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

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Q fever is a zoonotic disease caused by *Coxiella burnetii*. Its interest as a potential biological weapon stems from the fact that an aerosol of very few organisms could infect humans. Another route of transmission of *C. burnetii* could be through adding it to the food supply. Nevertheless, *C. burnetii* is considered to be one of the less suitable candidate agents for use in a bioterrorist attack; the incubation is long, many infections are inapparent and the mortality is low. In the case of an intentional release of *C. burnetii* by a terrorist, clinical presentation would be similar to naturally occurring disease. It may be asymptomatic, acute, normally accompanied by pneumonia or hepatitis, or chronic, usually manifested as endocarditis. Most cases of acute Q fever are asymptomatic and resolve spontaneously without specific treatment. Nevertheless, treatment can shorten the duration of illness and decrease the risk of complications such as endocarditis. Post-exposure prophylaxis is recommended after the exposure in the case of a bioterrorist attack.

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Introduction

Q fever (query fever) is a zoonotic disease caused by *Coxiella burnetii*, a rickettsial organism, which is distributed worldwide with the exception of New Zealand [1,2]. Cattle, sheep, goats, domestic pets (dogs, cats), wild rodents, birds and ticks are the primary reservoirs of this organism. Contrary to other rickettsias, ticks are not considered to be a major vector of infection for humans. Ticks are considered to be the natural primary reservoir of *C. burnetii* responsible for the spread of the infection in animals [1,2]. *C. burnetii* is not associated with rickettsial disease in these animals, but increased abortion rate in goats and sheep has been reported with *C. burnetii* infection. Humans are the only known host to develop illness as a result of infection [1].

C. burnetii is excreted in milk, urine and faeces of infected animals. Moreover, during birthing, the bacteria are shed in high numbers within the amniotic fluids and the placenta. The placenta of infected sheep contains up to 10^9 organisms per gramme of tissues [3].

Infection of humans can occur by consumption of contaminated food or water, or inhalation of *C. burnetii* in air that contains aerosolised particles from contaminated tissues or fluids such as dried placental material, amniotic fluids, or excreta of infected animals, which is the most common reported cause of human outbreaks [4]. Direct contact with infected animals or other contaminated material has been also associated with the spread of the disease. In Europe outbreaks mainly due to aerosolisation of the agent, involving between 4 and 150 or more patients are reported from many countries each year [5]. Person-to-person transmission does not usually occur (is extremely rare) [3,6], although case reports of sexual transmission and sporadic cases of human-to-human transmission following contact with an infected parturient woman have been reported[3]. Rare cases of transmission from blood or bone marrow transfusion have also been described. People at higher risk for Q fever are those working with infected animals such as farmers, veterinarians, laboratory workers, meat workers and sheep workers.

Q fever and bioterrorism

Interest in *C. burnetii* as a potential biological weapon stems from the fact that an aerosol of this agent could infect humans [7]. Humans are very susceptible to the disease. An infectious dose of very few organisms is required to cause infection. It has been estimated that as few as one to ten organisms could cause disease [8]. *C. burnetii* is resistant to heat, drying and many common disinfectants. These organisms can live for long periods in the environment in a spore-like form. Additionally, another route of transmission of *C. burnetii* could be through sabotage of the food supply. To our knowledge, this agent has never been used as a biological weapon. Nevertheless, *C. burnetii* is considered one of the less likely candidate agents for use in a bioterrorism attack; the incubation is long, many infections are inapparent and the mortality is low. Its use would rather be as an incapacitating agent. In case of an intentional release of *C. burnetii* by a terrorist, clinical presentation would be similar to naturally occurring disease.

Microbiological characteristics

Q fever is caused by *C. burnetii*, which is a pleomorphic coccobacillus with a Gram negative cell wall [3]. It is a member of the family Rickettsiacae. This bacterium, which is an obligate intracellular organism, can survive within the phagolysosomes in host cells, where the low pH is necessary for its metabolic functioning. A major characteristic of *C. burnetii* is its antigenic variation due to partial loss of lipopolysaccharide (LPS) [3]. This LPS is a major virulence factor for *C. burnetii*. When isolated from animals or humans, *C. burnetii* expresses phase I antigens and is very infectious. After subculture, modification of the LPS results in an antigenic shift to the phase II form, which is less infectious. This phenomenon is important for the serological differentiation between acute and chronic Q fever [3].

Clinical features

The clinical presentation of Q fever is highly variable and non-specific. It may be asymptomatic, acute, normally accompanied

by pneumonia or hepatitis, or chronic, usually manifested as endocarditis (TABLE 1).

