Treatment of anthrax

Author
Kenneth H Wilson, MD

Section Editor
Daniel J Sexton, MD

Deputy Editor
Anna R Thorner, MD

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INTRODUCTION — The incidence of anthrax in humans has decreased during the past century, and it is now very rare in developed countries including the United States. However, anthrax remains a concern in the developed world because of its potential as an agent of bioterrorism. Anthrax meningitis and the fulminant phase of inhalation anthrax are associated with extremely high mortality rates.

The treatment of anthrax will be reviewed here. The microbiology, pathogenesis, epidemiology, clinical manifestations, diagnosis, and prevention of anthrax are discussed separately. (See "Microbiology, pathogenesis, and epidemiology of anthrax" and "Clinical manifestations and diagnosis of anthrax" and "Prevention of anthrax".)

TREATMENT — The treatment recommendations presented here are in agreement with the recommendations of the United States Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) [1-3].

Important caveats — Treatment of patients suspected of having systemic anthrax should be started urgently and should include intravenous antimicrobial combination therapy, an antitoxin (raxibacumab or anthrax immunoglobulin), drainage of pleural effusions, supportive care, and consideration of adjunctive glucocorticoids [1]. Each of these therapies is discussed in detail below. When selecting an antimicrobial regimen for anthrax, the production of toxin, the potential for antimicrobial drug resistance, the frequent occurrence of meningitis, and the presence of latent spores must be taken into account.

- **Initial evaluation** – Patients suspected of having systemic anthrax should undergo similar testing as is done in other patients with an acute febrile illness, including pretreatment blood cultures and other appropriate cultures [1]. **Unless it is contraindicated, all patients suspected of having systemic anthrax should undergo lumbar puncture to evaluate for meningitis.** Other diagnostic testing is discussed separately. (See "Clinical manifestations and diagnosis of anthrax", section on 'Diagnosis'.)

- **Hospital admission** – All patients with systemic anthrax should be hospitalized [1]. Systemic anthrax is defined as cutaneous anthrax with systemic involvement; gastrointestinal, injection, or inhalation anthrax; anthrax meningitis; or bacteremia. Because inhalation anthrax can have a prodromal phase followed by a fulminant phase characterized by sudden decompensation, hospitalized patients should have careful hemodynamic monitoring, including continuous pulse oximetry and telemetry.

- **Antimicrobial therapy** – It is important to include bactericidal agents because of their immediate killing effect and a protein synthesis inhibitor to suppress toxin production [1]. The benefit of inhibiting toxin production has been demonstrated for streptococcal toxic shock syndrome and clostridial sepsis. (See "Treatment of streptococcal toxic shock syndrome", section on 'General principles' and "Clostridial myonecrosis", section on 'Treatment'.)

  Bacillus anthracis is highly susceptible to a variety of antimicrobial agents including penicillin, chloramphenicol, tetracycline, erythromycin, streptomycin, and fluoroquinolones [4-6]. *B. anthracis* is **not** susceptible to cephalosporins or trimethoprim-sulfamethoxazole [4-8]. Because *B. anthracis* possesses beta-lactamase genes, beta-lactam use can induce resistance during treatment; penicillin or amoxicillin use therefore warrants a high index of suspicion for emergence of resistance [1,9].

- **Risk of meningitis** – Meningitis and hemorrhagic brain infection has been observed in up to one-half of anthrax cases; thus, meningitis must be considered in all cases of systemic anthrax [1]. (See 'Meningitis' below and "Clinical manifestations and diagnosis of anthrax", section on 'Meningitis'.)

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Reporting cases – Suspected cases of anthrax should be reported to the local or state health department immediately. (See 'Public health reporting' below.)

- **Consulting public health officials** — Healthcare providers should consult their local or state public health departments for specific recommendations for the prevention or treatment of bioterrorism-related anthrax. This is critically important in order to ensure that an antimicrobial regimen is selected to which the isolate is fully susceptible.

Antimicrobial therapy

Meningitis — In the treatment of anthrax meningitis, early and aggressive multidrug therapy is crucial due to the rapid progression and high mortality of the disease [10-12]. Empiric treatment for anthrax cases in which anthrax meningitis is suspected or cannot be ruled out should include intravenous therapy with at least three antimicrobial agents with activity against *B. anthracis*, including at least two agents with bactericidal activity, and at least one protein synthesis inhibitor (to reduce exotoxin production), and all agents should have good central nervous system (CNS) penetration [1,2]. An antitoxin (raxibacumab or anthrax immunoglobulin) is also an essential part of the regimen. (See 'Antitoxins' below.)

For patients with systemic anthrax with suspected or proven meningitis and normal renal function, we suggest [1,2]:

- Ciprofloxacin – In adults: 400 mg intravenously (IV) every 8 hours; in children: 30 mg/kg per day divided every 8 hours, not to exceed 400 mg per dose **PLUS**
- Meropenem – In adults: 2 g IV every 8 hours; in children: 120 mg/kg per day divided every 8 hours, not to exceed 2 g per dose **PLUS**
- Linezolid – In adults: 600 mg IV every 12 hours; in children <12 years of age: 30 mg/kg per day divided every 8 hours, not to exceed 600 mg per dose; in children ≥12 years of age: 30 mg/kg per day divided every 12 hours, not to exceed 600 mg/dose

First-line and alternative agents are reviewed in the following Table (table 1). The treatment of pregnant, lactating, and postpartum women is similar to the treatment of nonpregnant adults, except that ciprofloxacin is strongly preferred as one of the bactericidal agents [3]. In addition, at least one agent that crosses the placenta is recommended for pregnant women; such agents include ciprofloxacin, levofloxacin, meropenem, ampicillin, penicillin, clindamycin, and rifampin. Pharmacokinetic data indicate that penicillin, ampicillin, and carbapenems may require higher doses in pregnant and postpartum women than those recommended for nonpregnant adults [3,13].

Ciprofloxacin is the agent of choice for the bactericidal component of therapy based upon efficacy data in nonhuman primate infection models and experience with its use for anthrax cases in humans [1]. Levofloxacin and moxifloxacin are acceptable alternatives. The fluoroquinolones have adequate CNS penetration. There have been no reports of naturally occurring resistance of *B. anthracis* to fluoroquinolones.

