JACC Vol. 49, No. 12, 2007
March 27, 2007:1398–406

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

[1]The 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	*Bacillus anthracis*	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	*Clostridium botulinum*	None†	None‖
Plague	*Yersinia pestis*	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	*Variola major*	DryVax (Wyeth)	DryVax (Wyeth)¶
Tularemia	*Francisella tularensis*	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	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	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	1. Histopathologic evidence of myocarditis by endomyocardial biopsy or on autopsy
Suspected pericarditis	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	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	1. Histopathologic evidence of pericardial inflammation in pericardial tissue from surgery or autopsy

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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/VaersDataEntryintro.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/anthrax/faq/vaccination.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 purpural 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 coinfected 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.