Bioterrorism Agents: What the Anesthesiologist Needs to Know

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Abstract

Reports and talk of terrorism is ubiquitous in most media outlets today. Many would dismiss the usage of biological agents as a mere theoretical threat. However, history dates bioterrorism as far back as 184 B.C. Biological agents have been shown to be a significant supplementary tool for war and terrorism. The United States local and national government have been preparing for what is called "not if, but when and how extensive" biological terrorism. Anesthesiologists also need to prepare and have a sound understanding of biological and chemical agents and how to treat victims of such attacks. Anesthesiologists are professionals in resuscitations and airway management and can be vital resources when aiding victims of biological warfare.

INTRO

Before the September 11th attacks on the United States, terrorism was rarely on the forefront of the American mind. Today, terrorism is reported and analyzed in almost every media outlet. Terrorism has become so prevalent, it is not a question of if but when another mass casualty like the events of September 11th will happen again, according to the Department of Defense (DOD). With this in mind, it is in the interest of every health care provider to aid in preparing for another mass casualty response. Anesthesiologists have a special knowledge of resuscitation and airway management that will make them a vital resource in the health care team when responding to these mass injuries. [1] The prior knowledge of bioterrorism agents including the history of their usage, pathophysiology, diagnosis and treatment of victims will result in more lives saved.

Terrorists have used many agents to further their cause including biological agents. [2] Bioterrorism “involves the threat or use of biological agents by individuals or groups motivated by political, religious, ecological, or other ideological objectives.” [3] It is also defined by the CDC as ‘‘the intentional release of bacteria, viruses or toxins for the purpose of harming or killing civilians'‘ [4]

Many would dismiss the usage of biological weapons as merely a theoretical possibility with these four arguments. l) The use of biological weapons is historically rare and they will not be an issue in the future. 2) Their usage is so morally repugnant that no one would have the impudence to release them. 3) The science behind biological warfare is so sophisticated and expensive that only highly technological refined laboratories could produce such agents. 4) The use of biological warfare is so destructive and unpredictable that its usage is unthinkable. [5] These four arguments fail to take in account a complete history of warfare.

A 2000 report of the U.S. intelligence agency described bioterrorism as “nontraditional” threat. However, many argue biological infectious disease is the most traditional threat. [6] It must be remembered that bioterrorism is not new to this century, it can be dated back as far as antiquity. [7]

HISTORICAL USAGE OF BIOTERRORISM PRE BACTERIAL

Some of the first known written description of bacterial and chemical weapons dates back to earlier Greek mythology. The stories of the Greek hero Hercules told of his battles with Hydra using burning firebrand. [8] In 184 B.C the great Carthaginian leader Hannibal, during a naval battle against King Eumenes, cast pots of snakes into the midst of their enemies. The attack of an unexpected biological weapon caused the Pergamene to lose the battle. [6]

Figure 1

Foul odor and filth, had been linked to “disease” and “contagion” long before science discovered the world of microbes. Thus, it should not be any surprise that human machinations used this association during wartime. [9] The crude use of diseased organisms and poor hygiene proved to be resourceful in weakening an opponent. [6] As early as 300 B.C, the Greeks used decaying bodies to pollute the water supply of their enemies to gain tactical advantage. The Romans and Persians used similar strategies. Diseased and decaying cadavers, as well as animal carcasses, would be catapulted over protective walls to infect the inhabitants of medieval cities. These diseased agents led to the spread of disease and death rendering the opponent, victims of such attacks, inept to defend themselves. [10] In 1346, the Tartar force, having been weakened by the plague would catapult their plague-stricken soldiers into the town of Kaffa (now Feodosia, Ukraine). [9] This led to an epidemic of the plague among the Genoese army who were forced to retreat and abandon Kaffa where they were stationed. In 1422, dead soldiers and 2000 cart loads of excrement were thrown into the enemy forces at Carolstein. Both of these battles contributed to the 25 million victims of the Black plague in Europe during the 14 th and 15 th century. [11]

POST CULTIVATION ERA

Many agree that the nineteenth century commenced the science of bacteriology. In 1877, Koch managed to culture bacteria using petri dishes in his laboratory replacing the crude usage of animal carcasses and cadavers with agar as a medium of growth. Starting with relatively simple cultivation methods, laboratory grown bacteria became the standard. [8]

The Geneva Protocol of 1925 called for the prohibition of bacteriological methods of warfare. It was the first multilateral agreement that prohibited the use of biological and chemical agents. [12,13] Viruses, fungi and rickettsiae were later included as biological agents. Though the Geneva Protocol was a milestone in defining and banning biological warfare, it lacked an enforcement authority. [14] Many countries, including the signatories of the new protocol stipulated that they would not follow the guidelines if their enemies used biological or chemical weapons. [15]

After the 1930's the major forces - United States, Britain, Japan, France, and Germany - continued production and expansion of their biological weaponry. The Japanese were frequently accused of releasing biological agents into neighboring countries. In 1940's the Japanese were accused of using planes to drop infected fleas, and contaminated rice and wheat, over multiple areas in China. It was reported that the granules contained gram-negative bacilli and other organisms that were associated with the plague. Thousands were infected and hospitalized and hundreds died, victims of the spreading bacilli. [12,13] .

Hundreds of prisoners of the Japanese Imperial Unit 731 were tortured and used as experimental victims of biological weapons. [12,16] Some of the agents allegedly used included anthrax, brucellosis, cholera, clostridium, meningococcal infection and the plague. [12] The Japanese continued to use and experiment with biological warfare from the 1930's clear up until the end of World War II.

