Clinical Impressions: Diphtheria, Pertussis and Streptococcal Infections

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Outline

• Diphtheria
  Clinical features, important epidemiology and immunizations
• Pertussis
  Clinical features, diagnosis, immunizations and epidemiology
• Group A Streptococcus
  Clinical features, non-suppurative complications

Diphtheria

• Corynebacterium diphtheriae
  • Gram + rods, aerobic, non-moblie
  • Nonspore-forming
  • Toxigenic or non toxigenic (lysogenic conversion; infected by Beta phage)
  • C. ulcerans & C. pseudotuberculosis also can be lysogenic

Corynebacterium Diphtheriae

• Humans only known reservoir
• Inhabits human mucous membranes and skin
• Asymptomatic carriers
• C. Diphtheriae in immunized carriers are less likely to be toxigentic

Diphtheria – Clinical features

• Diphtheria is from the Greek root for “leather”, describing the tough pharyngeal membrane of the disease
• 85-90% Sore throat, 50-85% low grade fever, 26-40% dysphagia, 50% membrane
• Toxin causing myocarditis, polyneuritis, renal tubular necrosis and other systemic toxic effects. A milder form can be restricted to the skin.

Diphtheria – Pharyngeal Membrane

• Gray-brown adherent pseudomembrane
• Removal leads to bleeding edematous submucosa
• Exotoxin – local tissue necrosis: dense necrotic coagulum of fibrin, RBCs, inflammatory cells, Gram+ rods
• Toxin can affect all eukaryocytes
Diphtheria – Membrane Formation
- “Strangling Angel of Children”
- Membrane + edema can cause airway obstruction
- Most common cause of death is suffocation due aspiration of the membrane.
- 2/3 with carditis, 10-25% clinical dysfunction
- Neurotoxicity is high in severe disease

Diphtheria – “Bull Neck”
- Fatality rate 5 – 10%, but in <5 or >40 year olds, could be 20%.
- 50-60% morality due to suffocation or cardiac failure
- Lymphadenitis & edema
- Paralysis of the palatal muscles
- Larynx

“Bull Neck”
- Nasopharyngeal and pharyngeal swab for culture
- Selective media Loeffler, Tinsdale, with tellurite
- Treatment with antibiotics (PCN, EES) and antitoxin
- Early recognition and diagnosis

Diphtheria - Epidemiology
- Spread by direct contact or breathing airborne particles
- Still endemic in multiple areas of the world
- Soviet Union 1991-98, >200,000 cases with >5000 deaths
- Outbreaks rare, but still occur even in developed nations

Diphtheria - Epi in the U.S.
- In the early 1990s, diphtheria was one of the leading causes of death in infants; 1920s: 200,000 cases/yr, 13,000 deaths.
- After immunization became available, 19,000 cases in 1945.
- 1970s, 196 cases/yr
- 1980 - 2004: 57 cases reported

Diphtheria in the U.S. Now
- Since 2000 there have been typically 0-2 cases per year reported in the US.
- These are usually isolated cases (Dade County, Florida in 1990), but there have been focal outbreaks – (South Dakota 11 cases in 1996).
- Why aren’t there more cases of Diphtheria seen in the United States?
Immunization
Diphtheria Toxoid-containing Vaccine
- Primary series – 2, 4, 6 months of age
  DTaP – Diphtheria, tetanus, and acellular Pertussis
- Boosters - at 15-18 months and 4-6 years
  DTaP
- Boosters at 11 years of age and every 10 years – Td or Tdap – reduced doses of diphtheria toxoid and acellular pertussis

Reasons for Dramatic Diphtheria Decline Unclear
Immunization expected to prevent symptoms of toxoid production, not colonization
- Historical evidence suggests epidemics in cycles with gaps of >100 years
- Immunization could counter hypothesized colonizing advantage of lysogenic strains
- Other unknown virulence factors

