Anthrax

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Number: 0483

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses anthrax.

1. **Medical Necessity**

    1. **Pre-Exposure Vaccination**

        Aetna considers anthrax immunization a medically necessary preventive service for indications recommended by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP). The ACIP recommends pre-exposure anthrax vaccination for the following groups:

        - Decontamination personnel and persons who work directly with the organism in the laboratory.*
        - Military personnel deployed to areas with high-risk for exposure to the organism (as when it is used as a biological warfare weapon).*
        - Persons who handle potentially infected animal products in high-incidence areas. (Incidence is low in the United States, but veterinarians who travel to work in other countries where incidence is higher should consider being vaccinated.)*
        - Persons who work with imported animal hides or furs in areas where standards are insufficient to prevent exposure to anthrax spores.*
        - Environmental investigators and remediation workers who, as part of their occupation, might repeatedly enter areas contaminated with B. anthracis spores.*
        - Responder units engaged in response activities that might lead to exposure to aerosolized *B. anthracis* spores.* (However, emergency and other responders are not recommended to receive routine pre-event anthrax vaccination because of the lack of a calculable risk assessment.)

        The immunization consists of 2 intramuscular injections given 4 weeks apart followed by 3 additional subcutaneous injections given at 6, 12, and 18 months. The ACIP recommends annual booster injections of the vaccine thereafter.

        ***Note**: In general, Aetna does not cover immunizations required solely for the purpose of employment, or because of incarceration. In addition, HMO plans usually exclude coverage of immunizations solely for the purpose of travel. Coverage of medically necessary preventive immunizations is available only to members with preventive service benefits. Check contract language, limitations and exclusions for coverage details.

    2. **Post-Exposure Vaccination**

        Aetna considers post-exposure anthrax vaccination medically necessary according to the ACIP guidelines. The ACIP guidelines recommend post-exposure anthrax vaccination for the following indications:

        - After aerosol exposure to *Bacillus anthracis* spores.
        - Following cutaneous or gastrointestinal exposure to *Bacillus anthracis*.

Note: Medically necessary post-exposure anthrax vaccinations are covered for medically necessary indications regardless of whether the member has preventive services benefits.

Aetna considers raxibacumab injection medically necessary for the prevention and treatment of inhalational anthrax.

Aetna considers obiltoxaximab (Anthim) injection in combination with appropriate anti-bacterial drugs medically necessary for the treatment of inhalational anthrax.

Aetna considers obiltoxaximab medically necessary for the prevention of inhalational anthrax when alternative therapies are not available or not appropriate.

Aetna considers intravenous human anthrax immune globulin (Anthrasil) medically necessary to treat persons with inhalational anthrax in combination with appropriate antibacterial drugs.

2. **Experimental, Investigational, or Unproven**

The following procedures are considered experimental, investigational, or unproven because the effectiveness of these approaches has not been established:

1. Anthrax vaccine for all other indications.
2. Intravenous anthrax immune globulin for the treatment of systemic anthrax soft tissue infection related to drug injection.

CPT Codes / HCPCS codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description

CPT codes covered if selection criteria are met:

***Intravenous human anthrax immune globulin (Anthrasil)* - no specific code:**

90581	Anthrax vaccine, for subcutaneous or intramuscular use

HCPCS codes covered if selection criteria are met:

***Obiltoxaximab (Anthim)* - no specific code:**

ICD-10 codes covered if selection criteria are met:

A22.1	Pulmonary anthrax
Z20.810	Contact with and (suspected) exposure to anthrax
Z23	Encounter for immunization

Background

The following discussion is based primarily on guidelines on use of anthrax vaccine from the Advisory Committee on Immunization Practices (ACIP) and information on anthrax from the Centers for Disease Control and Prevention (CDC).

Anthrax is an acute infectious disease caused by the spore-forming bacterium *Bacillus anthracis*. Anthrax most commonly occurs in wild and domestic lower vertebrates (antelopes, camels, cattle, goats, sheep, and other herbivores), but it can also occur in humans when they are exposed to infected animals or tissue from infected animals.

