Encephalitis, meningitis, myelitis, blood-brain barrier

Bacterial meningitis
   Fever, headache, stiff neck, neurologic dysfunction, long term neurologic problems
Diagnosis – clinical and CSF analysis
Therapy – empiric antibiotic therapy
Pathogenesis
   Colonization of nasopharyngeal epithelium, penetration of epithelial barrier,
   antiphagocytic polysaccharide capsule, invasion of CSF, inflammatory and ischemic
   damage of neurons.

*Haemophilus influenzae* B
   Gram-negative coco-bacillus
   6 months – 2 years of age
   almost eliminated in US by polysaccharide-protein conjugate vaccine

*Streptococcus pneumoniae*
   Gram-positive diplococci
   6 months – 2 years of age, elderly
   Most common cause of bacterial meningitis
   Many capsular serotypes, polysaccharide-protein conjugate, and polysaccharide-only
   vaccine

*Neisseria meningitidis*
   Gram-negative diplococcus
   Meningitis and sepsis
   Secretes endotoxin
   Epidemiology
      6 months – 2 years of age
      14-20 years – significant mortality
      School and community epidemics
      Major epidemics in sub-Saharan Africa
   Polysaccharide-protein conjugate vaccines protective against all serotypes except type B

*Streptococcus agalactiae* (Group B *Streptococcus*)
   Major cause of neonatal meningitis and sepsis
   Gram-positive cocci in chains
   Virulent capsular type is poorly immunogenic
   Early and late onset disease
   Prevention by screening pregnant women and antibiotic therapy at delivery
Poliomyelitis
  + sense ssRNA non-enveloped virus
  rapidly shuts off host cell mRNA translation, kills infected cells
Infection acquired by fecal-oral transmission, usually asymptomatic.
Symptoms include meningitis, paralysis varying from mild to extreme, and death

Pathogenesis
  Replicates in intestinal epithelium without causing symptoms.
  If viremia occurs, symptoms result.
  Penetration of blood brain barrier, infection of neurons. Damage results from death of infected neurons, inflammatory damage to uninfected neurons.

Diagnosis – clinical, serology, viral culture

No specific antiviral therapy

Prevention
  Inactivated and live attenuated vaccines.
  Vaccine-derived virulent strains.
  Disease “almost” eradicated.
  Three countries with endemic wild virus cases plus small numbers of vaccine-derived cases.
Nervous System Infections

- Anatomy
- Bacterial Meningitis
  - Streptococcus pneumoniae
  - Neisseria meningitidis
  - Haemophilus influenzae
  - Neonatal meningitis
    - Group B Streptococcus (S. agalactiae)
    - E.coli K1
  - Listeria monocytogenes
  - Polio

Nervous System Infections

- Bacterial Meningitis
  - Encephalitis
    - Inflammation of brain tissue (neurons, glial cells)
  - Meningitis
    - Inflammation of the meninges (membranes surrounding the brain and spinal cord)
  - Myelitis
    - Inflammation of the spinal cord (neurons and glial cells)
  - Meningoencephalitis, encephalomyelitis
  - Blood-brain barrier
    - Blood vessels in the brain are relatively impermeable to passage of proteins, microscopic particles, and large hydrophilic molecules, even during inflammation

Bacterial Meningitis

- The disease
  - Acute onset (few hours) of fever, headache, stiff neck, irritability, neurologic dysfunction
  - May follow several days of cold-like symptoms
  - Frequently rapidly progressive and fatal
  - Survivors frequently show long term neurological complications
    - deafness, learning disabilities, developmental delay
- Diagnosis
  - Clinical diagnosis – observation of signs and symptoms
  - Analysis of cerebrospinal fluid
    - Lumbar puncture
    - Microscopic analysis including Gram stain
    - Culture

Bacterial Meningitis

- Therapy
  - Antibiotics
    - Empiric, given upon suspicion of bacterial meningitis, may be changed depending on culture results
  - Dexamethasone (anti-inflammatory drug, inhibits recruitment of neutrophils, production of inflammatory cytokines)
    - limits continuing damage from inflammatory response to bacterial products released by antibiotic killing

