

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

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***Yersinia pestis* appears to be a good candidate agent for a bioterrorist attack. The use of an aerosolised form of this agent could cause an explosive outbreak of primary plague pneumonia. The bacteria could be used also to infect the rodent population and then spread to humans. Most of the therapeutic guidelines suggest using gentamicin or streptomycin as first line therapy with ciprofloxacin as optional treatment. Persons who come in contact with patients with pneumonic plague should receive antibiotic prophylaxis with doxycycline or ciprofloxacin for 7 days. Prevention of human-to-human transmission via patients with plague pneumonia can be achieved by implementing standard isolation procedures until at least 4 days of antibiotic treatment have been administered. For the other clinical types of the disease, patients should be isolated for the first 48 hours after the initiation of treatment.**

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Introduction

Plague is an acute bacterial infection caused by the organism *Yersinia pestis*. Historically, three plague pandemics have killed more than 200 million people, including the Black Death epidemic in 14th century Europe [1]. This disease, primarily the bubonic form, is still reported from several countries in Africa, Asia, South America and rural south-western parts of the United States (US) [2-6]. There is currently no plague in Europe: the last reported cases occurred after the second world war. Worldwide, it is estimated that 1000 to 6000 cases occur each year (mean: 1500 cases/year) [7]. The total number of human plague cases reported to the World Health Organization by 14 countries in 1997 was 5 419, of which 274 were fatal [8]. It remains an enzootic infection of rats and other rodents. Plague occurs in sylvatic rats, which may then spread among more domestic rat species and finally among humans. Bacteria are usually passed to humans through the bite of a flea that has previously fed on an infected rat. In nature, at least 200 species of mammals and 80 species of fleas serve as reservoirs [9]. Infection may also occur through direct contact with infected tissues or fluids from sick or dead plague-infected animals, by exposure of humans to respiratory droplets from infected animals, especially cats with plague pneumonia, or by laboratory exposure to plague bacteria.

Human-to-human transmission can occur through infectious respiratory droplets from pneumonic cases of plague [10-13]. Primary pneumonia appears as a consequence of this transmission. Bubonic and other forms of plague in humans, without secondary pneumonia, are not considered to be

infectious. It has been reported that inhalation from contaminated clothes could be also a route of transmission [10]. Propagation of a human plague outbreak depends upon the number and susceptibility of rodent populations, the flea-carrying capacity of the rodent species, the number and infectivity of the flea species, the degree of contact of people with infected rat fleas, climatic conditions, and the number and living conditions of susceptible people [13].

Plague and bioterrorism

Y. pestis appears to be a good candidate agent for a bioterrorist attack. The use of an aerosolised form of this agent could cause with an explosive outbreak of primary plague pneumonia in the exposed population, or alternatively the bacteria could be used to infect the rodent population and precipitate a secondary outbreak in humans living in poor conditions [12,13]. Intentional aerosol release should be suspected in patients presenting with plague pneumonia in non-endemic areas or in patients without risk factors.

Y. pestis is a relatively fragile organism that remains viable only an hour after an aerosol release. Nevertheless, as few as 1 to 10 bacteria are sufficient to infect rodents via the oral, intradermal, subcutaneous or intravenous routes [14]. Estimates of human infectivity by the respiratory route vary from 100 to 20 000 organisms [4,6,7]. The Tatars were the first to use plague as a biological weapon, in 1347, during the siege of the Genoese-controlled Black Sea port of Caffa: they hurled the bodies of their plague victims over the city walls [7,15]. It has been reported that the Japanese army dropped plague-infected fleas in China during the second world war [1,7]. In 1970, it was reported that if 50 kg of *Y. pestis* were released over a city of 5 million, plague pneumonia could occur in as many as 150 000 persons, including 36 000 deaths [16]. In May 2000, during the virtual exercise TOPOFF in the US (for 'top officials'), simulation of a deliberate release of an aerosol of *Y. pestis* at a performing arts centre estimated that 3 700-4 000 cases of plague pneumonia and between 950 to over 2 000 deaths might have resulted [12].

