Legionnaire’s Disease: Overview and Treatment
Sarah Newman, PharmD
PGY1 Pharmacy Practice Resident
Nicklaus Children’s Hospital

Disclosures

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

- Sarah Newman: nothing to disclose.

Objectives

- Describe the epidemiological risk factors for Legionnaire’s disease.
- Differentiate between the clinical features of Legionnaire’s disease and Pontiac fever.
- Design an antibiotic regimen for treatment of Legionnaire’s disease.
Quiz Question 1

T/F: A mild infection caused by *Legionella* bacteria is known as “Pontiac fever.”

Quiz Question 2

T/F: Levofloxacin 750 mg once daily for 10 days is an appropriate antibiotic treatment for Pontiac fever.

Quiz Question 3

T/F: Potable water systems, whirlpool spas, and cooling towers are common sources of Legionnaire’s disease outbreaks.
Philadelphia: 1968

- Annual convention of the American Legion at the Bellevue-Stratford Hotel
- 221 attendees contract a mysterious respiratory tract infection
  - 34 patients die
- The bacteria was finally isolated six months later by CDC researchers
- Source of the infection was traced to the hotel's water cooling system

Bronx, NY: 2015

- July
  - Legionnaire's outbreak infects more than 130 patients and kills 16
  - Traced to cooling tower above the Opera House Hotel
  - Deadliest Legionella outbreak in New York's history

Bronx, NY: 2015

- October
  - 13 new cases of Legionnaire's disease and one death reported
  - New outbreak appears to be unrelated to July outbreak
  - 15 cooling towers in the Morris Park area test positive for Legionella
  - Outbreak traced to cooling tower above Bronx Psychiatric Center
Bronx, NY: 2015

- Outbreaks in New York have increased dramatically over the last decade:
  - 73 cases in 2004 vs. 225 cases in 2014
- In August 2015, NY state government enacted legislation related to outbreaks
- Building owners must register and test water cooling towers within 30 days
  - All towers must be retested every 90 days

Epidemiology

- 8,000 – 18,000 cases/year in the United States
  - National reported cases tripled between 2001 and 2012
- Outbreaks typically occur in the summer and fall
- Caused by bacteria from the Legionella family
- Most frequent cause of waterborne illness in humans in the United States

Legionella Family

- Gram-negative aerobe
- At least 50 species
  - Most common human pathogen is Legionella pneumophila
- Prefer warm, moist environments
  - Outbreaks have been tied to cooling towers, whirlpool spas, decorative fountains, and grocery store “misters”
- Most common route of infection is via inhalation of the aerosolized particles → pneumonia
  - Human-to-human transmission has not been demonstrated
Signs and Symptoms

- In general, pneumonia symptoms accompanied by:
  - Fever >38.8°C (temperatures > 40°C common)
  - Dyspnea
  - Myalgia/arthralgia
  - Diarrhea
  - Nausea/vomiting
  - Neurological abnormalities
  - Chest pain
  - Non-specific lab findings
- Suspect Legionnaire’s disease in patients treated for pneumonia who do not respond to beta-lactam and/or aminoglycosides antibiotics

Diagnosis

- Atypical bacteria
- Typical gram stains will show neutrophils but few, if any, organisms
- If sputum culture is obtained, may be plated on black charcoal yeast extract
- Rapid diagnostic tests
  - Urinary antigen
  - Polymerase chain reaction (PCR)

Diagnosis

- Fever precedes any radiographic abnormalities, so diagnosis of pneumonia may be missed during the first 1-3 days of illness
- Begins with patchy, unilobar infiltrate that progresses to consolidations
- No characteristic chest x-ray finding
Common Pathogens

Community Acquired Pneumonia:
- *Streptococcus pneumoniae* 20-60%
- *Haemophilus influenzae* 3-10%
- *Staphylococcus aureus* 3-5%
- *Klebsiella pneumoniae, other GNRs* 3-10%
- *Mycoplasma pneumoniae* 4-6%
- *Chlamydia pneumoniae* 4-6%
- *Other bacteria* 3-5%
- *Legionella species* 2-4%
- *Viruses* 2-15%

Mortality Associated with Common Pathogens

Community Acquired Pneumonia
- *Psuedomonas aeruginosa* 61%
- *Klebsiella pneumoniae* 36%
- *Staphylococcus aureus* 32%
- *Legionella species* 15%
- *Streptococcus pneumoniae* 12%
- *Chlamydia pneumoniae* 10%
- *Haemophilus influenzae* 7%
- *Mycoplasma pneumoniae* 1%

Pontiac Fever
- Following identification of *Legionella*, analysis of stored serum from an earlier unidentified outbreak revealed *Legionella* was the cause
- Signs and symptoms
  - Milder course of disease compared to Legionnaire's disease
  - Fever
  - Chills
  - Fatigue
  - Headache
  - No respiratory complaints
- Usually self-limiting
  - No need to treat with antibiotics
Clinical Features of Legionellosis

