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Pediatric Q Fever

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Abstract

Purpose of Review—The non-specific presentation of acute Q fever makes it difficult to diagnose in children, but untreated Q fever can result in chronic infections that have severe complications.

Recent Findings—Pediatric Q fever cases continue to be infrequently reported in the literature, and primarily document cases of persistent infections with *Coxiella burnetii*. Standardized treatment protocols for chronic Q fever in children still do not exist. Doxycycline and hydroxychloroquine are the treatment combination most utilized by healthcare providers to treat Q fever endocarditis or osteomyelitis in children, but a variety of other antibiotic combinations have been reported with varying results. The use of adjunctive therapies, such as such as interferon gamma, has produced mixed outcomes.

Summary—The true impact of *Coxiella burnetii* on the health of children remains unknown; long-term longitudinal follow-up of children with acute or chronic Q fever has not been reported. Both the acute and chronic forms of Q fever are underreported and underdiagnosed. Healthcare providers should consider Q fever in pediatric patients with culture-negative endocarditis or osteomyelitis.

Keywords

Q fever; *Coxiella burnetii*; Pediatric; Children

Epidemiology

Q fever is a zoonotic disease caused by infection with the intracellular bacterium *Coxiella burnetii* [1]. The bacteria are commonly found in livestock such as sheep, goats, and cattle but can also infect a wide variety of domesticated and wild animal species [2•]. *C. burnetii* can be shed in urine, feces, milk, and birth products of infected animals, and infectious organisms are typically transmitted to humans when aerosols contaminated with dried waste products are inhaled. The highest concentrations of *C. burnetii* are in the placenta and birth products of infected ruminants. During birth, large numbers of *C. burnetii* are released into

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the environment, and outbreaks of Q fever often are associated with exposure to ruminant births [3]. The largest known outbreak of Q fever occurred in the Netherlands from 2007 to 2010 and was due to release of *C. burnetii* organisms into the environment from large numbers of infected goats [4]. *C. burnetii* can also infect cats and dogs and human infections have occasionally been linked to companion animals [5, 6].

Q fever is found all over the world, with only New Zealand thought to be free of the disease [1]. In many parts of the world, Q fever exists primarily as an occupational disease for those that come in contact with ruminants as part of their job [2]. Therefore, children usually are not at risk due to infrequent contact with livestock. Indeed, national Q fever surveillance reports from various countries show that only a small percentage of reported cases occur in children or young adults. In the USA, from 2000 to 2012, 3.4% of reported Q fever cases occurred in those 18 years or younger [7]. Australian national surveillance from 1991 to 2014 reported 7% of their cases in persons 0–19 years [8]. During a 3-year Q fever outbreak in the Netherlands, only 1.2% of cases were in pediatric patients [9•].

Several recent studies have tested for *C. burnetii* among febrile patient populations, with varied results on the number of pediatric patients identified. While none of the studies identified large numbers of Q fever patients in any age group, some studies did detect *Coxiella* primarily in pediatric patients. A study of febrile patients in several African countries found seven persons PCR positive for *Coxiella*, five of which were patients under the age of 18 years [10]. Another study in Mali identified only one patient PCR positive for *Coxiella*; the patient was in the 5–14 age group [11]. Six of nine patients diagnosed with Q fever in a Thailand study were ≤ 20 years [12]. Meanwhile, other acute febrile illness studies have identified smaller percentages of pediatric cases among patients with Q fever [13, 14].

Various theories exist as to why Q fever is rarely reported in children. Q fever might be a milder disease in pediatric patients or be underdiagnosed [15, 16]. One study following an exposed community in the Netherlands found that children had lower rates of infection than adults, leading investigators to hypothesize a possible protective role of young age in the pathophysiology of *C. burnetii* infection [16]. Despite the low number of reported pediatric cases, various serosurveys show that children are exposed to *C. burnetii*. Recent serosurveys in Turkey and Kenya reported the highest seropositivity rates in pediatric participants (24.1% of 8–20 year olds in Turkey; 34% of 5–14 year olds in Kenya) [17, 18]. In serosurveys in Afghanistan and Bhutan, pediatric patients were not the highest seropositive age group, but seropositivity among age groups varied minimally (≈ 58% in < 10 year olds in Afghanistan (range ≈ 58–71%); 7.4% of 13–25 year-olds in Bhutan (range 5.5–8.3%)) [19, 20]. More research is needed to ascertain the reasons for limited reports of pediatric Q fever cases given similar or higher seropositivity among pediatric compared to adult populations.

