Bioterrorism
Gregory J. Martin, M.D.
Captain
Medical Corps, U.S. Navy
Infectious Disease Service
National Military Medical Center
Uniformed Services University

The opinions expressed in this talk are mine and should not be construed as official views of the US Navy nor the Department of Defense

FDA unapproved use of antibiotics and vaccines will be discussed

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 morbidity 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 mortality rates and major health impact

www.bt.cdc.gov/bioterrorism

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

Off-Label Usage
- FDA unapproved use of antibiotics and Vaccines

Financial Relationships with Relevant Commercial Interests
- None

Resolution: N/A

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 6h post admission.
  - You arrive on the ward just as the patient is being transferred to the ICU for hypotension
Case 1

- While the patient is transferred you look at the peripheral smear that has been reported by the night tech as "GNRs" (Gram negative rods)
- When you point out that they look like GPRs (Gram positive rods) he says "probably a contaminant diphtheroid"
  - In 4/4 bottles in 6 hours?!
  - What is your differential dx?

Gram stain from blood culture bottle

Gram stain of colony from blood agar plate

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 IS systems
   - Blood cx likely positive early in Inhaled Illness
2) Two positive non-culture tests: PCR, γ phage or serology

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

Serology:
- FDA approved, Immunetics QuickELISA 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 >24h
- no role for Gram staining of nasal swabs

Anthrax: Case Definition

Anthrax Toxin Effects

Plasmid Mediated Toxin Production

Edema Factor (EF)
MW 89,000
Protective Antigen (PA)
MW 81,000
Lethal Factor (LF)
MW 90,000

Edema in Skin
(Rabbits, Guinea Pigs)
Increased Cyclic AMP

PA & LF or PA & LF bind on cell surface, are internalized and these toxins when released in cytosol causing cell damage or cell death

Pathology
(Rats, mice)
Macrophage lysis

Cutaneous Anthrax

>95% of naturally occurring cases

- Signs of cutaneous anthrax:
  - edema out of proportion to lesion size
  - lack of pain during initial stages
  - Gram stain: paucity of neutrophils
  - regional adenopathy common
  - >90% of lesions on exposed face, neck, arms and hands
- May occur in BW setting as spores are inoculated into skin
- Fatal only if untreated and progresses to bacteremia

Cutaneous Anthrax

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

CSF – Fatal Florida case

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

Human Dispersion

Fluorescence to Collector (%)
Gastrointestinal Anthrax
1-3% of naturally occurring cases

- Requires ingesting significantly more spores than inhalation to yield infection
- Typically undercooked or raw meat
- Oropharyngeal or intestinal disease
- Unlikely from BW use but high morbidity
- Treat like inhalational cases

Inhalational Anthrax
(<1% of natural cases)

- Incubation period:
  - 1 to 7 days (7-10 days or longer)
- Spore germination:
  - Taken into alveolar macrophages
  - Germination begins within hours
- Proliferation within macrophages:
  - NOT AN AIRSPACE PROCESS
- Transport to mediastinal nodes
- Continued proliferation within mac until eventual dissemination in the bloodstream to meninges, GI, etc.

Pathology:
- Arthritis and hemorrhage
- Hemorrhagic mediastinitis
- Sepsis
- Meningitis

Inhalational Anthrax Versus Influenza
Clinical Data

<table>
<thead>
<tr>
<th>Anthrax</th>
<th>Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBC:</strong></td>
<td>CBC:</td>
</tr>
<tr>
<td>- WBC high or normal</td>
<td>- WBC low or normal</td>
</tr>
<tr>
<td>- Hemocoagulation</td>
<td></td>
</tr>
<tr>
<td><strong>CXR:</strong></td>
<td>CXR:</td>
</tr>
<tr>
<td>- Widened mediastinum</td>
<td>- Normal or infiltrate in severe cases</td>
</tr>
<tr>
<td>- Pleural effusions = infiltrate</td>
<td></td>
</tr>
<tr>
<td><strong>CT scan:</strong></td>
<td>CT scan:</td>
</tr>
<tr>
<td>- Enlarged mediastinal nodes</td>
<td>- Negative, NO adenopathy</td>
</tr>
<tr>
<td>- Mediastinal edema</td>
<td></td>
</tr>
<tr>
<td><strong>Micro:</strong></td>
<td>Micro:</td>
</tr>
<tr>
<td>- Blood culture+ 6-24 hr (if before antigen)</td>
<td>- Rapid flu EIA + (70% sensitive)</td>
</tr>
</tbody>
</table>

