

Task Force I: Direct Cardiovascular Implications of Emerging Infectious Diseases and Biological Terrorism Threats

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Definition and Classifications

Emerging infections are those with a rising incidence over recent decades and those that threaten to increase, encompassing both newly emerging and re-emerging infections. The emergence of a new infectious agent in the population, the new recognition of a previously undetected circulating agent, or the realization that a noncommunicable disease is actually caused by infection contribute to this group of microbial threats, unrelated to any possible intentional release of biologic agents or bioterrorism (1). As with the scope of the larger body of all infections and infectious diseases, the capacity of emerging infections to affect the cardiovascular system varies from none to limited or increased risk. However, this task force report will focus on the possible cardiovascular implications of emerging infectious diseases and infection with select agents designated to have potential for intentional release.

A wide range of infectious agents that can emerge in spontaneous epidemics or be disseminated in bioterrorist attacks can affect the cardiovascular system. Many of these infectious agents have caused disease sporadically (e.g., botulism, tularemia) or endemically (e.g., viral hemorrhagic fevers) in certain parts of the world for centuries; others are relative newcomers (e.g., severe acute respiratory syndrome or SARS, *Nipah virus*). Some of these agents (e.g., smallpox) do not occur naturally at present and even one confirmed case would signal a likely bioterrorist event.

When focusing on the select potential agents of bioterrorism, as well as emerging infectious diseases, the clinical syndromes catalogued by the U.S. Department of Health and Human Services are as varied as the pathogens that produce them (2,3). With some, the direct clinical impact is limited to 1 organ system, as in the case of *Clostridium botulinum* toxin-induced neuroparalytic illness (4). Other agents can affect multiple organ systems, as in the case of *Coxiella burnetii* infection, which affects both pulmonary and hepatic systems (5). Additional factors accentuate the complexity of bioterrorism-related illnesses. The temporal onset of different clinical manifestations following exposure can vary. For example, Q fever endocarditis is an illness of chronic infection; whereas pneumonia is seen acutely following exposure (5).

However, naturally occurring infections with most of the designated bioterrorism agents are rarely seen in the U.S. today. Because of this, many clinicians are unfamiliar with the associated clinical syndromes and may not initially recognize when an illness stems from exposure to one of these agents, much less from intentional release in a bioterrorism attack (6).

The Centers for Disease Control and Prevention (CDC) has classified certain diseases and agents into 3 relatively high-priority categories (A, B, and C) (2,3). These diseases and agents are summarized in Tables 1 and 2. Diseases and agents in Category A have the highest priority because they can be disseminated or transmitted easily from person to person, result in high mortality rates, have the potential for major public health impact, may cause public panic and social disruption, and require special action for public health preparedness. Diseases and agents in Category B are moderately easy to disseminate, result in moderate morbidity rates and low mortality rates, and require specific enhancements of the diagnostic capacity and enhanced disease surveillance. Diseases and agents in Category C include emerging pathogens that could be engineered for mass dissemination in the future because of availability, ease of production and dissemination, and the potential for high morbidity and mortality rates and major public health impact.

This report focuses on the Category A, B, and C agents, but an unlimited number of other potential, nonbioterrorism, microbial threats exist from natural evolution, transformation, and transmission of existing pathogens, including emerging and re-emerging infectious diseases, as well as from genetically engineered variants or "mosaics" that can multiply the potential transmissibility, morbidity, and mortality of agents released in a terrorist attack.

Many of the Category A, B, and C agents injure the myocardium, pericardium, or endothelium by direct infection or infiltration or through a chemical toxin (e.g., ricin). For some, the evidence of direct effects stems from multiple observations. For others, information rests on a single or a small set of anecdotal reports. Although such direct injury could harm even healthy individuals with a previously normal cardiovascular system, the reality is that most of the currently known, high-risk agents are not directed at the cardiovascular

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Table 1 Categories of Bioterrorism Agents and Diseases and Associated Cardiovascular Syndromes

| Category | Agents and Diseases | Endocarditis | Myocarditis | Pericarditis | Vasculitis* |
|---|--|--|-------------|--------------|-------------|
| A Highest priority—these agents can be disseminated or transmitted easily from person to person, result in high mortality rates, might cause public panic and social disruption, and require special action for public health preparedness. | <u>Anthrax</u> (<i>Bacillus anthracis</i>) | | | | |
| | <u>Botulism</u> (<i>Clostridium botulinum</i> toxin) | | | | |
| | <u>Plague</u> (<i>Yersinia pestis</i>) | | | | |
| | Smallpox (<i>Variola major</i>) | | | | |
| | Tularemia (<i>Francisella tularensis</i>) | ++ | | + | + |
| B Moderate priority—moderately easy to disseminate, result in moderate morbidity rates and low mortality rates, and require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance. | Brucellosis (<i>Brucella species</i>) | + | + | + | + |
| | Epsilon toxin of <i>Clostridium perfringens</i> | | | | |
| | <u>Food safety threats</u> (e.g., <i>Salmonella species</i> , <i>Escherichia coli</i> O157:H7, <i>Shigella</i>) | ++++ | + | + | + |
| | Glanders (<i>Burkholderia mallei</i>) | | | | |
| | Melioidosis (<i>Burkholderia pseudomallei</i>) | | | + | + |
| | Psittacosis (<i>Chlamydia psittaci</i>) | + | + | + | |
| | Q fever (<i>Coxiella burnetii</i>) | +++++ | ++ | + | |
| | <u>Ricin toxin</u> from <i>Ricinus communis</i> (castor beans) | | | | |
| | <u>Staphylococcal enterotoxin B</u> | | | | |
| | Typhus fever (<i>Rickettsia prowazekii</i>) | | | | |
| | Alphaviruses (e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis) | | | | |
| | <u>Water safety threats</u> (e.g., <i>Vibrio cholerae</i> , <i>Cryptosporidium parvum</i>) | | | | |
| | C Low priority—could be engineered for mass dissemination because of availability, ease of production, and the potential for high morbidity/mortality rates. | Emerging infectious disease agents (such as <i>Nipah virus</i> , <i>hantavirus</i>) | | | |

The number of "+" indicates the strength of the evidence on the association. *Includes large, medium, and small vessel vasculitis plus cutaneous leukocytoclastic vasculitis.

system per se. Greater concern comes from secondary effects on the heart and vasculature when these agents cause prolonged or severe fever, sepsis, shock, dehydration, central and peripheral nervous system dysfunction, anemia, hypoxia, renal, and/or hepatic impairment.

Cardiovascular specialists should have a general working knowledge of the common bioterrorist agents (6). Table 2 highlights the clinical presentation, evaluation, and laboratory testing for a number of diseases and agents that are of particular concern to our national security (3,7). It is important for clinicians to remember that although most of the Category A, B, and C agents are disseminated and transmitted by aerosolized droplets or secretions that enter the victim via the respiratory route (e.g., weaponized anthrax spores, ricin), notable exceptions exist (e.g., cutaneous anthrax exposure).

Known Cardiovascular Syndromes Associated With Category A, B, and C Agents and Diseases

Four cardiovascular syndromes are caused by bioterrorism agents: 1) endocarditis, 2) myocarditis, 3) pericarditis, and

4) vasculitis. The heart is the primary site of endocarditis, myocarditis, and pericarditis pathology, while vasculitis affects the vascular tissues. The mechanisms of pathology are varied, ranging from direct tissue invasion by the microbe—transient or persistent—to complications of a local or systemic immune response to infection.

Distinguishing the microbial etiology of each syndrome can be challenging; whether intentionally released for bioterrorism or naturally occurring, different infectious agents can cause indistinguishably similar clinical signs and symptoms. Thus, it may not be obvious to clinicians, at least early in a bioterrorism attack, that a cardiovascular syndrome is due to biological warfare, especially if the biological agent does not grow or grows slowly in the culture media routinely used by clinical laboratories to detect naturally occurring pathogens. Characteristic signs and symptoms of each of the 4 cardiovascular syndromes are briefly outlined in the subsequent sections.

Endocarditis

The clinical features of infective endocarditis depend, in part, on the virulence of the infecting organism(s), the exposure dose, and the host response to that infection (8). With more aggressive pathogens, clinical evidence may

Table 2 Summary of Select Category A and B Diseases and Agents (3,7)

| Disease or Agent | Infection Routes, Signs, and Symptoms | Diagnostic Procedures |
|---|---|---|
| Category A Diseases and Agents | | |
| Anthrax (<i>Bacillus anthracis</i>) | <p>Cutaneous anthrax: About 95% of anthrax infections occur through a cut or abrasion on the skin. The skin infection begins as a raised itchy bump but within 1–2 days develops into a vesicle and then a painless ulcer, usually 1–3 cm in diameter, with a characteristic black necrotic (dying) area in the center. About 20% of untreated cases of cutaneous anthrax result in death.</p> <p>Inhalational anthrax: Initial symptoms may resemble those of the common cold—sore throat, mild fever, muscle aches, and malaise. After several days, the symptoms may progress to severe breathing problems and shock. Inhalation anthrax is usually fatal.</p> <p>Gastrointestinal anthrax: Gastrointestinal anthrax is characterized by acute inflammation of the intestinal tract. Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and severe diarrhea. Intestinal anthrax results in death in 25%–60% of affected individuals.</p> | <p>Anthrax is diagnosed by isolating <i>B. anthracis</i> from the blood, skin lesions, or respiratory secretions or by measuring certain antibodies in the blood.</p> <p>Health care providers should confirm the diagnosis by obtaining the appropriate laboratory specimens based on the clinical form of the suspected anthrax: specimens of vesicular fluid and blood for cutaneous anthrax, blood and cerebrospinal fluid (if meningeal signs are present) or chest X-ray for inhalational anthrax, and blood for gastrointestinal anthrax.</p> |
| Botulism (<i>Clostridium botulinum</i> toxin) | <p>The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. Infants with botulism appear lethargic, feed poorly, are constipated, and have a weak cry and poor muscle tone.</p> <p>These are all symptoms of the muscle paralysis caused by the bacterial toxin. If untreated, these symptoms may progress to cause paralysis of the arms, legs, trunk, and respiratory muscles. In foodborne botulism, symptoms generally begin 18–36 h after eating a contaminated food, but they can occur as early as 6 h or as late as 10 days later.</p> | <p>Patient history and physical examination may suggest botulism but are usually not enough to allow a diagnosis. Other diseases, such as Guillain-Barré syndrome, stroke, and myasthenia gravis, can produce symptoms that are similar to those of botulism, and certain tests may be needed to exclude these other conditions, including brain scan, spinal fluid examination, nerve conduction test (electromyography), and tensilon test for myasthenia gravis.</p> <p>The most direct way to confirm the diagnosis is to identify the botulinum toxin in the patient's serum or stool by injecting the samples into mice and looking for signs of botulism. The bacteria can also be isolated from the stool of persons with foodborne and infant botulism. These tests can be performed at some state health department laboratories and the CDC.</p> |
| Plague (<i>Yersinia pestis</i>) | <p>The typical sign of the most common form of human plague is a swollen and very tender lymph gland, accompanied by pain. The swollen gland is called a "bubo" (hence, the term "bubonic plague"). Bubonic plague should be suspected when a person develops a swollen gland, fever, chills, headache, and extreme exhaustion and has a history of possible exposure to infected rodents, rabbits, or fleas.</p> | <p>The diagnosis of plague is confirmed if 1 of the following conditions is met: 1) an isolated culture is lysed by a specific bacteriophage; 2) 2 serum specimens demonstrate a 4-fold anti-F1 antigen titer difference by hemagglutination testing; or 3) a single serum specimen tested by hemagglutination has an anti-F1 antigen titer of >1:128 and the patient has no known previous plague exposure or vaccination history.</p> |
| Smallpox (<i>Variola major</i>) | <p>Acute onset of fever of at least 101 °F (38.3 °C) followed by a rash characterized by firm, deep-seated vesicles or pustules in the same stage of development without other apparent cause.</p> | <p>Laboratory criteria for confirmation include: 1) PCR identification of variola DNA in a clinical specimen, or 2) isolation of smallpox (variola) virus from a clinical specimen (World Health Organization Smallpox Reference Laboratory or laboratory with appropriate reference capabilities) with variola PCR confirmation.</p> <p>The importance of case confirmation using laboratory diagnostic tests depends on the epidemiological situation.</p> |
| Tularemia (<i>Francisella tularensis</i>) | <p>Symptoms of tularemia include sudden fever, chills, headaches, diarrhea, muscle aches, joint pain, dry cough, and progressive weakness.</p> <p>People with tularemia may also develop pneumonia with chest pain and bloody sputum. They may experience difficulty breathing or even stop breathing.</p> <p>Other symptoms depend on the route of exposure to the tularemia bacteria. These symptoms include ulcers on the skin or mouth, swollen and painful lymph glands, swollen and painful eyes, and sore throat.</p> | <p>Laboratory diagnosis of tularemia is based on culture or serology. <i>F. tularensis</i> is a slow-growing, fastidious organism that requires media containing cystine or cysteine for optimal growth. Laboratory personnel should be alerted if tularemia is suspected to ensure that proper media are used and to prevent infection of laboratory workers. Serologic testing is available through reference laboratories. Confirmation requires a 4-fold change in anti-<i>F. tularensis</i> antibodies between paired sera.</p> |
| Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo]) | <p>Signs and symptoms vary by the type of VHF, but initial signs and symptoms often include marked fever, fatigue, dizziness, muscle aches, loss of strength, and exhaustion. Patients with severe cases of VHF often show signs of bleeding under the skin, in internal organs, or from body orifices such as the mouth, eyes, or ears.</p> | <p>The Special Pathogens Branch of the CDC works with Biosafety Level 4 viruses, which are highly pathogenic and require handling in special laboratory facilities.</p> |