Microbiology

C. burnetii was first isolated from ticks in the 1930s and the bacterium was soon linked to a disease afflicting abattoir workers in Australia, which at the time was called “Query” or “Q” fever [21]. *C. burnetii* was initially described to be a Rickettsia, and although it shares some

features with members of the *Rickettsia* genus (a small intracellular bacterium that can be found in ticks), later molecular analysis has demonstrated that it is a gammaproteobacteria most closely related to *Legionella* spp. [22]. In the 1950s, Stoker et al. demonstrated that *C. burnetii* can exist in two antigenic forms [23]. Phase 1 *C. burnetii* expresses complex lipopolysaccharide (LPS) side chains on its surface and is known to be infectious. Phase 2 *C. burnetii* expresses a truncated LPS on its surface is not infectious for animals and is not found in natural settings. Phase 2 is an antigenic form that develops after repeated passaging in the laboratory. The complex LPS side chains that are present on Phase 1 *C. burnetii* appear to be important for infection of animals and are considered a virulence factor for *C. burnetii* [24]. These complex side chains are not essential for growth in laboratory culture and Phase 2 will predominate after extended passage. Clones of the type strain of *C. burnetii* (Nine Mile strain) in Phase 1 and Phase 2 were described in the early 1980s [25].

Although *C. burnetii* is not a spore-forming bacterium, it does have impressive survival characteristics outside of a host cell. When not replicating, *C. burnetii* can form a small-cell variant (SCV) that has remarkable environmental stability [26]. It is resistant to heat, desiccation, and some disinfectants and can survive for weeks to years outside of a host cell [26]. These features, combined with the very low dose required for infection via inhalation (1–10 organisms), and the historical weaponization of *C. burnetii*, have resulted in its classification as a select agent in the United States [27]. This classification results in increased safety, security, and reporting requirements for the bacterium.

Clinical Features

Q fever presents in both an acute and chronic form. Acute infections are largely self-limited febrile illnesses, although hospitalization rates in specific outbreaks can be over 20% [28]. Many acute infections with *C. burnetii* do not result in clinical signs or symptoms [29]. For those who do develop clinical disease, the most common manifestations of acute Q fever are influenza-like illness, pneumonia, or hepatitis [1, 2•]. Chronic Q fever, also known as persistent localized *C. burnetii* infection, occurs after failure to clear a *C. burnetii* infection and can present weeks to months to years after an initial *C. burnetii* exposure [1]. Chronic Q fever clinical syndromes include endocarditis, vascular infections, and osteomyelitis. These infections are more serious and can be difficult to treat [2•]. A post-Q fever fatigue syndrome has also been described [30].

Acute Q fever in children, as with adults, primarily presents as a non-specific febrile illness, making the true burden of acute Q fever unknown [15, 31•]. The typical acute Q fever clinical appearance mimics common childhood pathogens, such as influenza-like illness, pneumonia, or respiratory infections; pediatric cases frequently have fatigue, cough, headache, and fever. Acute Q fever is difficult to accurately diagnosis in children, given these non-specific clinical signs and symptoms [31•]. The disease course is generally mild and uncomplicated [1, 31•]. Rare case reports of central nervous system involvement, such as meningitis or encephalitis, have been published [15, 32, 33]. Cases of Q fever hepatitis in children have been reported but appear to occur less frequently in children than adults [34, 35]. Literature reviews identified only one published pediatric meningitis case in the last 5

years [32] and no reports of acute Q fever hepatitis in children were found for the same time period.

It has been estimated that 1–5% of acute Q fever patients will develop a chronic form of the disease [36, 37]. In adults, the presentations of chronic Q fever are primarily endocarditis and vascular infections [1]. However, Q fever endocarditis and vascular infections are rarely reported in children [2•, 15]. An analysis of Q fever surveillance cases reported to the CDC between 1999 and 2015 found only one Q fever endocarditis case in a patient under 20 years of age [38]. In a study looking at Q fever in the Netherlands between 2007 and 2010, only 44 of 3522 reported cases of Q fever were in children. As of 2015, no pediatric cases of chronic Q fever had been identified in this group [9•]. Although rare, Q fever endocarditis cases in children do exist and have been reported in the literature. A review by Maltezou and Raoult in 2002 found five cases of Q fever endocarditis in children reported between 1966 and 2001 [15]. We conducted a search of the literature indexed in Medline for the years 2014–2019 found 13 reports of Q fever endocarditis in children. These cases were identified in France, Kuwait, Israel, and Portugal [39–43]. Of the 13 reported cases, 12 of these children had a pre-existing heart valve defect, with at least 11 of them having received a valve replacement and/or placement of a conduit. Two cases had tetralogy of fallot [40] and at least four of the children had undergone the Rastelli procedure to repair a ventricular septal defect [40–42, 43•]. Only 1 of the patients did not have a pre-existing heart condition. This patient was identified after diagnosis of an adult family member with Q fever endocarditis followed by serological screening of the family for possible Q fever [39]. This screening revealed an elevated Phase 1 antibody titer for this 14-year-old girl and echocardiography showed a vegetation on the mitral valve.