Because anthrax is considered to be a potential agent for use in biological warfare, the Department of Defense (DOD) has begun mandatory vaccination of all active duty military personnel who might be involved in conflict.

Anthrax is most common in agricultural regions where it occurs in animals. These include South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East. When anthrax affects humans, it is usually due to an occupational exposure to infected animals or their products. Workers who are exposed to dead animals and animal products from other countries where anthrax is more common may become infected with Bacillus anthracis (*B. anthracis;* industrial anthrax). Anthrax in wild livestock has occurred in the United States.

Anthrax infection can occur in 3 forms:

1. cutaneous (skin),
2. inhalation, and
3. gastrointestinal.

Symptoms of disease vary depending on how the disease was contracted, but symptoms usually occur within 7 days. Most (about 95 %) anthrax infections occur when the bacterium enters a cut or abrasion on the skin, such as when handling contaminated wool, hides, leather or hair products (especially goat hair) of infected animals. Skin infection begins as a raised itchy bump that resembles an insect bite but within 1 to 2 days develops into a vesicle and then a painless ulcer, usually 1 to 3 cm in diameter, with a characteristic black necrotic (dying) area in the center. Lymph glands in the adjacent area may swell. About 20 % of untreated cases of cutaneous anthrax will result in death. Deaths are rare with appropriate anti-microbial therapy.

Initial symptoms of anthrax inhalation may resemble a common cold. After several days, the symptoms may progress to severe breathing problems and shock. Inhalation anthrax is usually fatal. The intestinal disease form of anthrax may follow the consumption of contaminated meat and is characterized by an acute inflammation of the intestinal tract. Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and severe diarrhea. Intestinal anthrax results in death in 25 % to 60 % of cases.

Anthrax is diagnosed by isolating *B. anthracis* from the blood, skin lesions, or respiratory secretions or by measuring specific antibodies in the blood of persons with suspected cases.

Anthrax can be found globally. It is more common in developing countries or countries without veterinary public health programs. Certain regions of the world (South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East) report more anthrax in animals than others. Direct person-to-person spread of anthrax is extremely unlikely to occur. Communicability is not a concern in managing or visiting with patients with inhalational anthrax.

The World Health Organization and the CDC recommend that, in countries where anthrax is common and vaccination levels of animal herds are low, humans should avoid contact with livestock and animal products and avoid eating meat that has not been properly slaughtered and cooked. Also, an anthrax vaccine has been licensed for use in humans. The vaccine is reported to be 93 % effective in protecting against anthrax.

The anthrax vaccine is manufactured and distributed by BioPort, Corporation (Lansing, MI). The vaccine is a cell-free filtrate vaccine, which means it contains no dead or live bacteria in the preparation. According to the CDC, anthrax vaccines intended for animals should not be used in humans.

Anthrax pre-exposure prophylaxis consists of 2 intramuscular injections given 4 weeks apart followed by 3 additional subcutaneous injections given at 6, 12, and 18 months. Annual booster injections of the vaccine are recommended thereafter.

Mild local reactions occur in 30 % of recipients and consist of slight tenderness and redness at the injection site. Severe local reactions are infrequent and consist of extensive swelling of the forearm in addition to the local reaction. Systemic reactions occur in fewer than 0.2 % of recipients.

Pre-Exposure Vaccination

Occupational and Laboratory Exposures

According to the ACIP, routine vaccination with Anthrax Vaccine Adsorbed (AVA) is indicated for persons engaged in:

- Activities with a high potential for aerosol production
- Work involving production quantities or concentrations of Bacillus anthracis cultures.

The ACIP has concluded that laboratorians using standard Biosafety Level 2 practices in the routine processing of clinical samples are not at increased risk for exposure to *Bacillus anthracis* spores.

The CDC announced that decontamination personnel and state and private laboratory workers who are involved in analyzing possible anthrax exposures will be eligible for vaccination against anthrax.

The risk for persons who come in contact in the workplace with imported animal hides, furs, bone meal, wool, animal hair, or bristles has been reduced by changes in industry standards and import restrictions. ACIP recommends routine pre-exposure vaccination only for persons in this group for whom these standards and restrictions are insufficient to prevent exposure to anthrax spores.

