

BICHAT GUIDELINES* FOR THE CLINICAL MANAGEMENT OF ANTHRAX AND BIOTERRORISM-RELATED ANTHRAX

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The spore-forming *Bacillus anthracis* must be considered as one of the most serious potential biological weapons. The recent cases of anthrax caused by a deliberate release reported in 2001 in the United States point to the necessity of early recognition of this disease. Infection in humans most often involves the skin, and more rarely the lungs and the gastrointestinal tract. Inhalational anthrax is of particular interest for possible deliberate release: it is a life-threatening disease and early diagnosis and treatment can significantly decrease the mortality rate. Treatment consists of massive doses of antibiotics and supportive care. Isolation is not necessary. Antibiotics such as ciprofloxacin are recommended for post-exposure prophylaxis during 60 days.

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Introduction

Historically, human anthrax has been a disease affecting those who have close contact with animals or animal products contaminated with the spore-forming bacterium *Bacillus anthracis*. Anthrax is a zoonosis and is a normal commensal of many species of grazing mammals such as sheep, cattle and goats, which are infected through ingestion of soil contaminated by *B. anthracis* spores. The incidence of anthrax in herbivores has dramatically decreased in developed countries, but it remains an important health problem in developing countries. Wild and domestic animals in Asia, Africa, South and Central America, parts of eastern and southern Europe, the Caribbean and the Middle East are reported to be infected with the bacterium [1]. Human infections are usually the result of contact with infected animals or anthrax-contaminated animal products, or after direct exposure to *B. anthracis*, e.g. in a laboratory. One of the latest and largest epidemics of human anthrax occurred in Zimbabwe between 1979 and 1985 with 9445 human cases described, including 141 deaths [2]. Most of the cases were cutaneous, some very rare cases of the gastrointestinal form were noted, but eight cases of inhalational anthrax were also reported [2].

Anthrax and bioterrorism

Anthrax is seen as one of the most likely biological agents for use as a weapon. *B. anthracis* spores can be transmitted by aerosolisation. Inhalation anthrax has a high mortality rate and the organism's spores, compared with other potential biological warfare agents, are quite stable in the environment [3-10]. The use of anthrax in warfare has been recorded throughout history. In December 1941 the British

Government began testing the effect of anthrax on sheep on the Scottish island of Gruinard.

By 1945 the Japanese programme had stockpiled 400 kg of anthrax spores to be used in bombs. It has been estimated that 50 kg of *B. anthracis* spores released over an urban population of 5 million would sicken 250 000 and kill 100 000 [11]. The United States (US) has weaponised anthrax spores, as did other countries in the 1950s and 1960s; this was evidenced, for example, by the accidental aerosol release of *B. anthracis* spores from a Soviet military microbiology facility in Sverdlovsk in the former Soviet Union in April 1979 [9,12]. This was the largest known outbreak of inhalational anthrax in the 20th century. Cases have been also reported in animals located more than 50 km from the site.

During the first Gulf War, it was established that Iraq conducted research and development work on anthrax. In 1990 Iraq was in possession of 50 R400-bombs and 10 SCUD with anthrax. Iraq produced 8500 litres of concentrated anthrax.

In 2001 22 cases of bioterrorism-related anthrax were reported in the US: 11 confirmed inhalational, and 7 confirmed and 4 suspected cutaneous cases [13,14]. In March 2002, a laboratory worker in Texas presented with cutaneous anthrax after exposure to a contaminated surface in a laboratory [15]. No other bioterrorism-related or outbreak after deliberate release has been reported in the literature, though there are reports that the cult of Aum Shinrikyo in Japan tried on several occasions to disperse anthrax unsuccessfully in Tokyo before the sarin attack [9].

Infection in humans most often involves the skin, and more uncommonly the lungs and the gastrointestinal tract. Inhalation anthrax remains the most lethal form of the disease and is of particular interest for possible deliberate release [13,16-19]. However cases of cutaneous anthrax have also been associated with the deliberate release of the organism, as occurred in 2001 in the US [14]. Person-to-person transmission of inhalation anthrax has never been described [1].

