American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

FROM THE AMERICAN ACADEMY OF PEDIATRICS

Guidance for the Clinician in Rendering Pediatric Care

CLINICAL REPORT

Pediatric Anthrax Clinical Management

John S. Bradley, MD, FAAP, FIDSA, FPIDS, Georgina Peacock, MD, MPH, FAAP, Steven E. Krug, MD, FAAP, William A. Bower, MD, FIDSA, Amanda C. Cohn, MD, Dana Meaney-Delman, MD, MPH, FACOG, Andrew T. Pavia, MD, FAAP, FIDSA, and AAP COMMITTEE ON INFECTIOUS DISEASES and DISASTER PREPAREDNESS ADVISORY COUNCIL

KEY WORDS

anthrax, anthrax vaccine, biological weapon, bioterrorism, prophylaxis, children, pediatrics

ABBREVIATIONS

AAP—American Academy of Pediatrics
AIG—anthrax immune globulin
AVA—anthrax vaccine adsorbed
CDC—Centers for Disease Control and Prevention
CNS—central nervous system
CSF—cerebrospinal fluid
CT—computed tomography
FDA—US Food and Drug Administration
PCR—polymerase chain reaction
PEP—postexposure prophylaxis

Dr Bradley conceptualized, drafted, and revised the manuscript; and Drs Krug and Peacock reviewed and revised the manuscript. All authors contributed to the development of the content and recommendations and approved the final manuscript as submitted.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All policy statements from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

(Continued on last page)

abstract

FREE

Anthrax is a zoonotic disease caused by *Bacillus anthracis,* which has multiple routes of infection in humans, manifesting in different initial presentations of disease. Because *B anthracis* has the potential to be used as a biological weapon and can rapidly progress to systemic anthrax with high mortality in those who are exposed and untreated, clinical guidance that can be quickly implemented must be in place before any intentional release of the agent. This document provides clinical guidance for the prophylaxis and treatment of neonates, infants, children, adolescents, and young adults up to the age of 21 (referred to as "children") in the event of a deliberate *B anthracis* release and offers guidance in areas where the unique characteristics of children dictate a different clinical recommendation from adults. *Pediatrics* 2014;133:e1411–e1436

INTRODUCTION

Bacillus anthracis is often placed at or near the top of potential threat agents by biodefense experts.[1–3] Because of the potential use of *B anthracis* as a biothreat agent, clinical guidance that can be quickly implemented must be made available for review by clinicians before its use in a bioterrorism event, such as the intentional release of aerosolized spores. It is a rod-shaped bacterium present in the environment and may also exist in a spore form that is easy to disperse. It can remain a potential hazard for weeks to years after bioterror dispersal. Anthrax infection in humans can develop after exposure at different anatomic sites and can manifest in different clinical presentations, including cutaneous, inhalation, and gastrointestinal, all of which can disseminate and lead to meningoencephalitis. Another form of anthrax, injection anthrax, has recently been described in drug users and is associated with contaminated heroin use.[4] This form of anthrax will not be addressed in this report. Most types of anthrax carry a high mortality, including cutaneous infection if local disease of the skin or mucosal surfaces is untreated and progresses to systemic disease.[2,5,6] Toxins mediate much of the morbidity and mortality associated with *B anthracis*, including hemorrhage, edema, and necrosis.[7]

The potential danger of *B anthracis* as a bioweapon was dramatically illustrated after an accidental release of spores in 1979 from a military microbiology facility in Sverdlovsk, Union of Soviet Socialist Republics, that resulted in at least 77 cases of human anthrax and 68 deaths.[8] However, none of the cases reported in this incident involved children. *B anthracis* was also used as a bioweapon in 2001, when spores were intentionally distributed through the US postal system. Of

the 22 resulting cases, 18 had confirmed anthrax, 11 of which had inhalation anthrax; 5 of these cases were fatal.[9] The other 11 cases, both suspected and confirmed, were nonfatal cutaneous anthrax, 1 of which occurred in a 7-month-old infant, whose disease progressed to systemic illness.[10]

This document provides clinical guidance for the prophylaxis and treatment of children in the event of an intentional *B anthracis* release and offers guidance in areas in which the unique characteristics of children dictate a different clinical recommendation from that for adults. A comprehensive review of anthrax as it relates to naturally occurring infection is not provided. Rather, the document gives guidance on caring for children after an intentional release of *B anthracis* when public health officials are recommending prompt prophylaxis of individuals thought to be exposed and rapid treatment of individuals with potential anthrax infection. Guidelines for both treatment and prevention in adults have been developed and are not reviewed in this document.[11]

Children require special considerations for prophylaxis and treatment, because the clinical presentation and progression of disease for cutaneous, inhalation, gastrointestinal, meningoencephalitis, and disseminated anthrax infection may be different from those in adults. For example, children could be at a higher risk of developing disseminated, systemic disease and/or meningoencephalitis after focal infection. It may be more difficult to diagnose the infection in children by clinical signs and symptoms early in the course, because febrile and respiratory illnesses, which may mimic early symptoms of anthrax, are common in children compared with adults. Furthermore, the signs and symptoms for any type of anthrax infection in infants younger than 2 months are not well defined.[12]

In addition, antimicrobial selection and clinical care may be different for children. Young children, as well as children, adolescents, and young adults with disabilities, may have difficulty swallowing oral tablets; compliance also may be reduced with poor-tasting suspensions.[13] The safety and tolerability of some antimicrobial agents when prescribed for children continuously for weeks to months are not well-studied.

Although the provision of antimicrobial agents and vaccine to asymptomatic children for postexposure prophylaxis (PEP) falls under the aegis of public health authorities, local health care providers should be familiar with available resources during a public health emergency to be prepared to treat symptomatic children (ambulatory and hospitalized) who present with focal or systemic infection. In addition, pediatric health care providers will likely receive questions about antimicrobial prophylaxis regimens from families and will be called on to provide reassurance and guidance to families, specifically regarding adverse effects of the prophylactic antimicrobial agents. Pediatricians and others who provide health care to children will be involved in this process as trusted sources of health care information for their patients and families. Clear lines of communication between clinicians and public health practitioners will help families receive consistent messages, improve disease surveillance and adherence to prophylactic antimicrobial regimens, decrease panic among parents and caregivers, and possibly save lives in the midst of a public health emergency.

The American Academy of Pediatrics (AAP) has developed a Pediatric Preparedness Resource Kit[14] to encourage partnerships and joint decision-making between pediatricians and state and/or local health department representatives. This kit includes information and strategies that will help to promote strategic communications and effective messaging in a situation such as a *B anthracis* release (see www.aap.org/disasters/resourcekit).

Information and guidance that is specific to the identified exposure after a bioterror release in which spores intentionally target civilians will be provided on the Centers for Disease Control and Prevention (CDC) Web site to assist pediatric health care providers with critical decision-making when dealing with patients, families, health care facilities, and local health departments (www.cdc.gov/anthrax).

This guidance reflects a comprehensive review of the literature and the opinions of individual experts from the AAP and the CDC (referred to as the AAP and CDC Pediatric Anthrax Writing Group) at the time of publication, based on the proceedings of a jointly sponsored workshop, held at the CDC Tom Harkin Global Communications Center in Atlanta, Georgia, in November 2012.

Guidance for pediatric anthrax clinical management is provided in Appendices 1 through 8, which are ordered based on severity of disease to offer easy access in the event of a public health emergency.

CLINICAL PRESENTATIONS OF ANTHRAX

B anthracis is an aerobic, gram-positive, encapsulated, spore-forming, nonhemolytic, nonmotile, rod-shaped bacterium. It causes an acute infection called anthrax that can manifest differently according to the route of exposure: cutaneous, inhalation, and gastrointestinal. Each of these forms can progress to systemic disease, which may present clinically with signs of septicemia with the subsequent development of meningoencephalitis.[15]

Exposure to aerosolized *B anthracis* is likely to result in a predominance of inhalation and cutaneous anthrax cases; however, gastrointestinal cases also may occur. The clinical presentations as discussed herein are primarily from

reports of anthrax in previously healthy adults. Different clinical presentations may occur across the spectrum of pediatric age groups and in special pediatric populations, such as those with underlying comorbidities or disabilities.

Cutaneous Anthrax

Approximately 95% of naturally acquired cases of anthrax are cutaneous. Clinical disease in children appears to be similar to adults, spanning the spectrum from localized to systemic disease.[16] One of the youngest documented cases of cutaneous infection occurred in a 1-month-old infant who was hospitalized with *B anthracis* infection around the mouth, presumed to have been acquired from his mother with cutaneous anthrax.[17]

With cutaneous anthrax, after an incubation period of 1 to 12 days, the skin lesion progresses over 2 to 6 days from a pruritic papule or vesicle into a characteristic depressed black eschar surrounded by moderate to severe edema. The lesion is typically painless and can be accompanied by fever, malaise, headache, and painful lymphadenopathy.[12,18] The mortality rate for cutaneous anthrax is less than 1% if treated with antimicrobial agents but can be as high as 20% if untreated.[12,16,17,19] Those with symptoms or signs of systemic involvement or with lesions that involve the head, neck, or upper torso or that are large, bullous, multiple, or surrounded by significant edema have higher mortality rates.[16,19]

Inhalation Anthrax

Inhalation anthrax has the highest case-fatality ratio of the typical forms of the disease. After being inhaled into the lungs, *B anthracis* spores are transported by macrophages and other phagocytic cells to regional lymph nodes, where either en route or on arrival they can germinate into toxin-producing bacteria. The bacteria and toxins cause systemic anthrax. Spores may germinate as soon as 1 day or may remain dormant for weeks or months before germinating.[20,21] Depending on the circumstances of exposure, the inhalation form of anthrax may be the most prevalent form of serious, life-threatening disease after an anthrax attack. The incubation period for inhalation anthrax in humans is not well-defined and has ranged from 1 to 43 days, which may reflect delayed germination of inhaled spores or repeated inhalation of spores from the environment after the original exposure event.[8] Initial nonspecific signs and symptoms may include mild fever, fatigue, myalgia, and cough, and can resemble a viral respiratory illness.[22] Occasionally, these prodromal signs and symptoms briefly improve before abrupt deterioration[7,23,24] to a more fulminant disease characterized by diaphoresis, stridor, dyspnea, hypotension, or acute respiratory distress.[7,20,23,25] These patients may develop sepsis accompanied by cyanosis, shock, and hemorrhagic pneumonia. Hemorrhagic pleural effusions often develop. Other organ systems, particularly the central nervous system (CNS), also can be affected secondary to bacteremia, a frequent occurrence in children noted with certain bacterial pathogens. The risk of meningoencephalitis is not well-defined in children, but in adults with systemic disease, it appears to occur in approximately 50% of cases.[22,25,26]

In the 5 pediatric inhalation anthrax cases reported from 1900 to 2005, nausea, vomiting, headache, dyspnea, or meningeal signs were exhibited, and 3 of the 5 children died.[27] With prompt diagnosis, initiation of combination antimicrobial therapy, and modern critical care, the mortality rate observed in adults with inhalation anthrax dropped from more than 90% for the whole 20th century to 45% in the exposures linked to letters contaminated with *B anthracis* spores in 2001,[23] which suggests that better outcomes are also likely to occur in children. In 2006[28] and 2011,[29] adults in Pennsylvania and Minnesota, respectively, were successfully treated for naturally acquired inhalation anthrax, demonstrating the effectiveness of modern treatments.

Gastrointestinal Anthrax

Gastrointestinal anthrax can occur after the consumption of food contaminated with *B anthracis* vegetative cells or spores. After an incubation period of 1 to 7 days after ingestion of bacilli or spores, gastrointestinal anthrax presents with signs and symptoms that can include severe abdominal pain and tenderness, nausea, vomiting, hematemesis, anorexia, and fever progressing to more severe systemic illness.[20,30–32] With antimicrobial treatment, gastrointestinal anthrax exhibits a mortality rate of 40% or less.[31]

A report by Bravata et al[27] indicated that the most commonly reported pediatric gastrointestinal anthrax symptoms, in order from most to least common, were fever, abdominal pain, vomiting, diarrhea, and bloody stool.

Gastrointestinal anthrax also can manifest as oropharyngeal anthrax, which starts as a painless mucosal lesion in the oral cavity or oropharynx. Signs of oropharyngeal anthrax may include dysphagia with posterior oropharyngeal necrotic ulcers, unilateral neck swelling, cervical adenopathy, edema, pharyngitis, and fever. Gastrointestinal anthrax can progress to systemic infection.[20,31]

Meningeal Anthrax

In contrast to bacterial meningitis attributable to organisms, such as pneumococcus, meningococcus, or *Haemophilus influenzae* type b, *B anthracis* causes a hemorrhagic meningoencephalitis that involves both deep brain parenchymal hemorrhagic lesions as well as infection of the cerebrospinal fluid (CSF) in the subarachnoid space. All forms of

systemic anthrax can progress to meningoencephalitis, which, to date, has been nearly always fatal.[7,27] However, there is limited experience with treatment using currently available intensive care. In a systematic review of pediatric anthrax by Bravata et al,[27] meningoencephalitis developed in 7 of 22 patients with gastrointestinal anthrax and 1 of 37 patients with cutaneous anthrax; 6 children had primary meningoencephalitis with no apparent focus of entry. Only 1 patient survived. In an autopsy series of adult patients from Sverdlovsk, 50% of fatal cases had evidence of meningeal involvement.[33] Signs of meningoencephalitis include fever, altered mental status, meningeal signs, and seizures,[34] although in the review by Bravata et al,[27] pediatric cases of meningoencephalitis presented with fever, headache, delirium, seizures, emesis, and diarrhea. Too few cases exist to provide information on differences in the clinical presentation of meningitis between adults and children.

