Bioterrorism

Gregory J. Martin MD
Office of Medical Services
Department of State

DISCLOSURES

Financial Relationships with Relevant Commercial Interests
• None

Bioterrorism

– The opinions expressed in this talk are mine and should not be construed as official views of the US Department of State or the US government.

– FDA unapproved use of antibiotics and vaccines will be discussed

Bioterrorism on the ID Boards

• Material related to the naturally acquired syndromes have been ID Board topics since its inception.

• Some questions related to the unique aspects of use of an agent for bioterrorism now show up most years.

• Aspects to consider are:
  – Public health measures beyond the individual patient
  – Isolation and infection control issues
  – Immunization and antimicrobial prophylaxis
  – The possibility of bioengineering that may alter the characteristics of the agent from what occurs in the natural setting
  – Antimicrobial resistance profile
  – Virulence factors
  – Modification

CDC Threat Categories

Category A Diseases/Agents
• High-priority agents, organisms that pose a risk to national security:
  – easily disseminated or transmitted from person to person
  – high mortality rates, potential for major public-health impact
  – might cause public panic and social disruption
  – require special action for public health preparedness

Category B Diseases/Agents
• Second highest priority agents include those that are:
  – moderately easy to disseminate
  – result in moderate mortality rates and low mortality rates
  – require specific enhancements of diagnostic capacity and enhanced disease surveillance

Category C Diseases/Agents
• Third highest priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of:
  – availability
  – ease of production and dissemination
  – potential for high mortality and morbidity rates and major health impact

www.bt.cdc.gov/bioterrorism
Case 1

• 48 yo man admitted thru the ER the previous night with fever, chest pain and leukocytosis but no infiltrate on CXR.
  – Dx “Febrile bronchitis”
  – Began on oral azithromycin

• ID Consult called when admission BCx are reported positive for GNRs (Gram negative rods) 6h post admission.

• You arrive on the ward just as the patient is being transferred to the ICU for hypotension

---

Bacillus anthracis
Suspect Anthrax?

• Skin lesions or flu sx with potential exposure

• Painless skin lesion with black eschar and surrounding edema

• Unexplained sepsis, respiratory failure with:
  – large pleural effusion
  – bloody effusion
  – wide mediastinum

• GPRs in blood cultures, CSF or (rarely) sputum specimen

---

Anthrax: Case Definition

Definitive: Compatible clinical illness plus:
1) Positive culture from skin lesion, blood, CSF, pleural fluid
   - grows rapidly on standard media and automated BCx systems
   - blood is likely positive early in incubation illness
2) Two positive non-culture tests: PCR, y phage or serology

Suspected: Compatible clinical illness plus:
1) Single positive non-culture test: PCR, y phage or serology
2) Epidemiological link to source

Serology
- FDA approved, ImmunoTech QuickELISA-kit is neg acutely
- Positive one week after onset in nearly all anthrax cases (all types)
- Helpful in suspect cases with neg culture and neg PCR

Nasal swabs are NOT for diagnosis of disease:
- part of an epidemiologic work-up only
- performed within hours of exposure, little utility <48h
- no role for Gram staining of nasal swabs

---

Only spore aggregates <5 µM can reach terminal bronchioles
(Individual spores are 1-1.5 µM)

---

Role of Nasal Swabs
Many misconceptions

• Nasal swabs after exposure to anthrax spores are useful for defining the exposure zone but do NOT determine if an individual was exposed.
  – A negative nasal swab does not exclude a significant exposure
  – All those in the same room with someone with a positive nasal swab are considered exposed even if their swab is negative
• Nasal swabs are useful in the initial period after the exposure but the utility diminishes within hours
  – Swabs days after exposure should NOT be performed
Increased Edema
A

Anthrax
CT
Lethality
CXR

Typically

Micro

B

Cyclic

Inhalation

Influenza like Illness

Clinical Data

Anthrax

Influenza

• CBC:
  – WBC high or normal
  – Hemorrhage
• CXR
  – Wide mediastinum
  – Pleural effusions
• CT scan
  – Enlarged mediastinal nodes
  – Mediastinal edema
• Micro
  – Blood culture+ 6-24 hr (if before antitoxin)

