Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 64 / No. 4
December 4, 2015

Clinical Framework and Medical Countermeasure Use During an Anthrax Mass-Casualty Incident

CDC Recommendations

Continuing Education Examination available at http://www.cdc.gov/mmwr/cme/conted.html.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

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CDC, our planners, and our presenters wish to disclose that they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters with the following exception: Dr. Dan Hanfling has disclosed that he is a consultant for GlaxoSmithKline (GSK). GSK manufactures raxibacumab, which is FDA-approved for prophylaxis and treatment of inhalation anthrax.

Ciprofloxacin, levofloxacin, penicillin, doxycycline and anthrax antitoxins are FDA-approved for inhalational anthrax. While ampicillin, chloramphenicol, clindamycin, doripenem, imipenem, linezolid, meropenem, moxifloxacin, rifampin, and vancomycin do not have FDA-approved indication for anthrax, they are clinically recommended for treatment of anthrax.

The *MMWR* series of publications is published by the Center for Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30329-4027.

Suggested citation: [Author names; first three, then et al., if more than six.] [Title]. MMWR Recomm Rep 2015;64(No. RR-#):[inclusive page numbers].

Clinical Framework and Medical Countermeasure Use During an Anthrax Mass-Casualty Incident

CDC Recommendations

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Summary

In 2014, CDC published updated guidelines for the prevention and treatment of anthrax (Hendricks KA, Wright ME, Shadomy SV, et al. Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. Emerg Infect Dis 2014;20[2]. Available at http://wwwnc.cdc.gov/eid/article/20/2/13-0687_article.htm). These guidelines provided recommended best practices for the diagnosis and treatment of persons with naturally occurring or bioterrorism-related anthrax in conventional medical settings. An aerosolized release of Bacillus anthracis *spores over densely populated areas could become a mass-casualty incident. To prepare for this possibility, the U.S. government has stockpiled equipment and therapeutics (known as medical countermeasures [MCMs]) for anthrax prevention and treatment. However, previously developed, publicly available clinical recommendations have not addressed the use of MCMs or clinical management during an anthrax mass-casualty incident, when the number of patients is likely to exceed the ability of the health care infrastructure to provide conventional standards of care and supplies of MCMs might be inadequate to meet the demand required. To address this gap, in 2013, CDC conducted a series of systematic reviews of the scientific literature on anthrax to identify evidence that could help clinicians and public health authorities set guidelines for intravenous antimicrobial and antitoxin use, diagnosis of anthrax meningitis, and management of common anthrax-specific complications in the setting of a mass-casualty incident. Evidence from these reviews was presented to professionals with expertise in anthrax, critical care, and disaster medicine during a series of workgroup meetings that were held from August 2013 through March 2014. In March 2014, a meeting was held at which 102 subject matter experts discussed the evidence and adapted the existing best practices guidance to a clinical use framework for the judicious, efficient, and rational use of stockpiled MCMs for the treatment of anthrax during a mass-casualty incident, which is described in this report. This report addresses elements of hospital-based acute care, specifically antitoxins and intravenous antimicrobial use, and the diagnosis and management of common anthrax-specific complications during a mass-casualty incident. The recommendations in this report should be implemented only after predefined triggers have been met for shifting from conventional to contingency or crisis standards of care, such as when the magnitude of cases might lead to impending shortages of intravenous antimicrobials, antitoxins, critical care resources (e.g., chest tubes and chest drainage systems), or diagnostic capability. This guidance does not address primary triage decisions, anthrax postexposure prophylaxis, hospital bed or workforce surge capacity, or the logistics of dispensing MCMs. Clinicians, hospital administrators, state and local health officials, and planners can use these recommendations to assist in the development of crisis protocols that will ensure national preparedness for an anthrax mass-casualty incident.*

Introduction

Bacillus anthracis, the causative agent of anthrax, is classified as a Category A Priority Pathogen for biodefense because it is easy to acquire and disseminate and has a high case fatality rate (*1*–*3*). Models suggest that an aerosolized release of *B. anthracis* spores over a large urban population could result in a mass-casualty incident involving hundreds of thousands of illnesses and deaths (*4*,*5*). Among the types of anthrax expected in a mass-casualty incident (i.e., cutaneous, gastrointestinal [GI], inhalation, and meningeal), inhalation anthrax and anthrax meningitis have the highest case-fatality rates (*2*). In 1979, the accidental release of *B. anthracis* spores from a bioweapon facility in the city of Sverdlovsk in the former Soviet Union resulted in the deaths of 86% (68/79) of the

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patients with inhalation anthrax (*6*), including all 21 patients with documented meningitis (*7*). More recently, in 2001, a bioterrorism attack in the United States resulted in the deaths of five of 11 persons with inhalation anthrax (*8*,*9*), including at least one person with anthrax meningitis.

Since 2001, the U.S. government has developed anthrax prevention and treatment strategies and stockpiled medical countermeasures (MCMs), including vaccine, antimicrobials, and antitoxins. Focused on inhalation anthrax, these strategies emphasize antimicrobial and vaccine postexposure prophylaxis (PEP). Prioritization and allocation plans for anthrax PEP have been published previously (*10*). Preparedness plans are needed that address the treatment of hospitalized patients during a mass-casualty incident large enough to potentially exhaust or limit existing resources. This report provides recommendations for managing shortages of intravenous antimicrobials and antitoxins and diagnosing and managing common anthrax-specific complications in a mass-casualty incident that are based on published crisis standards of care. Clinicians, hospital administrators, state and local health officials, and planners can use this guidance to assist in the development of crisis protocols for an anthrax mass-casualty incident.

Background

Anthrax Pathogenesis

An understanding of pathogenesis is fundamental in the development of preparedness plans for prevention, treatment, and clinical management of anthrax. The spores of *B. anthracis* are the primary infectious form. Upon entry into a human host, *B. anthracis* spores germinate locally or in regional lymph nodes after transportation through the lymphatic system by phagocytic cells (*11*–*13*). Vegetative bacteria are capable of producing toxin upon germination (*14*). Bacteria and toxins enter the circulation and disseminate, resulting in systemic disease, sepsis, and, in some cases, septic shock (*9*,*15*).

B. anthracis has three major virulence factors: an antiphagocytic capsule and two exotoxins, edema toxin (ET) and lethal toxin (LT). Much of the morbidity and mortality observed with anthrax is attributed to the enzymatic effects of these toxins. Protective antigen (PA) combines with edema factor (EF) and lethal factor (LF) to form binary combinations of ET and LT (*16*) (Figure 1). PA is activated proteolytically in blood and tissue; once activated, complexes bind to anthrax toxin receptors (ATRs) on cell surfaces (*17*,*18*) and promote endocytosis of the toxin complex and translocation of EF and LF into the target cell cytoplasm. Within the cytoplasm of cells, EF and LF affect cell function (*19*) and cell proliferation and modulate the immune response (*20*). Together, ET and LT enhance the capacity of *B. anthracis* to downregulate and evade the host immune response. This downregulation fosters disease progression, bacteremia, toxemia, sepsis, and septic shock. Because anthrax toxins play such a key role in disease progression, antibody-based antitoxins are recommended as adjunctive therapeutics to prevent disease progression. Specific targeted steps for antibody-based antitoxin therapies include prevention of PA binding to the toxin receptor, inhibition of translocation, and acceleration of Fc receptor-mediated clearance.

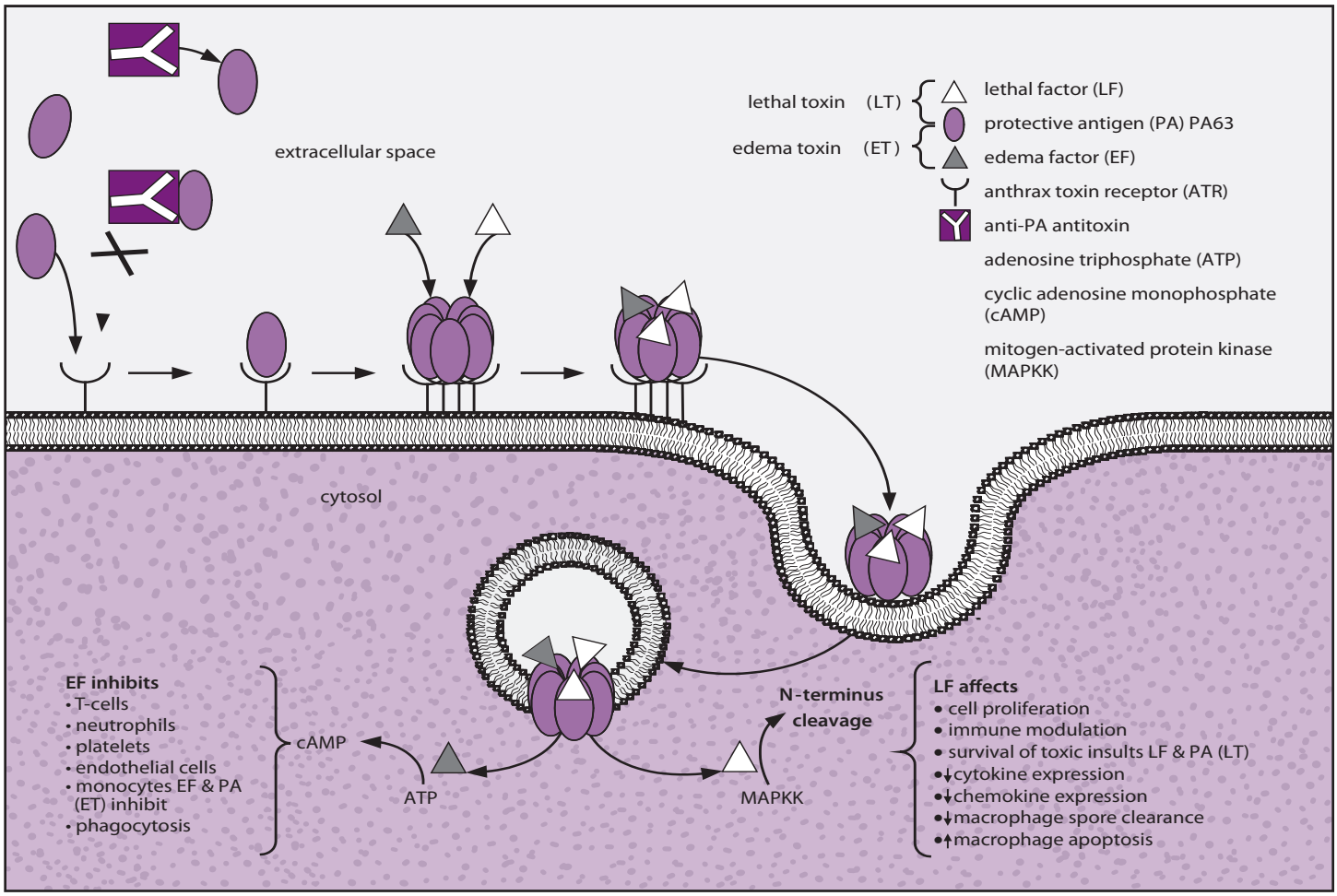
The route by which infectious spores enter the body determines the location of germination and the type of anthrax that manifests. Spores introduced through the skin lead to cutaneous anthrax, those ingested cause GI anthrax, and those inhaled cause inhalation anthrax. Anthrax meningitis results from dissemination of bacteria from primary inoculation sites to the meninges. Inhalation anthrax is most likely to occur following exposure to an aerosolized release of *B. anthracis* spores; however, meningeal, GI, and cutaneous anthrax can occur. Although injection anthrax, a type recently identified in heroin-injection drug users in northern Europe (*21*), is not expected to occur in an anthrax mass-casualty incident, information about injection cases has contributed to the understanding of systemic anthrax disease progression, toxin dynamics, and clinical response to MCMs.