Osteomyelitis is another manifestation of chronic Q fever. Published pediatric cases describe both single and multifocal osteolytic lesions in long and short bones, with recurrent/relapsing multifocal osteomyelitis accounting for most cases. Patients typically experienced months of symptoms prior to chronic Q fever diagnosis and had a variety of prior diagnoses including staphylococcal infection, culture-negative osteomyelitis, chronic relapsing multifocal osteomyelitis, and chondroblastoma [43•, 44–47]. Patients usually present with localized pain and inflammation but are afebrile and have low to mildly elevated inflammatory markers [45, 46•]. Unlike Q fever endocarditis patients, most pediatric Q fever osteomyelitis patients were previously healthy and have no known risk factors, such as heart valve defects. Not all patients have known exposures; some reside in urban areas [43•, 44]. Clinicians should consider Q fever as a differential for osteomyelitis, even if there are no known exposures.

Diagnostics

Serology is the most common approach for diagnosis of both acute and chronic Q fever, but it has notable limitations. Q fever serology is complicated by the specificity of the antibody response during acute and chronic Q fever infections. For reasons that have not been defined, the human antibodies during acute infection are primarily reactive with Phase 2 antigen [48]. A fourfold rise in the titer of serum IgG antibodies against Phase 2 Nine Mile strain is the gold standard for confirmation of acute Q fever by serology. Because of the need

to detect a rise in titer, ELISA tests are not often used for diagnosis. There are human ELISA tests commercially available, but these are primarily useful for serosurveys and screening of large numbers of samples. The indirect fluorescent antibody test (IFA) is the most common method to determine anti-*C. burnetii* IgG titers [2•].

Although serology can work well for epidemiologic purposes, it is not a practical method for acute diagnosis. During the first week of illness, it is common for results of an acute serology specimen to be non-reactive. It takes an average of 7–10 days following illness onset for IgG antibodies to reach detectable levels. A convalescent serum sample should be taken 3–6 weeks after the acute sample and results are not expected until 4–7 weeks after initial presentation [1, 2•]. Because of the diagnostic delay associated with serology, nucleic acid detection by PCR is essential for diagnosis of acute Q fever. PCR works well to detect *C. burnetii* DNA in serum or whole blood in the acute stage of the disease. PCR can give a positive result on Q fever patient serum or whole blood from 1 to 17 days after onset of symptoms. The ability of PCR to detect *C. burnetii* is reduced as anti-*C. burnetii* antibodies develop. When serum IgG against Phase 2 *C. burnetii* is detectable, PCR is only positive in 5% of patients [49]. Because PCR detects bacterial DNA, the ability to detect declines after appropriate antibiotic treatment. Therefore, the specimen should be collected before or shortly after (within 24–48 h) antibiotic administration [2•]. Ideally, PCR and serology should both be done on acute serum samples if Q fever is suspected [49].

Because Q fever is typically not initially suspected upon presentation with the non-specific symptoms typically found in acute Q fever, laboratory methods are not normally used to capture acute Q fever cases. Exceptions are in outbreak situations where clinical suspicion of Q fever is high and complicated cases that have prolonged symptoms, which increases the opportunity for multiple serum samples to be drawn.

For diagnosis of chronic Q fever, both serology and PCR can be used to confirm a diagnosis if there is a compatible clinical presentation [50]. Unlike acute Q fever, chronic infections are marked by high levels of IgG antibodies against Phase 1 *C. burnetii*. In the absence of an acute infection, a reciprocal antibody titer ≥ 1:1024 is considered laboratory evidence of chronic infection [50]; some chronic infections can result in extremely high titers (> 1:100,000). PCR is also often used to diagnose chronic infections, either on whole blood, serum, or tissue. Tissue surgically removed to physically reduce the bacterial burden is a useful diagnostic specimen and PCR performed on excised tissue can confirm the diagnosis. However, the first indication of chronic Q fever typically comes from detection of high Phase 1 antibody titers [51].

In addition to an elevated phase I IgG titer, an identifiable nidus of *C. burnetii* infection is typically used to diagnosis chronic Q fever [50]. Identification of the location of the persistent infection is important and imaging techniques such as echocardiography or ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET/CT are often required [50]. *C. burnetii* valvular infections are small and often missed on echocardiograms [52]. The transesophageal echocardiogram (TEE) is more sensitive than a transthoracic echocardiogram (TTE) [53]. When an echocardiogram is inconclusive, ^{18}F-FDG-PET/CT can be used to identify the

nidus of infection [54]. Whenever possible, surgical removal of the infected tissue is recommended. Patient outcomes improve with early surgical intervention and treatment [55].

