

Infections of Nervous System

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PATHOGENESIS

- CNS is normally sterile.
- parenchyma, coverings, and blood vessels of nervous system may be invaded by *virtually any pathogenic microorganism*.

Principal routes of entry:

- hematogenous spread** (bacteria, viruses) via septicemia, septic emboli - most common!
 - ordinarily through **arterial** circulation, but retrograde **venous** spread can occur (e.g. via anastomotic connections between veins of face and cerebral circulation).
 - most common sources: pneumonia, bronchiectases, bacterial endocarditis.
- direct implantation** (bacteria) - invariably traumatic (rarely – iatrogenic*); associated with congenital malformations (e.g. meningomyelocele).

*esp. LP, ventriculo-peritoneal shunts
- local extension** (bacteria) from established infection – **paranasal sinus** (most often frontal), **middle ear, tooth, surgical site** in cranium or spine (osteomyelitis → bone erosion → propagation into CNS).
- retrograde transport through PNS** (certain viruses - rabies, herpes simplex, poliovirus).

Infection becomes rapidly disseminated once organisms reach CSF.

- **CSF is area of impaired host defense** - lack of sufficient numbers of complement components and immunoglobulins for opsonization, contains no phagocytic cells; fluid medium impairs phagocytosis.

Damage to nervous tissue:

- 1) direct invasion by infectious agent
- 2) microbial toxins
- 3) destructive inflammatory / immune-mediated response - recently recognized as very important (even in bacterial meningitis).

Inflammatory reaction in confined intracranial space can cause **ICP**↑

CLASSIFICATION

- according to **major site of involvement**:

N.B. process frequently involves more than one of these structures (e.g. meningoencephalitis, encephalomyelitis)

1. **OSTEOMYELITIS** – inflammation of **bones**.
2. **MENINGITIS** – inflammation of **meninges**.
3. **ENCEPHALITIS** – **viral** invasion of **brain parenchyma**; often *diffuse*.
4. **CEREBRITIS** – *focal bacterial* invasion of **brain parenchyma**; no capsule or pus.
5. **MYELITIS** – inflammation of **spinal cord parenchyma**; no capsule or pus.
6. **ABSCESS** – *focal*, encapsulated, pus-containing cavity in **brain parenchyma** (rarely, in **spinal cord parenchyma**).
7. **EMPYEMA** – abscess in enclosed or potential **space**:
 - a) subdural
 - b) extradural
8. **GRANULOMA** – *focal*, more or less encapsulated, chronic inflammatory lesion without pus (e.g. sarcoidosis, syphilis, tuberculosis, fungi, larvae of intestinal parasites).

Infections of spine:

- 1) vertebral osteomyelitis/discitis
- 2) epidural abscess
- 3) subdural abscess*
- 4) meningitis
- 5) spinal cord abscess*

*exceedingly rare.

VIRUSES

Neuroinvasive - virus has ability to enter nervous system.

Neurotropic - virus infects nervous cells.

Neurovirulent - virus causes clinically recognizable neurologic symptoms.

ACUTE viral infections:

- a) **viral (aseptic) meningitis**
- b) **encephalitis**
- c) **myelitis**

DELAYED COMPLICATIONS of acute infection - **postinfectious polyneuritis**, **acute disseminated encephalomyelitis (ADEM)**, **acute cerebellar ataxia**.

LATENT infections with recurrences from time to time: **herpesviruses** (HSV, VZV).

SLOWLY PROGRESSIVE disorders (slow viral infections):

- a) **CONVENTIONAL viruses**:
 - 1) **subacute sclerosing panencephalitis (SSPE)** (measles virus)
 - 2) **progressive rubella panencephalitis (PRP)** (rubella virus)
 - 3) **progressive multifocal leukoencephalopathy (PML)** (JC virus)
 - 4) **human T-lymphotrophic virus (HTLV)-associated myelopathy (HAM) / tropical spastic paraparesis (TSP)** (HTLV-I)
 - 5) **acquired immunodeficiency syndrome (AIDS)** (HIV)
- b) **UNCONVENTIONAL transmissible spongiform encephalopathy agents (prions)**.

FUNGI

- **opportunistic** organisms – infect only **immunosuppressed** individuals.
(except few **pathogenic** fungi – *Histoplasma**, *Blastomyces**, *Coccidioides**, *Paracoccidioides*** – may infect **normal** hosts).
*endemic to some areas of North America
**endemic to some areas of Central-South America
- most fungi **invade brain** by **hematogenous dissemination** (but **direct extension** by *Mucor*).
- lungs / skin / hair are usual **primary sites**.

Cryptococcosis* is most common mycotic CNS infection!

*may be primary infection and occur in **normal** individuals!

