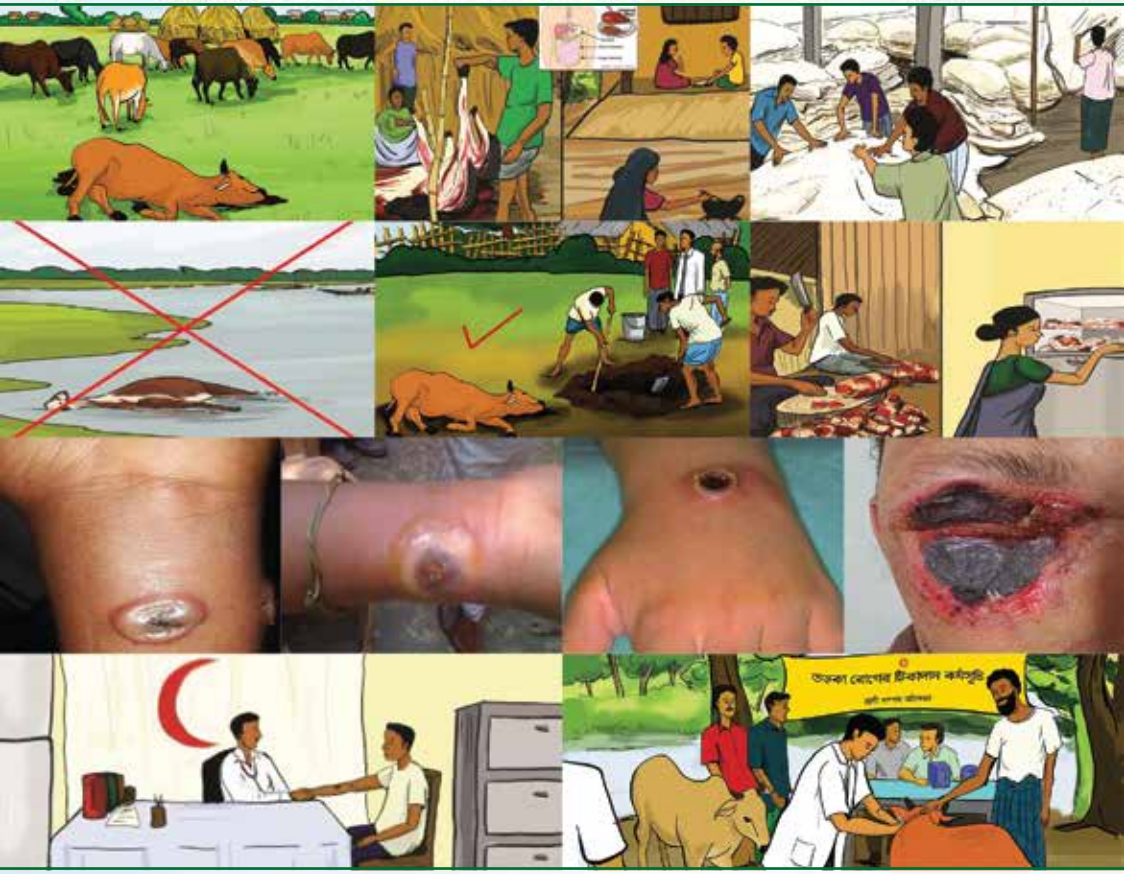
National Guideline for Management and Prevention of Human Anthrax



IEDCR

Institute of Epidemiology, Disease Control & Research (IEDCR)

Ministry of Health and Family Welfare

Government of the People's Republic of Bangladesh

NATIONAL GUIDELINE FOR MANAGEMENT AND PREVENTION OF HUMAN ANTHRAX

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FOREWORD OF DIRECTOR

Anthrax is primarily a disease if herbivorous mammals. Human generally acquires the disease from infected animals or occupational exposure to infected or contaminated animal products. Control in livestock is, therefore, the key to reduce incidence. Worldwide cutaneous anthrax occurs with an estimated of 20,000- 100,000 human cases annually and generally in low-income countries where livestock are not routinely vaccinated.

The first outbreak in Bangladesh was identified in August 2009 and since then outbreaks were reported every year at different areas especially in the northern part of Bangladesh. Institute of Epidemiology, Disease Control & Research (IEDCR) is conducting active surveillance of human anthrax in endemic zones. One health approach is recommended for anthrax control and prevention. During outbreak responses and surveillance activity need for updated information about the treatment and prophylaxis of the anthrax was felt. The first anthrax management guideline was prepared by IEDCR in 2015. Later, it was recommended in stakeholders meeting to incorporate the details of clinical management. Therefore, the current anthrax management guideline is being prepared with the objective to provide guidelines for the management of anthrax in humans based on updated knowledge on anthrax epidemiology, clinical profiles, laboratory diagnosis and control measures. This guideline also provides ready reference on all aspects of anthrax - diagnosis, treatment, outbreak investigation, surveillance and control program in Bangladesh.

I would like to congratulate and acknowledge the anthrax surveillance sub-committee, contributors and expert panel who were involved in preparing this anthrax management guideline. A special thanks to Bacterial Special Pathogen Branch (BSPB) of Centers for Disease Control and Prevention of United States (US-CDC) for providing the reference materials during preparation of this guideline.

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LIST OF ABBREVIATIONS

BID	Bis In Die
BSL	Bio-Safety Level
CDC	Centers for Disease Control and Prevention
CNS	Central Nervous System
CS	Civil Surgeon
CSF	Cerebro Spinal Fluid
DLS	Department of Livestock Services
DNA	Deoxyribonucleic Acid
EF	Edema Factor
IEC	Information Educational and Communication
IEDCR	Institute of Epidemiology, Disease Control & Research
IV	Intravenous
LF	Lethal Factor
LRI	Livestock Research Institute
LT	Lethal Toxin
MIC	Minimum Inhibitory Concentration
NRRT	National Rapid Response Team
OIE	World Organization for Animal Health
PA	Protective Antigen
PCR	Polymerase Chain Reaction
PEP	Post Exposure Prophylaxis
PPE	Personal Protective Equipment
QDS	Quarter Die Sumendum
TID	Ter Die Sumendum
UHC	Upazila Health Complex
UHFPO	Upazila Health and Family Planning Officer
US	Untied States
WHO	World Health Organization

1 INTRODUCTION

Anthrax is an acute infection caused by a spore forming bacterium called *Bacillus anthracis*, affecting both humans and animals. The bacilli can persist as spores in the soil for several decades. It is primarily a disease of herbivorous animals such as cattle, sheep, goats, horses, pigs etc. with clinical features of hyper-acute or acute symptoms and usually resulting into death in animals. Reports of the World Organization for Animal Health (OIE) show that the disease is still enzootic in most countries of Asia and Africa. *Bacillus anthracis* has always been high on the list of potential agents with respect to biological warfare and bioterrorism. Transmission may occur in human through direct contact with infected animal and/or indirect contact with animal materials such as meat, hides, hair, and bristles through microscopic or gross breach in the skin. There are three main forms of human anthrax, depending on the route of exposure: cutaneous, gastrointestinal, and pulmonary or inhalation. The cutaneous anthrax is the most predominant form in Bangladesh as well as in the other countries of the world.