The ACIP does not recommend routine vaccination of veterinarians in the United States because of the low incidence of animal cases. However, the ACIP guidelines note that vaccination might be indicated for veterinarians and other high-risk persons handling potentially infected animals in areas with a high incidence of anthrax cases.

Bioterrorism Preparedness

Although groups initially considered for pre-exposure vaccination for bioterrorism preparedness included emergency first responders, federal responders, medical practitioners, and private citizens, the ACIP does not recommend vaccination of these groups. The ACIP guidelines note that recommendations regarding pre-exposure vaccination should be based on a calculable risk assessment. The guidelines explain that, at present, the target population for a bioterrorist release of *Bacillus anthracis* can not be predetermined, and the risk of exposure can not be calculated. In addition, studies suggest an extremely low-risk for exposure related to secondary aerosolization of previously settled *Bacillus anthracis* spores. Because of these factors, the ACIP does not recommend pre-exposure vaccination for the above groups. The ACIP does state that pre-exposure vaccination may be indicated for the military, decontamination personnel, and other select populations or for groups for which a calculable risk can be assessed.

Options other than pre-exposure vaccination are available to protect personnel working in an area of a known previous release of *Bacillus anthracis*. According to the ACIP guidelines, if concern exists that persons entering an area of a previous release might be at risk for exposure from a re-release of a primary aerosol of the organism or exposure from a high concentration of settled spores in a specific area, initiation of prophylaxis should be considered with antibiotics alone or in combination with vaccine as is outlined in the section below on post-exposure prophylaxis.

Post-Exposure Prophylaxis - Chemoprophylaxis and Vaccination

Penicillin and doxycycline are approved by Food and Drug Administration (FDA) for the treatment of anthrax and are considered the drugs of choice for the treatment of naturally occurring anthrax. In addition, ciprofloxacin and ofloxacin have also demonstrated in- vitro activity against *Bacillus anthracis*. On the basis of studies that demonstrated the effectiveness of ciprofloxacin in reducing the incidence and progression of inhalation anthrax in animal models, the FDA approved the use of ciprofloxacin following aerosol exposure to *Bacillus anthracis* spores to prevent development or progression of inhalation anthrax in humans. Although naturally occurring *Bacillus anthracis* resistance to penicillin is rare, such resistance has been reported.

Antibiotics are effective against the germinated form of *Bacillus anthracis* but are not effective against the spore form of the organism. Following inhalation exposure, spores can survive in tissues for months without germination in non-human primates. This phenomenon of delayed vegetation of spores resulting in prolonged incubation periods has not been observed for routes of infection other than inhalation.

Currently, ciprofloxacin is the only antibiotic approved by the FDA for use in reducing the incidence or progression of disease after exposure to aerosolized *Bacillus anthracis*. Although post-exposure chemoprophylaxis using antibiotics alone has been effective in animal models, the definitive length of treatment is unclear. Several studies have demonstrated that short courses (5 to 10 days) of post-exposure antibiotic therapy are not effective at preventing disease when large numbers of spores are inhaled. Longer courses of antibiotics may be effective.

Studies have demonstrated that antibiotics in combination with post-exposure vaccination are effective at preventing disease in nonhuman primates after exposure to *Bacillus anthracis* spores. Vaccination alone after exposure was not protective. Because the current vaccine is labeled for use in specifically defined pre-exposure situations only, no FDA-approved labeling addresses the optimal number of vaccinations for post-exposure prophylaxis use of the vaccine. An estimated 83 % of human vaccines develop a vaccine-induced immune response after 2 doses of the vaccine and greater than 95 % develop a fourfold rise in antibody titer after 3 doses. Although the precise correlation between antibody titer and protection against disease is not clear, these studies of post-exposure vaccine regimens used in combination with antibiotics in non-human primates have consistently documented that 2 to 3 doses of vaccine were sufficient to prevent development of disease once antibiotics were discontinued.

Only 1 study has directly compared antibiotics plus vaccine with a longer course of antibiotics following aerosol exposure. This study documented no significant difference in survival for animals treated with doxycycline alone for 30 days or animals treated with 30 days of doxycycline plus two doses of anthrax vaccine post-exposure (9 of 10 versus 9 of 9, $p = 0.4$). However, the study suggests a possible benefit of post-exposure combination of antibiotics with vaccination.