Biological characteristics

Y. pestis is a Gram negative, non-motile, non-sporulating rod, which presents bipolar staining with Wayson stain and is a facultative anaerobic bacillus of the family Enterobacteriaceae. It grows aerobically on most culture media [6].

Clinical features

The most usual clinical presentations of plague are bubonic, primary septicaemic and pneumonic disease [4,6,7,11]. In a biological attack, the most likely clinical presentation would be primary pneumonic plague, as dispensed by aerosol is

considered the most likely way of dispersing the agent [7,12] (TABLE I).

Pneumonic plague may occur by primary respiratory infection, or as a complication of the bubonic and septicaemic forms of the disease (secondary pneumonia).

In this case, the incubation period is 1-6 days. It begins abruptly with intense headache and malaise, high fever, vomiting, abdominal pain, diarrhoea and marked prostration. Chest pain, cough, dyspnoea and haemoptysis develop thereafter [6]. Chest radiographs show evidence of multilobar consolidation, cavities or bronchopneumonia [6]. Laboratory findings are consistent with a bacterial infection with disseminated intravascular coagulation. Respiratory failure develops quickly with septic shock, and mortality is high. Without antibiotics, the disease is fatal in almost all patients within two or three days. Plague pneumonia is highly contagious to other humans by droplet transmission and in practice, patients are still contagious up to 3 days after starting appropriate antibiotic treatment. With the prompt use of antibiotics, the fatality rate decreases below 10% but the treatment should be started as soon as possible.

Bubonic plague is the most common clinical form of naturally occurring plague (75-97% of all cases). After an incubation period of 2 to 8 days, there is sudden onset of fever (38.5°C to 40°C), chills, headache, nausea, vomiting, malaise or prostration and weakness; 6 to 8 hours after the onset of symptoms a bubo develops [4,6,7]. The bubo is characterised by severe pain, swelling and marked tenderness. It develops in the area of an infected bite: groin (with femoral more frequent than inguinal lymph nodes affected), axillary and cervical nodes are most commonly affected. It becomes visible after 24 hours, and its size varies from 1 to 10 cm in diameter. There is surrounding oedema and the overlying skin is warm, erythematous and adherent. Pustules, vesicles, eschars, papules or skin ulcerations may occur at the site of the flea bite, which is usually in the lower extremities [7]. Rarely, the bubo may become fluctuant and suppurate. Other manifestations include apathy, confusion, fright, anxiety, oliguria or anuria, tachycardia, and hypotension [7]. Without specific treatment, complications are common and include primary (without discernible bubo) or secondary septicaemia, secondary pneumonia and meningitis. The mortality rate or case fatality rate for untreated bubonic plague is 60%, which becomes less than 5% with appropriate antibiotic treatment [11].

This form is unlikely to occur in a bioterrorist attack, except if fleas were used as a vector [7].

Septicaemic plague may occur as a complication of untreated bubonic plague or pneumonic plague (secondary septicaemic plague) and can develop in the absence of obvious signs of primary disease (primary septicaemic plague).

Symptoms and signs are indistinguishable from other Gram negative septicaemias, and include septic shock and disseminated intravascular coagulation with vasculitis, livid cyanotic petechiae, purpura and large ecchymoses that can mimic meningococcaemia [7,11]. Gangrene of acral regions, like the tip of the nose or the fingers and toes, due to small artery thrombosis may appear in advanced stages of the disease (Black Death). Left untreated, the mortality approaches 100%.

Plague meningitis is rare but may occur as a complication of inadequately treated infection elsewhere. There appears to be an association between the formation of a bubo and meningitis.

Pharyngeal plague is very rare and possibly a result of ingestion or inhalation of the organism. The tonsils are swollen and inflamed with anterior cervical lymphadenopathy and swelling of the parotid area.

