

# A Case of Pediatric Q Fever Osteomyelitis Managed Without Antibiotics

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Q fever osteomyelitis, caused by infection with *Coxiella burnetii*, is rare but should be included in the differential diagnosis of children with culture-negative osteomyelitis, particularly if there is a history of contact with farm animals, and/or granulomatous change on histologic examination of a bone biopsy specimen. We describe a case of Q fever osteomyelitis in a 6-year-old boy in which a decision was made not to treat the patient with combination antimicrobial agents, balancing possible risks of recurrence against potential side effects of prolonged antibiotic treatment. The patient had undergone surgical debridement of a single lesion and was completely asymptomatic after recovery from surgery. This case suggests that a conservative approach of watchful waiting in an asymptomatic patient with chronic Q fever osteomyelitis may be warranted in select cases when close follow-up is possible.

A previously well 6-year-old Caucasian boy from the Mid-North Coast of New South Wales, Australia, presented to his general practitioner with intermittent left knee pain and associated limp. The symptoms resolved within 2 weeks without any treatment but reappeared several weeks later. A knee x-ray revealed a lytic lesion in the left distal femur (Fig 1A). MRI demonstrated a T2 hyperintense lesion with sclerotic margins in the left lateral distal femoral epiphysis (Fig 1B). The patient had been systemically well throughout this time and was referred to an orthopedic surgeon with a working diagnosis of a chondroblastoma. Surgical management was undertaken 4 months after onset of symptoms, at which point the patient was completely asymptomatic.

During an open biopsy procedure, purulent material was discovered in the femoral epiphysis. A bone flap was elevated, and the lesion was washed out with 4 L of saline. A drain was left in situ for 2 days. The patient was administered empirical intravenous

flucloxacillin for 4 days, followed by oral cephalexin, while awaiting further results. The pus demonstrated numerous polymorphonuclear leukocytes, but standard bacterial cultures were negative. Histologic examination revealed necrotic material with diffuse inflammation, some granuloma formation and infiltration of plasma and lymphoid cells and histiocytes.

On further detailed review, it became apparent that the patient lived on a farm and had been exposed to calves, wallabies, and domestic cats and dogs. His father had previously worked in an abattoir. Both parents and 3 older siblings were well. Local laboratory investigations performed postoperatively demonstrated normal inflammatory markers and full blood count, with the exception of a raised platelet count ( $760 \times 10^9 /L$ ). *Brucella* (rose bengal test), Q fever phase II immunoglobulin (Ig)-G and IgM (by enzyme immunoassay), Quantiferon-Gold TB assay and Bartonella IgM (by indirect immunofluorescence [IFA]) were negative on serological testing.

## abstract

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Dr Khatami reviewed and revised the manuscript and was also involved in the clinical management of the patient whose case is described; Ms Sparks drafted the initial manuscript; Dr Marais reviewed and revised the manuscript and was involved in the clinical management of the patient whose case is described; and all authors approved the final manuscript as submitted.

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**FIGURE 1**  
A, left knee x-ray demonstrating lytic lesion in the distal femur (black arrow). B, left knee MRI demonstrating T2 hyperintense lesion with sclerotic margins in the lateral distal femoral epiphysis.

*Bartonella* IgG IFA titer was raised (1:256). Testing of the purulent material from a pellet of joint aspirate cultured in brain-heart-infusion broth using an in-house real-time polymerase chain reaction (PCR) targeting the first 500 bp of the 16S rRNA gene was positive for *Coxiella burnetii* (98% identity score). Testing of a separate sample of pus at a different laboratory by PCR was positive for *C burnetii* (Centre for Disease Control, US Laboratory Response Network *Coxiella burnetii* real-time PCR kit, using 3 primer and probe sets), and negative for *Bartonella*. Repeat serological testing at this laboratory for Q fever phase I and II antibodies was positive by complement fixation with a titer of 1:512 for both antigens using a commercial kit. The commercial kit included complement, antigen, and amboceptor (to sensitize sheep red blood cells) sourced from Virion/Serion (Würzburg, Germany). Inhibition of hemolysis, determined by manual inspection and  $\geq 75\%$  inhibition, is considered positive.

The patient remained asymptomatic. On review 2 months after surgery, minimal swelling of the left knee was observed around the surgical scar, with normal examination of all other bones and joints, without any fever or systemic illness. Repeat full blood

count, inflammatory markers, and liver function tests were normal, and a bone scan did not demonstrate sites of active osteomyelitis. An echocardiogram was not undertaken given that no murmur was detected and the child remained afebrile. After a discussion of treatment options with the parents, a decision was made to continue close clinical monitoring without antimicrobial therapy. No symptom recurrence or clinical deterioration occurred during the subsequent year. Repeat Q fever serology after 12 months showed that phase I and II antibodies had reduced to a titer of 1:128.

