Leptospirosis, Typhoid and Other Fevers

Global Health Course
Center for Global Health
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The Presentation

- Acute Febrile Illnesses
  - Quick Review
- Leptospirosis
  - Life cycle, natural history and epidemiology
  - Diagnosis, clinical course and management
- Typhoid
  - Natural history, clinical presentation, epidemiology
  - Diagnosis
  - Treatment
- Other fevers – meliodosis
What is an Acute Febrile Illness (AFI)?

- Frequently used criteria, since no internationally agree upon definition:
  - acute onset with temp $\geq 38^\circ C$ (measured or reported)
  - ‘non-localizing’ signs / symptoms
  - 2-7 days duration

- Fever is the ‘least common denominator’ for a large number of infectious diseases which have no pathognomonic signs/symptoms except in their severe/late stages.

- Limitations in knowledge (global, regional) to guide clinicians with regards to ‘what can I expect where I am working’
Differential Diagnosis of AFI

- Chikungunya
- Malaria
- Influenza
- Leptospirosis
- Typhoid
- Meliodosis
- Rickettsiodoses
- Bacterial sepsis
- Zika fever
- Measles
- Enterovirus
- Hepatitis A

- Erythema infectiosum (5th disease)
- Roseola infantum (6th disease)
- HIV seroconversion illness
- Rubella
- Epstein-Barr virus
- Scarlet fever
- Meningococcemia
- Adenovirus infections
- Viral hemorrhagic fevers
  (Hantavirus, Crimean-Congo HF virus, Ebola)
Leptospirosis
Leptospirosis

- **Re-emerging zoonotic disease**
  - Global distribution
  - *Leptospira* bacteria transmitted in urine of infected animals
  - ~550,000 hospitalizations/year
  - ~55,000 deaths/year

- **Acute febrile illness**
  - Common symptoms: fever, headache, chills, vomiting, diarrhea, myalgia
  - Complications: jaundice, kidney failure, pulmonary hemorrhage, shock, death
  - Case-fatality rate: 5–15%

Top image: [http://s02.middlebury.edu/BI330A/STUDENTS/scottr/Leptospira1.jpg](http://s02.middlebury.edu/BI330A/STUDENTS/scottr/Leptospira1.jpg);
Leptospirosis as a Dengue-like Illness
Reported Suspect Dengue, Puerto Rico, 2010
Epidemiology

- Higher incidence in warmer climates
- **Seasonal incidence**
  - Summer, fall in temperate regions
  - Rainy seasons in warm regions
- **Route of entry**
  - Non-intact skin
  - Conjunctiva, mucous membranes
  - Prolonged immersion in water
  - Rarely following animal bites, person-to-person
- **Outbreaks associated with point contamination of water supplies**
Epidemiology - animal hosts

- Maintain infection in nature
  - Chronic infection of renal tubules
  - Excretion in urine
  - Infection transmitted animal-to-animal

- Accidental (incidental)
  - Infected by maintenance hosts
  - Climate, population density, degree of contact
Taxonomy and Classification

• *L. biflexa* - environmental saprophytes

• *L. interrogans* - pathogenic
  – Over 200 serovars
  – Epidemiologically - useful serogroups

• 16 genomospecies
  – Do not correspond to serologic typing
  – Future reclassification likely
# Maintenance Hosts and Associated Serogroups and Serovars

<table>
<thead>
<tr>
<th>Mammal species</th>
<th>Serogroup, serovar</th>
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<tbody>
<tr>
<td>Rats</td>
<td>Icteroaemorrhagiae, Ballum</td>
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<tr>
<td>Mice</td>
<td>Ballum</td>
</tr>
<tr>
<td>Dairy cattle</td>
<td>hardjo, pomona, grippotyphosa</td>
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<tr>
<td>Pigs</td>
<td>pomona, tarrassovi, bratislava</td>
</tr>
<tr>
<td>Sheep</td>
<td>hardjo, pomona</td>
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<tr>
<td>Dogs</td>
<td>canicola</td>
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Epidemiology - exposures

- Occupational
  - Direct contact with infected animals
    - Farmers, vets, abattoir workers, meat inspectors
  - Indirect contact
    - Sewer workers, soldiers, taro and banana farmers,