Inhalation Anthrax vs Flu - ILI vs CAP

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Inhalation anthrax</th>
<th>Influenza like illness</th>
<th>Community acquired pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>82%</td>
<td>98% vs 88.6%</td>
<td>48% vs 8.9%</td>
</tr>
<tr>
<td>Lack of sore throat</td>
<td>83%</td>
<td>56% vs 66%</td>
<td>75% vs 6.9%</td>
</tr>
<tr>
<td>Lack of nasal symptoms</td>
<td>73%</td>
<td>19% vs 66%</td>
<td>56% vs 7.7%</td>
</tr>
<tr>
<td>Lack of headache</td>
<td>97%</td>
<td>14% vs 66%</td>
<td>62% vs 7.6%</td>
</tr>
<tr>
<td>Lack of myalgias</td>
<td>95%</td>
<td>9% vs 66%</td>
<td>58% vs 7.5%</td>
</tr>
<tr>
<td>Fever &gt; 37.8°C</td>
<td>73%</td>
<td>7% vs 66%</td>
<td>53% vs 7.3%</td>
</tr>
<tr>
<td>Cough</td>
<td>95%</td>
<td>39% vs 66%</td>
<td>76% vs 7.7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>100%</td>
<td>96% vs 66%</td>
<td>NA</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>27%</td>
<td>NA</td>
<td>23% vs 7.1%</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>8%</td>
<td>NA</td>
<td>20% vs 7.6%</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>83%</td>
<td>NA</td>
<td>35% vs 7.6%</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>64%</td>
<td>NA</td>
<td>32% vs 7.4%</td>
</tr>
</tbody>
</table>

Symptoms:
- Chills | 83% | NA | 59% vs 7.3% |

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 scan as mediastinal findings are better seen
- Pleural effusions are common
  - Bilateral
  - Bloody
  - Indication for early chest tube placement
Anthrax Infection Control

- 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 should be handled carefully as sporulation begins to occur 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

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>&lt; Byo or &lt;45 kg: 2.2 mg/kg bid</td>
<td>80 mg/kg/d divided tid</td>
</tr>
<tr>
<td>Amox</td>
<td>500 mg tid</td>
<td></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: amoxicillin 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

Treatment of Clinical Anthrax

**NOT prophylaxis**

- First Line:
  - Ciprofloxacin or other quinolones (linezolid, etc) are the backbone
  - Dose cysticercus resistant strains are more difficult to produce in vitro
- Penicillins and cephalosporins: effective but strains with potent β-lactamase activity occur. PCN achieves poor levels in granulomas.
- Shut Down Toxin production:
  - Clindamycin and rifampin act at ribosomal level to halt protein synthesis
- CNS penetration (cases present with concomitant meningitis):
  - Imipenem, meropenem, ceftriaxone, or chloramphenicol
- Ciprofloxacin, clinda and Doxy all get poor CNS levels
- Steroids:
  - Consider with extensive edema (cutaneous d/o, mediastinal edema, or meningitis
- Immune Therapy: (remain under IND for Emergency Use Authorization)
  - Anthrax immune globulin (AIG)
  - AntiPA monoclonal Ab: MAB-1301 (Valentis)
- Although pending FDA approval both are already in national stockpile

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
B. Staff who cared for the patient prior to the recognition of the anthrax dx should initiate ciprofloxacin or doxycycline prophylaxis
C. Blood agar plates in the lab are potentially sources of 2⁺ cases
D. Most automated blood culture systems will identify B. anthracis in this patient’s blood
E. Switching antibiotics to levofloxacin and rifampin is appropriate

Answer (and discussion) Question 1

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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

Case 2

- 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

Plague

- Gram-negative, non-motile, cocccobacillus
- Bipolar “safety-pin” appearance (Giemsa or Wayson Stain NOT Gram stain)
- Facultative intracellular pathogen
- Lymphotropism and ability to evade host immune response like other Yersiniae
- American and European populations have essentially no immunity
- Aerosols extremely sensitive to environmental degradation, esp daytime UV.
  - organisms viable at most for a few hours after dissemination in night scenarios.