PEP TO PREVENT INFECTION

Studies have demonstrated that spores with the potential to germinate in vitro could be found in the lungs of nonhuman primates up to 100 days after inhalation exposure.[35] However, the potential for long-term spore survival in the environment or subsequent disease is unknown.[36] In the setting of a large-scale release of *B anthracis* spores, the public health response will focus on protecting the exposed population with PEP. The CDC Advisory Committee on Immunization Practices and the AAP Committee on Infectious Diseases recommend a combination of antimicrobial prophylaxis for immediate protection during the first 60 days after exposure and immunization for long-term protection after exposure to *B anthracis* spores.[18,37] Antimicrobial prophylaxis and immunization in special pediatric populations, such as those with underlying comorbidities or disabilities, may differ from those provided below.

Antimicrobial PEP

Similar to adults, all children believed to be exposed to aerosolized *B anthracis* spores should receive at least 60 days of antimicrobial prophylaxis (Appendix 1). In response to an anthrax release, local points of dispensing will be identified and coordinated by public health officials, and will receive, and subsequently dispense, an initial 10-day supply of oral ciprofloxacin or doxycycline (or, if pathogens are documented to be susceptible to penicillin, oral amoxicillin, or phenoxymethyl penicillin may be used). Clindamycin and levofloxacin are considered effective alternative antimicrobial agents. Providing antimicrobial prophylaxis to the local population within 48 hours of the initial exposure is the public health goal, with local supplies being supplemented by antimicrobial agents from other regional or national sources. In the early phases of the response, data gathered by federal and state public health officials will better define the exposed population within the 10 days after that particular exposure. To minimize indiscriminate prescribing and use of antimicrobial agents during the early phases of the response to an event, practitioners are advised to seek advice from local public health officials to determine those in need of PEP. Individuals deemed exposed to aerosolized *B anthracis* spores will be notified by local health authorities in partnership with local professional organizations and health care providers to receive the first dose of anthrax vaccine adsorbed (AVA [BioThrax, Emergent BioSolutions, Rockville, MD]), instructions for the second and third AVA doses, and an additional 50-day supply of antimicrobial agents. This 60-day antimicrobial regimen covers the incubation period of the disease[8,38] and provides protection until the vaccine confers immunity.

A limited supply of oral suspension formulations of recommended PEP antimicrobial agents will be available, and distribution strategies will be determined by public health authorities at state and local levels. If oral suspensions are not readily available, doxycycline tablets will be provided with clear directions, as recommended by the US Food and Drug Administration (FDA), on how the tablets can be crushed and added to a food or liquid to create a formulation that is more palatable and designed to improve adherence for those who are unable to swallow a tablet.[39]

Tetracycline-based antimicrobial agents, including doxycycline, may cause permanent tooth discoloration for children younger than 8 years if used for repeated treatment courses. However, doxycycline binds less readily to calcium compared with older tetracyclines, and in some studies, doxycycline was not associated with visible teeth staining in younger children.[40,41] Although no prospective data exist on staining of teeth in children younger than 8 years taking a 60-day course of doxycycline, the benefits of preventing life-threatening anthrax infection outweigh the potential risks of injury to teeth. Similarly, although no prospective data exist on the risks of cartilage toxicity with ciprofloxacin, particularly for a 60-day course, the benefits of an extended course for prophylaxis in children outweigh the concerns for potential cartilage toxicity. On the basis of availability, either antimicrobial agent may be used and should provide equivalent efficacy, although prospective data after *B anthracis* bioterror exposure in children do not exist.[42] Some experts believe that if adverse events occurred with an equal incidence between doxycycline and ciprofloxacin, the potential for tooth staining as a sequela may be

less serious than the potential for long-term cartilage injury.

Additional liquid formulations, such as amoxicillin and liquid suspension forms of doxycycline and ciprofloxacin, may be available in this additional 50-day antimicrobial agent supply for infants and young children or children, adolescents, and young adults with disabilities after the initial 10-day prophylaxis supply has been completed and the antimicrobial resistance profile of the *B anthracis* strain has been determined.

Vaccine PEP

AVA contains proteins from a sterile, cell-free, culture fluid grown from a *B anthracis* strain and contains no live or dead bacteria. All exposed adults are expected to receive AVA intramuscularly or subcutaneously at 0, 2, and 4 weeks in addition to a total of 60 days of antimicrobial prophylaxis.[11] AVA has been shown to be safe and immunogenic in clinical trials in adults.[37] Serious adverse events after AVA administration in adults were infrequent. However, local adverse events, such as pain, erythema, induration, and swelling, were common.[37] Most of these local adverse events were not serious, and self-resolved. The vaccine, usually given as a 0.5-mL dose, contains 0.6 mg of aluminum (as aluminum hydroxide). A 0.5-mL dose of diphtheria, tetanus, acellular pertussis (DTaP [pediatric formulation] or TdaP [adolescent/adult formulation]) vaccine may contain up to 0.85 mg of aluminum. Local adverse events may be similar to those described in adults administered AVA and in children administered other vaccines, with similar aluminum hydroxide concentrations.

On the basis of routine and extensive use of similar vaccines in children 6 weeks of age and older, it is anticipated that AVA should demonstrate immunogenicity to *B anthracis* protective antigen necessary to provide protection against symptomatic infection in children 6 weeks and older. The safety profile should to be similar to that in adults, commensurate with prevention of life-threatening infection. However, studies of AVA in children younger than 18 years have not been conducted, and the vaccine is not currently approved by the FDA for use in children. Until there are sufficient data to support FDA approval, AVA will be made available for children at the time of an event as an investigational vaccine through an expedited process that will require institutional review board approval, including the use of appropriate consent documents. Information on the process required for use of AVA in children will be available on the CDC Web site at the time of an event (www.cdc.gov/anthrax), as well as through the AAP and the FDA. All exposed children 6 weeks and older should receive 3 doses of AVA at 0, 2, and 4 weeks in addition to 60 days of antimicrobial chemoprophylaxis. The recommended route of vaccine administration in children is subcutaneous, although both subcutaneous and intramuscular injections appear to achieve similar levels of immunogenicity in 60 days. Children younger than 6 weeks should immediately begin antimicrobial prophylaxis but delay starting the vaccine series until they reach 6 weeks of age.

For children, a local adverse event to a previous dose of AVA is not a contraindication to receiving additional doses, although the subsequent dose should be administered at an alternate site. Large local reactions or systemic adverse events should be evaluated before additional doses are administered. Given the short time intervals between the 3 doses recommended for PEP, parental concerns about local adverse events should be addressed prospectively to increase the likelihood of adherence with the full vaccination schedule.

PEP use of AVA is not yet an FDA-approved indication in any population. The doses for each pediatric age group that balance immunogenicity, safety, and protective efficacy have not yet been determined. Clinical guidance for use of AVA in infants and children is currently based on data from adult AVA clinical trials and expert opinion, although recommendations for pre-event limited investigation of AVA in children are under consideration. The Presidential Commission for the Study of Bioethical Issues recommends that pre-event pediatric research into medical countermeasures, including AVA administration, should pose only a minimal risk to children and should use an age de-escalation process to determine study participation risk.[43] This process would look at safety in 18-year-olds and then progressively assess safety and risk at younger ages. Studies that may cause "no more than a minor increase over minimal risk" will require national review under federal regulations. Local institutional review boards should be aware of their role, before a bioterror event, in facilitating the appropriate use of AVA in children during an event. Federal agencies are collaborating on ways to streamline the consent process in a public health emergency. The intent of all providers and federal agencies is to ensure that all children exposed during an event have appropriate access to vaccine.

Special Vaccination Considerations

AVA should not be coadministered routinely with standard childhood vaccines during an anthrax bioterror event. The coadministration of routine vaccines to children in addition to the recommended 3 doses of AVA within 6 weeks of the final AVA immunization could contribute to increased adverse reactions, resulting in a reduction in adherence to full vaccine schedules for both routine vaccines and AVA. In addition, research on the effect of anthrax vaccine on the immunogenicity of routine vaccines has not been performed. Infants and children who are

hospitalized yet still exposed during an anthrax bioterror event should be vaccinated by using the same schedule as outpatients. Given the host immune response normally documented with infection, those with anthrax infection may not require immunization, but systematically collected data on immunity after infection are not available; therefore, these children also should receive all 3 AVA vaccine doses.

Immunization of children exposed to aerosolized *B anthracis* spores with AVA is a priority, above routine immunizations. Although data are not available in children regarding the types and frequency of adverse events after immunization, or whether administering AVA as soon as a few days after the receipt of routine immunizations will lead to an increased frequency of adverse events, the benefits of AVA in children exposed to aerosolized *B anthracis* spores are currently believed to outweigh these risks.

Routine immunizations should resume 4 weeks after the last AVA dose.

INFECTION CONTROL IN THE HOSPITAL AND COMMUNITY

If patients have had recent exposure to aerosolized *B anthracis* spores, the risk of aerosolization of spores from clothing or skin and subsequent inhalation is unknown but not believed to be high.[44] Public health officials, in collaboration with the CDC, will issue recommendations, which will be available on the CDC Anthrax Web site (www.cdc.gov/anthrax), on how the public should decontaminate clothing and other surfaces after exposure, as well as how to decontaminate dwellings and public places where children may be present, such as schools and child care centers.

Human-to-human transmission of anthrax itself is exceedingly rare and described only in association with exposure to cutaneous lesions.[45] Transmission through nonintact skin contact with draining lesions is possible; therefore, use Contact Precautions if a large amount of uncontained drainage is present. Cutaneous lesions will no longer contain vegetative bacilli within 24 hours of starting antimicrobial therapy.[46] Hand washing with soap and water is preferable to use of waterless alcohol-based antiseptics, because alcohol does not have sporicidal activity. Patient care itself does not appear to pose a risk for transmission to health care providers.[47] Although Standard Precautions for patient care and disposal of blood and potentially contaminated body fluids adequately address contagiousness from vegetative bacilli, the presence of spores in contaminated body fluids, dressings, and patient linens may require additional sanitizing or disposal measures. Incineration or steam sterilization (121°C for 30 minutes) will destroy spores. Advice on infection control measures that address the need for incineration or steam sterilization will be made, specific to an anthrax event, on the CDC Anthrax Web site (www.cdc.gov/anthrax).

Anthrax PEP is not required for health care workers or other patient contacts as a result of exposure to the patient. However, health care workers and other patient contacts might require PEP depending on other exposure risks. A private room is unnecessary, and Standard Precautions should be used for patient care, including patient transport.

MANAGEMENT OF PATIENTS WITH SUSPECTED AND CONFIRMED ANTHRAX

General Diagnostic and Treatment Considerations

Diagnosis

The initial evaluation of patients with any form of anthrax after a biological weapon exposure should be based on careful clinical examination and laboratory testing of sites of presumed infection. A Gram stain is likely to be the only rapid method for identifying *B anthracis* readily available in a clinical laboratory. The organism is characterized as a gram-positive bacillus that forms long chains of vegetative cells with a "jointed bamboo-rod" appearance in culture or short chains of 2 to 4 cells in direct clinical samples. The organism can be isolated from specimen cultures of blood; skin; respiratory secretions; vesicular, pleural, or ascetic fluid; or stool, as well as from CSF (Appendix 7). Given the high rates of meningoencephalitis in children who have signs and symptoms of systemic anthrax, lumbar puncture should be performed as resources permit, unless clinically contraindicated (such as suspected increased intracranial pressure).[27] Gram-positive bacilli with typical morphology found on unspun peripheral blood smears or in vesicular fluid or CSF are highly suggestive of anthrax.[15]

Although most clinical laboratories can provide preliminary culture results, they may not be able to perform sophisticated confirmatory tests, such as polymerase chain reaction (PCR) assay on patient specimens (blood, serum, lesion swabs), lethal factor detection analysis, and immunohistochemical staining of tissue, which are available through local or state public health laboratories or the CDC. Public health laboratories in the Laboratory Response Network (www.bt.cdc.gov/lrn/), a national network of local, state, and federal public health laboratories, can identify *B anthracis* by standard culture methodology in addition to other methods and can perform antibacterial drug susceptibility testing. For current information on the availability and types of traditional confirmatory tests, as well as newly developed molecular tests, that can be performed by public health authorities,

particularly during a biological weapon exposure, visit the CDC Anthrax Web site. (www.cdc.gov/anthrax/labs/labresearch.html).

Treatment

The production of toxins and the frequent occurrence of meningoencephalitis, as well as the presence of latent spores, must be taken into account when selecting antimicrobial agents and the duration of treatment of anthrax. Most of the data used to make these recommendations are based on historical information collected before availability of many of the antimicrobial agents discussed, in vitro studies, and limited nonhuman primate studies. Treatment data that are available almost uniformly come from adult patients. For many of the antimicrobial agents discussed herein, limited pharmacokinetic data are available to make dosing recommendations for anthrax, particularly for young infants and neonates. However, systemic anthrax can be a rapidly lethal disease in humans, so in the absence of compelling, well-documented adverse safety data in children, the most effective antimicrobial agents used in the adult population also should be made available for use in children. Children may require larger doses per kilogram of body weight and more frequent dosing for certain antimicrobial agents to achieve a therapeutic exposure equivalent to that documented to be effective for adults. The recommended doses must be sufficient to ensure a therapeutic antimicrobial exposure required for life-threatening infection (ie, doses that achieve adequate exposure in more than 98% of all children treated). Antimicrobial dosing regimens, both empirical and definitive, for all anthrax clinical presentations in children and neonates are provided in Appendix 2 (cutaneous anthrax without systemic illness), Appendix 3 (systemic anthrax to include inhalation and gastrointestinal infection, without meningitis), Appendix 4 (systemic anthrax to include inhalation and gastrointestinal infection, with meningitis), and Appendix 6 (dosing in preterm and term neonates 32 to 44 weeks' postmenstrual age).

After an exposure to *B anthracis* aerosolized spores, patients treated for any form of anthrax are at risk for late-occurring inhalation anthrax from residual ungerminated spores that may remain in the lungs for several weeks or months after an inhalation event. Depending on the patient's immune status and age, as well as the type of antimicrobial agent used, some patients recovering from severe systemic disease will develop an immune response that would provide protection against germination of any remaining spores. However, if antimicrobial therapy is initiated early in the illness, the immune response may be blunted,[38] thus requiring continuation of antimicrobial therapy over several weeks to clear organisms as they emerge from the spore form. There is evidence that symptomatic nonhuman primates that are bacteremic with *B anthracis* and treated with antimicrobial agents for at least 10 days develop an immune response and do not develop clinical disease attributable to retained spores that germinate after discontinuation of antimicrobial therapy.[48] However, no data exist in either adults or children to identify which infected people may develop protective immunity and at what time after clinical infection. No commercially available assay currently exists that can determine adequate immunity to anthrax.

