



Coxiella burnetii pulmonary conduit endocarditis in a child with complex congenital heart disease: a case report

Ana-Maria Hodea^{1*}, Paolo Ciliberti², Eugen Sandica³, Carmen-Cristina Olteanu¹

Abstract

Background: *Coxiella burnetii* is a well-recognized cause of culture-negative endocarditis in patients with prosthetic cardiac material. In pediatric populations, diagnosis is uncommon and frequently delayed, particularly in the presence of immunological abnormalities that may impair serological responses.

Case presentation: We present a case of *Coxiella burnetii* endocarditis in an 11-year-old boy with complex congenital heart disease and multiple prior cardiac surgical interventions who developed chronic systemic manifestations associated with prosthetic conduit infection. He was first evaluated at our center at nine years of age, presenting with a two-year history of low-grade fever, hepatomegaly, hypoalbuminemia, hypogammaglobulinemia, peripheral edema, and progressive right-sided heart failure. His medical history was notable for splenectomy performed for severe unexplained splenomegaly with hypersplenism. Extensive investigations failed to identify an infectious etiology. Echocardiography demonstrated severe conduit stenosis without vegetations. Two years later, during hybrid surgical replacement of the stenotic conduit, fluorescence in situ hybridization of the explanted Contegra conduit detected *Coxiella burnetii*, while blood PCR and serology were initially negative. Following conduit replacement and initiation of doxycycline-hydroxychloroquine therapy, the patient showed rapid clinical improvement, with resolution of systemic manifestations and normalization of protein and immunoglobulin levels. Seroconversion with high phase I and II IgG titers occurred after three months of therapy.

Conclusions: In pediatric patients with congenital heart disease and prosthetic cardiac material, *Coxiella burnetii* infection may present with prolonged systemic manifestations. Despite negative initial serology, tissue-based detection from explanted material can establish the diagnosis when conventional investigations fail, and may support the initiation of targeted long-term antimicrobial therapy.

Keywords

Coxiella burnetii, Culture-negative endocarditis, Congenital heart disease, Pulmonary conduit, hypogammaglobulinemia, hepatosplenomegaly

Introduction

Coxiella burnetii is an obligate intracellular gram-negative bacterium that causes Q fever, a zoonotic disease with worldwide distribution transmitted primarily through inhalation of aerosolized particles from infected livestock.^[1] Q fever manifests clinically as a spectrum ranging from asymptomatic infection or self-limited acute febrile illness to chronic persistent focal infections, of which endocarditis represents the most common and clinically significant form.^[1] Q fever endocarditis is a well-recognized cause of culture-negative infective endocarditis that predominantly affects individuals with pre-existing valvular abnormalities, prosthetic cardiac material, or congenital heart disease.^[2]

Pediatric Q fever endocarditis is uncommon but increasingly recognized, particularly in children with congenital heart disease who have undergone cardiac surgical interventions involving prosthetic

material or conduit placement.^[3] National surveillance studies have documented only modest case numbers over extended periods, yet among affected pediatric patients, the majority have antecedent cardiac graft insertion or corrective procedures for congenital heart defects.^[3] Regional reviews have documented mean diagnostic delays exceeding 7 months, and this has contributed to increased morbidity, need for valve surgery, and risk of severe complications.^[4,5]

The diagnosis of Q fever endocarditis poses significant challenges due to its culture-negative nature and reliance on specialized serological testing, with phase I IgG antibody titers $\geq 1:800$ serving as a major diagnostic criterion.^[2] However, serological diagnosis can be complicated by variable antibody responses, particularly in immunocompromised patients or those with hypogammaglobulinemia.^[2,6] Molecular detection methods demonstrate limited sensitivity in blood samples but offer higher diagnostic yield when applied to excised valve tissue or prosthetic material.^[2] Early diagnosis is critical, as delayed treatment is associated with progressive valvular destruction, embolic complications, and risk of relapse, necessitating prolonged combination antimicrobial therapy with doxycycline and hydroxychloroquine.^[2,4]

