42nd Interscience Conference on Antimicrobial Agents and Chemotherapy

Convener: Nancy Khardori, M.D.

Faculty

Nancy Khardori, M.D., Ph.D. – Overview, Anthrax
David Carpenter, Ph.D. – Laboratory Diagnosis of Biological Weapons
Subhash Chaudhary, M.D. – Biological Terrorism – Care of Children
Janak Koirala, M.D., M.P.H – Botulism and Tularemia
James Goodrich, Ph.D., M.D. – Small Pox, Viral Hemorrhagic Fevers
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Nancy Khardori, M.D.
Division of Infectious Diseases
Southern Illinois University
School of Medicine
Springfield, Illinois, USA
“Infectious Disease is one of the few genuine adventures left in the world.”

“Infectious Disease is one of the great tragedies of living things - the struggle for existence between different forms of life . . Incessantly the pitiless war goes on, without quarter or armistice - a nationalism of species against species.”

Hans Zinsser- Rats, Lice and History (1934)
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Infectious Agents as Tools of Mass Casualties

- Bubonic plague killed a quarter (approx. 25 million) of the European population in the 14th century
- Small pox, measles, plague, typhus and influenza Estimated to kill 95% of pre-Colombian native American populations.
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Infectious Agents as Tools of Mass Casualties
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

IAATOMIC

Influenza Pandemic killed 21 million people between 1918 - 1919
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM
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OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

IAATOMC

In the US, approximately 170,000 people
die from infectious diseases each year

Worldwide Infectious Diseases remain the
major causes of death
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

IAATOMC
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

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Global nature and impact of Infectious Diseases threats

”The threat of bioterrorism and the spread of Infectious Diseases”

US Senate Committee on Foreign Relations
Heyman, WHO, September 5, 2001
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Definition

Bioterrorism “The intentional release of viruses, bacteria or toxins for the purpose of harming and killing civilians.”

CDC July, 2001
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Bioterrorism, National Security, and Law

Bioterrorism - “The intentional use of a pathogen or biological product to cause harm to a human, animal, plant or other living organism to influence the conduct of government or to intimidate or coerce a civilian population.”

Gostin et al, JAMA, August 7, 2002
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Bioterrorism, National Security, and Law

❖ The Model State Emergency Health Powers Act (MSEHPA)
  JAMA, August 7, 2002

❖ Bioterrorism, Public Health and Civil Liberties
  NEJM April 25, 2002
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Bioterrorism, National Security, and Law

- Public Health Security and Bioterrorism Preparedness and Response Act of 2002
- Public Law 107 - 188, June 12, 2002
- Title II - To balance Public Health concerns over safety and security with need to protect legitimate scientific research and diagnostic testing
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Bioterrorism, National Security, and Law

- New provisions for the possession, use and transfer of select agents
- Responsible Facility Official (RFO) - Reporting

CDC and ASM, May - August, 2002
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Bioterrorism, National Security, and Law
» Disease Reporting Laws
» CDC Commission

Journal of Law, Medicine and ethics,
30:262-266, 2002
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

✧ One of the first recorded events - 184 BC
✧ Carthaginian soldiers used snakes against King Eumenes
✧ Catapults - Plague infected bodies into Kaffa - 1346
✧ Diseased human and animal corpses
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

1763 — British Forces – Small pox
1877 — Koch’s Postulates
1910’s — Germany-Anthrax and Glanders
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

1930’s  
    Japanese - Plague

1940’s  

1970  
    Weather Underground - ??

1972  
    R.I.S.E. - Typhoid, Diphtheria, 
    dysentery, meningitis

1978  
    Bulgarian defector - Ricin
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Historical Perspective and Trends
Related to Bioterrorism

1979  Accidental release - Anthrax, USSR
1980  Red Army – Botulism ??
1984  Rajneeshees - Salmonella
1991  Minnesota Patriots Council - Ricin
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

1995 — Aum Shinrikyo - Anthrax, botulism, Q fever, Ebola
1996 — Laboratory Workers - Shigella
1998 — L.W. Harris - Anthrax
2001 — US Postal System - Anthrax
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Historical Perspective and Trends Related to Bioterrorism

The snakes to catapults to fleas
To
capsomers
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Chronology of Antibioterrorism (Biosafety) Actions

❖ The Geneva Protocol - 1925
❖ The Biological and Toxin Weapons Convention - (BWC) 1972*
❖ The Chemical Weapons Convention - 1997
❖ The Draft Protocol to Strengthen the BWC - July, 2001
❖ The Fifth BWC Review Conference - November, 2001

*143 states and 18 signatories
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The US Program