Yersinia pestis

Laboratory Characteristics

- Grows well on standard Blood or MacConkey agar plates.
- Grows readily in the 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
• Naturally acquired:
  – Mostly bubonic disease after the bite of an infected flea
  – Pneumonic plague presentations are less common, non specific and very varied.
  – Typically hematogenous spread from the bubo i.e. secondary pneumonic plague
  – Uncommon as primary plague pneumonia acquired from a coughing animal/human
    with pneumonic plague
  – Review of 27 cases in New Mexico from 1965-1989: 8 of 27 were fatal.
    – All 8 deaths patients <6 yo. and related to failure to initially treat with appropriate osteo.

• BW scenario:
  – primary inhalation pneumonia is most likely presentation
  – human to human transmission via fleas unlikely in developed world settings
  – secondary cases from pulmonary cases are possible.
  – Flea transmission from infected animals to humans is documented.

### Plague Clinical Presentations

![Image of Plague Clinical Presentations]

**Hospital Infection Control**

- One of the internationally quarantinable diseases.
- Uncomplicated, promptly treated cases - no risk to others.
- Cough or pneumonia- strict respiratory isolation for at least 48h or until sputum is negative.
  - negative pressure room
  - N95 masks for HCWs
- Universal precautions with aspirates, blood, etc.
  - Alert micro lab so appropriate precautions are taken.
  - Close contacts of pneumonic cases: doxycycline or ciprofloxacin x 7 days.

www.cdc.gov/ncidod/dvbid/plague  MMWR 1996;45:RR-14

### Pneumonic Plague

- Highest mortality of plague presentations.
  – Invariably fatal if antibiotics delayed > 24 hours after onset.
  – Exposure → Illness → Death may occur <24 hours.
- Current US mortality rates 18% overall.
  – Untreated bubonic plague: 40%.
  – Untreated septiemic 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></th>
<th>Plague</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>7 days antibiotics</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>doxycycline 2.2 mg/kg po bid or ciprofloxacin 500 mg po bid</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>doxycycline 1.6 mg/kg po bid or ciprofloxacin 500 mg po bid</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>streptomycin is no but generally not available; gentamicin or ceftriaxone can be substituted; change to po antx when stable</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>ceftriaxone 15 mg/kg IV q24h or gentamicin 3-5 mg/kg IV q8h</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>ceftriaxone 1.5-2.0 g IV q24h or gentamicin 150-300 mg IV q8h</td>
</tr>
</tbody>
</table>

Doxycycline or ciprofloxacin are alternative treatments.

- Chloramphenicol for penicillin allergic.
- 2nd gen cephalosporins not approved but effective
- Most wild strains sensitive to nearly all antx but some cases very resistant
- 25% resistant to ciprofloxacin in one US study

### Question 2

Which one of the following is TRUE regarding the diplomatic couple from Iran 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 Iran 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.

**Answer (and discussion) to Question 2**

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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 since the route of exposure was through the lungs and not a flea bite draining lymph nodes)
Case 3

• You are asked to see a 25 yo pregnant woman admitted to the ICU with “severe Varicella and viral pneumonia vs 2° bacterial pneumonia” requiring intubation

• She had been ill for “1 week prior to the onset of her rash with fever, malaise, headache and myalgias

• Her lesions started on her face, hands and feet 3 days ago at which point she rapidly developed cough and dyspnea. Admitted the previous night.

• She is currently on high dose IV acyclovir, ceftriaxone and vancomycin

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?

Variola - Smallpox

Variola vs Varicella vs Monkeypox

Smallpox

Varicella (Chickenpox):

• Monkeypox:

• Erythema multiforme:

• Contact dermatitis:

• Secondary syphilis:

• Other poxviruses:

Smallpox

Differential Diagnosis

• Varicella (Chickenpox):

• Monkeypox:

• Erythema multiforme:

• Contact dermatitis:

• Secondary syphilis:

• Other poxviruses:
Lesions

- Exanthem
  - Begins on face, hands, forearms
  - Spreads to lower extremities
  - Centrifugal distribution
  - Macules-papules-vesicles-pestules-scabs
  - 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
  - viremia
  - 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-hypopigmented-violaceous-erythematous-escabs
  - Scabs detach end of 3rd or 4th week
  - Patient infectious until all scabs detach

Specimen Collection

Attempt to “Rule In” Another Dx

- Uroof vesicle with sterile lancet
- Swab base of vesicle vigorously with sterile swab
- Smear swab onto 3 areas of a clean slide
- Allow to air dry
- To lab for immediate fixing and staining
- V2V+ may have zoster or chickenpox