Children with active infection, either cutaneous or systemic, whose original exposure source was aerosolized spores, should complete initial antimicrobial treatment, then transition to oral PEP to prevent relapse from surviving *B anthracis* spores within the lung that may subsequently germinate. The duration of antimicrobial therapy to prevent relapse is not well established. On the basis of incubation times of up to 43 days in humans and 58 days in animals exposed to aerosol challenge, a full 60-day course of an oral antimicrobial agent is recommended to complete treatment and prophylaxis.[8,38,49] Therefore, once the treatment course for the active infection is completed, patients should continue with antimicrobial prophylaxis so that they receive antimicrobial treatment for a total of 60 days.

Naturally occurring *B anthracis* is very likely to be susceptible to penicillin; although genetic material that codes for the presence of a penicillinase is present, regulation of these genes may be deficient.[50,51] Most strains are resistant to cephalosporins.[52] Further, the naturally occurring strains that are penicillin-resistant remain susceptible to amoxicillin/clavulanate. Given the relative safety and tolerability of the penicillin-class agents in children, most pediatric experts prefer these antimicrobial agents for treatment and antimicrobial prophylaxis if pathogens are documented to be susceptible. Other antimicrobial classes, such as fluoroquinolones or tetracyclines, are likely to exhibit poorer tolerance and increased toxicity, especially during prolonged treatment.

A theoretical concern exists that the use of penicillins as single antimicrobial agents could induce β-lactam resistance, especially if the number of organisms present is high, as can occur with systemic disease. In addition, infection with multidrug-resistant *B anthracis*, including bioengineered strains, is a concern.[53] Therefore, public health authorities will monitor for the development of penicillin resistance on an ongoing basis even if strains are initially susceptible.

Given the potential severity of the disease, the fluoroquinolone class of

antimicrobial agents and doxycycline (a tetracycline) are acceptable alternatives if amoxicillin and penicillin are not options, either because *B anthracis* susceptibility is unknown to either of these drugs or because there are other contraindications for their use in treatment. Levofloxacin and ciprofloxacin have been prospectively studied in children, with adequate pharmacokinetic data for levofloxacin use in children older than 6 months and for ciprofloxacin use in children older than 1 year, but less robust data are available for younger infants or neonates. Studies have shown a small but statistically significant increase in arthralgia in children but no documented increase in long-term bone or joint toxicity.[54] Tetracycline-class antimicrobial agents, in general, are not recommended for first-line therapy of acute bacterial infection in children younger than 8 years (with the notable exceptions of rickettsial, *Ehrlichia*, and *Anaplasma* infections) because of deposition of these compounds in teeth and bones. Although prospective, controlled data are not available, limited retrospective data suggest that children who receive up to 5 standard treatment courses of doxycycline are not likely to have clinically detectable tooth staining.[40,55]

Early diagnosis and initiation of combination antimicrobial therapy is considered essential for treatment of systemic *B anthracis* infection. Although it is always better to definitively identify the pathogen before treatment is administered, the rapid progression of anthrax may not support this approach. Samples for laboratory testing should be collected before treatment. The AAP and CDC Pediatric Anthrax Guidance Writing Group believe that severe systemic infection survival can improve with combination therapy on the basis of theoretical considerations of different mechanisms of antimicrobial activity, drug penetration characteristics, synergy with combinations, increased likelihood of effective drug activity in case of single or multidrug resistance, and decreased likelihood of emergence of resistance. Combinations recommended include both a bactericidal antimicrobial agent and a bacterial protein synthesis inhibitor (see the section "Treatment: Considerations for Combination Antimicrobial Therapy for Anthrax" later in this article). Compared with bacteriostatic agents, bactericidal antimicrobial agents are important for killing vegetative forms emerging from spores and are especially effective, in general, in clinical outcomes when used to treat bacterial meningitis.

The high morbidity and mortality observed with anthrax is attributable primarily to 2 exotoxins (lethal toxin and edema toxin) produced by *B anthracis*. Protein synthesis inhibitors, such as clindamycin, may decrease toxin production, as suggested with group A streptococcal toxic shock syndrome,[56–58] which may provide an added benefit; however, this potential benefit has not been demonstrated in animal infection models or human cases of anthrax. Additional benefits may be provided by immunologic agents (such as immunoglobulin or antitoxin) that bind to the protective antigen of *B anthracis* to prevent attachment to host cells, neutralize toxin activity, or promote clearance of toxin complexes.

For children with overwhelming, severe disease who are not likely to survive, pediatric palliative care teams, if available, may be of value to consult with treating physicians or to provide support to the family and child.

Cutaneous Anthrax

Diagnosis

If cutaneous anthrax is suspected, swabs of vesicular fluid, eschar tissue, or punch biopsy can be used to establish the diagnosis. Specimens should be submitted for Gram stain and culture. PCR assay and immunohistochemical staining of biopsies may be available through state or local public health laboratories or the CDC. The CDC provides a complete list of recommended specimens, including those listed previously and additionally blood for culture (or lethal toxin testing or antiprotective antigen serology) and swabs from beneath the eschar (www.cdc.gov/anthrax/labs/recommended_specimen.html).

Treatment

Localized or uncomplicated cutaneous anthrax is a less-severe disease. Historically, naturally acquired infection has been successfully treated in 7 to 10 days with a single oral antimicrobial agent, such as either amoxicillin for susceptible strains or ciprofloxacin, before susceptibility testing or for penicillin-resistant strains (Appendix 2). Many patients with uncomplicated cutaneous anthrax can be treated as outpatients. However, hospitalization is necessary for patients with symptoms or signs of systemic involvement, particularly those with lesions of the head or neck that may rapidly progress to include edema that can compromise the airway.

The use of surgical procedures, such as incision, in the treatment of cutaneous anthrax is usually not required, because the lesions do not contain pus. Use of surgical procedures may be associated with poor outcomes.[59,60] Treatment should focus instead on early initiation of antimicrobial agents and on local wound care. Exceptions to the general surgical contraindication include interventions to relieve airway obstruction or compartment syndrome, particularly for large or circumferential lesions of the extremities.[61,62]

As a child is started on therapy, cutaneous anthrax can evolve into disease

with systemic involvement, requiring the use of intravenous combination therapy (Appendices 3 and 4). Children who present with cutaneous anthrax during a biological weapon–related event also may have inhaled spores; after treatment, they should receive additional antimicrobial therapy to complete a total of 60 days of therapy.

Inhalation Anthrax

Diagnosis

For suspected inhalation anthrax, a chest radiograph should be performed to assess for a widened mediastinum, pleural effusions, and/or pulmonary infiltrates. In a review of 82 cases of inhalation anthrax, abnormal radiologic findings were reported in all 26 patients for whom chest radiographs were obtained; findings included pleural effusion in 69% of these patients and widened mediastinum in 54%.[25] Radiologic findings in children have been reported in only 2 children with inhalation anthrax, but typical findings, such as pleural effusions and widened mediastinum, were reported in both.[27] If there is strong suspicion of anthrax on the basis of exposure history and a questionable chest radiograph, a computed tomography (CT) scan of the chest may provide additional information to support the presumptive diagnosis.[63] However, during a biological weapon event, access to diagnostic radiology services may become difficult; therefore, assessing risk of anthrax exposure or clinical signs may be used initially to determine suspicion of inhalation anthrax and guide management accordingly.

Extrapolating from adult data, inhalation anthrax can have a biphasic presentation with initial improvement, followed by precipitous hemodynamic deterioration.[7,24] Because of this potential for sudden decompensation, patients who are hospitalized and treated for suspected anthrax should have careful hemodynamic monitoring, including continuous pulse oximetry and continuous cardiorespiratory monitoring for at least 24 to 48 hours, even if initial findings are reassuring.

Treatment: General Supportive Care and Ventilator Management

A review of inhalation anthrax cases from 1990 through 2005 showed a significant association between pleural fluid drainage and survival.[25] High concentrations of lethal toxin have been detected in pleural fluid and ascites; therefore, prompt and continuous drainage by chest and/or peritoneal tube is critical. Ultrasonography of the chest may be a useful way to detect and monitor pleural fluid. Thoracotomy may be required for loculated or gelatinous effusions.

Patients with anthrax may require mechanical ventilation because of respiratory distress or imminent shock. In addition, some patients with anthrax may require respiratory support for severe edema that may occur with cutaneous lesions involving the head, neck, oropharynx, or thorax. Intubation or tracheostomy may be required to maintain the airway. Although there are significant differences between the pathophysiology of anthrax and respiratory distress syndrome, standard principles of ventilator management apply in both situations. Standard pediatric sepsis guidelines for fluids, vasopressors, blood products, and hemodynamic monitoring should also be followed (Appendix 7).

Treatment: Considerations for Combination Antimicrobial Therapy for Anthrax

The antimicrobial treatment of inhalation anthrax should follow the guidance for severe, systemic anthrax, both for those children for whom a lumbar puncture can be performed and meningitis is unlikely (Appendix 3) and those in whom meningitis cannot be ruled out (Appendix 4). Patients presenting with signs or symptoms suggestive of pneumonia or systemic anthrax should be started on combination antimicrobial therapy as soon as possible while awaiting results of confirmatory tests. Before recognition of a *B anthracis* biological weapon event, the differential diagnosis for a severe systemic bacterial infection in a child usually warranted broad-spectrum antimicrobial coverage; however, cephalosporin therapy, often used empirically for community-acquired infections, is not active against *B anthracis*. Once the diagnosis of anthrax is confirmed, or in the midst of a biological weapon exposure, individuals presenting with illness consistent with anthrax would warrant therapy targeted more specifically to *B anthracis*. Given the unique drug disposition in preterm and term neonates during the first month of life, specific doses for this age group have been provided in Appendix 6.

Antimicrobial agents must penetrate into appropriate tissue sites, particularly into the CNS for children with systemic disease, especially if meningitis cannot be excluded. Meningitis and hemorrhagic parenchymal brain infection resulting from hematogenous spread must be considered in all children presenting with severe systemic anthrax.

For therapy of severe systemic anthrax in which anthrax meningitis is a consideration, treatment regimens for meningitis that include 2 bactericidal antimicrobial agents and 1 protein-synthesis inhibitor should be followed (Appendix 4). Before susceptibility testing, and for penicillin-resistant strains, ciprofloxacin remains the preferred bactericidal antimicrobial agent, in addition to meropenem. If those antimicrobial agents are not available, levofloxacin or imipenem should be

used. For susceptible strains, penicillin G (intravenous) or ampicillin are recommended, in addition to ciprofloxacin, as first-line antimicrobial agents, avoiding the unnecessary broad-spectrum activity of meropenem. Linezolid is the preferred protein-synthesis inhibitor for CNS infections on the basis of tissue penetration characteristics (Appendix 4).

However, if meningitis has been ruled out by CSF examination and/or imaging, treatment may be reduced to a combination of 2, rather than 3, antimicrobial agents with activity against *B anthracis*: 1 with bactericidal activity and 1 protein synthesis inhibitor (Appendix 3). If it is not possible to examine the CSF or perform imaging studies, but the clinical examination 2 to 3 days into therapy suggests that meningitis was not present by a normal neurologic examination, initial triple antimicrobial therapy can be stepped down to dual antimicrobial therapy (Appendix 3).

When meningitis is not a concern, clindamycin should be used as a protein synthesis inhibitor, rather than linezolid, primarily on the basis of concerns for safety. Doxycycline is an alternative protein synthesis inhibitor choice for treatment in all pediatric age groups for non-CNS anthrax. Rifampin is an additional option with the potential to provide synergistic antibacterial activity when used in combination with other agents if the preferred antimicrobial agents are not available or not tolerated.

After completing initial combination therapy for severe disease, all children with systemic illness, excluding meningitis, may switch to oral follow-up therapy (assuming that children can tolerate oral therapy and families are adherent to providing therapy) to complete a 14-day or longer treatment course (as dictated by clinical improvement), followed by prophylaxis, totaling 60 days (Appendix 5). Although data on the efficacy of oral follow-up therapy after short-course parenteral therapy of systemic anthrax are lacking, the recommended antimicrobial agents all have good oral absorption characteristics and have been used as oral therapy of other infections in children. Children who appear to be well, with no ongoing signs or symptoms of active infection, may be transitioned from parenteral therapy to monotherapy for the remainder of their 14 days of treatment. Those for whom there is some degree of concern about persistent deep infection or who are slower to recover may be transitioned to oral therapy that includes both a bactericidal antimicrobial agent and a protein synthesis inhibitor for the remainder of their 14 days of treatment (Appendix 5). Ciprofloxacin is the preferred antimicrobial agent for penicillin-resistant strains. Doxycycline, clindamycin, and levofloxacin should all provide adequate single-drug therapy. For penicillin-susceptible strains, amoxicillin is preferred therapy, although treating physicians should be aware of theoretical concerns for emergence of penicillin-resistance during monotherapy and be alert to the possibility of clinical deterioration as a result of resistance. In these situations, cultures should be obtained, if possible, to determine whether the organism has become resistant to amoxicillin, and the class of prescribed antimicrobial agent should be changed to those active against penicillin-resistant strains, as noted previously.

Gastrointestinal Anthrax

Diagnosis

When gastrointestinal anthrax is suspected, blood cultures should be performed before starting antimicrobial therapy, and culture and PCR of ascites fluid, stool or rectal swabs, or oropharyngeal lesions, if present, are recommended. Please see www.cdc.gov/anthrax/labs/recommended_specimen.html for all recommended diagnostic specimens for gastrointestinal anthrax.

Treatment

Antimicrobial therapy should follow the same guidance as that for systemic inhalation anthrax: 3 antimicrobial agents for children with possible or documented associated meningitis (Appendix 4) and 2 for those in whom meningitis can be excluded (Appendix 3).