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Table 2 Continued

| Disease or Agent | Infection Routes, Signs, and Symptoms | Diagnostic Procedures |
|---|---|---|
| Ricin toxin from <i>Ricinus communis</i> (castor beans) | <p>Inhalation: Within a few hours of inhaling ricin, typical symptoms are respiratory distress, fever, cough, nausea, and chest tightness. Heavy sweating may follow and fluid may accumulate in the lungs (pulmonary edema). Finally, low blood pressure and respiratory failure may occur, leading to death.</p> <p>Ingestion: Symptoms after swallowing ricin include vomiting, diarrhea that may become bloody, and severe dehydration followed by low blood pressure.</p> <p>Skin and eye exposure: Ricin in powder or mist form can cause redness and pain in the skin and eyes.</p> <p>Death from ricin poisoning may occur within 36 to 72 h of exposure, depending on the route of exposure and the dose received. If death has not occurred within 3 to 5 days, the victim is likely to recover.</p> | When an environmental sample is believed to contain ricin, the sample should be sent directly to a Laboratory Resource Network reference laboratory for testing using a time-resolved fluorescence immunoassay. If the sample tests positive for ricin, it may be sent to the CDC for additional PCR testing, defining, archiving, or storing. |
| Category B Diseases and Agents | | |
| Brucellosis (<i>Brucella</i> spp.) | <p>The most common route of infection is eating or drinking contaminated milk products. Brucellosis is rarely due to inhalation of <i>Brucella</i> organisms, but this may be a significant hazard for people in certain occupations. Persons working in slaughterhouses or meat-packing plants and veterinarians are at increased risk of contamination of skin wounds.</p> <p>Brucellosis can cause a range of symptoms that are similar to those of the flu, including fever, sweats, headaches, back pain, and physical weakness. Severe infections of the central nervous system or heart lining may occur. Brucellosis can also cause long-lasting or chronic symptoms, such as recurrent fevers, joint pain, and fatigue.</p> | Brucellosis is diagnosed in a laboratory by identifying <i>Brucella</i> organisms in samples of blood or bone marrow. In addition, blood tests can detect antibodies against the bacteria. To confirm a diagnosis using a blood test, the provider should collect an initial blood sample and a second blood sample 2 weeks later. |
| Q fever (<i>Coxiella burnetii</i>) | Only one-half of all people infected with <i>C. burnetii</i> show signs of clinical illness. Most acute cases of Q fever begin with sudden onset of one or more of the following: high fevers, severe headache, general malaise, myalgia, confusion, sore throat, chills, sweats, nonproductive cough, nausea, vomiting, diarrhea, abdominal pain, and chest pain. Fever usually lasts 1 to 2 weeks. Weight loss can occur and persist for some time. Up to one-half of all patients with a symptomatic infection develop pneumonia. Most people with Q fever have abnormal liver function test results, and some develop hepatitis. | Confirming a diagnosis of Q fever requires serologic testing to detect the presence of antibodies to <i>C. burnetii</i> antigens. In most laboratories, the indirect immunofluorescence assay is the most dependable and widely used method. <i>C. burnetii</i> may also be identified in infected tissues using immunohistochemical staining and DNA detection methods. |
| Psittacosis (<i>Chlamydia psittaci</i>) | <p>When a person breathes in <i>Chlamydia psittaci</i>, the lungs' defense mechanisms attempt to neutralize the bacteria. The bacteria that avoid this defense start an infection that ranges in severity from a mild flu-like illness to severe pneumonia. Generally, signs and symptoms appear within 4 to 15 days after exposure and include fever, chills, cough, weakness or fatigue, muscle and chest pain, loss of appetite, nausea, vomiting, diarrhea, headache, sweating, and abnormal intolerance to light.</p> <p>Psittacosis is primarily a lung disease, but it can involve several organs. Some reports show that inflammation can occur in the liver, heart cavity lining, heart muscle, and brain.</p> | Psittacosis can be diagnosed most often by 1) the isolation of <i>Chlamydia psittaci</i> from respiratory secretions, 2) a 4-fold or greater increase in antibody against <i>C. psittaci</i> by complement fixation or MIF to a reciprocal titer of greater than or equal to 32 between paired acute- and convalescent-phase serum specimens, or 3) the presence of immunoglobulin M antibody against <i>C. psittaci</i> by MIF to a reciprocal titer of greater than or equal to 16. |
| Salmonellosis (<i>Salmonella</i> spp.) | Most persons infected with <i>Salmonella</i> develop diarrhea, fever, and abdominal cramps within 12 to 72 h after infection. The illness usually lasts 4 to 7 days, and most persons recover without treatment. However, in some persons the diarrhea may be so severe that the patient needs to be hospitalized. In these patients, the <i>Salmonella</i> infection may spread from the intestines to the bloodstream and then to other body sites and can cause death unless the person is treated promptly with antibiotics. The elderly, infants, and those with impaired immune systems are more likely to develop severe illness. | To identify <i>Salmonella</i> as the cause of the illness, providers should send stool samples to the laboratory for testing to identify the presence of <i>Salmonella</i> . To ensure that the appropriate tests are conducted, providers must instruct the laboratory to look for <i>Salmonella</i> . Once <i>Salmonella</i> has been identified, further testing can determine its type and which antibiotics should be used to treat it. |

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Table 2 Continued

| Disease or Agent | Infection Routes, Signs, and Symptoms | Diagnostic Procedures |
|--|---|---|
| Melioidosis (<i>Burkholderia pseudomallei</i>) | <p>Transmission occurs by direct contact with contaminated soil and surface waters. In southeast Asia, the organism has been repeatedly isolated from agriculture fields, with infection occurring primarily during the rainy season. Humans and animals are believed to acquire the infection by inhalation of dust, ingestion of contaminated water, and contact with contaminated soil, especially through skin abrasions and, for military troops, by contamination of war wounds. Person-to-person transmission can occur.</p> <p>Illness from melioidosis can be categorized as acute or localized infection, acute pulmonary infection, acute bloodstream infection, and chronic suppurative infection. Inapparent infections are also possible. The incubation period (time between exposure and appearance of clinical symptoms) is not clearly defined but may range from 2 days to many years.</p> | <p>A definitive diagnosis can be made by growing <i>B. pseudomallei</i> from any site, including blood cultures, pus aspirated from an abscess, sputum, or urine cultures. A throat swab is not sensitive but is 100% specific if positive. Ashdown's medium, containing gentamicin, may be required for cultures from nonsterile sites. <i>Burkholderia cepacia</i> medium may be a useful alternative selective medium in nonendemic areas. A new medium derived from Ashdown known as Francis media can help differentiate <i>B. pseudomallei</i> from <i>B. cepacia</i> and helps in the early diagnosis of melioidosis. Diagnosis of melioidosis can be made as early as 18 h using Francis media.</p> |

Detailed description on these agents and diseases is available on the Web site of the Centers for Disease Control and Prevention. Bioterrorism Agents/Diseases: A to Z. <http://www.bt.cdc.gov/agent/agentlist.asp> (3).

CDC = Centers for Disease Control and Prevention; DNA = deoxyribonucleic acid; MIF = microimmunofluorescence; PCR = polymerase chain reaction; VHF = viral hemorrhagic fever.

develop within hours to days of establishment of infection. With less virulent microorganisms, the onset of infection is more subtle and initially nonspecific, often delaying diagnosis by weeks or even months.

A majority of patients manifest fever. Other signs of systemic toxicity or sepsis may be present with endocarditis due to aggressive pathogens but are usually absent in patients with subacute to chronic infection. Other nonspecific findings include chills, malaise, fatigue, night sweats, weakness, weight loss, myalgias, and arthralgias.

The development of secondary complications of endocarditis often prompts a consideration of the correct diagnosis. This includes the presence of a cardiac murmur due to valvular insufficiency (or rarely, stenosis) caused by destruction of components of the valve apparatus. Other indications of infective endocarditis are signs of left- or right-sided ventricular failure and systemic or pulmonary vascular embolic events, including acute evidence of tissue damage or organ dysfunction, such as stroke, pleuritic chest pain, extremity or digit ischemia, and visual loss.

Blood cultures are critical to establish the diagnosis and the etiology of infective endocarditis cases and other syndromes of intracardiac or intravascular infection. When a blood culture is negative due to recent administration of antibiotics or the fastidious growth characteristics of the infecting pathogen (such characteristics are manifested by some of the bioterrorism agents), the diagnosis of endocarditis may be less obvious, particularly if only nonspecific clinical findings are present. In such cases, echocardiography, particularly transesophageal echocardiography in adults, may be used to establish a diagnosis of endocarditis (8,9). Similarly, serology (detection of antibodies to the infectious agent), immunohistochemistry, and testing for the presence of pathogen deoxyribonucleic acid, may be key to the diagnosis of blood and tissue culture-negative endocarditis (10). These latter methods of diagnosis are partic-

ularly useful to identify certain naturally occurring pathogens that could be used for bioterrorism attacks, including *Coxiella burnetii*, *Francisella tularensis*, and *Chlamydia psittaci*.

Myocarditis

Myocarditis is associated with many more infectious and noninfectious causes than endocarditis. In addition, seasonal outbreaks of myocarditis may occur as a result of several viral etiologies. As a result, clinicians are likely to link an increased number of myocarditis cases to a viral epidemic, which could delay the recognition of a bioterrorism attack.

Unlike infective endocarditis, myocarditis can be asymptomatic and, depending on the etiology, may resolve itself without specific antimicrobial treatment (11,12). Thus, most cases of myocarditis are undiagnosed. This makes it difficult to quantify a background rate in the population and to detect any increased frequency of myocarditis induced by changing infectious exposures. When symptoms do occur, chest pain is predominant and palpitations, shortness of breath, and cough may be present. Additional signs of myocarditis include recent or current fever, tachycardia, pericardial friction rub, signs of congestive heart failure, and the presence of a third heart sound.

Cardiomegaly and vascular congestion on chest radiograph and ST-segment elevation and T-wave inversion on serial electrocardiograms may be present (11). Echocardiogram and cardiac magnetic resonance imaging (MRI) with gadolinium are useful for assessing ventricular wall motion and left ventricular ejection fraction (11). Inflammatory changes in the myocardium may be seen on MRI showing areas of reduced contrast perfusion and enhanced delayed ventricular wall uptake.

These symptoms, signs, and diagnostic indicators, however, are common to myocarditis of multiple etiologies. Laboratory studies that detect microbes and viruses, system-

ically or in myocardial tissue, and/or document the serologic response to a particular infection, are needed to delineate the infectious etiology—whether naturally occurring or due to an intentional bioterrorist release. The clinician must be prepared (perhaps educated or trained) to recognize the array of potential etiologies of myocarditis, including in this context, the rarer potential select agent causes and the rare possibility of a bioterrorism event. Clinicians should also be familiar with the route to appropriate testing of adequately collected and processed specimens at a proficient laboratory and to alerting public health officials of unusual findings so they might assess for a cluster or larger group of cases and, if found, investigate the cause.

Pericarditis

Many conditions affect both the myocardium and the pericardium. Primary involvement of one or the other cardiac structure, however, is usually clinically definable (13,14).

Chest pain is the most common symptom of pericarditis. The pain is usually, but not always, associated with a rub heard on cardiac auscultation and is typically worse when the patient lies supine, swallows, or takes deep breaths. The individual may experience fever, as well as dyspnea that could be a manifestation of cardiac tamponade due to pericardial effusion caused by pericarditis. Other evidence of tamponade may include a pulsus paradoxus greater than 10 mm Hg and a prominent X descent with loss of the Y descent in the jugular venous pressure.

An electrocardiogram usually shows ST-segment elevation in all lead tracings as early changes in pericarditis. Large pericardial effusions may cause reduced QRS voltage and electrical alternans. Echocardiography is an important tool to determine whether an effusion is present and to estimate its size and whether early hemodynamic compromise exists due to the effusion in the pericardial space (14). Identification of an infectious etiology is important since interventions are available for certain bacteria. Blood cultures, serology, polymerase chain reaction (PCR), or reverse transcriptase-PCR of blood, its components, and even pericardial fluid assist in this diagnosis.

Vasculitis

Infection of the peripheral vascular system has been reported with several of the potential infectious select agents of bioterrorism. In vasculitis, the involvement ranges from infection and inflammation with or without mycotic aneurysm of large and medium vessel walls to that of small vessels and even superficial cutaneous leukocytoclastic vasculitis; for each implicated infectious etiology, the available body of evidence varies from large to anecdotal. As with endocarditis and myocarditis, this complication of bacterial or viral infection is more often attributed to common agents than to the possible select agents of bioterrorism.

In some vasculitis cases, infection of the arterial wall may not be apparent. In some, local, systemic, or both clinical

manifestations occur (15,16). Local findings include pain due to aneurysmal dilation of the arterial wall. In addition, vessel rupture with bleeding can cause pain. Pain may also be due to arterial emboli that precipitate local or distal ischemia. The findings of distal ischemia include skin changes, diminishment or absence of palpable pulse, and eventual gangrene. A mass may be palpable with aneurysm or aneurysm formation. Bleeding, when in the brain or central nervous system, may present as severe headache, neurologic deficit, and/or mental status decline. Local soft tissue findings of inflammation may be apparent when more superficial arteries, usually in an extremity, are infected. Gastrointestinal bleeding, which can range from indolent to severe and sudden, may complicate abdominal aortic aneurysms that erode into the gastrointestinal tract.

The systemic findings of vasculitis include sepsis. In these patients, blood cultures are usually positive and leukocytosis is frequently present. Relapsing bacteremia following an initial course and response to antibiotics may be a valuable clue to the correct diagnosis. Depending on the cause, serology and PCR can be valuable adjuncts to the diagnosis of vasculitis and identification of an infectious etiology, as could culture, immunopathology, and molecular diagnostic tools (e.g., PCR) of any surgical resection or biopsy tissue.

The choice of imaging modality to evaluate whether an aneurysm is present varies depending on location of the infection. For intracranial evaluation, cerebral arteriography is optimal, although MRI angiography is also used. Computed tomography scanning is useful for aortic examination and for more distal arteries. Echocardiography is useful for evaluation of the most proximal segment of the aorta.

Select Diseases and Agents That May Affect the Cardiovascular System

Select Category A and B bioterrorism agents or diseases and the cardiovascular syndromes they may produce are summarized in Table 1 and described in more detail in the following text. These descriptions are based on the review of existing reports in the literature through a systematic literature search on PubMed. For all except Q fever, cardiovascular syndromes are uncommonly reported.

Category A Diseases and Agents

Tularemia

Direct involvement of cardiovascular structures by *Francisella tularensis*, the agent of tularemia, is clinically rare. Only 1 case of infective endocarditis has been described (17), so that characterization of the illness is not possible. Pericarditis has been reported in a small number of patients, both in the pre-antibiotic era (18) and recently (19). In these patients, concomitant pneumonia was frequent, and the presentation was acute.

Category B Diseases and Agents

Brucellosis

Infection due to *Brucella* species is uncommon in the U.S. Cardiovascular complications have been reported to occur in 2% or less of patients who develop brucellosis. Infective endocarditis is the most common cardiovascular syndrome in these individuals. Most reported cases of *Brucella*-associated endocarditis have occurred in males, age 40 years and younger (20,21). These individuals present with a chronic infection, and valvular cusp calcification (22).

Endocarditis can complicate both pre-existing normal and abnormal cardiac valves. The aortic valve is most often involved, but lack of use of transesophageal echocardiography could underestimate the frequency of mitral valve infection, in addition to structural complications. Myocardial abscess and systemic embolization may occur, although less frequently than with other types of bacterial endocarditis (23). The usual cause of death due to *Brucella* endocarditis is congestive heart failure (23).

Other rare cardiovascular syndromes associated with brucellosis include myocarditis, pericarditis, and infective arteritis. However, the numbers of cases with each syndrome is so small that characterization of these conditions is difficult (24–28). It is important to note, however, that aortic involvement with mycotic aneurysm formation is often associated with infective spondylodiscitis due to *Brucella* species (29,30).

Psittacosis

Cases of psittacosis-associated endocarditis, myocarditis, and pericarditis have been described (31–33). Mortality is frequent among patients with *Chlamydia psittaci*-associated infective endocarditis, who typically present with highly destructive valvular infection (33). Some patients experience pulmonary complaints, which is consistent with the route of exposure to the pathogen. Respiratory symptoms have also been identified in cases of myocarditis and pericarditis due to *C. psittaci*. Because congestive heart failure can complicate all 3 syndromes (endocarditis and myocarditis most commonly), it may be difficult to determine whether *C. psittaci* is directly or indirectly responsible for the pulmonary symptoms.