Pertussis
Whooping Cough
Bordetella pertussis
- Clinical picture
- Difficult lab diagnosis
- Antibiotics & Supportive care
- Acellular vaccine
- New epidemiology

Bordetella pertussis
- Fastidious, gram negative, pleomorphic bacillus
- Humans only host
- FHA, FIM factors
- Multiple toxins:
  - Adenylate cyclase
  - Pertussis toxin (PT)
  - Tracheal cytotoxin
  - Dermonecrotic T

Pertussis – Clinical Features
- Begins as mild URT symptoms: cough, sore throat, congestion, runny nose
- Fever absent or minimum
- Can progress to paroxysms of cough with vomiting
- Apnea in very young, Pneumonia and secondary infections, Toxin effects
- Azitromycin, Erythromycin treatment
Clinical presentation of *B. pertussis* disease

<table>
<thead>
<tr>
<th>Duration</th>
<th>Inhalation</th>
<th>Convalescent</th>
<th>Paroxysmal</th>
<th>Convalescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-10 days</td>
<td>1-2 weeks</td>
<td>2-4 weeks</td>
<td>3-4 weeks</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Primary infection, fever, sneezing, pneumonia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Paroxysmal cough with whoops, vomiting, lachrymation, development of secondary complications (pneumonia, otitis, encephalopathy)</td>
</tr>
</tbody>
</table>

**Pertussis in an Infant**

- No respiratory distress between paroxysms of cough
- Distress – consider pneumonia or another diagnosis
- Secondary bacterial pneumonia, often due to aspiration
- Pertussis toxin
- Tracheal cytotoxin

www.vaccineinformation.org/video/
look here for some good video clips

**Pertussis in a Child**

- Perihilar infiltrates or edema, atelectasis
- Frank consolidation – think secondary bacterial pneumonia
- Air trapping
- Extravasated air
- Pneumothorax

**Chest X-Ray in Pertussis**

- Perihilar infiltrates or edema, atelectasis
- Frank consolidation – think secondary bacterial pneumonia
- Air trapping
- Extravasated air
- Pneumothorax

**Pertussis – Encephalopathy**

- Anoxia, seizures and hemorrhage
- Rare - ~1:10,000 to 1:12,500
- More common in infants < 6 months

**Diagnosing Pertussis**

<table>
<thead>
<tr>
<th>Predictive Factors for Pertussis</th>
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</thead>
<tbody>
<tr>
<td>Positive Factors:</td>
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<tr>
<td>Coughing cessation</td>
</tr>
<tr>
<td>Sore throat, rhinitis, rhinorrhea</td>
</tr>
<tr>
<td>Pharyngitis, fever, rash</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Stridor, stridor</td>
</tr>
<tr>
<td>Photophobia</td>
</tr>
<tr>
<td>Pharyngitis, fever, rash</td>
</tr>
<tr>
<td>Negative Factors:</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Neurologic</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Lymphocytosis</td>
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</tbody>
</table>
Nasopharyngeal Swab for Culture

- Clinical diagnosis
- In the catarrhal or early paroxysmal phase
- NP swab to produce a cough
- Selective media – Regan-Lowe or Bordet-Gengou agar
- Incubate for 7 – 14 days
- Direct fluorescent assay (DFA)
- PCR – increased sensitivity

Pertussis and Immunization

Global Cases 1980-2008

- 50 million cases & 300,000 deaths / YR
- Up to 3% mortality in infants

Changing Epidemiology of Pertussis

- Transmission by close contact with respiratory secretions from infected
- 90% of unimmunized home contacts infected
- More severe <1yr old: 22% pneumonia, 3% seizures, 1% encephalopathy, and 1.3% mortality in <1mon olds hospitalized
- Adolescents/Adults can now be 50% of reported cases, but can occur at any age

Number of reported pertussis cases by age group in the United States in 2003.


Reported pertussis complications by age group in the United States from 1997 to 2000 (n = 28,187).