- Recreational - water

- Avocational - water, soil, animals
LEPTOSPIROSIS – TRANSMISSION CYCLES

Systemic vasculitis
Suspected Leptospirosis-Anicteric

- Acute febrile illness
- May have the following signs or symptoms
  - myalgia, calf tenderness, conjunctival suffusion, chills, abdominal pain, headache, retro-orbital pain,
  - aseptic meningitis (<25%)
  - rash (infrequent)
Icteric Leptospirosis

- Acute renal failure (16-40%)
  - Oliguria associated with death
  - Elevated serum amylase
  - Thrombocytopenia
- Pulmonary syndrome (16-67%)
  - Cough, dyspnea, hemoptysis
  - Acute respiratory distress syndrome
  - Intra-alveolar hemorrhage
- Cardiac involvement (10-40%)
  - EKG abnormalities
  - Severe myocarditis (high mortality)
Leptospirosis - Complications

- Ocular involvement (2-40%)
  - Conjunctival suffusion + scleral icterus pathognomonic for Weil’s disease
  - Recurrent anterior uveitis
- Abortion, fetal death
- Transmission through breastfeeding
- Rarely - nerve palsies, CVA, reactive arthritis
Laboratory Findings

- **Anicteric**
  - Elevated ESR
  - Slight elevation in transaminases, bilirubin
  - Proteinuria, pyuria, microscopic hematuria, hyaline and granular casts
  - CSF pleocytosis, elevated or normal protein

- **Severe, Icteric**
  - Peripheral leukocytosis, left shift
  - Thrombocytopenia
  - Elevated BUN, creatinine
Specific Diagnostic Testing

- Antibodies detectable 5-7 days after onset
  - Genus specific
  - Serogroup specific
- Microscopic agglutination test (MAT)
- IgM rapid tests
- PCR available but usually not positive until ~5 days after fever onset
Treatment

- Moderate-Severe disease
  - Penicillin G 1.5 MU q 6 hrs
  - Ceftriaxone 1 gm q 24 hrs
  - Ampicillin 1 gm q 6 hrs

- Mild cases
  - Doxycycline 100 mg BID PO
  - Amoxicillin 500 mg PO q 6 hrs

- Chemoprophylaxis
  - Doxycycline 200 mg once a week
Typhoid Fever
Typhoid Fever – Enteric Fever

- *Salmonella enterica* serovars Typhi, Paratyphi A, Paratyphi B, and Paratyphi C may be referred to collectively as typhoidal *Salmonella*.
  - Other serovars are grouped as nontyphoidal *Salmonella* (NTS)
- Typhoidal *Salmonella* strains are human host-restricted and cause typhoid fever and paratyphoid fever, together referred to as enteric fever
- NTS strains infect or colonize a broad range of vertebrate animals, or may be adapted or restricted to particular nonhuman animal species

Typhoid – Enteric Fever: Burden of Disease

- In 2000, typhoid fever estimated to cause 21.7 million illnesses and 216,000 deaths
  - paratyphoid fever caused 5.4 million illnesses
  - In 2010, estimated 11.9 million typhoid fever illnesses and 129,000 deaths in low- and middle-income countries (IVI estimates)
- Global Burden of Disease 2010 estimate = 12.2 million disability-adjusted life years and 190,200 deaths
- Children in south-central and southeast Asia are at particular risk.
- Typhoid fever appears to have become more common in sub-Saharan African countries or underappreciated there in the past.

After ingestion of *Salmonella* serovar Typhi or Paratyphi A, an asymptomatic period follows that usually lasts 7 to 14 days (range, 3 to 60 days).

- Human challenge models contributed to understanding of incubation period and very early symptoms in typhoid fever

A higher infecting dose is associated with a higher attack rate and shorter interval to bacteremia but not on time to symptom development or disease severity

- Recent human challenge studies have shown that a proportion of patients develop a subclinical or asymptomatic bacteremia

Fecal shedding can occur in period before symptom development, during primary infection
Typhoid – Enteric Fever: Course of Infection

- As symptomatic disease develops, the predominant symptom is the fever
  - Temperature rises gradually during the first week of the illness to high plateau of 39 to 40°C
  - Little diurnal variation, although the pattern may be modified by anti-pyretic medications
- Patients can have influenza-like symptoms, a dull frontal headache, malaise, anorexia, a dry cough, sore throat, and occasionally epistaxis
- Constipation is frequent early symptom
- Many patients will experience diarrhea at some point
Typhoid – Enteric Fever: Course of Infection