Microbiological characteristics

B. anthracis is a large (1-1.5 wide x 3-10 µm long), aerobic, Gram positive, non-haemolytic on sheep-blood agar, spore-forming, non-motile member of the *Bacillus* species with square and concave ends [20,21]. It forms a spore of 1 µm in diameter, which is resistant to drought, heat, ultraviolet light, gamma radiation and numerous disinfectants [20]. The *B. anthracis* spore can remain viable and infective in the environment for decades. Growing readily on all ordinary laboratory media at 37°C, *B. anthracis* forms rough grey-white colonies of 4-5 mm, with characteristic comma-shaped or comet-tail protrusions.

The two principal virulence factors of *B. anthracis* (capsule and toxins) are encoded on two plasmids. The bacteria can evade the immune system by producing an antiphagocytic capsule. The capsule material contains poly-D-glutamic acid, which helps protect the bacillus from ingestion by phagocytes [21]. The virulence of *B. anthracis* is also determined by the production of three proteins (protective antigen: PA; lethal factor: LF and oedema factor: EF) that act in association to form two exotoxins described as lethal toxin (PA+LF) and oedema toxin (PA+EF) [20]. Both lethal and oedema toxin require participation of a common transport protein (PA). These toxins cause local necrosis and extensive oedema.

Clinical features

There are three major forms of human disease depending on how infection is contracted: cutaneous, inhalation and ingestion. In scenarios of deliberate release by a bioterrorist attack, the spread of the bacteria is thought to be usually by aerosol, making inhalational anthrax the most common form of the disease, although the recent events in the US show that other clinical forms (cutaneous) need to be considered (TABLE I).

Inhalational anthrax

Aerosolised anthrax spores can be trapped in the upper airways, although spores of 2 to 3 µm can pass through the bronchi to the alveoli and be transported via the lymphatics to the hilar and mediastinal lymph nodes, where germination to the bacillary form may occur [22,23,33,34].

Spores do not immediately germinate and may continue to vegetate in the host for several weeks after inhalation. Germination has been described to occur up to 98 days later in non-human primates [24]. The very long incubation times described in the Sverdlovsk outbreak are also attributed to late germination [12]. It has been suggested that antibiotics, which are not effective against the non-vegetative or spore form of *B. anthracis*, may prolong the incubation period [1]. Spores germinate and begin replication only after having been taken up by alveolar macrophages. Replicating bacteria release several toxins leading to haemorrhagic thoracic lymphadenitis and mediastinitis, oedema and necrosis [9].

Typical bronchopneumonia is not found on clinical or postmortem examination. Haemorrhagic meningitis frequently develops and can be observed in up to half of patients. The median period from exposure to the onset of symptoms is approximately 4 days (range 1-6 days) but cases that occurred from 2 to 43 days after exposure have been reported in humans [12,25]. For the inhalation anthrax cases reported in the US in 2001, the median period was 7 days [13]. The incubation period seems to be inversely related to the dose of *B. anthracis* spores [1]. To cause inhalational anthrax, the estimated infectious dose by the respiratory route is 8000-50 000 spores, although it may be significantly smaller for some individuals [7,1].

Early diagnosis is very difficult or impossible, without a clinician's high index of suspicion. Initial non-specific symptoms are indistinguishable from a host of other diseases. The classic clinical presentation is a biphasic illness. The initial symptoms are non-specific, including mild fever, non-productive cough, myalgia, dyspnoea, headache, vomiting, chills, weakness, abdominal pain, malaise and chest pain, similar to a viral upper respiratory tract infection [9,13]. Physical examination is usually unremarkable, but chest examination can reveal bilateral decreased breath sounds, rhonchi and/or inspiratory rales [17-19]. Laboratory studies

at this stage are non-specific (leukocytosis and haemoconcentration) [13,17].

The illness progresses to the second phase within two to three days. In some patients, a brief period of apparent recovery follows, making it even harder to diagnose the disease. Usually, the second phase begins abruptly with sudden fever with chills, acute dyspnoea, retrosternal chest pressure, diaphoresis, cyanosis and shock [17]. Respiratory failure usually requires mechanical ventilation.

Stridor is present in some patients because of extrinsic obstruction of the trachea by enlarged lymph nodes, mediastinal widening and subcutaneous oedema of the chest and neck. Physical findings are decreased breath sounds, diffuse wheezes, crepitations, rales and/or rhonchi and pleural effusions when they are present. Laboratory investigations are again non-specific (leukocytosis, haemoconcentration, metabolic acidosis with hypoxaemia, azotaemia, elevated amylase and transaminase levels, disseminated intravascular coagulopathy) [13, 17-19]. At this stage, a chest radiograph most often shows a widened mediastinum consistent with mediastinal lymphadenopathy and haemorrhagic mediastinitis, pleural effusion and progressive bilateral perihilar infiltrates [13,17,18]. Tularaemia, caused by another high priority bioterrorism agent, may produce similar acute mediastinal lymphadenopathy [20].