Treatment

Doxycycline is the treatment of choice for acute Q fever. The pediatric dosage is 2.2 mg/kg (maximum 100 mg per dose) twice a day for 2 weeks [2•]. In short courses (≤ 5 days), doxycycline does not result in significant dental staining in children 8 years or younger [56]. However, the long-term dental effects from 2 weeks of doxycycline administration to children under 8 years have not been studied. Children with severe infection, regardless of age, should receive 2 weeks of doxycycline, but children aged less than 8 years with mild, uncomplicated illness may be treated with trimethoprim/sulfamethoxazole instead [1, 2•]. If neither doxycycline nor trimethoprim/sulfamethoxazole can be tolerated, newer macrolides such as clarithromycin or azithromycin can be considered [57].

The recommended treatment for adult Q fever endocarditis is doxycycline and hydroxychloroquine combination therapy for at least 18 months for native valve infections and 24 months for prosthetic valves [2•]. Specific guidelines for the treatment of pediatric Q fever endocarditis do not exist. In the recently reported pediatric Q fever endocarditis cases, 11 out of 13 were placed on long-term doxycycline plus hydroxychloroquine therapy. Duration of therapy ranged from 6 to 36 months, with 18 months being the most commonly reported duration [41, 43•]. The exceptions were one patient that was reported to be allergic to doxycycline plus hydroxychloroquine and was placed on moxifloxacin and rifampin as an alternative [40], and a second patient that was treated with doxycycline plus ciprofloxacin [43•]. Although this latter patient was reported in 2018, the diagnosis and treatment were in 1998. At that time, the combination therapy of doxycycline plus a quinolone was common. It was not until after the report by Raoult et al. in 1999 that the use of hydroxychloroquine was considered the preferred therapeutic regimen [58]. During treatment, monthly serologic testing should be established to evaluate if treatment is decreasing Phase I IgG titer levels [2•].

Medical management of Q fever osteomyelitis is challenging. Debridement of infected bone improves the patient's symptoms but does not always prevent reoccurrence [46•]. There are no established guidelines for the treatment of pediatric Q fever osteomyelitis and published case reports show that healthcare providers have used various combinations of rifampicin, ciprofloxacin, azithromycin, doxycycline, hydroxychloroquine, or trimethoprim/sulfamethoxazole for treatment (Fig. 1) [43•, 44–47]. Doxycycline plus hydroxychloroquine, which is the recommended treatment for adult Q fever endocarditis, was the most common therapy used at some point in the patient's treatment. Multiple patients experienced recurrent episodes while on antibiotic therapy, including patients on doxycycline and hydroxychloroquine treatment [43•, 46•]. However, some patients' osteomyelitis resolved after debridement without the aid of antibiotics [46•, 47]. Length of antibiotic therapy ranged from 1.5 to 43 months, although several patients were still on therapy at the time of publication [43•, 44–47]. Immunomodulatory therapies, such as interferon gamma, were not effective for some patients. High-dose steroids (i.e., methylprednisolone), similarly, did not prove to be consistently effective across patients [46•]. However, the number of reported

patients receiving these therapies is small, and thus, definitive conclusions on the effectiveness of adjunct therapies cannot be drawn.

Conclusions

Q fever remains a rare, and potentially under-recognized, disease in children. The acute disease clinical presentation is non-specific and mimics more common childhood diseases, making clinical suspicion for acute Q fever low. Chronic Q fever cases in children are even more infrequent and patients might receive multiple misdiagnoses prior to identifying persistent infection with *C. burnetii*. Q fever endocarditis can be an issue for pediatric patients, and almost all cases recently identified were in patients with a pre-existing cardiac valve repair. Pediatric patients with Q fever osteomyelitis often are misdiagnosed initially with the autoinflammatory disorder chronic relapsing multifocal osteomyelitis. Currently, there are no recommended guidelines for treatment of chronic Q fever in children. Recent published cases report use of doxycycline and hydroxychloroquine in pediatric Q fever endocarditis patients, but a variety of antimicrobial therapy combinations were utilized for pediatric Q fever osteomyelitis with varying degrees of success. Long-term follow-up of pediatric Q fever patients is lacking, and the impacts of childhood infection on adult health and quality of life remain unknown.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

1. Eldin C, Melenotte C, Mediannikov O, Ghigo E, Million M, Edouard S, et al. From Q fever to Coxiella burnetii infection: a paradigm change. Clin Microbiol Rev. 2017;30:115–90. 10.1128/CMR.00045-16. [PubMed: 27856520]

2•. Anderson A, Bijlmer H, Fournier PE, Graves S, Hartzell J, Kersh GJ, et al. Diagnosis and management of Q fever–United States, 2013: recommendations from CDC and the Q Fever Working Group. MMWR Recomm Rep. 2013;62(RR-03):1–30Recommendations for diagnosis and management of Q fever from the CDC.

