REVIEW ARTICLE

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Clinical Management of Potential Bioterrorism-Related Conditions

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In this article, we review the clinical management of deliberate infection with several pathogens of greatest bioweapons concern. On the basis of historical incidents coupled with information on ease of dissemination, contagiousness, mortality rates, public health impact, ability to engender panic, and the need for special preparedness,[1-3] the Centers for Disease Control and Prevention (CDC) stratifies pathogens and toxins into three risk categories — A, B, and C — with category A meriting the highest level of concern and preparedness.[4,5] In this review, we consider diseases that are caused by category A agents for which there are high-quality clinical data in the unclassified literature (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The category A viral hemorrhagic fever viruses are beyond the scope of this review.

Anthrax

Naturally occurring anthrax has been known since antiquity and is found worldwide. It has also been used as a bioweapon: there were 22 anthrax cases and 5 deaths after the 2001 attacks in which anthrax spores were sent through the U.S. mail.[6] Anthrax is caused by infection with the spore-forming, exotoxin-producing, gram-positive bacillus *Bacillus anthracis*. It is a disease of herbivores that ingest spores present in the soil that then germinate in the gut. In humans, three forms of anthrax are recognized: cutaneous (the most common), gastrointestinal, and inhalational (the most deadly).[7] After the 2009–2010 European outbreak linked to heroin injection, a fourth type, injectional, was recognized.[8] In all forms, the clinical manifestations are primarily caused by the toxins secreted by the vegetative bacterium.[7,9]

Cutaneous Anthrax

The most common and least lethal form of anthrax, cutaneous anthrax occurs after spores penetrate breaks in the skin and germinate. After a 1-day to 12-day incubation period, a pruritic papule appears at the site of inoculation, progresses to become a vesicle or pustule, and finally becomes the characteristic painless, coal-black eschar from which the disease derives its name. Marked edema of the affected region is present, as well as lymphadenopathy and fever. When untreated, cutaneous anthrax carries a mortality rate of less than 1%, but in rare cases it can disseminate throughout the body and produce high lethality.[9] Figure 1A shows the characteristic black eschar of cutaneous anthrax.

Gastrointestinal Anthrax

Gastrointestinal anthrax occurs after ingestion of vegetative *B. anthracis* bacteria from the meat of infected animals. The disease is divided into two phases: oropha-