CT scan of the chest can demonstrate parenchymal infiltrates or consolidation, large bilateral pleural effusions and a widened mediastinum with a complete infiltration of the mediastinal fat planes, bronchial mucosal thickening, encasement and compression of the hilar vessels, and haemorrhagic lymph nodes [13,17,18]. An echocardiogram can show pericardial effusion [18]. At this stage, up to half of patients may develop haemorrhagic meningitis.

Treatment may be successful in the early stages, but by the time respiratory symptoms develop, it is too late for it to have any effect and death usually occurs within 24-72 hours in almost 90% of cases, despite aggressive treatment [12,14,17]. Death usually occurs 7 days after the onset of symptoms [16,18]. At Sverdlovsk in 1979, 68 of the 79 patients with inhalational anthrax died [12]. In the cases reported from the US in October-November 2001, the mortality rate in patients with inhalational anthrax was significantly lower, closer to 50%, probably accounting for the significant advances in critical care medicine and aggressive antibiotic treatment [13]. Transmission of inhalation disease from person-to-person has never been reported.

Cutaneous anthrax

Cutaneous anthrax accounts for 95% of all naturally occurring anthrax infections with estimated 2000 cases annually worldwide (9). The clinical features of cutaneous anthrax are characteristic, but in the absence of frequent cases in the developed countries, the diagnosis could be missed by physicians not familiar with this disease. Cutaneous anthrax occurs following contact with spore-contaminated materials or infected animal products (e.g., contaminated meat, wool, hides, leather and bone or hair products from infected animals). Infection requires an existing break in the skin such as previous cuts or abrasions. Rare cases through certain species of biting flies have been reported [2,16,21]. Bacteraemia is a very rare complication. Direct exposure to secretions from human cutaneous anthrax lesions may result in secondary cutaneous infection but this is very rare.

The most common areas of exposure are the arms, hands, fingers, face, and neck, although any area can be involved. The incubation period is 1-5 days following cutaneous exposure although the primary lesion may occur up to 12 days

after [9,13,21]. After the spore germinates in the skin tissues, toxin production results in local oedema. The primary lesion is usually a painless, small, pruritic papule or macule. This lesion can resemble an insect bite. Subsequently, within 24 to 36 hours, a vesicle occurs (1 to 3 cm in diameter) and enlarges into a round ulcer. Two to six days later a characteristic black eschar develops surrounded by extensive local oedema and a number of purplish vesicles. The swelling tends to be much greater than would normally be expected for the size of the lesion. The eschar dries, loosens, and falls off in the next 1 to 3 weeks without complications or scarring in 80% to 90% of cases [21].

Cutaneous anthrax is a non-febrile disease. There is no liquefaction or abscess formation indicating that the lesions are not suppurative. Fever indicates a secondary infection (*Staphylococcus* or *Streptococcus*) or a systemic infection due to bacteraemia (20% of patients without antibiotics) [16]. Lymphangitis and painful lymphadenopathy can occur with associated systemic symptoms such as malaise and headache [1].

Antibiotic therapy only decreases the likelihood of systemic disease while not changing the progression of the skin lesion itself [9]. With antibiotic treatment, death due to cutaneous anthrax is rare (<1%); without antibiotic treatment, the mortality rate has been reported to be as high as 20% if cutaneous anthrax develops into systemic infection.

Gastrointestinal anthrax

Two clinical presentations are usually described: abdominal and oropharyngeal, neither of which have been reported after deliberate release of anthrax.