3. Angelakis E, Raoult D. Q Fever. Vet Microbiol 2010;140:297–309. 10.1016/j.vetmic.2009.07.016. [PubMed: 19875249]

4. Dijkstra F, van der Hoek W, Wijers N, Schimmer B, Rietveld A, Wijkmans CJ, et al. The 2007–2010 Q fever epidemic in The Netherlands: characteristics of notified acute Q fever patients and the association with dairy goat farming. FEMS Immunol Med Microbiol. 2012;64:3–12. 10.1111/j.1574-695X.2011.00876.x. [PubMed: 22066649]

5. Buhariwalla F, Cann B, Marrie TJ. A dog-related outbreak of Q fever. Clin Infect Dis. 1996;23:753–5. 10.1093/clinids/23.4.753. [PubMed: 8909839]

6. Pinsky RL, Fishbein DB, Greene CR, Gensheimer KF. An outbreak of cat-associated Q fever in the United States. J Infect Dis. 1991;164:202–4. 10.1093/infdis/164.1.202. [PubMed: 2056206]

7. Dahlgren FS, McQuiston JH, Massung RF, Anderson AD. Q fever in the United States: summary of case reports from two national surveillance systems, 2000–2012. Am J Trop Med Hyg. 2015;92:247–55. 10.4269/ajtmh.14-0503. [PubMed: 25404080]

8. Sloan-Gardner TS, Massey PD, Hutchinson P, Knope K, Fearnley E. Trends and risk factors for human Q fever in Australia, 1991–2014. Epidemiol Infect. 2017;145:787–95. 10.1017/S0950268816002843. [PubMed: 27927265]

9•. Slok ENE, Dijkstra F, De Vries E, Rietveld A, Wong A, Notermans DW et al. Estimation of acute and chronic Q fever incidence in children during a three-year outbreak in the Netherlands and a

comparison with international literature. BMC Res Notes. 2015;8(1). doi:10.1186/s13104-015-1389-0.An analysis of pediatric Q fever incidence in a large Q fever outbreak in the Netherlands.

10. Angelakis E, Mediannikov O, Socolovschi C, Mouffok N, Bassene H, Tall A, et al. Coxiella burnetii-positive PCR in febrile patients in rural and urban Africa. Int J Infect Dis. 2014;28:107–10. 10.1016/j.ijid.2014.05.029. [PubMed: 25245003]
11. Toure M, Petersen PT, Bathily SN, Sanogo D, Wang CW, Schioler KL, et al. Molecular evidence of malaria and zoonotic diseases among rapid diagnostic test-negative febrile patients in low-transmission season, Mali. Am J Trop Med Hyg. 2017;96:335–7. 10.4269/ajtmh.16-0700. [PubMed: 27821696]
12. Greiner AL, Bhengsri S, Million M, Edouard S, Thamthitiwat S, Clarke K, et al. Acute Q fever case detection among acute febrile illness patients, Thailand, 2002–2005. Am J Trop Med Hyg. 2018;98:252–7. 10.4269/ajtmh.17-0413. [PubMed: 29141767]
13. Esmaeili S, Mohabati Mobarez A, Khalili M, Mostafavi E, Moradnejad P. Genetic evidence of Coxiella burnetii infection in acute febrile illnesses in Iran. PLoS Negl Trop Dis. 2019;13:e0007181. 10.1371/journal.pntd.0007181. [PubMed: 30742631]
14. Njeru J, Henning K, Pletz MW, Heller R, Forstner C, Kariuki S, et al. Febrile patients admitted to remote hospitals in Northeastern Kenya: seroprevalence, risk factors and a clinical prediction tool for Q-fever. BMC Infect Dis. 2016;16:244. 10.1186/s12879-016-1569-0. [PubMed: 27260261]
15. Maltezou HC, Raoult D. Q fever in children. Lancet Infect Dis. 2002;2(11):686–91. [PubMed: 12409049]
16. Hackert VH, Dukers-Muijrers NH, van Loo IH, Wegdam-Blans M, Somers C, Hoebe CJ. Coxiella burnetii infection is lower in children than in adults after community exposure: overlooked cause of infrequent Q fever reporting in the young. Pediatr Infect Dis J. 2015;34:1283–8. 10.1097/inf.0000000000000871. [PubMed: 26252570]
17. Erturk R, Poyraz O, Gunes T. Serosurvey of Coxiella burnetii in high risk population in Turkey, endemic to Crimean-Congo haemorrhagic fever virus. J Vector Borne Dis. 2017;54:341–7. 10.4103/0972-9062.225839. [PubMed: 29460864]
18. Wardrop NA, Thomas LF, Cook EA, de Glanville WA, Atkinson PM, Wamae CN, et al. The sero-epidemiology of Coxiella burnetii in humans and cattle, Western Kenya: evidence from a cross-sectional study. PLoS Negl Trop Dis. 2016;10(10):e0005032. 10.1371/journal.pntd.0005032. [PubMed: 27716804]
19. Akbarian Z, Ziay G, Schauwers W, Noormal B, Saeed I, Qanee AH et al. Brucellosis and Coxiella burnetii infection in householders and their animals in secure villages in Herat Province, Afghanistan: a cross-sectional study. PLoS Negl Trop Dis. 2015;9(10). doi:10.1371/journal.pntd.0004112.
20. Tshokey T, Stenos J, Durrheim DN, Eastwood K, Nguyen C, Graves SR. Seroprevalence of rickettsial infections and Q fever in Bhutan. PLoS Negl Trop Dis. 2017;11(11):e0006107. 10.1371/journal.pntd.0006107. [PubMed: 29176880]
21. Davis GE, Cox HR. Public health weekly reports for DECEMBER 30, 1938. Public Health Rep. 1938;53:2259–309. [PubMed: 19315693]
22. Seshadri R, Paulsen IT, Eisen JA, Read TD, Nelson KE, Nelson WC, et al. Complete genome sequence of the Q-fever pathogen Coxiella burnetii. Proc Natl Acad Sci U S A. 2003;100:5455–60. 10.1073/pnas.0931379100. [PubMed: 12704232]
23. Stoker MG, Fiset P. Phase variation of the Nine Mile and other strains of Rickettsia burneti. Can J Microbiol. 1956;2:310–21. [PubMed: 13316625]
24. Hackstadt T The role of lipopolysaccharides in the virulence of Coxiella burnetii. Ann N Y Acad Sci. 1990;590:27–32. 10.1111/j.1749-6632.1990.tb42203.x. [PubMed: 2378455]
25. Hackstadt T, Peacock MG, Hitchcock PJ, Cole RL. Lipopolysaccharide variation in Coxiella burnetti: intrastrain heterogeneity in structure and antigenicity. Infect Immun. 1985;48:359–65. [PubMed: 3988339]
26. Minnick MF, Raghavan R. Developmental biology of Coxiella burnetii. Adv Exp Med Biol. 2012;984:231–48. 10.1007/978-94-007-4315-1_12. [PubMed: 22711635]