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Legionnaire's disease</th>
<th>Pontiac fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic pneumonia?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Incubation period</td>
<td>2-10 days</td>
<td>24-72 hours</td>
</tr>
<tr>
<td>Percent of persons</td>
<td>Less than 5%</td>
<td>Greater than 90%</td>
</tr>
<tr>
<td>Isolation of organism</td>
<td>Possible</td>
<td>Never possible</td>
</tr>
<tr>
<td>Radiographic pneumonia?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Incubation period</td>
<td>2-10 days</td>
<td>24-72 hours</td>
</tr>
<tr>
<td>Percent of persons</td>
<td>Less than 5%</td>
<td>Greater than 90%</td>
</tr>
<tr>
<td>Isolation of organism</td>
<td>Possible</td>
<td>Never possible</td>
</tr>
<tr>
<td>Outcome</td>
<td>Hospitalization common</td>
<td>Hospitalization uncommon</td>
</tr>
</tbody>
</table>

Outcome: Hospitalization common
Case fatality rate: 5-30%

Hospitalization uncommon
Case fatality rate: 0%

Patient Risk Factors

Legionnaire’s disease
- Recent travel with overnight stay
- Cigarette smoking
- Chronic lung disease
- Solid organ transplant patients
- Age > 50-years-old
  - Likely associated with increasing comorbidities as patients age

Pontiac fever
- Smoking and patient age do not appear to be risk factors
- Typically infects younger patients (mean age = 29)

Supportive Therapy

- Antipyretics
  - Acetaminophen
  - Ibuprofen
- Antitussives
  - Dextromethorphan
  - Codeine
- Bronchodilators
  - Albuterol
- Hydration and adequate nutrition
- Supplemental oxygen

Reproduced from www.cdc.gov
Pharmacological Therapy

- **Preferred:**
  - Levofloxacin 750 mg IV QD, then 750 mg PO x 10 days (high-dose)
  - Moxifloxacin 400 mg IV QD, then 400 mg PO QD x 10 days
  - Azithromycin 1000 mg IV QD on day 1, then 500 mg PO or IV QD x 10 days

- **Alternatives:**
  - Ciprofloxacin 500 mg IV BID, then 500 mg PO BID x 10 days
  - Doxycycline 100 mg IV BID, then 100 mg PO BID x 10 days

Fluoroquinolone Pharmacokinetics

- **Levofloxacin**
  - High-dose maximizes concentration-dependent killing
  - Increases plasma concentrations and penetration into the lungs
  - Prevents development of resistance

- **Ciprofloxacin**
  - Not considered a "respiratory fluoroquinolone" because of inactivity against *Streptococcus pneumoniae* species
  - In vitro activity against *Legionella* species
  - BID dosing

Fluoroquinolone Plasma Concentrations
Switching from IV to PO

- Recommend switching patients from IV to PO antibiotics when they have been afebrile for 48-72 hours and have no more than one of the following signs of clinical instability:
  - Temperature >37.8°C
  - Tachycardia
  - Tachypnea
  - Hypotension
  - O2 desaturation
  - NPO status
  - Mental status changes from baseline

Pediatric Legionella Infection

- Of the 23,076 cases of Legionnaire's disease reported between 1990 and 2005, only 1.7% of cases were in pediatric patients
  - Adolescents 15-19: 44.3%
  - Infants < 1-year-old: 18.1%
- Most cases are hospital-acquired
  - Many have been traced to hospital tap water
  - Two cases were reported in infants who were born in warm water during “water births”

Pediatric Treatment Options

- **Levofloxacin**
  - 2-6 months and <5 years: IV: 8 to 10 mg/kg/dose every 12 hours; maximum daily dose: 750 mg/day
  - 5-15 years and ≤16 years: IV: 8 to 10 mg/kg/dose once every 24 hours; maximum daily dose: 750 mg/day
- **Azithromycin**
  - 10 mg/kg IV once daily for at least two days, then transition to oral route with a single daily dose of 5 mg/kg to complete therapy course, max dose = 500 mg/dose
- **Ciprofloxacin**
  - Ciprofloxacin 10-15 mg/kg IV BID, max dose = 800 mg/day
Fluoroquinolone Use in Pediatrics

**Controversies:**
- Increased bacterial resistance
- Irreversible adverse effects on cartilage development demonstrated in animal models
- 3.3-21% absolute risk increase in arthropathies or musculoskeletal events
- At the time of the September 2011 FDA Pediatric Drugs Advisory Committee, 5 events of tendon rupture had been reported in pediatric patients
  - 122,000 patients had received prescriptions for a FQ during that time period

**Potential uses:**
- Multi-drug resistant infections
- Cystic fibrosis
- CAP caused by atypical pathogens

**FDA indications:**
- Anthrax: levofloxacin and ciprofloxacin
- Complicated UTI and pyelonephritis infections: ciprofloxacin

**Risk vs. benefit**
- Limit FQ use in pediatrics to selected respiratory infections and infections due to MDR organisms

Role of the Pharmacist

**Antimicrobial stewardship:** patients presenting with Pontiac fever do not require treatment with antibiotics

**Pharmacists may be helpful in recommending:**
- Appropriate antibiotic selection
- High-dose levofloxacin therapy to maximize PK parameters
- When to switch patients from IV to PO therapy
Quiz Question 1

T/F: A mild infection caused by *Legionella* bacteria is known as “Pontiac fever.”

Quiz Question 2

T/F: Levofloxacin 750 mg once daily for 10 days is an appropriate antibiotic treatment for Pontiac fever.

Quiz Question 3

T/F: Potable water systems, whirlpool spas, and cooling towers are common sources of Legionnaire’s disease outbreaks.
Any questions?

Thank you!

Sources


Sources