Offensive Biological Program – 1942
The War Reserve Service
Expanded During Korean War – 1950 – 1952
Simulants released in New York City, San Francisco etc. 1949 – 1968
Nosocomial epidemic – 1950 – 1951 of S. marcescens UTI
Termination of Program – 1969 – 1970
Defensive Program Against Biological Weapons – 1953
USAMRIID – Ft. Detrick, Maryland
# OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The US Program – Agents Used

<table>
<thead>
<tr>
<th>Weaponized</th>
<th></th>
<th>Incapacitating Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lethal Agents</strong></td>
<td><strong>Incapacitating Agents</strong></td>
<td></td>
</tr>
<tr>
<td><em>Bacillus anthracis</em></td>
<td><em>Brucella suis</em></td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td><em>Coxiella burnetii</em></td>
<td></td>
</tr>
<tr>
<td><em>Francisella tularensis</em></td>
<td>Staphylococcus Enterotoxin B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venezuela equine - Encephalitis virus</td>
<td></td>
</tr>
</tbody>
</table>
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The US Program – Agents Used

Stockpiled but not Weaponized

Anticrop Agents

Rice blast

Rye stem rust

Wheat stem rust
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Repositories and Sources (Pre BWC)

- Soviet Union Experimental Work - 1920’s
- Post War Military Building programs
  - The Soviet Union
  - The Allied Biological Weapons Program
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Repositories and Sources (Post BWC)

- Iraq’s Biological Weapons Program - 1974
- Vector in Kottsovo, Novosibirsk - visited 1997
- Obolensk in Moscow, visited 2000
- Estimated 10 (possibly 17) nations possess BWAs
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Repositories and Sources (Post BWC)

- Well financed organizations - Aum Shinrikyo
- Smaller less sophisticated organizations - Rajneeshees
- Smaller groups – R.I.S.E. Weather Underground
- Individuals - Larry Wayne Harris
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The Threat

Biological Weapons System

Payload - The agent itself

Munition - Protects and maintains potency

Delivery System

Missiles

Vehicles

Artillery Shells

Aerosol sprays

Dispersion System

Explosives

Food and Water
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The “Favorable” Characteristics

- 600 to 2000 times cheaper than other weapons of mass destruction
- 0.05% the cost of a conventional weapon to produce similar number of mass casualties per square kilometers
- Technology common and easy
- Delivery systems easily available
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The “Favorable” Characteristics

- Aerosols - The most effective means of dispersion
- Invisible, silent, odorless, tasteless
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

The “Favorable” Characteristics

- Incubation period - the natural lead time
- Confusion between sporadic/endemic disease and bioterrorism
- Secondary or tertiary transmission person to person and vectors
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Consequences of Biological Weapons’ Use

- Mass effect - 1 kg anthrax can kill 100,000 people
- Overwhelmed services and health care system
- Delayed diagnosis - unfamiliarity
- High morbidity and mortality
- Economic impact (26.2 billion/100,000 persons exposed to anthrax)
- Psychological impact
- Long term effects
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Types of Bioterrorism Attacks

- Overt versus covert (more likely)
- Announced versus unannounced (more likely)

Traditional

“First Responders” Health care providers for identification
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Clues to a Potential Bioterrorism Attack

- Outbreak of rare or new disease
- Non-endemic distribution
- Off season occurrence
- Unusual epidemiology, clinical presentation, age distribution, antimicrobial resistance
- Genetically identical pathogens in geographically different areas
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category A - Potential Agents of Bioterrorism

Highest priority agents that pose a threat to national security because they -

 رائع Can be easily disseminated or transmitted person to person
 رائع Can cause high mortality
 رائع Can cause public panic and social disruption
 رائع Require special action for Public Health preparedness
## OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

### Category A - Potential Agents of Bioterrorism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacillus anthracis</em></td>
<td>Anthrax</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Botulism</td>
</tr>
<tr>
<td><em>Franciscella tulareusis</em></td>
<td>Tularemia</td>
</tr>
<tr>
<td><em>Yersinia pestis</em></td>
<td>Plague</td>
</tr>
<tr>
<td>Variola major</td>
<td>Small pox</td>
</tr>
<tr>
<td>Vector borne viruses</td>
<td>Viral hemorrhagic fever</td>
</tr>
</tbody>
</table>
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Microbiology

- Family enterobacteriaceae and genus *Yersinia*
- Grows on blood agar and MacConkey agar
- Gram negative bipolar staining coccobacilli
  - non motile, non sporulating
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

**Microbiology**

- Non-lactose fermenting
- Microaerophilic, indole, oxidase and urease negative
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