Anthrax Meningoencephalitis

Diagnosis

Evaluation of CSF in the stable patient can provide laboratory evidence of meningoencephalitis as well as microbiologic confirmation of the etiology. For children too unstable to undergo lumbar puncture, CNS imaging by CT with contrast or magnetic resonance imaging with contrast should be able to document both meningeal enhancement characteristics of infection in addition to identification of hemorrhagic parenchymal lesions characteristic of anthrax meningoencephalitis. If imaging is not possible in the child with altered mental status or seizure activity, then clinical examination findings suggestive of meningitis (such as nuchal rigidity) should be presumed to be caused by meningoencephalitis and treated accordingly. If meningitis cannot be ruled out by laboratory, imaging, or physical examination, the child should be treated as though meningoencephalitis is present.

Treatment

Patients with confirmed or presumptive anthrax meningoencephalitis should be treated with 3 intravenous antimicrobial agents as noted previously in "Treatment: Considerations for Combination Antimicrobial Therapy for

Anthrax." All antimicrobial agents used should have good CNS penetration, at least 2 should have bactericidal activity, and at least 1 should inhibit protein synthesis (Appendix 4). It is assumed that during a biological weapon event, limited availability of some antimicrobial agents will exist; therefore, many alternative antimicrobial agents also have been listed, some lacking documented evidence of efficacy in CNS infections.

Intravenous ciprofloxacin is recommended as the primary bactericidal antimicrobial agent for meningoencephalitis on the basis of efficacy in nonhuman primate infection models and use in anthrax cases since 2001, unless ciprofloxacin use is contraindicated. Levofloxacin and moxifloxacin are considered equivalent alternatives to ciprofloxacin, although less experience is available with these antimicrobial agents in children. These fluoroquinolone antimicrobial agents have been shown to have adequate CNS penetration.[64,65] No reports exist to document naturally occurring fluoroquinolone-resistant strains. However, in vitro resistance can be induced, which has implications for bioengineered strains.

An antimicrobial agent from the β-lactam class with activity against *B anthracis* is recommended in combination with fluoroquinolones to treat systemic anthrax cases in which meningitis may be present. If antimicrobial susceptibilities are unknown or if the *B anthracis* strain is resistant to penicillin, meropenem is the preferred antimicrobial agent, because carbapenems are stable to the β-lactamases of *B anthracis,* and meropenem is approved by the FDA for use in pediatric meningitis; however, meningoencephalitis caused by *B anthracis* has not been prospectively studied. If meropenem is not available, imipenem/cilastatin is considered equivalent in antibacterial activity. However, imipenem/cilastatin is associated with an increased risk of seizures when used in the treatment of meningitis, presumably by lowering the seizure threshold,[66,67] and should be used with caution in patients with suspected meningitis. Pharmacokinetic data are available for use in children. Limited data are available for doripenem pharmacokinetics or clinical efficacy in children, but if meropenem and imipenem are not available, data from experimental animal models of meningitis suggest similar efficacy.[68] If the isolated *B anthracis* strain is susceptible to penicillin, penicillin G or ampicillin are preferred antimicrobial agents given their long history of use, safety profile, and narrower antimicrobial spectrum. However, as noted earlier, most strains contain a β-lactamase that is usually not associated with clinically relevant resistance but represents a potential for development of resistance to penicillin or ampicillin while on therapy. Emergence of resistance to penicillin would require treatment with meropenem or another carbapenem (Appendix 4).

Vancomycin has demonstrated in vitro activity against naturally occurring strains but has limited human clinical treatment data in anthrax. Vancomycin is bactericidal, achieves adequate CNS concentrations, has been used extensively in pediatric meningitis, and may be used as an alternative antimicrobial agent if β-lactam antimicrobial agents are not available (Appendix 4).[69]

At least 1 antimicrobial agent that inhibits protein synthesis is recommended for inclusion in the antimicrobial regimen to reduce production of exotoxins. Linezolid is recommended as the first-line protein synthesis inhibitor. It is recommended over clindamycin when meningitis is suspected or cannot be excluded, as it is likely to provide better CNS penetrance, although prospective, controlled data on the treatment of CNS infections with either antimicrobial agent do not exist.[70–73] Linezolid toxicity must be taken into consideration. Peripheral and optic neuropathy have been reported in both adults and children receiving prolonged courses of linezolid.[74–76] Myelosuppression is a potential adverse effect more commonly seen when linezolid is used for more than 14 days, but it is reversible and can be managed with marrow-stimulating agents.[77] Linezolid should be used with caution in patients with preexisting myelosuppression. If patients have contraindications to linezolid use or it is not available, clindamycin is an acceptable alternative. Rifampin, although not a protein synthesis inhibitor, has been widely used for antibacterial synergy with a primary drug and could be used in this capacity if neither linezolid nor clindamycin are available.

Chloramphenicol historically has been used to successfully treat anthrax[78]; it is a protein synthesis inhibitor with excellent CNS penetration. The intravenous form is not widely available in the United States, and the oral formulation is no longer available. Intravenous chloramphenicol would be an acceptable alternative if linezolid, clindamycin, and rifampin are not available for use. Doxycycline should not be used as first-line therapy if meningitis is suspected because of variable CNS penetration compared with fluoroquinolones and β-lactams, but it may be effective if other preferred antimicrobial agents are not available or are not tolerated.

Duration of initial intravenous combination therapy is determined by meningitis risk and clinical response to treatment. With mortality rates for meningoencephalitis approaching 100%, no prospective data exist on which to base recommendations for an effective

treatment duration.[69] For children with meningoencephalitis or in children for whom meningitis cannot be ruled out, combination therapy is recommended for a minimum of 2 weeks, depending on the severity of disease and presence of brain parenchymal hemorrhagic lesions. Intravenous therapy should continue until the patient is clinically stable, with all clinical signs and symptoms and laboratory and imaging data documenting resolution of inflammation, even if required for 3 to 6 weeks. As with other forms of anthrax secondary to a biological weapon exposure, ongoing oral PEP therapy should continue until antimicrobial therapy has been administered for a total of 60 days.

Use of Corticosteroids

There are limited data to guide use of corticosteroids in anthrax. Clinicians should maintain a high index of suspicion for adrenal failure and perform adrenal hormone replacement therapy with dosing appropriate for stressed patients if adrenal failure is suspected on the basis of history or pressor-refractory hypotension. Although there are no randomized trials of corticosteroid use in human anthrax, adjunctive corticosteroids in anthrax may be considered for management of severe edema or meningoencephalitis. In a systematic review of anthrax meningitis by Sejvar et al,[69] survival was slightly increased among patients with meningoencephalitis who received steroids compared with those who did not. Several small observational studies of anthrax involving the head and neck appeared to favor their use in this setting. Although corticosteroid doses have not been studied prospectively in anthrax, doses previously used in pediatric bacterial meningitis (dexamethasone 0.6 mg/kg per day, in divided doses every 6 hours for 4 days) should be appropriate.[79]

Antitoxins

Human data from the pre–antimicrobial era suggest that nonhuman anthrax antiserum reduced the mortality rate for cutaneous anthrax and that antiserum might be beneficial in inhalation anthrax. Two antitoxin products are in the Strategic National Stockpile: raxibacumab (a humanized monoclonal antibody) and Anthrax Immune Globulin (AIG [a polyclonal human immunoglobulin]). Raxibacumab is approved by the FDA for use in adults and children for the treatment or prevention of anthrax. On the basis of animal studies, pediatric population pharmacokinetic modeling was performed by the manufacturer, and proposed weight-based doses for children are provided on the package label (www.accessdata.fda.gov/drugsatfda_docs/label/2012/125349s000lbl.pdf). AIG is not currently approved by the FDA and will need to be administered under an Investigational New Drug application or Emergency Use Authorization during a mass exposure event.

Suggested doses of antitoxin preparations for children that reflect current knowledge of the product will accompany raxibacumab and AIG when these products are shipped to points of dispensing located in proximity to the anthrax exposure site. Both products inhibit *B anthracis* protective antigen binding to the anthrax toxin receptors on human cells and subsequent translocation of the 2 primary toxins into cells.[80]

In animal studies, both raxibacumab and AIG have been shown to be effective for treatment of inhalation anthrax when administered without antimicrobial agents.[1] Both have been studied in animals as adjunctive therapy with antimicrobial agents when treatment is delayed and appear to provide additional survival benefit. Both products have been studied in adult volunteers for pharmacokinetics and safety. AIG has been administered to 3 adults with inhalation anthrax, 1 with gastrointestinal anthrax, and 15 with injection anthrax. Raxibacumab has been used in animal models of inhalation anthrax but has not yet been used to treat human disease. The products appear to be safe and well-tolerated. Headache, sore throat, and nausea were the most commonly reported adverse effects with AIG, and rash occurred in a small number of recipients of raxibacumab. Pretreatment with diphenhydramine is recommended for patients who will be receiving raxibacumab (www.accessdata.fda.gov/drugsatfda_docs/label/2012/125349s000lbl.pdf).

The AAP and CDC recommend the use of antitoxin in addition to systemic antimicrobial agents for all patients with highly suspect (eg, child exposed during a bioterror event, with systemic signs and symptoms compatible with inhalation, gastrointestinal, or meningeal anthrax) or confirmed systemic anthrax. Antimicrobial agents alone can be effective if initiated early in the course of disease. However, given the high mortality rate of systemic anthrax and the apparently low risk of antitoxins, the potential benefits appear to greatly outweigh the risks. Data on the optimal timing are lacking, but most experts favor early administration. During a biological weapon event in which the number of patients with anthrax exceeds available antitoxin and ill patients may overwhelm the health care system, antitoxin should be reserved for patients most likely to benefit from it, including (1) noncritically ill, nonmoribund children with confirmed systemic anthrax in relatively stable clinical condition, and (2) critically ill nonmoribund children who may have progressive disease with dysfunction in 1 or more organ systems. In such an event, antitoxin should be added to combination antimicrobial therapy. Insufficient data are

available to recommend one antitoxin product routinely over the other. During an event, recommendations on dosing will be provided with the antitoxin products.

CONSIDERATIONS FOR BREASTFEEDING INFANTS

Unless breastfeeding mothers have untreated cutaneous lesions on their breasts, mothers should initiate and continue breastfeeding, if able, after exposure to *B anthracis* spores when they are undergoing treatment of disease and when they are receiving vaccine and antimicrobial agents for PEP. Cutaneous lesions are not considered contagious after 24 to 48 hours of effective antimicrobial therapy. Given the various considerations of the potential lethality of anthrax in both the infant and mother, antimicrobial efficacy, infant safety, and the well-known benefits of breastfeeding, the selection of antimicrobial agents and PEP for breastfeeding mothers should not be modified from those for the general adult population. More specific recommendations for compatibility of certain antimicrobial agents and breastfeeding can be found in Appendix 8.

The decision with respect to PEP therapy for breastfeeding mothers should be independent of that for the infant,[81] including the long-term use of fluoroquinolones or doxycycline. The safety of 60 days of infant exposure to maternal antimicrobial agents through human milk is largely unknown but should not in any way affect the need to appropriately treat the mother.[82] Breastfeeding infants should receive prophylaxis as recommended, regardless of the prophylaxis status of the mother. Additional guidance for pregnant and lactating mothers may be found in a recent review from the CDC by Meaney-Delman and colleagues.[83]

CONCLUSIONS

The use of *B anthracis* as a biological weapon is considered by the US government to be a potential national security threat. Therefore, the clinical and public health communities must be prepared to dispense prophylactic antimicrobial agents, antitoxin agents, and vaccines[115] to prevent disease and treat children who develop infection. To optimally manage children during an anthrax bioterror event, ready access to information from public health officials by health care providers and information communicated back to public health officials from health care providers is critical. Clear recommendations and consistent messaging to the public from both public health officials and health care providers will be extremely important.

Recommendations and key considerations (main points) in a mass *B anthracis* exposure scenario include the following:

Management of Exposed but Asymptomatic Children

1. Within 48 hours of exposure to *B anthracis* spores, public health authorities plan to provide a 10-day course of antimicrobial prophylaxis to the local population likely to have been exposed, contingent on available resources.
2. Within 10 days of exposure, public health authorities plan to further define those who have had a clear and significant exposure and will require an additional 50 days of antimicrobial PEP as well as the 3-dose AVA series under an Investigational New Drug application. For children younger than 6 weeks (who are not candidates for AVA), antimicrobial prophylaxis should begin immediately, but the vaccine series should be delayed until the child reaches 6 weeks of age.
3. A local adverse event to a prior dose of AVA is not a contraindication to receiving additional doses, although the subsequent dose should be administered at an alternate site and closely monitored.
4. Although not strictly contraindicated, AVA should not be coadministered with routine childhood vaccinations during an anthrax event.

Management of Disease

5. Anthrax may occur in different clinical forms, any of which may progress to systemic disease. Treatment will vary by clinical manifestation.
6. Cutaneous anthrax without systemic involvement that occurs in the context of an anthrax bioterror event should be treated with a single oral antimicrobial agent.
7. Inhalation, gastrointestinal, or other systemic disease without meningoencephalitis should be treated with at least 2 intravenous antimicrobial agents: a bactericidal agent and a protein synthesis inhibitor.
8. Systemic disease with possible or confirmed meningoencephalitis should be treated with 3 intravenous antimicrobial agents with adequate CNS penetration, including 2 bactericidal agents and a protein synthesis inhibitor.
9. Antitoxin (either AIG or raxibacumab) is recommended for children with anthrax systemic disease.
10. Corticosteroid adjunctive therapy may be considered in the management of children with severe cerebral edema or meningoencephalitis.
11. Once therapy has been completed for any form of systemic or cutaneous anthrax infection in children involved in an aerosol *B anthracis* dispersal event, appropriate oral antimicrobial agents

should be provided to complete a full 60 days of therapy.

12. Breastfeeding should continue for infants of mothers who require antimicrobial treatment or prophylaxis or anthrax vaccine.

ACKNOWLEDGMENTS

The authors acknowledge the members of the AAP and CDC Pediatric Anthrax Guidance Writing Group (www.aap.org/disasters/anthrax/mtg) for their assistance with writing and discussing recommendations in the article.