Inhalation anthrax has had historically high case-fatality rates, as high as 67%–88% even with antimicrobial or antiserum treatment (*15*). Early inhalation anthrax can be difficult to diagnose, often manifesting as an undifferentiated acute febrile illness with symptoms and signs such as fever, nonproductive cough, myalgia, and malaise. Initial symptoms and signs mimic those of other more common diseases such as influenza-like illnesses (ILI) and community-acquired pneumonia, creating diagnostic challenges (*22*–*24*). Clinical features at hospital admission of the 13 persons with inhalation anthrax cases diagnosed in the United States from 2001 through 2011 are listed (Table 1) (*8*,*9*,*25*,*26*).

Ingestion of spores or bacilli also can cause oral-pharyngeal disease, which manifests as oral, pharyngeal, or esophageal ulcerations and regional lymphadenopathy and edema. Spores that transit to and germinate in the lower GI tract can cause intestinal anthrax, which manifests with malaise, nausea, vomiting, bloody diarrhea, ascites, or an acute abdominal pain (*27*,*28*). The GI tract also can be affected from hematogenous spread, although resulting lesions are submucosal and nonulcerative.

Cutaneous anthrax develops after spore inoculation through breaks in the skin and manifests with nondescript, painless, pruritic lesions that progress to vesicles over 1–2 days. Classically, these lesions undergo central necrosis and form a

FIGURE 1. Formation and activity of main anthrax toxins



characteristic black eschar. Extensive local edema, often out of proportion to the size of the skin lesion, can occur in the surrounding area (*29*,*30*). Historically, approximately one third of patients with cutaneous anthrax develop fever (*31*).

Anthrax meningitis, a result of hematogenous bacterial dissemination and meningeal seeding, can occur as a complication of all types of anthrax and has been noted in up to half of persons with inhalation anthrax cases (*6*). Anthrax meningitis is an expected complication during an anthrax mass-casualty incident. The impact of early combination intravenous antimicrobial therapy on the incidence of this complication is unknown. The clinical presentation of anthrax meningitis resembles that of other forms of bacterial meningitis. Symptoms include altered mental status, fever, headache, nausea/vomiting, seizures, focal neurologic deficits, and meningeal signs such as nuchal rigidity and the Kernig and Brudzinski signs (*32*).

Methods

In partnership with the National Association of County and City Health Officials (NACCHO), CDC led the development of a clinical framework for the treatment of anthrax during a mass-casualty incident. Recommendations were developed in accordance with the standards outlined by the Institute of Medicine (IOM) (*33*). Initially, an internal CDC technical development group* identified issues for considerations during mass-casualty incident planning by reviewing the 2014 CDC anthrax guidelines (*34*). Subsequently, a guidelines steering committee comprising representatives from CDC, NACCHO, the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Office of the Assistant Secretary for Preparedness and Response (ASPR), the Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense (DoD) was established to

* A list of the members appears on page 22.

TABLE 1. Number and percentage of symptoms, signs, and diagnostic findings at hospital admission for patients in the United States with inhalation anthrax; 2001–2011

Characteristic	No.	(%)
Symptom		
Fever/Chills	12/13	(92)
Fatigue/Malaise	12/13	(92)
Cough	11/13	(85)
Nausea/Vomiting	9/13	(69)
Diaphoresis	8/13	(62)
Chest pain	7/13	(54)
Myalgia	6/13	(46)
Confusion	5/13	(38)
Headache	4/13	(31)
Sign		
Heart rate >90 beats/min	13/13	(100)
Abnormal core temperature fever >38.0°C or hypothermia <36.0°C)	8/13	(62)
Hypoxemia (PaO2 <85 mm Hg)	3/9	(33)
Tachypnea (>20 breaths/min)	2/13	(15)
Abnormal laboratory value		
Elevated transaminases (ALT or AST above normal limits)	9/11	(82)
Leukocytosis (WBC >12 x $10^3/\mu L$)	2/13	(15)
Radiographic finding		
Pleural effusion	9/13	(69)
Infiltrate	8/13	(62)
Mediastinal widening	5/13	(38)

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; PaO2 = arterial partial pressure of oxygen; WBC = white blood cell.

oversee and inform the recommendation development process. Together, the technical development group and the guidelines steering committee[†] prioritized topic areas and established the focus and scope of the clinical framework development process. Because antitoxin shortages might occur during an anthrax mass-casualty incident, antitoxin use was identified as the highest priority topic. Other topics recognized as vital to mass-casualty incident planning included the use of intravenous antimicrobials, the diagnosis of meningitis, and the management of pleural and ascitic fluid collections. These were identified as topics that would warrant modification of the 2014 CDC anthrax guidelines (*34*) if an anthrax mass-casualty incident were to occur.

As part of the guideline development process, three systematic literature reviews were performed to identify English-language articles that addressed use of antitoxins and intravenous antimicrobials and the diagnosis and management of common anthrax-specific complications. Twelve databases were searched from inception through October 2013: Commonwealth Agricultural Bureau (1973–2013), Cumulative Index to Nursing and Allied Health Literature (1981–2013), Defense Technical Information Center (1950–2013), EconLit (1886–2013), Embase (1988–2013) , Federal Research in Progress (1930–2013), Global Health (1910–2013), Medline (1946–2013), National Technical Information Service (1964–2013), Web of Science (1980–2013), WorldCat (1967–2013), and the World Health Organization Library Database (1948–2013). For antitoxin use, the systematic review included published human cases of anthrax treated with Anthrasil (Anthrax Immune Globulin Intravenous [AIGIV]) (Cangene doing business as Emergent BioSolutions, Inc.) and animal data from the experimental use of anthrax antitoxins. The other two systematic reviews of human anthrax case reports focused on survival outcomes with antimicrobial therapy and anthrax meningitis diagnostic considerations. These three reviews will be published separately (*35*,*36*) (Stefan Katharios-Lanwermeyer, unpublished data, 2015). Because the evidence base pertaining to the clinical management of anthrax fluid collections is limited, these recommendations were made on the basis of evidence from previously published reviews of the diagnosis and treatment of nonanthrax fluid collections (*37–45*).

Two workgroups[§] were formed to develop and draft preliminary recommendations in preparation for an in-person meeting of experts: the MCM Workgroup focused on antitoxins and intravenous antimicrobial use, and the Clinical Treatment and Diagnostic Workgroup focused on the diagnosis and management of common anthrax-specific complications. The workgroups reviewed data compiled from the systematic reviews and additional relevant unpublished data presented by the antitoxin manufacturers. Workgroup members represented themselves and provided individual input regarding expertise in anthrax pathophysiology and immunology, infectious diseases, antimicrobials and antitoxin use, emergency medicine, critical care medicine, triage and mass casualty, surgery, laboratory services, public health, radiology, obstetrics and gynecology, and pediatrics. Federal government agencies represented included CDC, NIH, FDA, ASPR, BARDA, and DoD. In addition to scientific subject matter experts, ethicists participated in each workgroup to provide input on fair allocation and effective stewardship of limited public resources such as antitoxins and other stockpiled MCMs. Ethical considerations overlaid on scientific discussions included how to maximize aggregate benefit effectively, fairly, and transparently and in a way that was respectful and inclusive and how to negotiate the ethical tensions inherent in transitioning from conventional to crisis standards of care. Achieving a balance between patient/physician autonomy within the normal context of physician-patient relations and the overriding obligation during an emergency situation to address public health needs of the entire affected population was integrated into the discussion. Workgroups met weekly to biweekly to discuss draft recommendations for the clinical use framework. A draft clinical framework and

[†] A list of the members appears on page 22.

[§] A list of the members appears on page 22.

algorithm was presented in March 2014 at an in-person Expert Panel Workshop consisting of the technical development group, MCM and Clinical Treatment and Diagnostic Workgroup members, and other invited participants[§] who provided individual expert opinions. Their individual expert opinions were used to assist CDC in guideline development for antitoxins and intravenous antimicrobial use and the diagnosis and management of common anthrax-specific complications during a mass-casualty incident. The final guidelines were based on the available scientific evidence and, where data were lacking, on a distillation of individual expert opinions. Although CDC sought individual expert opinion to inform the guidelines, consensus from participants was neither sought nor required.

The Expert Panel Workshop discussions were framed by oral presentations of evidence compiled from the systematic reviews addressing antitoxins, intravenous antimicrobial use, and the diagnosis and management of common anthrax-specific complications in the setting of a mass-casualty incident; presentations of unpublished animal studies on antitoxin effectiveness; and expert commentaries regarding considerations for special populations. Subsequent to discussions, CDC's technical development group revised and refined the clinical framework on the basis of discussions that took place during the workshop. The revised document was then distributed and reviewed by meeting participants. The recommendations presented in this report reflect a synthesis of evidence from systematic reviews conducted at CDC, along with analysis, discussion, and individual opinions from subject matter experts. These guidelines will be updated when new evidence becomes available or a critical preparedness need is identified.