Meropenem is the agent of choice as the second bactericidal agent for treatment of possible meningitis [1]. The carbapenems are highly resistant to beta-lactamases and have good CNS penetration. If meropenem is not available, doripenem and imipenem are acceptable alternatives. However, imipenem should be used with caution in patients with meningitis since it is associated with an increased seizure risk. If the *B. anthracis* strain is susceptible to penicillin (minimum inhibitory concentration [MIC] <0.125 mcg/mL), IV penicillin G or ampicillin is an acceptable alternative to the carbapenem. If beta-lactam agents are not available, vancomycin is an alternative agent for children [2].

Linezolid is the preferred protein synthesis inhibitor [1]. It is favored over clindamycin because it is likely to have better CNS penetration [1,14]. Potential toxicities of linezolid include myelosuppression, peripheral and optic neuropathies, and serotonin syndrome [1]. Linezolid should be used with caution in patients with preexisting myelosuppression. Clindamycin is an acceptable alternative if linezolid is unavailable or is not tolerated. Rifampin is not a protein synthesis inhibitor, but it has been used for its synergistic effect with other agents. Rifampin can be used if linezolid and clindamycin are unavailable. Chloramphenicol is a protein synthesis inhibitor with good CNS penetration. Where available, chloramphenicol can be used if linezolid, clindamycin, and rifampin are unavailable. Doxycycline is not recommended for adults with suspected meningitis because it

does not have adequate CNS penetration [1]. In contrast, the AAP guidelines state that doxycycline can be used in children with suspected meningitis if the preferred agents are unavailable or are not tolerated [2].

For patients being treated for anthrax meningitis, IV combination therapy should be continued for at least two to three weeks or until the patient is clinically stable, whichever is longer [1]. All clinical signs and symptoms and laboratory and imaging studies should show resolution of inflammation before antimicrobial therapy is discontinued [2]. In some patients, IV therapy will be necessary for three to six weeks.

Once the course of IV combination therapy has been completed, patients should be switched to single agent oral therapy to complete a 60-day course of antibiotics in order to prevent relapse from surviving *B. anthracis* spores [1]. Oral antimicrobial options are the same as those used for postexposure prophylaxis (table 2). (See "Prevention of anthrax", section on 'PEP antimicrobial regimens'.)

Adjunctive measures (including immunotherapy, glucocorticoids, and surgery) and supportive care are discussed below. (See 'Adjunctive therapies' below and 'Supportive care' below.)

Systemic anthrax without meningitis — Systemic anthrax is defined as anthrax meningitis; inhalation, injection, and gastrointestinal anthrax; and cutaneous anthrax with systemic involvement [1]. Antimicrobial therapy should be initiated promptly in any patient with suspected systemic anthrax. An antitoxin (raxibacumab or anthrax immunoglobulin) is also an essential part of the regimen. (See 'Antitoxins' below.)

As noted above, all patients suspected of having systemic anthrax should undergo lumbar puncture to evaluate for meningitis unless it is contraindicated. Patients in whom meningitis has not been ruled out should receive a regimen intended for patients with anthrax meningitis, as outlined above. (See 'Meningitis' above.)

Treatment for patients with systemic anthrax (eg, inhalation anthrax) in whom meningitis has been ruled out should include at least two agents with activity against *B. anthracis*, at least one agent with bactericidal activity, and at least one protein synthesis inhibitor (table 3). If the *B. anthracis* strain is susceptible to penicillin, penicillin G is considered equivalent to the fluoroquinolone options for primary bactericidal treatment.

For adults with systemic anthrax and normal renal function in whom meningitis has been ruled out, we suggest IV therapy with [1,3]:

- Ciprofloxacin 400 mg every 8 hours **PLUS**
- Clindamycin 900 mg every 8 hours **or** linezolid 600 mg every 12 hours

For children with systemic anthrax in whom meningitis has been ruled out, we suggest IV therapy with [2]:

- Ciprofloxacin 30 mg/kg per day divided every 8 hours (not to exceed 400 mg/dose) **or**, for penicillin-susceptible strains (MIC <0.125 mcg/mL), penicillin G 400,000 units/kg per day divided every 4 hours (not to exceed 4 million units/dose) **PLUS**
- Clindamycin 40 mg/kg per day divided every 8 hours (not to exceed 900 mg/dose)

First-line and alternative agents are reviewed in the following Table (table 3). The treatment of pregnant, lactating, and postpartum women is similar to the treatment of nonpregnant adults, except that ciprofloxacin is strongly preferred as one of the bactericidal agents [3]. In addition, at least one agent that crosses the placenta is recommended; such agents include ciprofloxacin, levofloxacin, meropenem, ampicillin, penicillin, clindamycin, and rifampin. Pharmacokinetic data indicate that penicillin, ampicillin, and carbapenems may require higher doses in pregnant and postpartum women than those recommended for nonpregnant adults [3,13].

Patients should be treated with IV therapy for at least two weeks and until clinically stable, whichever is longer [1]. Once the course of IV combination therapy has been completed, patients should be switched to single agent oral therapy to complete a 60-day course of antibiotics in order to prevent relapse from surviving *B. anthracis* spores [1]. Oral antimicrobial options are the same as those used for postexposure prophylaxis (table 2). (See "Prevention of anthrax", section on 'PEP antimicrobial regimens'.)

Children who appear to be well and have no ongoing signs or symptoms of active infection may be transitioned to oral monotherapy before completing two weeks of IV combination therapy [2]. Children who are slow to recover or in whom there is concern for persistent deep infection can be transitioned to oral therapy that

includes both a bactericidal antimicrobial agent and a protein synthesis inhibitor to complete the initial two weeks of therapy. More detailed recommendations can be found in the text and in Appendix 5 of the American Academy of Pediatrics guidelines.

Most data on the treatment of anthrax predate the availability of many of the antimicrobial agents that are recommended and/or are derived from animal studies [1]. In a systematic review of 82 cases of inhalation anthrax between 1900 and 2005, the 11 patients in the 2001 United States bioterrorist attack were significantly less likely to die than historical controls (45 versus 92 percent); they were also more likely to receive antibiotics during the prodromal phase of illness (64 versus 13 percent), multidrug regimens (≥2 antimicrobial agents or antiserum plus antimicrobial therapy; 91 versus 50 percent), and pleural fluid drainage (73 versus 11 percent) [10]. Patients who progressed to the fulminant phase had a mortality rate of 97 percent regardless of the treatment they received. All patients with anthrax meningoencephalitis died.