REFERENCES

1. MacIntyre CR, Seccull A, Lane JM, Plant A. Development of a risk-priority score for category A bioterrorism agents as an aid for public health policy. *Mil Med*. 2006;171(7):589–594
2. Inglesby TV, O'Toole T, Henderson DA, et al; Working Group on Civilian Biodefense. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA*. 2002;287(17):2236–2252
3. Franz DR. Preparedness for an anthrax attack. *Mol Aspects Med*. 2009;30(6):503–510
4. Booth MG, Hood J, Brooks TJ, Hart A; Health Protection Scotland Anthrax Clinical Network. Anthrax infection in drug users. *Lancet*. 2010;375(9723):1345–1346
5. Christopher GW, Cieslak TJ, Pavlin JA, Eitzen EM Jr. Biological warfare. A historical perspective. *JAMA*. 1997;278(5):412–417
6. Cieslak TJ, Eitzen EM Jr. Clinical and epidemiologic principles of anthrax. *Emerg Infect Dis*. 1999;5(4):552–555
7. Swartz MN. Recognition and management of anthrax—an update. *N Engl J Med*. 2001;345(22):1621–1626
8. Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlovsk anthrax outbreak of 1979. *Science*. 1994;266(5188):1202–1208
9. Jernigan DB, Raghunathan PL, Bell BP, et al; National Anthrax Epidemiologic Investigation Team. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. *Emerg Infect Dis*. 2002;8(10):1019–1028
10. Roche KJ, Chang MW, Lazarus H. Images in clinical medicine. Cutaneous anthrax infection. *N Engl J Med*. 2001;345(22):1611
11. Hendricks KA, Wright ME, Shadomy SV, et al; Workgroup on Anthrax Clinical Guidelines. Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. *Emerg Infect Dis*. 2014;20(2). doi:doi:10.3201/eid2002.130687
12. Centers for Disease Control and Prevention. Children and anthrax: a fact sheet for clinicians. Available at: www.bt.cdc.gov/agent/anthrax/pediatricfactsheet.asp. Accessed August 21, 2013
13. Steele RW, Thomas MP, Bégué RE. Compliance issues related to the selection of antibiotic suspensions for children. *Pediatr Infect Dis J*. 2001;20(1):1–5
14. American Academy of Pediatrics. *Pediatric Preparedness Resource Kit*. Elk Grove Village, IL: American Academy of Pediatrics; 2013 [toolkit]
15. American Academy of Pediatrics. Anthrax. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012: 228–232
16. Doganay M, Metan G, Alp E. A review of cutaneous anthrax and its outcome. *J Infect Public Health*. 2010;3(3):98–105
17. Akbayram S, Doğan M, Akgün C, et al. Clinical findings in children with

cutaneous anthrax in eastern Turkey. *Pediatr Dermatol*. 2010;27(6):600–606

18. Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012
19. Doust JY, Sarkarzadeh A, Kavoossi K. Corticosteroid in treatment of malignant edema of chest wall and neck (anthrax). *Dis Chest*. 1968;53(6):773–774
20. Glomski IJ. *Bacillus anthracis* dissemination through hosts. In: Bergman N, ed. *Bacillus Anthracis and Anthrax*. Hoboken, NJ: Wiley-Blackwell; 2011:227–249
21. Ross JM. The pathogenesis of anthrax following the administration of spores by the respiratory route. *J Pathol Bacteriol*. 1957;73:485–494
22. Kuehnert MJ, Doyle TJ, Hill HA, et al. Clinical features that discriminate inhalational anthrax from other acute respiratory illnesses. *Clin Infect Dis*. 2003; 36(3):328–336
23. Klempner MS, Talbot EA, Lee SI, Zaki S, Ferraro MJ. Case records of the Massachusetts General Hospital. Case 25–2010. A 24-year-old woman with abdominal pain and shock. *N Engl J Med*. 2010;363(8):766–777
24. Albrink WS, Brooks SM, Biron RE, Kopel M. Human inhalation anthrax. A report of three fatal cases. *Am J Pathol*. 1960;36: 457–471
25. Holty JE, Bravata DM, Liu H, Olshen RA, McDonald KM, Owens DK. Systematic review: a century of inhalational anthrax cases from 1900 to 2005. *Ann Intern Med*. 2006;144(4):270–280
26. Pile JC, Malone JD, Eitzen EM, Friedlander AM. Anthrax as a potential biological warfare agent. *Arch Intern Med*. 1998;158 (5):429–434
27. Bravata DM, Holty JE, Wang E, et al. Inhalational, gastrointestinal, and cutaneous anthrax in children: a systematic review of cases: 1900 to 2005. *Arch Pediatr Adolesc Med*. 2007;161(9):896–905
28. Walsh JJ, Pesik N, Quinn CP, et al. A case of naturally acquired inhalation anthrax: clinical care and analyses of anti-protective antigen immunoglobulin G and lethal factor. *Clin Infect Dis*. 2007;44(7):968–971
29. Stroud C, Viswanathan K, Powell T, Bass RR, edsInstitute of Medicine, Committee on Prepositioned Medical Countermeasures for the Public. *Prepositioning Antibiotics for Anthrax*. Washington, DC: National Academies Press; 2012
30. Sirisanthana T, Brown AE. Anthrax of the gastrointestinal tract. *Emerg Infect Dis*. 2002;8(7):649–651
31. Beatty ME, Ashford DA, Griffin PM, Tauxe RV, Sobel J. Gastrointestinal anthrax: review of the literature. *Arch Intern Med*. 2003;163(20):2527–2531
32. Ndyabahinduka DG, Chu IH, Abdou AH, Gaifuba JK. An outbreak of human gastrointestinal anthrax. *Ann Ist Super Sanita*. 1984;20(2–3): 205–208
33. Abramova FA, Grinberg LM, Yampolskaya OV, Walker DH. Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979. *Proc Natl Acad Sci U S A*. 1993;90(6):2291–2294
34. Centers for Disease Control and Prevention. Anthrax (*Bacillus anthracis*) 2010 case definition. Available at: wwwn.cdc.gov/nndss/script/casedef.aspx?CondYrID=609&DatePub=1/1/2010%2012:00:00%20AM. Accessed August 21, 2013
35. Henderson DW, Peacock S, Belton FC. Observations on the prophylaxis of experimental pulmonary anthrax in the monkey. *J Hyg (Lond)*. 1956;54(1):28–36
36. Manchee RJ, Broster MG, Stagg AJ, Hibbs SE. Formaldehyde solution effectively inactivates spores of *Bacillus anthracis* on the Scottish island of Gruinard. *Appl Environ Microbiol*. 1994;60(11):4167–4171
37. Wright JG, Quinn CP, Shadomy S, Messonnier N; Centers for Disease Control and Prevention (CDC). Use of anthrax vaccine in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep*. 2010;59 (RR-6):1–30
38. Friedlander AM, Welkos SL, Pitt ML, et al. Postexposure prophylaxis against experimental inhalation anthrax. *J Infect Dis*. 1993;167(5):1239–1243
39. US Food and Drug Administration. How to prepare doxycycline for children and adults who cannot swallow pills. Available at: www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM131001.pdf. Accessed August 21, 2013
40. Lochary ME, Lockhart PB, Williams WT Jr. Doxycycline and staining of permanent teeth. *Pediatr Infect Dis J*. 1998;17(5):429–431
41. Volovitz B, Shkap R, Amir J, Calderon S, Varsano I, Nussinovitch M. Absence of tooth staining with doxycycline treatment in young children. *Clin Pediatr (Phila)*. 2007;46(2):121–126
42. Meropol SB, Chan KA, Chen Z, et al. Adverse events associated with prolonged antibiotic use. *Pharmacoepidemiol Drug Saf*. 2008;17(5):523–532
43. Presidential Commission for the Study of Bioethical Issues. Safeguarding children. Pediatric medical countermeasure research. March 2013. Available at: http://bioethics.gov/node/833. Accessed August 21, 2013
44. Kournikakis B, Ho J, Duncan S. Anthrax letters: personal exposure, building contamination, and effectiveness of immediate mitigation measures. *J Occup Environ Hyg*. 2010;7(2):71–79
45. Yakupogullari Y, Koroglu M. Nosocomial spread of *Bacillus anthracis*. *J Hosp Infect*. 2007;66(4):401–402
46. Amidi S, Dutz W, Kohout E, Ronaghy A. Human anthrax in Iran. Report of 300 cases and review of literature. *Tropenmed Parasitol*. 1974;25(1):96–104
47. Davies JC. A major epidemic of anthrax in Zimbabwe. The experience at the Beatrice Road Infectious Diseases Hospital, Harare. *Cent Afr J Med*. 1985;31(9):176–180
48. Vietri NJ, Purcell BK, Tobery SA, et al. A short course of antibiotic treatment is effective in preventing death from experimental inhalational anthrax after discontinuing antibiotics. *J Infect Dis*. 2009; 199(3):336–341
49. 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). doi: 10.3201/eid2002.130687
50. Durmaz R, Doganay M, Sahin M, et al; Anthrax Study Group. Molecular epidemiology of the *Bacillus anthracis* isolates collected throughout Turkey from 1983 to 2011. *Eur J Clin Microbiol Infect Dis*. 2012; 31(10):2783–2790
51. Read TD, Peterson SN, Tourasse N, et al. The genome sequence of *Bacillus anthracis* Ames and comparison to closely related bacteria. *Nature*. 2003;423(6935):81–86
52. Turnbull PC, Sirianni NM, LeBron CI, et al. MICs of selected antibiotics for *Bacillus anthracis, Bacillus cereus, Bacillus thuringiensis*, and *Bacillus mycoides* from a range of clinical and environmental sources as determined by the Etest. *J Clin Microbiol*. 2004;42(8): 3626–3634
53. Brook I, Elliott TB, Pryor HI II, et al. In vitro resistance of *Bacillus anthracis* Sterne to doxycycline, macrolides and quinolones. *Int J Antimicrob Agents*. 2001;18(6):559–562
54. Bradley JS, Jackson MA; Committee on Infectious Diseases; American Academy of Pediatrics. The use of systemic and topical fluoroquinolones. *Pediatrics*. 2011;128 (4). Available at: www.pediatrics.org/cgi/content/full/128/4/e1034
55. Cale DF, McCarthy MW. Treatment of Rocky Mountain spotted fever in children. *Ann Pharmacother*. 1997;31(4):492–494