Anthrax is endemic in limited areas of the world although it has been found in most continents of the world and in some islands. In general, outbreaks are more common in areas characterized by alkaline soils rich in calcium and other minerals. Anthrax is particularly common in parts of Asia, Africa and the Middle East where control measures in animals are relatively inadequate. It also occurs in South and Central America. This disease is infrequently reported in North America and Europe.

Wildlife cycles have been documented in some regions, such as Africa and North America. *Bacillus cereus* biovar anthracis has been found in tropical forests of sub-Saharan Africa, where surveys suggest it may be widespread. Similar organisms that have only pX01- like (toxin) plasmids have been reported from human cases in several southern U.S. states (Florida, Texas, Louisiana).

Human anthrax cases in Bangladesh are often reported sporadically from the area where animal anthrax is considered as endemic. In the wave of 2010 outbreaks, 607 suspected cases of cutaneous anthrax were reported by health authorities from 12 out of 64 districts in Bangladesh. Several outbreaks were reported from Meherpur, Sirajgonj, Pabna and Rajshahi districts sporadically. Domestic animal anthrax is common in the country and passive surveillance system of Department of Livestock Services (DLS) reported 5,937 cases of animal anthrax during 2010-2012. Most of the human anthrax outbreaks were linked with animal anthrax outbreaks.

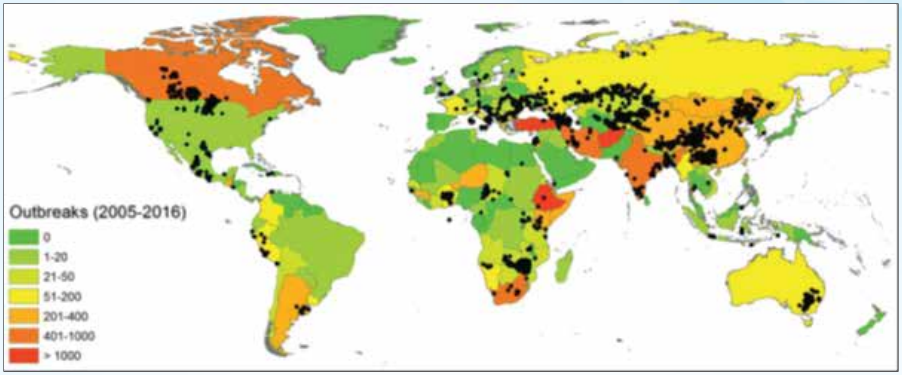


Figure1. Global database of anthrax occurrences (black dots), versus outbreaks of anthrax by country (Ref: Carlson et al. (2018)

Anthrax remains one of the most important zoonotic diseases (from animals to humans) in the world because of its effects on public health, agriculture, occupational health, and on the environment. The disease is more common in developing countries in the absence of well-developed widespread veterinary or public health programs.

1.1 Agent

The causative organism, *Bacillus anthracis* is a gram-positive, non-motile, non-haemolytic, and spore-forming bacillus. The virulence of the organism is determined by the capsule and exotoxins: Oedema toxin and lethal toxin. Fully virulent *Bacillus anthracis* isolates have two plasmids: pX01, which codes for a tripartite protein exotoxin complex, and pX02, which encodes the capsule genes. Anthrax is considered as an important biological warfare agent because (i) it is highly fatal when transmitted through inhalation, (ii) can be easily produced in large quantities at a very low cost and spores can remain viable for several decades and, (iii) it is an odorless and invisible aerosol. Therefore it is easy to weaponize which can affect thousands of people at the same time.

1.2 Chain of infection

Spores may remain viable in contaminated soil for many years. Dried or processed skins and hides of infected animals may also harbour spores for years. Animals (normally herbivores e.g. cattle, goat, sheep, horse, pig etc. of both livestock and wildlife) shed the bacilli in terminal hemorrhages or spilt blood at death. On exposure to the air, the vegetative forms sporulate.

Bacterial spores can travel to new area and spore density in soil can be enhanced due to flood and / or other ecological conditions. Soil can also be contaminated by vultures, which spread the organism from one area to another after feeding on anthrax infected carcasses.

Anthrax is usually transmitted by bacterial spores, although vegetative form of bacteria can cause some forms of anthrax infection (e.g., the oro-pharyngeal form). Humans usually develop the cutaneous form of anthrax after skin contact with infected animal tissues or animal products

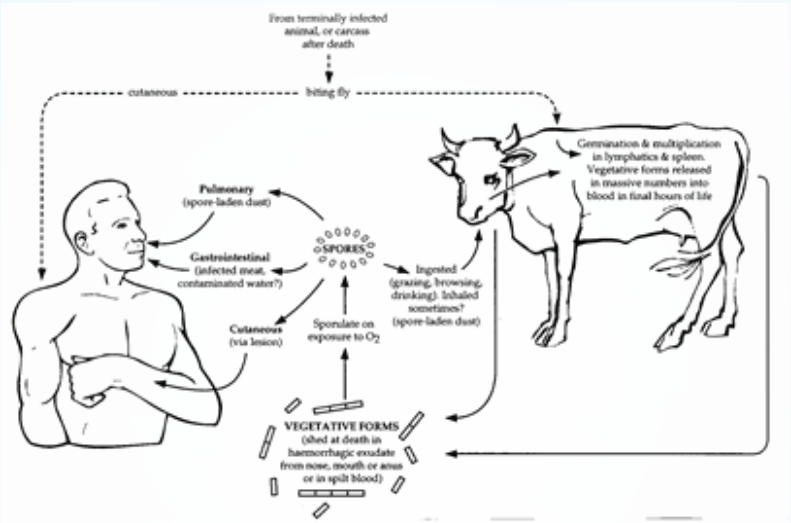
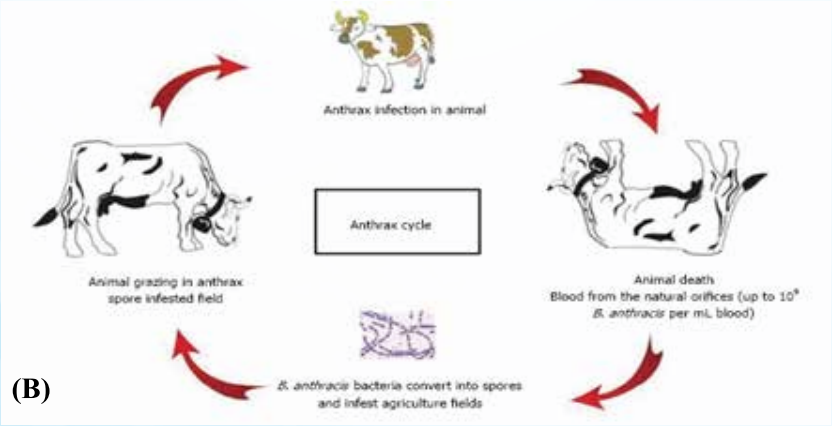


Figure 2: Transmission of anthrax in human (A) & animal cycle (B)



(if there is any breach in the skin). A few cases were suspected to have been acquired from biting flies. People can develop inhalation anthrax when spores from animal products, laboratory cultures or other sources are aerosolized. Gastrointestinal anthrax typically results from the ingestion of raw or undercooked tissues (e.g., meat) from an infected animal, although unusual sources (e.g., drumming on contaminated hides) have been reported. Person-to-person transmission of anthrax is very rare and has been seen only in cases of cutaneous anthrax. Animals are mainly thought to become infected when they ingest spores during grazing; however, inhalation could also play a role, and entry through skin lesions may be possible.

