Bioterrorism

John C. Rotschafer, Pharm. D.
Professor
College of Pharmacy
University of Minnesota
Overview

- Focus will be on biologic agents
- Discuss available prophylaxis & therapeutic measures
- Look at our state of preparedness on a local, state, & national level
- Consider measures for your own personal safety & that of your family
Overview

- **Terrorism (Code of Federal Regulations)**
  - The unlawful use of force and violence against persons or property to intimidate or coerce a government, the civilian population, or any segment thereof, in furtherance of political or social objectives

- **Bioterrorism**
  - Use of biological agents to intentionally produce disease or intoxication in susceptible populations to meet terrorist’s aims.

icanPREVENT webpage 2001
3 Critical Elements for Bioterrorism

- **Perpetrators**
  - State sponsored
  - Insurgent rebels
  - Doomsday/cult-type groups
  - Nonaligned terrorists
  - Splinter groups
  - Lone offenders

- **Biologic Agent**
  - >12 nations either have or are pursuing programs to develop biologic weapons
  - Reported loss of biologic agents from former Soviet Union

- **Technical means to disseminate agent**

  Osterholm, M. *Living Terrors* 2001
Logistics for Biologic Attack
Osterhom, M. Living Terrors 2001

- Variable access to biologic agents
  - Up until recently *B. anthracis* could be obtained from reference collections
  - Requires some technical know how and equipment but nothing out of the ordinary

- Methods to disperse agents generally available
  - Commercial products available that disperse small particles (≤10 microns)

- Likely a silent attack requiring several days before being detected
  - Expect unusual means of deployment
Biologic Agent Properties

- High infectivity
  - Small dose required to produce disease
  - Spread person to person for secondary effect
- Either fatal or highly incapacitating
- Can be dispersed and stable to environment once released
- No effective prophylactic or treatment measures
  - Potentially could genetically alter agent for this effect
Soviet Program

- Between 1972 & 1992 Soviet launched a full scale effort to generate biologic weapons
  - Biopreparat guise was as a pharmaceutical company
  - ~40 different facilities
  - Could produce 2 tons of anthrax spores / day

- At the program’s peak ≥ 30,000 people worked full time on this program

- Parts of program re-enacted in Iran, Iraq, & North Korea
Category A Agents

Agents that can:
- Easily disseminated or transmitted from person to person
- Causes high mortality & potential for major public health impact
- Could cause panic and social disruption
- Requires special action for public health preparedness

MMWR April 21, 2000
Class A Agents

- Variola major (Smallpox)
- *Bacillus anthracis* (Anthrax)
- *Yersina pestis* (Plaque)
- *Clostridium botulinum* toxin (Botulism)
- *Francisella tularensis* (Tularemia)
- Filioviruses
  - Ebola (Ebola hemorrhagic fever)
  - Marburg (Marburg hemorrhagic fever)
- Arenaviruses
  - Lassa (Lassa fever)
  - Junin (Argentine hemorrhagic fever)

MMWR April 21, 2000
Category B Agents

Agents that can:

– Moderately easily to disseminate
– Causes moderate mortality & low mortality
– Requires special enhancements of CDC’s diagnostic capacity and disease surveillance

MMWR April 21, 2000
Class B Agents

- *Coxiella burnetii* (Q Fever)
- *Brucella spp.* (Brucellosis)
- *Burkholderia mallei* (Glanders)
- Alphaviruses
  - Venezuelan encephalomyelitis
  - Eastern & Western encephalomyelitis
- Ricin toxin (castor beans)
- Epsilon toxin from *Clostridium perfringens*
- *Staphylococcus* enterotoxin B

MMWR April 21, 2000
Class B Agents Spread by Food and Water

- Salmonella spp.
- Shigella dysenteriae
- E. coli (O157:H7)
- Vibrio cholerae
- Cryptosporidium parvum
Category C Agents

Agents:
- Availability
- Ease of production and dissemination
- Potential for high morbidity and mortality and major health impact
Class C Agents

- Nipah virus
- Hantaviruses
- Tickborne hemorrhagic fever viruses
- Tickborne encephalitis viruses
- Yellow fever
- Multidrug-resistant tuberculosis

MMWR April 21, 2000
**Anthrax** (*Bacillus anthracis*)

- Routes of transmission: skin, GI tract, and inhalation of spores
  - Not spread person to person
- Most cases will occur in first two weeks of exposure but additional cases will present over next month *(Sverdlovsk, USSR)*
- Initial symptoms that of a cold or flu then abruptly turn to respiratory distress
  - Dyspnea and chest discomfort common
  - Rhinorrhea uncommon
- Untreated disease is ~90% fatal
  - Mediastinal widening & meningitis ~50%
  - High probability of bacteremia

Anthrax (*Bacillus anthracis*)

- Most countries attempting a biologic weapons program had or have anthrax in their arsenal (Vollum or Ames strain)
- To weaponize, product must be milled (1-5 micron size) & overcome electrostatic forces
  - Microencapsulation or surfactants (bentonite)
  - Infected dose data likely inaccurate with new forms
  - Aerial application depending on weather conditions in metro area could kill 100-400K or 1-3M people

- Pathogen attacks monocyte
  - Protective antigen with lethal factor & edema factor
  - Toxin causes release of IL-1beta & TNF-alpha
Shopping Mall Scenario
Osterholm, M.

