Objectives

For both plague and tularemia, review:

- Modes of transmission & clinical presentation
- Diagnosis
- Bioterrorism – history, signs of a bioterrorism attack, treatment, response
- CDC activities & resources

PLAGUE:
GENERAL INFORMATION

- Yersinia pestis – nonmotile, gram-negative bacillus
- Transmitted by:
  - Bites of infected rodent fleas (most common)
  - Handling infected animal tissues
  - Inhaling respiratory droplets from plague-infected animals, including pets
- Person-to-person transmission is possible but uncommon

Human Plague Cases Reported by Country, 2000-2009

Plague in the United States, 1965-2012

1 dot = 1 case, placed randomly within county of occurrence
Clinical Manifestations of Plague

- Bubonic
- Septicemic
- Pneumonic

- Less common forms – pharyngeal, meningeal
- 66% mortality prior to availability of antibiotics
- Mortality now 5-14% depending on clinical form

Frequency of Primary Plague Types, United States, 1965-2012

- Bubonic (80%)
- Septicemic (17%)
- Pneumonic (2%)
- Other (1%)


Initial Laboratory Testing for Plague

Collect primary specimen
- Bubo aspirate, blood, or sputum
- Inoculate for culture
  - General microbiologic media (e.g. sheep blood agar)
  - Grows slowly
- Staining
  - Gram-negative coccobacilli
  - Giemsa stain: bipolar staining organisms

Collect blood for acute and convalescent serology

Peripheral Blood Smear from Patient with Septicemic Plague

Smear shows characteristic bipolar (safety pin) staining of Y. pestis
Wright-Giemsa stain; magnification x 1000

Laboratory Testing for Plague - Continued

- Culture
  - Growth ~24-48 hours after inoculation
  - Automated bacterial identification systems may misidentify Y. pestis
  - Direct fluorescent antibody testing (F1 antigen detection) for rapid presumptive identification of isolate
  - Phage lysis for definitive identification of Y. pestis

- PCR

- Serology
  - Four-fold rise between acute and convalescent samples
  - Convalescent at least 2 weeks after acute sample

CDC research and prevention efforts

Uganda
- Rat control projects
- Treatment trial: doxycycline vs. ciprofloxacin

Plague “Dipstick” (Lateral Flow Assay)
- Rapid
- Inexpensive
- Technically simple
- Guide diagnosis and treatment, reduce the need for culture at remote sites
**Recent Events**

**Yosemite National Park – 2015**

**Child in California diagnosed with plague**

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---|---|---|---|---

**Comment** | **Share** | **Tweet** | **Stumble** | **Email**

Los Angeles: A child in southern California is recovering after contracting a rare case of plague. It's the first time the disease has been diagnosed in the state in almost a decade, authorities said Thursday.

On August 5, 2015, this report was posted on an MRFW Early Release on the MRFW website (http://www.mfrw.org)

Since April 1, 2015, 74 cases of human plague have been reported in residents of its states (two), California (five), Colorado (two), Georgia (one), New Mexico (two), Oregon (one). The two cases in Georgia and California residents have been linked to camping at Yosemite National Park in the northern Sierra Nevada Mountains of California. Nine of the 15 patients were male; median age was 52 years (range 1-79 years). Three patients aged 16, 52, and 79 years died.

**History of Plague as a Biological Weapon**

- **World War II**
  - Japanese Army Unit 731 dropped plague-infected fleas over populated areas of China

- **US and USSR bioweapons programs**
  - Techniques to aerosolize Y. pestis
  - US offensive program discontinued in 1970s
  - Soviet program continued through early 1990s

- **ISIS – August 2014**
  - "The [confiscated] laptop contains a 19-page document in Arabic on how to develop biological weapons and how to weaponize the bubonic plague from infected animals."