Adaptation of Existing Anthrax Guidelines for Use in a Mass-Casualty Incident

Previously published recommendations describe best practices for treatment of anthrax in conventional settings (*34*,*46*,*47*). However, these recommendations might require adjustment in an anthrax mass-casualty incident if the magnitude of the incident limits the ability to provide MCMs or conventional standards of care. In an anthrax mass-casualty incident, hospital beds (including both general inpatient beds and intensive-care beds) might become a limited resource. This limitation, compounded by potential lack of a sufficient health care workforce to care for all patients seeking evaluation and treatment, might require a change from the hospitalization criteria described in the 2014 CDC anthrax guidelines (*34*). Incident-specific factors (e.g., the number of persons presenting with illness, the acuity of their illnesses, and local/regional hospital bed availability and surge capacity) should determine this change. The workshop participants do not advocate a national standardized approach to hospital surge capacity issues because of local variability in response capabilities. This is consistent with the guidelines from IOM on crisis standards of care (*48*). Expert judgment of clinicians (e.g., emergency physicians, critical care specialists, and trauma surgeons) and of local and state health officials trained in standard triage principles and crisis management is best suited to guide these efforts (*49*).

Guidance on the use of MCMs for treatment of anthrax patients must be considered at the federal level because many of these MCMs will be deployed from CDC's Strategic National Stockpile, and judicious use will be required in an anthrax mass-casualty incident. The previously published 2014 CDC anthrax guidelines (*34*) assume the widespread availability of MCMs and recommend the use of two intravenous antimicrobials plus antitoxin for patients in whom anthrax meningitis has been excluded and three intravenous antimicrobials plus antitoxin for patients in whom meningitis has been diagnosed or cannot be excluded. During an anthrax mass-casualty incident, the availability of double and triple intravenous regimens and antitoxin will depend on many factors, including local availability, stockpiled MCMs, manufacturing surge capacity, and incident-specific factors such as the size of the event and the number of persons affected. First-line intravenous combination antimicrobial therapy in conjunction with antitoxin might not be available for all persons seeking care for whom there is a high level of clinical suspicion of systemic anthrax. In addition, modalities recommended for clinical assessment and management of patients, including the use of resource and labor-intensive diagnostic (e.g., lumbar punctures [LPs] and radiographic images) and fluid drainage procedures, might not be feasible. Imaging capacity (e.g., computed tomography scans and echocardiograms) might be limited, and less labor-intensive approaches might be needed for fluid drainage equipment and procedures, especially in light of expected health care workforce constraints.

This report is a companion to the 2014 CDC anthrax guidelines (*34*) and addresses antitoxins, intravenous antimicrobial use, and diagnosis and management of common anthrax-specific complications in the setting of an anthrax mass-casualty incident (*48–53*). This guidance does not address primary triage decisions, anthrax postexposure prophylaxis, hospital bed or workforce surge capacity, or the logistics of dispensing MCMs. This report is intended for use by clinicians treating patients in the event of an anthrax mass-casualty incident and by federal, state, and local public health officials and health care administrators in the development of crisis protocols for such an incident.

Crisis Standards of Care and Scarce Resource Allocation Strategies

Published guidance from IOM and the American College of Chest Physicians (ACCP) on catastrophic disaster response planning encourages state and local officials to develop comprehensive mass-casualty incident crisis response plans (*48*,*52*). Among the essential elements proposed in the IOM framework is the need to outline indicators, triggers, and processes involved in shifting patient care standards from those used in conventional settings to those that would be expected in contingency or crisis settings. IOM defines three standard of care levels (Box 1). The standard of care and the level of treatment will be adjusted on the basis of the prevailing circumstances and available resources. Under catastrophic conditions in which there is an overwhelming demand for limited resources, patient care interventions must be prioritized within a systems-based framework that maximizes fair, logical, and consistent approaches. Population-based outcomes might have priority over individual outcomes to provide the best possible care to the largest number of patients.

The recommendations provided in this report were developed for use only during a mass-casualty incident; conventional medical standards, as outlined in the 2014 CDC anthrax guidelines, should be followed in situations not involving anthrax mass casualties (*34*,*46*,*47*). Use of these recommendations will depend on the availability of MCMs and other resources, an indicator that will delineate when a shift from conventional to contingency to crisis standards of care is needed. As outlined in the IOM report, the adoption of contingency or crisis standards of care will be predicated on the exhaustion (or impending exhaustion) of the capability to provide conventional standards of care. This would occur after local, state, and federal distribution (and possible redistribution) of resources already has been maximized and, if possible, transportation of affected patients to alternative treatment facilities has been employed. The expectation is that the decisions to institute care that represent a shift away from conventional care will be made locally in consultation with state and federal partners on the basis of factors specific to the affected area and available resources. In an anthrax mass-casualty incident, factors to consider include the number of persons affected and expected to be affected based on epidemiologic projections, the acuity of illness among those affected, and the availability of treatment. As such, triggers for use of these recommendations include, but are not limited to, the recognition of a supply-demand imbalance, such that resources will not be available to diagnose or treat everyone presenting with illness (*48*).

An important aspect of crisis planning for anthrax treatment is that resource scarcity might not apply to all aspects of anthrax mass-casualty incident clinical management but rather might affect only one or a few aspects of anthrax diagnosis, management, or treatment. For example, some hospitals within an anthrax-exposed area might have enough first-line combination intravenous antimicrobials but might lack sufficient antitoxin or fluid drainage equipment. While operating within crisis standards of care, resource demand and supply, including health care capacity to treat patients, should be assessed continually. As additional resources become available, a shift back to conventional or contingency standards of care should occur at the earliest possible opportunity. For this to be accomplished, coordinated real-time communication is needed between health care facilities, local and regional disaster advisory councils, and local, state, and federal health officials.

Crisis planning should involve a local group of technical experts, referred to as triage teams (*49*,*54*), comprising persons with expertise in clinical and critical care, ethics, infectious disease, and triage. This group will use predefined triggers (e.g., shortage of antitoxin and inability to perform diagnostic or treatment procedures) for instituting shifts from conventional standards of care, providing a smooth and consistent transition between standards of care, guiding health care facilities to apportion resources to meet local needs in a fair manner, and developing, modifying, or adapting existing guidance or policies to support the disaster response. The primary role of this team is to ensure consistent, equitable, and fair practices in the face of fluctuating resource availability and local demand during an incident. The triage team is best suited to establish local triage criteria and define hospital admission criteria at the local and regional levels. If available, disease-specific prognostic indicators

BOX 1. Definitions of conventional, contingency, and crisis standards of care*

Conventional standard of care
Usual standard of care in noncrisis settings

Contingency standard of care
Equivalent care to conventional settings, except that the care might involve different methodologies, medications, and locations.

Crisis standard of care
Situations in which resource limitations require medical care prioritization. In crisis settings, care might not be initiated and might conceivably be withdrawn from persons to allow resources to be allocated to persons with the highest likelihood of survival or benefit.

* **Source:** Adapted from Institute of Medicine. Crisis standards of care: a systems framework for catastrophic disaster response. Washington, DC: The National Academies Press; 2012.

can help define treatment decisions in conjunction with clinical judgment. However, when these are not available, assessment of clinical status might be the major driving factor in decisions on resource allocation. A guiding tenet of the triage team approach to an anthrax mass-casualty incident is to give the highest priority to those persons most likely to benefit from treatment and to use resources in a manner expected to provide the greatest overall population benefit (*49*). While aiming to achieve the greatest amount of good, distribution of resources should not discriminate against persons who are economically or socially disadvantaged or who are members of minority population groups.

This clinical framework is intended to assist in the fair, efficient, and rational use of U.S. government–stockpiled anthrax antitoxins and intravenous antimicrobials and to guide the approach to treat anthrax-specific complications (i.e., meningitis and effusions). This guidance, although based on the best available evidence derived from reported cases and expert opinion at the time of publication, is not meant to replace expert clinical judgment. A clinical algorithm is presented that might assist with anthrax mass-casualty incident planning (Figure 2). This clinical algorithm should be used only after a predetermined trigger has defined a need for a shift away from the conventional standards of care for a given aspect of clinical management. The algorithm is focused on clinical treatment of symptomatic persons presenting for hospital care. Asymptomatic persons whose clinical status does not warrant hospital admission, as determined by the local triage team or similar group, are not addressed in this algorithm. Persons likely to meet criteria for hospitalization are those with known or probable exposures to *B. anthracis* spores on the basis of existing epidemiologic data and demonstrating symptoms and signs clinically compatible with systemic anthrax (Box 2). The clinical algorithm addresses four decision points where resource limitations might impact clinical management during an anthrax mass-casualty incident. The first decision point involves diagnostic evaluation of anthrax meningitis, which is necessary to determine optimal antimicrobial therapy. The second decision point involves treatment regimens of combination intravenous antimicrobial therapy. The third decision point involves administration of antitoxins, as an adjunctive therapy. The fourth decision point involves the identification and drainage of fluid collections, which have been associated with a survival benefit (*15*).