Following Inhalation Exposure

The ACIP recommends post-exposure prophylaxis against *Bacillus anthracis* following an aerosol exposure to *Bacillus anthracis* spores. Such exposure might occur following an inadvertent exposure in the laboratory setting or a biological terrorist incident.

Aerosol exposure is unlikely in settings outside a laboratory working with large volumes of *Bacillus anthracis*, textile mills working with heavily contaminated animal products, or following a biological terrorism or warfare attack. Following naturally occurring anthrax among livestock, cutaneous and rare gastrointestinal exposures among humans are possible, but inhalation anthrax has not been reported. Because of the potential persistence of spores following a possible aerosol exposure, the ACIP recommends 60 days of anti-microbial prophylaxis in conjunction with 3 doses of anthrax vaccine for optimal protection of previously unvaccinated persons after exposure to aerosolized *B. anthracis* spores. Because of concern about the possible antibiotic resistance of *Bacillus anthracis* used in a bioterrorist attack, the ACIP guidelines state that doxycycline or ciprofloxacin can be chosen initially for antibiotic chemoprophylaxis until organism susceptibilities are known. The guidelines note that antibiotic chemoprophylaxis can be switched to penicillin VK or amoxicillin once antibiotic susceptibilities are known and the organism is found to be penicillin susceptible with minimum inhibitory concentrations (MICs) attainable with oral therapy.

Although the shortened vaccine regimen has been effective when used in a post-exposure regimen that includes antibiotics, the duration of protection from vaccination is not known. Therefore, if subsequent exposures occur, additional vaccinations might be required.

Following Cutaneous or Gastrointestinal Exposure

No controlled studies have been conducted in animals or humans to evaluate the use of antibiotics alone or in combination with vaccination following cutaneous or gastrointestinal exposure to *Bacillus anthracis*. Cutaneous and rare gastrointestinal exposures of humans are possible following outbreaks of anthrax in livestock. In these situations, on the basis of pathophysiology, reported incubation periods, current expert clinical judgment, and lack of data, post-exposure prophylaxis might consist of antibiotic therapy for 7 to 14 days.

Vaccination During Pregnancy

No studies have been published regarding use of anthrax vaccine among pregnant women. The ACIP guidelines recommend anthrax vaccine as a component of post-exposure prophylaxis in pregnant women exposed to aerosolized *B. anthracis* spores. In a pre-event setting, in which the risk for exposure to aerosolized *B. anthracis* spores is presumably low, vaccination of pregnant women is not recommended and should be deferred until after pregnancy.

Vaccination During Lactation

No data suggest increased risk for side effects or temporally related adverse events associated with receipt of anthrax vaccine by breast-feeding women or breast-fed children. According to the ACIP guidelines, breast-feeding is neither a precaution nor a contraindication to vaccination, and vaccination does not need to be deferred in a pre-event setting if the occupation of the breast-feeding mother poses a risk for exposure to *B. anthracis*.

Allergies

Although anaphylaxis following anthrax vaccination is extremely rare and no anaphylaxis deaths associated with Anthrax Vaccine Adsorbed (AVA) have been reported, this adverse event can be life-threatening. The ACIP guidelines state that AVA is contraindicated for persons who have experienced an anaphylactic reaction following a previous dose of AVA or any of the vaccine components.

Previous History of Anthrax Infection

The ACIP guidelines note that anthrax vaccine is contraindicated in persons who have recovered from anthrax because of previous observations of more severe adverse events among recipients with a vaccine history of anthrax than among non-recipients.

Illness

According to the ACIP guidelines, in the context of the routine pre-exposure program, vaccination of persons with moderate or severe acute illness should be postponed until recovery. This prevents super-imposing the adverse effects of the vaccine on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine. The ACIP guidelines state that vaccine can be administered to persons who have mild illnesses with or without low-grade fever.