- Anthrax spores aerosolized into ventilation system
  - Of 10,000 people present 9,000 exposed
  - Attack announced 24 hours later
- 90% of those exposed are started on antibiotic by the end of day 2
- 4950 hospitalized
  - 2925 require ICU
    • 2601 require ventilator
  - 855 deaths
In-vitro Activity of Daptomycin, Sparfloxacin, Quinupristin/Dalfopristin & Other Antibiotics against *B. anthracis* Heine, H.S. ICAAC 2000-1

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Anthrax Adjunct Therapy

- **Newer fluoroquinolones**
  - Not FDA approved but likely effective:
    - Anthrax
    - Plague
    - Tularemia
    - Brucellosis
  - Offers advantage as once a day therapy
    - In emergency can treat twice the number of patients for same volume of drug

- **Efforts also directed at blocking anthrax toxin virulence**
  - Toxin made of three proteins, 1st attaches to cell & injects the 2 other proteins
  - Have identified cell receptor for toxin & structure of lethal factor
Ciprofloxacin
USA Today October 23, 2001

- Bayer has patent on oral Cipro until December of 2003
  - $1.6B in worldwide sales in 2000
- Barr laboratories has a 1997 agreement with Bayer not to produce generic Cipro for which Bayer pays $27M per year
  - Other companies have challenged patent
- New QD products in development
  - Ranbaxy (CiproQD, CiproUTI, or CiproOD)
  - DepoMed
- Government could set aside Bayer’s patent in wartime
Anthrax Vaccine
Pink Sheet September 24, 2001

- Formerly called Michigan Department of Public Health Protective Antigen (MDPH-PA)
  - Three 0.5 ml subcutaneous injections Q2weeks
  - Followed by three 0.5 ml boosters Q6months
  - Then annual booster

- BioPort (Lansing, MI)
  - Only U.S. manufacturer
  - Given Department of Defense contract to produce anthrax vaccine
    - 30 good manufacturing process deficiencies
  - Must submit plans to FDA for manufacturing plant renovation by mid October 2001
  - FDA expected to take 4-6 months to approve
Plague (Yersina pestis)

- Acute febrile lymphadenitis or bubonic plague
  - Result of infected flea bites, rodents serve as flea reservoir
    - Generally 2-8 day incubation period following flea bite
    - Bacteria move via cutaneous lymphatics to regional lymph node
    - Y. pestis phagocytized by PMN’s where bacteria multiply
    - Sudden onset of fever, headache, chills, & weakness
      - Within 24 hours classic genital, axilla, or neck bubo (Do not IND bubo—very infectious)
      - Can have pustules, vesicles, eschar, or papular lesions
      - Purpura can progress to necrosis and distal gangrene
        » Called the Black Death
Plague (*Yersina pestis*)

- Estimates to have killed ~25% of Europe’s population
- Septicemia, pneumatic, or meningeal forms
  - Cultures of blood, sputum, bubo, CSF likely to be positive

**Pneumonic form** *(Most likely form for terrorists)*
- Patients present with fever, lymphadenopathy, chest pain, hemoptysis
- Pneumonic form can be spread person to person
- CXR consistent with bronchopneumonia, confluent consolidation, & cavities may be present
- Untreated mortality >50%
Tularemia (*Francisella tularensis*)

- Named for work done by Dr Edward Francis & in Tulare County (CA)
  - Rabbit or Deerfly fever / Marketmen or Ohara’s Disease
  - Primarily occurs between 30 & 71 degrees latitude
  - Most common between June-August & again in December *(bug & hunting season)*
  - 6 classic forms (ulceroglandular, glandular, oculoglanular, pharyngeal, typhoidal, & pneumonic)
  - Symptoms: fever, chills, headache, malaise, anorexia, & fatigue. Cough, myalgia, emesis, pharyngitis, & diarrhea
Tularemia (*Francisella tularensis*)

**Continued**

- Fever (>101 F) typically for few days, then abates, then fever & symptoms return
- Spread by bite of blood feeding insect, contact with contaminated animal products, aerosolized droplets, contaminated water, or animal bites
- No human to human transmission
- 3-5 days after bug bite get local papule which over next few days ulcerates, organism spreads via lymphatics, affected tissue will show focal necrosis and may caseate
Smallpox