We present the case of *Coxiella burnetii* endocarditis in an 11-year-old boy with complex congenital heart disease and multiple

*Corresponding author: Ana-Maria Hodea; E-mail address: anajurcamaria@yahoo.com

¹Pediatric Cardiology Department, Grigore Alexandrescu Emergency Hospital for Children, Bucharest, Romania

²Pediatric Cardiology Unit Bambino Gesù Children's Hospital IRCCS, Rome, Italy

³Department of Surgery for Congenital Heart, Heart and Diabetes Center NRW, Ruhr University Bochum, Bad Oeynhausen, Germany

prior cardiac surgical interventions who developed chronic systemic manifestations associated with prosthetic conduit infection. This case illustrates the diagnostic complexity encountered in pediatric patients with congenital heart disease and concomitant immunological abnormalities, showing the critical role of tissue-based molecular diagnostics when conventional serological methods yield negative or delayed results.

Case presentation

We present the case of an 11-year-old boy with a history of complex congenital heart disease, pulmonary valve atresia, transposition of the great arteries, and ventricular septal defect. At birth, he underwent a Blalock-Taussig shunt. At the age of two years, a Rastelli procedure was performed with closure of the ventricular and atrial septal defects and implantation of a 14-mm Contegra right ventricle-to-pulmonary artery (RV-PA) conduit. Due to recurrent conduit stenosis, hybrid interventions were required at four and eight years of age, consisting of RV-PA conduit replacement (16-mm and 14-mm Contegra, respectively) and right pulmonary artery stent implantation with subsequent intrastent dilation.

The patient was first admitted to our center at the age of nine years for evaluation of palpebral and scrotal edema, reduced exercise tolerance, and a two-month history of progressive lower limb edema and ascites. For approximately two years, he had exhibited hepatomegaly associated with hypoalbuminemia and hypogammaglobulinemia, intermittent low-grade fever of unclear origin, and recurrent cutaneous rashes. He also experienced recurrent episodes of moderate transaminase elevation in the context of previously documented chronic aggressive hepatitis with reactive features on liver biopsy. Bilirubin levels remained within normal limits, and there were no clinical or biochemical features suggestive of acute liver failure. His medical history was also notable for a splenectomy performed for severe unexplained splenomegaly with hypersplenism.

On admission, his general condition was fair. No signs of respiratory distress or peripheral cyanosis were observed with oxygen saturation of 98% on room air. Physical examination revealed bilateral palpebral edema, lower limb and scrotal edema, hepatomegaly (3-4 cm below the right costal margin), and a grade IV/VI systolic murmur along the left parasternal border.

Laboratory investigations demonstrated microcytic anemia, thrombocytosis, marked hypoproteinemia and hypoalbuminemia, dyslipidemia, and hypocalcemia. No inflammatory syndrome, hepatocellular injury, or cholestasis was detected, and coagulation parameters were normal. Immunological testing showed reduced IgG and IgM levels. Extensive infectious, autoimmune, endocrine, renal, and metabolic investigations were unremarkable. Fecal alpha-1 antitrypsin levels were markedly elevated, consistent with protein-losing enteropathy.

Transthoracic echocardiography revealed dilated right-sided chambers, right ventricular hypertrophy with systolic dysfunction, mild tricuspid regurgitation, dilated inferior vena cava without respiratory

variation, and severe RV-PA conduit stenosis (Vmax 5.4 m/s; peak gradient 117.6 mmHg). There was no evidence of vegetations on echocardiography. Computed tomography angiography confirmed severe narrowing of the conduit to approximately 5 mm, with peripheral microcalcifications and a patent right pulmonary artery stent.

The patient was initially managed with nutritional support, diuretic therapy, intravenous albumin supplementation, and aspirin, and showed partial clinical improvement. He subsequently underwent balloon dilation of the RV-PA conduit, stent implantation in the common pulmonary trunk, and Melody valve implantation at a specialized cardiovascular center.