Acute disease

One half of patients infected with *C. burnetii* will have signs and symptoms of the disease. The incubation period varies from 9 to 39 days, but is usually 2 to 3 weeks. This period varies depending on the number of organisms that initially infect the patient [1,4]. A higher inoculum also increases the severity of the disease [4]. A self-limiting febrile illness is probably the most common form of Q fever mistaken for an acute viral illness lasting a few days to two weeks. Most of the signs and symptoms are non-specific. The onset of the disease is often abrupt with high fever, chills, profuse sweating, severe retrobulbar headache, myalgia, malaise, confusion, lethargy, nausea, vomiting, diarrhoea, abdominal pain, non-productive cough, sore throat and chest pain. Approximately 50% of these patients will develop pneumonia. This pneumonia may present like an atypical pneumonia, a rapidly progressive pneumonia or as febrile illness with no respiratory symptoms (probably the most common form) [9-12]. A chest radiograph can show non-segmental and segmental pleural-based opacities, which are frequent, multiple suggestive rounded opacities, pleural effusions, atelectasis and rarely hilar adenopathies [10]. Chest radiographs can also appear normal. The main differential diagnoses are with other pneumonias caused by *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia psitacci* and *Chlamydia pneumoniae*.

Acute or chronic granulomatous hepatitis is frequent [13]. Cases of meningoencephalitis or encephalitis, aseptic meningitis, myelitis, optic neuritis and peripheral neuropathy have also been reported [14]. Encephalitis signs are not specific, but behaviour or psychiatric disturbances are common. Cases of pericarditis have been reported; this manifestation may also be noted during the chronic phase [15].

In contrast to other rickettsioses, rash is rare: maculopapular or purpuric exanthema is found in only 10% of cases [3].

Other uncommon manifestations include: haemophagocytosis, haemolytic anaemia, transient hypoplastic anaemia, thyroiditis, gastroenteritis, pancreatitis, lymphadenopathy mimicking lymphoma, erythema nodosum, bone marrow necrosis, inappropriate secretion of anti-diuretic hormone, mesangioproliferative glomerulonephritis related to antiphospholipid antibodies and splenic rupture [3].

Pregnant women are at risk for in utero foetal death and abortion, even if clinically well, although most cases are asymptomatic [16]. Intrauterine transmission of *C. burnetii* has been reported [3].

Laboratory tests are usually without abnormalities except for mild elevations in the white blood cell count (30% of patients). Thrombocytopenia is noted in 25% of patients. The sedimentation rate is usually moderately elevated. Abnormal liver function tests are very common: elevated levels of alkaline phosphatase and transaminases (70%). Hyponatremia can be noted (28%) [10].

Chronic disease

Chronic Q fever is defined as disease that persists for more than 6 months. This chronic form may develop within a year or as long as 20 years after the initial infection. It occurs especially in patients with previous valvular heart disease, and to a lesser extent in patients with immunocompromising diseases such as transplant recipients, cancer or chronic kidney disease, and also in pregnant women.

The most common complication is endocarditis [17,18]. This endocarditis usually involves the aortic, and less commonly the mitral, heart valves in patients with pre-existing valvular heart diseases or valvular graft. Q fever endocarditis is the most important aetiology of blood culture negative endocarditis [18]. It occurs in patients with pre-existing valvular disease or with a valvular prosthesis [18]. Diagnosis is most often considered in the presence of an unexplained fever, heart failure with valvular dysfunction, haemolysis, glomerulonephritis or stroke [18].

Other complications include aseptic meningitis, encephalitis and osteomyelitis.

A chronic fatigue-like syndrome has been reported in some patients with chronic Q fever.

Laboratory results are those of an inflammatory syndrome.

Diagnosis

Case definitions of suspected and deliberate cases are reported in Tables 2 and 3.

Specific diagnosis of Q fever remains based upon serologic tests (indirect immunofluoresence is the reference method for the serodiagnosis). IgM and IgG antiphase II antibodies are detected 2 to 3 weeks after infection, whereas the presence of IgG antiphase I *C. burnetii* antibodies at titres $\geq$ 1:800 by microimmunofluorescence is indicative of chronic Q fever [2,3]. Antibodies to phases I and II antigens have been known to persist for months or years after initial infection.

Attempted isolation of *C. burnetii* from a clinical specimen by culture or blood cultures usually remains negative.

C. burnetii may also be identified in infected tissues by using immunohistochemical staining and DNA detection methods.

Treatment

Most of the cases of acute Q fever are asymptomatic and resolve spontaneously without specific treatment. Nevertheless, treatment can shorten the duration of illness and decrease the risk of complications such as endocarditis. Without treatment, the death rate in patients with acute Q fever is near 1%. Doxycycline is the first choice treatment for acute Q fever (200 mg/ day for 15-21 days) (TABLE 4) [19]. Fluoroquinolones have demonstrated good results and may also be recommended for the treatment of acute Q fever. In pregnant women, fluoroquinolones (if the woman is at term) or trimethoprim-sulfamethoxazole can be prescribed.