A history of avian contact is commonly reported among humans who develop cardiac infection due to *C. psittaci*. Culture of the organism from blood and infected tissues is difficult. Because of the rarity of cardiac infection produced by *C. psittaci*, clinicians rarely order serology or immunohistochemical studies for this agent, and the sensitivity and specificity of testing in clinical laboratories may vary. Thus, infection may remain undiagnosed.

Q Fever

Q fever is a worldwide zoonosis caused by *Coxiella burnetii*, a strictly intracellular, gram-negative bacterium, which lives in the monocyte/macrophage, its host phagocytic cell. It is

a particularly infectious organism, with the minimal infective dose being 1 to 5 organisms, and it is usually transmitted following contact with infected animals (34,35).

Clinically, the disease is polymorphic and nonspecific and may present in an acute or chronic form. The most common signs and symptoms of acute Q fever are prolonged fever or flu-like syndrome of unexplained origin, granulomatous hepatitis, and atypical pneumonia, although up to 50% of patients may be asymptomatic (5,36,37).

Infective endocarditis is the major manifestation of chronic Q fever (5,37), but routine blood cultures of affected patients are often negative for *C. burnetii* (38). Q fever endocarditis is estimated to account for at least 5% of the more than 800 cases of endocarditis diagnosed in France from 1949 through 2000 (36).

The major risk factors for developing chronic endocarditis following Q fever are pre-existing valvular disease, especially a prosthetic valve, and other comorbidities, such as cancer (39). Currently, most cases of Q fever endocarditis are diagnosed serologically by detecting antibodies to *C. burnetii* (40). High levels of anti-phase I antibodies are found in individuals with chronic Q fever, while anti-phase II antibodies predominate in acute Q fever. Diagnosis of Q fever endocarditis can also be made by isolating *C. burnetii* in cell culture, by PCR, or by immunohistochemistry (40).

Myocarditis has been reported as a manifestation of *C. burnetii* infection, with approximately 30 cases of acute and chronic Q fever cited in the literature over the last 20 years (41–43). Myocarditis occurred in 0.6% to 0.8% of patients with acute Q fever in 2 case series of 1276 and 1117 patients (41,42). Dyspnea, chest pain, and palpitation were the most common symptoms. Many patients also experienced dilated cardiomyopathy, which usually led to heart failure (41). Only 1 case of pericarditis with *C. burnetii* infection has been reported (44).

The long-term effects of Q fever on the cardiovascular system are not clear. A study of a large outbreak of Q fever in 1983 in Switzerland suggested that people with Q fever have an increased risk of vascular disease after 12 years of follow-up (45). However, another follow-up study of 147 patients from the 1989 Q fever outbreak in Birmingham, United Kingdom, did not find any increased risk (46).

Confirming a diagnosis of Q fever requires serologic testing to detect the presence of antibodies to *C. burnetii* antigens. In most laboratories, the indirect immunofluorescence assay is the most dependable and widely used method. *C. burnetii* may also be identified in infected tissues using immunohistochemical staining and deoxyribonucleic acid detection methods.

Salmonellosis

Infections due to salmonellae are common, and their incidence appears to be increasing in the U.S. and other countries (47,48). Although *S. Typhi* and *S. Paratyphi* infect humans only, the nontyphoidal salmonellae are widely spread in nature and are commonly found in some animal

species and occasionally in humans. In humans, the nontyphoidal salmonellae are important foodborne pathogens that cause gastroenteritis, bacteremia, and subsequent focal infection. In the U.S., an estimated 1.4 million *Salmonella* infections occur annually, resulting in approximately 45 000 hospitalizations and 600 deaths (48–50). Salmonellosis accounts for about 30% of deaths resulting from foodborne illnesses in the U.S. (48).

The major risk factors for salmonellosis and bacteremia are extremes of age and certain immunocompromised conditions, such as alteration of endogenous bowel flora of the intestine, diabetes, malignancy, autoimmune disorders, reticuloendothelial blockade, HIV infection, therapeutic immunodeficiency, and sickle cell anemia (51–53). Anatomical disruptions, including atherosclerotic endovascular lesions and prosthetic devices, may serve as foci for persistent *Salmonella* infection.

Salmonella infection may present in 5 different clinical forms: 1) asymptomatic chronic carrier status, 2) gastroenteritis, 3) enteric fever, 4) bacteremia, and 5) extraintestinal localized complications (54). The most serious (although rare) complication is the development of endovascular infection (e.g., endocarditis and infected aortic aneurysm). The prognosis for patients with these conditions is poor. *Salmonella* endocarditis usually occurs in patients with pre-existing heart problems and often causes severe valvular destruction, with a case fatality rate of 70% (54). About one-fourth of *Salmonella* endocarditic cases are nonvalvular (mural); and one-fourth of *Salmonella* endocarditic patients have associated lumbar osteomyelitis; however, their survival rates have not been reported (54). *Salmonella* pericarditis often presents with cardiac or pulmonary symptoms, but typical signs of pericardial disease (pulsus paradoxus, friction rub) or characteristic electrocardiograph changes (low voltage, elevated ST-segments) are uncommon. *Salmonella* may also infect the peripheral or visceral arteries, but the abdominal aorta is the most frequent site of vascular infection (55). Most of these patients are men over the age of 50 years with pre-existing atherosclerosis of the aorta who do not have a previous history of gastroenteritis and no survival with medical therapy alone has been reported. *Salmonellae* may also cause rare cases of myocarditis, but the pathogenesis is unclear (56,57).

The diagnosis of an endovascular infection is often not established until an advanced stage. But early diagnosis, before infection spreads to other areas of the circulatory system, is crucial for survival. To identify *Salmonellae* as the cause of the illness, providers should send stool samples to the laboratory for testing when gastrointestinal symptoms occur. Once *Salmonella* has been identified, further testing can determine its type and which antibiotics should be used to treat it.

In addition to antibiotic therapy, surgical removal of infected areas may be required. Guidelines for surgical removal have been proposed and these, along with increased

use of ampicillin for endovascular infection, may be responsible for the increased survival rates in recent years.

Melioidosis

Direct clinical involvement of cardiovascular structures by *Burkholderia pseudomallei*, the agent of melioidosis, is rare. Only 2 cases of pericardial melioidosis have been described (58,59) so characterization of this illness is not possible. Vasculitis (mycotic aneurysm) due to *B. pseudomallei* has been described but is also a rare event.

In 1 literature review that described 12 cases of mycotic aneurysm due to *B. pseudomallei*, only 2 of the patients had aortic arch involvement (60). The ages of these 12 patients ranged from 42 to 70 years, suggesting a possible predilection to atherosclerosis. Among 9 cases with a reported underlying illness, 1 had diabetes mellitus, 1 had hypertension, and 1 had prior *B. pseudomallei* infection. Trauma and soil exposure were noted in only 3 patients, and 3 patients died due to infectious complications. The areas of case origin include southeast Asia, Taiwan, Mainland China, and Australia, consistent with the indigenous distribution of the bacterium. A single case of cutaneous polyarteritis nodosa associated with *B. pseudomallei* has been also described in a young Thai woman (61).

Summary Statement

Recent events have demonstrated that bioterrorists have the ability to disseminate biologic agents in the U.S. and may be capable of causing widespread social panic. Health care providers including cardiologists can play a key role in the initial recognition of a potential bioterrorism attack (62,63). By being familiar with infectious agents of highest priority, providers can expedite diagnosis and initial management, and lead to a successful public health response to such attacks. Many resources are available to health care providers to learn more about relevant agents and diseases, as well as their effects on cardiovascular system.

The Task Force thus recommends that health care providers:

1. Be familiar with major agents and diseases that may be used for bioterrorism attacks, as categorized and described by the CDC (3,7). Detailed information on these agents and diseases can be obtained through CDC's Web site at <http://www.bt.cdc.gov/agent/agentlist.asp>. A summary description of the select Category A and B diseases and agents is presented in Table 2.
2. Be aware of signs and symptoms and the clinical diagnosis and management of the 4 major cardiovascular syndromes—endocarditis, myocarditis, pericarditis, and vasculitis—that certain potential bioterrorism agents might induce.

3. Consider the possibility of bioterrorism when one of the Category A agents is found to produce disease in a single patient in the absence of obvious risk factors. The likelihood of bioterrorism involvement increases significantly if more than 1 patient presents with illness from 1 of these agents.
4. Ensure that clinical laboratories save isolates from cases that may represent illness from biologic agents of bioterrorism and contact state health departments for guidance.
5. Obtain thorough family and environmental histories from patients to ascertain whether other close contacts have had similar illnesses.
6. Clinicians should be familiar with the public health reporting requirements in their locale. Contact infection control personnel and appropriate public health authorities if a patient is diagnosed with any of these agents or diseases.

Conclusions

We have shown that multiple infectious agents with the potential for use in a bioterrorist attack could have a profound impact on the cardiovascular system of the affected individuals, especially in those with underlying cardiovascular disease. Cardiologists and other health care providers need to familiarize themselves with these agents and diseases, as well as with symptoms they are likely to cause. In this way, they can be prepared to quickly identify the potential involvement of a bioterrorist agent or disease in a patient's condition to both provide appropriate treatment and assist the appropriate authorities in responding quickly to a potential attack.

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APPENDIX 1. ACCF/AHA/CDC CONSENSUS CONFERENCE REPORT ON EMERGING INFECTIOUS DISEASES AND BIOLOGICAL TERRORISM THREATS: TASK FORCE I—RELATIONSHIPS WITH INDUSTRY

Dr. Larry M. Baddour declared that his institution (Mayo Clinic) has financial relationships with infectious disease companies. The other authors of this report declared that they have no relationships with industry pertinent to this topic.

Task Force II: Indirect and Secondary Cardiovascular Effects of Biological Terrorism Agents and Diseases

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Background

Bioterrorist events can produce a variety of secondary cardiovascular effects. For example, mass vaccination campaigns to combat such potential bioterrorist agents as smallpox can lead to cardiovascular symptoms in some of those who receive the vaccine. The acute and posttraumatic psychological stress experienced by those affected (directly or indirectly) by the bioterrorist event may trigger acute cardiovascular events (such as heart attacks, sudden deaths, strokes) or exacerbate existing cardiovascular symptoms. In addition, a large-scale terrorist event could overwhelm the emergency medical and health care system, straining a

community's ability to provide timely care for patients with the more conventional but time-dependent medical and surgical cardiovascular emergencies.

In this report, we describe the secondary or indirect cardiovascular effects of the agents and diseases that are most likely to be used for bioterrorism. These include the impact of the stress produced by bioterrorism on cardiovascular health and the cardiovascular complications of smallpox vaccine. We then describe the pathophysiological processes through which bioterrorist attacks could trigger cardiovascular events, followed by suggestions for how to prevent or treat cardiovascular events during terrorist attacks and the implications for health care policy and future research.

Secondary and Indirect Cardiovascular Effects of Bioterrorism

Cardiovascular Effects of Smallpox Vaccination

Variola virus, which causes smallpox, does not produce cardiovascular complications directly, but vaccinia virus, which is used in the smallpox vaccine, has been linked to cardiovascular complications, especially myocarditis and myopericarditis (1,2). The pathogenic mechanism through which the vaccine precipitates myocarditis remains to be determined for 3 reasons. First, endomyocardial biopsy, which is the gold standard for diagnosing myocarditis, has limited sensitivity because the active inflammatory process is frequently patchy in distribution and has a diagnostic yield of only 10% (3). Second, because of the risks associated with endomyocardial biopsy, it is recommended for use only in patients with left ventricular dysfunction and symptoms not controlled by standard medical management. Third, the limited evidence currently available suggests that an abnormal immune mechanism is responsible for the development of myocarditis (4,5).

Several studies have examined the potential cardiovascular effects of smallpox vaccine. For example, Murphy et al. describe a case in which endomyocardial biopsy was obtained and primary vaccinia infection was excluded based on negative results of polymerase chain reaction (PCR) screening for the vaccinia genome (4). Histopathologic findings showed a mixed lymphocytic and eosinophilic infiltration, while immunoperoxidase stain demonstrated mainly CO3+ T-cells and the presence of major basic protein staining suggested an aberrant immunologic response with an eosinophil-mediated mechanism of myocyte injury. Examinations of autopsy-proven cases of myocarditis following smallpox vaccination from the 1960s also demonstrated both lymphocytic and eosinophilic infiltrations of the myocardium.

The Department of Defense (DOD) has collected data to determine the frequency of myopericarditis following smallpox vaccination among 230 734 U.S. military personnel who received vaccinia vaccines for the first time between December 2002 and March 2003 (2,4). The DOD study found that the rate of myopericarditis was 1 in 12 819 of those who received the vaccine for the first time. In those who developed acute myocarditis, clinical evidence appeared at 7 to 19 days (mean 10.5 days) following vaccination. However, no cases of myopericarditis developed among 95 622 individuals who received the vaccine but had previously been vaccinated.

Currently, a potential causal link is being examined between smallpox vaccination and ischemic cardiac events. Both fatal and nonfatal ischemic events have occurred in civilian and military populations 4 to 17 days following vaccination (4,6). Analyses of incidence data on current and past cardiac events from a vaccination campaign in New York City in 1947 did not find an increased number of cardiac ischemic events following smallpox vaccination (7). However, new vaccination screening guidelines were adopted to reduce the risk of poten-

tial ischemic events by excluding individuals with known cardiac disease or 3 or more known cardiac (ischemic) risk factors (8).

Stress-Related Effects

Natural disasters (e.g., earthquakes and blizzards) and “unnatural” disasters (i.e., caused by humans, such as missile attacks) have been associated with an increased incidence of cardiovascular events related to the sudden stress experienced by the affected population (1–4). On the day of the 1994 earthquake in Northridge, California, for example, the number of sudden cardiac deaths, acute myocardial infarctions (MIIs), and all atherosclerotic ischemic heart disease deaths increased.

Increases in emotional and physical stress can stimulate the sympathetic nervous system and increase the release of catecholamines, resulting in increased blood pressure, heart rate, and contractility (which can increase oxygen demand); changes in shear stress of blood against an atherosclerotic plaque, which may contribute to its rupture; and arrhythmias. At the same time, stimulation of alpha-receptors in the coronary arteries increases vascular resistance and reduces blood flow, leading to a decrease in oxygen supply.

The terrorist attacks of September 11, 2001, and the subsequent anthrax exposures created a very high level of psychological stress in those directly targeted as well as their friends and relatives. The attacks also increased psychological stress among the entire population of the U.S. Although the stress experienced by those who were not directly affected by the attacks may have been less severe than that experienced by those targeted directly, it may have produced far more cardiovascular events because it affected millions of individuals. However, the absolute number of cardiovascular events throughout the U.S. did not produce an unmanageable workload for cardiovascular treatment facilities.