During World War II the British tested anthrax in Gruinard Island off the coasts of Scotland. These tests contaminated the Island and led to costly clean-up years later. [17,18] Winston Churchill was purportedly ready to fight fire with fire if Hitler decided to use biological agents. [13]

There were many allegations during and after WWII of countries violating the Geneva Protocol without much evidence. The United States was accused of releasing biological warfare agents. In 1951, a Soviet newspaper claimed that the United States experimented with biological agents on the Eskimos living in Canada. The testing of these

biological agents was allegedly linked to an epidemic of plague in 1949. In 1950, Germany accused the United States of releasing Colorado beetles over crops in areas of their country. China, North Korea, and the Soviet Union also accused the United States of violating the Geneva Protocol by using biological weapons during the Korean War.

In 1972, 103 countries gathered together and committed to the prohibition of the development, production, and stockpiling of bacteriological and toxic weapons in the wake of increasing international concerns. This act was called the 1972 Biological Weapons Convention, whose purpose was the assurance that co-signing countries were to "never in any circumstances to develop, produce, stockpile or otherwise acquire or retain: (1) Microbial or other biological agents, or toxins whatever their origin, method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes [emphasis added]; (2) Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict." It called for destruction of banned items. [19]

The use of biological weaponry did not stop after the Biological Weapons Convention in 1972. In 1979, the Soviet Institute of Microbiology and Virology had a "mysterious" explosion that killed 66 persons, the majority of whom were down wind from the site (mostly due to the anthrax inhalation). [13,20] The "umbrella gun" (a concealed pellet gun that contained ricin toxin) was used in several assassinations by the Bulgarian government and others. [13,21]

In 1991, Iraqi government declared to the United Nations Commission Team 7 that they had researched anthrax, botulinum toxin and clostridium toxin for offensive use. This announcement was one of the first blatant admissions of the use biological agents as weapons by any country. Up until the Persian Gulf War, Iraq had produced 19,000L of botulinum toxin and close to 125,000 gallons of biological agents including anthrax and aflatoxin B. Later, they admitted to having 200 bombs, and missile warheads containing botulinum, anthrax, and aflatoxin and multiple rockets and spray tanks fitted to aircraft. [22] Iraq had multiple research and development facilities that were destroyed in the Persian Gulf War. Fortunately, the biological weaponry was never used against the American troops.

PURPOSE

The impact of bioterrorism on the US would have severe economical repercussions. A successful attack involving anthrax exposure to 100,000 persons has been estimated to cost $26.2 billion. [23]. These numbers do not take into account the price of decontaminating the areas of the affected environment. After 9/11, the Hart senate building in Washington, DC cost $23 million to decontaminate. [24] The US Postal Services irradiated multiple facilities in the Washington DC area. It was estimated that 32,000 persons received prophylactic antibiotics, and an additional 10,300 completed the 60 day antibiotic course prescribed for possible exposure to anthrax. [24] As was seen post 9/11, bioterrorism exposure can cause severe detrimental economical effects. The total budget for the homeland security agency for fiscal year 2008 is over 46 billion dollars. [25] Anti-Bioterrorism has funding increased from $297 million pre 9/11 to $6.2 billion post 9/11. [26]

Other purposes of bioterrorism are to instill fear, which leads to a change of lifestyle. The health care system was heavily taxed after 9/11 when fear replaced common sense. Any powdery substance was considered to be anthrax. One local health department reported a panicky mother who picked up her child from health care and saw white powdery substance on the child's clothes and instantly thought it was anthrax without considering the possibility of something like baby powder or formula. [8]

Bioterrorists are often politically motivated. There are multiple examples of bioterrorism attacks and failed attacks on the United States soil in addition to the anthrax released in 2001. In 1991, the "Minnesota Patriots Council" a right wing "Patriot" movement acquired ricin via mail order. The plan was to aerosolize the ricin and use it against the US Deputy Officials, the Internal Revenue Service, and local law enforcement officials. Fortunately, the Federal Bureau of Investigation agents infiltrated and prevented the plot. [27]

IDEAL AGENT

There are a multitude of agents that can be administered as weapons. Airborne release will affect more people than an agent being released into the food or water supply. Using an aircraft or other mode of transportation only furthers the agents' effect.

The ideal agent would have these characteristics 1) simple and cheap to mass-produce 2) capable of being dispersed as an inhaled aerosol [28] 3) low dose of infection. It should be mentioned that even small-scale causality substances like salmonella could be introduced into salad bars. Escherichia coli contamination of a meat processing line may not kill the victims, but could still fulfill terrorist objectives [28] 4) no

vaccine available 5) availability of a procurement (i.e., anthrax, which is in the soil unlike variola that is locked up in Atlanta and Novosibirsk) 6) stable in harsh environments. [26,29,30]

HOAXES

Bioterror hoax can cause just as much terror and consumes as many resources as a real threat. In 1997, a well-documented bioterror hoax occurred in the Washington, D.C area by a group known as the Counter Holocaust lobbyists of Hillel. This group left a paper bag containing a petri dish that was labeled “anthrix and Yersinia persits” in spite of both microbes being misspelled. First responders took elaborate measures including testing of the samples in the field, decontaminating persons in the street, quarantining others in the adjoining building, and cordoning off the surrounding city blocks. The sample was taken to a laboratory and was found to be negative of any virulent organisms. Tests revealed that the petri dish simply contained red gelatin void of any virulent agents. This hoax would have been less successful had there been a knowledge of these biological agents' characteristics. Had these agents been anthrax and yersinia, they would not have “jumped” from the paper bag to infect civilians in the streets and in the buildings. Familiarity with these agents can be the best tool in fighting bioterrorism. [28]