56. Stevens DL. Streptococcal toxic shock syndrome associated with necrotizing fasciitis. *Annu Rev Med*. 2000;51:271–288
57. Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. *N Engl J Med*. 1996;334(4):240–245
58. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive *Streptococcus pyogenes* infection. *Pediatr Infect Dis J*. 1999;18(12):1096–1100
59. Regan JC. The local and general serum treatment of cutaneous anthrax. *JAMA*. 1921;77:1944–1948
60. Pijper A. The treatment of human anthrax. *Lancet*. 1926;210:88–89
61. Binkley CE, Cinti S, Simeone DM, Colletti LM. *Bacillus anthracis* as an agent of bioterrorism: a review emphasizing surgical treatment. *Ann Surg*. 2002;236(1):9–16
62. Knox D, Murray G, Millar M, et al. Subcutaneous anthrax in three intravenous drug users: a new clinical diagnosis. *J Bone Joint Surg Br*. 2011;93(3):414–417
63. Wood BJ, DeFranco B, Ripple M, et al. Inhalational anthrax: radiologic and pathologic findings in two cases. *AJR Am J Roentgenol*. 2003;181(4):1071–1078
64. Thwaites GE, Bhavnani SM, Chau TT, et al. Randomized pharmacokinetic and pharmacodynamic comparison of fluoroquinolones for tuberculous meningitis. *Antimicrob Agents Chemother*. 2011;55(7):3244–3253
65. Ruslami R, Ganiem AR, Dian S, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. *Lancet Infect Dis*. 2013;13(1):27–35
66. Norrby SR. Neurotoxicity of carbapenem antibiotics: consequences for their use in bacterial meningitis. *J Antimicrob Chemother*. 2000;45(1):5–7
67. Wong VK, Wright HT, Jr, Ross LA, Mason WH, Inderlied CB, Kim KS. Imipenem/cilastatin treatment of bacterial meningitis in children. *Pediatr Infect Dis J*. 1991;10(2):122–125
68. Stucki A, Cottagnoud M, Acosta F, Egerman U, Laeuffer JM, Cottagnoud P. Efficacy of doripenem against *Escherichia coli* and *Klebsiella pneumoniae* in experimental meningitis. *J Antimicrob Chemother*. 2012;67(3):661–665
69. Sejvar JJ, Tenover FC, Stephens DS. Management of anthrax meningitis. *Lancet Infect Dis*. 2005;5(5):287–295
70. Yogev R, Damle B, Levy G, Nachman S. Pharmacokinetics and distribution of linezolid in cerebrospinal fluid in children and adolescents. *Pediatr Infect Dis J*. 2010;29(9):827–830
71. Villani P, Regazzi MB, Marubbi F, et al. Cerebrospinal fluid linezolid concentrations in postneurosurgical central nervous system infections. *Antimicrob Agents Chemother*. 2002;46(3):936–937
72. Shaikh ZH, Peloquin CA, Ericsson CD. Successful treatment of vancomycin-resistant *Enterococcus faecium* meningitis with linezolid: case report and literature review. *Scand J Infect Dis*. 2001;33(5):375–379
73. París MM, Shelton S, Trujillo M, Hickey SM, McCracken GH Jr. Clindamycin therapy of experimental meningitis caused by penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 1996;40(1):122–126
74. Lee E, Burger S, Shah J, et al. Linezolid-associated toxic optic neuropathy: a report of 2 cases. *Clin Infect Dis*. 2003;37(10):1389–1391
75. Bressler AM, Zimmer SM, Gilmore JL, Somani J. Peripheral neuropathy associated with prolonged use of linezolid. *Lancet Infect Dis*. 2004;4(8):528–531
76. Nambiar S, Rellosa N, Wassel RT, Borders-Hemphill V, Bradley JS. Linezolid-associated peripheral and optic neuropathy in children. *Pediatrics*. 2011;127(6). Available at: www.pediatrics.org/cgi/content/full/127/6/e1528
77. Gerson SL, Kaplan SL, Bruss JB, et al. Hematologic effects of linezolid: summary of clinical experience. *Antimicrob Agents Chemother*. 2002;46(8):2723–2726
78. Clarke PS. Chloramphenicol in treatment of cutaneous anthrax. *BMJ*. 1952;1(4749):86–87
79. Lebel MH, Freij BJ, Syrogiannopoulos GA, et al. Dexamethasone therapy for bacterial meningitis. Results of two double-blind, placebo-controlled trials. *N Engl J Med*. 1988;319(15):964–971
80. Moayeri M, Leppla SH. The roles of anthrax toxin in pathogenesis. *Curr Opin Microbiol*. 2004;7(1):19–24
81. Chung AM, Reed MD, Blumer JL. Antibiotics and breastfeeding: a critical review of the literature. *Paediatr Drugs*. 2002;4(12):817–837
82. Stern EJ, Uhde KB, Shadomy SV, Messonnier N. Conference report on public health and clinical guidelines for anthrax. *Emerg Infect Dis*. 2008;14(4). doi:doi:10.3201/eid1404.070969
83. Meaney-Delman D, Zotti ME, Creanga AA, et al; Workgroup on Anthrax in Pregnant and Postpartum Women. Special considerations for prophylaxis for and treatment of anthrax in pregnant and postpartum women. *Emerg Infect Dis*. 2014;20(2). doi:doi:10.3201/eid2002.130611
84. American Academy of Pediatrics. Antimicrobial therapy for newborns. In: Bradley JS, Nelson JD, eds. *2012–2013 Nelson's Pediatric Antimicrobial Therapy*. 19th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2013:17–35
85. Belet N, Haciömeroğlu P, Küçüködük S. Ciprofloxacin treatment in newborns with multi-drug-resistant nosocomial *Pseudomonas* infections. *Biol Neonate*. 2004;85(4):263–268
86. Kaguelidou F, Turner MA, Choonara I, Jacqz-Aigrain E. Ciprofloxacin use in neonates: a systematic review of the literature. *Pediatr Infect Dis J*. 2011;30(2):e29–e37
87. Aggarwal P, Dutta S, Garg SK, Narang A. Multiple dose pharmacokinetics of ciprofloxacin in preterm babies. *Indian Pediatr*. 2004;41(10):1001–1007
88. Anderson VR, Perry CM. Levofloxacin: a review of its use as a high-dose, short-course treatment for bacterial infection. *Drugs*. 2008;68(4):535–565
89. Hata A, Honda Y, Asada K, Sasaki Y, Kenri T, Hata D. *Mycoplasma hominis* meningitis in a neonate: case report and review. *J Infect*. 2008;57(4):338–343
90. Watt KM, Massaro MM, Smith B, Cohen-Wolkowiez M, Benjamin DK, Jr, Laughon MM. Pharmacokinetics of moxifloxacin in an infant with *Mycoplasma hominis* meningitis. *Pediatr Infect Dis J*. 2012;31(2):197–199
91. Bradley JS, Sauberan JB, Ambrose PG, Bhavnani SM, Rasmussen MR, Capparelli EV. Meropenem pharmacokinetics, pharmacodynamics, and Monte Carlo simulation in the neonate. *Pediatr Infect Dis J*. 2008;27(9):794–799
92. Smith PB, Cohen-Wolkowiez M, Castro LM, et al; Meropenem Study Team. Population pharmacokinetics of meropenem in plasma and cerebrospinal fluid of infants with suspected or complicated intra-abdominal infections. *Pediatr Infect Dis J*. 2011;30(10):844–849
93. van den Anker JN, Pokorna P, Kinzig-Schippers M, et al. Meropenem pharmacokinetics in the newborn. *Antimicrob Agents Chemother*. 2009;53(9):3871–3879
94. Böswald M, Döbig C, Kändler C, et al. Pharmacokinetic and clinical evaluation of serious infections in premature and newborn infants under therapy with imipenem/cilastatin. *Infection*. 1999;27(4–5):299–304
95. Giannoni E, Moreillon P, Cotting J, et al. Prospective determination of plasma imipenem concentrations in critically ill children. *Antimicrob Agents Chemother*. 2006;50(7):2563–2568

96. Reed MD, Kliegman RM, Yamashita TS, Myers CM, Blumer JL. Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. *Antimicrob Agents Chemother*. 1990;34(6):1172–1177
97. Metsvaht T, Oselin K, Ilmoja ML, Anier K, Lutsar I. Pharmacokinetics of penicillin g in very-low-birth-weight neonates. *Antimicrob Agents Chemother*. 2007;51(6):1995–2000
98. Muller AE, DeJongh J, Bult Y, et al. Pharmacokinetics of penicillin G in infants with a gestational age of less than 32 weeks. *Antimicrob Agents Chemother*. 2007;51(10):3720–3725
99. Dotis J, Iosifidis E, Ioannidou M, Roilides E. Use of linezolid in pediatrics: a critical review. *Int J Infect Dis*. 2010;14(8):e638–e648
100. Hoehn R, Groll AH, Schaefer V, Bauer K, Schloesser RL. Linezolid treatment of glycopeptide-resistant *Enterococcus faecium* in very low birth weight premature neonates. *Int J Antimicrob Agents*. 2006;27(3):256–258
101. Kocher S, Müller W, Resch B. Linezolid treatment of nosocomial bacterial infection with multiresistant gram-positive pathogens in preterm infants: a systematic review. *Int J Antimicrob Agents*. 2010;36(2):106–110
102. Kearns GL, Jungbluth GL, Abdel-Rahman SM, et al; Pediatric Pharmacology Research Unit Network. Impact of ontogeny on linezolid disposition in neonates and infants. *Clin Pharmacol Ther*. 2003;74(5):413–422
103. Shama A, Patole SK, Whitehall JS. Intravenous rifampicin in neonates with persistent staphylococcal bacteraemia. *Acta Paediatr*. 2002;91(6):670–673
104. Tan TQ, Mason EO, Jr, Ou CN, Kaplan SL. Use of intravenous rifampin in neonates with persistent staphylococcal bacteremia. *Antimicrob Agents Chemother*. 1993;37(11):2401–2406
105. van der Lugt NM, Steggerda SJ, Walther FJ. Use of rifampin in persistent coagulase negative staphylococcal bacteremia in neonates. *BMC Pediatr*. 2010;10:84
106. Shetty AK. Tetracyclines in pediatrics revisited. *Clin Pediatr (Phila)*. 2002;41(4):203–209
107. Lubani MM, Dudin KI, Sharda DC, et al. A multicenter therapeutic study of 1100 children with brucellosis. *Pediatr Infect Dis J*. 1989;8(2):75–78
108. Alexander JJ, Colangelo PM, Cooper CK, Roberts R, Rodriguez WJ, Murphy MD. Amoxicillin for postexposure inhalational anthrax in pediatrics: rationale for dosing recommendations. *Pediatr Infect Dis J*. 2008;27(11):955–957
109. Charles BG, Preechagoon Y, Lee TC, Steer PA, Flenady VJ, Debuse N. Population pharmacokinetics of intravenous amoxicillin in very low birth weight infants. *J Pharm Sci*. 1997;86(11):1288–1292
110. Huisman-de Boer JJ, van den Anker JN, Vogel M, Goessens WH, Schoemaker RC, de Groot R. Amoxicillin pharmacokinetics in preterm infants with gestational ages of less than 32 weeks. *Antimicrob Agents Chemother*. 1995;39(2):431–434
111. Pullen J, Stolk LM, Nieman FH, Degraeuwe PL, van Tiel FH, Zimmermann LJ. Population pharmacokinetics and dosing of amoxicillin in (pre)term neonates. *Ther Drug Monit*. 2006;28(2):226–231
112. Ahmed AS, Khan NZ, Saha SK, et al. Ciprofloxacin treatment in preterm neonates in Bangladesh: lack of effects on growth and development. *Pediatr Infect Dis J*. 2006;25(12):1137–1141
113. Zhanel GG, Ennis K, Vercaigne L, et al. A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs*. 2002;62(1):13–59
114. Grossman ER, Walchek A, Freedman H. Tetracyclines and permanent teeth: the relation between dose and tooth color. *Pediatrics*. 1971;47(3):567–570
115. Martin SW, Tierney BC, Aranas A, et al. An overview of adverse events reported by participants in CDC's anthrax vaccine and antimicrobial availability program. *Pharmacoepidemiol Drug Saf*. 2005;14(6):393–401

(Continued from first page)

www.pediatrics.org/cgi/doi/10.1542/peds.2014-0563

doi:10.1542/peds.2014-0563

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

APPENDIX 1 Postexposure Prophylaxis for *B anthracis* (for Children 1 Month of Age and Older)

1. For penicillin-resistant strains or prior to susceptibility testing

***Ciprofloxacin,* 30 mg/kg/day, by mouth (PO), divided every 12 h (not to exceed 500 mg/dose)**

OR

***Doxycycline,*[a] <45 kg: 4.4 mg/kg/day, PO, divided every 12 h (not to exceed 100 mg/dose)** >45 kg: 100 mg/dose, PO, given every 12 h

OR

Clindamycin,[b] 30 mg/kg/day, PO, divided every 8 h (not to exceed 900 mg/dose)

OR

Levofloxacin,[c] <50 kg: 16 mg/kg/day, PO, divided every 12 h (not to exceed 250 mg/dose) >50 kg: 500 mg, PO, given every 24 h

OR

2. For penicillin-susceptible strains[b,d]

Amoxicillin, 75 mg/kg/day, PO, divided every 8 h (not to exceed 1 g/dose)

OR

Penicillin VK, 50–75 mg/kg/day, PO, divided every 6 to 8 h

Duration of Therapy: 60 days after exposure

Bold font: preferred antimicrobial agent (when 2 bolded antimicrobial agents are present, both are considered equivalent in overall safety and efficacy).
Normal font: alternative selections are listed in order of preference for therapy for patients who cannot take first-line therapy or if first-line therapy is unavailable.
Doses are provided for children with normal renal and hepatic function. Doses may vary for those with some degree of organ failure.
Italicized font: indicates FDA approval for the indication in the pediatric population.
[a] A single 14-day course of doxycycline is not routinely associated with tooth staining, but some degree of staining is likely for a prolonged treatment course of up to 60 days.
[b] On the basis of in vitro susceptibility data.
[c] Safety data for levofloxacin in the pediatric population are limited to 14 days for duration therapy.
[d] Be aware of the possibility of emergence of penicillin-resistance during monotherapy with amoxicillin or penicillin.

APPENDIX 2 Treatment of Cutaneous Anthrax Without Systemic Involvement (for Children 1 Month of Age and Older)

1. For all strains, regardless of penicillin susceptibility or if susceptibility is unknown

Ciprofloxacin, 30 mg/kg/day, by mouth (PO), divided every 12 h (not to exceed 500 mg/dose)

OR

Doxycycline,[a] <45 kg: 4.4 mg/kg/day, PO, divided every 12 h (not to exceed 100 mg/dose) ≥45 kg: 100 mg/dose, PO, given every 12 h

OR

Clindamycin,[b] 30 mg/kg/day, PO, divided every 8 h (not to exceed 600 mg/dose)

OR

Levofloxacin <50 kg: 16 mg/kg/day, PO, divided every 12 h (not to exceed 250 mg/dose) >50 kg: 500 mg, PO, given every 24 h

OR

2. Alternatives for penicillin-susceptible strains[c]

Amoxicillin, 75 mg/kg/day, PO, divided every 8 h (not to exceed 1 g/dose)

OR

Penicillin VK, 50–75 mg/kg/day, PO, divided every 6 to 8 h

Duration of therapy:

For naturally acquired infection: 7–10 days.

For a biological weapon–related event: will require additional prophylaxis for inhaled spores, to complete an antimicrobial course of up to 60 days from onset of illness (see Appendix 1, Postexposure Prophylaxis).

Bold font: preferred antimicrobial agent.
Normal font: alternative selections are listed in order of preference for therapy for patients who cannot take first-line therapy or if first-line therapy is unavailable.
Doses are provided for children with normal renal and hepatic function. Doses may vary for those with some degree of organ failure.
Italicized font: indicates FDA approval for the indication in the pediatric population.
[a] A single 10- to 14-day course of doxycycline is not routinely associated with tooth staining.
[b] On the basis of in vitro susceptibility data.
[c] Be aware of the possibility of emergence of penicillin-resistance during monotherapy with amoxicillin or penicillin.

APPENDIX 3 Combination Therapy for Systemic Anthrax When Meningitis Can Be Ruled Out (for Children 1 Month of Age and Older)

1. A bactericidal antimicrobial

a. For all strains, regardless of penicillin susceptibility or if susceptibility is unknown

Ciprofloxacin, 30 mg/kg/day, intravenously (IV), divided every 8 h (not to exceed 400 mg/dose)

OR

Meropenem, 60 mg/kg/day, IV, divided every 8 h (not to exceed 2 g/dose)

OR

Levofloxacin <50 kg: 20 mg/kg/day, IV, divided every 12 h (not to exceed 250 mg/dose >50 kg: 500 mg, IV, given every 24 h

OR

Imipenem/cilastatin,[a] 100 mg/kg/day, IV, divided every 6 h (not to exceed 1 g/dose)

OR

Vancomycin, 60 mg/kg/day, IV, divided every 8 h (follow serum concentrations)

b. Alternatives for penicillin-susceptible strains

Penicillin G, 400 000 U/kg/day, IV, divided every 4 h (not to exceed 4 MU/dose)

OR

Ampicillin, 200 mg/kg/day, IV, divided every 6 h (not to exceed 3 g/dose)

PLUS

2. A Protein Synthesis Inhibitor

Clindamycin, 40 mg/kg/day, IV, divided every 8 h (not to exceed 900 mg/dose)

OR

Linezolid[b] (non-CNS infection dose): <12 y old: 30 mg/kg/day, IV, divided every 8 h≥12 y old: 30 mg/kg/day, IV, divided every 12 h (not to exceed 600 mg/dose)

OR

Doxycycline[c] <45 kg: 4.4 mg/kg/day, IV, loading dose (not to exceed 200 mg); ≥45 kg: 200 mg, IV, loading dose then <45 kg: 4.4 mg/kg/day, IV, divided every 12 h (not to exceed 100 mg/dose); ≥45 kg: 100 mg, IV, given every 12 h

OR

Rifampin,[d] 20 mg/kg/day, IV, divided every 12 h (not to exceed 300 mg/dose)

Duration of therapy: For 14 days or longer until clinical criteria for stability are met (see text). Will require prophylaxis to complete an antimicrobial course of up to 60 days from onset of illness (see Appendix 1).