- Prior to 1972, active immunization programs in the U.S. & worldwide
  - Even those previously immunized likely not protected now
- Incubation ~1-2 weeks
- Disease begins with chills, fever, headache, backache, and vomiting
- May begin with a rash which progresses on to enanthems a few days later
- Transmission person to person
- Mortality ~ 30%
Smallpox Meschede Hospital 1970

- Patient admitted with smallpox (6 day hospital stay)
- Placed in respiratory isolation, hospital was under isolation precautions for flu
- Responsible for 17 cases over following two weeks and 2 additional cases later
  - One case, patient just stayed a few minutes
- Cases occurred throughout hospital & despite patients & healthcare workers all likely being vaccinated
Smallpox Vaccine

- Currently we have 15.4 million doses of old cowpox vaccine in reserve
  - Likely not that entire supply still viable
- CDC has contract with Acambis PLC to manufacture smallpox vaccine
- Originally 20 year contract ($343M) to produce 40 million dose stockpile
- Plan to deliver new vaccine mid-2004
  - End of 2002 will have additional 54 million doses
  - U.S. contracted for additional 155 million doses

WSJ September 18, 2001
Smallpox

- Experiments underway to test cowpox vaccine using 1/5\(^{th}\) and 1/10\(^{th}\) dilutions
  - 650 patient forming 3 groups
    - Full strength, 1/5\(^{th}\), & 1/10\(^{th}\) dilutions
- Diluted could expand current 15.4 million doses into 77-154 million doses
- 4 day window to vaccinate after exposure
- Post exposure therapy
  - Cidofovir (Vistide-Gilead Sciences)
Preparation for Biological Attack
MMWR April 21, 2000

- Enhance epidemiological capacity to detect and respond to biologic attacks
- Supply diagnostic reagents to state and local public health agencies
- Establish communication programs to ensure delivery of accurate information
- Enhance bioterrorism related education and training for health care professionals
Preparation for Biological Attack
MMWR April 21, 2000

- Prepare educational materials that will inform and reassure the public during and after biologic attack
- Stockpile appropriate vaccines and drugs
- Establish molecular surveillance for microbiologic strains, including unusual or drug resistant strains
- Support the development of diagnostic tests
- Encourage research on antiviral drugs and vaccines
Officials Fear U.S. is Ill-Equipped to Deal with Biological or Chemical Terrorism

WSJ September 18, 2001
Lancet September 29, 2001

- Study of 200 hospitals, only 20% had any response plan for biochemical weapons
  - < 50% have decontamination unit with showers
  - < 33% had enough antidote for nerve gas attack
- Estimated ~3% domestic emergency responders trained in dealing with methods of mass destruction
- Last year test of preparedness in exercise simulating plague attack on Denver demonstrated our limited ability to respond
- War game exercise Dark Winter, smallpox virus released in 3 states, undetected for 9 days.
  - By end of 13 day exercise, thousands infected
  - Spread to 25 states and 15 countries
Department of Defense Armed Forces Epidemiology Board Recommendations for Prophylaxis

- **Anthrax** (*B. anthracis*)
  - Ciprofloxacin (Post Exposure & Treatment)
  - Doxycycline
- **Tularemia** (*Francisella tularensis*)
  - Ciprofloxacin
  - Doxycycline
  - Gentamicin (Treatment)
- **Plague** (*Yersina pestis*)
  - Ciprofloxacin
  - Doxycycline
  - Gentamicin (Treatment)
Department of Defense Armed Forces Epidemiology Board Recommendations for Prophylaxis

- **Q Fever** (*Coxiella burnetti*)
  - Doxycycline (Post Exposure & Treatment)

- **Glanders** (*Burkholderia mallei*)
  - Doxycycline

- **Brucellosis** (*Brucella spp.*)
  - Doxycycline
First Responder Equipment

- Tychem 10,000 Encapsulated Level A Vapor Proof Suit  
  – $780
- Air Boss PSS-100 Selfcontained Respirator  
  – $3,770
- APD 2000 Hand held Chemical Agent Detector  
  – $7655
- Mark I Nerve Agent Antidote Kit  
  – $540/case of 30
- Millennium Chemical Biological Gas Mask  
  – $297

WSJ October 15, 2001
Antibiotic Therapy

- **Two Scenarios**
  - Treatment for active infection
  - Prophylaxis following documented attack

- **Difficult to predict appropriate therapy**
  - Likely delay in identifying attack
  - Further delay in identification of agent & antibiotic susceptibility
    - Possible genetic modification could alter antibiotic susceptibility
  - Clinicians have no experience in diagnosing or treating these pathogens