Three antimicrobial agents have received US Food and Drug Administration (FDA) approval for the treatment of anthrax, including inhalation anthrax: ciprofloxacin, doxycycline, and penicillin G procaine [15,16]. The multidrug regimens found to be effective in the treatment of patients with inhalation anthrax during the 2001 bioterrorism attacks included ciprofloxacin plus rifampin plus either clindamycin or vancomycin [17].

Adjunctive measures (including immunotherapy, glucocorticoids, and surgery) and supportive care are discussed below. (See 'Adjunctive therapies' below and 'Supportive care' below.)

Cutaneous anthrax without systemic involvement — The recommendations in this section are intended for patients with cutaneous anthrax **without** systemic involvement, extensive edema, or lesions of the head or neck. Patients with cutaneous anthrax with systemic involvement, extensive edema, or lesions of the head or neck should be treated according to the recommendations presented above for systemic anthrax. (See 'Systemic anthrax without meningitis' above and 'Meningitis' above.)

For cutaneous anthrax without systemic involvement, we recommend monotherapy with one of the following agents:

- **Nonpregnant adults** — For nonpregnant adults, we suggest oral therapy with [1]:
  - Ciprofloxacin 500 mg every 12 hours **OR**
  - Doxycycline 100 mg every 12 hours **OR**
  - Levofloxacin 750 mg every 24 hours **OR**
  - Moxifloxacin 400 mg every 24 hours

  Alternatives include:
  - Clindamycin 600 mg every 8 hours **OR**
  - For penicillin-susceptible strains (MIC <0.125 mcg/mL), amoxicillin 1 g every 8 hours **or** penicillin VK 500 mg every 6 hours
- **Pregnant, lactating, and postpartum women** — For pregnant, lactating, and postpartum women, the agent of choice is ciprofloxacin 500 mg orally every 12 hours [3]. If ciprofloxacin is unavailable, alternative agents that are likely to cross the placenta adequately include levofloxacin, amoxicillin, and penicillin; amoxicillin or penicillin can be used for penicillin-susceptible strains. Clindamycin and doxycycline are also likely to cross the placenta, but data are limited.
- **Children** — For children, we suggest one of the following oral agents [2]:
  - Ciprofloxacin 30 mg/kg per day divided every 12 hours (not to exceed 500 mg/dose) **OR**
  - For penicillin-susceptible strains (MIC <0.125 mcg/mL), amoxicillin 75 mg/kg per day divided every 8 hours (not to exceed 1 g/dose)

  Alternatives include:
  - Doxycycline
    - <45 kg: 4.4 mg/kg per day divided every 12 hours (not to exceed 100 mg/dose)

- ≥45 kg: 100 mg every 12 hours **OR**

- Clindamycin 30 mg/kg per day divided every 8 hours (not to exceed 600 mg/dose) **OR**
- Levofloxacin
  - <50 kg: 16 mg/kg per day divided every 12 hours (not to exceed 250 mg/dose)
  - ≥50 kg: 500 mg every 24 hours **OR**
- For penicillin-susceptible strains (MIC <0.125 mcg/mL), penicillin VK 50 to 75 mg/kg per day divided every 6 to 8 hours

Adequate dosing of penicillin and amoxicillin is particularly important because resistance may emerge during treatment with subtherapeutic doses of these agents [1].

For bioterrorism-associated cases and cases in which an aerosol exposure is suspected, the duration of therapy is 60 days [1]. For naturally acquired infection (eg, animals with anthrax, hides from animals with anthrax), the duration of therapy is 7 to 10 days.

Antitoxins — In addition to antibacterial agents with activity against *B. anthracis*, a key component of therapy is an adjunctive agent with antitoxin effects [18]. Both raxibacumab, a monoclonal antibody, and anthrax immunoglobin derived from human plasma inhibit binding of protective antigen and translocation of the two primary toxins, lethal toxin (LT) and edema toxin, into cells [1]. Obiltoxaximab is another monoclonal antibody directed against the protective antigen of *B. anthracis*.

An antitoxin should be added to combination antimicrobial therapy in patients with suspected or proven systemic anthrax [1]. Raxibacumab, a monoclonal antibody, and anthrax immunoglobulin are discussed below. Clinicians should consult the CDC if these agents are indicated.

Animal origin antiserum was used with some success in the treatment of anthrax prior to the advent of antimicrobial therapy [19-21]. In a systematic review of inhalation anthrax cases from 1900 to 2005, mortality was significantly lower among patients who received antiserum than in those who received no treatment [10].

Two monoclonal antibodies, raxibacumab and obiltoxaximab, have been approved in the United States for the treatment of inhalational anthrax [22,23]. Raxibacumab, obiltoxaximab, or anthrax immunoglobulin should be used in combination with antibiotics and should be initiated when the diagnosis of inhalation anthrax is suspected or confirmed [1,24]. Supplies of raxibacumab and obiltoxaximab are held in the United States Strategic National Stockpile for use by the CDC in the event of an anthrax emergency. Clinicians in the United States should contact the CDC if raxibacumab or obiltoxaximab is indicated.

Raxibacumab — Raxibacumab, a human IgG1-gamma monoclonal antibody directed against protective antigen, was found to be effective for the treatment of anthrax in randomized trials involving rabbits, monkeys, and dogs [25,26]. In 2012, raxibacumab was approved by the US Food and Drug Administration for the treatment of inhalation anthrax [22].

Raxibacumab is given as a single dose following premedication with diphenhydramine; dosing recommendations are as follows [27]:

- Adults and children >50 kg: 40 mg/kg IV
- Children 15 kg to 50 kg: 60 mg/kg IV
- Children 15 kg or less: 80 mg/kg

The efficacy of raxibacumab has been evaluated only in animals since it is not possible to perform efficacy trials in humans given that inhalation anthrax is both rare and lethal. However, in phase II safety studies in humans, the therapeutic levels of the antibody achieved in humans were equal to or greater than those that provide protection in animal models [28]. Common adverse effects in 326 healthy humans included rash, extremity pain, pruritus, and drowsiness [22].