Studies examining the effect of the September 11, 2001, terrorist attacks on cardiac event rates show mixed results. A careful study of the cardiovascular deaths in New York City in the month following September 11, 2001, found no increase in cardiac mortality following the terrorist attack (9). In addition, in 1 analysis there was no significant increase in hospital admissions for cardiac events in a survey of several New York City hospitals (9,10). One potential explanation for these negative results was that patients with cardiac symptoms in New York City may have been directed away from hospitals near the site of attack. Conversely, a study from Brooklyn described an increase in acute MIIs and tachycardias following the terrorist attack (11). Studies from New Jersey (12) and Worcester, Massachusetts (13), also suggested that the terrorist attacks increased hospitalizations for MIIs in these locations more remote from the site of attack. It is also possible that cardiovascular events occurred at a lower level in New York City and nationwide that was not accounted for in this index. For example, cardiovascular events occurring in individuals within the World Trade Center towers on September 11, 2001, would not have been measurable due to the deaths caused by collapse of the buildings. In addition, it is not yet

clear whether those who inhaled toxic dust following the collapse of the World Trade Center will experience long-term cardiovascular effects as a result. Certainly some have experienced pulmonary manifestations (14).

Investigators have recently reported an increased firing of implantable cardioverter-defibrillators (ICDs) in the New York City area patients in the month following September 11, 2001. One study reported a 2.3-fold increase in ventricular tachyarrhythmias in the 30 days following the attack compared to the 30 days preceding the terrorist attack (15). Another study by some of the same investigators observed similar findings in Gainesville, Florida (16). However, seasonal variations in such arrhythmias and other cardiac events—which may even occur in mild climates—were not taken into account in these studies (17).

Pathophysiological Processes Through Which Terrorist Attacks Could Trigger Cardiovascular Events

Extensive data on the causes of cardiovascular events by external events provide a basis for understanding the cardiac events that future, potentially more widespread, attacks might cause. The distinct patterns of the onset of many acute cardiovascular conditions (e.g., acute MI, cardiac arrest, stroke) indicate that these events can be triggered by factors external to the atherosclerotic plaque.

Circadian Variation of MI

The onset of MI has a distinct pattern, with peak incidence in the hours after awakening and arising. Serum creatine kinase (CK) measurements obtained from 703 subjects in the MILIS (Multicenter Investigation of Limitation of Infarct Size) study were used to demonstrate a marked circadian variation in the incidence of MI, with a 3-fold increase at 9 AM compared to 11 PM (18). Goldberg et al. (19) and Willich et al. (20) have subsequently refined this evidence by determining that the increased incidence of MI occurs within the first few hours after awakening and onset of activity, independent of time of day. These data indicate that the activities after awakening trigger the onset of a sizeable percentage of acute coronary events. Thompson et al. (21) and others (22) have suggested that in the evening hours (between 6 PM and 12 AM), a secondary peak of MI onset may occur. Infarcts occurring in these hours may result from an evening meal or other triggers concentrated in the evening hours.

A variety of factors both related to and independent of activity level may create the milieu in the coronary plaque that leads to an increased incidence of MI onset in the morning hours. A morning systemic blood pressure surge due to increased cortisol and catecholamine secretion in combination with increased coronary artery tone could promote disruption of a vulnerable plaque (23,24). Increased coronary artery tone alone could worsen flow reduction produced by fixed stenoses (24). Prothrombotic processes—including increased platelet

adhesion and aggregability (25,26), increased factor VII, and plasminogen activator inhibitor activity (27), along with increased blood viscosity (28)—have been implicated in the onset of acute cardiac events and have been associated with decreased effectiveness of heparin and thrombolytics in the morning hours (29). Predisposition to plaque disruption and subsequent thrombosis added to reduced fibrinolytic activity in the morning could increase the likelihood that an otherwise harmless mural thrombus overlying a small plaque fissure would propagate and occlude the coronary lumen (30).

Epidemiologic and physiologic evidence suggests that the periodicity of MI onset is probably due to a combination of the true endogenous circadian rhythm and the daily rest-activity cycle. Cortisol secretion, a determinant of systemic blood pressure, is an established endogenous circadian process independent of daily activity (31), while enhanced platelet aggregability (25) and *in vitro* platelet responsiveness to adenosine diphosphate and epinephrine (26) increase only after the patient awakens and assumes an upright position. The peak morning incidence of MI probably results from the synchronization of adverse pathophysiologic processes.

Weekly Variations in Acute MI

Numerous investigators have reported a circaseptan (weekly) variation in MI onset, with a peak incidence on Mondays (32,33). Willich et al. (32) noted that this increase occurs primarily in the working population, who have a 33% higher relative risk of MI on this day of the week than the nonworking population. However, Spielberg et al. (33) observed a Monday increase in both working and retired subgroups. Some researchers have noted an increased incidence of MI on the weekend (34), while others have identified a weekend nadir (32).

Seasonal Variations in Acute MI and Coronary Artery Disease Deaths

Several investigators have reported a circannual (seasonal) variation in the incidence of acute MI onset, infarct size, and cardiac mortality, with a peak in the winter months (17,35,36). In the 83 541 subjects in the NRMI (National Registry of Myocardial Infarction) database between 1990 and 1993, 10% more acute cardiac events occurred in winter or spring than in summer ($p < 0.05$) (35). When Spencer et al. (36) reviewed data on 259 891 patients included in the second NRMI study from 1994 to 1996, they noted that at least 50% more cases of MI were reported in the winter (peak in January) than in the summer (nadir in July). Kloner et al. (37) demonstrated larger infarct size during the winter months by retrospective analysis of CK enzyme release in participants from the MILIS and Thrombolysis Myocardial Infarction-4 trial.

Sayer et al. (38) obtained prospective data on 1225 consecutive patients with acute MI admitted to a general hospital. Overall, these investigators noted a winter peak in the incidence of MI onset. However, patients who were

diabetic or of South Asian descent, or who were taking beta blockers or aspirin on admission did not demonstrate seasonal variation. Marchant et al. (39) noted a winter peak in the 633 consecutive patients with acute MI admitted to the coronary care unit during a 4-year period.

Interestingly, these authors noted an excess of infarctions on colder days in both winter and summer, suggesting that environmental temperature affects the onset of this disease. Colder weather has been shown to alter hemodynamic (blood pressure, sympathetic tone) and hematologic (platelet count, fibrinogen) factors favoring arterial thrombosis (40). In addition, cold weather may be associated with an increase in oxygen demand from such activities as shoveling snow and with an increase in the rate of respiratory infections (39). However, the increase in the incidence of cardiac events does not appear to depend on temperature alone. Even in the relatively mild climate of Los Angeles County, a study of 220 000 subjects revealed a peak cardiac death rate in December and January (17). The potential roles in MI onset played by dietary and psychological changes around the holidays, as well as the seasonal decrease in number of daylight hours, are under investigation.

Other Cardiovascular Triggers

The circadian, circaseptan, and circannual variations in the incidence of MI onset suggest that the onset of acute cardiac events is not random and can be triggered by endogenous rhythms in combination with external activities and exposures. The MIOS (Myocardial Infarction Onset Study) investigators have identified several of the activities and exposures that can trigger MI onset, including heavy physical exertion, anger, mental stress, sexual activity, cocaine use, marijuana use, and air pollution (41–45). According to these investigators, these triggers account for over 20% of infarctions, totaling more than 250 000 events, in the U.S. each year.

Heavy Physical Exertion

Several studies have identified heavy physical exertion as a trigger of acute MI. The MILIS trial (46), for example, found that 14% of patients engaged in moderate physical activity and 9% engaged in heavy physical activity prior to experiencing an MI. In the TIMI-2 trial (47), moderate or marked physical activity was reported at MI onset in 18.7% of patients. Compared to patients whose infarction occurred at rest or during mild activity, those with exertion-related infarction had fewer coronary vessels with greater than 60% stenosis and were more likely to have an occluded infarct-related vessel after thrombolytic therapy. Support for heavy exertion as a cause of plaque disruption has been further strengthened by an autopsy series on men who had died suddenly (48). Those who died during exertion were much more likely to demonstrate a plaque with a ruptured cap than those who died at rest.

Fifty-four (4.4%) of 1228 patients enrolled in the MIOS trial reported heavy exertion (6 or more metabolic equivalents) within 1 h of the onset of MI (41). The cardiac symptoms often began during the activity. Using the case-crossover study design developed by Maclure (49), the estimated relative risk of MI in the hour after heavy physical activity was 5.9 compared to less strenuous or no physical exertion. Relative risks were 107 among people who usually exercised less than once a week, 19.4 in those who exercised once or twice a week, 8.6 in those who exercised 3 to 4 times a week, and 2.4 in those who exercised 5 or more times per week. Therefore, habitually sedentary individuals were at greatest risk of MI after heavy exertion and increasing levels of regular physical exercise were associated with progressively lower coronary risk. Similarly, exercise appears to protect individuals from sudden cardiac death associated with heavy physical exertion (48,50).

Proposed mechanisms for triggering MI onset by heavy exertion include increased sympathetic nervous system activation leading to increased myocardial oxygen demand (50) and increased platelet activation in sedentary patients and those with prior MI (51). Interestingly, heavy exertion does not cause platelet activation in healthy active volunteers, which may help explain the protective effect of regular exercise. Additional benefits of regular exercise include blunted up-regulation of the sympathetic nervous system during exertion and activation of the fibrinolytic system (52). Thus, a patient's propensity for developing MI during or after heavy exertion appears to depend, in part, on the degree of sympathetic activity and of balance between prothrombotic and fibrinolytic effects. Despite the proposed importance of sympathetic activation and the potential net prothrombotic effect, it remains unclear whether beta blockers or aspirin decrease the relative risk of MI triggered by exertion.

Anger

The MIOS investigators interviewed 1623 individuals approximately 4 days after they experienced an acute MI to assess the intensity and timing of discrete episodes of anger (and other triggers) during the 26 h before the acute event (42). Anger was objectively assessed by the onset anger scale (a single-item, 7-level, self-report scale) and the state anger subscale of the State-Trait Personality Inventory. Based on the onset anger scale, 39 patients (2.4%) had experienced anger within the 2 h prior to onset of MI. This corresponded to a relative risk of MI of 2.3 in the 2 h following an outburst of anger relative to a control period using the case-crossover method (53). The state anger subscale corroborated these findings with a relative risk of 1.9. Of note, the relative risk of MI within the 2 h following an outburst of anger for patients on aspirin was 1.4, significantly lower than for those not on aspirin ($p < 0.05$), suggesting a possible role for aspirin in the prevention of anger-triggered MI onset. Reich et al. (54) noted that anger was the probable trigger for 15% of the life-threatening arrhythmias

in the 117 patients they studied. Fear, anxiety, and bereavement have also been implicated in an increased risk of cardiac events.

Mental Stress

Acute mental stress may be a trigger of transient myocardial ischemia (53,55), MI (56), and sudden cardiac death (57,58). Bairey et al. (53) noted that 75% of 29 patients with coronary artery disease and exercise-induced myocardial ischemia also demonstrated mental stress-induced wall motion abnormalities by radionuclide ventriculography. Barry et al. (55) performed ambulatory electrocardiographic monitoring supplemented with daily records in 28 subjects with coronary artery disease. The ECG monitoring identified 372 episodes of ST-segment depression over a span of 5 to 6 weeks. At least 22% of the ischemic episodes occurred at high levels of mental stress but low physical activity. In addition, transient ischemia was more likely to occur as the intensity level of mental activity increased.

Long-Term Cardiovascular Sequelae

The aforementioned studies indicate that a bioterrorist attack might trigger acute cardiovascular events among those who were not directly exposed to the attack. The kinds of terrorist attacks that have occurred in the past, such as airplane hijackings and car bombings, are unlikely to trigger cardiovascular events long after the event, although any acute events (congestive heart failure resulting from nonfatal MI) triggered immediately after the event could have long-term cardiovascular effects. However, other types of potential terrorist attacks, such as exposing a population to a virus that leads to inflamed plaques or cardiomyopathy might produce a massive number of cardiovascular events long after the attack occurred.

Preventing and Treating Cardiovascular Events During Terrorist Attacks

Pharmacoprevention

Given the compelling data on the circadian variation of MI onset, most physicians provide pharmacologic protection during the morning hours for patients already receiving anti-ischemic and antihypertensive therapy (18,19,59). Varying levels of evidence show that the 4 classes of agents most commonly administered to prevent acute coronary events (lipid-lowering agents, angiotensin-converting enzyme inhibitors, beta-adrenergic blocking agents, and aspirin) render plaques less likely to be disruptive. Lowering low-density lipoprotein levels to below 60 mg/dl, for example, appears to prevent infarction and death by stabilizing vulnerable plaques, and aspirin use has been associated with a reduced risk of anger-triggered MI onset. However, further study is needed to define the role of additional agents in trigger modulation (42).

The high likelihood that a terrorist attack will trigger acute cardiovascular events has led to questions about the need for preventive therapy in the event of a terrorist attack. The advisability of giving beta blockers or aspirin to the entire at-risk population when news of an attack is publicized must take into account the difference between absolute and relative risk of triggering. While it is true that some potent triggers, such as cocaine, increase the risk of an MI 20-fold (relative risk increase), the absolute risk that a 50-year-old, nonsmoking, nondiabetic male will have an MI in any given hour is 1 out of 1 million. The absolute number of infarctions that would result from a terrorist attack, therefore, is likely to be very low. As a result, the potential benefits of mass administration of beta blockers, aspirin, or other agents to millions of individuals are likely to be low, especially when compared to the side effects associated with these agents. The fact that the incidence of cardiovascular mortality did not increase in New York City after September 11, 2001, supports this conclusion (9).

The most promising approach to the prevention of cardiovascular events triggered by a conventional terrorist attack would be to improve methods for preventing such events in general. Improved methods to detect and treat vulnerable atherosclerotic plaques would protect the population against the many potential triggers that they experience daily, as well as the rare trigger of a massive terrorist attack. Furthermore, physical conditioning could also help reduce the likelihood of a stress-induced MI.

The additional threat remains that terrorists might launch a bioterrorism attack using a microorganism or toxin that causes cardiovascular disease, either by worsening atherosclerosis or directly attacking the cardiovascular system. The best defense against such an attack is continued research on the types of agents that might be used in such attacks and the development of drugs and vaccines to counteract their effects.

Surge Capacity for Emergency Medical Services

A bioterrorist attack is likely to have a significant, sustained, and harmful effect on the affected community's ability to manage everyday medical and surgical emergencies, similar to what commonly occurs following natural disasters (e.g., hurricanes, earthquakes, floods) (60–78). For example, in the 1 to 3 weeks following a major hurricane, the emergency department (ED) volume increases 17% to 40%, mostly due to an increase in patient visits relating to lacerations of all types, puncture wounds, stings, and falls (65,67). Unfortunately, sudden peaks in demand for emergency care are becoming increasingly difficult to handle because hospital surge capacity has eroded dramatically in the last decade due to: 1) decreased reimbursement by managed care organizations for inpatient care, resulting in a nationwide reduction of hospital beds, 2) the nursing shortage, 3) a more acute patient mix, and 4) a general deterioration in the health care safety net and an increase in ED visits by uninsured patients who cannot afford routine medical care (79).

Because of these factors, the EDs are overcrowded and ambulances are frequently diverted from their original destinations (80–83). The deleterious effects of ED overcrowding and ambulance diversion are most evident in patients with life-threatening cardiovascular conditions (e.g., cardiac arrest, heart attack, and stroke) for which effective, but highly time-dependent, treatments are available. Schull et al. (82) have shown that ED overcrowding is associated with significant increases in emergency medical services' ambulance response times and transport intervals for patients with chest pain.

