Blood culture negative infective endocarditis in adult congenital heart disease patients with prosthetic grafts: a case series

Myo Thidar Lwin, Victor Kwok Wai Tsoi, Tat Yam, Aisling Carroll, Tony Salmon, Stephen Harden, and Lindsay Smith

1Department of Cardiology, Wessex Congenital Cardiac Unit, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, Hampshire SO16 6YD, UK; and 2Department of Microbiology, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, Hampshire SO16 6YD, UK

Received 26 August 2020; first decision 7 October 2020; accepted 10 March 2021

Blood culture negative infective endocarditis (BCNIE) is often a diagnostic challenge in adult congenital heart disease patients leading to misdiagnosis, treatment delay and associated high mortality. Studies of BCNIE in adult congenital heart disease patients repaired with prosthetic cardiovascular grafts are limited.

Case summary
We report two cases of BCNIE where serology testing, multiple polymerase chain reaction testing of explanted valve material and multi-modality imaging including 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) were utilized not only to confirm the diagnosis but also to guide management strategy and inform prognosis. Both patients were treated successfully with cardiac surgery and prolonged anti-microbial therapy.

Discussion
Clinical presentation of BCNIE in repaired CHD patients is highly variable. The symptoms are often non-specific with sub-acute or chronic presentation. This may mislead initial diagnosis and subsequent management. Multi-modality imaging including PET/CT should be considered to support the diagnosis, define the extent of infection, decide the management strategy and inform prognosis in patients. A thorough history of animal exposure, and consideration of serology and multiple molecular testing to identify the causative organism, is critical in the management of BCNIE.

Keywords
Case series • Adult congenital heart disease • Blood culture negative infective endocarditis • Polymerase chain reaction • Positron emission tomography • Computed tomography

Learning points
- Clinical presentation of blood culture negative infective endocarditis (BCNIE) in repaired congenital heart disease patients is highly variable. Subacute or chronic presentation with non-specific symptoms may mislead initial diagnosis and subsequent management.
- A thorough history of animal exposure and consideration of serology and multiple molecular techniques to identify the causative organism is critical in the management of BCNIE.
- Multi-modality imaging including positron emission tomography/computed tomography should be considered to support the diagnosis, define the extent of infection, decide the management strategy and inform prognosis in patients.
Introduction

With the growing number of patients with repaired or palliated congenital heart disease (CHD) surviving into adulthood, a variety of serious complications such as infective endocarditis (IE) are becoming increasingly frequent despite advances in medical and surgical treatment. The reported proportion of CHD in patients with IE varies between 2% and 18%\(^2\) and blood culture negative infective endocarditis (BCNIE) accounts for approximately 10% of cases.\(^3\)\(^-\)\(^7\)

The clinical presentation of BCNIE in CHD can be highly variable, insidious, and non-specific resulting in underdiagnosis or misdiagnosis with considerable morbidity and mortality. A high index of suspicion and prompt diagnostic work up to confirm the diagnosis and identify the causative pathogen is crucial to guide appropriate treatment and improve outcome.

Standard clinical practice in the diagnosis of IE utilizes the Modified Duke Criteria which combines the findings of three domains: clinical, microbiological, and imaging. This then stratifies patients into three categories: definite, possible, and rejected IE. Blood cultures, transthoracic echocardiogram (TTE), and transoesophageal echocardiogram (TOE) are used to categorize patients by Modified Duke Criteria. Sensitivity of conventional imaging techniques such as TTE and TOE for diagnosing endocarditis in CHD is limited to 60–80%\(^8\).

Therefore, diagnosis of BCNIE caused by intracellular organisms often requires other microbiology tests such as serology and polymerase chain reaction (PCR) as well as multi-modality imaging including computed tomography (CT) and \(^{18}\)F-fluorodeoxyglucose positron emission tomography/CT (\(^{18}\)F-FDG PET/CT) particularly in cases with prosthetic cardiovascular grafts.\(^9\)

We report two cases of repaired CHD where a multidisciplinary and multi-modality approach was essential in the diagnosis and management of BCNIE.