In one trial, rabbits and monkeys were exposed to 200 times the median lethal dose of aerosolized *B. anthracis* spores and were monitored for the onset of signs of illness [25]. Animals with detectable protective antigen in the serum, an increase in temperature, or both, received a single intravenous dose of raxibacumab (20 mg/kg

or 40 mg/kg) or placebo. The primary endpoint was survival at 14 days in rabbits and survival at 28 days in monkeys. Rabbits that received 40 mg/kg of raxibacumab were significantly more likely to survive than those that received placebo (44 percent versus 0 percent). Likewise, monkeys that received 40 mg/kg of raxibacumab were more likely to survive than those that received placebo (64 percent versus 0 percent). The 20 mg/kg dose was also associated with improved survival in both rabbits and monkeys. In the same report, raxibacumab was well tolerated in humans who were given a single 40 mg/kg dose. It was also effective for the prevention of anthrax in rabbits and monkeys. (See "Prevention of anthrax", section on 'Raxibacumab'.)

In another trial, 40 mechanically ventilated dogs who were challenged with anthrax LT were given no treatment, hemodynamic support alone (fluids and norepinephrine), raxibacumab alone (administered at the start of the LT infusion or 9 or 12 hours later), or combination therapy with hemodynamic support plus raxibacumab [26]. Among the animals that received no treatment, all eight died, compared with six of eight animals who received hemodynamic support alone. In contrast, all five animals that received raxibacumab at the start of the LT infusion survived; however, only two of three animals that received raxibacumab at nine hours survived, and none of four animals that received raxibacumab at 12 hours survived. The animals that received both raxibacumab and hemodynamic support had the best outcomes, regardless of the delay in raxibacumab administration. Of the animals that received combined treatment, four of five animals that received raxibacumab at the start of the LT infusion survived, three of three animals that received raxibacumab at nine hours survived, and four of five animals that received raxibacumab at 12 hours survived.

Obiltoxaximab — Obiltoxaximab, a monoclonal antibody directed against the protective antigen of *B. anthracis*, was approved in 2016 by the US Food and Drug Administration for the treatment of inhalation anthrax (in combination with antimicrobial therapy) [23,29]. The evidence supporting its efficacy comes from studies in animal models of inhalational anthrax. It does not cross the blood-brain barrier and does not treat anthrax meningitis.

Obiltoxaximab is given as a single dose following premedication with diphenhydramine; dosing recommendations are as follows [29]:

- Weight >40 kg: 16 mg/kg IV
- Weight 15 to 40 kg: 24 mg/kg IV
- Weight ≤15 kg: 32 mg/kg IV

The efficacy of obiltoxaximab has been evaluated only in animals since it is not possible to perform efficacy trials in humans given that inhalation anthrax is both rare and lethal. The most common adverse effects in trials of 320 humans included headache, pruritus, upper respiratory tract infection, cough, vessel puncture site bruise, infusion site swelling, urticaria, nasal congestion, infusion site pain, and pain in an extremity [29]. Obiltoxaximab was discontinued in 8 of 320 individuals (2.5 percent) due to hypersensitivity reactions or anaphylaxis.

The efficacy of obiltoxaximab has been evaluated in studies of macaque monkeys and rabbits with inhalational anthrax [29]. Animals were challenged with aerosolized *B. anthracis* spores and were treated with obiltoxaximab or placebo after exhibiting signs or symptoms of anthrax. Among the animals that became bacteremic, those that received obiltoxaximab had significantly higher 28-day survival rates than the animals treated with placebo; survival rates ranged from 31 to 93 percent in the studies of animals that received obiltoxaximab compared with 0 to 6 percent with placebo. When obiltoxaximab was given in combination with antimicrobial therapy (levofloxacin, ciprofloxacin, doxycycline), it resulted in higher survival rates that obiltoxaximab alone.

Anthrax immunoglobulin — Anthrax immunoglobulin derived from the plasma of Anthrax Vaccine Adsorbed (AVA)-immunized persons is available from the CDC or through state and local health departments for the treatment of inhalation anthrax, in combination with antimicrobial therapy [30,31]. Anthrax immunoglobulin neutralizes toxins produced by *B. anthracis*.

Nineteen patients with anthrax were treated with anthrax immunoglobulin and antimicrobial therapy under an expanded access program [31]. Three had inhalation anthrax, one had gastrointestinal anthrax, and 15 had injection anthrax caused by contaminated heroin. Of these patients, 13 survived, including two of the three patients with inhalation anthrax.

The use of anthrax immunoglobulin for the treatment of inhalation anthrax has been best studied in animals. Rabbits exposed to an aerosolized dose of 200 times the LD_{50} of *B. anthracis* spores and treated with anthrax immunoglobulin at the time of protective antigenemia had 26 percent survival compared with 2 percent survival in animals given intravenous immunoglobulin. Of monkeys exposed to 200 times the LD_{50} of *B. anthracis* spores, survival with anthrax immunoglobulin was 36 to 70 percent, depending on the dose, compared with 0 percent in those who received placebo [31]. In another study in which anthrax immunoglobulin was added to levofloxacin in rabbits with systemic anthrax, there was a trend toward better survival in the rabbits who received anthrax immunoglobulin plus levofloxacin compared with those who received intravenous immunoglobulin plus levofloxacin, but only when treatment was delayed to 60 hours or later following anthrax exposure [31,32]. For animals treated earlier, survival was similar in the two groups. The number of animals evaluated was small, so it is difficult to draw conclusions about efficacy, although a post-hoc analysis suggested that animals with a moderate level of antigenemia benefited.

The safety of anthrax immunoglobulin was tested in 72 healthy human volunteers [31]. The most common side effects were headache, back pain, nausea, and infusion site pain and swelling.

Adjunctive therapies

Glucocorticoids — Glucocorticoids should be considered as adjunctive therapy for patients with anthrax meningitis, cutaneous anthrax with extensive edema involving the head and neck, anthrax in the setting of recent glucocorticoid therapy, or anthrax with vasopressor-resistant shock [1]. Supporting data are limited and there may be no benefit for reducing the inflammation resulting from toxin-mediated tissue edema. Small observational studies of patients with cutaneous anthrax of the head and neck suggest possible benefit [33,34]. A retrospective review of 70 cases of anthrax meningoencephalitis from 1966 to 2002 reported an overall mortality rate of 94 percent, but, among 10 patients treated with glucocorticoids as an adjunct to antimicrobial therapy, mortality was 80 percent [12]. However, it is not possible to draw conclusions from such a small study.