The effect of a terrorist attack on the health care system, and on the care of patients with cardiovascular problems in particular, will depend on the number of victims who survive and the need significant medical care, the nature of the attack, and how long the influx of patients and need for care continues. Following the World Trade Center attack on September 11, 2001, the New York metropolitan area health care system focused its attention on the hundreds of injured survivors, discharging patients with less critical problems and deferring their care. Because the event resulted in only a single burst of patients and did not threaten the hospitals directly, mortality of cardiac patients did not increase in the month following the attack compared to pre-attack control figures (9). However, on the first day of the 1991 Gulf War, the number of deaths from suffocation, asphyxiation, aspiration, MI, cardiac arrest, and cerebrovascular accidents increased abruptly in Israel, as did the number of sudden deaths associated with the use of tight-fitting masks with filters in sealed rooms. Much of the excess risk of death from cardiorespiratory complications during the first air raid alert may have been due to its duration (140 min).

A bioterrorism attack that leads to thousands or more of victims over a period of days, weeks, or months could have a catastrophic effect on health care facilities in the U.S. If the attack involved a highly infectious agent associated with high morbidity and mortality rates, particularly one for which immunization or effective prophylaxis does not exist, health care and public safety personnel (including police, firefighters, emergency medical technicians and paramedics, nurses, physicians) might not be willing to report for duty out of concern for their personal safety or to care for their own families. During such an event, Veterans Affairs and military hospitals, National Guard personnel and disaster management assistance teams, and other resources would probably be deployed, but this would typically take 12 to 24 h unless advance warning of the attack triggers activation and predeployment.

Cardiovascular (and presumably all other) emergency care would be highly compromised under such circumstances. Plans need to be developed to ensure emergency treatment and continuity of care (including supplies of needed medications) during a bioterrorist incident for those with known or emerging cardiovascular disease. Once the acute crisis subsides, more emphasis will need to be placed on managing

the mental and physical effects of the attack on the survivors and community at large.

Hospital surge capacity must be increased to accommodate the long-term consequences of a widespread, ongoing bioterrorism attack. The initial focus should be on the large Level 1 trauma center facilities throughout the country, particularly those that serve areas at increased risk of a terrorist attack based on Department of Homeland Security assessment.

The most promising new concept to emerge recently is ER One, a new congressionally funded ED renovation plan developed for the Washington Hospital Center. ER One allows a standard 60- to 70-bed ED to accommodate 4 times that number of patients with a less than 30-min notice and increase its normal patient volume 10-fold with only a few hours' notice. The design calls for rooms that are larger than standard size and can accommodate multiple patients during surges using collapsible walls to open up work areas. All medical equipment is modular and wired into the ceilings, allowing rapid influx of critical equipment in times of crisis. All public areas (corridors, waiting and registration areas, office spaces) are pre-wired and configured to be turned into patient care areas on short notice. Furthermore, all rooms are negative-pressure capable, allowing the ED to function effectively during a widespread bioterrorism attack.

Data and Health Care Policy Implications

Currently, the U.S. cannot track the incidence and outcomes of common cardiovascular emergency conditions (including heart attack, sudden death, and stroke) or quantify the direct and indirect cardiovascular effects of a bioterrorist event. A sophisticated tracking system is needed to provide early alerts concerning biological attacks, as well as outbreaks (e.g., influenza, SARS) that are not related to terrorism but could have a major impact on a population's health, including its cardiovascular health. A real-time electronic epidemiological and syndromic surveillance system is critically needed to track the types and numbers of patients with similar symptoms and diseases, beginning in the emergency medical system and continuing through the ED and hospital phases of care.

As more and more emergency medical, ED, and hospital systems convert to electronic medical records, common data elements with standardized definitions should be linked. Software manufacturers that produce electronic medical record products should be required to collect certain uniformly defined data elements that will support this Department of Homeland Security goal and build links into their program to export these encrypted data into a real-time national surveillance system. The system should also include a method to de-identify patient data early in the process to comply with HIPAA. Although the primary purpose of such a system would be to protect national security, it could

be used to increase the quality of care and support such government programs as Healthy People 2010 (84).

Recommendations

1. Additional research is needed on the cardiovascular complications of vaccines to determine whether individuals who react unfavorably can be identified prospectively and whether more effective preventive and therapeutic interventions are available for those who experience such complications.
2. Additional research is needed on the links between psychological stress and acute cardiovascular events, particularly with respect to whether any additional prophylactic measures can be used for individuals at increased risk.
3. Data should be collected from ICDs at the time of a bioterrorism incident to provide critical information on the effects of the associated stress on cardiac arrhythmias.
4. Further research is needed on the chronic, long-term effects of bioterrorist attacks.
5. The federal government should provide funds to help hospitals with trauma centers improve their surge capacity using the ER-One design. Such units must be staffed with adequately trained personnel who can sustain their functions during incidents that last for weeks or months.
6. Health care providers should be trained on how to address the consequences of a bioterrorism attack, including how and when to use personal protective equipment, and what information to report and to whom. Such training is now available through nationally standardized courses in core, basic, and advanced disaster life support (85,86).
7. Provide training to increase the general public's capability to help manage acute cardiovascular conditions. This should include recognizing acute cardiovascular conditions, calling 911 to report suspected events, performing cardiopulmonary resuscitation, and using automated external defibrillators (this is consistent with the Healthy People 2010 objectives). In addition, more large public facilities should be equipped with automated external defibrillators (87).
8. Establish a real-time, electronic epidemiological and syndromic surveillance system that can track the incidence of cardiovascular conditions (heart attack, sudden death, and stroke) that might be affected by a bioterrorist event.
9. Require manufacturers that produce electronic medical record products to collect certain uniformly defined data elements that will support this Homeland Security purpose and build links into the program that will export these encrypted data into a real-time national surveillance system.

10. Increase partnerships among multiple federal, state, local, public health, military, and private organizations to provide comprehensive, coordinated training, and response to a bioterrorist event.
11. Increase emphasis on preventing cardiovascular disease, including modifying risk factors.

Summary

In this report, we have discussed some of the secondary or indirect cardiovascular effects of the agents and diseases that are most likely to be used for bioterrorism, including the cardiovascular complications of the smallpox vaccine and the impact of the stress and anger produced by bioterrorism on both short- and long-term cardiovascular health. The pathophysiological processes through which bioterrorist attacks could trigger cardiovascular events include circadian variation of MI. We proposed that hospitals adopt plans, such as ER One, to increase their surge capacity quickly when needed to respond to a bioterrorist attack. In our recommendations, we called for additional research on the cardiovascular complications of the smallpox vaccine, the links between psychological stress and acute cardiovascular events, the effects of stress on cardiac arrhythmias, and the long-term cardiovascular effects of bioterrorism. Other recommendations were to train health care providers in addressing the indirect and secondary cardiovascular effects of bioterrorism, focus on preventing cardiovascular disease to reduce the risk of complications during a bioterrorist attack, and develop a surveillance system to monitor cardiovascular events associated with bioterrorism.

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APPENDIX 1. ACCF/AHA/CDC CONSENSUS CONFERENCE REPORT ON EMERGING INFECTIOUS DISEASES AND BIOLOGICAL TERRORISM THREATS: TASK FORCE II—RELATIONSHIPS WITH INDUSTRY

Dr. Robert A. Kloner declared that he received consulting fees and speaking honoraria in excess of \$10,000 from Pfizer. Dr. James E. Muller declared that he is a principal at InfraReDx, Inc. The other authors of this report declared that they have no relationships with industry pertinent to this topic.

Task Force III: Prevention and Control of Cardiovascular Complications of Emerging Infectious Diseases and Potential Biological Terrorism Agents and Diseases

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Introduction

Primary infection of cardiac and vascular structures by naturally occurring infectious disease pathogens, including emerging and re-emerging infections, in immunocompetent persons is uncommon. However, immunocompromised patients and patients with underlying chronic cardiovascular disease are potentially at risk for infection with these pathogens. More importantly, fever, tachycardia, hypotension, sepsis, toxemia, and shock associated with these infections can lead to life-threatening complications in persons with pre-existing cardiovascular disease and impaired ventricular function. When cardiovascular structures are primarily or secondarily involved in these infections, the well-recognized clinical manifestations may include endocarditis, myocarditis, pericarditis, and vasculitis. In addition, pre-event vaccination against potential biological terrorism may lead to cardiovascular complications, such as myopericarditis and acute coronary syndromes. For example, vaccination with vaccinia virus (to prevent smallpox) has been associated with myopericarditis, but not endocarditis or vasculitis.

In this report, we review current practices and recommendations for preventing and controlling the cardiovascular complications associated with the high-priority (Category A)¹ infectious and noninfectious biological agents of concern for their potential harm if used in bioterrorist attacks (see Task Force I, Table 1, Emerging infectious disease agents [1]). We first discuss the state of the science in clinical preventive practices and recommendations. Next, we review current management practices for endocarditis,

myocarditis, pericarditis, and vasculitis, the 4 predominant cardiovascular manifestations. Finally, we discuss the clinical manifestations of infection with specific pathogens and toxins and the best practices for managing patients exposed to bioterrorism agents.

Clinical Preventive Practices

Pre-event and postexposure vaccination and (sometimes) postexposure antimicrobial prophylaxis are the cornerstones of clinical preventive practices in addressing emerging infectious diseases and potential bioterrorist threats. The current Centers for Disease Control and Prevention (CDC) Category A potential bioterrorism agents and availability of U.S. Food and Drug Administration (FDA)-approved vaccines for pre-event and postexposure treatment are listed in Table 1. Anthrax is the only Category A disease for which both a pre-event and postexposure antimicrobial treatment is available. For smallpox, pre-event and postexposure vaccine is available, however, no cases of smallpox have been detected. No approved pre-event or postexposure countermeasures exist for viral hemorrhagic fevers. Overall, only a limited number of vaccines are available to prevent these diseases.

Smallpox

Although there is enough smallpox vaccine to vaccinate every person in the U.S., current indications for pre-event vaccination include essential health care workers who are part of the National Smallpox Vaccine program and who have no contraindications. The vaccinia vaccine (DryVax by Wyeth) is contraindicated in immunocompromized persons; people with life-threatening allergies to latex or to the smallpox vaccine or any of its ingredients (polymyxin B, streptomycin, chlortetracycline, neomycin); and people with cardiovascular disorders including congestive heart failure, ischemic or dilated cardiomyopathy, or a history of myocarditis or pericarditis. Serious adverse events following smallpox vaccination include eczema vaccinatum, progressive

¹The Centers for Disease Control and Prevention (CDC) has classified certain diseases and agents into 3 relatively high-risk categories (A, B, and C). Category A agents and diseases have the highest priority because they can be disseminated or transmitted easily from person to person, result in high mortality rates, have the potential for major public health impact, might cause public panic and social disruption, and require special action for public health preparedness. For more information on the CDC's classification system, see <http://www.bt.cdc.gov/agent/agentlist-category.asp>.

Table 1 Vaccines, Antitoxins, and Antimicrobials That Are Recommended for Prevention or Postexposure Prophylaxis in Category A Bioterrorism Threats

| Disease | Agent | FDA-Approved Vaccine | Recommended Postexposure Therapy* |
|-----------|-------------------------------|--------------------------------|--|
| Anthrax | <i>Bacillus anthracis</i> | Biothrax (Bioport Corporation) | 1. Adults: ciprofloxacin, levofloxacin, or doxycycline for 60 days 2. Pregnant women: amoxicillin may be used if exposure isolate is susceptible by in vitro testing 3. Children: ciprofloxacin and doxycycline for 60 days |
| Botulism | <i>Clostridium botulinum</i> | None† | None‖ |
| Plague | <i>Yersinia pestis</i> | None | 1. Preferred choice in adults: doxycycline or ciprofloxacin for 7 days 2. Alternative choice in adults: chloramphenicol for 7 days 3. Recommended choice in pregnant women: doxycycline or ciprofloxacin for 7 days 4. Preferred choice in children: doxycycline or ciprofloxacin for 7 days 5. Alternative choice in children: chloramphenicol for 7 days |
| Smallpox | <i>Variola major</i> | DryVax (Wyeth) | DryVax (Wyeth)¶ |
| Tularemia | <i>Francisella tularensis</i> | None‡ | 1. Adults: doxycycline or ciprofloxacin for 14 days 2. Pregnant women: doxycycline or ciprofloxacin for 14 days 3. Children: doxycycline or ciprofloxacin for 14 days |
| VHF | Several viruses | None§ | None |

*Only drug names are provided; an antibiotic reference guide should be consulted for the appropriate dose and routes of administration; †trivalent vaccine is available but not FDA-approved; ‡a live attenuated vaccine is available but not FDA-approved; §yellow fever vaccine available but it is in limited supply and is not considered useful in the setting of a bioterrorist event; ‖type-specific equine antitoxins are available but are not recommended for prophylaxis because of their scarcity and high prevalence of severe reactions; ¶optimal when administered within 4 days postexposure.

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FDA = U.S. Food and Drug Administration; VHF = viral hemorrhagic fever.

vaccinia, and acute myopericarditis developing within 3 to 21 days. Patients with myopericarditis may present clinically with congestive heart failure with diffuse ST-segment and T-wave abnormalities and elevated cardiac biomarkers. Several cases of cardiovascular death following vaccinia vaccination have been reported, however, the number of cases is similar to the number that normally occurs among unvaccinated military personnel of similar age.

Bioterrorism

Significant challenges threaten our ability to rely on vaccination for protection against bioterrorism agents. No effective vaccines have been approved for human use for the majority of pathogens that can be used in bioterrorist attacks, and it can take 10 to 15 years to develop a new vaccine for bioterrorism agents or emerging infections (2). Controlled human efficacy trials that will provide the evidence base for practice in children, adolescents, and most persons with underlying chronic diseases and immunocompromized patients are not feasible. Animal models may fill this requirement in some instances.

Management of Clinical Cardiovascular Syndromes Associated With Bioterrorism Agents

The 4 clinical cardiovascular syndromes most commonly associated with the Category A agents that could be used in bioterrorism attacks are myocarditis, pericarditis, endocarditis, and vasculitis (3). Vaccinia vaccination has been associated with myocarditis and myopericarditis but not isolated endocarditis or vasculitis. Endocarditis rarely occurs in individuals with tularemia but has been reported in slightly less than 10% of individuals with Q fever. Anthrax

and other biological terrorism can present as a sepsis-like syndrome with cardiovascular collapse.

Smallpox Vaccination

The risk of suspected and probable cases of myopericarditis following smallpox vaccine has been estimated at 5.5 per 10 000 based on a cohort receiving primary vaccines (4). A much higher number of vaccinations, up to 2% to 3%, may result in asymptomatic T-wave changes on electrocardiogram, without associated clinical manifestations (5). Most cases of myopericarditis associated with smallpox vaccination in healthy military personnel resolve without any short-term consequences. Because no studies have addressed the impact of administering vaccinia vaccine to patients with established heart disease, the precise risks in this population are not known, and any recommendations to exclude persons with 3 or more cardiovascular risk factors are based on expert consensus opinion.