## DISCUSSION

Q fever is caused by the obligate, intracellular anaerobe *C burnetii*, a small, Gram-negative coccobacillus with worldwide distribution sparing New Zealand. It is a notifiable disease in Australia.<sup>1</sup> *C burnetii* has reservoirs in many mammals, birds, and arthropods and is shed into the environment in milk, feces, and urine but is concentrated in birth products. The bacterium displays antigenic phase variation: the natural phase I variant is highly infectious and can survive and multiply within phagolysosomes of monocytes and macrophages; the phase II variant is

avirulent. Protective antibody against *C burnetii* is directed primarily against the phase I antigen.

Human Q fever infection usually occurs via inhalation of aerosols during handling of infected animal carcasses or products of parturition. Transmission via unpasteurized dairy products has been postulated.<sup>2</sup> An outbreak of acute Q fever in the Netherlands associated with proximity to goat farms,<sup>3</sup> as well as similar rates of seropositivity in metropolitan and rural Queensland,<sup>1</sup> suggest that other routes of exposure such as windborne spread, may occur.<sup>2</sup> Seropositivity in children is significantly lower than in adults,<sup>2</sup> due at least in part to fewer high-risk exposures, although differences in immune responses to infection between children and adults may also play a role.<sup>1</sup> Approximately 60% of infected individuals undergo asymptomatic seroconversion.<sup>4</sup> Acute Q fever typically presents with nonspecific symptoms of an acute febrile illness, less commonly as pneumonia or hepatitis. Data from pediatric populations are limited but suggest similar presentations with self-limited febrile illnesses resolving within a median of 7 days.<sup>2</sup> Headache is a common complaint in children and may reflect meningitis. In general, children have a better prognosis than adults after acute Q fever, and fatal events are extremely rare.<sup>5</sup>

Chronic Q fever occurs in 1% to 2% of infected adults,<sup>2</sup> usually presenting as culture-negative endocarditis (with absent or small vegetations), which is often fatal without antimicrobial therapy. Rarer manifestations include endovascular and osteoarticular infections and chronic hepatitis. In children, chronic Q fever is extremely rare. Presentations include osteomyelitis, which may be recurrent and multifocal, often associated with a delay in diagnosis,<sup>6</sup> and endocarditis, mainly in children with underlying cardiac

abnormalities.<sup>2</sup> Although not clearly elucidated, the variable clinical manifestations of Q fever may be due to bacterial virulence factors, host immune responses, the route of transmission, or the inoculating dose.<sup>4</sup>

Diagnosis of Q fever often relies on serological tests.<sup>7</sup> Complement fixation is highly specific but less sensitive than indirect IFA or enzyme-linked immunoassay, and also demonstrates seroconversion more slowly. Despite this, the initial Q fever enzyme immunoassay-based serology results on our patient were considered to be falsely negative. Antigenic phase variation and time from onset of infection also need to be considered when interpreting serology results, with different cutoff values indicative of acute or chronic infection for each assay. IFA can detect IgA, IgM, or IgG to both phase I and II antigens; however, cross-reactions occur with *Legionella* and *Bartonella* species.<sup>7</sup> The high *Bartonella* IgG titer in the case described may have represented previous infection or cross-reactive antibodies due to Q fever infection. DNA-based molecular tests can be used to confirm the diagnosis; however, current Q fever PCR techniques are mainly restricted to tissue samples with high organism loads; sensitivity in other samples is poor. Histologic examination of infected tissues usually shows noncaseating granuloma formation.

Trimethoprim-sulfamethoxazole for 14 days has been recommended for treatment of acute Q fever in children under 8 and doxycycline for the same duration in older children and adults. Dual therapy with doxycycline and

hydrochloroquine is recommended for at least 18 to 36 months in Q fever endocarditis,<sup>7</sup> with therapeutic drug monitoring to ensure adequate serum levels. A fall in antiphase I IgA and IgG titers to <1:200 is suggested to be indicative of cure<sup>7</sup>; however, some experts recommend lifelong treatment. Because of the rarity of infection, the optimal treatment regimen for Q fever osteomyelitis is less well established. Most adult cases reported in the literature have received a tetracycline-based regimen.<sup>8</sup> Pediatric cases received variable regimens of intracellularly active agents including rifampicin, trimethoprim sulfamethoxazole, ciprofloxacin, and linezolid, as well as doxycycline and hydrochloroquine.<sup>8</sup> A review of the limited number of reported Q fever osteoarticular infections advised combination treatment of at least 18 months, along with serological follow-up.<sup>8</sup>

Despite these prolonged antibiotic courses, treatment failures have been reported.<sup>6</sup> Given the lack of proven efficacy, the potential for significant side effects associated with prolonged antibiotic treatment, and the lack of symptoms in an otherwise well child, a decision was made to continue close observation without initiating antimicrobial therapy. We postulate that after a reduction in the bacterial load achieved by surgical drainage, the host immune responses in some individuals may be able to control the infection. In select patients with confirmed chronic Q fever osteomyelitis in whom adequate surgical debridement has occurred, a conservative approach may be indicated in those who remain completely asymptomatic. Surgical

debridement helps to establish the diagnosis but also has therapeutic value. Individuals should be followed closely to monitor for disease symptoms and to ensure that antibody levels show a persistent decline.

#### ABBREVIATIONS

IFA: immunofluorescence  
Ig: immunoglobulin  
PCR: polymerase chain reaction

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