2. CLINICAL MANIFESTATION OF ANTHRAX

2.1 Incubation period

The reported incubation period for cutaneous anthrax ranges from one to twenty days, but most clinical cases tend to develop within 7-10 days. Gastro-intestinal anthrax has been seen 1-7 days after exposure. The incubation period for inhalation anthrax is highly variable. While it was estimated to be 2-6 days in a limited number of cases, spores may remain viable in the lungs for several weeks (up to 100 days in nonhuman primate models), and these spores can germinate and cause inhalation anthrax during that time.

2.2 Patho-physiology

Bacillus anthracis is an important zoonotic pathogenic bacterium. Its major virulence factors are (a) the anthrax toxins and (b) an anti-phagocytic poly-glutamic capsule. As mentioned earlier these are encoded by two large plasmids, the former by pXO1 and the next one by pXO2. The expression of both is controlled by the bicarbonate-responsive transcriptional regulator, AtxA. The anthrax toxins are three polypeptides – protective antigen (PA), lethal factor (LF), and oedema factor (EF): that come together in binary combinations to form lethal toxin and edema toxin. PA binds to cellular receptors to translocate LF (a protease) and EF (an adenylate cyclase) into cells. The toxins alter cell signaling pathways in the host to interfere with innate immune responses in early stages of infection and to induce vascular collapse at late stages.

2.3 Clinical features

Anthrax infection occurs in three forms: Cutaneous, inhalation, and gastro-intestinal depending on the mode of transmission. Symptoms of

disease vary depending on how the disease was contacted. Any of these forms can develop into life-threatening septicemia or anthrax meningitis, but the frequency differs. Cutaneous anthrax is said to account for 95% or more of human cases globally. All three forms are potentially fatal if untreated but the cutaneous form is often self-limiting.

2.3.1 Cutaneous anthrax

Cutaneous anthrax initially appears as a papule, which may become surrounded by small fluid-filled vesicles that release clear or sanguineous discharge. The central papule quickly forms a vesicle or bulla, ulcerates, dries and develops into an eschar, which appears as a firmly adherent, depressed black scab. The satellite vesicles may also form ulcers. Cutaneous anthrax lesions are usually painless (can be painful if superadded bacterial infection is there), but they are typically surrounded by significant edema, and may be accompanied by regional lymphadenopathy.

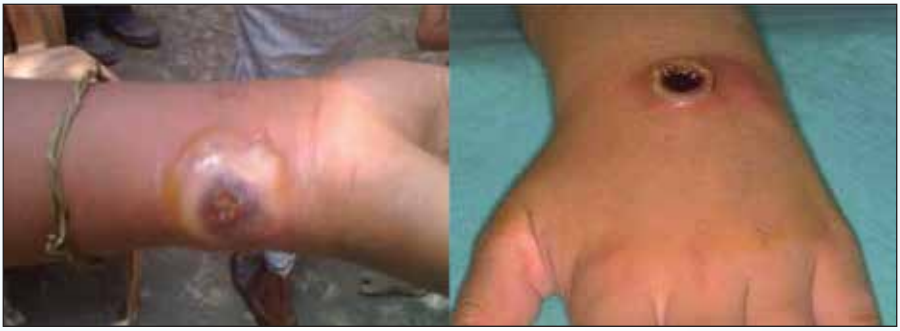


Fig 3: Cutaneous anthrax cases

An uncommon bullous form of cutaneous anthrax has also been described. It appears as a group of vesicles or bullae, which become hemorrhagic and necrotic. Co-infections with other organisms, including dermatophytes, can result in cutaneous anthrax cases with an atypical appearance. Pus is not usually seen in anthrax lesions unless they are secondarily infected. Low grade fever, malaise and headache may be apparent in more severe cases. Swelling on the face or neck can result in occlusion of the airways. Cutaneous anthrax often resolves spontaneously; however, the organisms can sometimes disseminate and cause life-threatening illnesses including septicaemia and meningitis. Face and neck lesions are more likely to spread to the CNS than lesions in other parts of the body Resolution of uncomplicated cutaneous anthrax may take weeks, even when the infection has been successfully treated with antibiotics. Small lesions usually heal with minimal scarring, but large lesions can leave significant damage. If the eyelids are affected, even smaller lesions may result in complications such as entropion.

2.3.2 Gastrointestinal anthrax

Gastrointestinal anthrax usually develops after eating contaminated, undercooked animal tissues including meat. Germinating spores can cause inflammation wherever they localize, and may, in severe cases, result in hemorrhages, obstruction or perforation. There are two clinical forms of gastrointestinal anthrax, i) abdominal form and ii) oropharyngeal form. In abdominal form any part of the gastrointestinal tract can be affected, but the ileum and colon are often involved. The initial symptoms of the abdominal form may be mild and can include malaise, a low fever and mild gastrointestinal symptoms such as nausea, vomiting, diarrhea and anorexia. In some cases, this is followed by the acute onset of severe abdominal pain, hematemesis and bloody diarrhea. Massive ascites may be present. Some patients have high fever. There may also be dyspnea, cyanosis, disorientation and other signs of septicemia. Meningitis is also possible. Severe cases progress rapidly to shock, coma and death. However, abdominal anthrax may not always be severe. Oropharyngeal form is characterized by clinical signs localized to that region. The initial symptoms include fever, a sore throat, dysphagia, hoarseness, and swelling of the neck from edema and cervical lymphadenopathy. Neck swelling can result in airway compromise. Lesions may be seen on the mucosa of the oropharyngeal region, including on the tonsils, pharynx and hard palate. In one report, these lesions initially appeared as areas of edema and congestion.

High index of suspicion is needed to diagnose gastrointestinal anthrax. The diagnosis should be suspected with alimentary symptoms developed during outbreak of anthrax. The suspicion of anthrax depends largely on awareness and alertness on the part of the physician as to the patient's history and to the likelihood that s/he had consumed contaminated food.

2.3.3 Pulmonary (inhalation) anthrax

Pulmonary anthrax occurs after inhaling spores. Suspicion of anthrax depends on the knowledge of the patient's history. The symptoms are nonspecific and may develop gradually. Early, vague symptoms can include fever, chills, tiredness and malaise, as well as a nonproductive cough and mild chest pain in some cases. These symptoms sometimes improve for several hours to a few days; however, this prodromal period ends with the acute onset of severe respiratory distress, tachycardia, diaphoresis, stridor and cyanosis, followed by fatal septicemia and shock within a day or two. Death occurs within 24 hours of onset of the hyper-acute phase.