Diagnosis

Case definitions of suspected or confirmed cases and cases due to deliberate release are summarised in Tables 2 and 3.

Y. pestis can be cultured from blood, sputum, bubo aspirate and cerebrospinal fluid (CSF) samples. Specimens for culture should be taken before initiation of antibiotic treatment. Smears may be stained with Gram, Giemsa or Wayson's stains to demonstrate bipolar staining coccobacilli [2-7]. The diagnosis of plague is then confirmed by culture. Antimicrobial susceptibility tests must be set up as early as possible. Serological diagnosis is possible but antibodies may not be detectable when the patient first presents. Detection of anti-capsular antibodies as either a ≥ 4 fold rise in titres from acute to convalescent serum or a single titre of $>1:128$ in patients not previously vaccinated, confirms the diagnosis [2-5].

Other tests include direct immunofluorescence for F1 antigen, specific phage lysis and PCR for the plasminogen activator gene (TABLE I).

Treatment

Treatment should be initiated as soon as the diagnosis is suspected (TABLE 4). Many antibiotics are active against *Y. pestis* (streptomycin, gentamicin, doxycycline, ciprofloxacin, chloramphenicol, sulfadiazine, trimethoprim-sulfamethoxazole) [2-5,17]. Most of the therapeutic guidelines suggest using gentamicin or streptomycin as first line therapy with ciprofloxacin as an alternative [2-7,17]. Chloramphenicol should be used for the treatment of meningitis. Persons who come in contact ($<2m$) with patients with pneumonic plague should receive antibiotic prophylaxis with doxycycline or ciprofloxacin for 7 days [2-7,17]. Other antibiotics (chloramphenicol, sulfadiazine, trimethoprim-sulfamethoxazole) could also be used [2-7,17].

Prevention of human-to-human transmission from patients with plague pneumonia can be achieved by implementing standard isolation procedures until at least 4 days of antibiotic treatment have been administered. For the other clinical types of the disease, patients should be isolated for the first 48 hours after the initiation of treatment. Healthcare workers should wear high efficiency respirators [2-5].

Vaccines

A killed whole cell plague vaccine that was efficacious against bubonic disease was available until 1999 in the US [4]. This vaccine was associated with a poor protection against pneumonic disease [9]. It was recommended for persons working with *Y. pestis* in a laboratory, for those working in plague-affected areas or with potentially infected animals [18]. A live attenuated vaccine is also available in the US, but it retains some virulence and is therefore not considered suitable for human use in most countries [9]. Recent vaccine research in Europe is focused on the development of a sub-unit vaccine containing F1 antigens and recombinant V antigens, which proved to be efficacious against pneumonic plague in mice [9,19].

Conclusion

In conclusion, *Y. pestis* is one of the major agents that could be as a biological weapon. The main clinical manifestations would be plague pneumonia if aerosolised bacteria were used, and

bubonic and/or septicaemic plague if fleas were used as infected vectors.

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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 and biological characteristics of plague