**Plague - Yersinia pestis**

**Epidemiology**

- Maintained in nature as a zoonotic infection in rodent hosts and fleas
- Epidemic bubonic plague described in biblical and medieval times
- Killed one fourth of Europe’s population in the middle ages
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

**Epidemiology**

- Most recent pandemic at the turn of 20th century originated in China
- Large outbreaks of pneumonic plague in Manchuria and India - 1910 - 1911 and 1920 - 1921
- Infected fleas released by Japan in Chinese cities - 1930’s and 1940’s
- Investigated as a biological weapon by Japan during WW II
- Studied by the US in the 1950’s
- Other countries suspected of weaponizing plague
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

**Plague - Yersinia pestis**

**Transmission**

- Contact (bite) with fleas
- Skin to regional lymph nodes
- Bacteremia, septicemia and endotoxemia
- Shock, DIC and coma
- Respiratory droplets from animals
- Respiratory droplets from infected humans
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Clinical Presentations

- Classical Bubonic plague - 84%* (14%)**
- Primary septicemic plague - 13%* (22%)**
- Primary Pneumonic plague - 2%* (57%)**

*US cases 1947 - 1996

** Mortality rate
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Clinical Presentations

- Secondary septicemic plague
- Secondary pneumonic plague
  - 12% of US cases over last 50 years
- Plague meningitis
- Plague pharyngitis
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

**Plague - Yersinia pestis**

Natural Disease Versus Bioterrorism

- Primary pneumonic plague most likely*
- Exposure to symptoms 1 - 6 (2 - 4) days
- Fever, cough, dyspnea
- Bloody, watery or purulent sputum*
- Prominent GI symptoms**

*Hemoptysis strongly suggests plague versus anthrax
**2 recent cases contracted from cats
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

**Laboratory Diagnosis** - Level A to Level B or C Lab

- Smear* and culture
  - Blood, respiratory secretions, CSF
- Acute and convalescent serology - EIA, PHA, PHIA - detect antibody to F1 antigen
- Rapid Diagnostic Tests - Antigen, IGM EIA, Immunostaining, PCR

*DFA, if available, Gram, Wright, Giemsa or Wayson*
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Antimicrobial Therapy

- Streptomycin or Gentamicin
- Tetracycline or Doxycycline
- Fluoroquinolones - In vitro and animal studies
- Chloramphenicol - Meningitis
- TMP/SMX - Sulfonamides only
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

Antimicrobial Resistance

- Rifampin, Aztreonam, Ceftazidime, Cefotetan and Cefazolin
- Rare natural resistance to tetracyclines
- Quinolone resistance
- Multidrug resistance - Plasmid mediated
- Multidrug resistance - Engineered??
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Plague - *Yersinia pestis*

Post Exposure Chemoprophylaxis

- Contact with a patient at less than 2 meters
- Prophylaxis for 7 days
- Doxycycline - First choice
- Tetracycline, sulfonamides, chloramphenicol
- Fluoroquinolones - studies in mice
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

**Vaccination**

- Killed whole cell vaccine
  - US 1946 - 1998
- Fusion Protein vaccine (F1-V antigen)
  - USAMRIID - Mice to primates
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Plague - *Yersinia pestis*

**Infection Control Procedures**

- Standard precautions for bubonic plague
- Strict isolation with droplet precautions for pneumonic plague - 48 hours of antibiotics/culture negative
- Surgical masks, gown, gloves, eye protection - HEPAF masks and negative pressure room - for aerosol generating procedures
- Dead bodies - routine strict precautions
- No need for environmental decontamination
- Rodent control measures, flea insecticides and flea barriers
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Potential Agents of Bioterrorism

Second highest priority agents because they

مرة

- Are moderately easy to disseminate
- Cause moderate morbidity and low mortality
- Require specific enhancement of CDC’s diagnostic capacity and enhanced disease surveillance
## Category B - Bacterial Agents of Bioterrorism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Coxiella burnetti</em></td>
<td>Q Fever</td>
</tr>
<tr>
<td><em>Brucella</em> species</td>
<td>Brucellosis</td>
</tr>
<tr>
<td><em>Burkholderia mallei</em></td>
<td>Glanders</td>
</tr>
<tr>
<td><em>Burkholderia pseudomallei</em></td>
<td>Melioidosis</td>
</tr>
<tr>
<td><em>Rickettsia prowazekii</em></td>
<td>Typhus Fever</td>
</tr>
<tr>
<td><em>Chlamydia psittaci</em></td>
<td>Psittacosis</td>
</tr>
</tbody>
</table>
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