Although his exercise tolerance improved transiently, his edema, hepatomegaly, hypoalbuminemia, and recurrent low-grade fever persisted, along with progressive increase in the RV-PA conduit gradient. Given the persistence of the symptoms and imaging evidence of severe conduit stenosis, a multidisciplinary team decision was made to proceed with surgical replacement of the Contegra conduit. The patient underwent a complex hybrid surgical intervention, including redo median sternotomy, removal of the previous 14-mm Contegra conduit, and replacement with a 16-mm Contegra valved conduit. Concomitant enlargement plasty of the pulmonary artery bifurcation was performed using a bovine pericardial patch, followed by balloon angioplasty of the right pulmonary artery via retrograde popliteal access under fluoroscopic guidance. Intraoperative Doppler evaluation confirmed adequate flow and conduit patency. The procedure was uneventful and did not require cardiopulmonary bypass.

To better illustrate the progression of symptoms, diagnostic evaluations, and therapeutic interventions from symptom onset to the current presentation, a chronological timeline is presented in Table 1.

Because of the long-standing recurrent febrile syndrome, infective endocarditis was suspected. Fluorescence in situ hybridization analysis of the explanted conduit identified *Coxiella burnetii*, while subsequent initial serological testing and polymerase chain reaction assays were negative. Epidemiological investigation revealed that the patient's family owned goats, and that the patient regularly consumed unpasteurized goat milk.

Postoperatively, the patient had a favorable clinical course, with preserved ventricular function and low gradients across the new pulmonary conduit. Treatment with doxycycline and hydroxychloroquine was initiated, while aspirin and spironolactone were continued. Following antibiotic therapy, fever and edema resolved, and serum albumin and protein levels normalized along with immunoglobulin levels. Therapeutic doxycycline plasma concentrations were achieved after 10 days of oral treatment. After three months of antimicrobial therapy and normalization of immunoglobulin levels, *Coxiella burnetii*-specific serology showed marked seroconversion and became strongly positive, with high phase I ($> 1/25.000$) and Phase II ($> 1/12.000$) IgG titers. At mid-term follow-up, the patient remains clinically well, with complete resolution of symptoms and good exercise tolerance. Laboratory parameters have improved, with normalization of serum protein and

Table 1 - Timeline of patient evolution.

Time point	Clinical status	Key investigations	Management
Birth	Pulmonary atresia, TGA, VSD	Echocardiography	Blalock-Taussig shunt
2 years old	Definitive repair		Rastelli procedure and 14-mm Contegra RV-PA conduit implantation
4 years old	Recurrent conduit stenosis	Echocardiography Angio-CT	Conduit replacement (16-mm Contegra)
8 years old		Hemodynamic assessment by cardiac catheterization	Conduit replacement (14-mm Contegra) + RPA stent implantation
~2 years before admission (age 7)	Hepatomegaly, hypoalbuminemia, hypogammaglobulinemia, intermittent fever, recurrent hepatitis, splenomegaly	Liver biopsy: aggressive chronic hepatitis	Splenectomy
Admission (age 9)	Palpebral, scrotal and lower limb edema, ascites, hepatomegaly, reduced exercise tolerance	Echocardiography: severe RV-PA stenosis; angio-CT: conduit narrowing	Initial supportive therapy (diuretics, albumin, aspirin)
Age 9		Hemodynamic assessment: cardiac catheterization severe (RV-PA) conduit stenosis, significantly elevated right ventricular systolic pressure, high transconduit gradient	Percutaneous transcatheter intervention: balloon dilation, pulmonary trunk stent, and Melody valve implantation
Following months	Persistent fever, edema, reduced exercise tolerance	Echocardiography: rising RV-PA gradient	
Reoperation (age 11)	Persistent fever, edema, reduced exercise tolerance	Echocardiography: severe conduit stenosis	Hybrid surgery: conduit replacement (16-mm Contegra), PA bifurcation plasty, RPA balloon dilation
Immediate Postoperative period	Favorable hemodynamics	FISH positive for <i>Coxiella burnetii</i> ; initial serology negative	Doxycycline and hydroxychloroquine
Three months follow-up	Clinical improvement; normalization of proteins and Ig levels	Seroconversion with high phase I and II IgG titers	Continued antimicrobial therapy