• CBC:
  – WBC low or normal
• CXR
  – Normal ± infiltrate in severe cases
• CT scan
  – Negative, NO adenopathy
• Micro
  – Rapid flu EIA + (~70% sensitive)

Inhalation Anthrax vs Flu-ILI vs CAP

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Inhalation anthrax</th>
<th>Influenza or Influenza like illness</th>
<th>Community acquired pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>103%</td>
<td>14%</td>
<td>69%</td>
</tr>
<tr>
<td>Lack of sore throat</td>
<td>99%</td>
<td>26%</td>
<td>75%</td>
</tr>
<tr>
<td>Lack of head aches</td>
<td>94%</td>
<td>19%</td>
<td>65%</td>
</tr>
<tr>
<td>Lack of headache</td>
<td>94%</td>
<td>19%</td>
<td>65%</td>
</tr>
<tr>
<td>Lack of myalgia</td>
<td>96%</td>
<td>19%</td>
<td>65%</td>
</tr>
<tr>
<td>Rash &gt; 3 days</td>
<td>73%</td>
<td>7%</td>
<td>65%</td>
</tr>
<tr>
<td>Tongue</td>
<td>96%</td>
<td>19%</td>
<td>65%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>100%</td>
<td>85%</td>
<td>65%</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>99%</td>
<td>NA</td>
<td>65%</td>
</tr>
<tr>
<td>Headache</td>
<td>96%</td>
<td>NA</td>
<td>65%</td>
</tr>
<tr>
<td>Low grade fever</td>
<td>96%</td>
<td>NA</td>
<td>65%</td>
</tr>
</tbody>
</table>


(c) 2013 Infectious Disease Board Review Course
Inhalational Anthrax

Review of 11 Cases

Epidemiology:
Documented exposure 9 (82%)

Clinical features:
- Chills, fever, sweats 11 (100%)
- Cough, non-productive 10 (91%)
- Nausea, vomiting 7 (73%)
- Coryza 1 (9%)

Inhalational Anthrax

Radiographic Findings

- CXR may be normal in early disease
- Airspace consolidation is NOT the primary process
- Mediastinal widening is characteristic
  - May not be evident on CXR early on
  - Consider CT - mediastinal findings better demonstrated
- Pleural effusions are common
  - Bilateral
  - Bloody
  - Indication for early chest tube placement
  - Effusions contain large amounts of toxin

Anthrax

Infection Control

- Patients arriving after exposure may have viable spores on clothing, skin and hair
  - Thorough showering and shampooing
  - Routine laundering of clothing
- No transmission from patient to household contact or healthcare workers
  - Most bacilli are in lymphatics and blood vessels NOT alveoli
- No special isolation necessary
- Cultures in lab must be handled carefully, sporulation begins on culture media in 24 hours and may infect lab personnel
- Anthrax spores released outdoors are very sensitive to UV light and are inactivated
  - If buried below the surface may survive for years
  - On non-soil surfaces inactivated in hours to days

Severe Anthrax

Measures in addition to antibx

- Immune Therapy: (obtained thru CDC or public health authorities)
  - Anthrax immune globulin [AIG]
  - antiPA monoclonal Ab: rabiesvacumab or MDX-1303 (Volurit)
- Steroids:
  - Consider with extensive edema (cutaneous dz), mediastinal edema, or meningitis
- Drainage:
  - Repeated thoracentesis (or chest tube) and repeated paracentesis are important to maintain pulmonary status and to remove fluids with high levels of bacilli and toxins

Treatment Severe Anthrax with Possible Meningitis

Two bactericidal agents plus a protein synthesis inhibitor

- First Line:
  - Ciprofloxacin or other quinolones (levo, mox, etc) are the backbone
  - Doxycline is secondary choice for treatment (but rare resistant strains)
  - Penicillins and cephalosporins - effective but strains with potent β-lactamase activity occur. PCN achieves poor levels in macrophages.
- 2nd agent with CNS penetration (esp with concomitant meningitis):
  - Meropenem, imipenem, rifampin, penicillin or chloramphenicol
  - (ciprofloxacin, clinda and doxy all get poor CNS levels)
- Shut Down Toxin production:
  - Linezolid, clindamycin and rifampin act at the ribosomal level to halt toxin synthesis