Timeline

| Patient 1 | Patient 2 |
|-----------|-----------|
| **Childhood diagnosis** | Tetralogy of Fallot | Bicuspid aortic valve and coarctation of aorta |
| Surgical interventions (before teen) | Waterston shunt and then a full repair with a pulmonary homograft | Coarctation of aortic repair and Bentall procedure with a 23 mm monoleaflet Medtronic aortic valve |
| Further interventions | Pulmonary valve replacement with a 24 mm CE Perimount Magna Ease valve mounted in a Dacron graft | Empirically treated with 6 weeks of antibiotics for blood culture negative infective endocarditis overseas over a year before presentation |
| At presentation | Worsening constitutional symptoms such as fevers, night sweats, lethargy, and loss of appetite while being treated for lower limb cellulitis with a second course of oral antibiotics in primary care | Constitutional symptoms consistent of infective endocarditis such as fevers, night sweats, and lethargy |
| Investigation | Elevated inflammatory markers, bicytopenia, transthoracic echocardiogram (TTE) was non-contributory to the diagnosis. Computed tomography (CT) chest showed linear echodensity in right ventricular outflow tract (RVOT). \(^{18}\)F-fluorodeoxyglucose positron emission tomography/CT (\(^{18}\)F-FDG PET/CT) confirmed high metabolic uptake in RVOT | TTE and transoesophageal echocardiogram demonstrated features of acute endocarditis with acute worsening of aortic valve haemodynamic and vegetation. CT and \(^{18}\)F-FDG PET/CT showed infection extending to ascending aorta, aortic arch, and sternum |

Case presentation

**Patient 1**

A 48-year-old Caucasian female with a history of Tetralogy of Fallot, initially palliated with a Waterston shunt, underwent full repair with a pulmonary homograft at the age of 8 years. In 2010, she required a pulmonary valve replacement (PVR) with a 24 mm CE Perimount Magna Ease valve mounted in a Dacron graft. The patient was placed under close surveillance for progressive right ventricular outflow tract (RVOT) obstruction secondary to valve degeneration.

In mid-2019, she presented with worsening constitutional symptoms such as fevers, night sweats, lethargy, and loss of appetite while being treated for lower limb cellulitis with a second course of oral antibiotics in primary care. Relevant medical history included recurrent skin infections secondary to frequent skin tears from cat scratches.

Initial work up revealed significantly elevated acute inflammatory markers and severe bicytopenia [haemoglobin 77 g/L (normal range: 115–165 g/L), white blood cell 1.7 × 10^9/L (normal range: 4–11 × 10^9/L), Neutrophil 0.4 × 10^9/L (normal range: 2.0–7.5 × 10^9/L)] which required treatment with intermittent G-CSF injections. Multiple sets of blood cultures with extended incubation were negative and the sub-optimal TTE demonstrated thickened PVR which was chosen as the next imaging modality to (i) exclude malignancy as a cause of bicytopenia, and (ii) investigate other possible infective sources. A linear echo-density was found in the region of RVOT which we further investigated with \(^{18}\)F-FDG PET/CT after discussion with the team.
in the adult congenital multidisciplinary team (MDT) meeting. This confirmed the presence of high metabolic uptake in the RVOT (Figure 1) and ruled out other infective sources and malignancy.

Consequently, the patient underwent surgical pulmonary valve and conduit replacement as she was failing anti-microbial therapy. Intraoperatively, the conduit was found to be severely narrowed in the proximal anastomosis with vegetations in the pulmonary valve. Real-time PCR from the explanted valve was positive for *Staphylococcus aureus* and 16s broad range PCR was positive for *Bartonella henselae* ultimately confirming the diagnosis of cat-scratch disease and IE. Post-operatively, she was treated with 6 weeks intravenous ceftriaxone and gentamicin followed by further 6 weeks of oral doxycycline resulting in complete resolution of constitutional symptoms, inflammatory markers, and normalization of bicytopenia. The patient remained well with satisfactory pulmonary valve haemodynamics at 12 months following surgery.

**Patient 2**

A 32-year-old Caucasian male from Sardinia with a history of bicuspid aortic valve and repaired coarctation of aorta had a Bentall procedure with a 23 mm monoleaflet Medtronic aortic valve for aortic regurgitation with associated aortopathy of proximal ascending aorta. This surgery was carried out in an overseas centre in Southern Europe at the age of 12 years. In 2017, the patient first presented to our centre with clinical symptoms suggestive of IE on a background of BCNIE overseas over a year ago. Importantly, he was empirically treated with 6 weeks intravenous ceftriaxone and gentamicin followed by further 6 weeks of oral doxycycline resulting in complete resolution of constitutional symptoms, inflammatory markers, and normalization of bicytopenia. The patient remained well with satisfactory pulmonary valve haemodynamics at 12 months following surgery.