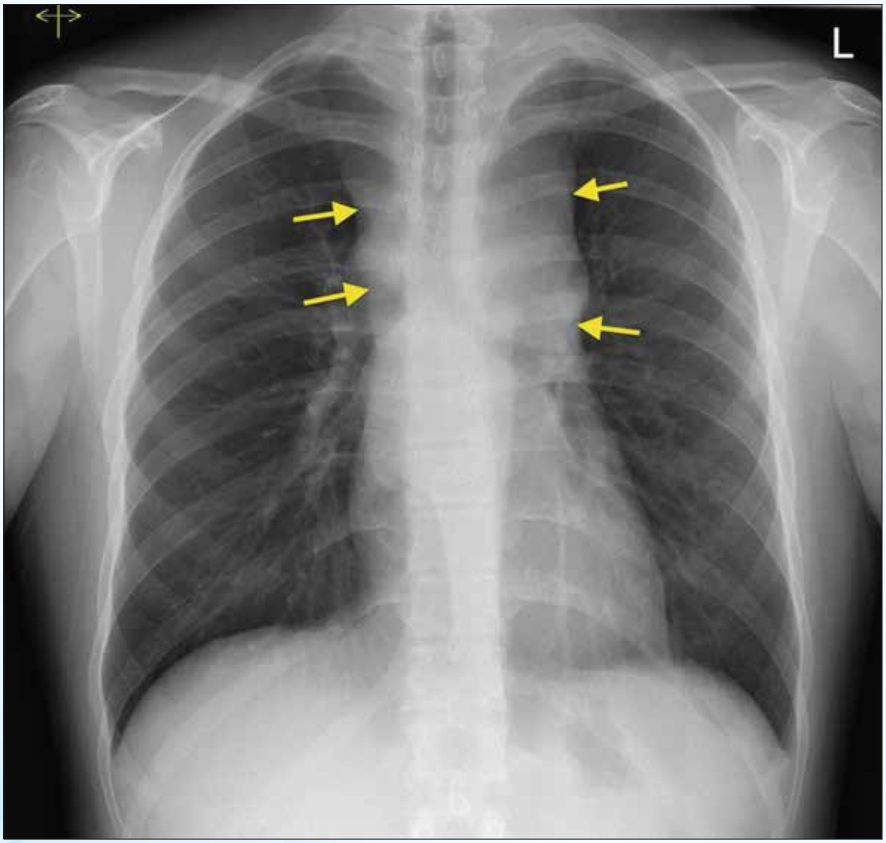


Figure 4: X-ray chest: Mediastinal widening

2.3.4 Anthrax meningitis

Meningitis due to anthrax is a serious clinical development which may follow any of the three forms of anthrax. The case fatality rate is almost 100%; the clinical signs of meningitis with intense inflammation of the meninges, markedly elevated cerebro spinal fluid (CSF) pressure and the appearance of blood in the CSF (the meningitis of anthrax is a haemorrhagic meningitis) are followed rapidly by loss of consciousness and death.

2.3.5 Anthrax sepsis

Sepsis develops after the lympho-hematogenous spread of *Bacillus anthracis* from a primary lesion (cutaneous, gastrointestinal or pulmonary). Clinical features include high fever, toxaemia, shock, and then death within short time.

3. LABORATORY DIAGNOSIS OF ANTHRAX AND BIOSAFETY

3.1 Diagnostic Tests

Specimens for an anthrax suspected case can be blood, swab from skin lesion or exudates, pleural or ascitic fluid, cerebrospinal fluid, or stool depending on the type of anthrax. Specimens should always be collected prior to antibiotic therapy. Culture will likely be negative if specimens are collected after starting of antibiotic therapy. The chance of getting positive result for antigen detection and /or molecular test decreases with the duration of antibiotic treatment prior to sample collection. Serology can be done even after antibiotic treatment. The available tests and expected findings are shown below:

Table 1: Laboratory tests for anthrax diagnosis and findings

Test	Findings
Gram stain	Gram-positive rods, square-ended, in pairs or short chains
Polychrome methylene blue stain (M'Fadyean stain)	Dark blue square-ended rods surrounded by pink capsule. Rods are in pairs or short chains, sometimes as single rods
Serology	Evidence of a four-fold rise in antibodies to protective antigen (PA)
Polymerase chain reaction (PCR)	Detection of toxin and capsule DNA
Culture (Gold standard)	Identification of *Bacillus anthracis* is done by observing it's colony morphology. Colonies have ground glass appearance with medusa head, lysis by gamma phage non-motile, non-hemolytic, penicillin-sensitive, and capsule producing

3.2 Principle of Bio-safety in handling anthrax

Bacillus anthracis is a risk group 3 micro-organism which needs very cautious handling especially during sample collection, processing, transport and testing in the laboratory or in the field. Therefore, practice of bio-safety guidelines, infection prevention measures and proper waste disposal should be ensured on regular basis.

Laboratory practice during sample collection, processing and transport

At Upazila (Peripheral laboratory)

- Use of personnel protective equipment (PPE) e.g. gloves, mask, shoe cover etc.
- Use of freshly prepared disinfectants e.g. 0.5 % hypochlorite solution
- Use of appropriate containers (screw capped)
- Prohibition of eating, drinking, in the laboratory
- Safe storage of contaminated material
- Laboratory tools should be housed safely
- Contaminated items and materials should be kept in a strong leak proof container

Infection prevention

- Incineration / autoclaving (if available) of infectious disposables (e.g. gloves, cotton, alcohol pad, specimen etc.) or using hypochlorite solution for the same purpose
- Minimizing aerosol production during slide/ sample preparation
- Thorough washing of hands with soap and water after completing sample handling
- Keep an accident and incident plan in place

At IEDCR (Central laboratory)

- Use of containment equipment like BSC, Centrifuge machine with lid
- Work for bacterial culture should be done in laboratories meeting BSL 3 criteria or at least BSL 2
- Manipulations of liquid cultures or suspension should be kept to minimum
- Good laboratory practice should be followed at all time

Infection prevention

- Autoclaving / incineration of infectious disposables
- Autoclaving, or fumigation of reusable materials
- Measures for minimizing aerosols
- Thorough washing of hands with soap before leaving laboratory
- An accident and incident plan should be in place

At community (if sample to be collected from community)

- Training of laboratory and field staff regarding sample collection
- Identify an isolated area for work at field
- Maintain good laboratory practice
- Hand hygiene before and after sample collection, processing and transport
- Use of PPE (mask, gloves and laboratory coat)
- Use of screw capped containers where required
- Avoidance of aerosol generating process like centrifugation of samples
- Collection of all infectious materials in a biohazard bag

4. MANAGEMENT OF ANTHRAX

4.1 Evaluation of patients and hospital admission criteria

Majority (95%) of human anthrax cases are cutaneous type and management of most cases can be done in outpatient department. The patients with symptoms and/or signs of systemic involvement (e.g., tachycardia, tachypnea, hypotension, hyperthermia, hypothermia, and leukocytosis) or with lesions that involve the head, neck, or upper torso or that are large, bullous, multiple, or surrounded by edema, have higher mortality rate.

