Diphtheria, Tetanus and Pertussis

Diphtheria, Tetanus and Pertussis Diseases and Associated Vaccines

Corynebacterium diphtheriae

- Aerobic gram-positive bacillus
- Toxin production occurs only when C. diphtheriae infected by virus (phage) carrying tox gene
- If isolated, must be distinguished from normal diphtheroid
- Toxoid developed in 1920s
Diphtheria Clinical Features

- Incubation period 2-5 days (range, 1-10 days)
- May involve any mucous membrane
- Classified based on site of infection
  - anterior nasal
  - pharyngeal and tonsillar
  - laryngeal
  - cutaneous
  - ocular
  - genital

Pharyngeal and Tonsillar Diphtheria

- Insidious onset
- Exudate spreads within 2-3 days and may form adherent membrane
- Membrane may cause respiratory obstruction
- Pseudomembrane: fibrin, bacteria, and inflammatory cells, no lipid
- Fever usually not high but patient appears toxic
Tonsillar Diphtheria

10 y/o boy with severe diphtheria
- conjunctivitis
- pharyngeal membrane
- bull neck
- severe myocarditis
- all vaccines contraindicated
Diphtheria - United States, 1940-2005

Year

Diphtheria - United States, 1980-2005

Year
Diphtheria Complications

- Most attributable to toxin
- Severity generally related to extent of local disease
- Most common complications are myocarditis and neuritis
- Death occurs in 5%-10% for respiratory disease

Diphtheria Epidemiology

- Reservoir: Human carriers
  - Usually asymptomatic
- Transmission: Respiratory, aerosols
  - Skin lesions
- Temporal pattern: Winter and spring
- Communicability: Up to several weeks without antibiotics
Diphtheria vaccine

- Detoxified bacterial, protein toxin
- Injectable, IM administration
- Toxigenic *Corynebacterium diphtheriae* (infected with $\beta$ phage)
- Produced in horses (old)
- First used in the U.S. in 1891
- Used only for treatment of diphtheria
- Neutralizes only unbound toxin
- Lifetime of Ab: 15 days – 3 weeks, wait 3-4 weeks before giving toxoid. Only given once.

Manufacturing Process

- Toxigenic strain of *C. diphtheriae* grown in Fenton medium with a bovine extract
- After suitable growth, toxin purified from cells by centrifugation
- Toxoided by incubation with formaldehyde for several weeks
- Concentrated with ultrafiltration
- Purified by precipitation, dialysis and sterile filtered
- Adsorbed onto aluminum hydroxide, Al(OH)$_3$
Routine DTaP Primary Vaccination Schedule

<table>
<thead>
<tr>
<th>Dose</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary 1</td>
<td>2 months</td>
</tr>
<tr>
<td>Primary 2</td>
<td>4 months</td>
</tr>
<tr>
<td>Primary 3</td>
<td>6 months</td>
</tr>
<tr>
<td>Primary 4</td>
<td>15-18 months</td>
</tr>
<tr>
<td></td>
<td>4-6 yrs</td>
</tr>
<tr>
<td></td>
<td>11-12 yrs</td>
</tr>
<tr>
<td></td>
<td>Every 10 yrs</td>
</tr>
</tbody>
</table>

Diphtheria Toxoids Adverse Reactions

- Local reactions (erythema, induration)
- Exaggerated local reactions (Arthus-type)
- Fever and systemic symptoms not common
- Severe systemic reactions rare
Tetanus

- First described by Hippocrates
- Etiology discovered in 1884 by Carle and Rattone
- Passive immunization used for treatment and prophylaxis during World War I
- Tetanus toxoid first widely used during World War II
**Clostridium tetani**

- Anaerobic gram-positive, spore-forming bacteria
- Spores found in soil, animal feces; may persist for months to years
- Multiple toxins produced with growth of bacteria
- Tetanospasmin estimated human lethal dose = 2.5 ng/kg
Tetanus Pathogenesis

- Anaerobic conditions allow germination of spores and production of toxins
- Toxin binds in central nervous system
- Interferes with neurotransmitter release to block inhibitor impulses
- Leads to unopposed muscle contraction and spasm