![Video 1](https://example.com/Video1)

Transthoracic echocardiogram (parasternal short-axis view) of Patient 1 demonstrating thickened pulmonary valve replacement with restricted opening.

| Management | Surgical pulmonary valve and conduit replacement and prolonged antibiotics | Surgical reconstruction of the aortic root with composite graft, reconstruction of ascending aorta, aortic arch, and proximal descending aorta along with coronary re-implantation and prolonged anti-microbial therapy |
|------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Follow-up  | Complete normalization of bicytopenia and inflammatory markers            | Four-fold reduction in his acute phase (Phase 2) IgG titre with negative real-time polymerase chain reaction at 5 months post-cardiac surgery |

Follow-up

Remained well with satisfactory pulmonary valve haemodynamics at 12 months after surgery

Clinically well with satisfactory echocardiographic findings

**Patient 2**

A 32-year-old Caucasian male from Sardinia with a history of bicuspid aortic valve and repaired coarctation of aorta had a Bentall procedure with a 23 mm monoleaflet Medtronic aortic valve for aortic regurgitation with associated aortopathy of proximal ascending aorta. This surgery was carried out in an overseas centre in Southern Europe at the age of 12 years. In 2017, the patient first presented to our centre with clinical symptoms suggestive of IE on a background of BCNIE overseas over a year ago. Importantly, he was empirically treated with 6 weeks intravenous ceftriaxone and gentamicin followed by further 6 weeks of oral doxycycline resulting in complete resolution of constitutional symptoms, inflammatory markers, and normalization of bicytopenia. The patient remained well with satisfactory pulmonary valve haemodynamics at 12 months following surgery.

With the acute presentation, multiple sets of blood cultures remained negative despite acute worsening of aortic valve haemodynamics and presence of vegetations in the mechanical aortic valve and aortic graft on TTE and TOE (Videos 2 and 3). Preoperative planning CT chest suggested potential infective involvement of ascending aorta and aortic arch. After discussion in the MDT, 18F-FDG PET/CT was carried out to define the extent of infection and guide the surgical management. This demonstrated an extensive metabolic uptake involving the mechanical aortic valve, ascending aorta, aortic arch, and the sternum (Figure 2A and 8). Subsequently, the patient was found to have a positive PCR for Coxiella burnetii in serum along with high level titre for Phase 2 (acute phase) IgG and low level titre for Phase 2 IgM which is highly suggestive of chronic aortic graft and mechanical aortic valve endocarditis due to Q fever.

The patient underwent cardiac surgery involving reconstruction of the aortic root and ascending aorta with 25 mm biointegral composite graft, bovine pericardial patch reconstruction of aortic arch and proximal descending aorta along with coronary re-implantation. The explanted mechanical valves and tissues had positive realtime PCR for *C. burnetii* though 16s broad range PCR was negative. Following surgery, the patient received prolonged treatment with oral doxycycline and hydroxychloroquine by the microbiology team.

Repeat convalescence Q fever antibodies titre (Table 1) showed a significant four-fold reduction in his acute phase (Phase 2) IgG titre with negative real-time PCR at 5 months post-cardiac surgery. The patient continued to receive oral doxycycline and hydroxychloroquine therapy with serial monitoring of Coxiella Serology (Table 1).
Discussion

True BCNIE caused by intracellular organisms such as Coxiella and Bartonella is increasingly reported in patients with underlying heart disease across Europe.\textsuperscript{10–12} The clinical manifestation can be protean and non-specific resulting in considerable diagnostic and therapeutic dilemma and mortality.

Our first case demonstrated acute on sub-acute presentation of right-sided endocarditis due to two pathogens namely, B. henselae and S. aureus in a patient with surgically repaired Tetralogy of Fallot and significant residual haemodynamic lesion in the homograft PVR. The symptoms were non-specific, and there was severe bicytopenia due to bone marrow suppression as a result of chronic Bartonella infection. Blood cultures were negative because (i) Bartonella is an intracellular pathogen that does not grow well in routine blood cultures and (ii) S. aureus was partially treated with antibiotics in primary care. Diagnosis of BCNIE was confirmed in this case by \textsuperscript{18}F-FDG PET/CT and PCR of the explanted conduit. Serology for Bartonella was not carried out initially after consultation with microbiology as there was sufficient evidence from other diagnostic modalities and a significant chance of sero-reactivity caused by previous infection secondary to cat scratches. \textsuperscript{18}F-FDG PET/CT was chosen over TOE in this case due to expected poor views with the anterior position of the pulmonary valve and RVOT.

The second case exemplified an acute presentation of left sided endocarditis due to \textit{C. burnetii} in a patient with prosthetic aortic material. The patient likely had previous animal exposure during his childhood in the rural area in Sardinia which is a farming and agricultural community. We believed his previous partially treated BCNIE was caused by the same pathogen. Though he fulfilled the Modified Duke criteria to diagnose endocarditis, serology and multiple molecular techniques were required to determine the causative organism. While \textsuperscript{18}F-FDG PET/CT defined the extent of the infection, it also provided crucial information to guide surgical management and inform perioperative risk and prognosis to the patient.