PREPARATION AND DEFENSE OBSTACLES

There exist many obstacles in defending against a biological attack. Defense is much more difficult than offense. A US Bio weapons specialist stated “It's a different world. Defense studies are so much more complicated. It takes 18 months to develop a weapons-grade agent and 10 more years to develop a good vaccine against it” [31] Bioterrorism can often times be disguised as a natural event. One example occurred when the terrorist group Rajneesh contaminated 10 salad bars with salmonella typhimurium in 1984. Over seven hundred people were infected and became ill by substance that could be prepared by an unskilled microbiologist spending less than $100. This bioterror attack by Rajneesh was considered natural food poisoning and it was not until a year later that Rajneesh was linked to the outbreak. Fortunately, today there exists a lower threshold for suspicious incidents like the one mentioned above. [28]

STOCKPILING

Stockpiling medications, hospital beds and other equipment is necessary when preparing for a mass casualty situation. Most hospitals are ill-equipped to handle such a volume of patients at any one time. [32] Many hospitals use a “just in time” mentality when providing health care to their patients and lack the necessary pharmaceuticals and equipment. [32] An inventory of supplies should be taken in every hospital to assess where the preparedness of the hospital to deal with such situations. Ventilators could be heavily in demand during a biological attack and acquiring portable ventilators should be a priority.

The Department of Health and Human Services (DHHS) has stockpiles maintained by the CDC of vaccines, antibiotics, and supplies that can be distributed to any state within 12 hours. In addition to the DHHS, vendor supplies, managed by pharmaceutical companies, can be distributed to the site within 24-32 hours upon request. [8] Supplies sent 12-32 hours after an anthrax release would be ideal. [32] However, if the attack is via a toxin then 6-12 hours could be too late to prevent mas casualties and a more local storage supply would be necessary. [32]

PROTECTIVE GEAR

Personal Protective equipment (PPE) may also become necessary upon a bioweaponary attack. As of now, no universal standard of PPE exist for health care providers. [3] Protection is a necessity when biological agents can be transmitted from person to person, often via the air through a respiratory droplet. In ideal circumstances, knowledge the size of the transmitted agent could determine what kind of mask to distribute for healthcare providers in case of crisis.

In addition to these issues is the possibility of illness debilitating the health care provider. Whether they were involved in the primary attack or exposed secondarily to an agent, this will significantly hinder response efforts. Some have also speculated that fear of contamination or infection may prevent some physicians from going to work, or that those fears may prevent the physician from functioning optimally. [32]

DECONTAMINATION

Many agree that decontamination is an important aspect of protecting the patient, physician, and equipment in a biological agent exposure. [8,33] Failure to decontaminate a patient before treatment carries risk of increasing the spread of a biological agent to other personnel and equipment. 1 Decontamination of a chemical agent is more essential than in the case of a biological agent. [33] With a biological agent, simply undressing the patient and applying the infection

control procedures would likely be enough. [33] For example, in the case of anthrax, simply decontaminating the patient with soap and water reduces the likelihood of secondary aerosolization of the spores. [30]

Decontamination following a biological or chemical agent should be performed before the patient enters the hospital facility and away from any ventilation ducts. Wet decontamination is the method of choice for mass causalities. [1] Mechanical and wet decontamination is performed by removing the victims clothing and washing the victim with water. This can be more effective in decontaminating the patients when soap or a bleach solution is added to the wash water. [1,8] Chemical decontamination products like hypochlorite, can render a biological agent harmless. [8] Hypochlorite is a safe decontaminate for equipment and fabric. [8] A more dilute solution of hypochlorite can be used to decontaminate the skin. It should be noted however, that hypochlorite is contraindicated for open wounds due to the possibility of spinal and brain injuries [8]

Heat and radiation techniques can be employed in the decontamination of tools and equipment. Solar UV radiation and dessication can be used in inactivation biological agents. Autoclaving and dry heat at 100 C for 2 hours can be used in sterilization of objects. [8]

ASSESSMENT

Many times with mass causalities, patients will not all come in at once to the emergency room but will trickle in and then the a wave of patients can inundate the emergency room. A physician assessment of the patient can help in detecting a possible “escalating crisis” of a biological attack and recovery of the patient. [34] This knowledge can possibly curtail any further causalities and best address the upcoming crisis. If such an attack is suspected the physician should notify the proper authorities including their infection control officer and any local control agencies. [34] The patient should be asked about any possible exposures to suspicious substances. A physician's knowledge of the clinical symptoms caused by agents of bioterrorism agent will not only help the affected patient, but can also help authorities stop the infection from spreading.

BIOLOGICAL AGENTS

BACTERIA

ANTHRAX

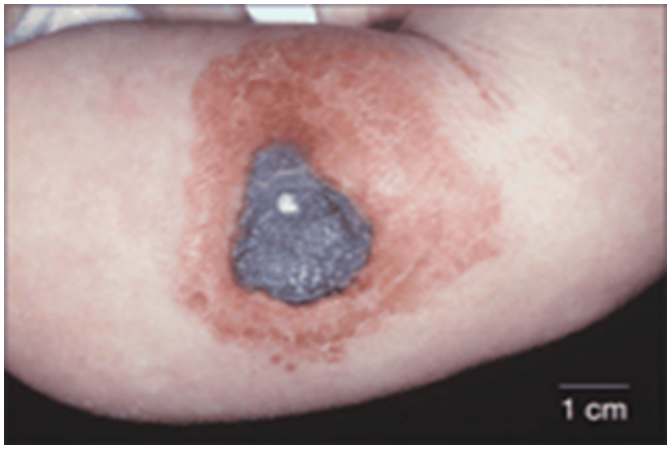
Infection with anthrax dates back to very early human society. It has even been postulated as a cause of the biblical Egyptian plagues. Since then there have been documented cases by ancient Romans, an epidemic in 1979 in Sverdlovsk, Russia, and most recently in 2001, 22 cases caused by the powder form of the bacteria circulating throughout the U.S. postal service. [35,36,37]

Anthrax is caused by Bacillus anthracis, a gram-positive, spore forming bacillus. Transmission occurs by inhalation, ingestion, or entry through breaks in the skin. Infections result from contact with infected animals or animal products. There are multiple clinical manifestations of anthrax: cutaneous, gastrointestinal, inhalational (Woolsorter's disease), and anthrax meningitis.

