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# 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

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

Category	Agents and Diseases	Endocarditis	Myocarditis	Pericarditis	Vasculitis*
<b>A</b> 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.	<b>Anthrax</b> ( <i>Bacillus anthracis</i> )				
	<b>Botulism</b> ( <i>Clostridium botulinum</i> toxin)				
	<b>Plague</b> ( <i>Yersinia pestis</i> )				
	Smallpox ( <i>Variola major</i> )				
	<b>Tularemia</b> ( <i>Francisella tularensis</i> )	++		+	+
<b>B</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.	<b>Viral hemorrhagic fevers</b> , including filoviruses (e.g., <i>Ebola</i> , <i>Marburg</i> ), and arenaviruses (e.g., <i>Lassa</i> , <i>Machupo</i> )				
	<b>Brucellosis</b> ( <i>Brucella</i> species)	+	+	+	+
	Epsilon toxin of <i>Clostridium perfringens</i>				
	<b>Food safety threats</b> (e.g., <i>Salmonella</i> species, <i>Escherichia coli</i> O157:H7, <i>Shigella</i> )	++++	+	+	+
	Glanders ( <i>Burkholderia mallei</i> )				
	<b>Melioidosis</b> ( <i>Burkholderia pseudomallei</i> )			+	+
	<b>Psittacosis</b> ( <i>Chlamydia psittaci</i> )	+	+	+	
	<b>Q fever</b> ( <i>Coxiella burnetii</i> )	+++++	++	+	
	<b>Ricin toxin</b> from <i>Ricinus communis</i> (castor beans)				
	<b>Staphylococcal enterotoxin B</b>				
	Typhus fever ( <i>Rickettsia prowazekii</i> )				
	Alphaviruses (e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis)				
	Water safety threats (e.g., <i>Vibrio cholerae</i> , <i>Cryptosporidium parvum</i> )				
<b>C</b> 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> )				<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
<b>Category A Diseases and Agents</b>		
Anthrax ( <i>Bacillus anthracis</i> )	<p><b>Cutaneous anthrax:</b> 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><b>Inhalational anthrax:</b> 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><b>Gastrointestinal anthrax:</b> 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 &gt;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><b>Inhalation:</b> 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><b>Ingestion:</b> Symptoms after swallowing ricin include vomiting, diarrhea that may become bloody, and severe dehydration followed by low blood pressure.</p> <p><b>Skin and eye exposure:</b> 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>	<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.</p>
<b>Category B Diseases and Agents</b>		
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>	<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.</p>
Q fever ( <i>Coxiella burnetii</i> )	<p>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.</p>	<p>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.</p>
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>	<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.</p>
Salmonellosis ( <i>Salmonella</i> spp.)	<p>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.</p>	<p>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.</p>

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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 endarteritis. 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.