Pleural fluid drainage — Pleural fluid drainage has been associated with improved survival in a case series of 82 patients with inhalation anthrax [10]. Drainage of both pleural fluid and ascites is thought to improve survival by reducing the toxin level and by decreasing mechanical lung compression [1]. Pleural fluid should be drained early and aggressively; chest tubes are preferred over thoracentesis because many effusions require prolonged drainage. Thoracotomy or video-assisted thoracic surgery might be required to remove gelatinous or loculated pleural effusions.

Other invasive procedures — Ascites should be drained and monitored for reaccumulation; continuous drainage is required in some patients [1]. Surgery should not be performed for cutaneous anthrax since it can lead to dissemination and poor outcomes. Tracheostomy may be required for patients with airway obstruction and surgery may be required for large or circumferential extremity lesions causing compartment syndrome. Surgery may be indicated for patients with gastrointestinal anthrax to address potentially fatal complications, including bowel ischemia, necrosis, and perforation. For injection anthrax, surgery may be performed to obtain diagnostic specimens and to differentiate the infection from necrotizing fasciitis and to remove the necrotic nidus of infection, which may serve as a reservoir for toxin and spores.

Supportive care — Because inhalation anthrax can have a prodromal phase followed by a fulminant phase characterized by sudden decompensation, hospitalized patients should have careful hemodynamic monitoring, including continuous pulse oximetry and telemetry [1]. Standard sepsis care should be administered to patients with systemic anthrax, including intravenous fluids, vasopressors, blood products, and invasive hemodynamic monitoring as needed.

Microangiopathic hemolytic anemia, coagulopathy, thrombocytopenia, and hemorrhage occur frequently with anthrax infection; these complications should be managed aggressively and may be contraindications to central venous catheter placement [1]. Patients with anthrax may require mechanical ventilation for respiratory distress, airway protection (for those with altered mental status), and/or airway edema. Substantial airway edema can occur with cutaneous lesions involving the head, neck, or thorax, and with oropharyngeal lesions.

More detailed recommendations for supportive care can be found in the CDC guidelines.

PREVENTION — Anthrax pre-event vaccination and postexposure vaccination, antimicrobial prophylaxis, and raxibacumab prophylaxis are reviewed separately. (See "Prevention of anthrax".)

PUBLIC HEALTH REPORTING — Anthrax is a reportable disease and immediate notification should be made to the local or state health department and public health laboratory even if there is only clinical or laboratory suspicion of anthrax or exposure to *B. anthracis*.

Healthcare providers should consult their local or state public health departments for specific recommendations for the prevention or treatment of bioterrorism-related anthrax. This is critically important in order to ensure that an antimicrobial regimen is selected to which the isolate is fully susceptible. For example, isolates from the bioterrorism-related cases in the United States in 2001 were susceptible to ciprofloxacin, doxycycline, tetracycline, rifampin, vancomycin, chloramphenicol, imipenem, clindamycin, and clarithromycin [35]. Although susceptible to penicillin and ampicillin, the presence of an inducible beta-lactamase in the isolates led the United States Centers for Disease Control and Prevention to advise against the use of these drugs as single agents for therapy of anthrax cases related to the 2001 bioterrorism event. (See 'Important caveats' above.)

OUTCOMES — Outcomes of anthrax vary depending on the site(s) of involvement:

- The case-fatality rate of cutaneous anthrax is <2 percent with antibiotic therapy; without therapy, mortality has ranged from 16 to 39 percent [1]. In the preantibiotic era in the early 20th century, the mortality rate in patients who received serum (antitoxin) ranged from 0 to 28 percent.
- Patients with inhalation anthrax frequently present late in the course of their illness. Prior to 2001, mortality rates for patients with inhalation anthrax were nearly 90 percent [1]. Since then, 8 of 15 patients (53 percent) with inhalation anthrax have survived. Patients who survived were diagnosed early, given combination antimicrobial therapy to eradicate *B. anthracis* and inhibit toxin production, and had aggressive management of pleural effusions.
- Even with antimicrobial therapy and modern intensive care, the mortality rates of injection, gastrointestinal, and inhalation anthrax have been estimated to be 28 percent, ≥40 percent, and 45 percent, respectively [1].
- With treatment, the mortality rate for anthrax meningitis approaches 100 percent [1,2].

SUMMARY AND RECOMMENDATIONS

- Sporadic cases and outbreaks of naturally occurring anthrax continue to occur worldwide, although they are rare in developed nations. However, anthrax remains a concern in the developed world because of its potential as an agent of bioterrorism. Anthrax meningitis and the fulminant phase of inhalation anthrax are associated with extremely high mortality rates. Anthrax is a reportable disease and immediate notification should be made to the local or state health department and public health laboratory even if there is only clinical or laboratory suspicion of anthrax or exposure to *Bacillus anthracis*. (See 'Introduction' above and 'Public health reporting' above.)
- Meningitis and hemorrhagic brain infection has been observed in up to one-half of anthrax cases. Unless it is contraindicated, all patients suspected of having inhalation anthrax should undergo lumbar puncture to evaluate for meningitis. Other important caveats are discussed above. (See 'Important caveats' above.)
- Treatment of patients suspected of having systemic anthrax should be started urgently and should include intravenous (IV) antimicrobial combination therapy, an antitoxin (raxibacumab or anthrax immunoglobulin), drainage of pleural effusions, supportive care, and consideration of adjunctive glucocorticoids. When selecting an antimicrobial regimen, the production of toxin, the potential for antimicrobial drug resistance, the frequent occurrence of meningitis, and the presence of latent spores must be taken into account. (See 'Important caveats' above.)
- For patients with systemic anthrax in whom meningitis is suspected or cannot be ruled out, we suggest ciprofloxacin **plus** meropenem **plus** linezolid (table 1) (**Grade 2C**). We also recommend that an antitoxin be administered to such patients (**Grade 1C**). Antitoxins include the monoclonal antibodies, raxibacumab and obiltoxaximab, and anthrax immunoglobulin derived from human plasma; these agents are available from the United States Centers for Disease Control and Prevention (CDC). (See 'Meningitis' above.)
- For patients with systemic anthrax (eg, inhalation anthrax) without meningitis, we suggest one of the antimicrobial regimens reviewed above and in the following Table (table 3) (**Grade 2C**). We also

recommend that an antitoxin be administered to such patients (**Grade 1C**). Raxibacumab and anthrax immunoglobulin are available from the CDC. (See 'Systemic anthrax without meningitis' above.)