Cutaneous anthrax results from inoculation of spores through skin lesions. Painless, pruritic papules will appear within 5 days of exposure. The papules develop into vesicles, which undergoes central necrosis in about 7 days, leaving a black eschar that eventually sloughs off. [38] (Figure 1). Luckily, this form is not usually fatal, as cutaneous anthrax affected half of the victims that received the powder form in the mail in the U.S. in 2001. [35]

Figure 2

Figure 1: Lesion of cutaneous anthrax. Reprinted from Feedman et al.



Gastrointestinal anthrax occurs after consuming contaminated meat. Symptoms of infection are pharyngeal ulcers and edema. This is important for the anesthesiologist to recognize because it may necessitate artificial maintenance of the airway. Hemorrhagic mesenteric adenitis, ascites, hematemesis, and melena may occur. [38] Morbidity is due to blood loss, fluid and electrolyte imbalances, and subsequent shock. Death results from intestinal perforation or anthrax toxemia. If the patient survives, most of the symptoms subside in 10 to 14 days. [40]

Inhalation anthrax, also result of the powder form, is usually fatal. The infective dose consists of 8,000-15,000 spores. Initial symptoms are flu-like and last about 4 days. Most cases lack a pulmonary infection; the primary damage occurs when the endospores are engulfed by alveolar macrophages and get transported to the mediastinal and hilar lymph nodes. The spores germinate and multiply in the lymph nodes, resulting in hemorrhagic mediastinitis. Peribronchial hemorrhagic lymphadenitis blocks pulmonary lymphatic drainage, leading to pulmonary edema. [37] The anthrax toxin gets released into circulation and death results from septicemia, toxemia, or pulmonary complications.

Diagnostic tests for B. anthracis are available. Enzyme-linked immunosorbent assay (ELISA) can rapidly detect the toxin in the blood. Peripheral blood smear and culture shows gram-positive bacilli (Figure 3A). A classic feature of inhalation anthrax is a widened mediastinum seen on chest X-ray. Chest CT scan would also show hyperdense mediastinal and hilar lymph nodes, as well as pleural effusion, and mediastinal edema. Thoracocentesis will demonstrate hemorrhagic pleural effusions. [36]

Unfortunately it would not be difficult to engineer penicillin resistant strains of anthrax. For this reason 400 mg of IV ciprofloxacin every 8 hours for 14 days is the standard treatment after exposure to anthrax. Doxycycline may be used as an alternative. Prophylaxis therapy consists of 500 mg oral ciprofloxacin every 12 hours. Disease can present 50 days or more after exposure, so prophylaxis should continue for 60 days unless exposure has been excluded. There is a 6-dose series vaccine available called anthrax vaccine adsorbed (AVA). As of 1997, all U.S. military personnel are required to receive it. The vaccine is injected subcutaneously at 0, 2, and 4 weeks, then at 6, 12, and 18 months followed by annual boosters. [36,38]

PLAGUE

One of the most feared diseases throughout history is the plague. No one is sure of the absolute number of deaths that the plague has caused, but some estimate it as much as 200 million. The first pandemic, the Justinian Plague, ripped through Egypt in A.D. 541. The second pandemic known as "Black Death" effected Europe in 1347. Cycles of the disease continued throughout history, and just when we thought the disease was something of ancient times, it reappeared in India in 1994. [41]

Yersinia pestis is a gram-negative, anaerobic coccobacillus. Y. pestis has been present throughout history due to the parasitic relationship of fleas and rodents. Fleas acquire the disease through an infected blood meal. The flea is not affected by the disease, and serves only as a carrier. The next mammal the flea feasts on becomes the plagues next victim. Y. pestis is transmitted to humans through fleas, rodents, or droplet infection. There are 3 forms of the disease: bubonic, septicemic, and pneumonic plague.

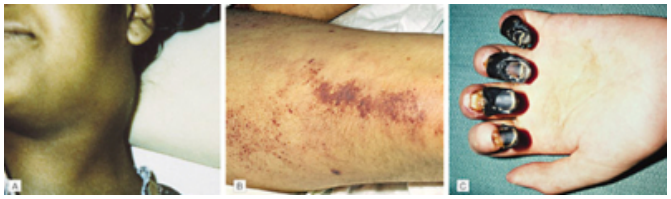
Bubonic plague is the classic form of the disease. After contact with the organism, symptoms appear such as fever, chills, gastrointestinal symptoms, and swollen, tender lymph nodes known as buboes. (Fig 2A). Axillary, inguinal, and/or cervical lymphadenitis is common. Bubonic plague can progress to septicemia or pneumonic plague and has a 40% fatality rate if left untreated. [38,41]

Septicemic plague usually occurs secondary to bubonic or pneumonic plague. Primary septicemic plague occurs when blood cultures are positive, but the patient lacks lymphadenopathy. Symptoms are typical for any gram-negative septicemia, including fever, chills, malaise, and headache. "Black death" gets its name from the septicemia leading to septic shock with cyanosis, causing gangrene in peripheral tissues. [42] Septicemic plague has a 100% fatality rate if left untreated. [38] (Figure 2B,C)

The most contagious and deadly of the three, pneumonic plague, has the potential for person-to-person airborne spread. Luckily, Y. pestis is not spore forming, and is viable for only 60 minutes as an aerosol. Symptoms begin as a flu-like illness and rapidly progress to pneumonia with hemoptysis. Anesthesiologists need to be on the look out for dyspnea, stridor, and cyanosis, which will likely need mechanical ventilation. Appropriate airborne precautions should be taken, as this form of disease is contagious through respiratory droplets with close contact (2 to 5 feet) to the infected patient. Pneumonic plague is 100% fatal unless treatment is given with 24 hours of the onset of symptoms. [41,42]

Figure 3

Figure 2: A. Cervical bubo; B. Petechial and ecchymotic bleeding of septicemic plague; C. Gangrene of the digits. (Figures from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.)