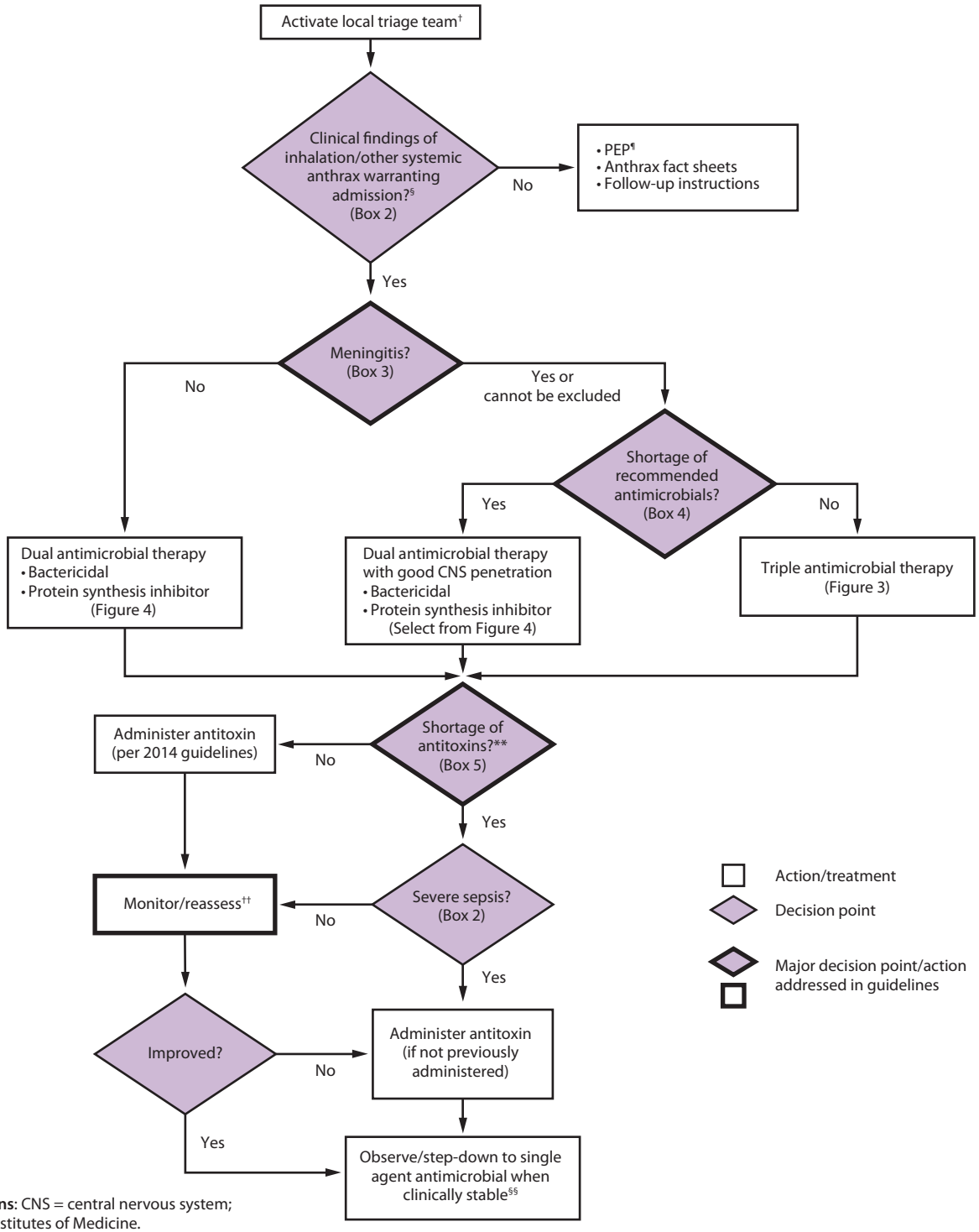
Evaluation for Anthrax Meningitis in Mass-Casualty Incident

Meningitis is a common complication of systemic infections caused by *B. anthracis*. Of the 40 patients who died from inhalation anthrax during the Sverdlovsk outbreak and on whom full autopsies were performed, 21 (52%) had histopathologic evidence of meningitis (*7*). In addition, 30 (42%) of the 71 persons with inhalation anthrax cases described in a review of published cases during 1900–2000 also had meningitis (*15*). Meningitis can complicate primary anthrax infections of the GI tract (*55*), skin (*32*), and soft tissue (*56*) and can occur in patients with systemic anthrax without a recognized port of entry (i.e., primary anthrax meningitis) (*57*). In 2001, only two of the 11 patients with inhalation anthrax underwent LP to rule out meningitis. One was confirmed to have meningitis (*8*,*9*); however, symptoms and signs suggestive of meningitis (confusion or photophobia) were present in five other patients who were not assessed for meningitis by LP. On the basis of historical data showing a high incidence of meningitis in patients with inhalation anthrax and their presenting symptomatology, at least some of these patients from the 2001 anthrax incident might have had meningitis (*32*). Meningitis is a common complication, and all patients with possible anthrax should be evaluated for meningitis. Because death is common but not inevitable in patients with anthrax meningitis (*32*), more aggressive antimicrobial therapy is indicated if meningitis is diagnosed or highly suspected.

A systematic review of the English-language clinical anthrax literature published during 1880–2013 was performed to establish an evidence base for distinguishing patients with anthrax meningitis from those with nonmeningitic systemic anthrax. This evidence was used to develop a clinical screening tool to differentiate systemically ill patients with anthrax meningitis from those without meningitis (Stefan Katharios-Lanwermeyer, unpublished data, 2015). During an anthrax mass-casualty incident (i.e., a setting in which few LPs or imaging studies would be feasible), such a tool could be used to empirically identify patients requiring meningitis-specific antimicrobial therapy.

A total of 363 patients with systemic anthrax met the inclusion criteria (i.e., they had anthrax and were systemically ill); one third had anthrax meningitis. Children comprised one sixth of patients with both systemic anthrax and anthrax meningitis. Descriptive statistics were calculated and multivariate regression was used on separate derivation and validation cohorts to identify potential diagnostic and prognostic factors for anthrax meningitis. An analysis suggests that a simple screening tool comprising four symptoms and signs can be used to reliably identify or exclude anthrax meningitis during an anthrax mass-casualty incident: 1) severe headache, 2) altered mental status, 3) meningeal signs (i.e., Kernig sign, Brudzinski sign, jolt accentuation test, nuchal rigidity, photophobia, and meningismus), and 4) other

FIGURE 2. Crisis standards of care* framework for medical countermeasure prioritization among hospitalized persons with known or potential exposure to anthrax



Abbreviations: CNS = central nervous system; IOM = Institutes of Medicine.

* Possible triggers indicating a shift in standards of care.

† As outlined in the IOM 2012 Crisis Standards of Care.

§ Admission criteria for nonsystemically ill patients may depend on local and regional bed space.

¶ Clinicians may choose to administer a second oral antimicrobial for patients with nonspecific symptoms of anthrax who do not meet criteria for hospitalization. Close follow-up is recommended.

** Patients with meningitis or in whom meningitis cannot be excluded should be treated aggressively and receive antitoxin even if an antitoxin shortage exists.

†† Drainage of effusions improves survival. Clinicians experienced with management of effusions should assess for significant fluid collections and drain as possible under the current standard of care (see Box 6).

§§ Patients with meningitis or in whom meningitis cannot be excluded should receive a minimum of 14 days of IV antimicrobials before stepping down to single agent.

neurologic signs (i.e., nonheadache nonmeningeal signs such as seizure, cranial nerve signs, limb weakness, and papilledema). Presence of one of these four symptoms or signs correctly identified 89% of adults and 83% of children with anthrax meningitis; presence of two or more symptoms or signs made the diagnosis very likely (LR+ = 26.5). These data comprise the basis for the recommendations (Box 3) (Table 2).

Antimicrobial Considerations for Mass-Casualty Incident Planning

Antimicrobials have been the mainstay of anthrax treatment since the 1940s, and combination therapy with multiple classes of antimicrobials seems to confer a survival advantage (*15*). Mice exposed to *B. anthracis* spores and treated with penicillin,

BOX 2. Diagnostic criteria for sepsis and severe sepsis*

Sepsis — documented or suspected infection plus one or more of the following:

General variables
Fever (>38.3°C)
Hypothermia (core temperature <36°C)
Heart rate >90/min or >2 SD above normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes

Inflammatory variables
Leukocytosis (WBC count >12 x$10^3/\mu$L)
Leukopenia (WBC count <4 x $10^3/\mu$L)
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein >2 SD above normal value
Plasma procalcitonin >2 SD above normal value

Hemodynamic variables
Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or an SBP decrease >40 mm Hg in adults or <2 SD below normal value for age)

Organ dysfunction variables
Arterial hypoxemia (PaO2/FiO_2 <300)
Acute oliguria (urine output <0.5 mL/kg/hr for at least 2 hours despite adequate fluid resuscitation)
Creatinine increase >0.5 mg/dL or >44.2 μmol/L
Coagulation abnormalities (INR >1.5 or aPTT >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100 x $10^3/\mu$L)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or >70 μmol/L)

Tissue perfusion variables
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

Severe sepsis — documented or suspected infection resulting in tissue hypoperfusion or organ dysfunction documented by one or more of the following:

Sepsis-induced hypotension
Lactate above upper normal limits of laboratory
Urine output < 0.5 mL/kg/hr for >2 hours despite adequate fluid resuscitation
Acute lung injury with PaO2/FiO_2 <250 in the absence of pneumonia as infection source
Acute lung injury with PaO2/FiO_2 <200 in the presence of pneumonia as infection source
Creatinine >2.0 mg/dL (176.8 μmol/L)
Bilirubin >2 mg/dL (34.2 μmol/L)
Platelet count <100 x $10^3/\mu$L
Coagulopathy (international normalized ratio >1.5)

Abbreviations: aPTT = activated partial thromboplastin time; INR = international normalized ratio; MAP = mean arterial pressure; SBP = systolic blood pressure; SD = standard deviation; WBC = white blood cell.
Source: Adapted with permission from Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580–637.
* Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5° or <35°C), tachycardia (might be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

BOX 3. Diagnosis of anthrax meningitis in conventional, contingency, and crisis standards of care

Conventional setting

Patients with systemic anthrax should undergo a lumbar puncture (LP) to determine whether they have anthrax meningitis, provided that no contraindications exist.

Contingency setting

- Patients with systemic anthrax who have two or more of the following — severe headaches, altered mental status including confusion, meningeal signs, or other neurological symptoms/signs — should be presumed to have anthrax meningitis (probable cases).
- When there is a need to cut back somewhat on the number of procedures, patients with fewer than two (i.e., one or none) of the screening symptoms and signs should have LPs.
- When there is a need to cut back severely on the number of procedures, patients with just one of the screening symptoms and signs should have LPs.
- Patients should be presumed to have meningitis if they have a contraindication to an LP.
- Identification of Gram-positive rods, pleocytosis, visible turbidity, or visible hemorrhage in cerebrospinal fluid is sufficient for a diagnosis of probable anthrax meningitis.

Crisis setting

A clinical case definition may be used to identify patients with probable anthrax meningitis. Patients with systemic anthrax and severe headache, altered mental status, meningeal signs, or other neurological signs should be considered to have anthrax meningitis.

dihydrostreptomycin, oxytetracycline, chlorotetracycline, or chloramphenicol monotherapy resulted in survival of approximately 55%. In contrast, 100% (16/16) of the mice treated with penicillin-streptomycin combination therapy survived (*58*). Data from human case reports suggest a similar finding. For patients with inhalation anthrax, a combination of antimicrobials was more likely curative than antimicrobial monotherapy (*15*).