**Q Fever - *Coxieilla burnetti***

**Microbiology/Epidemiology**
- Rickettsial organism - World wide zoonosis
- Cattle, sheep and goats - most common reservoirs
- Dogs, cats and birds
- No disease in infected animals
- Large number of organisms in body fluids
- Especially large number in placenta
Q Fever - *Coxieilla burnetti*

**Transmission**
- Resistant to heat and desiccation
- Highly infectious by aerosol - single organism
- Human infection - Inhalation
- Raw milk or fresh goat cheese
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

**Clinical Features**

- Incubation period 2 - 14 days
- Febrile illness
- Differential diagnosis - Atypical pneumonia, HPS, Tularemia, plague
- Culture negative endocarditis, chronic hepatitis, aseptic meningitis, encephalitis, osteomyelitis
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Natural Disease versus Bioterrorism

- Similar clinical presentation
- Incapacitating biowarfare agent
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

**Laboratory Diagnosis**
- IgM antibodies by ELISA - Diagnostic
- May detect by second week of illness
- IFA, ELISA and CFT - Reference laboratories
- Difficult to isolate
Q Fever - *Coxieilla burnetti*

**Antimicrobial Therapy**

- All cases treated to prevent complications
- Tetracycline or doxycycline for 5 - 7 days
- Erythromycin, Azithromycin and Clarithromycin?
- Tetracycline or Doxycycline + TMP/SMX or Rifampin
- Valve replacement

> 12 months for endocarditis
Q Fever - *Coxieilla burnetti*

**Post Exposure Chemoprophylaxis**

- **Immediate (1 - 7 days)** - Not effective
  - May prolong the onset of disease
- **Tetracycline or Doxycycline (8 - 12 days)** post exposure for 5 - 7 days
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxiella burnetti*

**Vaccination**

- Formalin inactivated whole cell vaccine
  - Licensed in Australia
  - Investigational in US - for at risk personnel
- Skin test required prior to vaccination
- Single dose - complete protection against natural disease
  - 95% protection against aerosol exposure within 3 weeks
- Protection for 5 years
- Live attenuated vaccine (Strain M44) - former USSR
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Q Fever - *Coxieilla burnetti*

Infection Control Procedures

- Standard precautions for health care worker
- No person-to-person transmission
- Decontamination – Soap and water or 0.5 hypochlorite
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

**Brucellosis - Brucella species**

**AKA** - Undulant Fever, Mediterranean Fever, Malta Fever

**Microbiology/Epidemiology**

- **Brucella species** - 6

  **Human pathogens** -
  
  - *B. melitensis* (goat)
  - *B. abortus* (cattle)
  - *B. suis* (pig)
  - *B. canis* (dog)

- Facultative intracellular gram negative coccobacilli
- Natural reservoirs - Herbivores
- Septic abortion and orchitis in animals
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

**Brucellosis - Brucella species**

**Microbiology/Epidemiology**

- Uncommon in the US - 0.5 cases per 100,000 population
  - Abbattier and veterinary workers
  - Unpasteurized dairy products
- Highly endemic - Southwest Asia (128 per 100,000)
  - Hazard to military personnel
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Transmission

- Stable to environmental conditions
- Long persistence in wet ground and food
- Ingestion - Infected raw milk or meat
- Inhalation - Contaminated aerosol
  Highly infectious
  10 - 100 bacteria
- Contact - Skin
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Clinical Features

- Incubation period 8 - 14 days (5 - 60 days)
- Nonspecific febrile illness
- Lumbar pain and tenderness - 60%
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Clinical Features

- GI symptoms - 7%
- Hepatosplenomegaly - 45 - 63%
- Sequale - Osteoarticular infections, Hepatitis, meningitis, encephalitis, endocarditis, pancytopenia
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

**Brucellosis - Brucella species**

Natural Disease versus Bioterrorism

- Natural disease prolonged, incapacitation and disabling
- Mortality rate 5% - Untreated
  - Endocarditis or meningitis
- Intentional large aerosol
  - Shorter incubation
  - Higher clinical attack rate
- Weaponized by the US in 1954
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Laboratory Diagnosis

- Blood cultures - 15 - 70%
- Bone marrow culture - 92%
- Longer incubation
- Slow growing oxidase positive colonies Level A
- Small faintly staining GNB Level B or C
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Laboratory Diagnosis

- Acute and convalescent serology
- SAT - IGM and IGG
  - Single titer $\geq 1:160$ active disease
- ELISA and PCR becoming available
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Antimicrobial Therapy