27. Madariaga MG, Rezai K, Trenholme GM, Weinstein RA. Q fever: a biological weapon in your backyard. Lancet Infect Dis. 2003;3:709–21. 10.1016/s1473-3099(03)00804-1. [PubMed: 14592601]
28. van der Hoek W, Morroy G, Renders NH, Wever PC, Hermans MH, Leenders AC, et al. Epidemic Q fever in humans in the Netherlands. Adv Exp Med Biol. 2012;984:329–64. 10.1007/978-94-007-4315-1_17. [PubMed: 22711640]
29. Raoult D, Marrie T, Mege J. Natural history and pathophysiology of Q fever. Lancet Infect Dis. 2005;5:219–26. 10.1016/S1473-3099(05)70052-9. [PubMed: 15792739]
30. Ayres JG, Flint N, Smith EG, Tunnicliffe WS, Fletcher TJ, Hammond K, et al. Post-infection fatigue syndrome following Q fever. QJM. 1998;91:105–23. 10.1093/qjmed/91.2.105. [PubMed: 9578893]
31•. Bart IY, Schabos Y, Van Hout RWNM, Leenders ACAP, De Vries E. Pediatric acute Q fever mimics other common childhood illnesses. PloS One. 2014;9(2). doi:10.1371/journal.pone.0088677.An evaluation of clinical symptoms in children with acute Q fever.
32. Figueiredo C, Candeias F, Brito MJ. Aseptic meningitis caused by Coxiella burnetii. Pediatr Infect Dis J. 2016;35:115. 10.1097/inf.0000000000000935. [PubMed: 26418239]
33. Ravid S, Shahar E, Genizi J, Schahor Y, Kassis I. Acute Q fever in children presenting with encephalitis. Pediatr Neurol. 2008;3:44–6. 10.1016/j.pediatrneurol.2007.09.004.
34. Berkovitch M, Aladjem M, Beer S, Cohar K. A fatal case of Q fever hepatitis in a child. Helv Paediatr Acta. 1985;40:87–91. [PubMed: 3843239]
35. Kuroiwa Y, Oyanagi R, Fuse S, Mori T, Ueno H, Tsutsumi H. Persistent hepatitis and repeated wheezing in an infant. Q fever. Pediatr Infect Dis J. 2007;26(763):8–9. 10.1097/INF.0b013e3180f60bfe. [PubMed: 17195698]
36. Fenollar F, Fournier PE, Carrieri MP, Habib G, Messana T, Raoult D. Risks factors and prevention of Q fever endocarditis. Clin Infect Dis. 2001;33:312–6. 10.1086/321889. [PubMed: 11438895]
37. Wielders CC, van Loenhout JA, Morroy G, Rietveld A, Notermans DW, Wever PC, et al. Long-term serological follow-up of acute Q-fever patients after a large epidemic. PLoS One. 2015;10(7):e0131848. 10.1371/journal.pone.0131848. [PubMed: 26161658]
38. Straily A, Dahlgren FS, Peterson A, Paddock CD. Surveillance for Q fever endocarditis in the United States, 1999–2015. Clin Infect Dis. 2017;65:1872–7. 10.1093/cid/cix702. [PubMed: 29140515]
39. Abu Rmeileh A, Khoury T, Meir K, Drori A, Shalit M, Benenson S, et al. Familial Q fever clustering with variable manifestations imitating infectious and autoimmune disease. Clin Microbiol Infect. 2015;21:459–63. 10.1016/j.cmi.2015.01.005. [PubMed: 25770747]
40. Alhadhoud SA, Vel MT, Qbandi MA. Q fever endocarditis after right ventricle to pulmonary artery conduit insertion: case series and review of the literature. Ann Pediatr Cardiol. 2018;11:60–3. 10.4103/apc.APC_37_17. [PubMed: 29440832]
41. Briggs BJ, Raoult D, Hijazi ZM, Edouard S, Angelakis E, Logan LK. Coxiella burnetii endocarditis in a child caused by a new genotype. Pediatr Infect Dis J. 2016;35:213–4. 10.1097/INF.0000000000000970. [PubMed: 26535879]
42. Maor Y, Sternik L, Orlov B, Rahav G, Keller N, Raanani E, et al. Coxiella burnetii endocarditis and aortic vascular graft infection: an underrecognized disease. Ann Thorac Surg. 2016;101:141–5. 10.1016/j.athoracsur.2015.06.075. [PubMed: 26428692]
43•. Sachs N, Atiya-Nasagi Y, Beth-Din A, Levy I, Ben-Shimol S, Tasher D, et al. Chronic Q fever infections in israeli children: a 25-year nationwide study. Pediatr Infect Dis J. 2018;37:212–7. 10.1097/INF.0000000000001790 [PubMed: 28938256] Review of 16 pediatric chronic Q fever infections in Israel over a 25-year period.
44. Britton PN, Macartney K, Arbuckle S, Little D, Kesson A. A rare case of Q fever osteomyelitis in a child from regional Australia. J Pediatr Infect Dis Soc. 2015;4:e28–31. 10.1093/jpids/piu095.
45. Costa B, Morais A, Santos AS, Tavares D, Seves G, Gouveia C. Q fever chronic osteomyelitis in two children. Pediatr Infect Dis J. 2015;34:1269–71. 10.1097/INF.0000000000000861. [PubMed: 26226441]
46•. Francis JR, Robson J, Wong D, Walsh M, Astori I, Gill D, et al. Chronic recurrent multifocal Q fever osteomyelitis in children: an emerging clinical challenge. Pediatr Infect Dis J.