CDC conducted a systematic review of the English-language clinical anthrax literature of antimicrobial-era patients treated for systemic anthrax to identify evidence to inform recommendations regarding antimicrobial therapy during an anthrax mass-casualty incident (*36*). From 98 citations, 149 persons were identified with a recorded clinical outcome who received an antimicrobial specifically recommended in the 2014 CDC anthrax guidelines (*34*) and had disease that could be categorized as cutaneous disease with systemic symptoms or signs (i.e., cutaneous disease with evidence of either the systemic inflammatory syndrome criterion (*59*,*60*) and/or meningitis), GI anthrax, inhalation anthrax, injection anthrax, or primary anthrax meningitis (i.e., central nervous system [CNS]) disease in the absence of other routes of infection. The primary routes of anthrax infection included cutaneous (40%), GI (19%), primary anthrax meningitis (13%), inhalation anthrax (17%), and injection anthrax (5%); 6% were classified as having multiple forms (e.g., GI plus cutaneous). As either a primary infection or as a secondary complication, 77 (52%) persons had confirmed anthrax meningitis (defined as cerebrospinal fluid [CSF] with gram-positive bacilli or a positive CSF culture for *B. anthracis*) or probable anthrax meningitis (defined as an anthrax case with reported altered mental status, meningeal signs, focal neurologic deficits, coma, CSF pleocytosis, presence of CSF red blood cells, CSF xanthochromia or a bloody CSF profile). Among the 59 persons classified as having cutaneous anthrax as the primary route of infection, the mortality rate was 44%, compared with 57% for the 28 persons with primary GI infection and 65% for the 26 persons with primary inhalation anthrax. Mortality was 89% for those with confirmed anthrax meningitis (n = 53), which is consistent with another large review of anthrax meningoencephalitis (*32*). Of note, among the 59 persons whose primary route of infection was categorized as cutaneous, mortality was 4% (1/26) for those persons without concomitant meningitis compared with 76% (25/33) for those persons with cutaneous disease complicated by meningitis. Because of the substantially lower mortality rate in persons with cutaneous anthrax without meningitis compared with the other forms of anthrax disease (i.e., cutaneous with meningitis, GI, and inhalation), these persons were excluded from the subsequent analyses evaluating the efficacy of different antimicrobial regimens for systemic anthrax.

Among the subset of 123 persons with severe anthrax disease (defined as cutaneous anthrax with secondary meningitis, inhalation, injection, GI anthrax, and primary anthrax meningitis), most patients received one antimicrobial (n = 79 [64%]), followed by equal numbers of patients who received either two or three or more antimicrobials (n = 22 [18%] each). Bactericidal therapy consisted of a penicillin class antimicrobial (n = 108), fluoroquinolones (n = 27), vancomycin (n = eight), and meropenem (n = four). Among those treated with protein synthesis inhibitors, patients received chloramphenicol (n = 20), clindamycin (n = 20), doxycycline (n = three), rifampin (n = eight), and linezolid (n = one).

Further analysis of persons who received, for any time period, combination therapy with a recommended bactericidal agent and a protein synthesis inhibitor demonstrated that overlapping bactericidal and protein synthesis inhibitor therapy was associated with higher percentage of survival

TABLE 2. Meningitis diagnosis by standard of care level

Standard of care level	Test	Result
Conventional	Lumbar puncture (LP) unless contraindicated by computerized tomography scan findings or clinical evaluation*	Culture and identification of *B. anthracis* from cerebrospinal fluid (CSF) by the Laboratory Response Network (LRN)
Contingency	History and physical	Consider patients to have meningitis if they have two or more of the following: • severe headache • altered mental status including confusion† • meningeal signs§ • other neurological symptoms/signs¶ OR • a contraindication to an LP • inability to tolerate an LP
	If resources for procedures are mildly constrained, LPs on patients with fewer than two (i.e., one or none) of the following: • severe headache • altered mental status • meningeal signs • other neurological symptoms/signs, as long as they also – lack a contraindication – can tolerate an LP If resources for procedures are severely restrained, LPs on patients with just one of the following: • severe headache • altered mental status • meningeal signs • other neurological symptoms/signs, as long as they also lack a contraindication and can tolerate an LP	Consider patients to have meningitis if they have any of the following CSF findings: • *Bacillus* spp. • gram-positive rods • pleocytosis • visible turbidity • visible hemorrhage
Crisis	History and physical	Consider patients to have meningitis if they have any of the following: • severe headache • altered mental status including confusion • meningeal signs • other neurological symptoms/signs

* **Source:** Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Engl J Med 2001;345:1727–33.
† Inability to correctly answer two consecutive questions or follow two consecutive commands.
§ Kernig sign, Brudzinski sign, jolt accentuation test (headache worsens on horizontally nodding head two to three times), nuchal rigidity, photophobia, and meningismus.
¶ Nonheadache nonmeningeal signs (e.g., recent seizures, focal signs such as cranial nerve signs or limb weakness, and papilledema).

(17 of 38 [45%]) compared with treatment that did not involve overlapping bactericidal and protein synthesis inhibitor antimicrobials (24 of 85 [28%]). These findings are consistent with previous findings demonstrating greater survival with combination antimicrobial therapy for inhalation anthrax (*15*). For patients with confirmed and probable meningitis, a greater percentage of those who received three or more recommended antimicrobials survived (three of four [75%]) compared with those who received one or two antimicrobials (12 of 73 [16%]).

Limited data were available to determine when to transition systemic anthrax patients from intravenous to oral therapy. Of the 123 patients in a systematic review (*36*), there were only 16 survivors with clearly documented duration of intravenous or intramuscular therapy. In this group, the median duration for either intravenous or intramuscular treatment was 14 days. These limited available data suggest that 14 days of intravenous therapy might be sufficient in stable patients before switching to oral therapy for prophylaxis against ungerminated spores. Because even fewer data are available on patients with confirmed or suspected meningitis, the recommendation is for these patients to receive at least 14 days of antimicrobials and be clinically stable and improving, before considering transition to oral monotherapy for prophylaxis against ungerminated spores.

The U.S. government has stockpiled enough 14-day combination intravenous treatment regimens to treat tens of thousands of patients with systemic anthrax. However, not all first-line treatment options are available through the CDC Strategic National Stockpile, warranting the use of commercially available sources or alternate antimicrobial therapy. Recommendations regarding the type, number, and duration of antimicrobials for use in the treatment of systemic anthrax during a mass-casualty incident were developed on the basis of data provided and opinion from clinical experts (Box 4) (Figures 3 and 4).

BOX 4. Parenteral antimicrobial choice for treatment of systemic anthrax in conventional, contingency, and crisis standards of care

Conventional setting

- Patients with probable, confirmed, or suspected meningitis should be treated with three recommended antimicrobials with good central nervous system penetration.
- Patients without evidence of meningitis should be treated with a minimum of one bactericidal agent plus one protein synthesis inhibitor.
- Parenteral combination treatment of systemic anthrax should be provided for at least two weeks or until the patient is clinically stable, whichever is longer; at that point, the patient may be transitioned to oral monotherapy for prophylaxis against ungerminated spores.

Contingency setting

Same as conventional setting, except that alternatives to first-line antimicrobial treatment recommendations may be used.

Crisis setting

- If triple antimicrobial therapy is not available, patients with probable, confirmed, or suspected meningitis may be treated with two recommended antimicrobials (one bactericidal agent and one protein synthesis inhibitor; both with good central nervous system penetration).
- Patients without evidence of meningitis
  - Should be treated with a bactericidal antimicrobial combined with a protein synthesis inhibitor.
  - Parenteral therapy may be stopped based on clinical judgment that the patient is clinically stable and improving; at that point, the patient may be transitioned to oral monotherapy for prophylaxis against ungerminated spores.
- Patients with confirmed or suspected meningitis are recommended to receive at least 14 days of antimicrobials and be clinically stable and improving, before considering transition to oral monotherapy for prophylaxis against ungerminated spores.

Antitoxin Prioritization in a Mass-Casualty Incident

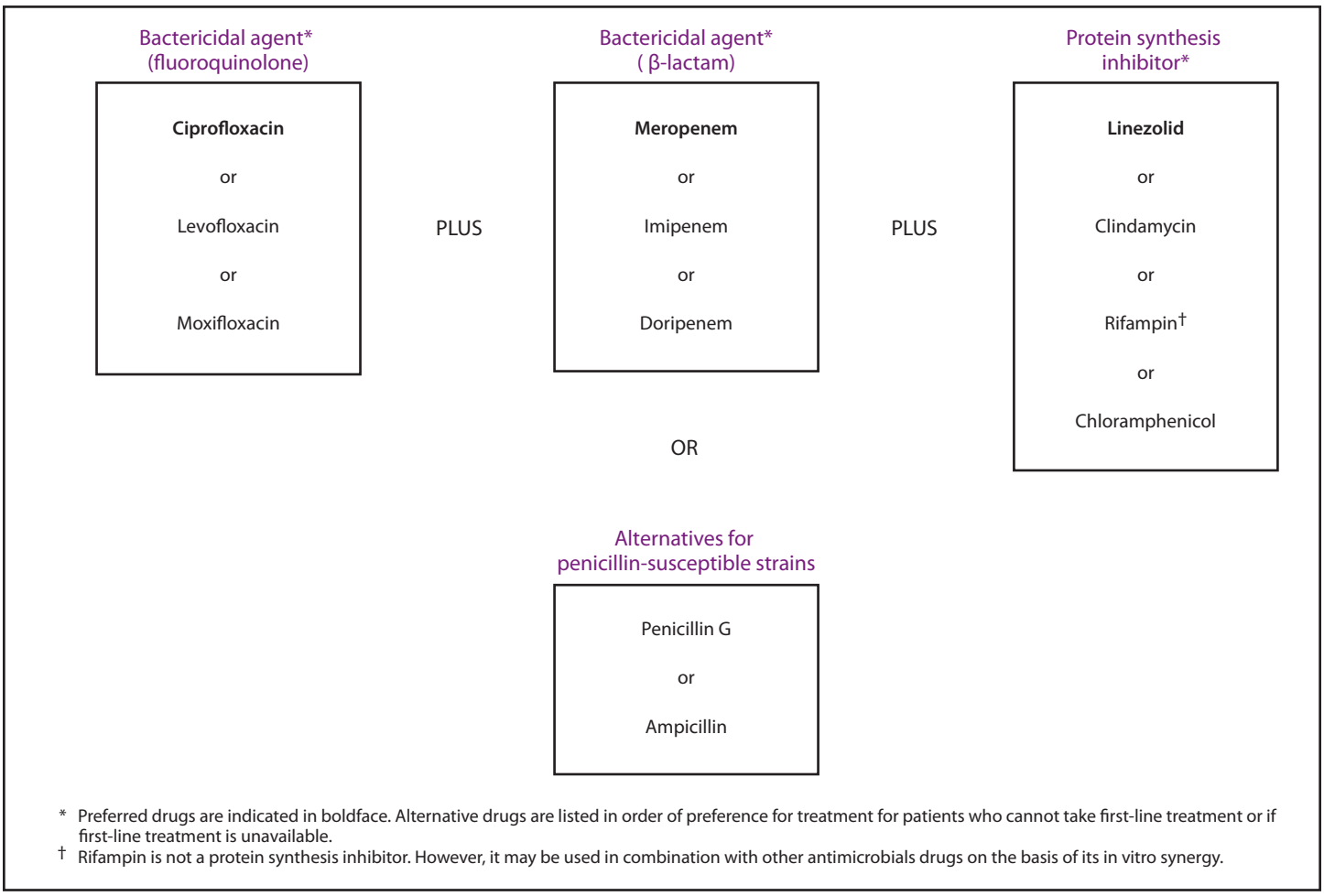
The U.S. government stockpiles antibody-based antitoxins for the treatment of adult and pediatric patients with inhalation anthrax for use in combination with appropriate antimicrobial therapy. These antitoxins bind to PA with high affinity in a dose-dependent manner. CDC's Strategic National Stockpile contains monoclonal and polyclonal antitoxins. Although polyclonal antitoxins bind PA at multiple sites, and bind other antigens besides PA, available data do not provide enough evidence to preferentially recommend one antitoxin over another (*34*). Stockpiled antitoxins not FDA-approved for anthrax, or for a particular type of anthrax might require use under an Investigational New Drug (IND) protocol or Emergency Use Authorization (EUA). These regulatory mechanisms allow access and clinical use of unapproved medical products but differ in their criteria, scope and requirement. IND is a means by which a drug can be made available for use before it is licensed by FDA and is limited to clinical trials or expanded access and requires informed consent. EUA is a mechanism that facilitates the availability and use of MCMs during a declared public health emergency and is intended for broad access to an unapproved product (e.g., drugs, biologics, or devices) during a declared public health emergency and does not require informed consent (*61*).