Gastrointestinal anthrax is very rarely reported and occurs following deposition of spores or vegetative bacilli in the upper or lower gastrointestinal tract after ingestion of raw or undercooked contaminated meat. Outbreaks are reported in Africa and Asia in patients who have eaten contaminated meat [9]. Information concerning the risks of direct contamination of food with *B. anthracis* spores as a biological weapon is not available. The initial symptoms appear 2 to 7 days after the ingestion of spores and are non-specific [22]. The symptoms of abdominal anthrax consist of nausea, vomiting, loss of appetite, malaise, fever and abdominal pain due to an acute inflammation of the intestinal tract. Ulcerations occur mainly in the terminal ileum or caecum. The clinical manifestations progress rapidly to severe, bloody diarrhoea, with an acute abdomen and sepsis [26]. Gastric ulcers may be associated with haematemesis. Haemorrhagic mesenteric lymphadenitis and massive ascites may occur. With further progression toxemia develops, with shock, cyanosis and death. An early diagnosis is difficult and the mortality rate is very high (>50%). The differential diagnosis includes diseases that are associated with severe gastroenteritis such as shigellosis, salmonellosis and *Yersinia* gastroenteritis. The time between the onset of the manifestations and death is usually short, from 2 to 5 days.

Oropharyngeal anthrax

This is even less common. Symptoms include fever, cervical oedema and local adenopathy with dysphagia, sore throat and dyspnoea. Ulcers covered with a pseudomembrane may be seen in the oral cavity involving the posterior wall, the hard palate and the tonsils [27]. The symptoms might suggest severe streptococcal pharyngitis. This presentation is very rare; most of the patients die with toxemia and sepsis.

Meningitis

Meningitis may be a complication of any of the forms of anthrax, if bacteraemia is present. Despite aggressive therapy, this meningitis is almost always fatal. Clinical symptoms are those of common meningitis. The cerebrospinal fluid (CSF) is haemorrhagic in most instances. Gram staining of CSF can reveal many polymorphonuclear white cells (>4000/mm³), elevated protein level, hypoglycorachia and numerous large, encapsulated, Gram positive bacilli [28].

Diagnosis

The clinical diagnosis is easier in the case of cutaneous anthrax, but is difficult in the other forms of the disease where the evolution is extremely rapid. Case definitions of suspected or confirmed cases and cases due to deliberate release are reported in Tables 2 and 3.

Samples should be drawn prior to antibiotic treatments because sterilisation of cultures is possible after one dose of antibiotics. Gram stain of the vesicular fluid from cutaneous lesions or of the pleural effusion, CSF and ascites fluid should be obtained [3-10]. If cutaneous anthrax is suspected, punch biopsy may also be performed for immunohistochemistry.

The most useful microbiological test remains the standard blood culture. Organisms must be tested for sensitivity to antibiotics for natural existence of resistant species and possible genetic manipulation before deliberate release. The initial diagnosis of anthrax can also be made by positive cultures of CSF, pleural fluid, pleural or bronchial biopsy, or skin lesion. The rate of positive culture of tissues is poor [16]. Sputum culture and Gram stain are unlikely to be diagnostic of inhalational anthrax given the frequent lack of frank pneumonia.

Rapid identification of *B. anthracis* can be made by direct fluorescent antibody testing and gamma-phage lysis. Confirmatory diagnostic tests such as polymerase chain reaction (PCR) can also be used and may help in early diagnosis [3-10]. Antibody testing by ELISA may yield positive results in convalescent serum specimens. Therefore, serologic testing is useful only retrospectively. The predictive value of the nasal swab test for the diagnosis or following exposure to *B. anthracis* spore is unknown. A negative swab does not indicate that the patient has not been exposed to *B. anthracis*.

In inhalational anthrax, postmortem findings are thoracic haemorrhagic necrotising lymphadenitis and mediastinitis, pleural effusions and, in 50% of cases, haemorrhagic meningitis. Usually, there are no signs of pneumonia.

Treatment

Many guidelines have been published for treatments and prophylaxis of anthrax [4-10,29,30]. Treatment recommendations for humans have been based on historical information and in vitro findings (TABLE IV). Private room placement for patients with inhalational anthrax is not necessary. In case of cutaneous anthrax, healthcare workers should use standard precautions with gloves (in this case person-to-person transmission is possible during the first days before antibiotic treatment sterilises the skin lesion). Historically, penicillin was the drug of choice for anthrax [9]. It is still approved by the European Medicine Evaluation Agency (EMA), as an alternative first line treatment of inhalational anthrax infection when the strain is susceptible to this drug [29]. However, naturally resistant strains to penicillin have been reported. Furthermore it might not be difficult to induce resistance to penicillin through laboratory manipulation of organisms. Naturally occurring resistant *B.*