immunoglobulin levels. Echocardiography demonstrates a patent RV-PA conduit with mild pulmonary regurgitation and preserved ventricular function; no treatment-related adverse effects have been observed to date.

Discussion

This case illustrates several important diagnostic and therapeutic challenges associated with suspected *Coxiella burnetii* endocarditis in a pediatric patient with complex congenital heart disease, repeated prosthetic material implantation, and concomitant hypogammaglobulinemia.

1. Diagnostic considerations

Chronic Q fever endocarditis is classically diagnosed by high titers of phase I IgG antibodies, often in the absence of fever or overt inflammatory markers.^[7] The modified Duke criteria considers phase I IgG titers of $\geq 1:800$ to be diagnostic for infective endocarditis in the appropriate clinical context.^[8] However, our patient initially tested negative for *Coxiella*-specific antibodies and blood PCR, findings that would typically argue against chronic Q fever.

Importantly, this patient had documented hypogammaglobulinemia with persistently low total IgM and IgG levels, a condition known to impair humoral immune responses and potentially lead to false-negative serological testing.^[6,9] The history of splenectomy may have further contributed to impaired immune surveillance and atypical

presentation. While the impact of hypogammaglobulinemia on *Coxiella* serology has not been extensively studied in the pediatric literature, similar cases of culture-negative endocarditis with atypical serological patterns have been reported in immunocompromised patients.^[9,10]

Despite negative serology and PCR, *Coxiella burnetii* was detected by FISH analysis in the explanted Contegra conduit. Direct identification of *Coxiella* in cardiac tissue or prosthetic material is uncommon, but it has been reported, and it is considered highly specific when present.^[11] Molecular detection from valve or prosthetic tissue can confirm infection when blood cultures and serology are negative, as demonstrated in several pediatric cases where tissue PCR or next-generation sequencing provided a definitive diagnosis.^[12,13]

As highlighted by Buijs et al., FISH has methodological limitations and variable sensitivity to cardiac tissue infections.^[14] It is not a standardized first-line diagnostic method for chronic Q fever endocarditis, and its sensitivity may be influenced by bacterial load, tissue preservation, and uneven microorganism distribution. Furthermore, interpretation of fluorescence signals may be operator-dependent. For these reasons, FISH findings should be interpreted in conjunction with clinical, serological, and molecular data rather than in isolation. FISH techniques do not replace the other already-approved diagnostic techniques, but they can be used as complementary tools, especially in complex cases where the causative agent is difficult to identify.^[15]

In this context, the positive FISH result, combined with the patient's history of splenectomy for splenomegaly, as well as his long-standing systemic manifestations, including recurrent low-grade fever, hepatomegaly, chronic hepatitis, hypoalbuminemia, and rapid conduit degeneration, support the hypothesis of a chronic infection.

Chronic Q fever is a systemic disease that may involve multiple organs beyond the endocardium, most frequently the liver, skeletal system, vascular structures, and skin. In retrospect, the constellation of clinical findings observed in our patient is consistent with this chronic systemic form of *Coxiella burnetii* infection.^[1] As described in other pediatric case reports involving prosthetic materials used for the correction of congenital heart disease, the association of hepatosplenomegaly and prolonged culture-negative febrile episodes should raise suspicion of chronic *Coxiella* infection.^[12]