Diagnostic tests for plague can be taken from blood cultures, bubo aspirates, or sputum. Gram, Giemsa, and Wright stains can also aid in the diagnosis (Figure 3). ELISA and PCR analysis provide a more rapid diagnosis. Chest x-ray is nonspecific when looking at pneumonic plague.

The standard treatment of bubonic, septicemic, or pneumonic plague is 30mg/kg of intramuscular streptomycin every 12 hours for 10 days. The drawback is that this drug has limited availability due to the fact that it is manufactured by 1 pharmaceutical company. More readily available alternatives include chloramphenicol, gentamicin, or doxycycline. [43] Chemoprophylaxis includes treatment with tetracycline or doxycycline. The Greer vaccine is an inactivated form of the disease, and requires a course of injections over 6 months. A recombinant sub-unit vaccine is being investigated. [44]

TULAREMIA

Francisella tularensis is the etiological agent responsible for tularemia. It is an aerobic, gram-negative, intracellular coccobacillus that is found in the water, soil, and vegetation. Small mammals such as rabbits, squirrels, and mice are the natural reservoirs for the disease. Humans become infected through contact with contaminated environments, insect bites, contact with infected mammals, or inhalation. The last mode of transmission is what makes F. tularensis an ideal agent for bioterrorism. [45]

The type of tularemia infection that results depends on the mode of transmission. A few types of the disease include ulceroglandular, oroglandular, and pneumonic. Ulceroglandular form is the most common. It occurs after a bite from an infected arthropod or from handling an infected mammal. Symptoms begin as flu-like and an ulcer appears at the site of infection. Regional lymph nodes enlarge and may resemble buboes. The patient may become bacteremic. This form of the disease has a very low mortality rate, but may take quite a long time to recover from. [46]

Oroglandular tularemia results from ingestion of contaminated water or can even occur from inhalation. Symptoms include stomatitis, exudative pharyngitis or tonsillitis. Cervical or retropharyngeal lymphadenopathy will occur.

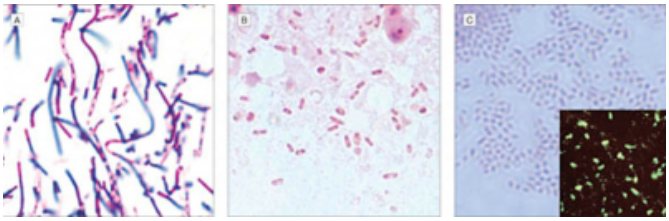
The most clinically severe form of the disease is pneumonic tularemia. Transmission occurs through inhalation of the aerosolized bacteria. It can also occur secondary to hematogenous spread. Symptoms include fever, non-productive cough, pleuritic chest pain, chills, headache, and malaise. It may resemble community-acquired pneumonia. The patient does not need to be isolated because the disease is not transmissible from person-to-person. This form of the disease has a mortality rate of 30-60%. [46,47]

Chest x-ray may show infiltrates, hilar adenopathy, or pleural effusion. It may be confused with tuberculosis by exhibiting miliary infiltrates or caseating granulomas seen on lung biopsy. Culture of F. tularensis will grow in about 24-48 hours, and can make the definitive diagnosis (Fig 3C). PCR or ELISA may also be used to aid in the diagnosis. [45]

Treatment of tularemia is 30mg/kg streptomycin intramuscularly bid for 10-14 days. An alternative is 5mg/kg gentamicin intramuscularly or intravenously once a day for 10-14 days. There does exist a live attenuated vaccine against tularemia. It has reduced the development of pneumonic tularemia in lab personnel who are in contact with F. tularensis. A live vaccine strain has been developed; however, to date this vaccine has not yet become available. Vaccination is not recommended as a post-exposure prophylaxis. In the event of a bioterrorist act with F. tularensis, oral doxycycline or ciprofloxacin are recommended as post-exposure prophylaxis. [38,45,46]

Figure 4

Figure 3: Gram Stain Smears of the Agents of Anthrax (), Plague (), and Tularemia ()



TOXINS

BOTULISM

Botulism toxin is the most poisonous substance known. A single gram of the crystalline toxin could kill up to 1 million people. Botulism has been used as a bioterrorism agent for the past 70 years. In the 1930's, Japan fed cultures of C. botulinum to prisoners while occupying Manchuria. In the early 1990's the Japanese cult Aum Shinrikyo dispersed the toxin in aerosol form in Tokyo, Japan and at U.S. military sites located in Japan. Fortunately they were unsuccessful in their attack. In the Persian Gulf War Iraq possessed warheads with botulinum toxins, making the weaponized toxin the number one biological agent they produced. [48,49]

Botulism is a neuroparalytic illness caused by the toxin formed by Clostridium botulinum. This gram-positive anaerobe forms spores and is commonly found in soil. [50] There are three naturally occurring forms of botulism: foodborne, wound, and intestinal. The toxin enters the bloodstream via mucosal surface or breaks in the skin. Botulinum toxin acts at the neuromuscular junction. Here it irreversibly binds to the presynaptic neuron and is endocytosed. The light chain of the toxin cleaves SNARE proteins, which inhibits the synaptic vesicle from fusing with the terminal membrane. This in turn inhibits acetylcholine release into the synaptic cleft, resulting in flaccid paralysis. [49]

Foodborne botulism is a result of ingesting the preformed toxin of C. botulinum. The most common culprits are home-canned foods and honey. The incubation period is short, usually 12 to 72 hours. [51] Clinically, the initial symptom will be gastrointestinal upset i.e. abdominal cramps, nausea, vomiting, or diarrhea. These are followed by the onset of neurological symptoms. The patient will be afebrile with symmetric descending paralysis beginning in bulbar musculature and multiple nerve palsies producing diplopia, ptosis, blurred vision, enlarged or sluggishly reactive pupils, photophobia, facial weakness, dysphonia, dysphagia and dysarthria. [48] As paralysis progresses, hypotonia and generalized muscle weakness will occur. Anesthesiologist should be aware that dysphasia and loss of gag reflex may indicate intubation and mechanical ventilation. If left untreated, death will ensue due to upper airway muscle paralysis leading to airway obstruction. Tidal volume will also decrease to a fatal level due to diaphragmatic and accessory respiratory muscle paralysis. Death occurs in 5% to 10% of cases of foodborne botulism. [52]

With the exception of gastrointestinal symptoms, wound botulism is similar clinically to foodborne botulism. The introduction of the toxin is from colonization of a break in the skin with C. botulinum. The fatality rate for wound botulism is around 15%. Intestinal botulism occurs most commonly in infants. The intestinal tract becomes colonized with C. botulinum which produces its toxin. Symptoms are similar to foodborne botulism. [50] If the toxin was used as a bioterrorism agent, it would most likely be in the aerosol form. The toxin would enter the body through the lung mucosa and cause its classic neurologic symptoms.

Diagnosis of botulism is clinical. There are some laboratory tests to confirm the diagnosis, but these require days to complete, and the patient may experience respiratory distress before these are completed. Laboratory tests for botulism are currently only available at the CDC and approximately 20 states and municipal public health laboratories. Serum, stool, gastric aspirate, or vomitus may be used as a specimen for mouse bioassay. This is the standard lab test for botulism, in which type-specific antitoxin protects mice against any toxin present in the sample. Another diagnostic tool is an electromyogram. The characteristic electromyographic findings of botulism include normal nerve conduction velocity, normal sensory nerve function, a pattern of brief, small-amplitude motor potentials, and, most distinctively, an incremental response (facilitation) to repetitive stimulation often seen only at 50 Hz. [49]

The number one priority in the treatment of a patient with botulism is to protect the airway. The patient will need to be admitted to the intensive care unit with mechanical ventilation anywhere from sixty days to 7 months. Passive immunization should be started intravenously with trivalent (A, B, and E) equine antitoxin. [48] The antitoxin should be started as soon as possible. A retrospective analysis of 134 cases of type A botulism showed an overall mortality rate of 10% among patients who received early treatment with antitoxin (within 24 hours of symptom onset) compared with 15% among those who received late treatment (> 24 hours after symptom onset) and 46% among those who did not receive antitoxin. In addition, survivors who received antitoxin early had a median hospital stay of only 10 days compared with 41 days for those who received antitoxin late and 56 days for those who did not receive antitoxin. [53] A pentavalent (A, B, C, D, and E) botulinum toxoid vaccine is used for laboratory workers and military personnel. [48]

VIRUSES

SMALLPOX

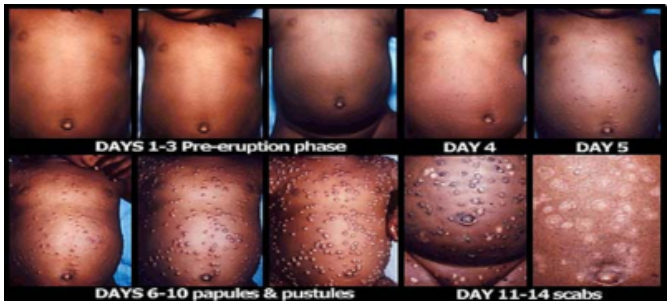
Several times in history the use of smallpox was passed as a

biological weapon in America. Pizarro was guilty of distributing variola-laced clothing to the Indians in South Americas during the 15 th century. Sir Jeffery Amherst of the English presented Native Americans loyal to the French with variola-infested blankets in the French and Indian War (1754–1767) [54] . During the American Civil War, confederate surgeon Dr. Luke Blackburn was guilty of distributing small pox laced clothing to the Union army. [55,56] The last endemic of smallpox occurred in 1977 in Somalia, with the last case infecting a laboratory worker in 1978 in the United Kingdom. The World Health Organization (WHO) declared smallpox eradicated in 1980. There are only 2 known countries that continue to carry stocks of the virus: United States and Russia. [57,58]

Smallpox is caused by the variola virus, a member of the genus orthopoxvirus. It is transmissible person-to-person and is spread by inhalation of aerosol droplets. The virus replicates in the spleen, bone marrow, and lymph nodes. On the 12 th to 14 th day the patient becomes febrile. Viremia develops and the virus localizes in the dermis and oropharynx. Within a couple of days a maculopapular rash forms on the oropharynx, face, and upper extremities, later spreading to the trunk. The lesions of smallpox are all in the same stage, unlike chickenpox. The rash becomes vesicular, pustular, and then scabs over (Fig 4). Within the second week of infection, death ensues due to toxemia and is associated with immune complexes and hypotension. [57,58,59]

Figure 5

Figure 4: The stages of smallpox in an infant.



There are a few different subtypes of smallpox. 90% of cases are variola major, which was described above. This has a mortality rate of 30%. Hemorrhagic smallpox is very deadly, but fortunately accounts for only 3% of cases. The incubation period is shorter, and the disease is characterized by petechiae with hemorrhaging into the skin and intestinal tract. Within seven days the patient dies. The malignant form of the disease has a slower progression. The lesions do not become pustular, but give the skin a crepe rubber appearance. This form is also frequently fatal. [57,58]

The diagnosis of smallpox can be made clinically, and usually a thorough history would rule out other forms of rashes. A specimen can be collected by lysing a lesion and swabbing the fluid. The virus can be identified under an electron microscope in a high contaminate facility. Definitive identification occurs through polymerase chain reaction techniques or restriction fragment-length polymorphisms. [57,58]

In 1972, routine vaccination against smallpox in the United States ended. There are some stockpiles of the vaccine. The CDC has enough vaccine for 6 to 7 million people from a 1970's New York City Board of Health freeze-dried strain. The WHO has enough for about 500,000 doses. [57] Studies performed in the 1960s showed that the risk for serious complications from the smallpox vaccine were greater than the threat of reintroduction of the smallpox virus. [60] Complications include postvaccinal encephalitis and progressive vaccinia. The risk of postvaccinal encephalitis is about 1/1,000,000, with 40% of those cases being fatal. Progressive vaccinia occurs in immunocompromised patients, in which the virus continues to grow. This can be treated with vaccinia immune globulin (VIG). VIG is made from the blood of highly immune, recently vaccinated donors. [57,59,60]

The CDC reports that the smallpox vaccine provides a high level of immunity for about 3 to 5 years. [61] The amount of people that were vaccinated and still have some immunity has been speculated. One source suggests about 30 to 80% immunity in persons vaccinated once, and greater than 90% immunity in persons who were vaccinated and received multiple revaccinations. [62]

A person with suspected smallpox should be kept in a negative-pressure room and strict respiratory and contact precautions should be taken. If the patient is in the early stages of the disease, vaccination can lessen the course of the virus. Supportive therapy is the most that can be offered. Penicillinase-resistant antimicrobials can be given for secondary infections, bacterial infections that threaten the eyes, or if the eruption is dense and widespread. Cidofovir can be given immediately after exposure to prevent cowpox, vaccinia, and monkeypox. [57,58]

HEMORRHAGIC FEVER

Viral hemorrhagic fever can be caused by a number of RNA viruses. The family of Arenaviridae causes Lassa, Junin,

Machupo, Sabia, and Guanarito fever. Bunyaviridae leads to Crimean-Congo HF, Rift Valley fever, and Hantavirus fever. Filoviridae results in Ebola and Marburg HF, and Flavivirdae in Yellow and Dengue fever. [63] VHF can be transmitted to humans by contact or inhalation of contaminated material from animal reservoirs or from arthropod vectors. Certain VHF could make potentially dangerous biological weapons due to their ease of dissemination and transmission and high mortality rates. However, the Working Group on Civilian Biodefense recently excluded the viruses causing dengue HF, Crimean-Congo HF, and the agents of HF with renal syndrome as potential biological weapons. Dengue fever is not transmissible by aerosol. Congo-Crimean HF is difficult to achieve in high concentrations in cell culture, making it unfavorable as a biologic weapon. [63]

VHF generally has an incubation period of 2 to 35 days. There is a prodrome period with symptoms of malaise, fever, myalgia, headache, and nausea lasting about one week. VHF targets the vascular system, causing microvascular damage and increased vascular permeability. Conjunctival injection, hypotension, flushing, petechial hemorrhage, and ecchymoses may be seen. This progresses to shock, coagulopathy, and hemorrhage from mucous membranes. [38,63]

Diagnosis of VHF is largely clinical. Laboratory findings may include thrombocytopenia or leukopenia. Prothrombin time (PT), activated partial thromboplastin time (APTT), and bleeding time are often prolonged. [63] Enzyme-linked immunosorbent assay or reverse transcriptase-polymerase chain reaction may be used for definitive diagnosis. [38]

Treatment of VHF is mainly supportive. Isolation and contact precautions must be taken, especially if the patient is hemorrhaging. Blood pressure needs to be maintained, however IV access may be difficult due to hemorrhage from the venipuncture sites. Prothrombotics should be avoided unless there is severe hemorrhage or disseminated intravascular coagulopathy. [38] There is no cure for VHF; however Ribavirin may be beneficial. Ribavirin seems to help with arenavirus and bunyavirus, but not with filovirus. The antiviral drug reduces morbidity and mortality in Lassa fever, and may aid in Crimean-Congo HF. Ribavirin is also approved for postexposure prophylaxis for Lassa fever. [64] Vaccines have been developed for Rift Valley fever and research has shown that one can be made for Lassa Fever [38,65] Passive immunization has been attempted with varying results. [63,66]

VIRAL ENCEPHALITIS

There are three main players that cause viral encephalitis and are a bioterrorism threat. Venezuelan, Eastern, and Western equine viruses (VEE, EEE, and WEE respectively) are all members of the Togaviridae family. Equine viruses have caused epidemics beginning in the 1930's. The most recent outbreaks occurred in 1993 in Venezuela, and then again in 1995 in Columbia afflicting nearly 100,000 people and causing nearly 300 deaths. [67] These viruses are choice bioterrorism agents due to causing incapacitating illness in humans, ability to be spread as an aerosol, and ease of mass production. [68]

In the United States, there are four main viral agents that cause encephalitis: EEE, WEE, St. Louis Encephalitis, and La Crosse Encephalitis. [69] West Nile virus (WNV) is usually seen in the Eastern hemisphere; however, in 1999 WNV caused an outbreak in New York City , causing 59 people to be hospitalized for muscle weakness. WNV is asymptomatic in nearly 80% of those infected. The disease is usually seen in the summer months and in older individuals. [68]

Natural infection with this virus is spread from infected horses to humans through a mosquito vector. Upon infection with VEE the patient will exhibit chills, fever, malaise, myalgia, nausea, vomiting, headache, and photophobia. Less than 5% will develop clinical encephalitis. In patients who do progress to fatal meningoencephalitis, the predominant pathological findings include edema, hemorrhages, and encephalitis in the CNS. Alveolar hemorrhage, interstitial pneumonia, edema and congestion are found in the lungs. Lymphoid tissue shows follicular necrosis and lymphocyte depletion, while the liver shows diffuse hepatocellular degeneration. [70] EEE and WEE have a longer incubation period, followed by fever, nausea, vomiting, headache, and myalgia. This intensifies and the patient will begin exhibiting neurological symptoms such as confusion, delirium, ataxia, seizures, paresis, and cranial nerve palsies. EEE has high fatality rates and persistent neurological deficits. [38,71]

The diagnosis of viral encephalitis can be made early in the disease by isolating the virus in the patient's serum. Serum aspartate transaminase will be elevated in VEE infections. Once neurological symptoms are present, the cerebrospinal fluid may show lymphocytic pleocytosis. Definitive diagnosis is accomplished through ELISA and isolation of

the virus. [38,71]

Treatment is mainly supportive. Neurological morbidity may be reduced through neurological protection strategies, ventilatory support, anticonvulsant therapy, and antipyretics. [38] A vaccine is available to laboratory workers and military personnel for VEE. It is the live attenuated TC-83 strain, which has been used on 8,000 humans in the last four decades. About 40% of people vaccinated developed symptoms of a viremia. It has also been used on horses; however, viremia levels are sufficient enough to infect mosquitoes and initiate a transmission cycle. [70] There is no commercially available vaccine for humans against EEE or WEE. [69]

CHEMICAL AGENTS

NEUROLOGIC

TABUN, SARIN, SOMAN, AND VX

Tabun, Sarin, Soman, and VX are human-made chemical warfare agents classified as nerve agents. They were originally developed in 1930s in Germany as pesticides. [72] Tabun was the first to be synthesized, followed by Sarin and Soman. VX was an insecticide used in the United Kingdom, and is much more toxic than the other pesticides. Once military forces got a hold of these agents code names GA, GB, and GD were given to Tabun, Sarin, and Soman respectively. [73] Among other nerve agents, sarin was used in the 1980s as chemical warfare during the Iran-Iraq war. On March 20, 1995, terrorists released sarin into the Tokyo subway system, causing over 5,500 people to seek medical care and leaving 12 people dead. [74]

GA, GB, and GD agents are a clear, colorless, tasteless liquid in their pure form. They can be vaporized and release into the air. People can absorb the agents through the skin, eyes, and through inhalation. They may also be ingested into the gastrointestinal tract. [72] VX is a sulfur-containing organophosphate. It is mainly a liquid contact hazard. [73]

An organophosphate is a compound that irreversibly binds to acetylcholinesterase. This results in an excess of acetylcholine that accumulates in the synaptic cleft. Symptoms of nerve agent poisoning would include miosis, salivation and dysphagia, bronchospasm, flaccid paralysis, and possible seizures. The vapors of the nerve agent may accumulate on the skin and clothing, continuing to release the agent for 30 minutes after contact with the vapor if the patient is not decontaminated properly. [75]

Treatment of nerve gas poisoning is by administration of a muscarinic receptor antagonist such as atropine, scopolamine, or pralidoxime. Pralidoxime reactivates acetylcholinesterase by dephosphorylating the organophosphate. This must be given before the phosphorylated bond between the nerve agent and acetylcholinesterase ages, becoming irreversible.

Treatment of patients exposed to chemical agents will extend beyond the emergency room. Patients will rely on anesthesia and critical care services. Anesthesiologists have played major roles in mechanical ventilation during a mass exposure to nerve agents. [76] Patients exposed to nervous agents will pose a different type of challenge to the hospital than one typically seen. Typically, patients in the emergency room or intensive care unit will not require the same amount of airway manipulation as patients in the operating room. Seldom patients will deteriorate on other hospital floors be rushed to another location for emergency airway intervention. In a mass casualty where patients are exposed to nervous agents will more times than not require emergency airway outside the operating room. Patients will have copious amount of pulmonary secretions and bronchoconstrictions that lead to respiratory failure. These patients will typically be more acutely ill than patients in the operating room. Many will have altered mental status and express agitation leading to difficulties in securing an airway. [1]

Management of the airway in the past has long been endotracheal intubation, providing a secure airway with the usage of positive pressure ventilation. [1] Most recently, in the short-term management of perioperative and emergency patients, other methods such as the laryngeal mask airway have been used. [77,78,79] Tight fitting face mask requiring no invasive techniques have been used more frequently in the many clinical scenarios including acute respiratory failure [80] . However, the none invasive techniques have been found unfavorable in patients exposed to nervous agents. [1] With the usage of the LMA and noninvasive face masks, studies have showed the seal is inadequate when ventilating patients suffering from severe bronchospasms. The ineffective seal will cause air leakage, which in turn leads to “ineffective ventilation.” [1] Noninvasive techniques will provide the least protection against aspiration of oral or gastric secretions. Endotracheal intubation will provide the patient with the most effective and safest way of managing the airway.

CONCLUSION

The use of biological agents by terrorists is a real threat for which anesthesiologists need to prepare. History has shown biological agents to be a significant supplementary tool in war and terrorism. It has only been six years since the United States has seen the anthrax letters attack. Biological agents can cause mass amounts of causalities and have a number of different presentations. The physician should be able to recognize the threat early, diagnose, treat and prepare for the possibility of mass causalities. Anesthesiologist should know the hospital's emergency preparedness plan and familiarize themselves with the resources at their institutes. [81]

Anesthesiologists have special training in critical care and can be an asset when providing a compromised patient with airway management, breathing and circulation. Anesthesiologists' skills of vascular access and the provision of on-site anesthesia and general anesthesia have a particular importance. [82] The anesthesiologist can also provide instructions to other health care providers in these three life-sustaining managements. In addition, the anesthesiologist should be continually aware and prepared to deal with any new biological threat that they may face in the future.

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