2016;35:972–6. 10.1097/inf.0000000000001211 [PubMed: 27294309] Review of 12 pediatric Q fever osteomyelitis cases in Australia over a 14-year period.

47. Khatami A, Sparks RT, Marais BJ. A case of pediatric Q fever osteomyelitis managed without antibiotics. Pediatrics. 2015;136:e1629–e31. 10.1542/peds.2015-0024. [PubMed: 26574586]
48. Dupuis G, Peter O, Peacock M, Burgdorfer W, Haller E. Immunoglobulin responses in acute Q fever. J Clin Microbiol. 1985;22:484–7. [PubMed: 3908466]
49. Schneeberger PM, Hermans MH, van Hannen EJ, Schellekens JJ, Leenders AC, Wever PC. Real-time PCR with serum samples is indispensable for early diagnosis of acute Q fever. Clin Vaccine Immunol. 2010;17(2):286–90. 10.1128/CVI.00454-09. [PubMed: 20032219]
50. Kampschreur LM, Wegdam-Blans MC, Wever PC, Renders NH, Delsing CE, Sprong T, et al. Chronic Q fever diagnosis- consensus guideline versus expert opinion. Emerg Infect Dis. 2015;21:1183–8. 10.3201/eid2107.130955. [PubMed: 26277798]
51. Peacock MG, Philip RN, Williams JC, Faulkner RS. Serological evaluation of O fever in humans: enhanced phase I titers of immunoglobulins G and A are diagnostic for Q fever endocarditis. Infect Immun. 1983;41:1089–98. [PubMed: 6885155]
52. Million M, Thuny F, Richet H, Raoult D. Long-term outcome of Q fever endocarditis: a 26-year personal survey. Lancet Infect Dis. 2010;10:527–35. 10.1016/S1473-3099(10)70135-3. [PubMed: 20637694]
53. Shively BK, Gurule FT, Roldan CA, Leggett JH, Schiller NB. Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. J Am Coll Cardiol. 1991;18:391–7. 10.1016/0735-1097(91)90591-v. [PubMed: 1856406]
54. Rouzet F, Chequer R, Benali K, Lepage L, Ghodbane W, Duval X, et al. Respective performance of 18F-FDG PET and radiolabeled leukocyte scintigraphy for the diagnosis of prosthetic valve endocarditis. J Nucl Med. 2014;55:1980–5. 10.2967/jnumed.114.141895. [PubMed: 25453046]
55. Botelho-Nevers E, Fournier PE, Richet H, Fenollar F, Lepidi H, Foucault C, et al. Coxiella burnetii infection of aortic aneurysms or vascular grafts: report of 30 new cases and evaluation of outcome. Eur J Clin Microbiol Infect Dis. 2007;26:635–40. 10.1007/s10096-007-0357-6. [PubMed: 17629755]
56. Todd SR, Dahlgren FS, Traeger MS, Beltran-Aguilar ED, Marianos DW, Hamilton C, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever. J Pediatr. 2015;166:1246–51. 10.1016/j.jpeds.2015.02.015. [PubMed: 25794784]
57. Kersh GJ. Antimicrobial therapies for Q fever. Expert Rev Anti-Infect Ther. 2013;11:1207–14. 10.1586/14787210.2013.840534. [PubMed: 24073941]
58. Raoult D, Houpikian P, Tissot Dupont H, Riss JM, Arditi-Djiane J, Brouqui P. Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. Arch Intern Med. 1999;159:167–73. 10.1001/archinte.159.2.167. [PubMed: 9927100]