Bacterial Meningitis

- Pathogenesis
  - Colonization of the nasopharyngeal respiratory epithelium
  - Invasion of the epithelial barrier
    - Bacterial binding to receptors that are naturally internalized
    - Bacterial inhibition of cellular tight junction function
  - Avoidance of phagocytosis and establishment of bacteremia
  - Anti-phagocytic polysaccharide capsule
  - Invasion of cerebrospinal fluid from blood vessels in the choroid plexus (where CSF is produced)

Bacterial Meningitis

- Pathogenesis (cont.)
  - Invasion of cerebrospinal fluid from blood vessels in the choroid plexus (where CSF is produced)
    - Replication in CSF and induction of inflammatory response
    - Recruitment of neutrophils, but no phagocytosis
      - Very low levels of complement in CSF, even during inflammation
    - Anti-phagocytic polysaccharide capsule
    - Production of reactive oxygen and nitrogen species
      - Diffusion into brain tissue, damage to neurons and glial cells, induction of apoptosis in these cells
    - Cerebral blood circulation disturbances
      - Ischemia (insufficient oxygen supply to tissue)
**Bacterial Meningitis**

- *Haemophilus influenzae* B
  - Prior to the introduction of a polysaccharide-protein conjugate vaccine, this was the most common cause of meningitis
  - Meningitis in infants 6 months – 2 years of age
  - Gram-negative coccobacillus
  - Single capsular serotype (B) in invasive strains
  - Pneumonia, arthritis, epiglottitis
  - Non-encapsulated strains are members of normal pharyngeal flora
  - otitis media, sinusitis, chronic pneumonia in elderly
  - Vaccine protects against invasive disease, not otitis, sinusitis, chronic pneumonia in elderly

- *Neisseria meningitidis*
  - Gram-negative diplococcus
  - 5 serotypes of antiphagocytic polysaccharide capsule
  - Invasive meningococcal disease includes meningitis and sepsis (≈50:50)
  - Bacterial cells "secrete" endotoxin, may contribute to severity of sepsis
  - Disease can be rapidly progressive

- *Streptococcus pneumoniae*
  - Currently the most common cause of meningitis
  - Meningitis in infants 6 months – 2 years of age
  - Meningitis in adults with immunocompromising conditions and >65 years old
  - Gram-positive diplococcus
  - Many capsular serotypes
  - Acute pneumonia, sepsis, otitis media, sinusitis
  - Multi-valent polysaccharide-protein conjugate vaccine protects against invasive disease, AND otitis, sinusitis
  - Most cases presently caused by serotypes not included in vaccine
  - Multi-valent polysaccharide-only vaccine given to adults >65

- *Neisseria meningitidis*
  - Epidemiology
    - 6 months – 2 years (second to *S. pneumoniae*)
    - 14 – 20 years (leading cause)
    - significant mortality
  - Epidemic disease
    - School and community-level epidemics in U.S. and Europe
    - ~500 cases per year in U.S., declining
    - Major epidemics in sub-Saharan Africa
      - 1996 – 250,000 cases; 25,000 deaths
      - 2009 – 78,000 cases; 4,000 deaths

- *Neisseria meningitidis*
  - Prevention
    - Antibiotic prophylaxis of contacts
    - Polysaccharide-protein conjugate vaccine
      - Protects against 4 (out of 5) capsular serotypes
      - Does NOT protect against type B (~1/3 of cases in U.S.)
      - Administered at age 10 with booster at age 16
  - MenAfriVac
    - Low cost (<$.50 per dose) monovalent (type A) polysaccharide-protein conjugate vaccine developed by PATH and Gates Foundation for Africa
    - Campaign started in Sept. 2010 and by the end of 2012, 120,000,000 doses will have been administered.
    - Type A W. meningitidis appears to have been eradicated in the vaccine area
  - Outer membrane protein vaccine for type B strains
    - Recommended for approval in European Union, Nov. 15, 2012