Tetanus Clinical Features

- Incubation period; 8 days (range, 3-21 days)
- Generalized tetanus: descending symptoms of trismus (lockjaw), difficulty swallowing, muscle rigidity, spasms
- Spasms continue for 3-4 weeks; complete recovery may take months
- Fatality rate ~90% w/o treatment
  ~30% w/ treatment
Neonatal Tetanus

- Generalized tetanus in newborn infant
- Infant born without protective passive immunity
- Estimated >215,000 deaths worldwide in 1998

Complications
- Laryngospasm
- Fractures
- Hypertension
- Nosocomial infections
- Pulmonary embolism
- Aspiration pneumonia
- Death

>270,000 cases worldwide per year
### Tetanus Epidemiology

- **Reservoir**
  - Soil and intestine of animals and humans
- **Transmission**
  - Contaminated wounds
  - Tissue injury
- **Temporal pattern**
  - Peak in summer or wet season
- **Communicability**
  - Not contagious

### Tetanus toxins

- **Tetanolysin** - possible role in establishing infection at inoculation site
- **Tetanospasm**
  - Accumulates intracellularly during log-phase growth
  - Released into medium upon autolysis
  - Minimum human lethal dose ~ 2.5 ng/kg
Tetanus disease

- Tetanospasms
  - localized - spasm of muscles close to site of injection; weeks to months duration; rare but may precede generalized symptoms
  - generalized - 80% of cases
- Complications of the spasms:
  - fractures of the long bones and vertebrae
  - asphyxia from glottic obstruction

Nervous system effects

- Toxin travels up nerve endings by intra-axonal transport
- Gains entry to neuromuscular junctions by binding to gangliosides
- Interferes with release of neurotransmitters from presynaptic inhibitory fibers
- Excitatory reflexes multiply unchecked, causing spasms
Tetanus Transmission

- Not a communicable disease
- The only vaccine-preventable infection that is not communicable
- Disease acquired through exposure to bacterial spores in the environment
  - inoculation of bacterial spores into body by puncture or deep cut

Tetanus—United States, 1947-2005
Manufacturing Process

- Growth of *C. tetani* in modified Latham broth in fermenters
- Harvest extracellular toxin by filtration
- Purify
- Detoxify with formaldehyde for ~3 weeks
- Adsorb with Alum adjuvant
- Diafiltration

Tetanus Toxoid

- Formalin-inactivated tetanus toxin
- Schedule Three or four doses + booster
  
  Booster every 10 years

- Efficacy  Approximately 100%
- Duration  Approximately 10 years
- Should be administered with diphtheria toxoid as DTaP, DT, Td, or Tdap
Pertussis (Whooping Cough)

- Highly contagious respiratory infection caused by *Bordetella pertussis*
- Outbreaks first described in 16th century
- *Bordetella pertussis* isolated in 1906
- Estimated 294,000 deaths worldwide in 2002
- Primarily a toxin-mediated disease

**Bordetella pertussis**

- Fastidious gram-negative bacteria
- Antigenic and biologically active components:
  - pertussis toxin (PT)
  - filamentous hemagglutinin (FHA)
  - agglutinogens
  - adenylate cyclase
  - pertactin
  - tracheal cytotoxin
**Pertussis Pathogenesis**

- B. pertussis binds to and multiplies on ciliated cells (respiratory mucosa). The infection is not systemic.
- Inflammation occurs which interferes with clearance of pulmonary secretions.
- B. pertussis binds via at least 2 adhesion proteins to the ciliated cells:
  - Filamentous hemagglutinin
  - Pertussis toxin (Ptx, A5B exotoxin)
- Ptx is also released into the extracellular fluid and can affect host cells.

**Pertussis Clinical Features**

- Incubation period 5-10 days (range 4-21 days)
- Insidious onset, similar to minor upper respiratory infection with nonspecific cough
- Fever usually minimal throughout course of illness
- Catarrhal stage 1-2 weeks
- Paroxysmal cough stage 1-6 weeks
- Convalescence Weeks to months
## Pertussis Epidemiology

- **Reservoir**: Human  
  - Adolescents and adults
- **Transmission**: Respiratory droplets
- **Communicability**:  
  - Maximum in catarrhal stage  
  - Secondary attack rate up to 80%