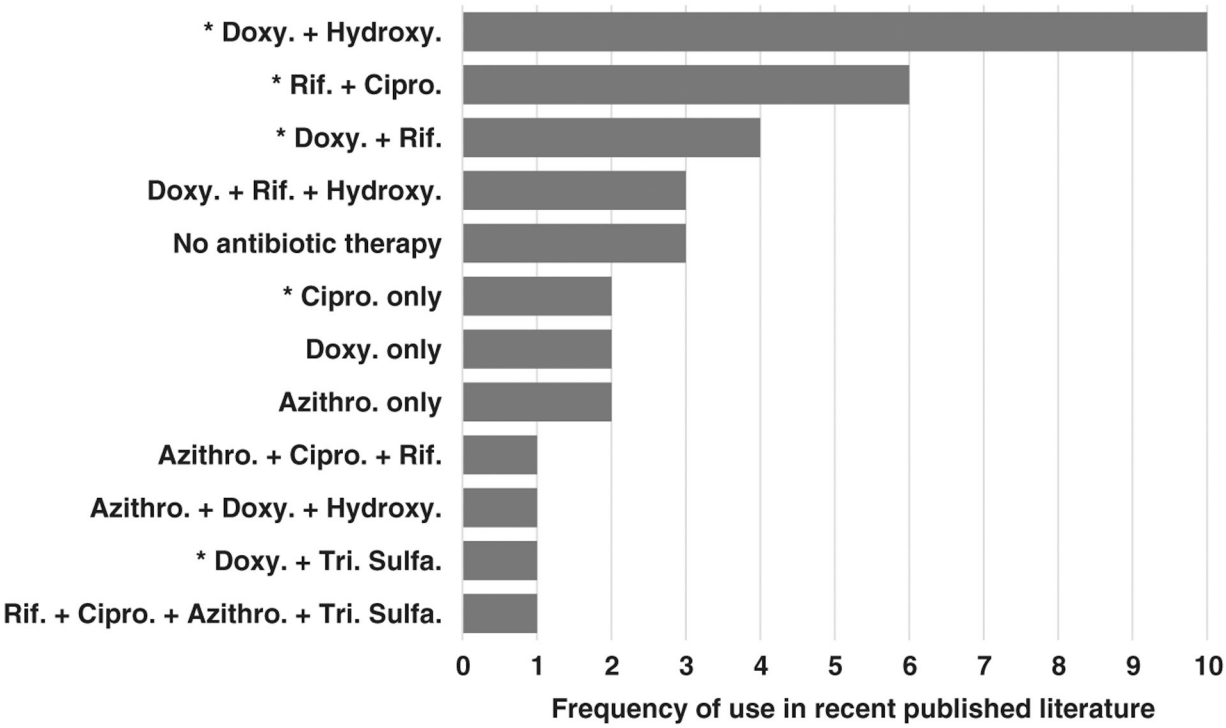

Fig. 1.

Antibiotic therapy combinations used for the treatment of pediatric osteomyelitis, as reported by published case reports from 2014 to 2018 [43•, 44–47]. No established guidelines exist for the treatment of pediatric osteomyelitis. Healthcare providers have tried a variety of antibiotics after surgical debridement and often switch drug combinations after osteomyelitis recurrence. Some patients experienced clinical resolution on a certain drug combination, while other patients had their osteomyelitis recur. Three patients in recent literature improved without any antibiotic therapy. Doxy., doxycycline; Hydroxy., hydroxychloroquine; Rif., rifampin; Cipro., ciprofloxacin; Azithro., azithromycin; Tri. Sulfa., trimethoprim/sulfamethoxazole. A single asterisk indicates some reports of reoccurrence while on this antibiotic therapy