- Doxycycline + Rifampin - 6 weeks
- Doxycycline 6 weeks + Streptomycin 2 - 3 weeks
- TMP/SMX - Less effective
- Tetracycline + Rifampin + Streptomycin for long term therapy - Endocarditis or meningoencephalitis
OVERVIEW OF POTENTIAL AGENTS

OF BIOTERRORISM

Brucellosis - Brucella species

Post-Exposure Chemoprophylaxis

 관한 Not generally recommended

 관한 High risk exposures*

 3 - 6 weeks of one of treatment regimens

*Vaccine - Needlestick
*Laboratory exposure
*Bioterrorism
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Vaccination

✱ Live vaccine for animals
  Widely used
  Eliminated from domestic herds in the US
✱ No licensed human vaccine in the US
✱ *B. abortus* (S19-BA) - USSR and China
  Limited efficacy and annual revaccination
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Brucellosis - Brucella species

Infection Control Procedures

- Standard precautions for health care workers
- Rare person-to-person transmission - Tissue transplantation and sexual contact
- BSL - 3 Laboratory practices
- Environmental decontamination - 0.5% hypochlorite
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Melioidosis - *Burkholderia pseudomallei*

**Microbiology/Epidemiology**

- Gram negative bacilli “safety pin” appearance
- Widely distributed in the soil and water in tropics
- Endemic in Southeast Asia and Northern Australia
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Melioidosis - *Burkholderia pseudomallei*

Transmission

- Widely distributed
- Common cause of community-acquired septicemia in northeastern Thailand
- Inhalation
- Contaminated injuries
- Long incubation period - Imported
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - *Burkholderia mallei*

**Microbiology/Epidemiology**

- Gram negative bacilli - “Safety pin” appearance
- Occurs primarily in horses, mules and donkeys
- Acute form - Mules and donkeys
- Chronic form or Farcy - Horses
- Human disease uncommon
- Not found in water, soil or plants
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Glanders - *Burkholderia mallei*

**Transmission**
- Veterinarians and animal handlers
- Low transmission rate - low concentration, less virulence
- Inhalation
- Contaminated injuries
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Clinical Features
- Incubation period - 10 - 14 days
- Acute pneumonic illness*
- Acute fulminant septicemic illness*
- Acute oral, nasal, conjunctival infections
- Chronic - Skin and muscle abscesses, osteomyelitis, meningitis and brain abscess
- Reactivation disease

*Expected in case of bioterrorism
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Natural Disease versus Bioterrorism

- WW I - Glanders spread by central powers - Russian horses and mules
- Human cases in Russia increased during and after WW I
- WW II - Japanese infected horses, civilians and POWs in China
- US studied B.mallei and B. pseudomallei as BW agents - 1943 - 1944 - Not weaponized
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Natural Disease versus Bioterrorism

- USSR believed to be interested/experiments
- Aerosols (cultures) - highly infectious to laboratory workers*
- Shorter incubation period
- Acute pneumonic or septicemic illness

*Recent case - Military Research Microbiologist
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Laboratory Diagnosis

- Gram stain
- Irregular staining - methylene blue or Wright’s stain
- Culture - Standard methods
- Serology - Agglutination
  - Complement Fixation
    - More specific > 1:20
    - Single titers > 1:160 active infection
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Antimicrobial Therapy

- Oral tetracycline, amoxacillin/clavulante or TMP/SMX for localized disease for 60 - 150 days
- I/V ceftazidime + TMP/SMX for 2 weeks - PO TMP/SMX for 6 months
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Post Exposure Chemoprophylaxis

TMP/SMXX Trial
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Vaccination

No vaccine for human use
No vaccine for animal use
Candidate vaccines
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Glanders - Melioidosis

Infection Control Procedures

✎ Standard precaution for health care workers

✎ BSL 3 practices in the laboratory
# Overview of Potential Agents of Bioterrorism

## Category B - Viral Agents of Bioterrorism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
</tr>
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<tbody>
<tr>
<td>Venezuelan Encephalitis virus</td>
<td>Febrile illness - Encephalitis</td>
</tr>
<tr>
<td>Eastern Equine Encephalitis virus</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Western Equine Encephalitis virus</td>
<td>Encephalitis</td>
</tr>
</tbody>
</table>
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Viral Agents

- Mosquito-borne Alpha viruses
- VEE, WEE, EEE
- Difficult to distinguish clinically
- Encephalitis in horses, mules and donkeys precedes human cases
- VEE acute febrile illness - Encephalitis less common
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Viral Agents