2. Infection versus hemodynamic consequences

An alternative explanation for the patient's clinical picture is severe right-sided heart failure secondary to progressive RV-PA conduit stenosis. Hepatomegaly, hypoalbuminemia, peripheral edema, ascites, and protein-losing enteropathy can all be explained by chronic systemic venous congestion. Indeed, imaging in this patient demonstrated severe conduit stenosis with right ventricular dysfunction, and many symptoms improved after surgical correction. However, several elements argue against a purely hemodynamic etiology: the presence of prolonged, unexplained low-grade fever over several years, recurrent inflammatory-like episodes (including rash responsive to corticosteroids), aggressive conduit degeneration, and the identification of *Coxiella burnetii* within the conduit material. The marked clinical improvement following both conduit replacement and initiation of doxycycline-hydroxychloroquine therapy further supports a contributory infectious component, although causality cannot be definitively established.

3. Graft contamination hypothesis

Another important consideration is whether the detection of *Coxiella burnetii* represents contamination of the Contegra conduit rather than true infection. Possible explanations include residual bacterial DNA within the xenograft material, contamination during manufacturing, or persistence of non-viable organisms without active infection in the host. Contegra conduits are derived from bovine jugular veins, and although manufacturing processes are designed to eliminate pathogens, the theoretical risk of residual microbial DNA cannot be completely excluded.

However, the patient's clinical evolution, systemic manifestations, and response to targeted antimicrobial therapy make isolated graft contamination less likely to fully explain the presentation. Furthermore, the development of strongly positive *Coxiella burnetii*-specific serology after three months of targeted antimicrobial therapy and normalization of immunoglobulin levels argues against graft contamination and supports the presence of a true infection.

4. Epidemiological and risk factor considerations

Q fever endocarditis predominantly affects patients with underlying valvular disease or prosthetic cardiac material.^[1,5] Pediatric

cases, though rare, have been repeatedly reported in children with congenital heart disease who have undergone cardiac surgery with prosthetic valve or conduit placement.^[5] A national cohort study from Israel identified chronic Q fever in children over a 25-year period, with endovascular infections occurring particularly frequently in those with prior cardiac graft insertion.^[3]

The primary route of *Coxiella burnetii* transmission is inhalation of aerosols from infected animals, particularly cattle, sheep, and goats.^[16] Our patient's family-owned goats and patient had a history of regular consumption of unpasteurized goat milk, which represents a recognized exposure risk, although direct transmission through ingestion is less common than aerosol inhalation. Similar epidemiological exposures have been documented in other pediatric Q fever endocarditis cases.^[2,17]

5. Therapeutic implications

Given the high morbidity associated with untreated chronic Q fever endocarditis and the patient's immunocompromised status, a decision was made to initiate standard combination therapy with doxycycline and hydroxychloroquine.^[2] This regimen is recommended for chronic Q fever endocarditis, with treatment duration typically ranging from 18 to 24 months in adults.^[1,2] Pediatric experience with prolonged hydroxychloroquine therapy is limited, and careful monitoring for adverse effects is essential.^[2,17]

Recent outcome data suggest favorable prognoses with doxycycline-hydroxychloroquine combination therapy, with significantly lower mortality rates compared to alternative regimens or untreated cases.^[18] In a comprehensive review of 185 reported Q fever endocarditis cases, no deaths were observed among patients treated with this combination, supporting its efficacy.^[18] Although doxycycline use in children under 12 years of age has traditionally been limited due to concerns regarding dental discoloration, current evidence and international recommendations suggests that this risk is low and support its use in severe or life-threatening infections when the benefits clearly outweigh potential risks, and chronic Q fever endocarditis meets the criteria for such a condition.^[19,20] Guidance from expert bodies notes that chronic Q fever treatment decisions in pediatric patients should be individualized in consultation with infectious disease specialists, and that doxycycline remains the drug of choice despite historical age restrictions.^[21]

Our patient's marked clinical improvement following treatment initiation, with resolution of fever, edema, hepatomegaly, and normalization of serum protein levels, is consistent with these favorable outcomes.