Anthrax Prophylaxis

Adults, Pediatrics and Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Peds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For 60 days</td>
<td>For 60 days</td>
</tr>
<tr>
<td>Cipro</td>
<td>500 mg bid</td>
<td>10-15 mg/kg bid</td>
</tr>
<tr>
<td>Doxy</td>
<td>100 mg bid</td>
<td>&gt;8 yo and &gt;45 kg: 100 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 8yo or &lt;45 kg: 2.2 mg/kg bid</td>
</tr>
<tr>
<td>Amax</td>
<td>500 mg tid</td>
<td>80 mg/kg/d divided tid</td>
</tr>
</tbody>
</table>

- Due to the presence of inducible β lactamases, amoxicillin should be considered 2nd line until full sensitivity profile.
  - PCN sensitive strains: amox may be used in pregnancy, lactating women and children.
- Due to drug intolerance may need to use other quinolones, macrolides or cephalosporins – base on in vitro sensitivities

(c) 2013 Infectious Disease Board Review Course
**U.S. Anthrax Vaccine**

AVA (anthrax vaccine alum adsorbed)

- Highly immunogenic:
  - >85% serologic response after 1 dose
  - >90% seropositive after 3 doses
  - 100% develop rise in titer after yearly booster
  - Simplified pre-exposure regimen approved 2009
  - 6/4 weeks, 6 months, 12 months, 18 months, then annually

- Excellent safety profile but reactions common:
  - Mild local reactions in ~30% (erythema, tenderness)
  - Moderate reactions in ~4% (erythema, pruritis)
  - Subcutaneous nodules ~35-50%
  - Systemic transient reactions 0.2 to 0.4% (malaise, fever)
  - No long term sequelae demonstrated

- NOT FDA approved for POST exposure prophylaxis but still recommended
  - CDC recs use under IND in a 3 dose regimen at 0,2 & 4 weeks even in pregnancy

---

**Answer (and discussion) Question 1**

Which one of the following is FALSE regarding the 48yo man admitted with inhalational anthrax <12 hours ago?

A. Azithromycin, although not the drug of choice, probably is an effective therapy for anthrax. (Although azithromycin has activity vs anthrax it is not a drug of choice and unless multiple drug allergies preclude other choices a quinolone and/or dox are preferred)

B. Staff who cared for the patient prior to the recognition of the anthrax should initiate ciprofloxacin or doxycycline prophylaxis (someone who is still covered with anthrax spores after an exposure would be a risk but after the patient has changed clothes and showered he/she is NOT an infection control risk even if they develop fulminant clinical anthrax in any of its forms, since this is not an air space disease even inhalational anthrax patients are not a risk to contacts)

C. Blood agar plates in the lab are potentially sources of 2+ cases (11)

D. Most automated blood culture systems will identify B. anthracis in this patient's blood

E. Switching antibiotics to levofloxacin and rifampin is appropriate

---

**Case 2**

- A 52 yo diplomat and her 48 yo husband returned from Iraq yesterday and have both been admitted with cough, fever, WBCs >18k and pulmonary infiltrates.
  - Presumptive dx from the ER ?pneumococcal pneumonia
  - IV azithromycin initiated

---

**Yersinia pestis**

Plague

- Sputa stains are shown
  - Many PMNs
  - Gram neg cocccobacillary organisms 1-2 μ long

- Characteristic appearance ONLY on Wright-Giemsa or Wayson's staining
  - NOT on Gram's stain
Yersinia pestis

Laboratory Characteristics

• Grows well on standard Blood or MacConkey agar.
• Grows readily in liquid media of automated blood culture systems.
• Serology is not readily available and may be negative in early disease:
  – Direct fluorescent antibody (DFA)
  – Hemagglutination and ELISA serologies available but may take too long for acute diagnosis
• Negative serology will not rule out acute disease

Pneumonic Plague

• Highest mortality of plague presentations.
  – Invariably fatal if antibiotics delayed > 20 hours after onset.
  – Exposure → Illness → Death may occur <24 hours.
• Current US mortality rates 18% overall.
  – Untreated bubonic plague: 40%.
  – Untreated septicemic and pneumonic plague: 100%.
• How contagious by airborne transmission?
  – Some controversy about efficiency
  – Most tests – highly contagious; but little data to support
  – Infected animals, especially cats, with plague pneumonia may infect humans.
Antibiotics for Plague

