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BIOLOGICAL AGENTS
Q Fever¹

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AETIOLOGY

Q Fever is caused by the rickettsial pathogen *Coxiella burnetii*, a minute bacterium-like organism which may vary in size and shape. The smaller organisms will pass through microbial filters (pore size 2.1 μm)¹.

The pathogen is able to produce a highly resistant spore which enables it to remain stable in the environment and in the presence of many disinfectants. It can withstand temperatures from -52°C to 40°C. 0.5 percent phenol is relatively resistant to desiccation and is able to persist on surfaces for five to 60 days.

Two distinct antigenic phases exist: Phase I is found in nature, and Phase II in the laboratory, after multiple passages through cell cultures or eggs.

EPIDEMIOLOGY

The disease has been reported in continents, especially the United States (particularly California), Australia, Europe, South America and Africa.

Although this organism infects wild animals via arthropod bites, the human disease is acquired primarily through inhalation of aerosols. Animal reservoirs include sheep, cattle, cats, feral rodents and ticks⁶. Although these animals are often asymptomatic, massive numbers of microorganisms can be shed in urine, faeces, milk and placenta.

PATHOLOGY

Virulence Factors

The molecular basis of Q fever pathogenesis is still poorly understood. It appears that different isolates of *C. burnetii* possess surface lipopolysaccharides (LPS) which vary antigenically and cause different host cell responses and clinical manifestations. Host characteristics (immune status, predisposing factors such as cardiac or immunological anomalies) may also be important in the clinical manifestations of Q fever¹.

Correlations have been found between the LPS type and the form of the disease - either chronic or acute. Virulent Phase I pathogens possess a "smooth" LPS, whereas LPS of avirulent Phase II organisms is truncated or "rough".

Phase I LPS has been shown to induce toxic responses, such as hyperthermia, weight loss, hepatomegaly, lipid infiltration of the liver, and leukocytosis^{7,8}. Phase II isolates are able to survive in phagolysosomes but not the humoral and cell-mediated immune responses⁹. Phase II LPS does not induce the pathological reactions characteristic of Phase I strains¹⁰.

The precise role of LPS in pathogenesis is not known, but it may involve toxicity, attachment to host cells or influence on the immune response.

Other virulence factors are probably involved in pathogenesis but have not yet been identified.

Relationship between isolate and disease manifestation

Q fever can occur either as a short-term acute disease, or as a chronic illness which may last for months or years. Approximately five percent of patients with acute Q fever will develop chronic disease. There is some evidence to suggest that the form of the disease is very much dependent on the particular strain of *C. burnetii* involved.

Pathogenic Sequence

Coxiella burnetii is an obligate intracellular parasite which can grow in monocytes, macrophages and pneumocytes. The pathogens enter the cell passively by endocytosis (they are engulfed by the phagocyte) and grow in the highly acidic phagolysosomes, where huge colonies may form.

The organism is able to resist degradation by lysosomal enzymes and requires acidic conditions for the metabolism and transport of nutrients such as sugars and amino acids". The organisms may disseminate via the bloodstream and may cause major pathological changes in organs - especially the lungs and liver. Granulomas and necrotic lesions are common symptoms.

Pathogens which are able to persist in the body may cause chronic illness, although the physiological mechanism of persistence is not well understood. It has been demonstrated in vitro that *C. burnetii* is able to induce the presentation of antigens on the surface of the host cell, and that the degree of presentation varies with different isolates. Strains which are associated with acute disease cause more antigen presentation than those strains implicated in chronic infection. If this is also relevant in vivo, chronic isolates may be able to survive for a longer period in the host because they are not as visible to the immune system¹².

CLINICAL MANIFESTATIONS

Q fever can occur either as an acute illness, or a persistent, chronic disease. The symptoms are non-specific, making diagnosis purely from clinical observations difficult. Mortality in untreated cases is less than 1 per cent.

Acute illness

The acute form of Q fever typically manifests as a pneumonitis with malaise, anorexia, muscle pain, fever, chills, and intense pre-orbital headache" which may last nine to 14 days. The onset of symptoms is sudden and usually occurs 14 to 39 days after inhalation of spores¹³.

A dry cough may be present in some patients. Unlike other rickettsial diseases, no rash develops.

Complications are not uncommon and may include encephalitis (involving headache, arthralgia, fever, speech difficulties, diarrhoea, influenza-like symptoms, dry cough, ataxia and dysphagia) and meningoencephalitis⁵.

Chronic Illness

Chronic Q fever usually appears as endocarditis, commonly involving the aortic or mitral valves¹⁻⁶. This form of the disease has a poor prognosis and may persist for years. Pericarditis and hepatitis may also develop.

DIAGNOSIS

Laboratory diagnosis

Positive identification can be made by specific antibody response, isolation of the pathogen from inoculated animals or cell cultures, or fluorescent antibody staining of blood or tissue smears. However, these techniques have limitations.

Serologic testing is the most useful technique, although diagnosis is not usually made early enough to affect the management of the disease". Techniques include immunofluorescent antibody assays, ELISA, latex agglutination, immunoperoxidase assays and haemagglutination. Several of these methods are useful in field situations.

Detection of antibodies using microscopy is difficult because organisms are present in relatively small numbers in tissues or blood (except postmortem tissue)¹⁷.