- EEE and WEE - Encephalitis predominantly
- No evidence for horse-to-human or human-to-human transmission
- Diagnosis - Virus isolation, serology, PCR
- No natural aerosol transmission
- Infective dose of VEE is 10 - 100 organisms
- Viruses killed by heat and standard disinfectants
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Viral Agents

- Stable during storage and manipulation
- VEE tested as a BW agent by the US in 1950’s and 1960’s
- In a bioterrorism event - Human cases precede or concurrent with animals
- No specific therapy
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Category B - Viral Agents

- Alpha interferon and poly ICLC - Effective post exposure prophylaxis in experimental animals
- Live attenuated vaccine - IND
- Formalin-inactivated vaccine – IND*
- Standard precautions and vector control

*Booster immungen
### OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

#### Category B – Toxin Agents of Bioterrorism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ricin</td>
<td>Necrosis - ARDS</td>
</tr>
<tr>
<td>Epsilon Toxin</td>
<td>Cytotoxic - ARDS</td>
</tr>
<tr>
<td>Staphylococcal Enterotoxin B</td>
<td>Cytokines - ARDS</td>
</tr>
<tr>
<td>T2 - Mycotoxins</td>
<td>Dermal, Ocular, Respiratory and GI</td>
</tr>
</tbody>
</table>
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Ricin Toxin

- Beans of castor plant (*Ricinus communis*)
- Ubiquitous plant
- Toxin highly stable and easy to extract
- Protein cytotoxin
- Toxic by multiple routes
- Inhalation - ARDS (1-3 days) - Death
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Category B - Biological Toxins

Ricin Toxin

- Ingestion - GI, hepatic, splenic and renal necrosis
- IM injection - Necrosis of muscle and regional lymph nodes
  Moderate visceral involvement
- Antigen detection by ELISA - serum and respiratory secretions
- Paired serology
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Ricin Toxin

- PCR - Castor bean DNA
- No specific therapy
- Gastric lavage and cathartics
- Charcoal - Not useful
- Protective mask for inhalation
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Ricin Toxin

- Standard precautions for health care workers
- Hypochlorite (0.1% sodium hypochlorite) solution inactivates ricin
- Immunization - Promising in animal models
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Category B - Biological Toxins

Epsilon (Alpha) Toxin

- *C. perfringens* - 12 toxins
- One or more can be weaponized
- Alpha toxin - highly toxic phospholipase
- Inhalation - ARDS
- Thrombocytopenia and hepatic damage
- Immunoassay for toxin
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Epsilon (Alpha) Toxin

- Bacteria cultured easily
- Penicillin the antibiotic of choice
- Clindamycin or rifampin - Reduce toxin
- Veterinary toxoids widely used
- Toxoids for enteritis necroticans - humans
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Staphylococcal Enterotoxin B

- SEB - one of the exotoxins produced by S. aureus
- Protein (23-29 kd)
- Pyrogenic and GI toxicity
- Food poisoning - Improperly handled or refrigerated food
- Inhaled SEB - Lower dose (1/100th) toxic
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Staphylococcal Enterotoxin B

- ARDS - Within 12 hours
- Concomitant GI symptoms
- Contamination of food or small volume water supplies
- One of 7 agents in the US BW program prior to 1969
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Staphylococcal Enterotoxin B

- No specific therapy
- Experimental immunization reported
- A candidate human vaccine - advanced development
- Standard precautions for health care workers
- Decontamination - Soap and water
- Destroy contaminated food
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

T-2 Mycotoxins

- Trichothecene mycotoxins - Over 40
- Fusarium, Myrotecium, Trichoderma, Stachybotrys and others
- “Yellow Rain” - pigmented oily fluids
- Extremely stable in the environment
- Resist hypochlorite and autoclaving
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

T-2 Mycotoxins

- Dermal, ocular, respiratory and GI exposures
- Rapid and severe symptoms
- No specific therapy – Superactivated charcoal if swallowed
- Decontamination - soap and water
Category B - Biological Toxins

T-2 Mycotoxins

- **Contact precautions** - Standard precautions for health care workers
- **Environmental decontamination**
  - 1% sodium hypochloride and 0.1 NAOH with 1 hour contact time
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category B - Biological Toxins

Other Toxins - Potential for Bioterrorism

- Tetanus toxin - *C. tetani* - Tetanus
- Saxitoxin - paralytic shellfish poisoning
- Tetrodotoxin - fish, frogs, etc.
- Toxins - Blue green algae
  - Anatoxin – A (s)
  - Microcystin
<table>
<thead>
<tr>
<th>Agents</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella species</td>
<td>Enteritis</td>
</tr>
<tr>
<td><em>Shigella dysenteriae</em></td>
<td>Typhoid Fever</td>
</tr>
<tr>
<td><em>E. coli 157:H7</em></td>
<td>Dysentery</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Bloody Diarrhea</td>
</tr>
<tr>
<td><em>Cryptosporidium parvum</em></td>
<td>Cholera</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>
Category C - Potential Agents of Bioterrorism