- Collect at least three specimens from each patient:
  - DFA: rapid but need good specimen
  - DFA: as above
  - Variola PCR: CDC, USAMRIID
  - Some state labs
  - Serology: IgG for evidence of prior Variola (should be negative at time of rash)
  - VZV culture: results in days, place in viral transport media
  - EM: takes days

Laboratory Diagnosis

difficult to differentiate vaccinia, cowpox or monkeypox

- Electron microscopy
  - Virions on EM of vesicular scrapings

- Light microscopy
  - Eosinophil 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

WHO Website: http://www.who.int/mediacentre/factsheets/smallpox/en/index.html
NI Whitley 2003, Avantgarde Rev. 17:7-12
Smallpox Vaccination

Pre exposure
- Inclusions:\n  - Pregnancy
  - He of atopic dermat
  - Steroids
  - Cardiac risk factors
  - Immunocompromising illnesses

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

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-outbreak 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 Acambis 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 chemotherapy currently available
- Candidates:
  - Most promising is SIGA ST-246 with broad orthopoxvirus inhibition and excellent protection in animal models
    - Has been used in human cases of disseminated vaccinia as well
    - Being stockpiled even before FDA approval
    - Will be used under IND for smallpox, monkeypox and vaccinia
  - Active in vitro vs varicella
    - idoxifur cyclo idoxifur
    - adebolvar ribavirin
    - Vidarabine
      - Shows promise in small animal trials
    - Methisazone
      - Not licensed efficacy in varicella

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/BT exposure 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 cares for this patient who has severe eczema treated with steroids should be exempted from vaccination because of the increased risk of disseminated Vaccinia.

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 healthcare 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>Prophylaxis</th>
<th>Anthrax</th>
<th>Plague</th>
<th>Tularemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (do not exceed prophylaxis)</td>
<td>ciprofloxacin 500 mg po bid</td>
<td>doxycycline 2.2 mg/kg po bid</td>
<td>ciprofloxacin 100 mg po bid</td>
</tr>
<tr>
<td>Adults</td>
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<td>ciprofloxacin 100 mg po bid</td>
</tr>
</tbody>
</table>

**Treatment**

| Children (do not exceed prophylaxis) | ciprofloxacin 500 mg po bid | doxycycline 2.2 mg/kg po bid | ciprofloxacin 100 mg po bid |
| Adults | ciprofloxacin 500 mg po bid | doxycycline 2.2 mg/kg po bid | ciprofloxacin 100 mg po bid |

**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.

**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, acral vessels.
    - purpura, necrosis, gangrene, DIC.

**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**
- Caissiella burnetti (Q fever)
- Brucella species (brucellosis)
- Burkholderia mallei (glanders)
- Rickettsia conorii (eastern louer)
- Staphylococcus enterotoxin B

**Category C**
- Nipah virus
- Hantaan virus
- Tickborne encephalitis viruses
- Tickborne hemorrhagic fever viruses
- Yellow fever
- Multidrug-resistant tuberculosis
Tularemia

- Contagious: no
- 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%
- 1969 WHO estimate: aerosol dispersal of 50 kg of F. tularensis over an area with 5 million would result in 250,000 incapacitating casualties, including 10,000 deaths
- Illness expected to persist for several weeks and disease relapses to occur during ensuing weeks or months.
- Vaccinated individuals only partially protected against aerosol exposure.
- CDC estimates of economic impact of aerosol attack to be $5.4 billion for every 100,000 persons exposed.

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 foul play 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 Outbreak

Meschede, Germany 1970

"Unusual in the extent of transmission that took place in a non-endemic smallpox area and in that a number of cases occurred in persons who had not face-to-face contact with the patient"


Clinical Course of Smallpox from Handbook of the Common Acute Infectious Diseases. Auralgan Research Division.
**Smallpox Clinical Disease**

- Scabs form 8-14 days after disease onset
  - Leave depressed depigmented scars
  - Virus readily recovered from scabs throughout convalescence
  - Patients should be isolated until all scabs separate

![Early Vesiculation, day 6](image)

---

**Smallpox Complications**

- **Encephalitis**
  - 1 in 500 cases of Variola major
  - 1 on 2000 cases of Variola minor
- Keratitis, corneal ulceration
  - Blindness in ~1% of cases
- Infection in pregnancy
  - High perinatal fatality
  - Congenital infection

---

**Botulinism**

- Most cases are associated with home canned vegetables
- Seven serotypes (A to G) of Bot tox
  - "Type A most fatal, & least frequent"
- The most toxic substances known:
  - LD50 1 ng/kg
  - 1g could kill 5 million people
- Slightly less toxic via inhalation:
  - 3 ng/kg
- Same 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](image)

---

**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

---

**Clostridium botulinum Botulism**

In 1995 Iraq admitted to the UN inspection team to having produced 10,000 L of concentrated botulinum toxin; ~10,000L were loaded into military weapons.