- meningitis
- intraparenchymal abscess / granuloma
- vasculitis → thrombosis → infarction (often strikingly hemorrhagic) - *Mucor*, *Aspergillus*

PREDISPOSING FACTORS

1. **Recent infection** that may progress to meningitis (e.g. upper respiratory infection, pneumonia, otitis media leading to pneumococcal meningitis; mumps, chickenpox).
2. **Exposure to others with infectious illness** (e.g. meningococcus or *Haemophilus influenzae*).
3. **Recent travel** (e.g. mosquitoes → arbovirus encephalitis; Central America → cysticercosis).
4. **Occupation** (e.g. painter exposed to *Cryptococcus* in pigeon droppings)
5. **Underlying disease**:
 - 1) lymphoma, leukemia, other malignancy
 - 2) renal failure
 - 3) AIDS and other immunodeficiency states
 - 4) alcoholism
 - 5) diabetes
6. **Drugs** (chemotherapy, immunosuppressant, steroids)
7. **Recent head injury** (precedes 10% of pneumococcal meningitis), penetrating skull trauma.
8. **Recent neurosurgical procedure**.
9. **Recent insect bite** (e.g. Lyme disease, rickettsial infection).
10. History of **positive PPD**.

DIAGNOSIS

- **CT / MRI** is indicated in any patient with syndrome compatible with CNS infection!
- **CSF** is indicated in any patient (after exclusion of intracranial mass).
- **brain biopsy** (→ immunostaining techniques, electron microscopy, injection into susceptible animals and tissue culture cell lines) is still standard of diagnosis in some specific CNS infections.
- **CBC with differential** is nonspecific adjunct in diagnostic evaluation.
CBC may be normal in elderly or immunosuppressed patients!
- 2-3 **blood cultures** should be obtained from all patients (even when antimicrobial therapy has already been administered).
- in suspected **any viral CNS infection**, draw **serum specimen** acutely and save to compare with convalescent sera (3-5 weeks after onset of illness) – ≥ 4-fold rise in **IgG titers**?
- **search of infection source** – chest X-ray (!), echocardiography, cultures of other body fluids, bone scans.
- **serum** electrolytes, glucose*, urea nitrogen, creatinine.

*for interpretation of CSF glucose level.

TREATMENT

With exception of **viral meningitis**, all but **most chronic** CNS infections require **initial inpatient evaluation and treatment**:

1. Bed rest
2. Analgesics
3. IV antimicrobials
4. Fluid balance

ANTIBIOTICS

DRUG IV	NEONATES (0-7 days → 8-28 days)	CHILDREN	ADULTS
PENICILLIN G	100,000-150,000 U/kg/d (divided every 12 hr) → 150,000-200,000 U/kg/d (divided every 6-8 hr)	250,000-400,000 U/kg/d (divided every 4 hr)	20-24 million U/d* (divided every 4 hr)
AMPICILLIN	50-75 mg/kg q12h → 50-100 mg/kg q6-8h	50-100 mg/kg q6h	2 g q4h
METHICILLIN		50 mg/kg q6h	
OXACILLIN	50-75 mg/kg q12h → 50 mg/kg q6-8h	33 mg/kg q4h or 50 mg/kg q6h	2 g q4h
NAFCILLIN		33 mg/kg q4h	1.5-2 g q4h
TICARCILLIN	75-100 mg/kg q12h	75 mg/kg q6h	3 g q4h
GENTAMICIN	2.5 mg/kg q12h → q8h	2.5 mg/kg q8h	1.66 mg/kg q8h
AMIKACIN	7.5-10 mg/kg q12h → q8h	10 mg/kg q8-12h	7.5 mg/kg q12h
CEFOTAXIME	50 mg/kg q12h → 50 mg/kg q6-8h	50 mg/kg q6h	1.5-2 g q4h
CEFTRIAZONE	- (displaces bilirubin from albumin-binding sites)	40-50 mg/kg q12h	2-3 g q12h
CEFTAZIDIME	30 mg/kg q12h → q8h	40-50 mg/kg q8h	2 g q8h
VANCOMYCIN	15 mg/kg q12h → q8h	10 mg/kg q6h	500 mg q6h
CHLORAMPHENICOL	25 mg/kg q24h → q12h	20-25 mg/kg q6h	1 g q6h
METRONIDAZOLE		7.5 mg/kg q8h	500 mg q6h
oral RIFAMPIN		> 1 yr.: 10 mg/kg q12h < 1 yr.: 5 mg/kg q12h	600 mg q12h

*may produce convulsions if large concentrations are introduced into CSF

N.B. only **3rd generation cephalosporins** are used; CEFUROXIME enters CSF, but frequent treatment failures!

Antibiotic	Ratio CSF to serum
PENICILLIN G	2-5%
AMPICILLIN	15-20%
CEFOTAXIME	27-63%
NAFCILLIN	10-15%
VANCOMYCIN	10-15%

ANTIVIRALS

1. **GANCICLOVIR** 5 mg/kg q12h IVI over 1 h for minimum 14-21 days → 6 mg/kg/d for indefinite period.
2. **FOSCARNET** 40-60 mg/kg q8h (or 100 mg/kg q12h) IVI over 1 h for 14-21 days → maintenance 60-120 mg/kg/d IV for indefinite period.
3. **ACYCLOVIR**
 - a) 10 mg/kg (or 500 mg/m²) IVI q8h over 60 min (to minimize risk of renal dysfunction).
 - dilute to concentration ≤ 7 mg/mL (e.g. 70-kg person - 700 mg is diluted in 100 mL).
 - extravasation → local inflammation and phlebitis.
 - excellent CSF penetration.
 - acyclovir-resistant strains are problem only in AIDS patients.
 - b) 800 mg orally ×5/d.
4. **VALACYCLOVIR** 1.0 g orally ×3/d.
5. **FAMCICLOVIR** 500-750 mg orally ×3/d.

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