- *Streptococcus agalactiae* – Group B Streptococcus (GBS)
  - Major cause of neonatal meningitis
  - Gram-positive cocci in chains
  - Normal intestinal flora, vaginal colonization common
  - Capsular polysaccharide type III most frequently associated with neonatal disease
    - Poorly immunogenic because of similarity to host antigens
  - Early onset disease – acquired at birth
    - Apparent at birth or in first few days of life
    - Severe pneumonia, sepsis, meningitis
    - Frequently fatal
  - Late onset disease – acquired from mother (nursing) or other contacts
    - 1 month of age (1 week – 3 months)
    - Bacteremia, meningitis
Bacterial Meningitis

- Streptococcus agalactiae – Group B Streptococcus (GBS) (cont.)
  - Diagnosis
    - Clinical diagnosis difficult in young infants
    - Lethargic, refuse to feed, high-pitched crying, seizures
  - Therapy
    - Antibiotics without dexamethasone
  - Prevention
    - Universal screening for rectal and vaginal GBS colonization at 35-37 weeks gestation
    - For GBS-positive women, administration of antibiotics during labor

Poliovirus

- Poliovirus
  - Small positive-sense ssRNA non-enveloped virus
  - Picornavirus family, genus Enterovirus
  - Enteroviruses replicate in the intestine, but cause disease when they spread to other sites
- The disease – poliomyelitis, polio
  - Acquired by fecal-oral transmission
  - Infants < 6 months are infected but protected from disease by maternal antibody
  - This infection stimulates active life-long immunity
- ~90% of infections are very mild or inapparent
- ~8-9% of infections are meningitis
- Fever, mild meningeal symptoms for a few days, complete recovery
- <2% of infections result in paralysis
- Ranges from mild paralysis of legs, to severe paralysis of arms and legs with atrophy of limbs, most severe form affects respiratory muscles.

Paralytic poliomyelitis

- Paralytic poliomyelitis
  - Paralysis most severe within a few days, then partial recovery begins and proceeds for up to 6 months
  - Post-polio syndrome
    - 30-40 years after infection: fatigue, pain, weakness
    - Thought to involve motor neuron failure from over-use rather than reactivation of infection

Poliomyelitis

- Diagnosis
  - Clinical observation
  - Serology
    - Isolation of virus from CSF and culture in tissue culture
    - Sequence analysis of viral genome important to differentiate vaccine-derived strains from wild poliovirus

- Therapy
  - No specific antiviral therapy

Poliomyelitis

- Prevention
  - Vaccines
    - Oral Polio Vaccine (OPV): live attenuated vaccine
    - Inactivated Polio Vaccine (IPV): administered by injection
    - IPV (1955)
      - Protects against paralytic polio, but has no effect on intestinal infection and transmission
    - OPV (1962)
      - Infects intestine, induces mucosal and systemic immunity
      - Prevents subsequent intestinal infection
      - Can be transmitted via fecal-oral route; provide protection to contacts of immunized individuals
      - Can mutate to virulent form and recombine with other enteroviruses if allowed to circulate over long periods in populations with poor vaccine coverage (40 cases in 2012 vs. ~193 cases of wild poliovirus)
Epidemiology and Eradication of Polio

• Epidemics of paralytic polio began in Europe and the U.S. at the end of the 19th century.
  • Improved sanitation delayed initial infection of children beyond the period of protection against invasive disease by maternal antibody
  • U.S. – 1952
    • 58,000 cases; 21,000 paralyzed; 3,000 deaths

• 1988 – World Health Organization began campaign to eradicate polio
  • ~350,000 cases annually at that time

• 2012 – ~200 cases to date (+40 vaccine-derived cases)
  • Wild poliovirus is endemic in only three countries: Nigeria, Pakistan, Afghanistan

Eradication is being achieved by

• Intensive surveillance for cases of polio
• General and targeted immunization campaigns

• Cessation of OPV will be implemented after eradication to prevent emergence of of vaccine-derived virulent poliovirus