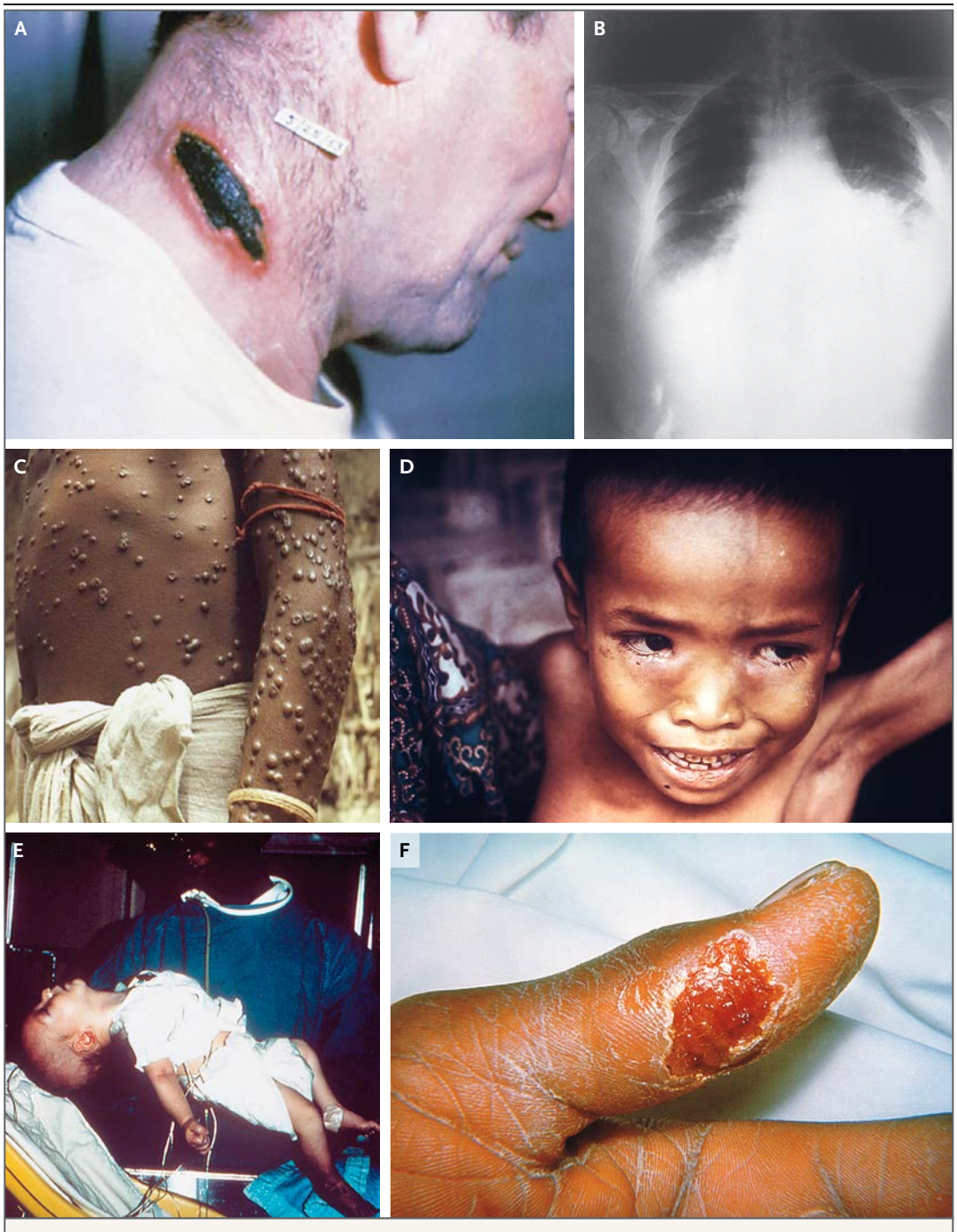

Figure 1. Characteristic Features of Diseases Caused by Category A Agents.

Panel A shows a cutaneous anthrax lesion. Panel B is a chest radiograph of a patient with anthrax, showing mediastinal widening and pleural effusions. Panel C shows a smallpox rash. Panel D shows a patient with bubonic plague with axillary lymphadenopathy. Panel E shows paralysis in a patient with botulism. Panel F shows a tularemia skin ulcer. Images courtesy of the CDC Public Health Image Library.

ryngeal and lower gastrointestinal. After an incubation period of 3 days, oral or esophageal ulcers, cervical lymphadenopathy, and dysphagia occur. Fever and constitutional symptoms are also present. Lower gastrointestinal involvement is signaled by the appearance of abdominal pain, nausea, vomiting, bloody diarrhea, and abdominal distention. Ascites and inflammatory changes in the bowel wall may be present and visible on imaging. Mortality can reach 60% if the disease is untreated.[7,10]

INJECTIONAL ANTHRAX

Injectional anthrax is characterized by skin lesions similar to those seen in "skin-popping" drug users. These lesions may progress rapidly and require surgical débridement. Dissemination with systemic symptoms, including meningitis and shock, may occur. Unlike cutaneous anthrax, injectional anthrax is not associated with eschar formation on the skin, and the mortality, even with treatment, is considerably higher, at 34%.[11]

INHALATIONAL ANTHRAX

The most lethal form of anthrax, and the form that would follow an intentional aerosol release of spores, inhalational anthrax results from the inhalation of bacterial spores that later germinate in the lung. The incubation period of inhalational anthrax can be as short as 1 day; has been as long as 6 weeks, in the case of the Sverdlovsk outbreak[12]; and has also been as long as 9 weeks in experimentally exposed monkeys.[13] Disease onset begins with nonspecific influenza-like symptoms, with the exception that rhinorrhea is absent.[14] After the disease progresses through this stage, which lasts hours to days, a severe advanced phase occurs and includes high fever, shock, and respiratory distress. Inhalational anthrax does not cause pneumonia but nevertheless can progress to the acute respiratory distress syndrome. Hemorrhagic mediastinitis, as well as toxin-laden pleural and pericardial effusions, can be present.[15] Spread of the disease to the meninges, with resultant hemorrhagic meningitis, is a frequent complication of systemic forms of anthrax, occurring in up to 50% of cases[16]; this complication confers a higher degree of mortality. In the 2001 attacks, all persons with meningitis died, a finding consistent with other cases.[17] Traditionally, inhalational anthrax has carried a 90% case fatality rate; however, during the 2001 attacks, the case fatality rate was halved, to 45%.[6] The reason for the decrement in mortality is probably multifactorial and includes the benefits of modern critical care, the drainage of toxin-laden pleural effusions, and the use of antimicrobial therapies.