<table>
<thead>
<tr>
<th>Plague</th>
<th>Prophylaxis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>doxycycline 2.2 mg/kg po bid</td>
<td>doxycycline is not generally available, gentamicin or tobramycin can be substituted, change to po or IV when stable</td>
</tr>
<tr>
<td>Adults</td>
<td>doxycycline 100 mg po bid</td>
<td>ciprofloxacin or gentamicin 500 mg po or 400 mg IV bid</td>
</tr>
</tbody>
</table>

**Question 2**

Which one of the following is TRUE regarding the diplomatic couple from Iraq hospitalized in the US with pneumonic plague?

A. Nasal swabbing for Y. pestis exposure for remaining staff in Baghdad should be urgently initiated.

B. Since plague is endemic in Iraq this is unlikely to represent a bioterrorism incident.

C. Staff that initially cared for these patients do NOT need to be given prophylaxis with a quinolone or doxycycline.

D. A logical antibiotic regimen would be ceftriaxone and gentamicin.

E. It is likely that the patients will develop bubo(es) during the course of their illness.

Answer (and discussion) to Question 2

Which one of the following is TRUE regarding the diplomatic couple from Iraq hospitalized in the US with pneumonic plague?

A. Nasal swabbing for Y. pestis exposure for remaining staff in Baghdad should be urgently initiated. (nasal swabbing is useful only immediately after exposure and there is no utility in swabbing staff days after exposure)

B. Since plague is endemic in Iraq this is unlikely to represent a bioterrorism incident. (it would be highly unusual for two people to develop inhalational plague who live in the city and have no animal contact, even in a plague endemic country)

C. Staff that initially cared for these patients do NOT need to be given prophylaxis with a quinolone or doxycycline (inhalational plague, although not efficiently transmitted among contacts can be transmitted in a health care center and those treating the patient in the first 48 hours who were not properly protected should be given prophylaxis)

D. A logical antibiotic regimen would be ceftriaxone and gentamicin.

E. It is likely that the patients will develop bubo(es) during the course of their illness (it is highly unlikely that they will develop bubo(es) if the route of exposure was through the lungs and not a flea bite draining to lymph nodes).

**Case 3**

- The chief resident took this photo while the patient was still in the ER

- A scraping of the one lesion was sent for DFA for HSV and VZV but the tech was not available last night

- Even with no further tests available what concerns you about the dx of Varicella?

**Case 3**

- The chief resident took this photo while the patient was still in the ER

- A scraping of the one lesion was sent for DFA for HSV and VZV but the tech was not available last night

- Even with no further tests available what concerns you about the dx of Varicella:
  - Prodomal illness is not typical for Varicella, this woman had 1 week
  - Varicella typically starts on the trunk and later moves to the extremities and face, her lesions started on her face
Variola - Smallpox

Differential Diagnosis

- Varicella (Chickenpox):
- Monkeypox:
- Erythema multiforme:
- Contact dermatitis:
- Secondary syphilis:
- Other poxviruses:

Variola vs Varicella vs Monkeypox

<table>
<thead>
<tr>
<th>Incubation</th>
<th>Smallpox</th>
<th>Varicella</th>
<th>Monkeypox</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-17 days</td>
<td>14-21 days</td>
<td>7-17 days</td>
<td></td>
</tr>
<tr>
<td>(typically ~12)</td>
<td></td>
<td>(typically ~12)</td>
<td></td>
</tr>
<tr>
<td>Prodrome</td>
<td>1-4 days before rash</td>
<td>None or minimal</td>
<td>1-3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(occasionally longer)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Centrifugal (first lesions face, hands, arms)</td>
<td>Centripetal (first lesions face or trunk)</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(inoculation site or face first)</td>
</tr>
<tr>
<td>Palms/Soles</td>
<td>Frequently</td>
<td>Rarely</td>
<td>Unusual</td>
</tr>
<tr>
<td>Evolution</td>
<td>Synchronous (in each body region)</td>
<td>Asynchronous Rapid evolution</td>
<td>Asynchronous</td>
</tr>
<tr>
<td>Scabs form</td>
<td>10-14 days</td>
<td>4-7 days</td>
<td>5-10 days</td>
</tr>
<tr>
<td>Scabs separate</td>
<td>14-28 days</td>
<td>&lt;14 days</td>
<td>*10-14 days</td>
</tr>
<tr>
<td>Infectivity</td>
<td>Up to scab separation</td>
<td>Up to lesions scabbed</td>
<td>? Up to scab separation</td>
</tr>
</tbody>
</table>