The diagnosis of myopericarditis after vaccinia vaccination should be based on a standard case definition (Table 2). Clinical symptoms that suggest myopericarditis after vaccinia vaccination include chest pain, shortness of breath, palpitations, syncope, and edema. The standard diagnostic studies that should be performed when clinical symptoms suggest vaccinia vaccine-related myopericarditis include electrocardiogram (ECG), chest X-ray, troponin, and creatinine kinase-MB (6). The interpretation of troponin testing is difficult because the assays lack standardization (7). Nonetheless, values greater than the 99th percentile of a normal reference population should be considered abnormal. Because of analytic variability, values that are near the 99th percentile might require additional laboratory confirmation with the use of a higher sensitivity assay. Indeed, minor elevations in troponin may occur without overt disease in viral myocarditis, and the long-term clinical

Table 2 Case Definition of Myopericarditis for Use in Smallpox Adverse Events Monitoring

| Level of Suspicion | Description of Criteria |
|------------------------|---|
| Suspected myocarditis | <ol style="list-style-type: none"> 1. Symptoms (dyspnea, palpitations, or chest pain) 2. ECG abnormalities beyond normal variants, not documented previously (ST/T abnormality, paroxysmal supraventricular tachycardia, ventricular tachycardia, atrioventricular block, frequent atrial or ventricular ectopy) OR focal or diffuse depressed LV function of uncertain age by an imaging study 3. Absence of evidence of any other likely cause |
| Probable myocarditis | <ol style="list-style-type: none"> 1. Meets criteria for suspected myocarditis 2. In addition, meets 1 of the following: elevated levels of cardiac enzymes (creatine kinase-MB fraction, troponin T or I), OR new onset of depressed LV function by imaging, OR abnormal imaging consistent with myocarditis (MRI with gadolinium, gallium-67 scanning, antithyosin antibody scanning) |
| Confirmed myocarditis | <ol style="list-style-type: none"> 1. Histopathologic evidence of myocarditis by endomyocardial biopsy or on autopsy |
| Suspected pericarditis | <ol style="list-style-type: none"> 1. Typical chest pain (made worse by supine position, improved with leaning forward, pleuritic, constant) 2. No evidence for alternative cause of such pain |
| Probable pericarditis | <ol style="list-style-type: none"> 1. Meets criteria for suspected pericarditis 2. Has one or more of the following: pericardial rub on auscultation OR ECG with diffuse ST-segment elevations or PR-segment depressions not previously documented OR echocardiogram revealing an abnormal pericardial effusion |
| Confirmed pericarditis | <ol style="list-style-type: none"> 1. Histopathologic evidence of pericardial inflammation in pericardial tissue from surgery or autopsy |

Reprinted from Cassimitis DC, Atwood JE, Engler RM, et al. Smallpox vaccination and myopericarditis: a clinical review. *J Am Coll Cardiol* 2004;43:1503-10 (6) with permission from Elsevier. ECG = electrocardiogram; LV = left ventricle; MRI = magnetic resonance imaging.

significance of troponin elevation in this setting is not known. Research is needed to determine the sensitivity of specific troponin assays for myocarditis and the prognostic significance of a mildly elevated troponin level.

Additional diagnostic studies such as an echocardiogram, coronary angiography, and endomyocardial biopsy (EMB) may be needed, depending on the clinical presentation. If acute myocardial infarction is suspected, coronary artery disease and coronary dissection may be excluded by coronary angiography. An EMB may be indicated to distinguish a direct vaccinia infection from a postvaccine autoimmune reaction in those patients who develop high-grade heart block, or sustained ventricular tachycardia who fail to respond to usual care and exhibit progressive hemodynamic deterioration.

Any adverse events after smallpox vaccination should be reported to the Vaccine Adverse Event Reporting System, a cooperative program for vaccine safety of the CDC and the FDA (<https://secure.vaers.org/Vaers/DataEntryintro.htm>).

Treatment for myopericarditis is dictated by the presence of left ventricular dysfunction and abnormalities in ECG and cardiac biomarkers. For pericarditis in the absence of left ventricular dysfunction, nonsteroidal anti-inflammatory drugs and analgesics are indicated, with frequent follow-up (6). For acute severe myocarditis with left ventricular dysfunction, particularly if associated with ventricular tachycardia or new heart block, therapy may be guided by the results of an EMB. If polymerase chain reaction (PCR) results are positive for vaccinia genome, then a course of vaccinia immune globulin may be considered. If PCR for vaccinia genome is negative and an acute eosinophilic myocarditis is present, then a short course of steroids in addition to usual treatment for heart failure may be beneficial (8). Treatment of acute coronary syndromes in the postvaccine period should follow standard guidelines (9,10).

Anthrax (*Bacillus anthracis*)

Diagnosis

The pathogenesis and diagnosis of inhalation anthrax is addressed in the report of Task Force I. Briefly, the diagnosis may be suspected on the basis of clinical findings when unexplained biphasic pulmonary illness progresses to severe respiratory decompensation in patients with radiographic findings of mediastinal widening, mediastinal lymphadenopathy, bilateral pulmonary infiltrates, and pleural effusion (11,12). The etiologic diagnosis is confirmed once clinical specimens are sent to specific referral laboratories that function as part of a Laboratory Response Network (LRN), which was established in the U.S. through a collaboration of the Association of Public Health Laboratories and the CDC (12). An array of laboratory methodologies can be used by the LRN to confirm a diagnosis including immunohistochemical staining, gamma phage assays, and nucleic amplification techniques (13).

Therapy

Table 3 shows the recommended therapy for inhalation anthrax infection in the contained casualty setting. Initial intravenous therapy with ciprofloxacin or doxycycline and 1 or 2 additional antibiotics is recommended as shown. When susceptibility tests were performed on the isolates of *B. anthracis* recovered from patients who were victims of the 2001 bioterrorist attack in the U.S., the strains of *B. anthracis* were susceptible in vitro to ciprofloxacin, doxycycline, chloramphenicol, clindamycin, rifampin, vancomycin, and clarithromycin. A few of the tested strains were susceptible to imipenem or meropenem. Intermediate susceptibility to erythromycin and borderline susceptibility to azithromycin were noted. *B. anthracis* strains were susceptible to penicillin and amoxicillin, but some strains produce beta-lactamase, so penicillin or amoxicillin should not be used alone to treat a *B. anthracis* infection. *B. anthracis* produces

Table 3 Recommended Therapy for Inhalation Anthrax Infection in the Contained Casualty Setting*†

| Category | Initial IV Therapy‡§ | Duration |
|---------------------------|---|---|
| Adults | Ciprofloxacin, 400 mg every 12 h or Doxycycline, 100 mg every 12 h¶ and 1 or 2 additional antimicrobials§ | IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg twice daily or Doxycycline 100 mg twice daily Continue oral and IV treatment for 60 d†† |
| Children | Ciprofloxacin, 10–15 mg/kg every 12 h#** or Doxycycline ¶§§ for those aged >8 yrs and weight >45 kg: 100 mg every 12 h; >8 yrs and weight ≤45 kg: 2.2 mg/kg every 12 h; ≤8 yrs: 2.2 mg/kg every 12 h and 1 or 2 additional antimicrobials§ | IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 10–15 mg/kg every 12 h** or Doxycycline for those aged >8 yrs and weight >45 kg: 100 mg twice daily >8 yrs and weight ≤45 kg: 2.2 mg/kg twice daily ≤8 yrs: 2.2 mg/kg 2 daily Continue oral and IV treatment for 60 d†† |
| Pregnant women‡‡ | Same for nonpregnant adults | IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate†; oral therapy regimens are the same for nonpregnant adults |
| Immunocompromised persons | Same for nonimmunocompromised adults and children | |

*For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax. †Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax. ‡Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies. §Other agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible β -lactamases in *Bacillus anthracis*, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised. ||Initial therapy may be altered based on clinical course of the patient; 1 or 2 antimicrobial agents may be adequate as the patient improves. ¶If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration. #If intravenous (IV) ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are attained 1 to 2 h after oral dosing but may not be achieved if vomiting or ileus is present. **In children, ciprofloxacin dosage should not exceed 1 g/day. ††The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (i.e., Rocky Mountain spotted fever). ‡‡Because of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days. §§Although tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones of fetus are dose related; therefore, doxycycline might be used for a short time (7–14 days) before 6 months of gestation. The high death rate from the infection outweighs the risk posed by the antimicrobial agent. Reproduced with permission from Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA* 2002;287:2236–52. © American Medical Association (12).

a cephalosporinase, so cephalosporins should not be used to treat patients with a *B. anthracis* infection. *B. anthracis* is resistant to trimethoprim-sulfamethoxazole. Recommendations for postexposure prevention of inhalation anthrax are provided in Table 1. Additional information on the diagnosis and treatment of anthrax infection is available on the CDC Web site (<http://www.bt.cdc.gov/agent/anthrax/anthrax-hcp-factsheet.asp>).

Vaccination

The anthrax vaccine available in the U.S. is an inactivated cell-free vaccine licensed to be given in a series of 6 doses. Vaccine administration was mandated for all U.S. military active- and reserve-duty personnel. Like all vaccines, anthrax vaccine can cause soreness, itching, redness, and swelling at the injection site. A total of 1% to 5% of vaccinees report 1 to 5 inches of redness at the injection site. Muscle aches, nausea, chills, and fever are common, but the rate of hospitalization and major adverse events are the same in vaccinated and unvaccinated military personnel (<http://www.vaccines.mil/documents/854AVASafetyRvw.pdf>).

In a study of experimental infection in monkeys, the vaccine was completely protective following an aerosol challenge with *B. anthracis*. Postexposure vaccination following a biologic attack with anthrax is recommended along with postexposure antibiotic prophylaxis as shown in Table 1. (For more information, see <http://www.bt.cdc.gov/agent/>

<http://www.bt.cdc.gov/agent/anthrax/anthrax-hcp-factsheet.asp> and <http://www.bt.cdc.gov/agent/anthrax/anthrax-hcp-factsheet.asp>).

Public Health Measures

Anyone who notices a suspicious substance and fears that inhalation anthrax may have resulted from a bioterrorist attack should contact the public health authorities immediately. Local and state public health authorities have been trained in the proper management of suspected biohazardous materials, including *B. anthracis*, so members of the public should not attempt to handle the suspicious material (<http://www.bt.cdc.gov/agent/anthrax/anthrax-hcp-factsheet.asp>).

Botulism (*Clostridium botulinum* toxin)

Clostridium botulinum neurotoxin (BoNT) blocks the release of acetylcholine at the neuromuscular junction, leading to paralysis of skeletal and smooth muscle. As a weapon, BoNT can be aerosolized and spread by inhalation or ingestion. Symptoms of BoNT depend on the route of infection or toxin exposure. When ingested, preformed BoNT causes nausea, vomiting, abdominal pain, and constipation. Cranial nerve palsies may develop, and death results from respiratory failure (14). Although BoNT is not directly associated with cardiovascular toxicity, persons with established cardiovascular diseases, such as heart failure, could be at increased risk from BoNT exposure.

Supportive care, including critical care support, is central to managing patients with botulism (15). The only specific treatment for this illness is administration of a botulism antitoxin. Antitoxin can prevent further progression of paralysis and diminish both the duration of paralysis and dependence on ventilatory support (15). Thus, its administration as early (<24 h after symptom onset) as possible is pivotal. The botulism antitoxin is not recommended for prophylactic use because of its limited availability and high prevalence of severe reactions (16).

Plague (*Yersinia pestis*)

Several different clinical forms of plague result from infection with *Yersinia pestis*. Although bubonic plague is the most common form of the infection (17), primary systemic plague and primary pneumonic plague are more lethal. Primary pneumonic plague is the most lethal presentation and usually results in death within 24 h of onset of illness (18).

Previous reviews have emphasized that an extracellular envelope of lipopolysaccharide has the pathophysiological properties of endotoxin and initiates disseminated intravascular coagulation. The host response to bacterial endotoxin may result in a wide spectrum of pathological events including intravascular coagulation, multiple organ failure, and adult respiratory distress syndrome. Disseminated intravascular coagulation can lead to arteriolar thrombosis, hemorrhage in skin, serosal surfaces, and organ parenchyma (2,19). The fulminant pathology in the lungs may result in cor pulmonale.

A whole-cell vaccine for *Y. pestis* was available in the U.S. until 1999 but the efficacy of this vaccine in humans, particularly against inhalation plague, was never proven. Because of multidrug-resistant *Y. pestis* (17), a safe and effective vaccine is greatly needed.

Prevention and Management

For postexposure prophylaxis, oral doxycycline or ciprofloxacin for 7 days has been recommended (2). As with the other bioterrorism agents, the management of cardiovascular complications is aimed at maintaining adequate systemic perfusion during the acute illness with supportive measures.

Smallpox (*Variola major*)

Smallpox is caused by the variola virus, a member of the orthopox family that includes monkeypox. After an incubation period of 9 to 17 days, patients develop high fever, body aches, headache, and general malaise. Within 2 to 3 days of nonspecific symptoms, a rash appears in the face and spreads to the trunk, legs, and arms. Over the next 2 weeks, maculae and vesicles develop and eventually dry into crusts. A milder form of smallpox may occur in those who have been previously vaccinated (20,21).

Diagnosis

The diagnosis of smallpox can be confirmed by serology or electron microscopy of skin lesions. Fast diagnostic tests based on deoxyribonucleic acid recognition have been developed, together with sequencing methods for rapid determination of the poxvirus type. Serum antibody levels suggest a specific humoral immune response to the variola virus (21).

Any cases of smallpox suggest a bioterrorism attack. If a bioterrorism attack is suspected, a distribution of associated cases should be sought. For example, identification of an unusual epidemic cluster of chickenpox-like rash or illness could be the first stages of smallpox, but smallpox is generally more severe than chickenpox.

Therapy

Smallpox disease has not been seen anywhere since 1976. Consequently, no antiviral drugs are known to be effective against smallpox. General supportive care should include nutritional and hemodynamic support and prevention of secondary bacterial infections. Patients who have cardiac disorders and develop smallpox may have reduced cardiac reserve capacity and may be more likely to experience cardiovascular collapse.

Q Fever

Coxiella burnetii can cause infection by aerosol, arthropod-borne carriage, and possibly milk ingestion (22,23). The presenting manifestations can include mild flu-like symptoms, as well as symptoms of pneumonitis. A review of the available literature suggests that slightly less than 10% of individuals infected with *C. burnetii* (Q fever) develop endocarditis. However, when patients with Q fever do develop endocarditis, it may be more chronic than other forms of infectious endocarditis. Other primary cardiovascular complications due to *C. burnetii* have also been reported (24). Myocarditis, pericarditis, and myopericarditis can occur in acute disease. In chronic infection, vasculitis, including infection of vascular grafts, has been described (24). There are no FDA-approved vaccines for prevention or treatment of Q fever. Antimicrobial prophylaxis using doxycycline or tetracycline is recommended.

Tularemia

Infection with *Francisella tularensis* (a pleomorphic gram-negative rod), known as tularemia, may result in several different clinical syndromes (25). Although there are anecdotal reports of "pericarditis" in tularemia, this does not appear to be a common manifestation. Endocarditis has been reported, but isolation of the organism from the blood of patients with tularemia is rare (26). Although primary cardiovascular manifestations are very rarely associated with this infection, substernal chest pain has been described with pneumonitis (27). Streptomycin and gentamicin have been used for treatment, and for more severe infections, some advocate the addition of ciprofloxacin (28). The latter agent

has been used for milder infections and for maintenance therapy following initial aminoglycoside treatment (28).

Viral Zoonotic Infections

In the last 2 to 3 decades, the incidence of viral zoonotic infections (including hantavirus, avian influenza virus, and West Nile virus [WNV]) has been observed. These emerging infectious diseases result when viruses broaden their host range or develop high mutation rates (29). Some are transmitted by insects (e.g., WNV) or rodents (e.g., hantaviruses). The emergence and increased incidence of these diseases are a consequence of environmental changes and distortions of the ecological balance, changes in agriculture, the uncontrolled growth of cities in tropical and subtropical regions without improvement of public health measures, increases in international animal trade, and increases in international travel (29,30).

Although many types of zoonotic viruses have been reported; we focus on hantavirus, avian influenza virus, and WNV because these are most likely to have cardiovascular effects.

Hantavirus

Hantavirus belongs to the Bunyaviridae family of viruses that cause hemorrhagic fevers with renal syndrome, resulting in abnormal vascular regulation and damage, cardiopulmonary syndrome, or hantavirus pulmonary syndrome. Naturally occurring human infections arise from inhalation of aerosolized excreta of persistently infected rodents (30,31). The number of reported cases, and possibly of actual cases, has increased in the Americas over the past 10 to 15 years.

The Bunyaviridae category of virus could be a potential bioterrorism tool due to its ability to induce a fatal or seriously incapacitating illness, the ease of cultivating this virus and production of large quantities, the virus' relative infectivity in human patients, its transmissibility by aerosol, and the lack of adequate control measures (32). Hantavirus has been categorized by the CDC as a Category C agent (relatively low risk) as a biologic threat (30). Although hantavirus is an important potential biological threat to address, the phlebovirus (Rift Valley fever) of the Bunyaviridae category is viewed as a more serious risk as a possible biological weapon (32).

The clinical manifestations of hemorrhagic fever include febrile illness, hemorrhage or purpurral rash, and petechial hemorrhages and ecchymoses of the skin and mucous membranes. Bleeding may occur in the form of epistaxis, hematemesis, hemoptysis, and hematochezia. At autopsy, lesions are found on internal organs along with necrosis of the liver and lymphoid tissue, and diffuse alveolar damage (30). Extensive central nervous system involvement has also been documented in infected mice (33). Patients with hantavirus pulmonary syndrome typically present with interstitial infiltrates or pleural effusions, and signs and symptoms of reduced oxygen saturation due to alveolocapillary lesion. However, patients exposed to hantavirus rarely

present with cardiac dysfunction (34). Travel history and potential exposures must be assessed (35).

PREVENTION AND THERAPY. Vaccines to control the infections induced by hantavirus are in various stages of development. Interferon and interferon inducers have been shown to significantly inhibit hantavirus infections in animal models. Bunyaviridae viruses that produce hemorrhagic fever with renal syndrome are generally sensitive to ribavirin, which has been recommended as an emergency measure, although it has not yet been approved for this purpose by the FDA (36). However, to date, no vaccines, antiviral drugs, or immunologic agents are effective in preventing or treating hantavirus pulmonary syndrome (37,38).

The primary goals of caring for patients exposed to hantavirus are supportive and may include treating hypovolemia by closely monitoring fluid and electrolyte balance to avoid pulmonary edema and treating fever. Aspirin, nonsteroidal anti-inflammatory drugs, and steroids are contraindicated in patients exposed to hantavirus (32). Depending on the patient's symptoms, mechanical ventilation or renal dialysis may be indicated. If viral encephalitis develops, frequent neurological assessments and seizure precautions are needed. Families and others in close contact with the patient should be educated about the course of the illness and its potentially grave outcome (39).

Avian Influenza Virus

An epidemic of avian influenza, originating in Asian birds, poses a risk to human and animal health due to its potential for cross-species transmission and re-assortment of avian and human influenza viruses in coinfecting individuals (40) (see <http://www.cdc.gov/flu/avian/index.htm>). The risk of transmission is increasing as more humans contract infections of H5N1 (the avian influenza subtype involved in the current epidemic). Epidemiologists have noted that, like the Spanish flu epidemic in 1918, the avian flu virus infects humans and is highly fatal, and human populations around the world have low levels of antibodies to the disease. However, unlike the Spanish flu, avian flu is not efficiently transmitted from human to human. More than 200 human cases of Influenza A (H5/H7/H9) worldwide have occurred due to poultry-to-human transmissions, with fatality rates greater than 50% for AH5N1 (41). A limited number of sporadic human-to-human transmissions have been reported; however, with viral replication, this pattern could change (42).

A review of clinical data from 10 humans with confirmed cases of H5N1 avian influenza in Vietnam showed that these individuals ranged in age from 5 to 24 years, and 9 had a history of direct contact with poultry 2 to 4 days prior to onset of symptoms (43). The primary clinical features were fever, shortness of breath, cough, and diarrhea. Sore throat, coryza, and conjunctivitis were notably absent. Pronounced lymphopenia and thrombocytopenia and diffuse multifocal infiltrates were key features on chest X-ray. H5N1 reported

in other parts of the world has presented as a flu-like illness with pneumonia, reactive hemophagocytic syndrome, and gastrointestinal symptoms (41).

DIAGNOSIS. If a patient has a severe respiratory illness that cannot be readily diagnosed and is suspected to have avian influenza, the health care provider should inquire about the patient's history of travel to an area with outbreaks of avian flu in poultry. Recommended tests in high-risk patients who present with fever and respiratory symptoms and have recently been in contact with poultry include a throat swab or nasopharyngeal aspirate for antigen detection or reverse transcriptase-PCR for influenza prior to antiviral therapy and within 3 days of symptom onset (41). Because of the risk of hemodynamic compromise, ongoing assessments should include monitoring vital signs, cardiac rate, and cardiac rhythm. A rapid diagnostic assay was approved by the FDA and is available through public health laboratories.

THERAPY. Treatment of H5N1 involves supportive care and patient isolation using precautions similar to those required for severe respiratory syndrome (42). Oral ribavirin or corticosteroids appear to provide little benefit (43), but no rigorous clinical trials of these agents for H5N1 have been conducted.

For H7, full recovery was reported after treatment with oseltamivir, but the low number of human infections precludes generalization (44). Antiviral effectiveness against Influenza A continues to be studied in single and combined forms (41). Vaccine development continues, with a focus on both traditional vaccine approaches and combined vaccine and adjuvants, but no products have been released to date.

WNV

The WNV is an emerging infectious disease in North America and Europe, but it is not categorized as a potential bioterrorist threat. The WNV was first identified in 1937 in Uganda, and the first human WNV infection in the U.S. was reported in 1999 (45). Since then, the distribution of WNV has expanded across North America, through infected mosquitoes and birds. Avian, animal, and human cases have been detected in all 48 states in the continental U.S. (<http://www.cdc.gov/ncidod/dvbid/westnile/surv&control04Maps.htm>; <http://www.cdc.gov/ncidod/dvbid/westnile/background.htm>) and 6 of 10 provinces in Canada (http://dsol-smed.phac-aspc.gc.ca/wnv/map600_e.phtml).

The WNV can produce devastating clinical illness in elderly or immunocompromised individuals with cardiovascular disease. A single-stranded ribonucleic acid (RNA) flavivirus, WNV is transmitted between birds by mosquitoes that act as bridge vectors to humans (46). Transmission of WNV to humans by organ transplantation, transfusion of blood products, transplacental transmission, breastfeeding, and laboratory acquired infection has also been documented (47–49).

WNV infection can result in clinical illness 2 to 14 days after exposure, but only a small number of infections become clinically apparent (50,51). Symptoms include fever, headache,

and stiff neck with progression to altered mental states ranging from confusion to coma if encephalitis ensues. The WNV is the most common cause of epidemic viral encephalitis in the U.S. (52). Additional neurological manifestations involving cranial nerves, sensory deficits such as visual loss, and weakness or paralysis from West Nile poliomyelitis (<http://www.cdc.gov/ncidod/dvbid/westnile/qa/Poliomyelitis.htm>) have also been reported (53). Mortality is around 10% and older patients are at higher risk of death. Severe neurologic illness, meningitis, and encephalitis are the most common clinical syndromes due to the ability of the WNV to cross the blood-brain barrier, (51) and these syndromes may be more severe or fatal in immunocompromised patients, such as transplant recipients (54,55).

DIAGNOSIS. Symptoms include fever, headache, and stiff neck with progression to altered mental states ranging from confusion to coma if encephalitis ensues. Diagnosis of WNV includes detecting WNV RNA in cerebrospinal fluid or tissue or by assessing WNV immunoglobulin M antibody with an enzyme-linked immunosorbent assay. A 4-fold increase in immunoglobulin G antibodies between acute and convalescent sera is typically identified 4 weeks later (56).

PREVENTION AND TREATMENT. No human vaccine is currently available to prevent WNV, although testing is underway. The best way to prevent WNV is to prevent mosquito bites. Treatment should be supportive, with an emphasis on respiratory support, managing cerebral edema, and preventing secondary bacterial infection. Treatment with ribavirin, interferon, osmotic agents, gamma globin, and steroids has been suggested, but no controlled trials have ascertained the efficacy of these approaches (51,57). Outcomes vary with only 37% achieving full recovery and persistent cognitive and motor impairment noted at 1-year follow-up (52). Our literature search revealed no specific cardiovascular complications or indications associated with WNV.

Preventing the Spread of Infection or Disease in Cardiac Catheterization Laboratories and Cardiac Care Units

Patients infected with emerging infectious diseases or agents used for bioterrorism—including those with a high likelihood of airborne or blood transmission—may develop acute coronary syndromes requiring special cardiac procedures in a cardiac catheterization laboratory or cardiac care unit (58). Careful infection control measures are essential to avoid nosocomial spread of infection in these settings. However, infection control guidelines published by the World Health Organization and the CDC do not provide specific recommendations on infection control in cardiac catheterization laboratories where positive pressure ventilation is usually employed (59–61). Specific recommendations for preventing the spread of highly contagious bloodborne or respiratory infec-

tions in cardiac care units and catheterization laboratories, similar to those developed for other hospital settings (62,63), need to be incorporated into available guidelines (64).

Catheterization laboratory and cardiac care unit personnel should be trained in proper hand washing, universal protection measures, and the use of protective clothing (gowns, gloves, masks, caps, and face shields) to avoid direct contact with airborne agents, respiratory droplets, and blood (64). More advanced barriers may be used during high-risk operations associated with severe blood spill or aerosolization, including blood sampling, intubation, and resuscitation. Closed-system suction for mechanical ventilators and high-efficiency microbial filters in the exhalation circuit may be particularly useful (61). When necessary, appropriate disinfection and decontamination measures (compatible with the patient and environment) need to be implemented. Appropriate cleaning and disinfection measures should be employed when equipment will be reused. Special ventilation systems (e.g., negative pressure or one-way airflow systems) may be deployed when caring for patients with highly contagious respiratory infections. These efforts should be coordinated with each institution's environmental safety unit.

Summary Statements and Conclusions

Primary infection of cardiac and vascular structures by organisms discussed in this report is relatively uncommon. However, the indirect impact of associated fever, tachycardia, hypotension, and other manifestations of toxemia and shock can be substantial in patients with underlying cardiovascular diseases. Appropriate evaluation of and treatment for related endocarditis, myocarditis, pericarditis, and vasculitis is essential. Prompt notification of the appropriate local, state, and federal public health authorities is required when any of the organisms discussed is suspected of having been used as a bioweapon. In this setting, effective, FDA-approved vaccines are available only for anthrax and smallpox. Within the Category A agents, postexposure antimicrobial prophylaxis is available for all except botulism and viral hemorrhagic fevers. In light of these findings, Task Force III recommends the following:

1. Further research is needed to improve our understanding of the natural history, pathophysiology, and management of the cardiovascular complications of infectious agents classified as potential bioterrorist agents and emerging or re-emerging infections.
2. All health care workers involved in the care of acutely ill patients should receive continuing education on methods of prevention and treatment for the different forms of bioterrorist threats and emerging or re-emerging infections, including how to recognize them based on the clinical manifestations and diagnostic tests.
3. Additional strategies for preventing biological threats, including vaccines and chemoprophylaxis measures, should be developed.

In this report, we have reviewed measures for preventing and controlling the cardiovascular complications associated with infectious and noninfectious biological agents of concern for their potential cardiovascular impact if used as bioweapons. Anthrax is the only agent we discussed that has actually been used for bioterrorism, but all of the other agents have the potential to be spread deliberately in a population by a terrorist. Therefore, efforts are needed to familiarize health care providers with the cardiovascular complications associated with potential bioterrorist threats and how to prevent and manage these complications.

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APPENDIX 1. ACCF/AHA/CDC CONSENSUS CONFERENCE REPORT ON EMERGING INFECTIOUS DISEASES AND BIOLOGICAL TERRORISM THREATS: TASK FORCE III—RELATIONSHIPS WITH INDUSTRY

Dr. Larry M. Baddour declared that his institution (Mayo Clinic) has financial relationships with infectious disease companies. Dr. Leslie T. Cooper declared that he received consulting fees from Acambis in an amount less than \$10,000. The other authors of this report declared that they have no relationships with industry pertinent to this topic.

Task Force IV: Cardiovascular Effects of Emerging Infectious Diseases and Biological Terrorism Threats

Basic, Clinical, and Population Science Research and Training Needs

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Introduction

The role of infectious agents in cardiovascular disease has been well-recognized since the early 20th century (1), when in a few decades, introduction of antibiotics and public health efforts made it possible to control many infectious diseases. Subsequently, considerable attention was paid to the role of multiple noninfectious risk factors in the atherosclerotic process. More recently, investigators have addressed the possibility that infections may complicate existing cardiovascular diseases and advance the atherosclerotic process. It is also possible that exposure to infectious agents and toxins may have more direct cardiovascular effects and play an important role in inflammation (2). The significant role of inflammation in many cardiovascular diseases (2) and the identification of new emerging infections (e.g., HIV, Ebola, SARS, and avian influenza) have renewed interest in the potential role of infections in cardiovascular diseases. Current knowledge of these relationships is largely based on anecdotal reports; no prospective studies or well-developed research programs on this issue are currently available.

Task Force IV discussed issues surrounding basic, clinical, and population science research and training needs with regards to emerging infectious diseases and biological threats. Although some data are available on the manifestations of and therapies for some infectious agents (e.g., influenza) (3) and some preventive interventions have been developed (e.g., smallpox vaccination) (4), little information is available on the cardiovascular effects of most emerging infectious diseases and potential bioterrorism agents. Comprehensive, targeted research is needed to assess the nature and extent of the effects of emerging and re-emerging infections, as well as other biologic threats, such as Category A, B, and C agents,¹ on the

cardiovascular system. This research should address clinical manifestations, diagnostic methods, and the efficacy of various preventive and therapeutic interventions. Translational and interdisciplinary research approaches are also needed to analyze data from basic, animal, clinical, and population-based studies to reach a comprehensive understanding of this topic.

The group recognized that lessons can be learned from the effects of both natural and unnatural disasters for assessing the secondary effects of emerging diseases and biological agents on the cardiovascular system (5–7). In general, epidemiologic, clinical, and basic research can help clarify the pathogenesis, identify people at highest risk for potential cardiovascular complications, identify the most effective diagnostic and therapeutic approaches, and establish effective prevention and rehabilitation methods.

In this report, we provide an overview of the limited epidemiologic research that has been conducted connecting cardiovascular and infectious diseases and identify gaps in the literature. We describe the need for surveillance systems that might increase our ability to quickly identify disease outbreaks and track their course and cardiovascular impact. We also address the clinical studies required to improve our ability to diagnose, prevent, and treat the potential cardiovascular complications of bioterrorist agents and diseases, as well as the basic research that could be useful for clarifying the mechanisms of infectious disease. We describe the training needs required for both health care professionals and high-risk members of the public to help them recognize and respond appropriately to bioterrorist threats that could have cardiovascular effects. The report ends with our suggestions for basic, clinical, and epidemiological research and for training for professional and lay populations.

Epidemiologic Studies

Traditionally, epidemiologic or population studies have played a key role in gaining insight into the different aspects of infectious diseases, including emerging or re-emerging infections and their complications. The epidemiologic literature focuses primarily on the immediate morbidity and

¹Based on the categorization scheme of the Centers for Disease Control and Prevention (CDC). Agents in Category A are the highest priority because they can be easily disseminated or transmitted from person to person; result in high mortality rates and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness. Agents in Categories B and C have lower priority. For more information on this categorization scheme and a list of agents in each category, see the CDC's list of bioterrorism agents and diseases at: <http://www.bt.cdc.gov/agent/agentlist-category.asp>.

mortality or the long-term noncardiovascular complications of these infectious diseases.

New epidemiologic studies are needed to identify, characterize, and prioritize different classes of emerging infections as well as biological toxins with a potential for causing cardiovascular complications and quantify their cardiovascular burden. These effects may be direct or indirect, or even occur as iatrogenic complications of preventive or therapeutic efforts. These infections may occur sporadically or in epidemics or pandemics (8–12). They may occur naturally (e.g., epidemic and pandemic influenza, West Nile virus), accidentally (e.g., accidental release of smallpox virus), or through acts of bioterrorism (e.g., smallpox, anthrax in the U.S. in 2001, and ricin) (9,13–16). Also worthy of consideration are potential side effects of mass public health interventions, such as smallpox or anthrax vaccination, in response to potential threats (4,17,18).

Infectious disease outbreaks have been associated with excess cardiovascular mortality (19–21). Epidemiological studies are needed to identify both the acute (e.g., assessment of influenza epidemics) and potential chronic effects (e.g., increased risk of atherosclerotic events) of such outbreaks (22). Studies of available data on cardiac patients after major disasters such as earthquakes or the September 11, 2001, attacks could be helpful in predicting the long-term psychological and other effects of other events such as infectious disease outbreaks or biological threats on individuals with existing cardiovascular disease (23–25).

Available databases and retrospective studies should be used to assess whether historical outbreaks of infectious diseases and interventions to control them (e.g., flu epidemics, SARS, smallpox vaccination programs) were consistently associated with an increase in cardiovascular complications (19–21,24,26–29). When possible, such studies might examine issues such as identifying the excess risk of cardiovascular complications associated with each threat, time–response relationships, whether the disease is associated with both long-term chronic cardiovascular effects and acute effects, and whether certain populations have an increased risk following such events. Potential data sources include death certificates, clinical examinations of survivors, medical records, emergency room admission records, and billing records. Predefined criteria should be established to identify whether the number of cardiovascular events actually increases following an outbreak, assess possible cause–effect relationships, and evaluate the impact in vulnerable populations, such as persons with pre-existing cardiovascular disease or atherosclerosis.

Emerging infections may have primary or secondary effects on the cardiovascular system. The primary impact of a disaster should be evaluated in the immediate vicinity of the threat. Indirect and secondary impacts (such as psychological effects) may be evaluated in locations that were not direct targets of the event. These psychological evaluations should be incorporated into an evaluation program designed to assess cardiovascular implications, because they could

have a significant impact on the pathogenesis of cardiovascular disease and have implications for therapy (30–32).

Research Infrastructure for Surveillance and Response

When indicated, a cardiovascular component needs to be designed and implemented into surveillance systems at regional, national, and global levels to increase our ability for early detection of cardiovascular effects of diseases of interest (33). Surveillance should also include monitoring of disease outbreaks in animals for diseases affecting nonhuman hosts (34).

Syndromic surveillance is comprised of systems designed to detect in a timely manner signals of increasing events based on monitoring patterns of hospitalizations, emergency room visits, emergency medical services data, billing records, prescriptions, and so on (35–38). Adhering to standard national protocols for data definition and collection, as well as ensuring compatibility of electronic medical record systems, are critical factors for developing syndromic surveillance systems. State and federal law should permit syndromic surveillance to ensure morbidity and mortality follow-up because syndromic surveillance may often include cardiovascular data and can potentially detect disease outbreaks sooner and with a higher sensitivity than traditional surveillance systems, which depend on active reporting of diagnosed cases (38–41). The growing use of electronic medical records could facilitate timely surveillance and easy inclusion of cardiovascular data.

In the meeting the group discussed that although issues of privacy and confidentiality are important, the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 allows necessary disclosures of protected personal health information to public health authorities for the purpose of preventing or controlling disease, injury, or disability.

Clinical Studies

Very little information is available about the likely impact of most emerging infections and potential bioterrorism agents on the cardiovascular system. Most prior studies have concentrated on noncardiac effects and few experimental studies have been done. Clinical studies, therefore, are needed to assess the pathophysiology of each threat's impact on the cardiovascular system and its components (28).

Potential cardiovascular effects of emerging infectious diseases and biological threats include damage to the myocardium, endocardium, pericardium, and blood vessels; destabilization of vulnerable plaques; accelerated progression of atherosclerosis; modification of risk factors; valvular damage; conduction system abnormalities; prothrombotic effects; and psychological sequelae. Bioterrorism agents may serve as a primary cause of cardiac disease in people without pre-existing cardiovascular disease and may have secondary

cardiovascular effects in populations with atherosclerosis or other chronic cardiovascular diseases.

It may be possible to conduct clinical trials/observational studies in healthy volunteers for low-risk interventions (e.g., smallpox vaccination in military service members) (17,28). Clinical observations and case series in the setting of disasters may be feasible, but these will be unplanned and unpredictable (26,27). When experimental studies are impractical or not possible for ethical reasons, disease effects may be monitored in subjects with known exposures or who are at high risk for exposure and in health care professionals caring for exposed people. Cardiovascular effects should be carefully recorded and subjects' responses to different interventions should be monitored. Careful monitoring of these groups may help develop diagnostic methods for rapid identification of an emerging infectious disease or terrorist threat and facilitate the identification of effective preventive or therapeutic interventions.

Examples of potential natural experiments include studies of military personnel after experimental vaccinations and treatments and of individuals who have survived disasters, as well as long-term follow-up of people who have survived infections (e.g., influenza, anthrax) (28). To study the cardiovascular effects of mass smallpox vaccination efforts, for example, investigators could monitor electrocardiography, echocardiography, and troponin measurements in a subset of asymptomatic subjects following smallpox vaccination. Different risk groups could be followed to determine whether the number of cardiac events increases after the vaccine is administered. Different therapeutic measures could also be assessed in these individuals, and the results could be compared to yield the best strategy. Since plaque disruption has been proposed as an etiology for cardiac effects, analyzing the mechanisms of known plaque disruption triggers could yield a pathogenesis model of infectious etiologies (24,25,32,42).

In addition to specific therapies for each infectious agent (e.g., antibiotics against specific infectious agents, antidotes for toxins), nonspecific cardioprotective medications may be tested in these natural settings. Recent reports suggest potential benefit from the use of beta blockers for immediate survivors following major stressful events to reduce the risk of posttraumatic stress disorder (43). Beta blockers may also be effective and merit further research in preventing acute coronary syndromes, especially in high-risk patients, following terrorist events or disasters. Other potentially effective therapies for various cardiac complications include aspirin, antiplatelet drugs, anti-inflammatory drugs, and intravenous immunoglobulins. The efficacy and cost-benefit ratio of such interventions when many patients are already receiving these drugs are largely unknown.

Outbreaks of emerging infections are unpredictable, and it is difficult or even impossible to make substantial changes in the clinical care of high-risk individuals within a short time period. Therefore, considerable effort should be focused on increasing the adoption rate of proven preventive

therapies in people with cardiovascular disease to decrease their likelihood of cardiovascular complications in a crisis. For example, the best way to improve vaccine coverage rates during influenza pandemics is to improve interpandemic vaccine coverage rates (44).

Vaccination

Although the influenza vaccine has been shown to reduce the risk of cardiovascular events (3), a small number of cardiovascular events have been reported following smallpox vaccination, including myopericarditis and rare ischemic events associated with pre-existing atherosclerotic disease or risk factors, although the relationship of acute myocardial infarction to smallpox vaccination is uncertain. The cardiovascular effects of vaccines for other infectious agents are not readily recognized; however, as new vaccines are developed and used, their cardiovascular effects should be closely monitored. With any vaccination, a general stimulation of the immune system could cause a flare-up of the inflammatory process in the atherosclerotic plaques, endocardium, myocardium, or pericardium, exacerbating inflammatory disease. Also, the widespread activation of inflammatory cells could be associated with activation of macrophages in vulnerable plaques, triggering heart attacks. Therefore, an increased early hazard is a possibility after any vaccination program and needs to be monitored and ruled out if possible. However, B-cell activation (part of the humoral response) may be protective against atherosclerosis (45). Research is needed on the potential cardiovascular benefits and complications of immunization and on public attitudes regarding the benefits and risks of vaccination in general.

Clinical Guidelines

Recommendations on the diagnosis, prevention, and treatment of cardiovascular complications of biological threats are critically needed. When applicable, consensus guidelines for different infectious agents that could be used for bioterrorism (14,46–50) should address cardiovascular effects and the related diagnostic, preventive, and therapeutic approaches.

Basic Studies

In the absence of controlled clinical experiments and given the high-risk nature of many threats that make clinical studies either difficult or impossible, basic laboratory and animal studies may provide valuable information on the cardiovascular mechanisms of infectious disease and help prepare for bioterrorism threats.

The availability of several good animal models of atherosclerosis should enable scientists to determine the effect of many infections and biological toxins (e.g., ricin) on atherosclerotic plaques, the coagulation system, circulatory and hemodynamic components, and the conducting system (51–54). Infections may trigger acute destabilization of

vulnerable plaques, leading to acute coronary syndromes (in short-term) or they can accelerate the atherosclerosis process and increase patients' risk over years (3,51,55,56). The efficacy of different classes of medications in preventing complications could also be assessed in these animal models.

Training

Professional Training

Training strategies should target professional leadership, workforces, and organizations. Issues of the cardiovascular effects of emerging infections need to be added to and incorporated into existing training programs. These educational programs may also be incorporated into continuing medical education programs for health care providers.

When applicable, a cardiovascular component may be incorporated into current infectious disease and biologic agent outbreak training programs. Consensus-based recommendations for responding to different bioterrorist threats describing the measures to be taken by medical and public health professionals can be used as educational materials for this purpose (14,47–50,57).

Public Education

As the first and third leading causes of death in the U.S., Task Force IV members noted that cardiac and cerebrovascular events will continue during infectious disease outbreaks and bioterrorist events. Individuals who have or are at risk for cardiovascular disease should adhere to the well-documented evidence-based guidelines for primary and secondary prevention of cardiovascular diseases (such as those developed by the American College of Cardiology and American Heart Association) (58–60). The best way to ensure that patients will follow these guidelines at the time of a crisis is to improve general adherence to these guidelines. The public can provide additional protection for those at risk of cardiovascular complications by learning cardiopulmonary resuscitation techniques and how to use automated external defibrillators (61). Educational materials should be developed for the public regarding the potential impact of emerging infectious diseases and biological threats on cardiovascular disease.

Future Considerations

Based on this discussion of the research and training needs related to the cardiovascular effects of potential bioterrorist agents, Task Force IV suggested that addressing the following issues may help to improve response and cardiovascular outcomes of potential emerging infectious diseases and biological threats:

1. Multidisciplinary translational research should assess the full spectrum of the effects of potential bioterrorism agents on the cardiovascular system.
2. To determine the incidence and significance of cardiovascular complications of smallpox or other vaccinations, epidemiologic studies should be conducted in conjunction with vaccination programs, and animal studies should be conducted to further delineate the extent and nature of potential cardiovascular complications.
3. Public health surveillance should be established to monitor incidence and trends of cardiovascular diseases. The proposed surveillance system should be capable of detecting increased rates of cardiac events (e.g., acute coronary syndromes, myocarditis) with high sensitivity and in a timely manner. Following relevant events (e.g., massive vaccination programs or disease outbreaks) with a high risk for cardiovascular adverse effects, reporting of cardiac complications should be encouraged and even required. The feasibility of reporting cardiac events following relevant events should be explored. Privacy and legal issues need to be addressed.
4. When applicable, a cardiovascular disease response component must be incorporated into response plans for emerging infections and bioterrorism events with potential adverse cardiac effects. Health care providers and first responders should be trained about the common and important cardiac effects of emerging infections. Related scenarios should be tested in drills and tabletop exercises. When necessary, educational material on potential cardiac effects of biological agents should be developed for the public and made widely available.
5. An influenza pandemic is considered likely to occur and, therefore, must be considered a high-priority research issue. The lessons learned in trying to prepare for such a pandemic might be applied to preparations for outbreaks of other emerging infections and bioterrorist threats.
6. The legal and ethical issues regarding equitable distribution of scarce resources to cardiac patients at times of crisis require attention, and solutions for different scenarios should be outlined.
7. Environmental safety procedures for catheterization laboratories and coronary or intensive care units that care for patients infected with highly contagious agents must be defined and implemented.
8. In the absence of clinical trials, the role of vaccination, antitoxins and anti-infective therapy, and nonspecific cardioprotective therapies in bioterrorism threats should be analyzed and published by consensus panels.
9. Research is needed on public attitudes regarding the benefits, risks, and acceptance of vaccination from a cardiovascular point of view.
10. Animal models should be used to evaluate the cardiovascular effects of potential threats related to emerging infections (e.g., avian influenza or smallpox vaccine) as well as the efficacy of preventive and therapeutic measures.

Conclusions

Natural outbreak of emerging infections or release of biologic agents during a bioterrorism attack could have a considerable impact on the cardiovascular systems of those exposed to the agents, but little information is available on related mechanisms, clinical presentations, or appropriate diagnostic, preventive, and therapeutic measures. Therefore, research on these issues is needed at the population, clinical, and basic science levels. In addition, health care providers need training on how to identify and care for those who experience cardiovascular effects from a bioterrorist attack.

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APPENDIX 1. ACCF/AHA/CDC CONSENSUS CONFERENCE REPORT ON EMERGING INFECTIOUS DISEASES AND BIOLOGICAL TERRORISM THREATS: TASK FORCE IV—RELATIONSHIPS WITH INDUSTRY

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