CONSIDERATIONS FOR ANTHRAX IN SPECIAL POPULATIONS

Children and pregnant women are populations that may require special consideration. In a recent systematic review of 20 natural cases — most of which were cutaneous — reported in pregnant women, high rates of maternal and fetal death were noted.[18] It is unclear whether this represents a heightened proclivity for severe disease among pregnant women or a reporting bias. A systematic review of 73 pediatric cases, most of which were cutaneous or gastrointestinal, yielded no striking differences in the presentation of anthrax in children, as compared with adults.[19]

DIAGNOSIS OF ANTHRAX

Although clinical suspicion is of utmost importance, laboratory confirmation is required for diagnosis, because the clinical findings in anthrax may overlap with those of other infections. *B. anthracis* grows rapidly in culture, and patients with systemic disease can be identified with the use of routine blood cultures. Because other bacillus species are frequent contaminants, there is the potential for delayed diagnosis if results are disregarded. Cultures from skin, ascites, pleural fluid, cerebrospinal fluid, and pericardial fluid may be positive. Biopsy can also be used to identify cases of cutaneous anthrax. A serologic test that has been cleared by the Food and Drug Administration (FDA) is available, but it does not yield positive results until late in the disease course. Reference laboratories, such as a state health laboratory, can perform definitive testing, including polymerase-chain-reaction (PCR)–based assays.[9]

Chest imaging may reveal a widened mediastinum, pleural effusions, or both, as well as apparent infiltrates due to effusions, atelectasis, and changes consistent with the early phase of the acute respiratory distress syndrome (Fig. 1B); in addition, many patients may have characteristic hyperdense (hemorrhagic) mediastinal lymphadenopathy on unenhanced computed tomography of the chest. An echocardiogram may reveal a pericardial effusion.[9]

Laboratory studies may reveal hemoconcentration, abnormal transaminases, anemia, thrombocytopenia, and coagulopathy, depending on disease severity. Lumbar puncture is required to rule out meningitis.[9] There are decision support tools available to facilitate the diagnosis of anthrax after a known release of the bacillus.[20]

TREATMENT OF ANTHRAX

Several antimicrobial agents have activity against *B. anthracis*, although concerns regarding engineered drug resistance influence the choice of treatment regimens.[2] Because the disease is toxin-mediated, therapies that inhibit protein synthesis or disable toxins are preferred in the published CDC guidelines.[21]

The form of the disease and context of exposure (natural vs. intentional) determine the specifics of treatment. Treatment regimens can be divided into those for systemic disease and those for limited cutaneous disease.[21]

Uncomplicated cutaneous anthrax can be treated with an oral fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) or doxycycline. Penicillin can be used if the isolate is known to be susceptible. The recommended duration of treatment is 7 to 10 days; however, a recent study suggests that shorter courses for naturally occurring cases are effective.[22] In the setting of an intentional attack, in which inhalation of spores may also have occurred, the duration should be extended to 60 days to cover the full incubation period of inhalational anthrax.[21]

Ideally, systemic forms of anthrax should be treated in an intensive care unit, where interventions such as mechanical ventilation, hemodynamic monitoring, fluid resuscitation, vasopressor support, prophylaxis for deep-vein thrombosis, and prophylaxis for gastrointestinal bleeding can be provided, consistent with the current sepsis protocols.[23] Anthrax-specific treatments include combination antimicrobial therapy. If meningitis has not been ruled out, the CDC recommends a regimen including a fluoroquinolone, such as ciprofloxacin; a drug that inhibits protein synthesis, such as linezolid; and a drug that penetrates the central nervous system, such as meropenem. If meningitis has been ruled out with the use of a lumbar puncture, a two-drug regimen that includes a fluoroquinolone plus linezolid or clindamycin is recommended. Glucocorticoid treatment could be initiated for anthrax meningitis in accordance with the protocols for bacterial meningitis. The treatment duration is 2 to 3 weeks.[21]