anthracis to multiple antibiotics have been produced in different laboratories (resistance to penicillin, doxycycline, chloramphenicol, macrolides, and rifampicin) [20]. No case of *B. anthracis*, in vitro or in vivo, to our knowledge, has ever been reported to be resistant to quinolones. That is why ciprofloxacin is the recommended first line treatment, due to its ease of administration, good safety profile and predictable activity. Alternative antibiotics are amoxicillin and doxycycline after susceptibility has been confirmed. These drugs are associated with fewer side effects but can induce resistance to *B. anthracis*. Despite the absence of studies, it is recommended to use one or two additional antibiotics in inhalational anthrax such as rifampicin, chloramphenicol, clindamycin, clarithromycin, erythromycin, gentamicin, streptomycin or vancomycin (29). *B. anthracis* is resistant to extended-spectrum cephalosporins, cefuroxime, aztreonam, and trimethoprim-sulfamethoxazole. For inhalational anthrax, the duration of treatment is 60 days (8 weeks). Duration of treatment for cutaneous anthrax is 7-10 days. The same antibiotics are recommended for post-exposure prophylaxis. Oral ciprofloxacin is also recommended as first choice for prophylaxis for persons at risk of inhalational anthrax and must be taken for at least 60 days, unless exposure has been excluded. It has been demonstrated that treatment with antibiotics beginning one day after exposure to a lethal aerosol can provide significant protection against death [31].

In the United Kingdom, there is only one vaccine licensed for use. This culture supernatant-derived vaccine is produced by the UK Health Protection Agency Porton Down and formulated in a similar way to the American vaccine [36]. The human anthrax vaccine licensed in the US consists of a non-infectious sterile filtrate from a formalin-treated culture of an attenuated strain of *B. anthracis*, adsorbed to the adjuvant, aluminium hydroxide [32]. Severe side effects due to this vaccine are infrequent in humans [32]. The US vaccine is administered in a series of six subcutaneous injections: after the initial dose, injections are given at 2 weeks, 4 weeks, 6 months, 12 months and 18 months (immunity following vaccination is short-lasting). The UK vaccine is given in a series of four intramuscular injections at 0, 3, 6 weeks and a fourth booster 6 months after the third dose, followed by annual boosters. The effectiveness of the anthrax vaccine has been reported in monkeys [32]. It has been demonstrated in these monkeys that this vaccine provided complete protection against an aerosol of *B. anthracis* at week 8 after exposure and 88% protection at week 100. Over half a million military personnel have received this vaccine in the US. The use of this vaccine could, in association with antibiotics, decrease the period of recommended post-exposure antimicrobial therapy (30 to 45 days) [20].

Both currently available products can be regarded as first generation vaccines, for which improvements are needed. A recent report on this vaccine concluded that while the vaccine is acceptable, safe and effective in protecting humans against anthrax, including inhalational anthrax, there was an urgent need for an improved vaccine [35]. This improved vaccine should not cause severe local reactions or severe systemic reactions. Further, it should require only 2 or 3 injections, elicit protection lasting at least one year and remain stable over long periods of time to enable stockpiling. Clinical trials on the safety and efficacy of a new recombinant Protective Antigen (rPA) based anthrax vaccine have recently been initiated in the US [37].

In conclusion, the spore-forming *B. anthracis* must be considered as one of the most likely to be used and to cause terror or the most deaths potential biological weapons. The recent cases of bioterrorism-related anthrax reported in 2001 in the US point to the necessity of early diagnosis of this disease. Inhalational anthrax is a life-threatening disease and early diagnosis and treatment can significantly decrease the mortality rate. This form of the disease begins with non-specific symptoms followed in 2 to 3 days by the sudden onset of acute respiratory distress, which is rapidly fatal. Treatment consists of massive doses of antibiotics and supportive care.

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- * **BICHAT**, the European Commission's Task Force on Biological and Chemical Agent Threats, has developed this set of guidelines that may be the basis of national authorities' guidance, and may also be used directly by clinicians, general practitioners and specialists when confronted with patients infected by agents that may be due to deliberate release of biological agents. Ref. Bossi P, Van Loock F, Tegnell A, Gouvras G. Bichat clinical guidelines for bioterrorist agents. *Euro Surveill*. 2004; 9(12)
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Editorial note: These clinical guidelines were reviewed by the Task Force and by two experts designated by each Member State of the European Union. This review was completed at the end of February 2003. The revised guidelines were submitted to the Health Security Committee which approved them in April 2003 and agreed their publication in a widely disseminated journal so as to allow access to as large an audience as possible. The editorial process of Eurosurveillance also introduced modifications that improved the contents of these guidelines.