## Pertussis Among Adolescents and Adults

- Disease often milder than in infants and children
- Infection may be asymptomatic, or may present as classic pertussis
- Persons with mild disease may transmit the infection
- Older persons often source of infection for children
# Pertussis Complications*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>4.9</td>
</tr>
<tr>
<td>Seizures</td>
<td>0.7</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0.1</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>16</td>
</tr>
<tr>
<td>Death</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Cases reported to CDC 2001-2003 (N=28,998)

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# Pertussis Complications by Age

*Cases reported to CDC 1997-2000 (N=28,187)
Pertussis (vaccines)

• Killed Whole cell -
  – old, not licensed in U.S. or Europe
  – still used in developing countries
  – relatively cheap
• Acellular (aP) -
  – currently licensed in U.S., Japan and Europe
  – some are recombinant
  – expensive

Pertussis-containing Vaccines

• DTaP (pediatric)
  – approved for children 6 weeks through 6 years (to age 7 years)
  – contains same amount of diphtheria and tetanus toxoid as pediatric DT
• Tdap (adolescent and adult)
  – approved for persons 10-18 years (Boostrix) and 11-64 years (Adacel)
  – contains lesser amount of diphtheria toxoid and acellular pertussis antigen than DTaP
Interchangeability of Different Brands of DTaP Vaccine

- Whenever feasible, the same DTaP vaccine should be used for all doses of the series
- Limited data suggest that “mix and match” DTaP schedules do not adversely affect safety and immunogenicity
- If vaccine used for earlier doses is not known or not available, any brand may be used to complete the series

DTaP Adverse Reactions

- Local reactions 20%-40% (pain, redness, swelling)
- Temp of 101°F 3%-5% or higher
- More severe adverse reactions not common
- Local reactions more common following 4th and 5th doses
DTaP Contraindications

- Severe allergic reaction to vaccine component or following a prior dose
- Encephalopathy not due to another identifiable cause occurring within 7 days after vaccination

DTaP Precautions*

- Moderate or severe acute illness
- Temperature ≥105°F (40.5°C) or higher within 48 hours with no other identifiable cause
- Collapse or shock-like state (hypotonic hypo responsive episode) within 48 hours
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours
- Convulsions with or without fever occurring within 3 days

*may consider use in outbreaks
# DTaP Vaccine Formulations

<table>
<thead>
<tr>
<th>Component, per 0.5 mL dose</th>
<th>GSK Infanrix, Pediatrix</th>
<th>AP Inc (sanofi pasteur) Tripedia</th>
<th>AP LTD (sanofi pasteur) Daptacel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria Toxoid</td>
<td>25 LF</td>
<td>6.7 LF</td>
<td>15 LF</td>
</tr>
<tr>
<td>Tetanus Toxoid</td>
<td>10 LF</td>
<td>5 LF</td>
<td>5 LF</td>
</tr>
<tr>
<td>PT, inactivated</td>
<td>25 µg</td>
<td>23.4 µg</td>
<td>10 µg</td>
</tr>
<tr>
<td>FHA, inactivated</td>
<td>25 µg</td>
<td>23.4 µg</td>
<td>5 µg</td>
</tr>
<tr>
<td>PRN (69kD OMP)</td>
<td>8 µg</td>
<td></td>
<td>3 µg</td>
</tr>
<tr>
<td>Fimbriae 2</td>
<td>0</td>
<td>0</td>
<td>5 µg</td>
</tr>
<tr>
<td>Fimbriae 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-phenoxycetanol (PE), preservative NaCl</td>
<td>2.5 mg</td>
<td>0</td>
<td>0.6%</td>
</tr>
<tr>
<td>Aluminum adjuvant</td>
<td>&lt;0.625 mg</td>
<td>&lt;0.17 mg</td>
<td>0.33 mg</td>
</tr>
<tr>
<td>Formaldehyde, residual</td>
<td>100 µg</td>
<td>&lt;100 µg</td>
<td>&lt; 0.02%</td>
</tr>
<tr>
<td>Glutaraldehyde, residual</td>
<td></td>
<td></td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>Polysorbate 80 (Tween 80)</td>
<td>100 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thimerosal, preservative</td>
<td>0</td>
<td>Trace (single -dose)</td>
<td>25 µg/dose (multi -vial)</td>
</tr>
</tbody>
</table>