Because historical studies of anthrax showed benefit with the use of antiserum, modern antibody therapies directed against anthrax toxins have been developed as adjunctive treatment. Two antibody-based therapies are available: raxibacumab and anthrax immune globulin. Raxibacumab is an FDA-approved monoclonal antibody targeted at the protective antigen component of the toxins and is administered in a single dose. In studies in animals, the use of raxibacumab without the concomitant use of antimicrobials was highly protective against lethal disease.[24] However, when raxibacumab was combined with antimicrobials, the protective effect was no longer significant, although a trend in favor of the effectiveness of the therapy was apparent.[21] Similar findings were seen with anthrax immune globulin.[21,25] The CDC recommends antitoxin treatments in cases of systemic anthrax.[21] However, it is difficult to determine what added benefit they confer for patients who are effectively treated with antimicrobials.

Another recommended adjunctive therapy is drainage of pleural effusions, ascites, and pericardial effusions, all of which are toxin-laden. In a historical review, such treatment of pleural effusions was shown to be partly responsible for the diminished fatality rate in modern cases of anthrax.[26] Surgical resection may be required in cases of gastrointestinal and injectional anthrax.[21]

Anthrax does not spread from person to person. Standard precautions are sufficient for infection control.[9]

PREVENTION OF ANTHRAX

Anthrax vaccine adsorbed (AVA) is the FDA-licensed vaccine used for the prevention of anthrax. AVA was initially administered in a series of six subcutaneous injections followed by annual booster injections. A randomized clinical trial, however, showed noninferior immunogenicity results when five intramuscular injections were used.[27] The intramuscular regimen is now the recommended method of vaccination. Evidence suggests that this schedule may be further simplified.[28] Other anthrax vaccines are in development.

For postexposure prophylaxis, AVA would probably be recommended for off-label (or Emergency Use Authorization) use in a three-dose schedule[21]

on the basis of studies in animals.[29] Antimicrobial therapy is coupled with vaccination for postexposure prophylaxis; ciprofloxacin and doxycycline are the preferred antimicrobials. The duration of prophylaxis, derived from the longest germination time of inhaled spores, is 60 days.[21] After the 2001 anthrax attacks, approximately 10,000 persons received antimicrobial prophylaxis and had no resultant disease, despite compliance rates of less than 50%; this suggests that some modification of antibiotic recommendations is possible.[30] On the basis of studies in animals, raxibacumab can also be used as single-agent postexposure prophylaxis when no other option is available,[21,24] although the circumstances in which ordinary postexposure prophylaxis could not be used are limited.

SMALLPOX

Smallpox, a viral disease, has the distinction of being the only human infectious disease that has been eradicated. Because of this success, routine vaccination ceased, which allowed immunity to wane and has created a large susceptible population, should the virus be released from a laboratory. A recent study, however, indicates that some residual immunity may remain in persons vaccinated in the past.[31]

CARDINAL FEATURES OF SMALLPOX

Infection with the smallpox virus, variola, occurs through droplet or aerosol exposure. After an incubation period of 10 to 14 days, a prodrome of fever and constitutional symptoms begins. Rash appears 1 to 4 days after the onset of fever. The rash is characteristically centrifugal, with lesions progressing synchronously from macules to papules to vesicles (umbilicated) to pustules to scabs over a period of a couple of weeks (Fig. 1C). A person is contagious during the period when the rash is present, and infectiousness ceases after the scabs have sloughed. The fatality rate of smallpox is approximately 25%, and severe complications such as blindness can also occur.[32]

DIAGNOSIS OF SMALLPOX

The initial suspicion of smallpox infection is likely to arise from the presence of a characteristic febrile rash. Definitive diagnosis is based on serologic testing, cell culture, PCR, or electron microscopy performed at reference facilities. Because a single case represents a public health emergency, authorities should be notified immediately on initial suspicion.[32]

TREATMENT AND PREVENTION OF SMALLPOX

There are currently no FDA-licensed treatments for smallpox, although two compounds are in late development stages (tecovirimat and liposomal cidofovir).[33] Indications for their use are not yet available, but their availability during an outbreak would probably be through emergency-use authorization. The prevention of smallpox is based on the efficacy of the vaccine and is derived from the strategy of surveillance and containment pursued during the global eradication campaign.

The current vaccine, ACAM2000 (Sanofi Pasteur Biologics), is based on the traditional Jenner vaccine (using the related virus, vaccinia) and is administered in a single percutaneous dose. Vaccination after exposure — but before the rash is present — can abort or attenuate the clinical manifestations of the disease. This live vaccine is contraindicated for persons with severe immunosuppression, and newer-generation vaccinations have been developed for these populations.[34]

The vaccine is not without risk: it is estimated that pericarditis or myocarditis may develop in 5.7 per 1000 vaccinees.[35] In addition, eczema vaccinatum, generalized vaccinia, progressive vaccinia, and vaccinia encephalitis can also occur.[36] Table 1 provides definitions of the dermatologic forms of vaccinia. Patients with eczema vaccinatum, generalized vaccinia, or progressive vaccinia benefit from the administration of vaccinia immune globulin and possibly antiviral therapy.[37,38] Accidental inoculation of the vaccine from the administration site to the eye or to other persons can also occur.[36]

Newer-generation vaccines (LC16 and Imvamune [Bavarian Nordic]) exist and have shown promise in safety and immunologic studies involving populations for whom the traditional vaccine is contraindicated. Neither vaccine is FDA-approved for use, although Imvamune is stockpiled and would be expected to be available through emergency-use authorization.[39,40]

Smallpox is contagious. Patients with smallpox should be placed under airborne precautions.[32]

Table 1. Dermatologic Vaccinia Reactions.

Reaction	Feature or Features
Progressive vaccinia	Necrosis in the area of vaccination
Eczema vaccinatum	Local or generalized spread of vaccine virus in persons with eczema
Generalized vaccinia	Skin lesions that are remote from the vaccination site

PNEUMONIC PLAGUE

Pneumonic plague is caused by infection with the fleaborne bacterium *Yersinia pestis*. This organism, found worldwide and responsible for the "Black Death," can cause several forms of illness: bubonic (the most common) (Fig. 1D), septicemic, and pneumonic plague.[41] Because of the focus of this review, only pneumonic plague is discussed.

CARDINAL FEATURES OF PNEUMONIC PLAGUE

In a deliberate attack, primary pneumonic plague — rather than secondary spread from bubonic or septicemic forms — would occur 1 to 3 days after inhalation of the released bacterium or after droplet transmission from another infected person. The initial presentation of pneumonic plague is nonspecific and is difficult to differentiate from an ordinary pneumonia in its early stages. Hemoptysis, a unique feature, might be present, and rapid progression to respiratory failure and death would occur with greater frequency than in ordinary pneumonias.[41]

DIAGNOSIS OF PNEUMONIC PLAGUE

Because the clinical features of pneumonic plague are nonspecific, diagnosis is largely based on the results of culture. Sputum, blood, or lymph-node aspirates could yield positive culture results. Chest radiography would reveal a severe pneumonic process. Serologic testing can also be useful but would not play much of a role during acute illness.[41] Rapid antigen tests are available in regions in which plague is endemic, but none are FDA-approved.

TREATMENT AND PREVENTION OF PNEUMONIC PLAGUE

The treatment of pneumonic plague involves a 10-day course of an aminoglycoside antibiotic agent, such as streptomycin or gentamicin. Doxycycline is considered a second-line treatment.[41] However, a randomized, controlled trial of potential treatments for bubonic plague revealed equivalency between gentamicin and oral doxycycline; it is unclear whether these results can be extrapolated to pneumonic plague.[42] There has been increased interest in the use of fluoroquinolones as primary treatment in mass-casualty settings.[42] A 7-day course of doxycycline or ciprofloxacin would be used as postexposure prophylaxis.[41] No vaccine against plague is available. Because pneumonic plague can be transmitted from person to person through respiratory droplets, droplet precautions must be implemented for all patients.[41]

BOTULISM

Botulism is the result of toxin elaboration by the gram-positive, spore-forming bacillus *Clostridium botulinum*. Several forms of botulism occur, including infantile, wound, gastrointestinal, iatrogenic, and inhalational botulism. In a deliberate attack, inhalational botulism would be anticipated, although gastrointestinal botulism is also a possibility. Because of the dearth of naturally occurring cases of inhalational botulism, gastrointestinal botulism is taken as a surrogate for the pathophysiological aspects of inhalational botulism.[43]

CARDINAL FEATURES OF INHALATIONAL BOTULISM

Approximately 6 hours after the inhalation of botulinum toxin, persons exposed would have a descending paralysis (Fig. 1E) with symptoms of cranial-nerve dysfunction, such as diplopia, dysphagia, pupillary dilation, and ptosis. This would progress to ventilatory failure necessitating mechanical ventilation. Fever and altered mental status are absent.[43]

DIAGNOSIS OF BOTULISM

The diagnosis of botulism is largely clinical and is confirmed with the use of mouse bioassays, through culture, or through laboratory detection of the toxin in contaminated materials, blood, or stool. New methods of diagnosis are being developed. Nerve-conduction studies can also be used. Newer methods involve the use of PCR-based detection.[43]

There are currently eight known toxin types (A through H) that can be elaborated by *C. botu-*

Table 2. Selected Features of the Conditions Discussed.