Lesions

- Exanthem
  - Begins on face, hands, forearms
  - Spreads to lower extremities
  - Centrifugal distribution
  - Macules-papules-vesicles-pustules-scales
  - Infectious until scab separates
- Enanthem (mucous membrane eruption)
  - Concomitant with exanthem
  - Infectious oropharyngeal secretions!

Poxviruses as Bioterrorist threats

- WHO: “produced and weaponized with relatively simple techniques”
- Other virulent poxviruses such as Monkeypox as a BW agent?
  - Recombinant technology
  - Potential modification of poxvirus with genes for enhanced virulence
- Cadavers in permafrost / dry crypts and leftover specimens from eradication programs as potential sources for terrorists?
  - Freeze dried for storage: viable for decades
  - Viable for weeks in scabs but tightly bound in fibrin
- Infectious via aerosol
  - Viability in environment for only short periods
  - Sprayed outdoors: highly susceptible to UV
  - Person to person transmission after initial cases established
- Clinical inexperience throughout the world
- Confusion and panic.

Variola Epidemiology

- Reservoir – only humans
- Transmission: person-to-person
  - Respiratory droplet
    - Most cases acquired by face-to-face contact
  - Coughing, sneezing
  - Typically SLOW spread thru communities
- Contact
  - Contaminated fingers - oral / nasal mucosa
  - Intact skin - rare
- Fomites
  - Inhalation of contaminated dust from clothing, bed linen - not common
**Smallpox**

After exposure to aerosolized virus:

- Incubation typically 12 days
  - (range 7-17 d)
- Infected respiratory mucosa → regional lymphatics ➔ spread to liver, spleen, lung, bone marrow
- Prodrome with fever, chills, headache and severe backache
- Non-infectious until exanthem appears
- 2–4 days after prodrome: rash appears—typical evolutes—papule—vesicle—bulla—scab
- Scabs detach end of 3rd or 4th week
  - Patient infectious until all scabs detach

**Laboratory Diagnosis**

Difficult to differentiate vaccinia, cowpox or monkeypox

- Electron microscopy
  - Virology on EM of vesicular scrapings
- Light microscopy
  - Enzyme-immunoassay intracytoplasmic inclusions
  - (Guarnieri bodies with viral inclusions)
  - Black inclusions on silver stain
- Gel diffusion test
  - Incubate fluid with vaccinia hyperimmune serum
- Growth characteristics in tissue culture
- PCR
  - More accurate, less cumbersome
  - Best for distinguishing which poxvirus

**Smallpox Vaccination**

**Pre exposure**

- Exclusions (in patient or household):
  - Pregnancy
  - History of atopic dermat
  - Steroids
  - Antiviral drug use
  - Cardiac risk factors
  - Immune-compromising illnesses
  - Immunocompromised household contact

**Post exposure**

- Immediate vaccination (or boosting) of all potential contacts:
  - Clinical “take” within three years
  - Confers immunity
  - Given within 4 days (or up to 7 days) of exposure
  - Most effective if given <24 h post exposure
  - Limited data: vaccine + VIG more effective than vaccine alone

**Specimen Collection**

Attempt to “Rule In” Another Dx

- Unroof vesicle with sterile lancet
- Swab base of vesicle vigorously with sterile swab
- Swab swab onto 3 areas of a clean slide
- Allow to air dry
- To lab for immediate fixing and staining
- VZV may have asper or chickenpox
  - Collect at least three specimens from each patient:
    - DFA: rapid but need good specimen
    - IFA: as above
    - Vario1 PCR: CDC, USEARRS, some state labs
    - Serology IgG for evidence of prior VZV (should be negative at time of rash)
    - VZV culture: results in days, place in viral transport media
    - EM: taken days