Systemic anthrax defined as cutaneous anthrax with systemic involvement; gastrointestinal, injection or inhalation anthrax; anthrax meningitis; or bacteremia may need hospital admission and treatment. As 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. 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 cultures. All patients suspected of having systemic anthrax should undergo lumbar puncture to evaluate for meningitis unless it is contraindicated.

4.2 Supportive therapy

Despite potential pathophysiologic differences between *Bacillus anthracis* septic shock and septic shock caused by other bacteria, standard sepsis and septic shock guidelines should be followed for anthrax patients, including guidelines for fluids, vasopressors, blood products, and invasive hemo-dynamic monitoring. Micro-angiopathic hemolytic anemia, coagulopathy, thrombocytopenia, and hemorrhage commonly occur with anthrax infections; these complications must be aggressively managed, and might pose contraindications to invasive central catheter placement. Fresh frozen plasma and plasmapheresis should be considered, and fibrinogen levels should be kept >100 mg/dL. Because of the risk for coagulopathy, mechanical rather than pharmacologic prophylaxis is preferred for prevention of deep vein thrombosis. An echocardiogram might be needed to identify pericardial effusions.

4.3 Antimicrobial selection for prevention and treatment

The approach to prevention and treatment of anthrax differs from that for other bacterial infections. The production of toxin, potential for antimicrobial drug resistance, frequent occurrence of meningitis, and presence of latent

spores must be taken into account when selecting post-exposure prophylaxis (PEP) or a combination of antimicrobial drugs for treatment of anthrax. Patients hospitalized for systemic anthrax should be immediately treated with a combination of broad-spectrum intravenous antimicrobial drug treatment before getting laboratory test results because any delay may prove fatal. Meningitis and hemorrhagic brain parenchymal infection has been observed in ≤50% of human anthrax cases. Thus, all cases of systemic anthrax which are treated with antimicrobial drugs must have good penetration to central nervous system (CNS) considering occurrence of meningitis. Persons exposed to aerosolized *Bacillus anthracis* are at risk of having inhalation anthrax from ungerminated spores retained in their lungs, including patients treated for any form of anthrax who were exposed to aerosolized spores. There is need to continue antimicrobial drug therapy for 60 days to clear germinating organisms

4.3.1 Anthrax prevention for post exposure prophylaxis

A timely given effective Post Exposure Prophylaxis (PEP) can potentially save thousands of lives. In our country, the mode of exposure with anthrax bacilli is mainly by natural exposure (e.g. contact with animal having anthrax, during processing of anthrax infected meat, cooking etc.) The duration of therapy in naturally occurring cutaneous anthrax is 7 to 10 days. So PEP for naturally occurring cases would be for 10 days. But any person exposed to aerosolized *Bacillus anthracis* spores should receive PEP for 60 days, irrespective of their vaccination status, (vaccine is not available in Bangladesh). Ciprofloxacin or doxycycline is recommended as preferred drugs for PEP. The alternative drugs are levofloxacin or moxifloxacin; amoxicillin and penicillin V (if penicillin susceptible), and clindamycin to be used when preferred drugs are not available or who can't tolerate the preferred drugs. The antimicrobial drug linezolid cannot be used for extended periods. The risk for development of resistance must be kept in mind if using β-lactam drugs.

Table 2: Oral antimicrobial post-exposure prophylaxis for anthrax*

Non-pregnant adults	Pregnant, postpartum, and lactating women	Duration
For all strains, regardless of penicillin susceptibility or if susceptibility is unknown:		
Preferred drug		
Ciprofloxacin 500 mg every 12 hours OR	Ciprofloxacin 500 mg every 12 hours	10 days
Doxycycline 100 mg every 12 hours		10 days
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	10 days
Moxifloxacin 400 mg every 24 hours OR		
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	10 days
Penicillin V potassium 500 mg every 6 hours◊	Penicillin V potassium 500 mg every 6 hour ◊	10 days

MIC: minimum inhibitory concentration;

* 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.

◊ Be aware of the possibility of emergence of penicillin resistance during monotherapy with amoxicillin or penicillin

4.3.2 Treatment for uncomplicated cutaneous anthrax (without systemic involvement)

Uncomplicated cutaneous anthrax has been successfully treated with a single oral antimicrobial drug. Oral fluoroquinolone (e.g. ciprofloxacin, levofloxacin, and moxifloxacin) or doxycycline is the preferred drug. If the preferred drugs are contraindicated or unavailable, clindamycin is an alternative option. For pregnant women amoxicillin is the second choice of drug. Anthrax can also be treated with alternative drugs like penicillin, amoxicillin and penicillin V if the organism is known to be susceptible to penicillin. However, adequate dosage must be ensured because of the potential for development of drug resistance during treatment with sub-therapeutic dose. Duration of treatment for localized or uncomplicated cutaneous disease depends on the *Bacillus anthracis* exposure source.

If naturally acquired (e.g., from animals with anthrax, products such as hides from animals with anthrax), a 10 days course of antimicrobial drugs is sufficient. If bioterrorism -related exposure or an aerosol exposure is suspected, the recommendation is 60 days because the patient is likely to have inhaled spores too.

Table 3: Oral Antimicrobial Treatment for Cutaneous Anthrax without Systemic Involvement*

Non-pregnant Adults	Pregnant Women	Duration of treatment
A. For all strains, regardless of penicillin susceptibility or if susceptibility is unknown		10 days
Ciprofloxacin 500 mg every 12H OR **Doxycycline** 100 mg every 12H OR **Levofloxacin** 750 mg every 24H OR **Moxifloxacin** 400 mg every 24H OR Clindamycin† 600 mg every 8H	**Ciprofloxacin** is preferred 500 mg every 12H	
OR		
B. Alternatives for penicillin-susceptible strains		
Amoxicillin 1 g every 8H OR Penicillin VK 500 mg every 6H	Amoxicillin 1 g every 8H	

*Recommendations are specific to cutaneous anthrax where natural transmission is suspected.

Boldface indicates preferred agent. Alternative selections are listed in order of preference for treatment for patients who cannot take first-line treatment, or if first-line treatment is unavailable.

†Based on in vitro susceptibility data, rather than studies of clinical efficacy.

The treatment duration of cutaneous anthrax (without systemic manifestation) will be 60 days in the setting of bioterrorism only

4.3.3 Antimicrobial treatment for systemic anthrax with possible meningitis

For treatment of anthrax meningitis, early and aggressive multidrug therapy should be started as because the rapid progression and high mortality of

the disease. When anthrax meningitis is suspected or cannot be ruled out the empiric treatment for anthrax cases should include intravenous therapy with at least three antimicrobial agents with activity against *Bacillus 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. Intravenous combination treatment should be provided for 2 to 3 weeks or until the patient is clinically stable, whichever is longer. As mortality rate is high with meningitis, some expert panelists favor 3 weeks of treatment.

Intravenous ciprofloxacin is preferred as the primary bactericidal component in the treatment of systemic disease. Levofloxacin and moxifloxacin are considered equivalent alternatives to ciprofloxacin. The fluoroquinolones have adequate CNS penetration and there are no reports of natural resistance.

The carbapenem class of antimicrobial drugs is highly resistant to β-lactamases and provides good CNS penetration. Meropenem is preferred as the second antimicrobial drug in the combination antimicrobial drug regimen for anthrax meningitis. If meropenem is unavailable, doripenem and imipenem are considered equivalent alternatives. Imipenem is associated with increased seizure risk and should be used with caution in patients with suspected meningitis. If the *Bacillus anthracis* strain is susceptible to penicillin (MIC <0.125 μg/mL), penicillin G or ampicillin are acceptable alternatives to carbapenems.

At least one antimicrobial drug that inhibits protein synthesis should be used to reduce exotoxin production. Linezolid is preferred as the first-line protein synthesis inhibitor. It is preferred over clindamycin because it is likely to provide better CNS penetration. However, linezolid toxicity issues must be taken into consideration.

Rifampin, although not a protein synthesis inhibitor, has been widely used for its synergistic effect with a primary drug and can also be used in this capacity if linezolid or clindamycin are unavailable. The protein synthesis inhibitor chloramphenicol has good CNS penetration and has historically been used to successfully treat anthrax. Where available, it can be an acceptable alternative if linezolid, clindamycin, and rifampin are unavailable. Doxycycline should not be used if meningitis is suspected because it does not adequately penetrate the CNS. Once the course of intra-venous 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 *Bacillus anthracis* spores. Oral antimicrobial options are the same as those used for post-exposure prophylaxis.

The treatment of pregnant, lactating, and postpartum women is similar to the treatment of non-pregnant adults, except that ciprofloxacin is strongly preferred as one of the bactericidal agents. 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 non-pregnant adults.

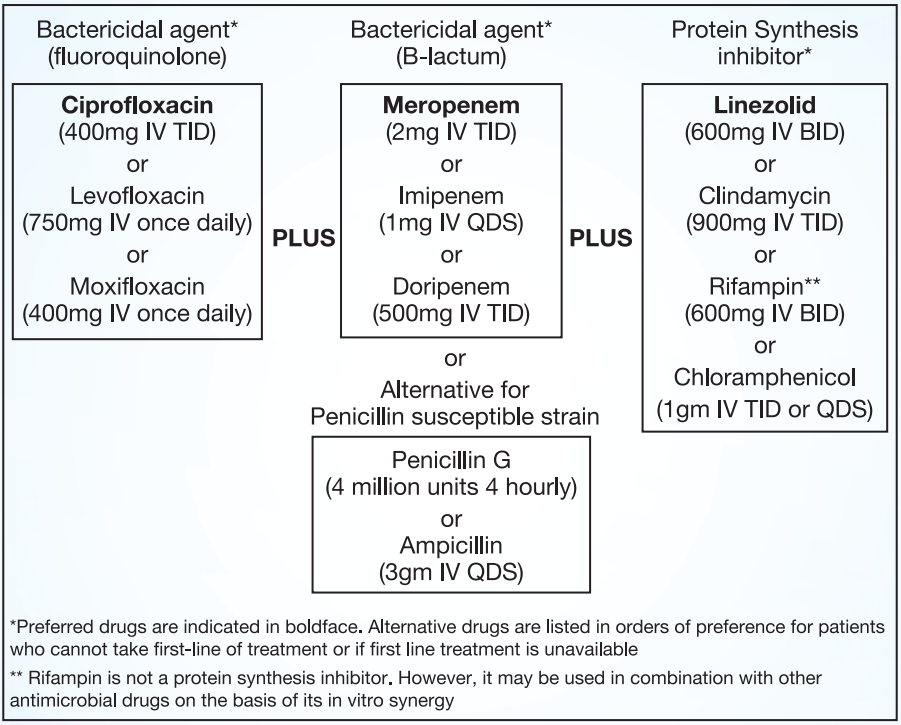


Figure 5: Intravenous treatment for systemic anthrax with possible meningitis cases

4.3.4 Antimicrobial treatment for systemic disease if meningitis is ruled out

Treatment for patients with systemic anthrax in whom meningitis has been ruled out should include at least two agents; at least one agent with bactericidal activity, and at least one protein synthesis inhibitor. Initial intravenous combination treatment should be given for two weeks or until the patient is clinically stable, whichever is longer. If the *Bacillus anthracis* strain is susceptible to penicillin, then penicillin G is considered equivalent

to the fluoroquinolone options for primary bactericidal treatment. Treatment with antimicrobial drugs that have good CNS penetration is not a crucial factor. Ciprofloxacin or similar combinations are considered equivalent first-line choices for protein synthesis inhibitors. Doxycycline may be added as an alternative to protein synthesis inhibitor option if linezolid or clindamycin are contraindicated or unavailable.

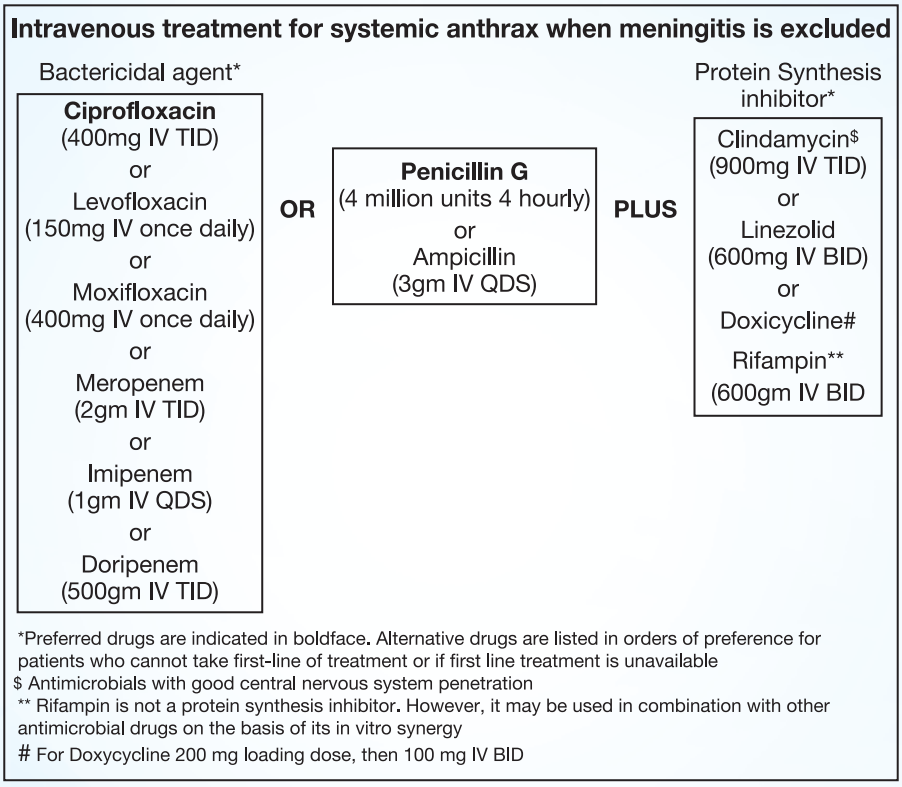


Figure 6: Intravenous treatment for systemic anthrax when meningitis is ruled out