Additional Information

The anthrax vaccine is made by BioPort Corp. (Lansing, MI), which is awaiting U.S. FDA approval to resume shipping the vaccine. The FDA stopped production at BioPort in 1998 because of quality concerns. Virtually all the U.S. stockpile of the vaccine is under the control of the Pentagon, which has long worried that its soldiers will face enemy use of anthrax on the battlefield.

Raxibacumab: Prevention and Treatment of Anthrax

Raxibacumab is a monoclonal antibody that neutralizes toxins produced by B. anthracis that can cause massive and irreversible tissue injury and death. On December 14, 2012, FDA approved raxibacumab injection to treat inhalational anthrax. Raxibacumab also is approved to prevent inhalational anthrax when alternative therapies are not available or not appropriate. The FDA granted raxibacumab fast track designation, priority review, and orphan product designation. The drug demonstrated the potential to fill an unmet medical need, has the potential to provide safe and effective treatment where no satisfactory alternative therapy exists, and is intended to treat a rare disease, respectively.

Raxibacumab is the first monoclonal antibody approved under the FDA's Animal Efficacy Rule, which allows efficacy findings from adequate and well-controlled animal studies to support FDA approval when it is not feasible or ethical to conduct trials in humans. In this case, because inhalational anthrax is a rare and lethal disease, it is not possible to conduct adequate efficacy trials in humans. Raxibacumab's effectiveness for inhalational anthrax was demonstrated in 1 study in monkeys and 3 studies in rabbits. All animals were administered aerosolized B. anthracis spores, and efficacy was determined by survival at the end of the studies. Animals received varying doses of raxibacumab, placebo or antibiotics normally used to treat anthrax. More animals treated with raxibacumab lived compared to animals treated with placebo; 64 % of animals in the monkey study and 44 % of animals in 1 rabbit study receiving the 40 mg/kg dose of raxibacumab survived exposure to anthrax, compared with none in the placebo groups. All surviving animals developed toxin-neutralizing antibodies. Another study in rabbits showed that 82 % of animals treated with antibiotics and raxibacumab survived exposure to anthrax compared with 65 % of animals receiving antibiotic treatment alone. The safety of raxibacumab was evaluated in 326 healthy human volunteers. Common side effects included rash, extremity pain, itching and drowsiness.

Combined Raxibacumab and Anthrax Vaccine for Post-Exposure Prophylaxis Against Inhalational Anthrax

Skoura and colleagues (2020) noted that raxibacumab is a monoclonal antibody against protective antigen, which is the cell-binding part of Bacillus anthracis toxin; and was FDA-approved for the treatment and post-exposure prophylaxis of inhalational anthrax. Anthrax Vaccine Adsorbed (AVA), for anthrax prophylaxis, consists primarily of adsorbed protective antigen. In a post-approval study, these researchers examined the effect of raxibacumab on immunogenicity of AVA. In a randomized, open-label, parallel-group, non-inferiority study at 3 centers in the U.S., these investigators enrolled healthy volunteers (aged 18 to 65 years) with no evidence of exposure to protective antigen. Subjects were randomly allocated (1:1) according to a pre-generated balanced independent randomization schedule to either subcutaneous 0.5 ml AVA on days 1, 15, and 29 or raxibacumab intravenous infusion (40 mg/kg) immediately before AVA on day 1, followed by AVA only on days 15 and 29. It was an open-label study to researchers and subjects; however, the sponsor remained blinded during the study. The primary outcome was the ratio of geometric mean concentrations (GMCs) of anti-protective antigen antibodies (attributable to the immune response to AVA) between AVA and AVA plus raxibacumab 4 weeks after the 1st AVA dose in the per-protocol population. The per-protocol population comprised all individuals who received the allocated treatment within the protocol-specified visit window and completed the primary study outcome assessment, without a protocol deviation requiring exclusion. The non-inferiority margin for the ratio of GMCs was pre-defined (upper limit of 90 % CI < 1.5). Between February 24, 2015 and June 6, 2017, a total of 873 subjects were screened for eligibility, of whom 300 were excluded; 573 were randomly allocated either AVA (n = 287) or AVA plus raxibacumab (n = 286). The per-protocol population comprised 276 individuals assigned AVA and 269 allocated AVA plus raxibacumab. At week 4, the GMC of anti-protective antigen antibodies in subjects allocated AVA was 26.5 µg/ml (95 % CI: 23.6 to 29.8) compared with 22.5 µg/ml (20.1 to 25.1) among individuals allocated AVA plus raxibacumab. The ratio between groups was 1.18 (90 % CI: 1.03 to 1.35; p = 0·0019), which met the pre-defined non-inferiority margin; AEs in the safety population were similar across groups (87 [30 %] of 286 in the AVA group versus 80 [29 %] of 280 in the AVA plus raxibacumab group) and no treatment-related serious AEs were reported. The authors concluded that co-administration of raxibacumab with AVA did not negatively affect AVA immunogenicity. These researchers stated that this finding suggested that combining raxibacumab with AVA might provide added benefit in post-exposure prophylaxis against inhalational anthrax.