This case shows the importance of individualized, multidisciplinary decision-making when classic diagnostic criteria are not fully met. The combination of tissue-based molecular detection, along with the patient's prolonged systemic manifestations, known risk factors, and dramatic response to targeted therapy, collectively supported the decision to treat, despite the absence of initial serological confirmation.

We acknowledge that there is a limitation to this case report in that we did not have access to the system used for the in-situ hybridization, which was performed in another medical center.

Conclusion

This case highlights the complexity of diagnosing suspected *Coxiella burnetii* endocarditis in pediatric patients with congenital heart disease and hypogammaglobulinemia. Detection of *Coxiella* in explanted prosthetic material, even in the absence of serological or molecular confirmation from blood samples, should prompt careful clinical evaluation and consideration of targeted therapy. The presence of hypogammaglobulinemia may contribute to false-negative serology, complicating diagnosis in immunocompromised patients. The favorable clinical response to doxycycline-hydroxychloroquine therapy in our patient supports the decision to treat, despite initial incomplete fulfillment of classic diagnostic criteria. Further studies are needed to clarify the significance of *Coxiella* detection in bioprosthetic grafts, and to establish diagnostic and management strategies in similar challenging scenarios.

Acknowledgements

We acknowledge the multidisciplinary team involved in the care of this patient, including cardiologists, pediatricians, cardiac surgeons, infectious disease specialists, and nursing staff.

REFERENCES

1. Eldin C, Mélenotte C, Mediannikov O, et al. From Q fever to *Coxiella burnetii* infection: A paradigm change. Clin Microbiol Rev 2017;30(1):115-190. doi:10.1128/CMR.00045-16. Available from URL: <https://doi.org/10.1128/CMR.00045-16>
2. Melenotte C, Protopopescu C, Million M, Edouard S, Carrieri MP, Eldin C, et al. New insights in *Coxiella burnetii* infection: Diagnosis and therapeutic update. Expert Rev Anti Infect Ther 2020;18(1):75-86. Available from URL: <https://doi.org/10.1080/14787210.2020.1699055>
3. Sachs A, Bialik A, Mazar J, Peled N, Somekh E, Tasher D. Chronic Q fever infections in Israeli children: A 25-year nationwide study. Pediatr Infect Dis J 2017; 36(12):1237-1239. Available from URL: <https://doi.org/10.1097/INF.0000000000001790>
4. Cotar AI, Badescu D, Oprea M, Dinu S, Banu O, Dobreanu D, et al. Q fever endocarditis in Romania: The first cases confirmed by direct sequencing. Int J Mol Sci 2011; 12(12):9504-9513. Available from URL: <https://doi.org/10.3390/ijms12129504>
5. Alhadhoud SA, Vel MT, Al Qbandi M. Q fever endocarditis after right ventricle to pulmonary artery conduit insertion: Case series and review of the literature. Ann Pediatr Cardiol 2018; 11(1):60-63.
6. Das I, Guest N, Steeds R, Hewins P. Chronic Q fever: An ongoing challenge in diagnosis and management. Can J Infect Dis Med Microbiol 2014; 25(1):35-37.
7. Boattini M, Almeida A, Moura RB, Abreu J, Santos AS, Toscano Rico M. Chronic Q fever with no elevation of inflammatory markers: A case report. Case Rep Med 2012; 2012:249705. doi: 10.1155/2012/249705. Epub 2012 Jun 26. PMID: 22792113; PMCID: PMC3389709.
8. Fowler VG, Durack DT, Seldon-Suty C, Athan E, Bayer AS, Chamis AL, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases criteria for infective endocarditis: Updating the modified Duke criteria. Clin Infect Dis 2023; 77(4):518-526. doi: 10.1093/cid/ciad271. Erratum in: Clin Infect Dis 2023; 77(8):1222. doi: 10.1093/cid/ciad510. PMID: 37138445; PMCID: PMC10681650.
9. Kampschreur LM, Oosterheert JJ, Koop AM, Wegdam-Blans MC, Delsing CE, Bleeker-Rovers CP, et al. Microbiological challenges in the diagnosis of chronic Q fever. Clin Vaccine Immunol 2012;19(5):787-790.
10. Rolain JM, Lecam C, Raoult D. Simplified serological diagnosis of endocarditis due to *Coxiella burnetii* and *Bartonella*. Clin Diagn Lab Immunol

Funding

There was no funding for this work.

