Infections of Nervous System

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) hemogenous spread (bacteria, viruses) via sepsisemia, septic emboli - most common! - ordinarily via arterial circulation, but retrograde venous spread can occur (e.g. via anastomotic connections between veins of face and cerebral circulation).
• most common sources: pneumonia, bronchiectasis, bacterial endocarditis.

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

• *esp. L.P. ventriculo-peritoneal shunts

c) local extension (bacteria) from established infection - parannual sinus (most often frontal), middle air, tooth, surgical site in cranium or spine (osteonmyelitis → 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 a reservoir of host defense - lack of sufficient numbers of complement components and immunoglobulins for opsonization, contains no phagocytic cells; fluid medium impairs impaired host defense rapidly.

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:

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. ARACHNOIDITIS - focal, encapsulated, pus-containing cavity in brain parenchyma (rarely, in spinal cord parenchyma).

7. EMPYEMA - abscesses 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, tuberculosi, fungi, larvae of intestinal parasites).

Infections of spine:

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

*exceedingly rare.

INFECTIOUS AGENTS

1. BACTERIA - cause acute and chronic infections of the nervous system.

2. VIRUSES - cause clinical acute and chronic infections of the nervous system.

3. PARASITES - cause clinical acute and chronic infections of the nervous system.

SLOWLY PROGRESSIVE DISEASES (sow viral to time):

a) CONVENTIONAL DISEASES:

1) subacute sclerosing panencephalitis (SSPE) (measles virus)
2) progressive multifocal leukoencephalopathy (PML) (JC virus)
3) human T-lymphotropic virus (HTLV)-associated myelopathy (HAM) / tropical spastic paraparesis (TSP) (HTLV-I)
4) acquired immunodeficiency syndrome (AIDS) (HIV)

b) UNCONVENTIONAL transmissible spongiform encephalopathy agents (prions).
**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. meningococcal or Haemophilus influenzae).
3. Recent travel (e.g. mosquitoes → arbovirus encephalitis; Central America → cisticercosis).
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, tickbiter 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 nonadjuvant 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 specimens acutely and save to compare with convalescent sera (3-5 weeks after onset of illness) (± 2-fold rise in IgG titters).
- search of infection source – chest X-ray (±), echocardiography, cultures of other body fluids, bone scans.
- serum electrolytes, glucose*, area nutrition, creatinine.

   *for interpretation of CSF glucose level.

**TREATMENT**

With exception of viral meningitis, all but most chronic CNS infections require initial empiric evaluation and treatment:
1. Bed rest
2. Analgesics
3. IV antimicrobials
4. Fluid balance

**ANTIBIOTICS**

<table>
<thead>
<tr>
<th>Drug IV</th>
<th>Neonates (0-7 days)</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>PENICILLIN G</td>
<td>100,000-350,000 U/kg/d (divided every 12 hr)</td>
<td>250,000-400,000 U/kg/d (divided every 4 hr)</td>
<td>20-24 million U/kg* (divided every 4 hr)</td>
</tr>
<tr>
<td>AMPICILLIN</td>
<td>50-75 mg/kg q6h</td>
<td>50-100 mg/kg q6h</td>
<td>2 g q6h</td>
</tr>
<tr>
<td>MECillin</td>
<td>50 mg/kg q6h</td>
<td>50 mg/kg q6h</td>
<td>2 g q6h</td>
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<tr>
<td>COACILLIN</td>
<td>75-100 mg/kg q24h</td>
<td>50-100 mg/kg q6h</td>
<td>2 g q6h</td>
</tr>
<tr>
<td>NITROCEF</td>
<td>7.5-15 mg/kg q12h</td>
<td>50 mg/kg q12h</td>
<td>2 g q12h</td>
</tr>
<tr>
<td>AMIKACIN</td>
<td>15 mg/kg q12h</td>
<td>50 mg/kg q12h</td>
<td>7.5 mg/kg q12h</td>
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<tr>
<td>CEFOTAXIME</td>
<td>25 mg/kg q12h</td>
<td>50 mg/kg q12h</td>
<td>1.5-2 g q12h</td>
</tr>
<tr>
<td>CEFTRIAZONE</td>
<td>30 mg/kg q12h</td>
<td>50 mg/kg q12h</td>
<td>2-3 g q12h</td>
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<tr>
<td>PENTAMETHYLDIAMINE</td>
<td>25 mg/kg q24h</td>
<td>40-50 mg/kg q12h</td>
<td>2 g q12h</td>
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<tr>
<td>TROMBUCUR</td>
<td>15 mg/kg q12h</td>
<td>10 mg/kg q6h</td>
<td>20-30 mg/kg (max. 3000 mg)</td>
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<tr>
<td>SMX/TMP</td>
<td>75 mg/kg q24h</td>
<td>750 mg/kg q24h</td>
<td>500 mg q24h</td>
</tr>
<tr>
<td>NATAMICIN</td>
<td>25 mg/kg q24h</td>
<td>50 mg/kg q12h</td>
<td>1 g q12h</td>
</tr>
</tbody>
</table>

* may produce convulsions if large concentrations are introduced into CSF

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

**ANAMNESIS**

- opportunistic – infect only immunosuppressed individuals.
- most fungi invade brain by hematogenous dissemination (but direct extension by Mucor).
- lungs / skin / hair are usual primary sites.

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

- Cryptococcus is most common mycotic CNS infection!

N.B. only 3rd generation cephalosporins are used; CEPCeX/mono enters CSF, but frequent treatment failures!
INFECTIONS OF NERVOUS SYSTEM (GENERAL)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Ratio CSF to serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>PENICILLIN G</td>
<td>2-5%</td>
</tr>
<tr>
<td>AMPICILLIN</td>
<td>15-20%</td>
</tr>
<tr>
<td>CEPHALAXIN</td>
<td>27-63%</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>10-15%</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>10-15%</td>
</tr>
</tbody>
</table>

**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)
   - Dilution 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 x5d.

4. **Valacyclovir**
   - 1.0 g orally x3d.

5. **Famciclovir**
   - 500-750 mg orally x3d.

**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 bio-polymer wares 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 Candidurias?

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/day 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/day, 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 >>