New techniques, such as nucleic acid amplification by the polymerase chain reaction (PCR), allow detection of DNA from very small samples, and have been useful in the early detection of acute phase Rocky Mountain spotted fever and murine typhus (other rickettsial diseases).

Differential diagnosis

Q fever may be mistaken for influenza, legionellosis, mycoplasmal pneumonia, tularaemia, pulmonary brucellosis, typhoid fever, cytomegalovirus and EBV mononucleosis, and psittacosis.

TREATMENT

Q fever can be successfully treated with tetracycline, doxycycline or chloramphenicol. Because of the intracellular nature of the pathogen, antibiotics must have good cell membrane permeability.

Acute Q Fever

Acute Q fever is usually a self-limiting disease which resolves within a few weeks if untreated.

Treatment only reduces the time of fever.

Recommended therapy is:

- doxycycline 100 mg every 12 hours for five to six days, or
- tetracycline 750 mg every six hours for five to six days, or for three days after the patient becomes afebrile, or
- erythromycin 500 mg every six hours plus rifampicin 600 mg per day for five to six days.

Other antibiotics successfully used include ofloxacin, perfloxacin, chloramphenicol and cotrimoxazole.

Tetracycline can also be used for post-exposure prophylaxis. Treatment with 750 mg of tetracycline every six hours for five to six days starting eight to twelve days after exposure prevents the development of the clinical disease. However, if this regimen is begun one day after exposure (and stopped on day six or seven), clinical disease occurs about three weeks after the cessation of treatment.

Chronic Q fever

Q fever endocarditis has been treated with most success with a combination of drugs. Therapy with one drug alone often results in prolonged illness or death²⁰. Antibiotic treatment should continue for at least three years^{20,21}.

Recommended therapy is:

- doxycycline 200 mg per day plus rifampicin 900 mg per day or a quinolone (pefloxacin or ofloxacin 400 mg per day)²⁰.
- Tetracycline only appears to be effective for as long as it is given - once treatment is stopped, relapse of ten occurs²¹.
- Several fluoroquinolones have been shown to be ineffective in the treatment of Q fever endocarditis unless used in combination with other antibiotics such as rifampicin²².

In the event of a biological warfare attack, and if possible, the surrounding area should be disinfected. The pathogen is very hardy and can resist elevated temperature, osmotic shock, desiccation, ultraviolet radiation and many chemical disinfectants²³. Formaldehyde gas, 0.5 per cent sodium hypochlorite, 2 per cent roccal, 5 per cent lysol and 5 per cent formalin all fail to inactivate the microorganism after 24 hours at 25°C²³. Pathogens in 70 per cent ethyl alcohol, 5 per cent chloroform or 5 per cent Enviro-chem are inactivated within 30 minutes²³.

SUSCEPTIBILITY OF POPULATION

Susceptibility is high in previously unexposed individuals. Prior exposure generally gives solid, long-lasting immunity. The pathogen is extremely infectious inhalation of one to ten microorganisms is enough to cause disease.

PREVENTION

Two inactivated vaccines are currently in use and appear to be effective.

A formalin-killed whole-cell vaccine ("Q-vax" made by the Commonwealth Serum Laboratories, Melbourne) has been successfully tested on at-risk abattoir workers in Queensland and South Australia^{25,26}. The vaccine consists of a formalin-inactivated Phase I strain. One 30 11g doses appeared to confer immunity 10 to 15 days after vaccination, and immunity seems to last for at least five years²⁵.

A trichloroacetic acid (TCA) extracted Phase I antigen from an attenuated strain of *C. burnetii* has also been used successfully in the former Czechoslovakia²⁷.

It is important to pretest individuals for antibodies before vaccination, as severe local reactions often occur if vaccines are given to individuals who have prior immunity. A skin test (20 ng of antigen) measuring delayed-type hypersensitivity is the best measure of immunity (antibody titres do not necessarily correlate with protection). Because of the high immunogenicity of *C. burnetii*, the skin test alone may be enough to cause seroconversion¹³.

Recently, chloroform-methanol extractions of antigens have been tested, and these appear to be effective in preventing aerosol infections in mice. These vaccines do not produce the local reactions characteristic of the whole-cell vaccines, and are probably safe to administer to individuals with prior immunity (therefore eliminating the need to skin-test).

POTENTIAL AS A BIOLOGICAL WEAPON

A biological warfare attack of *C. burnetii* would involve aerosolised organisms and would cause disease very similar to naturally acquired Q fever. The very high infectivity means that only a few organisms (between one and ten) are necessary to cause disease.

The hardy nature of *C. burnetii* and its resistance to desiccation, heat and other environmental conditions, makes dissemination of the organism by aerosol feasible. It will also persist on dry or wet surfaces for a long period of time. Decontamination of the surrounding environment would be difficult because of the pathogen's survival in many chemical disinfectants.

Although fatalities would be rare, the illness is very debilitating and could seriously drain manpower and medical resources. The onset of acute disease could be any time between 14 and 40 days after exposure, causing prolonged disruption. The development of chronic disease would have a long-term effect on the individual infected and medical costs associated with the years of therapy would be considerable.

The current vaccines, although apparently effective, require testing of the patient for prior exposure - this is time-consuming and expensive. Local skin reactions are also associated with these vaccines. Recent development of better vaccines is promising.

FUTURE DIRECTIONS

New vaccines are currently being developed and should be available for use in the next few years. Antibiotic regimens for chronic illness should continue to be improved.

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