**Local Plague Death Confirmed**

Santa Fe County woman dies of plague; health department is testing those in contact with her

**Possible Human-to-Human Transmission of Plague**

**Outbreak of Human Pneumonic Plague with Dog-to-Human and Possible Human-to-Human Transmission – Colorado, June-July 2014**

**Patient** | **Date of exposure (source)** | **Onset of illness** | **Chest radiograph findings**
---|---|---|---
D | June 25 (dog) | July 5 | PNA
Intentional Release of *Y. pestis*

- 1970 World Health Organization (WHO) report
  - 50 kg of *Y. pestis* released as aerosol
  - Metropolitan area of 5 million

- Outcomes
  - 150,000 pneumatic plague cases
  - 36,000 deaths
  - *Y. pestis* would remain viable as an aerosol for one hour for a distance of up to 10 km
  - Further spread could occur

Intentional Release of *Y. pestis*

- Factors influencing size of outbreak:
  - Quantity of biological agent used
  - Characteristics of the strain
  - Environmental conditions
  - Methods of aerosolization

- Indications of artificial dissemination:
  - Occurrence of disease in areas with no enzoonotic foci
  - Occurrence in persons with no known risk factors
  - Absence of prior rodent deaths

Working Group on Civilian Biodefense

- Series of articles in JAMA
  "Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of the Working Group on Civilian Biodefense"

- Representatives from academic medical centers, research, government, military, public health, and emergency management institutions and agencies

- Critical biological agents

Plague as a Biological Weapon – Clinical Manifestations

- Primary pneumatic plague
- Incubation period: 2-4 days (range 1-6)
- First signs of illness
  - Fever with cough and dyspnea
  - Bloody, watery, or purulent sputum
  - Gastrointestinal symptoms may be present

Plague as a Biological Weapon

- Absence of buboes (except, rarely, cervical buboes)
- Pulmonary disease with areas of profound lobular exudation & bacillary aggregation
- Consolidation on CXR
- Treat suspect plague patients without waiting for lab confirmation
- Without treatment, death quickly follows onset of symptoms

Specimen cup containing purulent, bloody sputum from a pneumatic plague patient, Uganda.

Treatment of Pneumonic Plague in the Contained Casualty Setting

**Preferred Choices**

- Gentamicin, 5mg/kg IM or IV once daily or 2mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 times daily
- Streptomycin, 1 g IM twice daily

**Alternative Choices**

- Doxycycline, 100 mg IV twice daily or 200 mg IV once daily
- Ciprofloxacin, 400 mg IV twice daily
- Chloramphenicol, 25 mg/kg IV 4 times daily

For children – same antibiotics but different dosing

CXR of patient with primary pneumatic plague shows extensive lobular consolidation in left lower and left middle lung fields.
Treatment of Pneumonic Plague in the Contained Casualty Setting

**Preferred Choice**
- Gentamicin, 5mg/kg IM or IV once daily or
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**Alternative Choices**
- Doxycycline, 100 mg IV twice daily or 200 mg IV once daily
- Ciprofloxacin, 400 mg IV twice daily

Treatment of Pneumonic Plague in the Mass Casualty Setting and for Postexposure Prophylaxis

**Preferred Choices**
- Doxycycline, 100 mg orally twice daily
- Ciprofloxacin, 500 mg orally twice daily

**Alternative Choice**
- Chloramphenicol, 25 mg/kg orally 4 times daily

For children – same antibiotics but different dosing

Infection Control Measures for Pneumonic Plague Patients

- **Respiratory droplet precautions** until at least 48 hours of antibiotic therapy and clinical improvement is seen
  - Disposable surgical masks
  - Gown, gloves, and eye protection
- **Bodies of patients who have died** should be handled with strict precautions
  - Aerosol-generating procedures during autopsy not recommended

Environmental Decontamination Recommendations for Plague

- **Plague bacilli** are sensitive to sunlight and heating
  - No spore form in *Y. pestis* life cycle
  - Does not survive long outside the host
- **No evidence** that plague bacilli pose an environmental threat following dissolution of primary aerosol
- **Standard precautions** for cleaning patient rooms and linens

Tularemia - Overview

- **Caused by** *Francisella tularensis* – small, nonmotile, aerobic, gram-negative cocobacillus
- **Hardy** – survives well in water, moist soil, straw, decaying animal carcasses
- **First identified** in 1911 as plague-like illness of ground squirrels in Tulare County, CA
- **Aka** “rabbit fever”
**Francisella basics**