Reasons for Pertussis Increase

- Decreasing immunization of the young
- Waning immunity in adolescents/adults
- Atypical presentation in older patients
- Possible carrier state even with immunization

Streptococcal Infection - Group A
*Streptococcus pyogenes*

- **Ubiquitous** GPC
- Beta-hemolytic
- >100 M types:
  - 1,3,5,6,18,19,24 - RF;
  - 49,55,57,59 - pyoderma
  - 1,6,12 - pharyngitis, AGN
- Streptolysins A & S, DNases, exotoxins including TSS superAg

**Streptococcus pyogenes**
*GAS*

- **Acute infection** of pharynx, skin or any organ system
- **Suppurative complications**
- Major non-suppurative complications:
  - **Toxin** mediated disease
  - **Post-infection** complications
    - a) Acute rheumatic fever
    - b) Acute glomerular nephritis

**Streptococcus (Group A) pyogenes**–Clinical Manifestations

- Pharyngitis
- Skin/Impetigo/Erysipelas
- Scarlet Fever
- Rheumatic fever
- Acute glomerulonephritis
- Necrotizing fasciitis
- Toxic Shock

**Streptococcus (Group A) pyogenes**
*Pharyngitis (GAS most common cause)*

* fever, exudative tonsils, lymphadenitis
* should not have cough, rhinorrhea, URI-like
* 4 criteria: fever; no cough; exudate; ant. C node
* Culture is still gold standard but rapid test is good
* growing azithromycin resistance makes Pen a better choice.

**Palatal petechiae in GAS pharyngitis**
Tonsillitis and Palatal Pettechiae

Exudative Pharyngitis #1

Exudative Pharyngitis #2

Pharyngitis / Tonsillitis

“Beefy” Red Tonsillitis

Streptococcus (Group A) pyogenes

**Epidemiology**

* direct contact, resp secretions
* crowding, schools, food borne
* Pharyngitis - late fall, winter, spring
* Pyoderma - warm seasons
* assoc. with *Varicella* infection
**Streptococcus (Group A) pyogenes**

**Diagnosis**
- GPC in pairs, chains; catalase negative
- beta-hemolytic in blood agar
- Rapid
- Culture

**Treatment**
- Pen V 2-3x/d for 10d, Erythomycin x10d, narrow-spectrum cephalos x10d

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**Suppurative COMPLICATIONS:**

- Peritonsilar abscess
- Cervical lymphadenopathy
- Empyema
- Osteomyelitis, septic arthritis, endocarditis, or any body site.

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**Peritonsillar Abscess**

- Trismus, muffled or altered speech, unilateral pain
- Trismus, Distorted anterior tonsillar pillar, erythema and swelling
- Drainage, antibiotics and an interval tonsillectomy

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**Posterior Cervical Lymphadenitis**

Streptococcal Infection Potentially Suppurative

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**Acute Rheumatic Fever**

Nonsuppurative Complication

- Migratory Polyarthritis
- Carditis = pancarditis
- Erythema Marginatum
- Chorea (late manifestation)
- Subcutaneous Nodule

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**Modified Jones Criteria for RF 1992**

**Major Criteria**
- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

**Minor Criteria**
- Arthralgia
- Fever
- Elevated ESR, CRP
- EKG evidence of prolonged PR interval

Diagnosis requires 2 major or 1 major & 2 minor criteria along with evidence of preceding GAS infection. Presence of chorea or carditis may not require preceding GAS infection. Recurrence may only require 1 major or several minor criteria with evidence of preceding GAS infection.
Clinical Case

- 13 year old female is referred to Rheumatology Clinic because of pain in joints, fevers and fatigue.
- Upon presentation to the clinic, she is tachypneic and has to pause when speaking.
- She has distant heart sounds, a diffuse PMI, but loud systolic and diastolic murmurs.