In human safety trials, serious adverse reactions to antitoxins were rare, and overall these drugs appear well-tolerated (*62*); however, the small size of the human trials limited the ability to detect rare, serious adverse events. Criteria for choosing a particular antitoxin might change once the results of ongoing antitoxin studies that directly compare antitoxin efficacy become available.

In conventional settings, CDC recommends that antitoxin should be administered as an adjunct to intravenous antimicrobials whenever there is a high level of clinical suspicion for systemic anthrax in a given patient (*34*). During an anthrax mass-casualty incident, the number of antitoxin doses and the resources needed to administer and monitor the 2–4-hour infusion might become limited. Therefore, antitoxin might not be available to treat every person for whom there is a high level of clinical suspicion for systemic anthrax. Prioritization of antitoxin selection in this setting would be informed by answers to three questions: 1) Is there a therapeutic window during which antimicrobials alone will provide effective treatment?; 2) Is there an optimal therapeutic window for adjunctive antitoxin therapy?; and 3) Is there a point at which patients are so ill that antitoxin no longer provides a clinical benefit?

CDC conducted a systematic review of the literature to evaluate data related to these questions and to inform antitoxin use during an anthrax mass-casualty incident (*35*). Because no human or animal studies published to date examine the questions above as the primary outcome, indirect evidence was examined. Evidence from 28 animal studies and three human studies was reviewed. In animal studies, fluoroquinolone monotherapy administered early in disease (i.e., at the detection of increased body temperature or serum PA) was associated with higher survival rates compared with no treatment (*63*). Higher rates of survival were demonstrated

FIGURE 3. Intravenous treatment for systemic anthrax with suspected, possible, or confirmed meningitis



Source: Adapted from Hendricks KA, Wright ME, Shadomy SV, et al. Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. Emerg Infect Dis 2014;20(2). Available at http://dx.doi.org/10.3201/eid2002.130687.

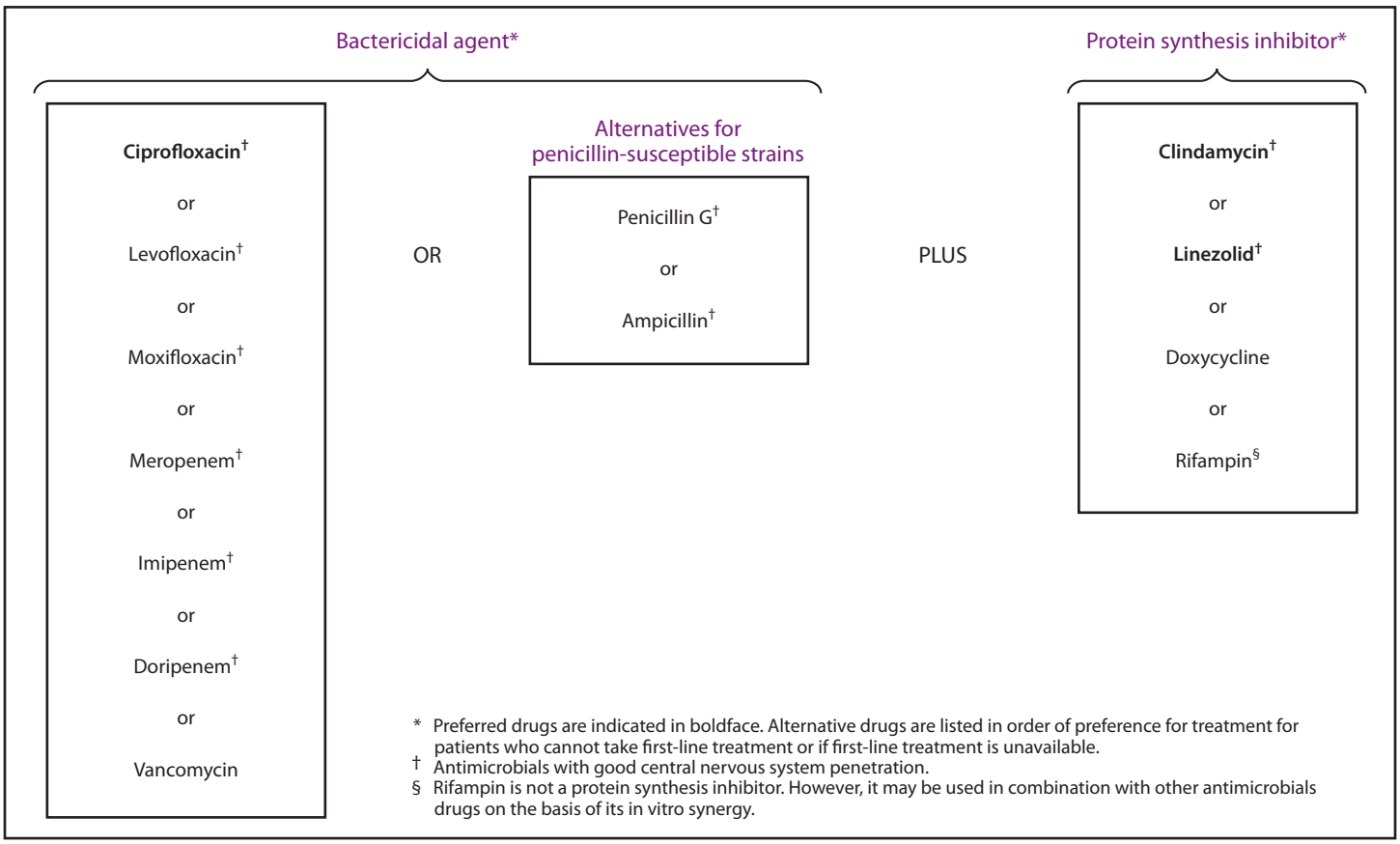
with antitoxin-antimicrobial treatment compared with antimicrobial treatment alone when treatment was initiated late in disease; however, sample sizes were small, and the results were not statistically significant. Among persons with cases of inhalation anthrax, the addition of antitoxin to antimicrobial treatment after symptom onset was associated with survival in two of the three cases, although the contribution of AIGIV to survival is unknown (*25*,*26*,*64*,*65*). However, serum lethal factor levels declined subsequent to AIGIV treatment, suggesting that an improvement in toxin-related sequela might be associated with antitoxin use.

These data do not define an antitoxin therapeutic window but suggest that antitoxin might provide therapeutic benefit after onset of bacteremia and toxemia and support the recommendation that antitoxin be considered adjunctive therapy to combination intravenous antimicrobials. However, the therapeutic window for adding antitoxin to antimicrobials is unknown (*35*). The mechanism of action of antitoxins (i.e., binding and inactivation of extracellular PA to prevent intracellular translocation of EF and LF) suggests that the maximal effect of antitoxins is likely before cellular uptake or the accumulation of lethal amounts of intracellular toxin.

Clinical markers or diagnostic tests that correlate to stages of anthrax disease progression could be used to define an antitoxin therapeutic window. However, no such markers or tests are available. In the absence of clinical markers of anthrax toxemia, clinical status must be used to determine antitoxin use in mass-casualty incident settings. Use of clinical indicators to base treatment decisions in scarce resource settings aligns with existing critical care allocation strategies (*48*,*49*,*66*). An established principle in crisis-care settings is to identify persons expected to derive the greatest benefit from available interventions for the purpose of prioritizing the allocation of scarce resources provided there is a reasonable chance of survival (*48*,*49*,*66*,*67*). The challenge with applying this principle for anthrax is defining

FIGURE 1. Formation and activity of main anthrax toxins

FIGURE 4. Intravenous treatment for systemic anthrax when meningitis has been excluded



Source: Adapted from Hendricks KA, Wright ME, Shadomy SV, et al. Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. Emerg Infect Dis 2014;20(2). Available at http://dx.doi.org/10.3201/eid2002.130687.

clinical parameters that can be used to determine which patients will derive the greatest clinical benefit.

AIGIV has been used to treat 15 persons with injection anthrax cases, a type of anthrax not expected to occur in an anthrax mass-casualty incident but one that might elucidate the benefits of antitoxin. Of the 15 patients who received AIGIV for injection anthrax, 10 (67%) had LF levels collected under the IND protocol. Two (13%) received AIGIV after LF levels had declined to below the level of detectability; the rest showed either no change or only a modest drop in LF levels after receiving AIGIV. It is unclear why the patients with injection anthrax did not experience the same decrease in serum toxin levels as seen in those with inhalation anthrax that received AIGIV. Overall, 10 (67%) patients with injection cases who were treated with AIGIV survived (William Bower, unpublished data, 2013).