4.3.5 Antimicrobial Treatment for children

Information regarding the treatment of anthrax infection in adults is scarce and is even more limited in children. Children, however, may be at a greater risk for developing an infection and systemic disease if exposed to anthrax than adults. The mortality rates in children, however, are unknown. Also unknown is the likelihood of cutaneous anthrax progressing to a systemic infection, or, worse yet, meningitis. As the risks of anthrax infections are great, The Centers for Disease Control and Prevention (CDC) recommends

the use of doxycycline or ciprofloxacin for prophylaxis and treatment in children. Doxycycline currently is not indicated for use in children <8 years old, due to staining of teeth and inhibition of bone growth associated with tetracyclines. Doxycycline, however, may have less adverse effect on teeth than its precursors.

The recommended agents for the treatment of anthrax in children are shown below:

Table 4: Treatment of anthrax in children

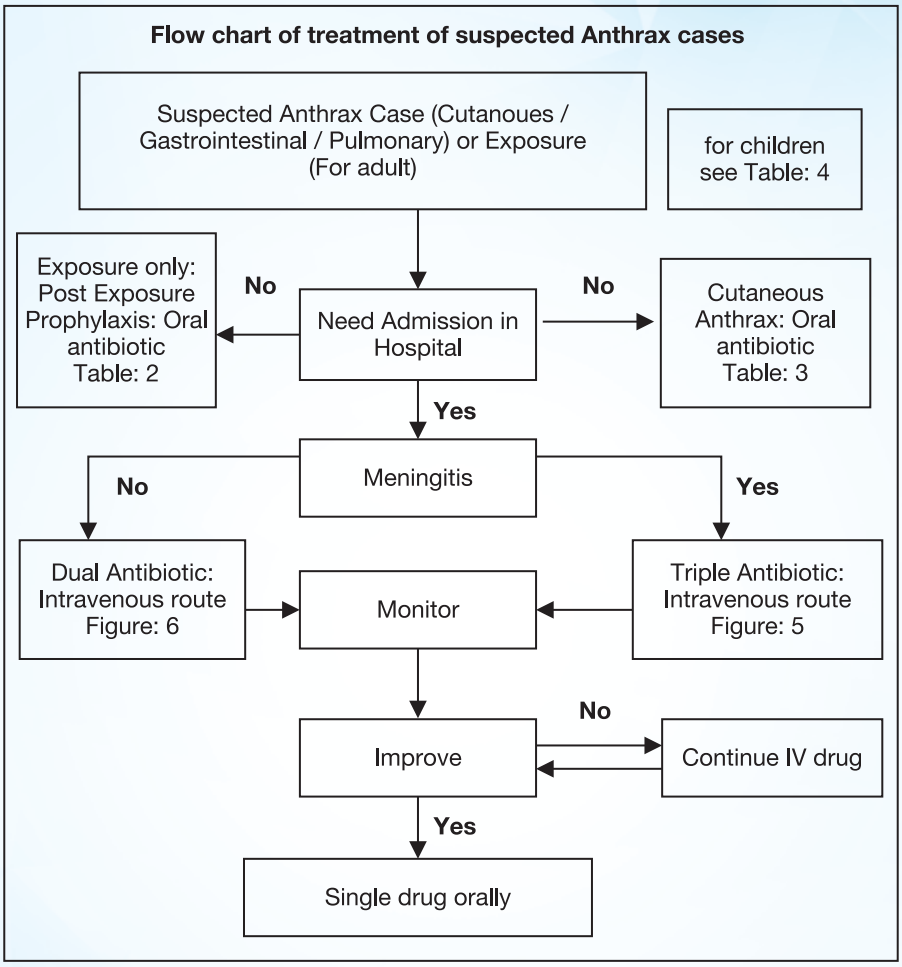
Indication	Antibiotics	Duration
Post exposure prophylaxis [a]	Ciprofloxacin 10–15 mg/kg orally BID [b] OR Doxycycline [c] orally BID >8 y and >45 kg: 100 mg >8 y and ≤45 kg: 2.2 mg/kg ≤8 y: 2.2 mg/kg	10 days
Cutaneous anthrax [a]	Ciprofloxacin 10–15 mg/kg orally BID [b] OR Doxycycline [c] orally BID >8 y and >45 kg: 100 mg >8 y and ≤45 kg: 2.2 mg/kg ≤8 y: 2.2 mg/kg	10 days
Inhalation / Systemic / Meningitis anthrax	Ciprofloxacin 10–15 mg/kg IV BID OR Doxycycline orally BID >8 y and >45 kg: 100 mg >8 y and ≤45 kg: 2.2 mg/kg ≤8 y: 2.2 mg/kg 1 or 2 additional antimicrobials (iv): ampicillin chloramphenicol , clarithromycin, clindamycin, imipenem, penicillin, rifampin, vancomycin	Inhalation / Systemic anthrax: 2 weeks or longer until clinical criteria for stability are met Anthrax Meningitis: 3 weeks or longer until clinical criteria for stability are met

[a] Ciprofloxacin and doxycycline are considered first-line therapy. Amoxicillin 80 mg/kg/d divided every 8 h (not to exceed 500 mg/dose) should be used for post-exposure prophylaxis if the anthrax strain is susceptible and for treatment once the patient is clinically improving on either doxycycline or ciprofloxacin.

[b] Ciprofloxacin not to exceed 1 g/d in children.

[c] Doxycycline can be considered first-line therapy for children with cutaneous anthrax who are <8 y because the benefits outweigh the risks.

Algorithm for Treatment of Anthrax Suspected cases



4.3.6 Use of corticosteroids

Clinicians should maintain a high index of suspicion for adrenal failure and perform adrenal hormone replacement therapy with dosing appropriate for stressed patients if adrenal failure is suspected on the basis of history or pressor-refractory hypotension. Adjunctive corticosteroids in anthrax may be considered for management of severe edema or meningo-encephalitis. Doses of dexamethasone used in pediatric bacterial meningitis as 0.6 mg/kg per day, in divided doses every 6 hours for 4 days should be appropriate. Use of corticosteroid in adult for anthrax is not mentioned.

4.3.7 Consideration for breastfeeding infants

Unless breast feeding mothers have untreated cutaneous lesions on their breasts, mother should initiate and continue breast feeding, if able, after exposure to *Bacillus anthracis* spores when they are undergoing treatment of disease. Cutaneous lesions are not considered contagious after 24-48 hours of effective antimicrobial therapy. Breast feeding infants should receive prophylaxis as recommended, regardless of the prophylaxis status of the mother.