Furthermore, an UpToDate review on "Prevention of anthrax" (Wilson, 2021) does not mention combined raxibacumab and anthrax vaccine for post-exposure prophylaxis.

Obiltoxaximab: Prevention and Treatment of Anthrax

Biron et al (2015) stated that the B. anthracis anti-toxin monoclonal antibody (MAb) ETI-204 is a high-affinity chimeric de-immunized antibody that targets the anthrax toxin protective antigen (PA). In this study, a partial protection New Zealand White (NZW) rabbit model was used to evaluate the protective effectiveness of the adjunct therapy with the MAb. Following detection of PA in the blood, NZW rabbits were administered either an antibiotic (doxycycline) alone or the antibiotic in conjunction with ETI-204. Survival was evaluated to compare the effectiveness of the combination adjunct therapy with that of an antibiotic alone in treating inhalational anthrax. Overall, the results from this study indicated that a sub-therapeutic regimen consisting of an antibiotic in combination with an anti-PA MAb results in increased survival compared to the antibiotic alone and would provide an effective therapeutic strategy against symptomatic anthrax in non-vaccinated individuals.

Huang et al (2015) noted that clinical guidelines for the treatment of anthrax recommend anti-toxin therapy in combination with intravenous anti-microbials; however, a large-scale or mass anthrax incident may exceed anti-toxin availability and create a need for judicious anti-toxin use. These researchers conducted a systematic review of anti-toxin treatment of inhalation anthrax in humans and experimental animals to inform anti-toxin recommendations during a large-scale or mass anthrax incident. A comprehensive search of 11 databases and the FDA website was conducted to identify relevant animal studies and human reports: 28 animal studies and 3 human cases were identified. Anti-toxin monotherapy at or shortly after symptom onset demonstrated increased survival compared to no treatment in animals. With early treatment, survival did not differ between anti-microbial monotherapy and anti-microbial-antitoxin therapy in non-human primates and rabbits. With delayed treatment, anti-toxin-antimicrobial treatment increased rabbit survival. Among human cases, addition of anti-toxin to combination anti-microbial treatment was associated with survival in 2 of the 3 cases treated. Despite the paucity of human data, limited animal data suggested that adjunctive anti-toxin therapy may improve survival. Delayed treatment studies suggested improved survival with combined anti-toxin-antimicrobial therapy, although a survival difference compared with anti-microbial therapy alone was not demonstrated statistically. In a mass anthrax incident with limited anti-toxin supplies, anti-toxin treatment of individuals who have not demonstrated a clinical benefit from anti-microbials, or those who present with more severe illness, may be warranted.

Obiltoxaximab (ETI-204) is a MAb that neutralizes toxins produced by B. anthracis. Obiltoxaximab's effectiveness for treatment and prophylaxis of inhalational anthrax was demonstrated in studies conducted in animals based on survival at the end of the studies. More animals treated with obiltoxaximab lived compared to animals treated with placebo. Obiltoxaximab administered in combination with anti-bacterial drugs resulted in higher survival outcomes than anti-bacterial therapy alone. The safety of obiltoxaximab was evaluated in 320 healthy human volunteers. The most frequently reported side effects were bruising, cough, headache, hives, nasal congestion, pruritus, swelling and pain at the infusion site, and upper respiratory tract infections.