- *Francisella tularensis* recovered from >200 animal species, soil, water
  - *F. tularensis* subsp. *tularensis* (type A)
  - *F. tularensis* subsp. *holarctica* (type B)

- Genus also comprised of other organisms widespread in environment, including:
  - *F. novicida*, *F. philomiragia* (brackish or salt water)
  - *F. noatunensis*, *F. halioticida*, *F. piscicida* (fish/mollusks)
  - Several other species not fully characterized

**Transmission**

Multiple modes of infection
- Arthropod bites (ticks, deerflies)
- Handling infected tissues or fluids
- Ingestion of contaminated water
- Inhalation of infective aerosols (agricultural dusts, laboratory)

Person-to-person transmission not documented

**Tularemia**

"I know of no other infection of animals communicable to man that can be acquired from sources so numerous and so diverse. In short, one can but feel the status of tularemia, both as a disease in nature and of man, is one of potentiality."

R.R. Parker (1934)

**Geographic Distribution of Reported Tularemia Cases, United States, 2004-2013**

**Clinical Presentation**

Symptoms & severity vary based on route of infection
- Ulceroglandular – cutaneous ulcer/papule & regional lymphadenopathy
- Glandular – regional lymphadenopathy
- Oculoglandular – conjunctivitis & regional lymphadenopathy
- Oropharyngeal – pharyngitis/tonsillitis
- Typhoidal – fever without localizing signs
- Pneumonic – respiratory disease
Summary of Surveillance Data

- NNDSS data tabulated annually after finalized
- Usually 100-200 cases per year in recent decades
- Most cases (~70%) are ulceroglandular or glandular – Arthropod bites or other cutaneous exposure
- More than 1/3 of cases diagnosed serologically

Laboratory Diagnosis

- Clinical samples: blood, lymph node aspirate, or respiratory sample (sputum, bronchoalveolar lavage, biopsy)
- Wright, Giemsa or Wayson stain may show tiny, gram-negative coccobacilli
- Culture
- DFA – rapid identification of *F. tularensis* in primary specimens or isolates
- PCR (does not distinguish between species)
- Serology

Recent Events

Notes from the Field: Increase in Human Cases of Tularemia — Colorado, Nebraska, South Dakota, and Wyoming, January—September 2015

Public Health Response to Tularemia

- Alerts triggered by confirmed cases in human accompanied by positive carcasses
- Alerts include signage in affected areas, HANs, MMWR articles, and public service announcements

Tularemia in an Age of Bioterrorism

- *F. tularensis* is one of the most infectious bacteria known → inoculation with only 10 organisms can cause disease
- Weaponized by US in the 1950s and 1960s, parallel effort by USSR until early 1990s
- Other countries suspected to have weaponized it as well
- Can be cultured and engineered for antimicrobial resistance
- Contamination of the water supply also a concern
**Intentional Release of *F. tularensis***

- Bioterrorist attack would most likely occur via aerosolization of *F. tularensis*
- 1970 WHO expert committee report
  - 50 kg of virulent *F. tularensis* released as aerosol
  - Metropolitan area of 5 million
- Outcomes
  - 250,000 incapacitating casualties
  - 100,000 deaths
  - Illness expected to persist for several weeks

**BioWatch**

- Federal government program to detect the release of pathogens into the air as part of a terrorist attack on major American cities
- Created in 2001 in response to anthrax attacks
- System of filters located within existing Environmental Protection Agency air filters that monitor air quality
- Cross-reactivity with naturally-occurring *Francisella* spp.
- CDC provides SME support on national calls and on-site investigations

**Inhalational Tularemia**

- Incubation: 3-6 days for acute symptoms (range 1-14 days)
  - Only 25-50% of patients may have radiologic evidence of pneumonia in early stages of infection
- Acute illness with one or more of the following signs/symptoms:
  - Pharyngitis
  - Bronchiolitis
  - Pleuropneumonitis
  - Hilar lymphadenitis
  - Manifestations of systemic illness
- Inhalational exposures can present as systemic illness with few signs of respiratory disease