- Enteric fever can present as a diarrheal illness and occasionally with bloody diarrhea
- Most patients have abdominal pain that is diffuse and poorly localized
  - Nausea is common, and vomiting occurs in more severe cases.
- Rigors are uncommon and can distinguish the illness from malaria
Typhoid – Enteric Fever: Course of Infection

- Few other signs and symptoms, similar to other AFI
  - Slightly distended abdomen and diffuse tenderness
  - Occasionally pain and tenderness in the right iliac fossa, mimicking appendicitis
  - Moderate soft and tender hepatomegaly and splenomegaly
  - Rose spots, a blanching erythematous maculopapular rash with lesions approximately 2 to 4 mm in diameter, reported in 1-30% - easily missed in dark-skinned patients
  - Scattered wheezes, are common and can suggest pneumonia, but with normal chest x-ray

- Children have greater frequency of diarrhea and vomiting, jaundice, febrile convulsions, nephritis, or typhoid meningitis
Typhoid – Enteric Fever: Complications

- GI bleeding or intestinal perforation (terminal ileum)
- Encephalopathy with hemodynamic shock
- Hepatitis or Cholecystitis
- Pneumonia (2° other organisms *S. pneumoniae*).
- Myocarditis
- Acute kidney injury, nephritis
- Deep abscess (e.g., spleen, large joint, bone)
- Anemia
- Meningitis (in infants)
- Cerebellar ataxia
- Miscarriage
- Disseminated intravascular coagulation
- Chronic carriage (fecal or urinary carriage for >1 yr)
Typhoid – Enteric Fever: Diagnostic Testing

- Blood culture = gold standard
- Rapid diagnostic tests – antibody to specific antigens or LPS
  - Variable sensitivity / specificity
  - Use a good one – problem is lack of reference standard – most are not worth using
Typhoid – Enteric Fever: Treatment

- Prompt diagnosis
- Chloramphenicol had been effective
- Ampicillin, amoxicillin and TMP-SMX
- MDR = chloramphenicol, ampicillin, TMP-SMX
  - Resistance now widespread globally
- Fluoroquinolones – initially had high cure rates but now resistance is widespread
- Azithromycin and extended-spectrum cephalosporins (e.g., ceftriaxone) have shown good efficacy
  - Used for the treatment of enteric fever
  - Sporadic reports of resistance
Burkholderia pseudomallei

- Aerobic, Gram-negative bacillus found in water and moist soil
- Motile, saprophytic
  - Normally infects amoebas
- Opportunistic pathogen in humans and animals
  - Infects phagocytic cells
- Category B bioterrorism agent
Worldwide Distribution of \textit{B. pseudomallei}
Epidemiology

- **Endemic in tropics and subtropics**
  - Southeast Asia, Australia, Middle East, India, China…Caribbean?
  - U.S. cases linked with travel abroad

- **Wet season**
  - Heavy rainfall
  - High humidity or temperature

- **Classically a disease of rice farmers**
  - 5–20% of Thai agricultural workers have anti-\(B. \text{pseudomallei}\) antibodies
Transmission

- Bacterium enters the body via skin wounds, ingestion, or inhalation
  - Wound infection: Contact with contaminated soil or water
  - Ingestion: Contaminated water
  - Inhalation: Dust from contaminated soil; droplets from aerosolized water

- Incubation time
  - Median: 9 days; typical range: 1–3 weeks
  - Longest documented: 62 years

- Person-to-person transmission is possible, but very rare
Clinical Events

Diagnosis

- **Isolation of organism is the gold standard**
  - Vitek (screening)
  - Culture from blood, urine, sputum, throat swab, pus from abscesses in selective medium
    - But >20 different colony morphologies

- **Sero logic tests**
  - Indirect Hemagglutination Assay
    - High background in endemic areas
Treatment

- **Frequent antimicrobial resistance**
  - Penicillins and cephalosporins
  - Aminoglycosides
  - Quinolones and macrolides

- **Systemic antibiotics**
  - Intensive phase: IV ceftazidime, imipenem or meropenem for 10–14 days or until clinical improvement
  - Eradication phase: Oral co-trimoxazole for 12–20 weeks

- **Surgical drainage of abscesses**