On March 18, 2016, the FDA approved obiltoxaximab (Anthim) injection for the treatment of inhalational anthrax in combination with appropriate antibacterial drugs. Anthim is also approved for the prevention of inhalational anthrax when alternative therapies are not available or not appropriate. Anthim was approved under the FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support FDA approval when it is not feasible or ethical to conduct efficacy trials in humans. Anthim carries a "Boxed Warning" alerting patients and health care providers that the drug can cause allergic reactions, including anaphylaxis. Anthim should be administered in settings where patients can be monitored and treated for anaphylaxis. However, given that anthrax is a very serious and often deadly condition, the benefit of Anthim for treating anthrax is expected to out-weigh this risk.

Intravenous Anthrax Immune Globulin

The FDA approved intravenous human anthrax immune globulin (Anthrasil, Cangene Corp, Winnipeg, Canada) to treat patients with inhalational anthrax in combination with appropriate antibacterial drugs (FDA, 2015).

Human anthrax immune globulin is manufactured from the plasma of individuals vaccinated against anthrax. The plasma contains antibodies that neutralize toxins produced by the anthrax bacteria.

The efficacy of human anthrax immune globulin was studied in animals because it was not feasible or ethical to conduct adequately controlled efficacy studies in humans (FDA, 2015). Rabbits and monkeys were exposed to a lethal aerosolized dose of B. anthracis spores, then treated with human anthrax immune globulin or a placebo, and evaluated for survival. Survival in anthrax-infected monkeys treated with anthrax immune globulin ranged from 36 to 70 percent compared to 0 percent survival in the placebo group with a trend toward increased survival at higher doses of anthrax immune globulin. Rabbits treated with a moderate dose of anthrax immune globulin after infection exhibited 26 percent survival compared to 2 percent survival in the placebo group. Another study in rabbits showed that a combination of anthrax immune globulin and antibiotics resulted in 71 percent survival compared to 25 percent survival in animals treated with antibiotics alone.

The FDA concluded that the results of studies in research animals provided sufficient evidence that human anthrax immune globulin is reasonably likely to benefit humans with inhalational anthrax (FDA, 2015). The FDA's Animal Rule allows efficacy findings from adequate and well-controlled animal studies to support FDA approval when it is not feasible or ethical to conduct trials in humans.

The safety of the product was tested in 74 healthy human volunteers (FDA, 2015). The most commonly observed side effects were headache, back pain, nausea and infusion site pain and swelling.

Cui and colleagues (2017) studied anthrax immune globulin intravenous (AIG-IV) use from a 2009 to 2010 outbreak of Bacillus anthracis soft tissue infection in injection drug users in Scotland, UK, and compared findings from 15 AIG-IV recipients with findings from 28 non-recipients. Death rates did not differ significantly between recipients and non-recipients (33 % versus 21 %). However, whereas only 8 (27 %) of 30 patients at low risk for death (admission sequential organ failure assessment score of 0 to 5) received AIG-IV, 7 (54 %) of the 13 patients at high risk for death (sequential organ failure assessment score of 6 to 11) received treatment. AIG-IV recipients had surgery more often and, among survivors, had longer hospital stays than did non-recipients; AIG-IV recipients were sicker than non-recipients. The authors concluded that whether AIG-IV treatment is effective for systemic anthrax soft tissue infection related to drug injection cannot be answered with currently available data.

Combined Antitoxin and Anti-Microbial Therapy in the Prevention and Treatment of Anthrax Disease