Condition	Contagious	Clinical Form or Forms	Vaccine Available	Treatment
Anthrax	No	Three primary forms: cutaneous, inhalational, and gastrointestinal	Yes	Combination antimicrobials, effusion drainage, monoclonal antibody
Smallpox	Yes	Centrifugal rash with same-stage lesions	Yes	Supportive treatment
Plague	Yes	Pneumonic or bubonic	No	Antimicrobials
Botulism	No	Inhalational or gastrointestinal	No	Antitoxin
Tularemia	No	Inhalational or ulceroglandular	No	Antimicrobials

linum, and knowing which type is present can provide epidemiologic clues regarding the source of exposure.[44] For example, toxin type G does not cause disease naturally in humans, and toxin type E is found almost exclusively in seafood.[45]

TREATMENT OF BOTULISM

The treatment of botulism involves the administration of the equine-derived heptavalent (A–G) antitoxin, which has been approved by the FDA and is available exclusively from the CDC.[43] In a deliberate attack, the bivalent human-derived antitoxin, BabyBIG (Baxter Healthcare), which is used for infant botulism, should not be administered. A diagnosis of inhalational botulism should prompt attention to any signs of impending respiratory failure, along with consideration of admission to an intensive care unit and initiation of mechanical ventilation. In addition, given the equine origin of the antitoxin, there is the potential for hypersensitivity. There is no vaccine against botulinum toxin, although the antitoxin may induce host immunity to the toxin and therefore may be efficacious when used as a vaccine.[46] A program for vaccination of workers at high risk has ended.[47] Botulism is not contagious, and standard precautions are sufficient for infection control.[43]

TULAREMIA

Tularemia is caused by infection with *Francisella tularensis*, a gram-negative bacillus that occurs naturally in many parts of the United States. Colloquially known as "rabbit fever," the infection can be transmitted from contaminated animals or through tick bites.[48] The infectious dose is very low. Several forms of tularemia occur; however, a deliberate release would be expected to cause pneumonic tularemia rather than the more common ulceroglandular form (Fig. 1F).

CARDINAL FEATURES OF PNEUMONIC TULAREMIA

After an average incubation period of 3 to 5 days, pneumonic tularemia would manifest with signs and symptoms similar to those of community-acquired pneumonia, including fever, cough, and dyspnea. However, septic shock, acute respiratory distress syndrome, and respiratory failure can ensue. Because there is no distinguishing characteristic of pneumonic tularemia, clinical suspicion must be high.[48]

DIAGNOSIS OF TULAREMIA

Tularemia can be diagnosed with the use of culture, although enriched culture medium must be used. Immunofluorescence staining, serologic testing, and PCR can also be used for diagnosis. In addition, because of the highly infectious nature of tularemia bacilli, laboratory personnel must be alerted, so that they can work in proper biosafety conditions. Chest imaging results in tularemia are nonspecific and would reveal changes consistent with pneumonia.[48]

TREATMENT AND PREVENTION OF TULAREMIA

The treatment of tularemia consists of a 10-day course of an aminoglycoside antibiotic, such as streptomycin or gentamicin. Ciprofloxacin and doxycycline are alternatives. For postexposure prophylaxis, a 7-day course of doxycycline or ciprofloxacin can be prescribed. There is no vaccine for tularemia. Standard precautions are adequate for infection control.[48]

CONCLUSIONS

The purpose of this review is to highlight clinically useful issues related to CDC category A pathogens. Because most of these conditions can occur naturally, suspicion for bioterrorism depends on clinicians being alert to unusual patterns, such as unexplained clusters of infection. Table 2 summarizes the key facts about the agents we have discussed. In all situations, a close collaboration between public health officials and clinicians is essential.

Dr. Adalja reports holding stock in Siga, Biocryst, Cubist, and Luminex. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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