Erythema Marginatum

Subcutaneous Nodule

Mitral Valve Regurgitation
Aortic Valve Insufficiency

Pericardial effusion

Streptococcus (Group A) pyogenes

Rheumatic fever (RF)
* only associated with pharyngitis
* treatment protects against RF

Acute glomerular nephritis
* associated with both pharyngitis and skin infections
* can occur even after treatment
Post-Streptococcal Glomerulonephritis

- Group A Streptococcal Skin Infection
- IgG develops in 2-3 weeks
- Antigen-Antibody complexes
- Activation of complement system
- Deposited on glomerular capillary wall
- Proliferation of mesangial and epithelial cells
- Infiltration of PMNs in mesangium
- Immunofluorescence IgG and C3 deposits

Streptococcus (Group A) pyogenes

Non-Suppurative COMPLICATIONS:

Toxic Shock
- BCxs may grow faster/more likely positive (50%) than with Staph (5%)
- Tx with Vanco & Clinda (inhibit protein production, no inoculum & post-antib effect)
- IVIG may help by binding to toxins

Necrotizing fasciitis
- debridement critical

GAS – Necrotizing faciitis

Toxic-Shock Syndrome (TSS) – 1997 CDC Case Definition

- Fever: ≥102.0°F (greater than or equal to 38.9°C)
- Rash: diffuse macular erythema
- Desquamation: 1-2 weeks after onset of illness, esp. on the palms and soles
- Hypotension: systolic <90 mm Hg for adults or less than fifth percentile by age;
  orthostatic drop in diastolic blood pressure greater than or equal to 15 mm Hg from
  lying to sitting, orthostatic syncope, or orthostatic dizziness
- Multisystem involvement (2 or more of the following):
  - Gastrointestinal: vomiting or diarrhea at onset of illness
  - Muscular: severe myalgia or CPK level >the upper limit of normal
  - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  - Renal: BUN or Cr >the upper limit of normal for laboratory or urinary sediment
  - Hematologic: platelets <100,000/mm3
  - Hepatic: T.Bili, ALT, or AST >twice the upper limit of normal
  - Central nervous system: disorientation or alterations in consciousness
    without focal neurologic signs when fever and hypotension are absent

Streptococcus (Group A) pyogenes

Impetigo
- most common cause is now Staph
- Clindamycin could cover both staph/strep

Scarlet Fever
- fever, sandpaper rash, +/- desquamation
- assoc. with pharyngitis, skin/wound infection

Erysipelis
- tender, indurated cellulitis with clear margins of demarcation
GAS - Impetigo

Scarlet Fever
- Strawberry tongue
- Red cracked lips
- Circumoral pallor
- Red cheeks
- Palpable, red, blanching diffuse rash
- "Sandpaper feel"
- What causes the syndrome of Scarlet Fever?

“Strawberry” Tongue

“White Strawberry” Tongue

Palpable Rash

Post-Streptococcal Peeling
GAS - Erysipelis

Clinical:
* Acute pharyngitis (like GAS) with fever, exudate, lymphadenopathy, rash, pruritis
* mac-pap or scarlatiniform rash on extremities spreading to trunk, sharing palms/soles
* sinusitis, pneumonia, cellulitis & more severe...

Etiology: facultative anaerobic GP bacillus

Epidemiology:
* Humans primary reservoir
* person to person, presumptively resp droplet
* .5 – 3% of acute pharyngitis; asymptomatic CX rare

Arcanobacterium Haemolyticum

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* Humans primary reservoir
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Arcanobacterium Haemolyticum

Diagnosis:
* Cx from infected site
* may take 48-72hr to grow

Treatment:
* Erythromycin drug of choice
* clindamycin, tetracycline
* susceptibility to Pen variable, R to Septra common
* Disseminated infection – empiric Pen + Gent IV

Fusobacterium necrophorum

• Gram (-) rod, non-spore forming anaerobe
• Up to 10% of pharyngitis cases
• Implicated in 20% of recurrent/chronic pharyngitis
• Associated with Lemierre’s syndrome: pharyngitis, jugular vein thrombosis, septic emboli
• Clindamycin, metronidazole treatment