In patients with chronic Q fever, the death rate may be as high as 30% to 60%. Treatment should include combinations of doxycycline and fluoroquinolone or rifampicin or trimethoprim-sulfamethoxazole for at least four years, or doxycycline plus hydroxychloroquine for 1.5 to 3 years. Surgery is needed in some cases.

It is recommended that post-exposure prophylaxis be started 8 to 12 days after the exposure (TABLE 4).

Only an inactived whole cell (Q-Vax) vaccine is available and recommended for workers with occupational risk of exposure to *C. burnetii* (laboratory workers, abattoir workers, veterinarians etc). It is not available for the general population and is not recommended as pre-event prophylaxis. A chloroform:methanol residue (CMR) vaccine has been developed [20]. The efficacy of this vaccine has been reported in mice and guinea pigs. The CMR vaccine dose required to protect 50% of mice (PD_{50}) against lethal aerosol challenge (11 LD_{50}) was one-third of the Q-Vax dose. However, the PD_{50} for CMR was four times the Q-Vax dose in guinea pigs challenged by aerosol (60 LD_{50}). It was concluded that CMR is an efficacious alternative to cellular Q fever vaccines for the prevention of Q fever.

In conclusion, Q fever has been reported as a possible agent for use in biowarfare. The agent is stable and could be transmitted via the airborne route. The disease is associated with low mortality and relatively high morbidity, therefore making it a comparatively limited-impact agent.

References

1. Norlander L. Q fever epidemiology and pathogenesis. *Microbes Infect* 2000; 2: 417-24
2. Maurin M, Raoult D. Q fever. *Clin Microbiol Rev* 1999; 12: 518-53
3. Fournier PE, Marrie T, Raoult D. Diagnosis of Q fever. *J Clin Microbiol* 1998; 36: 1823-34
4. Byrne W. Q fever. In Zajtchuk R, ed. Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare. Washington, DC: US Department of the Army, Surgeon General, and the Borden Institute 1997: 523-37
5. Anonymous. Q fever in Europe. *Eurosurveillance Monthly* 1997; 2: 13-5
6. Mann J, Douglas J, Inglis J et al. D fever; person to person transmission within a family. *Thorax* 1985; 41: 974-5
7. Franz D, Jahrling P, Friedlander A et al. Clinical recognition and management of patients exposed to biological warfare agents. *JAMA* 1997; 278: 399-411
8. Sawyer L, Fishbein D, McDale D. Q fever; current concepts. *Rev Infect Dis* 1987; 9: 935-46
9. Marrie T. Coxiella burnetii (Q fever). Gerald L Mandell, John E Bennett and Raphael Dolin, Eds. Principles and practice of Infectious Diseases. 4th ed: New York: Churchill Livingstone, Inc, 1995: 1727-35
10. Caron F, Meurice JC, Ingrand P et al. Acute Q fever pneumonia: a review of 80 hospitalized patients. *Chest* 1998; 114: 808-13
11. Antony S, Schaffner W. Q fever pneumonia. *Semin Respir Infect* 1997; 12: 2-6
12. Marrie T. Coxiella burnetii (Q fever) pneumonia. *Clin Infect Dis* 1995; 21 suppl 3: S253-64
13. Zaidi S, Singer C. Gastrointestinal and hepatic manifestations of tick borne diseases in the United States. *Clin Infect Dis* 2002; 34: 1206-12
14. Bernit E, Pouget J, Janbon F et al. Neurological involvement in acute Q fever: a report of 29 cases and review of the literature. *Arch Intern Med* 2002; 162: 693-700
15. Levy P, Carrieri P, Raoult D. *Coxiella burnetii* pericarditis; report of 15 cases and review. *Clin Infect Dis* 1999; 29: 393-7
16. Stein A, Raoult D. Q fever during pregnancy: a public health problem in southern France. *Clin Infect Dis* 1998; 27: 592-6
17. Stein A, Raoult D. Q fever endocarditis. *Eur Heart J* 1995; 16 suppl B: 19-23
18. Salamand A, Collart F, Caus T et al. Q fever endocarditis: over 14 years of surgical experience in referral centre for rickettsioses. *J Heart Valve Dis* 2002; 11: 84-90
19. The European Agency for the Evaluation of Medicinal Products/CPMP guidance document on use of medicinal products for treatment and prophylaxis of biological agents that might be used as weapons of bioterrorism. July 2002; www.emea.eu.int
20. Waag D, England M, Pitt M. Comparative efficacy of a *Coxiella burnetii* chloroform:methanol residue (CMR) vaccine and a licensed cellular vaccine (Q-Vax) in rodents challenged by aerosol. *Vaccine* 1997; 15: 1779-83
21. Commission decision of 19 March 2002. Case definitions for reporting communicable diseases to the Community network under decision N° 2119/98/EC of the European Parliament and the Council. *Official Journal of the European Communities.* OJ L 86, 3.4.2002; 44
22. Amending Decision N°2119/98/EC of the European Parliament and of the Council and Decision 2000/96/EC as regards communicable diseases listed in those decisions and amending decision 2002/253/EC as regards the case definitions for communicable diseases. *Official Journal of the European Union.* OJ L 184, 23.7.2003;35-9