Clinical status is defined by various clinical symptoms and signs, progressing from bacteremia to sepsis to severe sepsis/septic shock. According to the 2012 Surviving Sepsis Campaign guidelines (*59*), sepsis is defined as an infection (suspected and documented) associated with signs of systemic inflammation, severe sepsis is defined as sepsis and accompanying organ dysfunction or tissue hypoperfusion (Table 2), and septic shock is defined as sepsis-induced hypotension despite adequate fluid resuscitation. In the absence of disease-specific indicators of worsening status in anthrax patients, progression along the continuum of systemic infection provides a framework to define clinical status. These well-established criteria for stages of sepsis are widely recognized and categorize severity of illness among patients with systemic infections. Because anthrax sepsis has features similar to other causes of sepsis, the standard clinical definitions of sepsis, severe sepsis, and septic shock can be applied reasonably to categorize patients with systemic anthrax (i.e., inhalation, GI, meningeal, and cutaneous with signs of systemic involvement) and can differentiate between groups of patients who are potential candidates for antitoxin administration in anthrax mass-casualty incident settings. The use of clinical status and disease progression is the basis for the recommendations listed regarding antitoxin use during an anthrax mass-casualty incident (Box 5).

Anthrax meningitis has been associated historically with high mortality (*32*). Although the clinical benefit of combined

bactericidal-protein synthesis inhibitor antimicrobials plus antitoxin regimen for anthrax meningitis treatment is unknown, combination intravenous antimicrobial therapy is standard treatment for bacterial meningitis. Because anthrax is a toxin-mediated disease and anthrax meningitis is associated with bacteremia and toxemia, combination antimicrobial plus antitoxin might decrease the mortality rate. Thus, in the proposed framework, antitoxin prioritization remains high among patients with anthrax meningitis or in whom meningitis cannot be excluded. Because of historical mortality rates, it will be necessary to closely monitor, and potentially refine, this component of the algorithm if it is determined that mortality rates remain extremely high for anthrax meningitis, even with combined antimicrobials and antitoxin treatment. As the availability of antitoxin becomes increasingly scarce, more importance will be placed on the ability to predict survival when selecting which persons should receive therapy.

MCM Allocation and Indicators of Disease Severity and Prognosis

The optimal allocation strategy for MCMs in a mass-casualty incident would use anthrax-specific clinical indicators to define prioritization and use. However, because anthrax-specific clinical indicators do not exist, these recommendations outline a framework using clinical status that aligns with existing sepsis guidelines. The 2012 IOM report on crisis standards of care (*48*) recommends use of decision tools to predict prognosis and to aid resource allocation decisions. In resource-limited settings, the underlying tenet that guides decision-making is that resources should be used in patients with a reasonable chance of survival and that patients most likely to benefit from a given resource should be identified and given a higher priority to receive MCMs in order to save the greatest number of lives (*49*). However, these variations in standards of care should occur only in the setting of a formal activation of an incident command structure that involves both the affected health care systems and local and state public health departments.

Real-time anthrax clinical outcome data could greatly inform clinical decisions surrounding anthrax mass-casualty incident care and would be informative to the local clinician-based triage team. Because very limited data exist on predictors of clinical outcome for patients with anthrax treated in the era of modern critical care, extrapolation from historical cases often is required and might not reflect expected outcomes. For certain patients with anthrax, toxin-mediated cellular damage might induce irreversible organ failure and death, for which treatment would be futile. However, the point at which this would occur has not been well-defined. Observational studies in the setting of careful hemodynamic monitoring and intensive critical care could identify possible prognostic indicators for systemic anthrax. In the absence of such indicators, decisions will be based not on anthrax-specific indicators but rather on clinical judgment.

Multiple illness severity scoring systems have been developed to assess organ dysfunction among critically ill patients,

BOX 5. Antitoxin prioritization for treatment of systemic anthrax in conventional, contingency, and crisis standards of care

Conventional setting

An antitoxin should be added to the combination antimicrobial treatment for patients for whom there is a high level of clinical suspicion for systemic anthrax.

Contingency setting

- Patients for whom there is a high level of clinical suspicion of systemic anthrax, with clinical symptoms or signs consistent with any of the general or inflammatory sepsis variables and in whom severe sepsis has not been diagnosed, should receive.
  - Combination parenteral antimicrobial therapy.
  - Short term re-evaluation and observation is recommended.
  - Based on the clinical judgment of the local triage team, an antitoxin may be added to the antimicrobial regimen for patients who do not display rapid clinical improvement or who demonstrate any signs or symptoms of clinical deterioration.
- Patients for whom there is a high level of clinical suspicion for systemic anthrax, with clinical signs or symptoms consistent with severe sepsis or septic shock with a reasonable expectation of survival based on clinical judgment of the local triage team, should receive combination parenteral antimicrobial therapy plus antitoxin without delay.
- Patients with probable, confirmed, or suspected meningitis should receive combination parenteral antimicrobial therapy plus antitoxin without delay.
- Mechanisms should be in place to capture critical care and organ dysfunction measurements among septic anthrax patients, including measurements included in the sequential organ failure assessment (SOFA) score and other objective scoring systems.
- Disease-specific prognostic indicators should be defined based on real-time data and may inform and augment decisions of the local triage team regarding resource allocation.

Crisis setting

Same as contingency setting.

the most well-known being the Sequential Organ Failure Assessment Score (SOFA) scoring system. Although some data suggest that high SOFA scores are associated with mortality, recent experience with influenza has called into question the predictive utility of such scores (*68*,*69*). SOFA scores have not been studied extensively with respect to anthrax. One small retrospective study of patients with injection anthrax demonstrated that a low SOFA score was associated with survival, but the subset of patients was small, and injection anthrax might differ from other forms of anthrax (*70*). The respiratory and hemodynamic parameters of the SOFA score show promise as a reliable decision-support tool on the basis of observations from recent patients; however, it is premature to suggest that SOFA is predictive of mortality in systemic anthrax or in anthrax meningitis. Despite this, a few points can be made about SOFA: 1) monitoring organ dysfunction over time might be most useful; 2) failure of clinical improvement or increasing scores across multiple organ systems generally indicates poor prognosis; and 3) very high total scores are worrisome. In the proposed framework, the SOFA scoring system is provided as an example of an objective scoring system. This might not be the best objective score, but it is a tool that might be adapted to address systemic anthrax as more data become available. SOFA scores have not been validated as a predictor of mortality in infants and children.

Because laboratory capacity might be severely limited in a mass-casualty incident, scoring systems that rely less on laboratory testing should be considered. In addition, some critical care experts propose the use of basic clinical discriminators (e.g., the need for mechanical ventilation, hemodynamic instability requiring vasopressors) to define clinical status and resource prioritization. In this schema, patients requiring maximum ventilator settings or with vasopressor resistant shock would generally be lower priority to receive limited resources, such as antitoxin or intensive care beds. This is consistent with other critical care resource allocation strategies (*49*,*67*,*71*).

Use of standard criteria for sepsis, severe sepsis, and septic shock as indicators of clinical status is rational in the setting of limited data, but the need for more data to fill critical gaps is evident. To the extent possible in an anthrax mass-casualty incident, disease-specific clinical indicators of prognosis should be collected and analyzed. Until anthrax-specific markers are identified, obtainable elements of existing objective scoring systems, such as the SOFA, modified SOFA, or other objective scoring systems can be used. Near real-time, intra-event data collection and analysis will be valuable in the development of decision tools to guide scarce resource allocation and to help define exclusion criteria.

Fluid Drainage Considerations for Mass-Casualty Incident Planning

Fluid collections (pleural, pericardial, and peritoneal) are common in systemic anthrax. Among the 42 patients on whom autopsies were performed following the accidental release of *B. anthracis* spores in Sverdlovsk in 1979, all had pleural effusions, seven (17%) had pericardial effusions, and nine (21%) had up to 1.5 liters of ascites (*7*). Fluid accumulation is not restricted to inhalation anthrax; pleural effusions have been noted in patients with gastrointestinal anthrax (*65*) and primary anthrax meningitis (*72*) and ascites has been observed in patients with injection anthrax (*73*). Although the mechanism has not been elucidated, lymphatic destruction, vascular leakage, and edema toxin all have been suggested as the underlying pathogenesis of the effusions in systemic anthrax.

Clinically apparent fluid collections that accompany systemic anthrax should be drained, provided the procedure itself does not pose an undue risk. Drainage of pleural fluid appears to confer a survival advantage. Among patients with inhalation anthrax during 1900–2005, 83% of the survivors received pleural fluid drainage compared with only 9% of nonsurvivors ($p < 0.001$) (*15*). Drainage of over 50 liters of ascites likely contributed to survival in the 2009 U.S. patient with GI anthrax (*65*). Among the three 2001 patients with known pericardial effusions, one died from a complication related to cardiac tamponade (*8*,*9*). Fluid collections also might serve as toxin reservoirs. An LF level measured in pleural fluid was higher than any of the LF levels in serum in the 2006 patient with inhalation anthrax (*25*). In addition, LF was detected in ascitic fluid 3 weeks after it became nondetectable in serum in the 2009 U.S. GI anthrax case (Anne Boyer, unpublished data, 2013). Finally, fluid drainage might improve lung function by preventing segmental lung collapse induced by hydrostatic pressure within the pleural space. The six 2001 inhalation anthrax survivors all received pleural fluid drainage, and none were intubated, suggesting a clinical benefit of the procedure. In contrast, only two of the five nonsurvivors had fluid collections drained, and all five were intubated (*8*,*9*).

Fluid collections are dynamic. They might not be clinically apparent on admission to the hospital, and they can reaccumulate after drainage. In the 2009 U.S. GI anthrax patient, despite multiple exploratory laparotomies during which peritoneal fluid was removed, ascites reaccumulated throughout hospitalization, necessitating multiple paracenteses (*65*). In inhalation anthrax cases, repeated thoracenteses or continuous pleural drains are often necessary. In an anthrax mass-casualty incident, chest tubes and pre-assembled closed

chest drainage systems might be in short supply; should this occur, locally available supplies may be adapted into chest tubes and water seals or intermittent thoracentesis performed (although this requires substantially more provider time and increases the potential for complications) (*74*). The recommendations for diagnosis and management of fluid collections in an anthrax mass-casualty incident are listed (Box 6) (Table 3).

