy → RECURRENT BACTERAL 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 → PENICILLIN G.
  b) meningitis more than 3 days after trauma - often Gr. organisms → CEFTAXIME
  c) in children, posttraumatic meningitis may be due to Haemophilus influenzae.
- CSF: rhinorrhea / otorrhea (detected by significant concentration of glucose in nasal or aural secretions) may be transient (H: monitoring course of radiodense-labelabcu albumin instilled radiographically or CT after intrathecal injection of metrizamide).
- prophylaxis: pneumococcal vaccine + long-term prophylactic penicillin (**) + surgical closure of CSF fistula.
- see p. 564

HOSPEDAL MENINGITIS
- temperature may be elevated for first few days after most cranborstones.
- if fever continues > 72 hours (in setting of good pulmonary toilet), aseptic 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).

SPINAL MENINGITIS (ARACHNOIDITIS)
- injury to central sheaths traverses 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 - atrophic (myelography performed with iophendylate (Myodil) - involves caudal sac (rarely ascending above L3/4 disc), lumbar disc surgery itself is rarely cause.
  b) trauma
  c) intradural infections - tuberculous, fungal and parasitic (esp. cysticercosis)
  d) spinal SAH
  e) intraspinal tumors (rarely)
  f) spinal sarcoidosis
- 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).
- see p. 564
- prophylactic antibiotics are not recommended in acute setting in CSF leaks caused by basilar skull fractures.

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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 >>

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Please visit website at www.NeurosurgeryResident.net