* **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 Q fever

Clinical features
• The clinical presentation is polymorphic and non-specific
Acute disease
• 50% of patients have signs and symptoms of the disease • Incubation period: 2 to 3 weeks • The most common form: self-limiting febrile illness • Symptoms: abrupt onset of high fever, chills, profuse sweating, severe retrobulbar headache, myalgia, malaise, confusion, lethargy, nausea, vomiting, diarrhoea, abdominal pain, non-productive cough, sore throat and chest pain • 50% of symptomatic patients develop pneumonia • Acute hepatitis is frequent • Pregnant women are at risk for in utero foetal death and abortion • Laboratory findings: ↑ transaminases and alkaline phosphatase, mild leucocytosis (30%), thrombocytopenia (25%)
Chronic disease
• Disease that persists for more than 6 months • Patients with previous valvulopathy, immunocompromising diseases, pregnant women • Most common complication: endocarditis • Patients with pre-existing valvular disease or with a valvular prosthesis
Diagnosis

• Isolation of *C. burnetii* from a clinical specimen
• Demonstration of *C. burnetii* in a clinical specimen by PCR
• Specific diagnosis is indirect immunofluorescence:
  • IgM and IgG antiphase II antibodies are detected 2 to 3 weeks→ acute Q fever
  • IgG antiphase I antibodies at titres of ≥ 1:800→ chronic Q fever

TABLE 2

Case definitions of Q fever

Possible case
• not applicable for Q fever
Suspected case
• clinically compatible case that fulfils the laboratory criteria for a probable case or has an epidemiological link
Confirmed case
• laboratory confirmed case that is clinically compatible or has an epidemiological link

Source: [21-22]

TABLE 3

Case definitions of Q fever due to deliberate release

Suspected deliberate release
• Large-scale outbreak of confirmed Q fever which are not likely to be from a natural source

TABLE 4

Recommendations for treatment and post-exposure prophylaxis of Q fever

		Treatment of suspected or confirmed clinical cases (1-3 weeks)	Post-exposure prophylaxis (1 week)
Adults **Pregnant women**	**First line treatment and prophylaxis**	- Doxycycline: 100 mg IV bid followed by 100 mg orally bid	- Doxycycline: 100 mg orally bid
It is recommended, when possible, to stop breastfeeding.	**Second line treatment and prophylaxis**	- Erythromycin: up to 1g IV 4 times daily followed by 500 mg orally 4 times daily. **or** - Clarithromycin: 500 mg IV bid followed by 500 mg orally bid **or** - Roxithromycin: 150 md per os bid (2-3 weeks)	- Erythromycin: 500 mg orally 4 times daily. **or** - Clarithromycin: 500 mg orally bid **or** - Roxithromycin: 150 md per os bid
	First line treatment in case of meningoencephalitis (2-3 weeks)	- 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	
Children	**First line treatment and 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)
	Second line treatment and prophylaxis	- Erythromycin: 50 mg/kg/day IV in 4 divided doses followed by: . > 35 kg: 500 mg orally 4 times daily. . < 35 kg: 50 mg/kg/day orally in 2 divided doses daily **or** - Clarithromycin: . > 40 kg: adult dose . < 40 kg: 7.5 mg/kg per os bid (max 500 mg daily) **or** - Roxithromycin: 8 mg/kg/day per os in 2 divided doses (2-3 weeks)	- Erythromycin: . > 35 kg: 500 mg orally 4 times daily. . < 35 kg: 50 mg/kg/day orally in 2 divided doses daily **or** - Clarithromycin: . > 40 kg: adult dose . < 40 kg: 7.5 mg/kg per os bid (max 500 mg daily) **or** - Roxithromycin: 8 mg/kg/day per os in 2 divided doses
	First line treatment in case of meningoencephalitis (2-3 weeks)	- Ciprofloxacin: 10-15 mg/kg IV bid followed by 10-15 mg/kg per os bid	

Source: [19]