**Smallpox Infection Control**

- Use of smallpox vaccine up to 4 days after exposure should protect those exposed from developing disease or markedly attenuate the severity of their illness.
  - Contraindications to vaccination apply only in pre-event scenario
  - In the event of actual disease outbreak there are no absolute contraindications to vaccination.
  - Atopic dermat, active eczema, even pregnancy should not preclude vaccination
- In 2007 Acardis live attenuated vaccine ACAM 2000 approved by the FDA and is in the national stockpile as the older Dryvax is no longer manufactured.
  - New product is grown in Vero cells and not calf skin
- Quarantine of individuals in their homes for a period of 17 days

**Therapy: Variola**

- Supportive care
- No FDA approved chemotheraphy currently available
- Most promising:
  - Tecovirimat (SIGA STA-246 or Anectyl) an acyclocide inhibitor with broad orthopoxvirus inhibition and excellent protection in animal models
  - Has been used in human cases of disseminated vaccinia as well
  - Two million treatment courses being stockpiled even before FDA approval
  - Will be used under IND for smallpox, monkeypox and vaccinia
  - Capsid, suspension and IV formulations
  - No serious side-effects reported
- Other drugs with in vitro activity vs variola:
  - Cidofovir: cidofovir ribavirin
  - Adenovir: adenovirin
  - Vidarabine: adenine arabinoside, only benefit in small animal models
  - Methisoxime: no therapeutic efficacy vs variola

**Variola (c) 2013 Infectious Disease Board Review Course**
Question 3
Which one of the following is FALSE regarding the pregnant woman with smallpox and pneumonic symptoms?
A. There is a high incidence of spontaneous abortion or neonatal infection in cases of smallpox in pregnancy
B. Continuation of acyclovir is not indicated once the smallpox diagnosis is confirmed
C. Considering her pulmonary symptoms this patient should be considered exceptionally infectious to HCWs
D. The patient's family members should be quarantined for two weeks in their home
E. A nurse who cared for this patient who has severe eczema treated with steroids should be exempted from vaccination because of the increased risk of disseminated Vaccinia.

Answer (and discussion) Question 3
Which one of the following is FALSE regarding the pregnant woman with smallpox and pneumonic symptoms?
A. There is a high incidence of spontaneous abortion or neonatal infection in cases of smallpox in pregnancy (true, this is why in the event of true outbreak/epidemic even pregnant women will be recommended to be vaccinated)
B. Continuation of acyclovir is not indicated once the smallpox diagnosis is confirmed (acyclovir has no activity against Variola)
C. Considering her pulmonary symptoms this patient should be considered exceptionally infectious to HCWs (even non coughing patients can transmit smallpox, this woman with possible Variola pneumonia may be even more infectious)
D. The patient's family members should be quarantined for two weeks in their home (they should be examined and vaccinated immediately but they should be quarantined as well during the incubation period)
E. A nurse who cared for this patient who has severe eczema treated with steroids should be exempted from vaccination because of the increased risk of disseminated Vaccinia. (In a non outbreak setting severe eczema is a contraindication for vaccination, in an actual exposure the risk of developing clinical smallpox is a worse outcome than those associated with the complications of vaccination and exemptions are removed)

Conclusions
• With the exception of anthrax, none of the Category A agents has environmental stability after release, especially outdoors
• With the exception of smallpox and pneumonic plague the category A agents are NOT transmissible in a health care setting
• Release indoors may allow for significant exposure to many individuals
• The use of quinolones and tetracyclines is protective for anthrax, plague and tularemia and are initial rec for all ages and pregnancy
• Early recognition of the disease is critical to saving lives with each of these agents

Summary Recommendations
Bacterial Threat Agents

<table>
<thead>
<tr>
<th></th>
<th>Anthrax</th>
<th>Plague</th>
<th>Tularemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children (non-contact)</td>
<td>60 days antitoxin 7 days antitoxin 14 days antitoxin</td>
<td>60 days antitoxin 7 days antitoxin 14 days antitoxin</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children (non-contact)</td>
<td>60 days antitoxin 7 days antitoxin 14 days antitoxin</td>
<td>60 days antitoxin 7 days antitoxin 14 days antitoxin</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children (non-contact)</td>
<td>60 days antitoxin 7 days antitoxin 14 days antitoxin</td>
<td>60 days antitoxin 7 days antitoxin 14 days antitoxin</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Supplementary Material
• Due to time constraints, the following material could not be included in a 40 minute lecture but is included for your review.
• Some questions from this additional material will be in the review questions.
**Viral hemorrhagic fevers**