- Patients with systemic anthrax in whom meningitis is suspected or cannot be ruled out should be treated with IV antimicrobial therapy for at least two to three weeks and until clinically stable, whichever is longer. Patients with systemic anthrax without meningitis should be treated with IV therapy for at least two weeks and until clinically stable, whichever is longer. Once the course of IV combination therapy has been completed, patients should be switched to single agent oral therapy to complete a 60-day course of antibiotics in order to prevent relapse from surviving *B. anthracis* spores. Oral antimicrobial options are the same as those used for postexposure prophylaxis (table 2). (See 'Systemic anthrax without meningitis' above.)

- Patients with cutaneous anthrax without systemic involvement should receive oral antimicrobial therapy with a single agent. For nonpregnant adults, we suggest ciprofloxacin **or** doxycycline **or** levofloxacin **or** moxifloxacin (**Grade 2C**). For pregnant, lactating, and postpartum women, we suggest ciprofloxacin (**Grade 2C**). For children, we suggest ciprofloxacin **or**, for penicillin-susceptible strains (minimum inhibitory concentration <0.125 mcg/mL), amoxicillin (**Grade 2C**). For bioterrorism-associated cases and cases in which an aerosol exposure is suspected, the duration of therapy is 60 days. For naturally acquired infection (eg, animals with anthrax, hides from animals with anthrax), the duration of therapy is 7 to 10 days. (See 'Cutaneous anthrax without systemic involvement' above.)

- Glucocorticoids should be considered as adjunctive therapy for patients with systemic anthrax, meningitis, or cutaneous anthrax with extensive edema involving the head and neck. (See 'Glucocorticoids' above.)

- Pleural fluid should be drained early and aggressively; chest tubes are preferred over thoracentesis because many effusions require prolonged drainage. (See 'Pleural fluid drainage' above.)

- Standard sepsis care should be administered to patients with systemic anthrax, including intravenous fluids, vasopressors, blood products, and invasive hemodynamic monitoring as needed. (See 'Supportive care' above.)

- Anthrax postexposure prophylaxis is discussed separately. (See "Prevention of anthrax".)

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Topic 15309 Version 16.0

GRAPHICS

Intravenous antimicrobial regimens for the treatment of systemic anthrax with possible or confirmed meningitis*

Nonpregnant adults	Pregnant, postpartum, and lactating women	Children and adolescent (age ≥1 month through 17 years)
First bactericidal agent:		
Preferred:		
Ciprofloxacin 400 mg every 8 hours	Ciprofloxacin 400 mg every 8 hours NOTE: The treatment of pregnant, postpartum, and lactating women is similar to that for nonpregnant adults, except that **ciprofloxacin is strongly preferred as the first bactericidal agent** At least one agent with transplacental passage is recommended; agents with transplacental passage include ciprofloxacin, levofloxacin, meropenem, ampicillin, penicillin, clindamycin, rifampin	Ciprofloxacin 30 mg/kg per day divided every 8 hours, not to exceed 400 mg per dose
Alternatives if ciprofloxacin is unavailable or contraindicated, in order of preference:		
Levofloxacin 750 mg every 24 hours **OR**	Levofloxacin 750 mg every 24 hours **OR**	Levofloxacin ▪ <50 kg: 16 mg/kg per day divided every 12 hours, not to exceed 250 mg per dose ▪ ≥50 kg: 500 mg every 24 hours **OR**
Moxifloxacin 400 mg every 24 hours	Moxifloxacin 400 mg every 24 hours	Moxifloxacin ▪ 3 months to <2 years: 12 mg/kg per day divided every 12 hours, not to exceed 200 mg per dose ▪ 2 to 5 years: 10 mg/kg per day divided every 12 hours, not to exceed 200 mg per dose ▪ 6 to 11 years: 8 mg/kg per day divided every 12 hours, not to exceed 200 mg per dose ▪ 12 to 17 years, <45 kg: 8 mg/kg per day divided

		every 12 hours, not to exceed 200 mg per dose ▪ 12 to 17 years, ≥45 kg: 400 mg every 24 hours
PLUS		
Second bactericidal agent:		
Preferred for all strains, regardless of penicillin susceptibility or if susceptibility is unknown:		
Meropenem 2 g every 8 hours	Meropenem 2 g every 8 hours[Δ]	Meropenem 120 mg/kg per day divided every 8 hours, not to exceed 2 g per dose
Alternatives if meropenem is unavailable or contraindicated, in order of preference:		
Imipenem 1 g every 6 hours[◇] **OR**	Imipenem 1 g every 6 hours[Δ◇] **OR**	Imipenem 100 mg/kg per day divided every 6 hours, not to exceed 1 g per dose[◇] **OR**
Doripenem 500 mg every 8 hours	Doripenem 500 mg every 8 hours[Δ]	Doripenem 120 mg/kg per day divided every 8 hours, not to exceed 1 g per dose **OR**
		Vancomycin 60 mg/kg per day divided every 8 hours, not to exceed 2 grams per dose; maintain serum trough concentration of 15 to 20 mcg/mL
Alternatives for penicillin-susceptible strains (MIC <0.125 mcg/mL):[§]		
Penicillin G 4 million units every 4 hours **OR**	Penicillin G 4 million units every 4 hours[Δ] **OR**	Penicillin G 400,000 units/kg per day divided every 4 hours, not to exceed 4 million units per dose **OR**
Ampicillin 3 g every 6 hours	Ampicillin 3 g every 6 hours[Δ]	Ampicillin 400 mg/kg per day divided every 6 hours, not to exceed 3 g per dose
PLUS		
Protein synthesis inhibitor (preferred):		
Linezolid 600 mg every 12 hours[¥]	Linezolid 600 mg every 12 hours[¥]	Linezolid[¥] ▪ <12 years old: 30 mg/kg per day divided every 8 hours, not to exceed 600 mg per dose ▪ ≥12 years old: 30 mg/kg per day divided every 12 hours, not to exceed 600 mg per dose
Alternatives if linezolid unavailable or contraindicated, in order of preference:		
Clindamycin 900 mg every 8 hours **OR**	Clindamycin 900 mg every 8 hours **OR**	Clindamycin 40 mg/kg per day divided every 8 hours, not to exceed 900 mg per dose **OR**
Rifampin 600 mg every 12 hours[‡] **OR**	Rifampin 600 mg every 12 hours[‡]	