Systemic anthrax includes inhalation anthrax; injection, gastrointestinal, or cutaneous anthrax with systemic involvement, extensive edema, or lesions of the head or neck.

Children with altered mental status, signs of meningeal inflammation, or focal neurologic deficits should be considered to have CNS infection if CSF examination is not possible. A normal CSF may not completely exclude deep brain hemorrhage/abscess. See Appendix 4 for therapy of CNS infection.

Bold font: preferred antimicrobial agent.

Normal font: alternative selections are listed in order of preference for therapy for patients who cannot tolerate first-line therapy or if first-line therapy is unavailable.

Doses are provided for children with normal renal and hepatic function. Doses may vary for those with some degree of organ failure.

[a] Increased risk of seizures associated with imipenem/cilastatin therapy.

[b] Linezolid should be used with caution in patients with thrombocytopenia, as it may exacerbate it. Linezolid use for >14 days carries additional hematopoietic toxicity.

[c] A single 14-day course of doxycycline is not routinely associated with tooth staining.

[d] Rifampin is not a protein synthesis inhibitor; it may also be used in combination therapy based on in vitro synergy.

APPENDIX 4 Triple Therapy for Systemic Anthrax (Anthrax Meningitis or Disseminated Infection and Meningitis Cannot Be Ruled Out) for Children 1 Month of Age and Older

1. A bactericidal antimicrobial (fluoroquinolone)

Ciprofloxacin, 30 mg/kg/day, intravenously (IV), divided every 8 h (not to exceed 400 mg/dose)[a]

OR

Levofloxacin <50 kg: 16 mg/kg/day, IV, divided every 12 h (not to exceed 250 mg/dose); >50 kg: 500 mg, IV, every 24 h

OR

Moxifloxacin 3 mo to <2 y: 12 mg/kg/day, IV, divided every 12 h (not to exceed 200 mg/dose)
2–5 y: 10 mg/kg/day, IV, divided every 12 h (not to exceed 200 mg/dose)
6–11 y: 8 mg/kg/day, IV, divided every 12 h (not to exceed 200 mg/dose)
12–17 y, ≥45 kg body weight: 400 mg, IV, once daily
12–17 y, <45 kg body weight: 8 mg/kg/day, IV, divided every 12 h (not to exceed 200 mg/dose)

PLUS

2. A bactericidal antimicrobial (β-lactam or glycopeptide)

a. For all strains, regardless of penicillin susceptibility testing or if susceptibility is unknown

Meropenem, 120 mg/kg/day, IV, divided every 8 h (not to exceed 2 g/dose)

OR

Imipenem/cilastatin,[b] 100 mg/kg/day, IV, divided every 6 h (not to exceed 1 g/dose)

OR

Doripenem,[c] 120 mg/kg/day, IV, divided every 8 h (not to exceed 1 g/dose)

OR

Vancomycin, 60 mg/kg/day, IV, divided every 8 h

b. Alternatives for penicillin-susceptible strains

Penicillin G, 400 000 U/kg/day, IV, divided every 4 h (not to exceed 4 MU/dose)

OR

Ampicillin, 400 mg/kg/day, IV, divided every 6 h (not to exceed 3 g/dose)

PLUS

3. A Protein Synthesis Inhibitor

Linezolid[d]: <12 y old: 30 mg/kg/day, IV, divided every 8 h≥12 y old: 30 mg/kg/day, IV, divided every 12 h (not to exceed 600 mg/dose)

OR

Clindamycin, 40 mg/kg/day, IV, divided every 8 h (not to exceed 900 mg/dose)

OR

Rifampin,[e] 20 mg/kg/day, IV, divided every 12 h (not to exceed 300 mg/dose)

OR

Chloramphenicol,[f] 100 mg/kg/day, IV, divided every 6 h

Duration of therapy: for 2–3 wk or greater, until clinical criteria for stability are met (see text). Will require prophylaxis to complete an antimicrobial course of up to 60 days from onset of illness (see Appendix 1).

Systemic anthrax includes anthrax meningitis; inhalation anthrax; or injection, gastrointestinal, and cutaneous anthrax with systemic involvement, extensive edema, or lesions of the head or neck.

Children with altered mental status, signs of meningeal inflammation, or focal neurologic deficits should be considered to have CNS infection if CSF examination is not possible. Normal CSF may not completely exclude deep brain hemorrhage/abscess.

Bold font: preferred antimicrobial agent.

Normal font: alternative selections are listed in order of preference for therapy for patients who cannot tolerate first-line therapy or if first-line therapy is unavailable.

Doses are provided for children with normal renal and hepatic function. Doses may vary for those with some degree of organ failure.

[a] A 400-mg dose of ciprofloxacin, IV, provides an equivalent exposure to that of a 500-mg ciprofloxacin oral tablet.

[b] Increased risk of seizures associated with imipenem/cilastatin therapy.

[c] Doripenem is approved in Japan at this dose for the treatment of community-acquired bacterial meningitis.

[d] Linezolid should be used with caution in patients with thrombocytopenia, as it may exacerbate it. Linezolid use for >14 days carries additional hematopoietic toxicity.

[e] Rifampin is not a protein synthesis inhibitor; it may also be used in combination therapy based on in vitro synergy for some strains of staphylococci. Not evaluated for *B anthracis*.

[f] Should be used only if other options are not available, because of toxicity concerns.

APPENDIX 5 Oral Follow-up Combination Therapy for Severe Anthrax (for Children 1 Month of Age and Older)

1. A bactericidal antimicrobial

a. For all strains, regardless of penicillin susceptibility or if susceptibility is unknown

Ciprofloxacin, 30 mg/kg/day, by mouth (PO), divided every 12 h (not to exceed 500 mg/dose)

OR

Levofloxacin <50 kg: 16 mg/kg/day, PO, divided every 12 h (not to exceed 250 mg/dose) ≥50 kg: 500 mg, PO, given every 24 h

OR

b. Alternatives for penicillin-susceptible strains

Amoxicillin, 75 mg/kg/day, PO, divided every 8 h (not to exceed 1 g/dose)

OR

Penicillin VK, 50–75 mg/kg/day, PO, divided every 6 to 8 h

PLUS

2. A protein synthesis inhibitor

Clindamycin[a] 30 mg/kg/day, PO, divided every 8 h (not to exceed 600 mg/dose)

OR

Doxycycline[b] <45 kg: 4.4 mg/kg/day, PO, divided every 12 h (not exceed 100 mg/dose) ≥45 kg: 100 mg, PO, given every 12 h

OR

Linezolid[c] (non-CNS infection dose):

<12 y old: 30 mg/kg/day, PO, divided every 8 h

≥12 y old: 30 mg/kg/day, PO, divided every 12 h

(not to exceed 600 mg/dose)

Duration of therapy: to complete a treatment course of 14 days or greater. May require prophylaxis to complete an antimicrobial course of up to 60 days from onset of illness (see Appendix 1).

Severe anthrax includes inhalation anthrax; injection, gastrointestinal, or cutaneous anthrax with systemic involvement, extensive edema, or lesions of the head or neck.

Bold font: preferred antimicrobial agent.

Normal font: alternative selections are listed in order of preference for therapy for patients who cannot take first-line therapy or if first-line therapy is unavailable.

Doses are provided for children with normal renal and hepatic function. Doses may vary for those with some degree of organ failure.

[a] Based on in vitro susceptibility data rather than studies of clinical efficacy.

[b] A single 14-day course of doxycycline is not routinely associated with tooth staining.

[c] Linezolid should be used with caution in patients with thrombocytopenia, as it may exacerbate it. Linezolid use for >14 days carries additional hematopoietic toxicity.

APPENDIX 6 Dosing in Preterm and Term Neonates 32 to 44 Weeks' Postmenstrual Age (Gestational Age Plus Chronologic Age)

THESE ANTIMICROBIALS AND DOSAGES HAVE NOT BEEN REVIEWED OR APPROVED BY THE FDA FOR USE IN NEWBORN INFANTS, UNLESS SPECIFICALLY NOTED. THESE DOSES ARE PROVIDED ONLY AS GUIDANCE DURING AN EMERGENCY BIOLOGICAL WEAPON EVENT, ON THE BASIS OF AVAILABLE LITERATURE OR EXTRAPOLATION FROM PHARMACOKINETIC DATA FROM OLDER CHILDREN, WITH KNOWLEDGE OF MATURATION OF NEONATAL CLEARANCE MECHANISMS.

Dosing guidance for anthrax in newborn infants has not been proposed earlier because of the paucity of pharmacologic data describing kinetics, safety, and efficacy and the broad range of developmental changes that will affect therapy in this immature population. This guidance accommodates not only term newborn infants but also neonates who may be born at 32 wk postmenstrual age (PMA). For neonates of earlier gestational age, please consult with a neonatologist, pharmacologist, or infectious diseases physician for appropriate dosing. Doses are provided for newborns with developmentally appropriate renal and hepatic function. Doses may vary for those with some degree of organ failure.

By convention, the neonatal period ends 28 d (4 wk) after birth, but at 4 wk of age, the physiologic maturity of a preterm infant lags significantly behind a term infant. Preterm infants continue to undergo developmental changes through 44 wk PMA that affect pharmacokinetics, with maturation of mechanisms of renal elimination and hepatic enzymatic drug inactivation that occur at different rates for different antimicrobial agents, some closely linked to PMA or chronologic age, but most demonstrate aspects of both. Hence, we provide guidance for all newborn infants through 44 wk PMA while recognizing that many physiologic processes mature during this developmental period and that new dosing recommendations are likely to follow as additional data become available. Should these medications be required for treatment or prophylaxis, it will be especially important to plan prospectively to monitor serum/plasma concentrations in a systematic fashion to acquire good data that relate dose of drug to concentration, efficacy, and occurrence of adverse effects.

Antimicrobial-related adverse effects are always possible; however, the benefit of antimicrobial therapy for life-threatening infection justifies assuming greater risk during therapy. In general, the frequency and severity of adverse events seem to be less, rather than more, in neonates.

A. Triple therapy for severe anthrax[a] (anthrax meningitis or disseminated infection and meningitis cannot be ruled out[b])

Duration of therapy: For ≥2–3 wk, until clinical criteria for stability are met (see text). Will require prophylaxis to complete an antibiotic course of up to 60 days from onset of illness (see Appendix 6E).

Antimicrobial[84]	**32–34 wk Gestational Age**		**34–37 wk Gestational Age**		**Term Newborn Infant**	
	0–1 wk of Age	**1–4 wk of Age**	**0–1 wk of Age**	**1–4 wk of Age**	**0–1 wk of Age**	**1–4 wk of Age**
1. A bactericidal antimicrobial (fluoroquinolone)						
Ciprofloxacin IV[85–87]	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**
		OR				
Levofloxacin IV[88]	—	—	—	—	—	—
		OR				
Moxifloxacin IV[89,90]	5 mg/kg/day, q24h	5 mg/kg/day, q24h	5 mg/kg/day, q24h	5 mg/kg/day, q24h	10 mg/kg/day, q24h	10 mg/kg/day, q24h
		PLUS				
2. A bactericidal antimicrobial (β-lactam)						
a. For all strains, regardless of penicillin susceptibility or if susceptibility is unknown						
Meropenem IV[91–93]	60 mg/kg/day, divided q8h	90 mg/kg/day, divided q8h	60 mg/kg/day, divided q8h	90 mg/kg/day, divided q8h	60 mg/kg/day, divided q8h	90 mg/kg/day, divided q8h
		OR				
Imipenem[c] IV[94–96]	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h
		OR				
Doripenem[d] IV	20 mg/kg/day, divided q12h	30 mg/kg/day, divided q8h	20 mg/kg/day, divided q12h	30 mg/kg/day, divided q8h	20 mg/kg/day, divided q12h	30 mg/kg/day, divided q8h
		OR				
b. Alternatives for penicillin-susceptible strains						
Penicillin G[97,98]	200 000 Units/kg/day, divided q12h	300 000 Units/kg/day, divided q8h	300 000 Units/kg/day, divided q8h	400 000 Units/kg/day, divided q6h	300 000 Units/kg/day, divided q8h	400 000 Units/kg/day, divided q6h
		OR				
Ampicillin	100 mg/kg/day, divided q12h	150 mg/kg/day, divided q8h	150 mg/kg/day, divided q8h	200 mg/kg/day, divided q6h	150 mg/kg/day, divided q8h	200 mg/kg/day, divided q6h
		PLUS				
3. A protein synthesis inhibitor						
Linezolid[e] [99–102]	20 mg/kg/day, divided q12h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h
		OR				
Clindamycin	10 mg/kg/day, divided q12h	15 mg/kg/day, divided q8h	15 mg/kg/day, divided q8h	20 mg/kg/day, divided q6h	15 mg/kg/day, divided q8h	20 mg/kg/day, divided q6h
		OR				

APPENDIX 6 Continued

Rifampin[f] [103–105]	10 mg/kg/day, divided q12h	10 mg/kg/day, divided q12h	10 mg/kg/day, divided q12h	10 mg/kg/day, divided q12h	10 mg/kg/day, divided q12h	20 mg/kg/day, divided q12h
		OR				
Chloramphenicol[g]	25 mg/kg/day, q24h	50 mg/kg/day, q12h	25 mg/kg/day, q24h	50 mg/kg/day, q12h	25 mg/kg/day, q24h	50 mg/kg/day, q12h

B. Therapy for severe[a] anthrax when meningitis can be ruled out[b]

Duration of therapy: For ≥2–3 wk, until clinical criteria for stability are met (see text). Will require prophylaxis to complete an antimicrobial course of up to 60 days from onset of illness (see Appendix 6E).