Hesse et al (2022) noted that bacillus anthracis is a high-priority threat agent because of its widespread availability, easy dissemination, and ability to cause substantial morbidity and mortality. Although timely and appropriate anti-microbial therapy can reduce morbidity and mortality, the role of adjunctive therapies continues to be examined. These investigators searched 11 databases for studies that reported the use of anthrax antitoxins in treatment or prevention of systemic anthrax disease published through July 2019. They identified other data sources via reference search and communication with experts. These researchers included English-language studies on antitoxin products with approval by the FDA for anthrax in humans, non-human primates, and rabbits. Two researchers independently reviewed studies for inclusion and abstracted relevant data. They abstracted data from 12 publications and 2 case reports. All 3 FDA-approved anthrax antitoxins demonstrated significant improvement in survival as monotherapy over placebo in rabbits and non-human primates. No study found significant improvement in survival with combination antitoxin and anti-microbial therapy compared to anti-microbial monotherapy. Case reports and case series described 25 patients with systemic anthrax disease treated with antitoxins, 17 survived. Animal studies that used antitoxin monotherapy as post-exposure prophylaxis (PEP) showed significant improvement in survival over placebo, with greatest improvements coming with early administration. The authors concluded that limited human and animal evidence demonstrated that adjunctive antitoxin treatment may improve survival from systemic anthrax infection. Antitoxins may also provide an alternative therapy to anti-microbials for treatment or PEP during an intentional anthrax incident that could involve a multidrug-resistant B. anthracis strain, or when anti-microbials are not tolerated.

The authors stated that this review had several drawbacks. First, there was a dearth of relevant human clinical data on the use of antitoxins in the treatment of systemic anthrax; obiltoxaximab has never been used to treat anthrax in humans. Of the human case studies that do exist, there was no standardization of anti-microbial or adjunctive therapies, an inherent challenge when examining treatment of rare and often fatal diseases. Second, the FDA approved all 3 antitoxin products based on animal studies that conformed to the “Animal Rule”. When antitoxin was compared to or added to an anti-microbial regimen in animal studies, the anti-microbials were administered for sub-therapeutic durations, compared to what would be administered to human patients. Many of these animal studies also failed to capture clinical indices, even when those were available, and the pathophysiology of rabbits and non-human primates was difficult to correlate with those of humans. Third, these researchers limited their search to studies available in English, which may have excluded animal or human case studies published elsewhere. Fourth, this review was subject to publication and reporting biases, which are intrinsic to all systematic reviews.

Kennedy et al (2022) stated that without effective anti-microbial PEP (PEPAbx) and treatment, the mortality of systemic anthrax is high. To inform clinical guidelines for PEPAbx and treatment of B. anthracis infections in humans, these researchers systematically examined animal anthrax treatment model studies. They searched for survival outcome data in 9 scientific search engines for studies describing anti-microbial PEPAbx or treatment of anthrax in animals in any language through February 2019. These investigators carried out meta-analyses on the effectiveness of anti-microbial PEPAbx and treatment for each drug or drug combination using random-effects models. Pharmacokinetic/pharmacodynamic relationships were developed for 5 anti-microbials with available pharmacokinetic data. Monte Carlo simulations were employed to predict unbound drug exposures in humans. These researchers synthesized data from 34 peer-reviewed studies with 3,262 animals. For PEPAbx and treatment of infection by susceptible B. anthracis, effective monotherapy could be accomplished with fluoroquinolones, tetracyclines, β-lactams (including penicillin, amoxicillin-clavulanate, and imipenem-cilastatin), and lipopeptides or glycopeptides. For naturally occurring strains, unbound drug exposures in humans were predicted to adequately cover the minimal inhibitory concentrations (MICs; those required to inhibit the growth of 50 % or 90 % of organisms [MIC50 or MIC90]) for ciprofloxacin, levofloxacin, and doxycycline for both the PEPAbx and treatment targets. Dalbavancin covered its MIC50 for PEPAbx. The authors concluded that these animal studies demonstrated many reviewed anti-microbials are good choices for PEPAbx or treatment of susceptible B. anthracis strains, and some are also promising options for combating resistant strains. Monte Carlo simulations suggested that oral ciprofloxacin, levofloxacin, and doxycycline are especially robust choices for PEPAbx or treatment. Combination antitoxin and anti-microbial therapy is not mentioned as a management option.

An UpToDate review on treatment of anthrax (2023) stated: "Treatment of patients suspected of having systemic anthrax should be started urgently and should include intravenous (IV) antimicrobial combination therapy, an antitoxin (raxibacumab, obiltoxaximab, 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."

References

The above policy is based on the following references:

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Policy History

- Last Review 07/12/2024

  Effective: 01/08/2002

  Next Review: 05/08/2025

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes