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:

a) **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.

b) **direct implantation** (bacteria) - invariably traumatic (rarely – iatrogenic*); associated with congenital malformations (e.g. meningomyelocele).

*esp. LP, ventriculo-peritoneal shunts

c) **local extension** (bacteria) from established infection – ***paranasal sinus*** (most often frontal), ***middle air***, ***tooth***, ***surgical site*** in cranium or spine (osteomyelitis → bone erosion → propagation into CNS).

d) **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!

a) meningitis
b) intraparenchymal abscess / granuloma
c) 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**. see p. Op120 >>
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
CEFTRIAXONE	- (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 R	15 mg/kg q12h → q8h	10 mg/kg q6h	Load 25-30 mg/kg (max. 3000 mg) ↓ 500-750 mg q6h (check trough level after 3rd dose)
CHLORAMPHENICOL	25 mg/kg q24h → q12h	20-25 mg/kg q6h	1 g q6h
METRONIDAZOLE		7.5 mg/kg q8h	500 mg q6h
SMX/TMP			15-20 mg/kg/d divided equally as q6h or q8h doses
oral RIFAMPIN		> 1 yr.: 10 mg/kg q12h < 1 yr.: 5 mg/kg ql2h	600 mg q12h

*may produce convulsions if large concentrations are introduced into CSF

R dose adjustment necessary for Creatinine Clearance < 60 mL/min

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/m^2) 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.

ANTIFUNGALS

CANDIDA

From 2016 guidelines:

What Is the Treatment for Central Nervous System Infections in Neonates?

Recommendations

45. For initial treatment, AmB deoxycholate, 1 mg/kg intravenous daily, is recommended *(strong recommendation; low-quality evidence).*
46. An alternative regimen is liposomal AmB, 5 mg/kg daily *(strong recommendation; low-quality evidence).*
47. The addition of flucytosine, 25 mg/kg 4 times daily, may be considered as salvage therapy in patients who have not had a clinical response to initial AmB therapy, but adverse effects are frequent *(weak recommendation; low-quality evidence).*
48. For step-down treatment after the patient has responded to initial treatment, fluconazole, 12 mg/kg daily, is recommended for isolates that are susceptible to fluconazole *(strong recommendation; low-quality evidence).*
49. Therapy should continue until all signs, symptoms, and cerebrospinal fluid (CSF) and radiological abnormalities, if present, have resolved *(strong recommendation; low-quality evidence).*
50. Infected central nervous system (CNS) devices, including ventriculostomy drains and shunts, should be removed if at all possible *(strong recommendation; low-quality evidence).*

XIII. What Is the Treatment for Central Nervous System Candidiasis?

Recommendations

92. For initial treatment, liposomal AmB, 5 mg/kg daily, with or without oral flucytosine, 25 mg/kg 4 times daily is recommended *(strong recommendation; low-quality evidence).*
93. For step-down therapy after the patient has responded to initial treatment, fluconazole, 400–800 mg (6–12 mg/kg) daily, is recommended *(strong recommendation; low-quality evidence).*
94. Therapy should continue until all signs and symptoms and CSF and radiological abnormalities have resolved *(strong recommendation; low-quality evidence).*
95. Infected CNS devices, including ventriculostomy drains, shunts, stimulators, prosthetic reconstructive devices, and biopolymer wafers that deliver chemotherapy should be removed if possible *(strong recommendation; low-quality evidence).*
96. For patients in whom a ventricular device cannot be removed, AmB deoxycholate could be administered through the device into the ventricle at a dosage ranging from 0.01 mg to 0.5 mg in 2 mL 5% dextrose in water *(weak recommendation; low-quality evidence).*

Related:

IX. Does the Isolation of *Candida* Species From the Respiratory Tract Require Antifungal Therapy?

Recommendation

58. Growth of *Candida* from respiratory secretions usually indicates colonization and rarely requires treatment with antifungal therapy *(strong recommendation; moderate-quality evidence).*

XIV. What Is the Treatment for Urinary Tract Infections Due to *Candida* Species?

What Is the Treatment for Asymptomatic Candiduria?

Recommendations

97. Elimination of predisposing factors, such as indwelling bladder catheters, is recommended whenever feasible *(strong recommendation; low-quality evidence).*
98. Treatment with antifungal agents is NOT recommended unless the patient belongs to a group at high risk for dissemination; high-risk patients include neutropenic patients, very low-birth-weight infants (<1500 g), and patients who will undergo urologic manipulation *(strong recommendation; low-quality evidence).*
99. Neutropenic patients and very low–birth-weight infants should be treated as recommended for candidemia (see sections III and VII) *(strong recommendation; low-quality evidence).*
100. Patients undergoing urologic procedures should be treated with oral fluconazole, 400 mg (6 mg/kg) daily, OR AmB deoxycholate, 0.3–0.6 mg/kg daily, for several days before and after the procedure *(strong recommendation; low-quality evidence).*

What Is the Treatment for Symptomatic Candida *Cystitis?*

Recommendations

101. For fluconazole-susceptible organisms, oral fluconazole, 200 mg (3 mg/kg) daily for 2 weeks is recommended *(strong recommendation; moderate-quality evidence).*
102. For fluconazole-resistant *C. glabrata*, AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days OR oral flucytosine, 25 mg/kg 4 times daily for 7–10 days is recommended *(strong recommendation; low-quality evidence).*
103. For *C. krusei*, AmB deoxycholate, 0.3–0.6 mg/kg daily, for 1–7 days is recommended *(strong recommendation; low-quality evidence).*
104. Removal of an indwelling bladder catheter, if feasible, is strongly recommended *(strong recommendation; low-quality evidence).*
105. AmB deoxycholate bladder irrigation, 50 mg/L sterile water daily for 5 days, may be useful for treatment of cystitis due to fluconazole-resistant species, such as *C. glabrata* and *C. krusei (weak recommendation; low-quality evidence).*

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