- Appropriate duration is at best a guess

- No chemotherapy for viral infections
National Pharmaceutical Stockpile

- **Immediate Supply of Antibiotics**
  - 12 hour push packages
  - Under Federal government control
    - Centers for Disease Control and Prevention
  - Initial shipment 50 tons of material for anthrax, smallpox, tularemia, and plague for 2 million

- **Reserve Supply of Antibiotics**
  - Vendor Managed Inventory Packages (VMI)
  - Under Federal government control
    - Centers for Disease Control and Prevention
    - Shipped within 24-36 hours

- Antibiotic supply will be increase to service ~12 million patients with new funding
Patient’s Plea for Antibiotics

- Daily sales of Ciprofloxacin prescriptions
  - Average sales of $1- $5M per day prior to September 11th
  - Sales have increased to $40-$45M/day
    - University of Pennsylvania Physicians memo
      October 2001 from Dr Neil Fishman
        - Rx limited to 10 day supply & Dx must be included on Rx
  - Pressure brought to bear on family physicians
  - Personal stockpiling
    - Expensive ~$1000 drug expense for family of four x 60 days
    - Fluoroquinolones not indicated in pediatrics
    - Produces local shortages
    - Potentially prevents identification of an attack
    - Self medication of patient &/or family members
      - Initial symptoms of anthrax and viral infection indistinguishable
  - Pharmacies could be at security risk in panic scenario

WSJ October 15, 2001
Antibiotic Prophylaxis ADR’s
MMWR 50(November 30):1053, 2001

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*Self administer survey in NYC & DC, NJ done by RN 7-10 days into Tx
8,424 Postal workers studied October 26 – November 6, 2001

LH/DZ- Lightheaded/Dizziness
R/HV-Rash/Hives
HB-Heartburn
F/U- Required follow-up
D/C- Drug stopped due to ADR
Minnesota Situation

- Fairly low profile target
- No real mass transit system
- Excellent State Department of Health
  - Laboratory capable of working with category A-C agents
  - 1 of 27 National Guard units trained in biohazard
- Level of preparedness likely much higher than national norm
  - Previous preparation drills
  - Twin City level 1 hospitals have been preparing
- State has a MMRS plan of action
  - Communication is an issue
  - Stockpile of pharmaceuticals
Minneapolis Metropolitan Medical Response System

Department of Defense Program

- Response Plan
  - Locally treat 1000 patients for 24 hours
  - Locally provide prophylaxis to 25,000 patients for 24 hrs
- Provide for necessary equipment
- Provide for necessary pharmaceuticals
  - Develop drug formulary
  - Purchase and store pharmaceuticals
  - Allocate appropriate personnel
- Identify plan for temporary morgue
- Plan for necessary law enforcement
- Conduct mock drills

Integrates Local, State, & Federal planning
Minnesota Drug Formulary for Antibiotics

- **Ciprofloxacin**
  - 500mg tablets
  - 400 mg minibags

- **Doxycyline**
  - 100mg / 20ml vials
  - 100 mg capsules

- **Gentamicin**
  - 100mg premixed bags
Push Package Inventory

- **Ciprofloxacin**
  - 432,000 tablets
  - 4,008 bottles of suspension
  - 26,952 IV bags

- **Doxycycline**
  - 5,004,000 tablets
  - 16,032 bottles of suspension
  - 6,300 IV vials

- **Erythromycin**
  - 81,000 vials

- **Gentamicin**
  - 18,000 multi-dose vials
Bioterrorism Summary

“...it’s not a matter of if, but when, which agent, & how bad will it be.” M. Osterholm

- Incredibly complicated situation, likely to worsen over time
  - Everyone has been drafted for this war
  - Glass half empty vs half full syndrome

- Virtually, everyone in the world is affected

- Solutions to bioterrorism will likely begin to unfold, vaccination programs will grow

- At the present time, we are probably not adequately prepared but we are closing that gap quickly
Bioterrorism Summary

- Virtually no U.S. trained physician has seen a clinical case of smallpox, anthrax, plague, etc.
- In initial stages symptoms of biological agents infection are fairly nonspecific
  - Difficult to identify & determine timing of attack
- Clustering of cases may be the clue
  - Syndromic surveillance of ED’s
  - Work attendance & demand for OTC medications
- Would still need to identify pathogen and if a bacteria, antibiotic susceptibilities
- Response plans are dramatically improving
  - 7000 emergency personnel ready to go
  - Would still expect significant public panic
- Morbidity and mortality would be significant for persons initially exposed
Resources

- Centers for Disease Control & Prevention
  - www.bt.cdc.gov
- ASM Website
  - www.asm.org
- Center for the study of Bioterrorism
  - http://bioterrorism.slu.edu
- Treatment handbook that can be downloaded to Palm Pilot
  - www.usamriid.army.mil/education/bluebook.html
- Center for Infect Dis Research & Policy
  - www1.umn.edu/cidrap/index.html