Clinical description
<ul style="list-style-type: none"> - Incubation period: 1-6 days
Pneumonic plague
<ul style="list-style-type: none"> - Abrupt onset of intense headache and malaise, high fever, vomiting, abdominal pain, diarrhoea and marked prostration, chest pain, cough, dyspnoea and haemoptysis - Chest X-ray: multilobar consolidation, cavities or bronchopneumonias - Respiratory failure develops quickly with septicaemic shock
Bubonic plague
<ul style="list-style-type: none"> - Fever (38.5°C to 40°), chills, headache, weakness and bubo - Surrounding oedema and the overlying skin is warm, erythematous and adherent
Septicaemic plague
<ul style="list-style-type: none"> - Septic shock, vasculitis, livid cyanotic petechiae, large ecchymoses, gangrene of acral regions and multi-organ failure - Meningitis occurs in 5% of cases
Presumptive diagnosis
<ul style="list-style-type: none"> - Staining of specimens - ELISA, direct immunofluorescence, PCR
Diagnosis
<ul style="list-style-type: none"> - Isolation of <i>Y. pestis</i> from a clinical specimen - Demonstration of a specific antibody response to <i>Y. pestis</i> fraction 1 (F1) antigen - Elevated serum antibody titres to <i>Y. pestis</i> F1 antigen (without documented specific change) in a patient with no history of plague vaccination - Detection of F1 antigen in a clinical specimen by fluorescent assay
Management of treatment
<ul style="list-style-type: none"> - If plague pneumonia, isolation in a negative pressure room (if possible) - Gentamicin or streptomycin as first line therapy with ciprofloxacin as an alternative (Table 4) - Chloramphenicol should be used for the treatment of meningitis - Persons in contact (<2m) with patients with pneumonic plague should receive antibiotic prophylaxis with doxycycline or ciprofloxacin for 7 days. Other antibiotics (chloramphenicol, sulfadiazine, trimethoprim-sulfamethoxazole, etc) could also be used

TABLE 2**Case definitions of possible, probable and confirmed cases**

Possible case
<ul style="list-style-type: none">• Sudden onset of severe, unexplained febrile respiratory illness• Unexplained death following a short febrile illness• Sepsis with Gram negative coccobacilli identified from clinical specimens
Probable case
<ul style="list-style-type: none">- A case that clinically fits the criteria for suspected plague, and in addition, positive results are obtained on one or more specimens
Confirmed case
A clinically compatible case with confirmatory laboratory results
<ul style="list-style-type: none">• Culture of <i>Y. pestis</i> from a clinical specimen and confirmation of identification by phage lysis• A significant (4-fold) change in antibody titre to F1 antigen in paired serum samples• A definitive diagnosis, by positive PCR or detection of F1 antigen on suspect isolates, will be available within one working day

Source: [20,21]

TABLE 3**Criteria for suspecting a deliberate release of plague**

Deliberate release
<ul style="list-style-type: none">• A single confirmed case in the European Union must be regarded with a high degree of suspicion of deliberate release*• A confirmed case of plague in a person without history of being outdoors or having contact with animals• ≥ 2 suspected cases of plague that are linked in time and place, especially if the suspected cases are geographically related according to a particular wind pattern

* Cases that occur in people, who have returned from endemic areas should be investigated to ascertain that the illness did not occur with intent to deliberately release *Y. pestis*

TABLE 4

Recommendations for treatment and post-exposure prophylaxis of plague

		Treatment of suspected or confirmed clinical cases (10 days)	Post-exposure prophylaxis (7 days)
Adults Pregnant women	First line treatment	- Gentamicin: 5 mg/kg IV in 1 or 2 doses daily or - Streptomycin: 1 g IM twice daily	
It is recommended, when possible, to cease breastfeeding.	Second line treatment; first line prophylaxis	- Ciprofloxacin: 400 mg IV bid followed by 500 mg per os bid or - Ofloxacin: 400 mg IV bid followed by 400 mg per os bid or - Levofloxacin: 500 mg IV once a day, followed by 500 mg per os once a day	- Ciprofloxacin: 500 mg per os bid or - Ofloxacin: 400 mg per os bid or - Levofloxacin: 500 mg per os once a day
	Third line treatment; second line prophylaxis	- Doxycycline: 100 mg IV bid followed by 100 mg bid per os	- Doxycycline: 100 mg bid per os
Children	First line treatment	- Gentamicin: 2.5 mg/kg IV in 3 doses daily or - Streptomycin: 15 mg/kg IM twice daily (max, 2g)	
	Second line treatment; first line prophylaxis	- Ciprofloxacin: 10-15 mg/kg IV bid followed by 10-15 mg/kg per os bid	- Ciprofloxacin: 10-15 mg/kg per os bid
	Third line treatment; second line prophylaxis	- 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)	- 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)

Source: [17]