TABLE 1

Summary of clinical description and laboratory criteria for diagnosis of anthrax

<p style="text-align: center;">Clinical description</p> <ul style="list-style-type: none">◦ Incubation period is generally 1-6 days.◦ Physical findings are non-specific <p style="text-align: center;">Inhalational anthrax</p> <ul style="list-style-type: none">◦ Following inhalation of <i>B anthracis</i> and a brief prodrome acute febrile respiratory failure develops with hypoxia, dyspnoea and radiological evidence of mediastinal widening <p style="text-align: center;">Cutaneous anthrax</p> <ul style="list-style-type: none">◦ A skin lesion evolving from a papule, through a vesicular to a depressed black eschar with surrounding oedema. The lesion is usually painless but there may be constitutional disturbance (fever and malaise) <p style="text-align: center;">Gastrointestinal anthrax</p> <ul style="list-style-type: none">◦ Following consumption of raw contaminated food a syndrome of severe abdominal pain, diarrhoea, fever and septicaemia

TABLE 2

Case definitions of suspected and confirmed cases

Case definition
<ul style="list-style-type: none">◦ Possible: NA◦ Probable: A probable case is defined as:<ul style="list-style-type: none">- a clinically compatible case of illness without isolation of <i>B. anthracis</i> and no alternative diagnosis, but with laboratory evidence of <i>B. anthracis</i> by one supportive laboratory test- a clinically compatible case of anthrax epidemiologically linked to confirmed environmental exposure, but without corroborative laboratory evidence of <i>B. anthracis</i> infection◦ Confirmed: A clinically compatible case that is laboratory confirmed

NA: Not applicable

Source: [38,39]

TABLE 3

Case definition of a deliberate release of anthrax

Deliberate release
<ul style="list-style-type: none">• >1 confirmed case of inhalation anthrax• >1 confirmed case of cutaneous anthrax arising in individuals who do not routinely have contact with animals or animal hides• >2 suspected cases of anthrax that are linked in time and place, especially geographical related groups of illness following a wind direction pattern

Source: [38,39]

TABLE 4

Recommendations for treatment and post-exposure prophylaxis of inhalation/intestinal anthrax

		Treatment of suspected or confirmed clinical cases of inhalation/intestinal anthrax (60 days)	Post-exposure prophylaxis (60 days)
Adults Pregnant women	First line	Ciprofloxacin: 400 mg IV bid followed by 500 mg per os bid	Ciprofloxacin: 500 mg per os bid
It is recommended, when possible, to stop breastfeeding.	Alternative to ciprofloxacin	- Ofloxacin: 400 mg IV bid followed by 400 mg per os bid - Levofloxacin: 500 mg IV once a day, followed by 500 mg per once a day	- Ofloxacin: 400 mg per os bid - Levofloxacin: 500 mg per once a day
	Alternative first line treatment and follow-up when susceptibility is confirmed Alternative first line prophylaxis if susceptibility is confirmed	- Doxycycline: 100 mg IV bid followed by 100 mg bid per os - Penicillin G: 2.4 to 3 millions IV, 6 times daily - Amoxicillin: 1 g IV 3 times daily, followed by 500 mg per os 3 times daily	- Doxycycline: 100 mg bid per os - Amoxicillin: 500 mg per os 3 times daily
Children	First line	Ciprofloxacin: 10-15 mg/kg IV bid followed by 10-15 mg/kg per os bid	Ciprofloxacin: 10-15 mg/kg per os bid
	Alternative first line treatment and follow-up when susceptibility is confirmed Alternative first line prophylaxis if susceptibility is confirmed	- Doxycycline: . >8 years and > 45 kg: adult dose . >8 years and < 45 kg or < 8 years: 2.2 mg/kg IV bid followed by 2.2 mg/kg per os bid (max 200 mg/d) - Penicillin G: . > 12 years: 2.4 to 3 millions IV, 6 times daily . < 12 years: 30 mg/kg IV, 4 times daily - Amoxicillin: 80 mg/kg IV daily in 3 divided doses, followed by 80 mg/kg per os daily in 3 divided doses	- Doxycycline: . >8 years and > 45 kg: adult dose . >8 years and < 45 kg or < 8 years: 2.2 mg/kg per os bid (max 200 mg/d) - Amoxicillin: 80 mg/kg per os daily in 3 divided doses

Source: [29]