		Rifampin 20 mg/kg per day divided every 12 hours, not to exceed 300 mg per dose‡ **OR**
Chloramphenicol 1 g every 6 to 8 hours†	Chloramphenicol 1 g every 6 to 8 hours†	Chloramphenicol 100 mg/kg per day divided every 6 hours, not to exceed 1 g per dose†

In addition to antimicrobial therapy, antitoxin therapy (raxibacumab or anthrax immunoglobulin) should also be given. Patients should be treated with IV antimicrobial therapy for at least two to three weeks and until clinically stable, whichever is longer. These recommendations are based on the susceptibilities of *B. anthracis* isolated during the 2001 bioterrorism event in the United States. In the event of another bioterrorism event, susceptibilities must be rechecked and antimicrobial therapy modified accordingly. Following completion of IV antimicrobial therapy, patients exposed to aerosolized spores will require PEP to complete 60 days of therapy from onset of illness. Refer to the related topic reviews and table on anthrax PEP for additional details.

MIC: minimum inhibitory concentration; IV: intravenous; PEP: postexposure prophylaxis.
* The doses recommended above are intended for patients with normal renal function; the doses of some of these agents must be adjusted in patients with renal insufficiency.
Δ Pharmacokinetic data indicate that penicillin, ampicillin, and carbapenems may require higher doses in pregnant and postpartum women than those recommended for nonpregnant adults.
◇ Imipenem is associated with an increased risk of seizures.
§ Penicillin-based antimicrobial drug use requires a high index of suspicion for emergence of resistance.
¥ Linezolid should be used with caution in patients with thrombocytopenia because it might exacerbate it. Linezolid use for >14 days has additional bone marrow toxicity.
‡ Rifampin is not a protein synthesis inhibitor. However, it may be used as an alternative agent based on its in vitro synergy for staphylococci in place of a protein synthesis inhibitor if they (linezolid, clindamycin) cannot be given. It has not been evaluated for *B. anthracis*.
† Because of toxicity concerns, chloramphenicol should only be used if other options are not available.

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3. *Bradley JS, Peacock G, Krug SE, et al. Pediatric anthrax clinical management. Pediatrics 2014; 133:e1411.*

Graphic 96170 Version 3.0

Oral postexposure prophylaxis for anthrax*

Nonpregnant adults	Pregnant, postpartum, and lactating women	Children and adolescents (age ≥1 month through 17 years)
For all strains, regardless of penicillin susceptibility or if susceptibility is unknown:		
Preferred:		
Ciprofloxacin 500 mg every 12 hours **OR**	Ciprofloxacin 500 mg every 12 hours	Ciprofloxacin 30 mg/kg per day divided every 12 hours, not to exceed 500 mg per dose **OR**
Doxycycline 100 mg every 12 hours		Doxycycline¶ ▪ <45 kg: 4.4 mg/kg per day divided every 12 hours, not to exceed 100 mg per dose ▪ ≥45 kg: 100 mg every 12 hours
Alternatives if preferred agent(s) are unavailable, in order of preference:		
Levofloxacin 750 mg every 24 hours **OR**	Clindamycin 600 mg every 8 hours **OR**	Clindamycin 30 mg/kg per day divided every 8 hours, not to exceed 600 mg per dose **OR**
Moxifloxacin 400 mg every 24 hours **OR**	Doxycycline 100 mg every 12 hours	Levofloxacin△ ▪ <50 kg: 16 mg/kg per day divided every 12 hours, not to exceed 250 mg per dose ▪ ≥50 kg: 500 mg every 24 hours
Clindamycin 600 mg every 8 hours		
Alternatives for penicillin-susceptible strains (MIC <0.125 mcg/mL):		
Amoxicillin 1 g every 8 hours◇ **OR**	Amoxicillin 1 g every 8 hours◇ **OR**	Amoxicillin 75 mg/kg per day divided every 8 hours, not to exceed 1 g/dose◇ **OR**
Penicillin V potassium 500 mg every 6 hours◇	Penicillin V potassium 500 mg every 6 hours◇	Penicillin V potassium 50 to 75 mg/kg per day divided every 6 to 8 hours not to exceed 500 mg per dose◇

PEP is started as soon as possible for suspected aerosolized exposure to *Bacillus anthracis*, pending risk assessment. All patients who meet criteria for receiving PEP should also receive three doses of anthrax vaccine adsorbed by subcutaneous administration at zero, two, and four weeks. Recommendations for PEP regimens are based on the susceptibilities of *B. anthracis* isolated during the 2001 bioterrorism event in the United States. In the setting of another bioterrorism event, susceptibilities must be rechecked and antimicrobial therapy modified accordingly. The duration of therapy for PEP is 60 days. Refer to the UpToDate topic on prevention of anthrax for additional details.

MIC: minimum inhibitory concentration; PEP: postexposure prophylaxis.
* The doses recommended above are intended for patients with normal renal function; the doses of some of these agents must be adjusted in patients with renal insufficiency.
¶ A single 14-day course of doxycycline is not routinely associated with tooth staining, but some degree of staining is likely with a prolonged treatment course of up to 60 days in children <8 years of age.
Δ Safety data for levofloxacin are limited to 14 days for duration of therapy in children and 30 days in adults.
◇ Be aware of the possibility of emergence of penicillin resistance during monotherapy with amoxicillin or penicillin.

References:

1. *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. *Meaney-Delman D, Zotti ME, Creanga AA, et al. Special considerations for prophylaxis for and treatment of anthrax in pregnant and postpartum women. Emerg Infect Dis 2014; 20.*
3. *Bradley JS, Peacock G, Krug SE, et al. Pediatric anthrax clinical management. Pediatrics 2014; 133:e1411.*

Graphic 58905 Version 5.0

Intravenous therapy for systemic anthrax when meningitis has been excluded*

Nonpregnant adults	Pregnant, postpartum, and lactating women	Children and adolescents (age ≥1 month through 17 years)
A bactericidal agent:		
Preferred for all strains, regardless of penicillin susceptibility or if susceptibility is unknown:		
Ciprofloxacin 400 mg every 8 hours	Ciprofloxacin 400 mg every 8 hours NOTE: The treatment of pregnant, postpartum, and lactating women is similar to that for nonpregnant adults, except that **ciprofloxacin is strongly preferred for the bactericidal agent** At least one agent with transplacental passage is recommended; agents with transplacental passage include ciprofloxacin, levofloxacin, meropenem, ampicillin, penicillin, clindamycin, and rifampin	Ciprofloxacin 30 mg/kg per day divided every 8 hours, not to exceed 400 mg per dose
Alternatives if ciprofloxacin is unavailable or contraindicated, in order of preference:		
Levofloxacin 750 mg every 24 hours **OR**	Levofloxacin 750 mg every 24 hours **OR**	Meropenem 60 mg/kg per day divided every 8 hours, not to exceed 2 g per dose **OR**
Moxifloxacin 400 mg every 24 hours **OR**	Moxifloxacin 400 mg every 24 hours **OR**	Levofloxacin ▪ <50 kg: 20 mg/kg per day divided every 12 hours, not to exceed 250 mg per dose ▪ ≥50 kg: 500 mg every 24 hours **OR**
Meropenem 2 g every 8 hours **OR**	Meropenem 2 g every 8 hours[Δ] **OR**	
Imipenem 1 g every 6 hours[◇] **OR**	Imipenem 1 g every 6 hours[Δ◇] **OR**	Imipenem 100 mg/kg per day divided every 6 hours, not to exceed 1 g per dose[◇] **OR**
Doripenem 500 mg every 8 hours **OR**	Doripenem 500 mg every 8 hours[Δ] **OR**	
Vancomycin 60 mg/kg per day divided every 8 hours, not to exceed 2 g per dose; maintain serum trough concentration of 15 to 20 mcg/mL	Vancomycin 60 mg/kg per day divided every 8 hours, not to exceed 2 g per dose; maintain serum trough concentration of 15 to 20 mcg/mL	Vancomycin 60 mg/kg per day divided every 8 hours, not to exceed 2 g per dose; maintain serum trough concentration of 15 to 20 mcg/mL
Alternatives for penicillin-susceptible strains:		
Preferred:		

Penicillin G 4 million units every 4 hours	Penicillin G 4 million units every 4 hours[Δ]	Penicillin G 400,000 units/kg per day divided every 4 hours, not to exceed 4 million units per dose
Alternative:		
Ampicillin 3 g every 6 hours	Ampicillin 3 g every 6 hours[Δ]	Ampicillin 200 mg/kg per day divided every 6 hours, not to exceed 3 g per dose
PLUS		
A protein synthesis inhibitor:		
Preferred:		
Clindamycin 900 mg every 8 hours **OR**	Clindamycin 900 mg every 8 hours **OR**	Clindamycin 40 mg/kg per day divided every 8 hours, not to exceed 900 mg/dose **OR**
Linezolid 600 mg every 12 hours[§]	Linezolid 600 mg every 12 hours[§]	
Alternatives if clindamycin and linezolid (for adults) or clindamycin (for children) are unavailable or contraindicated, in order of preference:		
		Linezolid (non-CNS infection dose)[§] ▪ <12 years old: 30 mg/kg per day divided every 8 hours, not to exceed 600 mg/dose ▪ ≥12 years old: 30 mg/kg per day divided every 12 hours, not to exceed 600 mg/dose **OR**
Doxycycline 200 mg loading dose, then 100 mg every 12 hours **OR**	Doxycycline 200 mg loading dose, then 100 mg every 12 hours[¥] **OR**	Doxycycline[¥] ▪ <45 kg: 4.4 mg/kg loading dose, not to exceed 200 mg; then 4.4 mg/kg per day divided every 12 hours, not to exceed 100 mg per dose ▪ ≥45 kg: 200 mg loading dose; then 100 mg every 12 hours **OR**
Rifampin 600 mg every 12 hours[‡]	Rifampin 600 mg every 12 hours[‡]	Rifampin 20 mg/kg per day divided every 12 hours, not to exceed 300 mg/dose[‡]

Systemic anthrax includes anthrax meningitis; inhalation, injection, and gastrointestinal anthrax; and cutaneous anthrax with systemic involvement, extensive edema, or lesions of the head or neck. In addition to antimicrobial therapy, antitoxin therapy (raxibacumab or anthrax immunoglobulin) should also be given. Patients should be treated with IV antimicrobial therapy for two weeks and until clinically stable, whichever is longer. These recommendations are based on the susceptibilities of *B. anthracis* isolated during the 2001 bioterrorism event in the United States. In the event of another bioterrorism event, susceptibilities must be rechecked and antimicrobial therapy modified accordingly. Following completion of IV antimicrobial therapy,

patients exposed to aerosolized spores will require PEP to complete 60 days of therapy from onset of illness. Refer to the related topic review and table on anthrax PEP.

CNS: central nervous system; IV: intravenous; PEP: postexposure prophylaxis.
* The doses recommended above are intended for patients with normal renal function; the doses of some of these agents must be adjusted in patients with renal insufficiency.
Δ Pharmacokinetic data indicate that penicillin, ampicillin, and carbapenems may require higher doses in pregnant and postpartum women than those recommended for nonpregnant adults.
◇ Imipenem is associated with an increased risk of seizures.
§ Linezolid should be used with caution in patients with thrombocytopenia because it might exacerbate it. Linezolid use for >14 days has additional bone marrow toxicity.
¥ A single 10 to 14 day course of doxycycline is not routinely associated with tooth staining.
‡ Rifampin is not a protein synthesis inhibitor. However, it may be used as an alternative agent based on its in vitro synergy for staphylococci in place of a protein synthesis inhibitor if linezolid and clindamycin cannot be given. Rifampin has not been evaluated for *B. anthracis*.

References:

1. *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. *Meaney-Delman D, Zotti ME, Creanga AA, et al. Special considerations for prophylaxis for and treatment of anthrax in pregnant and postpartum women. Emerg Infect Dis 2014; 20.*
3. *Bradley JS, Peacock G, Krug SE, et al. Pediatric anthrax clinical management. Pediatrics 2014; 133:e1411.*

Graphic 74184 Version 6.0

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