1. A bactericidal antimicrobial

a. For all strains, regardless of penicillin susceptibility or if susceptibility is unknown

	32–34 wk Gestational Age		**34–37 wk Gestational Age**		**Term Newborn Infant**	
	0–1 wk of Age	**1–4 wk of Age**	**0–1 wk of Age**	**1–4 wk of Age**	**0–1 wk of Age**	**1–4 wk of Age**
Ciprofloxacin IV	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**
		OR				
Meropenem IV	40 mg/kg/day, divided q8h	60 mg/kg/day, divided q8h	60 mg/kg/day, divided q8h	60 mg/kg/day, divided q8h	60 mg/kg/day, divided q8h	60 mg/kg/day, divided q8h
		OR				
Levofloxacin IV	—	—	—	—	—	—
		OR				
Imipenem[c] IV	40 mg/kg/day, divided q12h	50 mg/kg/day, divided q12h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h
		OR				
Vancomycin IV (dosing based on serum creatinine for infants ≥32 wk gestational age). Follow vancomycin serum concentrations to modify dose.	Serum creatinine <0.7			15 mg/kg/dose		q12h
	Serum creatinine 0.7 -0.9			20 mg/kg/dose		q24h
	Serum creatinine 1–1.2			15 mg/kg/dose		q24h
	Serum creatinine 1.3–1.6			10 mg/kg/dose		q24h
	Serum creatinine >1.6			15 mg/kg/dose		q48h
	Begin treatment with a 20-mg/kg loading dose					
	OR					

b. Alternatives for penicillin-susceptible strains

Penicillin G IV	200 000 U/kg/day, divided q12h	300 000 U/kg/day, divided q8h	300 000 U/kg/day, divided q8h	400 000 U/kg/day, divided q6h	300 000 U/kg/day, divided q8h	400 000 U/kg/day, divided q6h
		OR				
Ampicillin IV	100 mg/kg/day, divided q12h	150 mg/kg/day, divided q8h	150 mg/kg/day, divided q8h	200 mg/kg/day, divided q6h	150 mg/kg/day, divided q8h	200 mg/kg/day, divided q6h
		PLUS				
2. A protein synthesis inhibitor						
Clindamycin IV	**10 mg/kg/day, divided q12h**	**15 mg/kg/day, divided q8h**	**15 mg/kg/day, divided q8h**	**20 mg/kg/day, divided q6h**	**15 mg/kg/day, divided q8h**	**20 mg/kg/day, divided q6h**
		OR				
Linezolid IV[e]	20 mg/kg/day, divided q12h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h
		OR				
Doxycycline IV (loading dose 4.4 mg/kg)[106,107]	—	—	—	—	4.4 mg/kg/day, divided q12h	4.4 mg/kg/day, divided q12h
		OR				
Rifampin IV[f]	10 mg/kg/day, q24h	10 mg/kg/day, q24h	10 mg/kg/day, q24h	10 mg/kg/day, q24h	10 mg/kg/day, q24h	10 mg/kg/day, q24h

C. Oral follow-up combination therapy for severe[a] anthrax

Duration of therapy: to complete a treatment course of 10–14 days or greater. May require prophylaxis to complete an antimicrobial course of up to 60 days from onset of illness (see Appendix 6E, Postexposure Prophylaxis).

1. A bactericidal antimicrobial

a. For all strains, regardless of penicillin susceptibility or if susceptibility is unknown

	32–34 wk Gestational Age		**34–37 wk Gestational Age**		**Term Newborn Infant**	
	0–1 wk of Age	**1–4 wk of Age**	**0–1 wk of Age**	**1–4 wk of Age**	**0–1 wk of Age**	**1–4 wk of Age**
Ciprofloxacin[h] PO	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**
		OR				
Levofloxacin PO	—	—	—	—	—	—
		OR				

b. Alternatives for penicillin-susceptible strains

Amoxicillin PO[108–111]	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q8h
		OR				
Penicillin VK PO	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q6–8h
		PLUS				
2. A protein synthesis inhibitor						
Clindamycin[i] PO	**10 mg/kg/day, divided q12h**	**15 mg/kg/day, divided q8h**	**15 mg/kg/day, divided q8h**	**20 mg/kg/day, divided q6h**	**15 mg/kg/day, divided q8h**	**20 mg/kg/day, divided q6h**
		OR				
Doxycycline[j] PO (loading dose 4.4 mg/kg)	—	—	—	—	4.4 mg/kg/day, divided q12h	4.4 mg/kg/day, divided q12h
		OR				
Linezolid PO[e]	20 mg/kg/day, divided q12h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h	30 mg/kg/day, divided q8h
		OR				

D. Treatment of cutaneous anthrax without systemic involvement

Duration of therapy:

For naturally acquired infection: 7–10 days

For a biological weapon–related event, may require additional prophylaxis for inhaled spores to complete an antimicrobial course of up to 60 days from onset of illness (see Appendix 6E).

1. For all strains, regardless of penicillin susceptibility or if susceptibility is unknown

	32–34 wk Gestational Age		**34–37 wk Gestational Age**		**Term Newborn Infant**	
	0–1 wk of Age	**1–4 wk of Age**	**0–1 wk of Age**	**1–4 wk of Age**	**1–4 wk of Age**	**0–1 wk of Age**
Ciprofloxacin[h] PO	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**
		OR				
Doxycycline[j] PO (Loading dose 4.4 mg/kg)	—	—	—	—	4.4 mg/kg/day, divided q12h	4.4 mg/kg/day, divided q12h
		OR				
Clindamycin[h] PO	10 mg/kg/day, divided q12h	15 mg/kg/day, divided q8h	15 mg/kg/day, divided q8h	20 mg/kg/day, divided q6h	15 mg/kg/day, divided q8h	20 mg/kg/day, divided q6h
		OR				
Levofloxacin[h] PO	—	—	—	—	—	—
		OR				
2. Alternatives for penicillin-susceptible strains						
Amoxicillin[k] PO	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q8h
		OR				
Penicillin V[k] PO	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q6–8h

E. Postexposure prophylaxis for *Bacillus anthracis*

Duration of therapy: 60 days from exposure

1. For all strains, regardless of penicillin susceptibility or if susceptibility is unknown

	32–34 wk Gestational Age		**34–37 wk Gestational Age**		**Term Newborn Infant**	
	0–1 wk of Age	**1–4 wk of Age**	**0–1 wk of Age**	**1–4 wk of Age**	**0–1 wk of Age**	**1–4 wk of Age**
Ciprofloxacin[h] PO	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**20 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**	**30 mg/kg/day, divided q12h**
		OR				
Clindamycin PO	10 mg/kg/day, divided q12h	15 mg/kg/day, divided q8h	15 mg/kg/day, divided q8h	20 mg/kg/day, divided q6h	15 mg/kg/day, divided q8h	20 mg/kg/day, divided q6h
		OR				
Doxycycline[j] PO (loading dose 4.4 mg/kg)	—	—	—	—	4.4 mg/kg/day, divided q12h	4.4 mg/kg/day, divided q12h
		OR				
Levofloxacin[h] PO	—	—	—	—	—	—
		OR				

APPENDIX 6 Continued

2. Alternatives for penicillin-susceptible strains						
Amoxicillin[k] PO	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q8h
		OR				
Penicillin V[k] PO	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	50 mg/kg/day, divided q12h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q8h	75 mg/kg/day, divided q6–8h

div, XXX; q, every.

Bold font: preferred antimicrobial agent.

Normal font: alternative selections are listed in order of preference for therapy for patients who cannot tolerate first-line therapy, or if first-line therapy is unavailable.

[a] Severe anthrax includes anthrax meningitis; inhalation anthrax; or injection, gastrointestinal, or cutaneous anthrax with systemic involvement; extensive edema; or lesions of the head or neck.

[b] Neonates with irritability, vital sign instability, bulging fontanel, or focal neurologic deficits should be considered to have CNS infection if CSF examination is not possible. Normal CSF may not completely exclude deep brain hemorrhage/abscess.

[c] Increased risk of seizures associated with imipenem/cilastatin therapy.

[d] Doripenem is approved in Japan at this dose for the treatment of community-acquired bacterial meningitis in older children.

[e] Linezolid should be used with caution in newborn infants with thrombocytopenia, as it may exacerbate it. Linezolid use for >14 days may be associated with additional hematopoietic toxicity.

[f] Rifampin is not a protein synthesis inhibitor; it also may be used in combination therapy based on in vitro synergy.

[g] Should be used only if other options are not available because of toxicity concerns; obtain chloramphenicol serum concentrations, if possible.

[h] Safety data are unavailable for fluoroquinolones for duration of therapy >30 days. Tendinopathy and arthralgia have been reported with fluoroquinolone antimicrobial agents in ambulating animals and humans. These problems appear to be much less, if they occur at all, in pediatric patients, especially in newborn infants.[54,112,113]

[i] On the basis of in vitro susceptibility data rather than studies of clinical efficacy.

[j] A single 10- to 14-day course of doxycycline is not routinely associated with tooth staining in older children but may stain developing teeth in neonates.[40,41,114]

[k] Be aware of the possibility of emergence of penicillin-resistance during monotherapy with amoxicillin or penicillin.

APPENDIX 7 Diagnostic Assessment and Monitoring for Systemic Anthrax (Based on Recommendations for Adults)

Test	Unique Findings in Systemic Anthrax Infections	
	Initial	Serial Monitoring
Complete blood cell count	Marked hemoconcentration; thrombocytopenia may not be present; white blood cell count frequently normal	Anemia can suddenly develop; thrombocytopenia onset often associated with hemolytic anemia; leukocytosis usually not seen until severe sepsis stage
Electrolytes, blood urea nitrogen, lactate	Decreased sodium; bicarbonate can be normal even with severe sepsis; increased blood urea nitrogen	
Liver panel, serum albumin	Mild transaminitis; hypoalbuminemia related to acute infection	
Prothrombin time (PT), partial thromboplastin time (PTT), D-dimer, Fibrinogen	Normal PT/PTT at admission does not exclude coagulopathy or disseminated intravascular coagulopathy	Low threshold for disseminated intravascular coagulation workup, including haptoglobin, lactate dehydrogenase, fibrin split products. If evidence of hemolytic anemia, assess ADAMTS 13 (von Willebrand factor–cleaving protease).
Erythrocyte sedimentation rate, C-reactive protein	Useful for characterizing inflammatory response	
Gram stain, cultures, serum for toxin assays	Any accessible fluid: blood, sputum, cerebrospinal, urine, wound, gastric ulcers	Cultures usually negative after antimicrobial agents, but toxin may be detectable at multiple time points.
Cardiac enzymes (troponin) +/—B-type natriuretic peptide	Troponin leak as a result of increased cardiac demands from acute infection (especially if atrial fibrillation with rapid ventricular response)	
Electrocardiogram/continuous cardiorespiratory monitoring telemetry	Atrial fibrillation with rapid ventricular response commonly observed.	
Posterior-anterior and lateral chest radiograph	Any abnormality: mediastinal widening may not be seen in inhalation and pleural effusion can be subtle	Daily chest radiographs or other thoracic imaging until pleural effusions are stable or decreasing
Chest CT	Evaluate for severity of pleural effusions, presence of mediastinal widening, and to rule out thromboembolic disease with CT angiography	Repeat if significant clinical status change. Ultrasonography of the chest may be useful for following pleural effusion.
Lumbar puncture	With severe or systemic disease, perform as soon as clinically feasible; meningeal signs are usually not present until late stage, if meningitis is present.	—
Other imaging	As relevant to site of exposure; to evaluate edema, inflammation, and necrosis	—
Echocardiogram	Evaluate for pericardial effusion in addition to myocardial dysfunction.	

APPENDIX 8 Recommendations for Compatibility of Antimicrobial Agents and Breastfeeding

Antimicrobial Agent	US National Library of Medicine LACTMED[a]	Briggs' Pregnancy and Lactation[b]
Amoxicillin	Acceptable to use	Compatible
Ampicillin	Acceptable to use	Compatible
Chloramphenicol	Alternate drug is preferred	Potential toxicity
Ciprofloxacin	Short-term[c] use is acceptable	Limited human data—potential toxicity
Clindamycin	Not a reason to discontinue breastfeeding Alternate drug is preferred	Compatible
Doxycycline	Short-term use is acceptable Avoid prolonged[d] or repeat courses	Compatible
Imipenem	Acceptable to use	Limited human data—probably compatible
Levofloxacin	Short-term[c] use is acceptable	Limited human data—probably compatible
Linezolid	Not a reason to discontinue breastfeeding	No human data—potential toxicity
Meropenem	Not expected to cause adverse effect	No human data—probably compatible
Moxifloxacin	Short-term[c] use is acceptable	No human data—probably compatible
Penicillin	Acceptable to use	Compatible
Rifampin	Not expected to cause adverse effects	Compatible

[a] toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT.

[b] Briggs GG, Freeman RK, Yaffe SJ, eds. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

[c] 7–14 days.

[d] More than 14 days.

Pediatric Anthrax Clinical Management

John S. Bradley, Georgina Peacock, Steven E. Krug, William A. Bower, Amanda C. Cohn, Dana Meaney-Delman, Andrew T. Pavia and AAP COMMITTEE ON INFECTIOUS DISEASES and DISASTER PREPAREDNESS ADVISORY COUNCIL

Pediatrics; originally published online April 28, 2014;
DOI: 10.1542/peds.2014-0563

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Pediatric Anthrax Clinical Management

John S. Bradley, Georgina Peacock, Steven E. Krug, William A. Bower, Amanda C. Cohn, Dana Meaney-Delman, Andrew T. Pavia and AAP COMMITTEE ON INFECTIOUS DISEASES and DISASTER PREPAREDNESS ADVISORY COUNCIL

Pediatrics; originally published online April 28, 2014;
DOI: 10.1542/peds.2014-0563