- *Francisella tularensis* (tularemia)
- *Clostridium botulinum* toxin (botulism)
- *Yersinia pestis* (plague)
- *Bacillus anthracis* (anthrax)
- *Variola major* (smallpox)

**CDC’s Threat Agent Categories**

**Category A**
- *Bacillus anthracis* (anthrax)
- *Yersinia pestis* (plague)
- *Variola major* (smallpox)
- *Clostridium botulinum* toxin (botulism)
- *Francisella tularensis* (tularemia)
- Viral hemorrhagic fevers

**Category B**
- *Coxiella burnetii* (Q fever)
- *Brucella species* (brucellosis)
- *Burkholderia mallei* (glanders)
- *Ricinus communis* (castor beans) ricin toxin
- *Staphylococcus enterotoxin B*

**Category C**
- Nipah virus
- hantaviruses
- tickborne hemorrhagic fever viruses
- tickborne encephalitis viruses
- yellow fever
- yellow fever multiresistant tuberculosis

**Septicemic Plague**

- All bubonic and pneumonic plague patients have intermittent low level bacteremia.
- Moribund patients with plague have high density bacteremia (>100/μL) i.e. peripheral smear positive.
- Some patients develop high level bacteremia rapidly after inoculation without developing detectable lymphadenitis - septicemic plague.
- Higher mortality than bubonic plague.
- Hematogenous seeding of almost any organ in all forms of plague.
  - Liver & spleen most commonly infected in autopsy series.
  - Secondary toxin effects on heart and kidneys.
  - Clots in small, aerial vessels

**Francisella tularensis**

**Tularemia**

- Contagious: not from patients
- Infective dose: 10-50 organisms
- Incubation period: 1-21 days (average 3-5 days)
- Duration of illness: ~2 weeks
- Mortality:
  - treated: low
  - untreated: moderate
- Persistence of organism: months in moist soil
- Vaccine efficacy: ~80% but not generally available

**Tularemia Diagnosis**

- Suspect if:
  - Pneumonia with negative blood cultures
  - No response to β-lactam antibiotics
- Consider if:
  - Clustering of acute, severe respiratory illness in previously healthy persons
- Suspect focal if:
  - Clustering of cases in urban setting
  - No difference in outbreak epi by age or sex

**Tularemia Therapy**

- Streptomycin 1 g IM bid x 10-14 d
  - "Drug of Choice"
- Gentamicin 3-5 mg/kg IV/d x 10-14 d
  - The drug you’ll actually have

AlTERNATIVES:

- Ciprofloxacin 400mg IV q 12hr
- Doxycycline 100mg IV q 12hr
- Chloramphenicol 15mg/kg IV qid: Relapse common if duration of Rx < 14 days
Tularemia
Post-Exposure Prophylaxis

• Aerosol exposures
  – Doxycycline 100 mg PO bid x 14 d
  – Ciprofloxacin 500mg po bid x 14 d

• Not advised for possible natural exposures

Smallpox
Additional material

Smallpox Outbreak
Meschede, Germany 1970

Smallpox Complications

• Cough and bronchitis (occasional)
  – Implications for transmission

• Pulmonary edema
  – Frequent in hemorrhagic and flat-type variants

• Arthritis and osteomyelitis
  – 1-2% of cases, usually children
  – Destruction of growth plate
  – Bilateral joint involvement, usually elbows
  – Permanent osteoarticular deformities

Scabs form 8-14 days after disease onset

– Leave depressed depigmented scars
– Virus readily recovered from scars throughout convalescence
– Patients should be isolated until all scabs separate

(c) 2013 Infectious Disease Board Review Course


**Botulinism**

- Most cases are associated with home canned vegetables.
  - Seven serotypes (A to G) of Bot tox
    - Type A most lethal, 6 least
  - The most toxic substances known:
    - <10 μg 1 mg/kg
    - 1g could kill 1 million people
  - Slightly less toxic via inhalation:
    - 3 mg/kg
  - Some disease whether ingested, inhaled or injected
  - Very difficult to identify in body fluids due to extreme toxicity even at low doses
  - When "weaponized" into crystalline form is highly stable