Outbreaks of foodborne botulism by state, 1950-1996

Botulism in the United States, 1899-1994. CDC National Center for Infectious Diseases

---

**Botulism**

- Aerosolized or foodborne botulinum toxin weapon would cause:
  - acute symmetrical descending flaccid paralysis
  - prominent bulbar palsy: dyspnea, 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 treatment with antitoxin and supportive care
- Potentially mechanical ventilation for weeks or months
- Treatment with antitoxin should not be delayed for microbiological testing.
- Diagnosis of botulism is made clinically

CDC Botulism: Information and Guidance for Clinicians www.bt.cdc.gov/agent/botulism/clinicians/index.asp

16 June 2006

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Botulism misdiagnoses

Misdiagnosis
- Guillain-Barre
  - esp Miller-Fischer variant
- Myasthenia gravis
- Eaton-Lambert syndrome
- Tick paralysis
- CVA
- Drug overdose
- Hypothyroidism
- Conversion disorder
- Inflammatory myopathy

How to distinguish from botulism
- Ascending paralysis
  - EMG findings
- Recurrent hx, response to edrophonium
- Increased strength with sustained response to edrophonium
- Paresthesias, ascending paralysis
- Paralysis often asymmetric, CT/MRI
  - Hx of exposure; tox screen
  - TTFs
- Normal EMGs despite paralysis
- Elevated CPK

Arnon et al. JAMA. 2001;285:1059-1070

Inhalation botulism: humans and primates
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>3rd day post-exposure:</td>
<td>12-18 h post-exposure:</td>
</tr>
<tr>
<td>-recess in throat</td>
<td>-respiratory weakness</td>
</tr>
<tr>
<td>-dysphagia</td>
<td>-gag</td>
</tr>
<tr>
<td>-dilatation</td>
<td>-dysphagia</td>
</tr>
<tr>
<td>Followed by:</td>
<td>-sustained weakness of facial and neck muscles</td>
</tr>
<tr>
<td>4th day post-exposure:</td>
<td>-respiratory failure</td>
</tr>
<tr>
<td>-difficulty rising</td>
<td>-difficulty swallowing</td>
</tr>
<tr>
<td>-several nasal discharge</td>
<td>-nasal discharge</td>
</tr>
<tr>
<td>-markary disfunct and nystagmus</td>
<td>-nystagmus, dysphagia</td>
</tr>
<tr>
<td>-reduced speech</td>
<td>-vomiting</td>
</tr>
<tr>
<td>-marked ptosis</td>
<td>-ptosis</td>
</tr>
<tr>
<td>-sustained weakness</td>
<td>-generalized weakness</td>
</tr>
<tr>
<td>2nd-4th day post-exp:</td>
<td>-death in some animals</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%
  - Hyporeflexia/areflexia 40%
  - Nystagmus 22%
  - Ataxia 17%

- Symptoms:
  - Dysphagia 96%
  - Dry mouth 93%
  - Diplopia 91%
  - Dysarthria 84%
  - Fatigue 77%
  - Arm weakness 73%
  - Constipation 73%
  - Leg weakness 69%
  - Blurred vision 65%
  - Nausea 64%
  - Dysphagia 60%
  - Vomiting 59%
  - Sore throat 54%
  - Dizziness 51%
  - Abdominal cramps 42%
  - Diarrhea 19%
  - Paresthesia 14%

Foodborne Botulism
- 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

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Potential Viral BW agents

- Chordopoulosviridae
  - Variola, monkeypox, others
- Togaviridae
  - VEE, EEE, WEE, others
- Arenaviridae
  - Lassa, SAHFs
- Bunyaviridae
  - CCHF, RVF, HPS, HFRS
- Filoviridae
  - Ebola, Marburg
- Flaviviridae
  - DEN, SLE, WNV, JE, YF

- Smallpox
- Hemorrhagic fevers
- Viral Encephalitides
- Pulmonary syndromes

Naturally Zoonoses
- Vector-borne
- Aerosol transmitted

Viral Hemorrhagic Fevers

- 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