Third highest priority agents include emerging pathogens that could be engineered for mass dissemination

- Availability
- Ease of production and dissemination
- Potential for high morbidity and mortality
- Major health impact
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Nipah virus
Hantavirus
Tickborne Hemorrhagic Fever viruses
Tickborne encephalitis viruses
Yellow Fever
Multidrug resistant Tuberculosis
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Nipah Virus

- Outbreak in Malaysia - 1998 - 1999
- 1 Million deaths in swine
- Encephalitis in 265 humans
- Direct contact with swine
- Mortality rate - 40%
- Eradicated from swine
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Nipah Virus

- Likely to be present in fruit bats
- Human to human transmission not documented
- No cases documented in the US
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Tickborne Encephalitis Viruses

Far Eastern, Central European, Kyasanur Forest, Louping ill, Powassan and Negishii
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Category C - Potential Agents of Bioterrorism

Tickborne Hemorrhagic Fever Viruses

Crimean-Congo Hemorrhagic Fever
Omsk Hemorrhagic Fever
Kyasanur Forest Disease
AGENTS OF BIOTERRORISM
OVERVIEW OF POTENTIAL

Detection

Biological Integrated Detection System (BIDS)

Long Range Biological Stand Off Detection System - (LRBSDS)

Short Range Biological Stand Off Detection System - (SRBSDS)
AGENTS OF BIOTERRORISM
OVERVIEW OF POTENTIAL

Personal Protection

Protective Mask - M40*
Battle Dress Overgarment (BDO)
Protective Gloves
Overboots

*HEPA-filter masks or surgical mask protection against BWs but not CWs
AGENTs OF BIOTERRORISM OVERVIEW
OF POTENTIAL

Decontamination
Mechanical Decontamination
Water filtration
Air filtration
AGENTS OF BIOTERRORISM OVERVIEW
OF POTENTIAL
Decontamination

Chemical Decontamination
M291 Skin Decontamination Kit
Soap and water
Hypochlorite solution
  0.5% for 10 - 15 minutes for gross contamination*
  5% for clothing or equipment

*Except open body cavity wound, brain and spinal cord injuries
AGENTS OF BIOTERRORISM OVERVIEW
OF POTENTIAL

Decontamination

Physical Decontamination

Dry Heat (160°C) for 2 hours

Autoclaving (121°C) for 20 minutes

Solar Ultraviolet radiation
Patient Isolation Precautions

Standard Precautions - All patients

Handwashing
Gloves*
Mask*, eye protection*, face shield*
Patient care equipment and linen

*As needed
AGENTS OF BIOTERRORISM
OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Contact Precautions - Standard Precautions Plus

- Private room - Cohort same infection
- Gloves when entering
- Gown when entering
- Limit movement or transport of the patient
- Patient care items - Surfaces - Daily cleaning
- Dedicate noncritical patient care equipment or disinfect between patients
AGENTS OF BIOTERRORISM OVERVIEW
OF POTENTIAL

Patient Isolation Precautions

Contact Precautions

Conventional Diseases
MRSA, VRE, *C. difficile*
RSV, Parainfluenza, Enteroviruses

Biothreat Diseases
Viral Hemorrhagic Fevers
Draining anthrax lesions

Enteric Infections – Incontinence
SSSS, HSV, Impetigo, Lice, Scabies
Hemorrhagic conjunctivitis
AGENTs OF BIOTERRORISM
OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Droplet Precautions - Standard Precautions Plus

- Private room - Cohort with same infection or maintain 3 feet between patients
- Mask - Within 3 feet of patient
- Limit movement and transport of the patient - place mask if needed
AGENTS OF BIOTERRORISM
OVERVIEW OF POTENTIAL

Patient Isolation Precautions

**Droplet Precautions**

**Conventional Diseases**
- Invasive *H. influenzae* disease
- Invasive Meningococcal disease
- Drug resistant pneumococcal disease
  - Diphtheria – Pertussis - Mycoplasma
  - Group A streptococcus
- Influenza - Rubella - Mumps - Parvovirus

**Biothreat Diseases**
- Pneumonic plague
PATIENT ISOLATION PRECAUTIONS

Airborne Precautions - Standard Precautions Plus

- Monitored negative air pressure room
- Respiratory protection on entry
- Limit movement and transport of the patient
  - place mask if needed
AGENTS OF BIOTERRORISM
OVERVIEW OF POTENTIAL