Conflicts of interest

None declared.

Informed Consent Statement

Written informed consent has been obtained from the patient to publish this paper.

Ethics compliance

We confirm that the article was conducted in compliance with ethical guidelines.

2003;10(6):1147-1148. doi: 10.1128/cdi.10.6.1147-1148.2003. PMID: 14607881; PMCID: PMC262450.

11. Angelakis E, Edouard S, Lafranchi MA, Pham T, Lafforgue P, Raoult D, et al. Q fever endocarditis and new *Coxiella burnetii* genotype, Saudi Arabia. Emerg Infect Dis 2014; 20(4):726-728. Available from URL: <https://doi.org/10.3201/EID2004.131603>

12. Briggs HM, Pati S, Schlager R, Milla SS, Stence NV, Greenberg J, et al. *Coxiella burnetii* endocarditis in a child caused by a new genotype. Pediatr Infect Dis J 2016; 35(3):331-333. Available from URL: <https://doi.org/10.1097/INF.0000000000000970>

13. Kondo M, Bitterman P, Cockrill B, Kanjilal S, Patel R. 154. Diagnosis and genotyping of *Coxiella burnetii* causing endocarditis in a patient with prosthetic pulmonary valve replacement (PVR) using next-generation sequencing (NGS) of plasma. Open Forum Infect Dis 2018; 5(Suppl 1):S67. Available from URL: <https://doi.org/10.1093/OFID/OFY209.024>

14. Buijs SB, Weehuizen JM, Jensen TK, Boye M, Hermans MH, Nooijen PT, et al. Fluorescence in situ hybridization for detecting *Coxiella burnetii* in tissue samples from chronic Q fever patients. Clin Microbiol Infect 2022; 28(11):1502.e1-1502.e5.

15. Prudent E, Raoult D. Fluorescence in situ hybridization, a complementary molecular tool for the clinical diagnosis of infectious diseases by intracellular and fastidious bacteria. FEMS Microbiol Rev 2019; 43(1):88-107.

16. Delsing CE, Warris A, Bleeker-Rovers CP. Q fever: Still more queries than answers. In: Curtis N, Finn A, Polard AJ, editors. Hot Topics in Infection and Immunity in Children VIII. Springer; 2011. pp. 153-166. Available from URL: https://doi.org/10.1007/978-1-4614-0204-6_12

17. Robinson JL. *Coxiella burnetii* infection in children. Curr Infect Dis Rep 2020; 22(5):12.

18. Jaltotage B, Sliwa K, Zuhlke L, Ntsekhe M, Comitis G, Russell JB, et al. Q fever endocarditis: A review of local and all reported cases in the literature. Heart Lung Circ 2021; 30(9):1313-1322. Available from URL: <https://doi.org/10.1016/J.HLC.2021.04.022>

19. Ma K, Lu M, Li H, Yuan X, Zhang Y, Ni Q, et al. Incidence and influencing factors of tooth discoloration in children using doxycycline: A meta-analysis. Front Pediatr 2025; 13:1644231.

20. Cherry CC, Kersh GJ. Pediatric Q fever. *Curr Infect Dis Rep* 2020; 22(4):10. Available from URL: <https://doi.org/10.1007/s11908-020-0719-0>
21. Centers for Disease Control and Prevention [Internet]. 2025 Mar 5. Q fever: Clinical guidance. Available from URL: <https://www.cdc.gov/q-fever/hcp/clinical-guidance/index.html>