**Botulism**

- Aerosolized or foodborne botulinum toxin weapon would cause:
  - Acute symmetric, descending flaccid paralysis
  - Prominent bulbar palsy: diplopia, dysarthria, dysphagia, and dysphonia
  - Normal mental status i.e. alert and oriented
  - Typically present 12 to 72 hours after exposure
- Effective response to a deliberate release of botulinum toxin will depend on:
  - Timely clinical diagnosis
  - Case reporting
  - Epidemiological investigation.
- Potentially exposed to botulinum toxin:
  - Closely observed
  - Those with signs of botulism require prompt tx with antitoxin and supportive care
  - Potentially mechanical ventilation for weeks or months
  - Treatment with antitoxin should not be delayed for microbiological testing.
- *Botulinum toxin is made clinically*

(Botulinum in the United States, 1989-1996. CDC National Center for Infectious Diseases 1996)

**Clostridium botulinum**

In 1995 Iraq admitted to the UN inspection team to having produced 10,000 L of concentrated botulinum toxin, “10,000 L were loaded into military weapons, none was discovered after the US invasion in 2003

3 German workers exposed to Bot A toxin during an animal necropsy

<table>
<thead>
<tr>
<th>Humans (n=3)</th>
<th>Monkeys (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th day post-exposure:</td>
<td>12-18 h post-exposure:</td>
</tr>
<tr>
<td>Muscle weakness:</td>
<td>respiratory weakness</td>
</tr>
<tr>
<td>Diplopia:</td>
<td></td>
</tr>
<tr>
<td>Dysarthria:</td>
<td></td>
</tr>
<tr>
<td>Dysphonia:</td>
<td></td>
</tr>
<tr>
<td>Supranuclear gaze:</td>
<td></td>
</tr>
<tr>
<td>Nystagmus:</td>
<td></td>
</tr>
<tr>
<td>Dystonia:</td>
<td></td>
</tr>
<tr>
<td>Ptosis:</td>
<td></td>
</tr>
<tr>
<td>Pseudobulbar signs:</td>
<td></td>
</tr>
<tr>
<td>Hemiparesis:</td>
<td></td>
</tr>
<tr>
<td>Normal EMGs despite paralysis:</td>
<td></td>
</tr>
<tr>
<td>Elevated CPK:</td>
<td></td>
</tr>
</tbody>
</table>

Foodborne Botulism

US cases types A and B in 1973-74 (n=35-55)

- Signs:
  - Alert Mental status 90%
  - Arm weakness 75%
  - Ptosis 73%
  - Leg weakness 69%
  - Gaze paralysis 65%
  - Diminished gag 65%
  - Facial palsy 63%
  - Tongue weakness 58%
  - Pupils dilated/fixed 44%
- Symptoms:
  - Dysphagia 96%
  - Dry mouth 93%
  - Diploplia 91%
  - Dysarthria 84%
  - Fatigue 77%
  - Arm weakness 73%
  - Constipation 73%
  - Leg weakness 65%
  - Blurred vision 65%
  - Nausea 64%
  - Dyspnea 60%
  - Vomiting 59%
  - Sore throat 54%

- Infective dose: 0.001 µg/kg
- Incubation period: 18 - 36 hours
- Dry mouth, double vision, droopy eyelids, dilated pupils
- Progressive descending bilateral muscle weakness & paralysis
- Respiratory failure and death
- Mortality 5-10%, up to 25%

Botulism

Control of Intoxication Spread

- No person to person transmission
- Minute quantities acquired by ingestion, inhalation, or by absorption can cause death and may be on carried on the skin of an exposed individual
- All materials suspected of containing toxin must be handled with CAUTION!
- Toxin is denatured with heat (>85°C for 5 min) and rapidly by routine chlorination or aeration of water.
- May retain potency in untreated food, water or beverages for several days

Hemorrhagic Fever Viruses

- Contagious --- Moderate
- Infective dose --- 1-10 virions
- Incubation period --- 4-21 days
- Duration of illness --- 7-16 days
- Mortality --- variable
- Persistence of organism --- unstable
- Mostly non-endemic in U.S.
- No FDA approved vaccines