Patient Isolation Precautions

Airborne Precautions

Conventional Diseases
- Measles
- Varicella
- Pulmonary TB

Biothreat Diseases
- Small Pox
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Preparedness for Public Health and Medical Communities

- CDC * - Designated by DHHS
- Cooperative agreements with states and large cities
- Five areas emphasized (1999 - 2001)
  i) Preparedness, planning and readiness assessment
  ii) Surveillance and epidemiology capacity
  iii) Biological laboratory capacity
  iv) Chemical laboratory capacity
  v) Health alert network and training

*Disease reporting - a tool for preparedness
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Preparedness for Public Health and Medical Communities

_dept of defense – federal effort

_trained first responders in 120 cities

_handed over to dept of justice – 2000
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Preparedness for Public Health and Medical Communities

- FDA - Interagency group
- USAMRIID - Aeromedical isolation team
- ACP/ASIM - Pocket guide
- APIC - CDC - Bioterrorism Readiness plan
- County and City level preparedness
- Small town level preparedness
- Detection of clusters - AACERDAIC
- Immediate Immunity - Passive Antibody Administration
- Executive order – 13139 – September, 1999
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO

Privileged Access

Geographic Resources

Headquarters Geneva

Regional Offices - 6

Country Offices - 141
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM
Global Alert and Response

WHO

Collaborating Centers
Laboratories and Institutions - 250
- CDC
- USAID
- Do D-GEIS*
- Counterparts in other countries

*US Dept of Defense Global Emerging Infections Surveillance and Response System
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO

Surveillance Networks

Electronic “detective” system* and databases

International health regulations

*FluNet (> 50 yrs) 110 labs in 84 countries
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO

- Welcome Assistance

- “Deep” Experience
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Surveillance and Response

- Containing Known Risks
- Responding to the Unexpected
  - Semiautomatic electronic system
    - Health Canada
  - US based Pro-MED
  - Local online newspapers
  - Scan the world-outbreak verification
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Surveillance and Response

- Global outbreak alert and Response Network
  April 2000
- Standardized procedures
- Communication
- Guidelines for foreign nationals
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Surveillance and Response
Improving Preparedness
HealthMap
NASA and Other Satellites
TEPHINET - CDC Training Program*
Lyon, France - 2001 - Specialized training program

*Training program in Epidemiology and Public Health Interventions Network
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Surveillance and Response

Improving Preparedness

Long term preparedness working group

Early Warning and Response Network (EWARN)

Capacity building - National epidemic detection

Births and Deaths Registry
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Preparedness for Bioterrorism

- Updated Standard Guide
- Epidemiological techniques for natural outbreak
- Exchange between Public health and Veterinary Sectors
- Overseeing remaining stocks of small pox virus
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Global Alert and Response

WHO - Proactive Role

✔ Consensus resolution - World Health Assembly

✔ Investigate and verify outbreaks prior to official notification

✔ Global solutions for Global causes and consequences
OVERVIEW OF POTENTIAL AGENTS
OF BIOTERRORISM

Global Alert and Response

WHO - US Support
CDC*
USAID - First Global Strategy for Containment of Antimicrobial Resistance
NIH* - Fogarty International Center
Bureau of PRM - Malaria control

*Grants to Global Outbreak Alert and Response Network and WHO collaborating Centers
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

**Economic Impact**

- **Brucellosis scenario** - 477.7 million/100,000 exposed
- **Anthrax scenario** - 26.2 billion/100,000 exposed
- **Post attack prophylaxis program**
- **Rapid implementation**
- **Single most important means** - reducing losses
- **Economic justification**

*Kaufman et al, EID, April - June 1997*
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Preparedness for Public Health and Medical Communities

Balance
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Preparedness for Public Health and Medical Communities
OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Nature’s Biowarfare

“Modern adventurers like to up the ante, but even the most extreme sports wouldn’t produce the adrenaline of a race against pandemic influenza or a cloud of anthrax at the Super Bowl. In the field of Infectious Diseases, reality is stranger than anything a writer could dream up. The most menacing bioterroist is Mother Nature herself.”

OVERVIEW OF POTENTIAL AGENTS OF BIOTERRORISM

Frank and Ernest

Infectious Microbe Research Lab

The most important thing in this job is not letting the little things get to you.
Laboratory Diagnosis of Biological Weapons: Conventional and New Methods

David Carpenter, Ph.D.
Associate Professor
Department of Microbiology/Immunology
Southern Illinois University
School of Medicine
Springfield, Illinois, USA