4.4 Anti-toxin

In addition to antibacterial agents with activity against *Bacillus anthracis* , a key component of therapy is an adjunctive agent with antitoxin effects. 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. Obiltoxaximab is another monoclonal antibody directed against the protective antigen of *Bacillus anthracis* . An antitoxin should be added to combination antimicrobial therapy in patients with suspected or proven systemic anthrax if available. But unfortunately these antitoxins are not available in Bangladesh.

4.5 Vaccine for Human

No vaccine is available in Bangladesh for human anthrax. Therefore, using antimicrobial agents are the mainstay of treatment and prophylaxis. However, vaccine is used in some countries. For humans, almost all vaccines in use or development rely on protective antigen as the primary immunogen. The vaccine is a course of 5 shots over 18 months, with annual boosters thereafter. The vaccine is recommended for certain high-risk groups and is recommended as a post-exposure regimen alongside appropriate antimicrobial prophylaxis for people 18 years or older.

4.6 Referral of anthrax patient

Patients with naturally occurring exposure to anthrax suspected sick animal or products like meat, hide, bone, horn, biological fluids, etc. and uncomplicated cutaneous anthrax can be treated in Upazilla health complex by a physician as an outpatient. Cutaneous anthrax with suspected systemic involvement or with severe lesion in head and neck region, gastro-intestinal or pulmonary type anthrax with or without meningitis should be referred to district sadar hospital or medical college or chest disease hospital as required for better treatment.

5. PREVENTION AND CONTROL OF ANTHRAX

5.1 Surveillance of Anthrax

Effective surveillance is essential to prevent and control of anthrax and encompasses mechanisms for disease detection, confirmation of diagnosis, reporting, collation of data and feedback of the data to the source. IEDCR is conducting surveillance for anthrax at present where following activity are ensured from the field.

1. Regular reporting of anthrax cases which is important for anthrax prevention and control.

2. Field staffs from sentinel sites collect information related to human anthrax cases and report to Upazilla health complex. From Upazilla health complex samples are being collected and send to IEDCR for microbiological and molecular testing. Monthly reports are also sent regularly from sites.

Continued surveillance is required at sentinel sites as well as in area where an outbreak has occurred to monitor anthrax status so that appropriate control measures can be developed or revised. Routine cross-notification between the veterinary and human health surveillance systems should be part of any zoonotic disease prevention and control programme and so in anthrax. Close collaboration between the two health sectors is particularly important during epidemiological surveillance and outbreak investigations. Epidemiological case definition is needed to classify anthrax cases for surveillance and outbreak control purpose. Case definitions are given below:

Epidemiological Case definitions:

Suspected case: A case that meets the clinical description (describe in chapter 3.3) for cutaneous or systemic anthrax but with no epidemiological link relating to anthrax or has no laboratory evidence (presumptive or confirmatory) will be considered as suspected anthrax case.

Probable case: A suspected case that has an epidemiological link and / or has presumptive laboratory test results (characteristic gram positive bacilli identified in gram staining or demonstrated capsule in McFadyean's reaction with poly-chrome methylene blue) will be considered as probable anthrax case.

Epidemiological link means exposure to environment, food, animal, materials, or objects that is suspected or confirmed to be contaminated with *Bacillus anthracis* ; consumption of food that is suspected or confirmed to be contaminated with *Bacillus anthracis* ; exposure to the same environment, food, animal, materials, or objects as another person who has laboratory-confirmed anthrax; consumption of the same food as another person who has laboratory-confirmed anthrax.

Confirmed case: A suspected or probable case that has confirmatory laboratory test results

5.2 Community intervention

Infectious diseases including anthrax are not only biologically determined rather some social factors are also responsible to remain the infections in the community. Yet, most of the interventions employed for the control of anthrax are largely derived from technical measures with limited consideration of the social conditions existing in the affected communities. To address social factors, interventions need to consider such as training of farmers, community leaders, health care provider using information, education and communication (IEC) material in order to increase community awareness which will be more appropriate and acceptable to local communities.

Figure 7: Poster for Community Awareness

5.3 Anthrax control and prevention in animal

The most effective prevention strategy is mass vaccination of animals those are susceptible to anthrax infection especially in endemic areas. Ring vaccination to be ensured during an anthrax outbreak in animal. cold chain maintenance of vaccine should be ensured.

a) The most effective prevention strategy is mass vaccination of animals those are susceptible to anthrax infection. At first all the cattle in the affected area, and later all the cattle of the country will have to be vaccinated. Since Bangladesh is an endemic zone of anthrax, cattle in all area of the country is vulnerable to anthrax infection

b) Vaccination for goat is very important because some goat owner does not like to vaccinate their goat due to side effect like irritation. Therefore, vaccination for goat to be ensured and/or strategy to be sought for effective coverage of goat vaccination.

c) Avoidance of slaughtering sick animal is an important strategy to prevent contracting anthrax in human.

d) Deep burial (at least 6 feet deep) of anthrax infected dead animal is a must for preventing the spread of anthrax. Many people throw away the carcasses in the water bodies, river or in the open field. It facilitates the spreading of anthrax spores both in the nature and human who comes in contact with the contaminated carcasses.

e) Handling of infected animal (both living and dead) with bare hands is another source of infection. Using of gloves or any other protective barrier prevent transmission of the infection.

5.4 Human anthrax outbreak preparedness and response

The objective of anthrax outbreak investigation is to control and contain the anthrax outbreak, prevention of further outbreaks by mass vaccination of animal and increase community awareness about anthrax. The following activities are suggested:

- Community mobilization
- Reinforce health education messages and community awareness

- Organize intense community mobilization
- Deliver simple and targeted messages
- Create multiple social mobilization teams
- Orientation of field workers for prevention and control
- Conduction of several advocacy meeting with local leaders, public
- representative and other professionals in the affected areas
- Establishment of co-ordination with livestock department
- Information sharing between health and livestock personnel and working together during outbreak and afterwards

6. ONE HEALTH APPROACH FOR PREVENTION AND CONTROL OF ANTHRAX

Anthrax as being a zoonotic disease needs one health approach for control and prevention. For an effective response to anthrax, it is necessary to coordinate the knowledge, expertise, and experience of physicians, veterinarians, and allied health professionals. The key success factor will be the extension of one health approach to the local and community levels. Partnership is critical to success. People from both animal and human health are critical for controlling and preventing anthrax cases among human as well as in animal. IEDCR is running active anthrax surveillance in 9 sentinel sites in 5 districts and passive surveillance throughout the country. The staffs from both human and animal part are involved to conduct anthrax surveillance at local level to central following one health approach.

7. COMMUNITY AWARENESS

Communication effort should be made to educate the farmers and general public on various aspects of anthrax with an aim to prevent and control the disease. The concerned officials (animal and human health) should provide correct and relevant information to the general public through awareness build up using posters, leaflets, flip charts, banners, arranging health education program to avoid miscommunication and misinformation. This management guideline can be useful for physicians and veterinarians too.

8. FURTHER READING:

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