Special Populations

Certain populations might be more vulnerable to anthrax and anthrax complications as a result of differences in physiology, ability to access specialized care, or reticence to use MCMs because of lack of data regarding MCM safety and efficacy. For these populations, there is a paucity of data to inform specific recommendations for the allocation of clinical care and MCMs. However, because of the potential for these population groups to be at increased risk for morbidity and mortality during a mass-casualty incident, local and state preparedness planning should address these populations (*51*). Given the dearth of evidence, many clinical decisions will need to be made locally and require the input of local or hospital ethics committees and specialists. Recommendations to diagnose and treat anthrax in pregnant, postpartum, and lactating women and in children already exist (*46*,*47*), and the principles outlined in the anthrax mass-casualty incident recommendations contained in this guidance are largely applicable to these populations as well.

Pregnant and Lactating Women

An estimated 6.5 million pregnancies occur each year in the United States (*75*). Pregnancy causes physiologic changes resulting in a shift from cell-mediated to humoral immunity; decreased maternal oxygen reserve, lung compliance, and GI motility; and increases in volume of distribution, glomerular filtration, and renal secretion. These physiologic changes can affect a pregnant woman's susceptibility to and severity of infectious diseases; certain infectious diseases (e.g., influenza, hepatitis E, and listeriosis) have disproportionately

BOX 6. Diagnosis and therapy of fluid collections in conventional, contingency, and crisis standards of care

Conventional setting

- Patients with systemic anthrax should be evaluated for pleural effusions, pericardial effusions, and ascites by physical exam, computed tomography (CT) scan or ultrasound (e.g., thoracic and abdominal ultrasound and echocardiography). The presence of pleural, pericardial, or abdominal collections identified on physical exam should be confirmed by CT scan, thoracic ultrasound, echocardiography, or abdominal ultrasound.
- Early and aggressive drainage is recommended for any clinically/radiographically apparent pleural effusions.
  - Chest tube drainage is recommended over thoracentesis because of high reaccumulation rates.
  - Drainage should be continuous via thoracostomy to either suction or underwater seal.
  - Thoracotomy or video assisted thoracic surgery (VATS) might be required to remove gelatinous or loculated collections.
- Ascites also should be drained and monitored for reaccumulation; continuous drainage is preferred.
- Hemodynamically significant pericardial effusions should be addressed by experienced staff with access to radiographic, echocardiographic, ultrasonographic, and hemodynamic monitoring.

Contingency setting

- Patients with systemic anthrax should be evaluated for the presence of pleural fluid and ascites and for impending cardiac tamponade.
- If patients develop a coagulopathy, the risk/benefit argument will favor drainage of detectable pleural fluid and ascites in most cases.
- Continuous drainage for both pleural fluid and ascites is preferred.
  - When continuous drainage can no longer be maintained, intermittent thoracentesis for pleural fluid or intermittent paracentesis for ascites may be used.
- The smaller volumes associated with pericardial effusions and the technical difficulty of the procedure weigh against aspiration of all pericardial effusions. However, pericardial effusions still can pose a risk of tamponade.
  - Cardiac tamponade should be considered in dyspneic patients with systemic anthrax, particularly if they have findings such as tachycardia or have elevated neck veins, hypotension, pulsus paradoxicus, or cardiomegaly on chest radiography.
- Hemodynamically significant pericardial effusions should be addressed by experienced staff with access to radiographic, echocardiographic, and hemodynamic monitoring.

Crisis setting

Same as contingency setting.

higher mortality during pregnancy (*76*). Physiologic changes associated with pregnancy also make critical care management (e.g., mechanical ventilation and effusion drainage) more complex. In addition, there are few pharmacokinetic data on the distribution of antimicrobials or antitoxins in pregnant women or fetuses (*77*).

A systematic review of anthrax cases in pregnancy indicated that the maternal mortality proportion among the cases was 80% (16 of 20 mothers) and the fetal/neonatal mortality rate was 71% (12 of 17 infants) (*78*). Evidence of anthrax was documented in the placenta, amniotic fluid, and fetal tissues, indicating in utero infection. Because these data are limited and include cases from the pre-antimicrobial era, whether pregnant women and infants are at increased risk from anthrax with modern critical care management is unknown. However, these findings suggest that anthrax is associated with similar morbidity and mortality during pregnancy (*78*). Pregnant women should be considered as high a priority as nonpregnant adults for mass-casualty incident care and require close monitoring and specialized care (*46*).

Pediatric Population (Children Aged <18 Years)

Approximately 24% of the U.S. population is aged <18 years. The physiologic differences between children and adults can be marked and depend on the age of the child. Data on the presentation of anthrax in children are limited, and the ability to diagnose anthrax might be more difficult because clinical symptoms and signs might not be as apparent. Younger children (i.e., those aged <12 years) can have difficulty communicating symptoms (e.g., fatigue, chest pain, headache, myalgias, and confusion) and might not present with classic signs associated with early anthrax (*79*,*80*). Furthermore, the thymic shadow might obscure the mediastinum in chest imagery in infants. Children should be considered as high a priority as adults and might require closer monitoring for clinical deterioration by health care personnel with pediatric experience (*47*). Physicians administering antimicrobials and antitoxins to children also should be aware of the regulatory requirements associated with MCMs. Some MCMs will be available for use in children only under an IND protocol or EUA. If the use of the MCM will be under IND or EUA, clinicians will need to plan for the time and staff needed to fulfill the regulatory requirements that might be needed (e.g., securing informed consent of a parent or guardian if MCMs are used under IND).

Future Directions

A review of the literature has revealed gaps in knowledge regarding optimal medical treatment of anthrax and tools needed to respond to an anthrax mass-casualty incident. A reliable point-of-care assay for staging anthrax toxemia is needed (*25*). On the basis of findings presented at the March 2014 Expert Panel Workshop, anthrax toxin components show promise as reliable markers of anthrax disease progression and could provide objective, evidence-based approaches to guide resource allocation in a mass-casualty incident. To date, limited data are available on the measurement of quantitative serum toxin levels; however, patterns of promising markers of clinical stages of anthrax are emerging (*25*,*26*,*64*,*81*,*82*). Potential markers that might be reasonable to study include toxin-associated biomarkers, serum PA (*25*), anti-PA, LF, EF, LT or ET levels and organism-associated markers such as the poly-γ-D-glutamic acid capsule antigen (*81*). However, many questions remain, including the correlation of serum and toxin levels with clinical status and mortality, and the contribution of CNS toxin levels to meningeal symptoms and high fatality associated with anthrax meningitis.

LF shows promise as a clinical marker because it can be detected in a culture-independent fashion in all types of anthrax (*25*,*26*,*81*–*84*) and is the earliest marker of infection, preceding the onset of signs of infection in animal studies (*85*). In addition, LF detection is not subject to interference from antimicrobials and antitoxins and thus can be used to monitor therapeutic interventions and disease status

TABLE 3. Effusion drainage techniques by standard of care level

Standard of care level	Pleural effusions	Ascites	Pericardial effusions
Conventional	Continuous drainage to suction	Continuous drainage of ascites via indwelling drain (e.g., Jackson-Pratt or peritoneal dialysis catheter)	Drain hemodynamically significant effusions
Contingency	Continuous drainage to underwater seal	Same as conventional setting	Same as conventional setting
Crisis	• Continuous drainage if possible • Intermittent thoracentesis, preferably ultrasound guided	Continuous drainage if possible • Intermittent paracentesis, preferably ultrasound guided	Same as conventional setting

(*25*,*26*,*84*). Point-of-care assays for LF, other toxins, and capsule are under development and might assist with resource allocation, particularly for antitoxin use. In addition, animal data suggest relative levels of LF, FT, and EF toxins appear to correlate with disease severity and support the notion that toxemia varies at different stages of illness (*86*). Rather than a single quantitative measurement of toxin, relative differences in toxin levels might improve our understanding of anthrax pathogenesis and ultimately help guide the use of therapeutics (Anne Boyer, unpublished data, 2013).

Quantitative evaluation of PA levels in animals also might help elucidate anthrax disease progression, as well as define optimal treatment timing. Survival rates with antimicrobial alone and with antimicrobial-antitoxin treatment were higher when treatment was provided at lower PA levels, suggesting that treatment before a large toxemic burden develops is beneficial (Judith Hewitt, unpublished data, 2013) (*87*). Although these preliminary data require more robust analysis and extrapolation to anthrax human disease, in nonhuman primates, PA levels appear to correlate well with bacteremia. Serum PA threshold might be able to define different toxin loads and perhaps even stages of illness that correlate with toxemia. Amount or level of toxemia could then be assessed as a trigger for treatment and driver for antitoxin allocation.

Limitations

These guidelines have at least three limitations. First, much of the data used to develop the guidelines were compiled from systematic reviews of historical human data and animal studies, and these studies, although helpful, were not designed to answer questions of optimal antitoxins and intravenous antimicrobial use and diagnosis and management of common anthrax-specific complications in a mass-casualty incident. Second, the data from case reports span over a century, during which time antimicrobials and supportive care have changed tremendously. Finally, cases were geographically diverse and included outcomes that resulted from care in countries with differing health care capacities. Although the recommendations provided in this guidance are evidence-based, the quality of the evidence is inherently limited as this topic does not lend itself to controlled trials or even high-quality observational studies. For this reason, these recommendations rely heavily on extrapolation and interpretation of indirect data and individual expert clinical judgment.

Conclusion

CDC has developed guidelines for the prevention and treatment of naturally occurring or bioterrorism-related anthrax in conventional medical settings (*34*,*46*,*47*). However, during an anthrax mass-casualty incident, resource limitations might warrant a shift to contingency or crisis standards of care. The U.S. government preparedness plan calls for preplanning for the possibility of an anthrax attack, including one in which the number of persons seeking inpatient care following a large release of *B. anthracis* spores could overwhelm stockpiled resources (*88*). These guidelines were developed to help address mass-casualty incident considerations and gaps in preparedness planning, specifically pertaining to MCM use and the treatment of anthrax-related complications.

This guidance provides a framework for fair, efficient, judicious, and rational antimicrobial and antitoxin utilization and addresses common anthrax-specific complications in the context of an anthrax mass-casualty incident. Clinicians, hospital administrators, state and local health officials, and planners can use this guidance to assist in the development of crisis protocols for an anthrax mass-casualty incident.

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ISSN: 1057-5987

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