**Inhalational Tularemia - Continued**

- Earliest radiographic findings may be:
  - Peribronchial infiltrates – typically advancing to broncho-pneumonia in one or more lobes
  - Accompanied by pleural effusions and hilar lymphadenopathy
- However, signs may be minimal or absent
  - Some patients show only one or several small, discrete pulmonary infiltrates, or
  - Scattered granulomatous lesions of parenchyma or pleura

**Epidemiology of Tularemia Following Intentional Release**

- First indication of clandestine release
  - Cluster of acute, severe respiratory illness with unusual epidemiologic features
- Early diagnosis of inhalation tularemia requires a high index of suspicion
- Unlikely that serendipitous lab identification would be sentinel event
  - Identification of *F. tularensis* in clinical specimens may be missed or delayed for days when routine screening procedures for bacterial pathogens are followed

**Dispersal after Intentional Release**

- Under natural conditions, *F. tularensis* can survive for extended periods in cold, moist environment
- Survival of intentionally dispersed particles is unknown but expected to be limited
  - Expect a short half-life due to desiccation, solar radiation, oxidation, and other environmental factors
  - Very limited risk from secondary dispersal
Treatment of Tularemia in the Contained Casualty Setting

**Adults**

**Preferred Choices**
- Streptomycin, 1 g IM twice daily
- Gentamicin, 5mg/kg IM or IV once daily

**Alternative Choices**
- Doxycycline, 100 mg IV twice daily
- Chloramphenicol, 15 mg/kg IV 4 times daily
- Ciprofloxacin, 400 mg IV twice daily

*For children – same antibiotics but different dosing*

**Pregnant Women**

**Preferred Choices**
- Gentamicin, 5mg/kg IM or IV once daily
- Streptomycin, 1 g IM twice daily

**Alternative Choices**
- Doxycycline, 100 mg IV twice daily
- Ciprofloxacin, 400 mg IV twice daily

Treatment of Tularemia in the Mass Casualty Setting and for Postexposure Prophylaxis

**Adults (including pregnant women)**

**Preferred Choices**
- Doxycycline, 100 mg orally twice daily
- Ciprofloxacin, 500 mg orally twice daily

**Children**

**Preferred Choices**
- Doxycycline
  - If ≥ 45 kg, give adult dose
  - If < 45 kg, give 2.2 mg/kg orally twice daily
- Ciprofloxacin, 15 mg/kg orally twice daily

Infection Control Measures for Inhalational Tularemia Patients

- No human-to-human transmission of tularemia documented
- Standard precautions are appropriate
- Isolation of patients is not recommended
- Bodies of patients should be handled using standard precautions
  - Autopsy procedures likely to produce aerosols should be avoided
- **Caution for laboratory workers**

Differential Diagnosis: Inhalational Tularemia, Plague and Anthrax

- **Plague:** progress rapidly to severe pneumonia
  - Copious watery or purulent sputum production
  - Hemoptysis, respiratory insufficiency, sepsis and shock
- **Tularemia:** slower progression of illness and lower case fatality rate
- **Anthrax:** characteristic findings of prominent mediastinitis
  - Absence of bronchopneumonia
  - Develop fulminating, toxic, fatal illness despite antibiotic treatment

**IN SUMMARY...**
CDC RESOURCES & ACTIVITIES

• Track and report on national epidemiology
• Subject matter expertise for health departments and clinicians
• Health communications assistance
• Ecologic and entomologic guidance
• Outbreak response
  e.g. Devils Tower, Wyoming

CDC Laboratory Resources & Activities

• WHO Collaborating Center on Vector-Borne Bacterial Diseases
• National strain reference collections
  2,500 Yp + 1,200 Ft strains
• Reference diagnostic services and training
  – Molecular characterization and antimicrobial susceptibility testing
  – Laboratory Response Network coordination and reagent distribution
• R&D for new diagnostics

Questions?

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