The Modified Duke Criteria provides a reference framework for diagnosing IE but it performs poorly in patients with CHD repaired or palliated with prosthetic material. It also performs poorly if the endocarditis is caused by a fastidious intracellular organism. Application of non-conventional microbiology testing with serology and molecular techniques along with multi-modality imaging is critical in such patients if the clinical suspicion remains high despite negative blood cultures, in order to aid the diagnosis and select an appropriate treatment. Out of all serology for fastidious organisms, Coxiella and Bartonella serology have been found to be highly contributory in the diagnosis of BCNIE.\textsuperscript{13} As such, the latest European Society of Cardiology guideline recommends routine use of Coxiella and Bartonella serological testing in patients with BCNIE, and \textsuperscript{18}F-FDG PET/CT in the assessment of prosthetic valve infection when echocardiogram is inconclusive.\textsuperscript{9}
However, it is important for clinicians to recognize the limitation of these tests, and thereby utilize them as a complementary investigation tool in aiding diagnosis rather than a standalone diagnostic tool. Limitations of serology tests include sero-cross-reactivity from another organism or sero-reactivity from prior exposure. For PCR assays, testing histology specimens with organism-specific PCR assays is more sensitive than blood, due to a relatively higher abundance of bacterial DNA in histology specimens.\textsuperscript{14,15} It has been shown that the broad range 16S rDNA PCR assay was able to provide additional diagnostic value in 62\% of BCNIE cases.\textsuperscript{16} Studies comparing TTE and TOE with \textsuperscript{18}F-FDG PET/CT in evaluating patients with suspicious IE found that \textsuperscript{18}F-FDG PET/CT can provide a significantly superior diagnostic yield.\textsuperscript{17–19} However, it is worth noting that \textsuperscript{18}F-FDG-PET/CT uptake is often identified in recently implanted prosthetic valves, where uptake can remain increased at 1 year after surgery.\textsuperscript{20} Additionally, \textsuperscript{18}F-FDG as a metabolic substrate is frequently taken up by the left ventricle in the absence of infection, and this can make assessment more difficult, although methods of suppression of myocardial uptake can be used.\textsuperscript{21}

Once the organism is identified in BCNIE, prolonged antimicrobial treatment is often necessary to eradicate the infection and prevent recurrence. The recommended treatment for Bartonella endocarditis is a beta-lactam antibiotic or doxycycline for four weeks in combination with gentamicin for the first 2 weeks. For Coxiella endocarditis, the treatment is doxycycline and hydroxychloroquine until Phase 1 antibody titre is <800 for IgG and <50 for IgM.\textsuperscript{9,22} However, antimicrobial treatment alone is often insufficient because prostheses are usually polytetrafluoroethylene tubes, which requires surgical re-intervention to explant the contaminated foreign material.

In summary, with more CHD patients surviving into adulthood as a result of improved paediatric care and surgical techniques, serious long-term complications including IE are increasingly common. It is very important that clinicians recognize the atypical presentation of BCNIE, the diagnostic pathway, and utilize a multi-modality approach of imaging, serology testing and PCR of explanted valve material to confirm the diagnosis and identify the causative organism. In particular, we believe that \textsuperscript{18}F-FDG PET/CT should be routinely considered in high-risk cases with prosthetic cardiovascular grafts to support the diagnosis, quantify the extent of the infection, define management strategy and inform prognosis.

\begin{table}[h]
\centering
\begin{tabular}{lcccccc}
\hline
Date & 30 September 2017 & 17 October 2017 & 27 February 2018 & 19 December 2018 & 02 December 2019 \\
\hline
Month & 0 & 0.5 & 5 & 15 & 27 \\
Phase 1 IgG & 10240 & 5120 & 5120 & 5120 & 2560 \\
Phase 1 IgA & 1280 & 5120 & 640 & 320 & 160 \\
Phase 2 IgG & 40960 & 10240 & 10240 & 10240 & 10240 \\
Phase2 IgM & 640 & 2560 & 0 & 0 & 0 \\
PCR & Positive & Negative & Negative & Negative & Negative \\
\hline
\end{tabular}
\caption{Serial Coxiella Serology}
\end{table}
Lead author biography

Dr Myo Thidar Lwin completed her undergraduate education at the University of Medicine 2, Yangon, Myanmar. She then completed her general physician and cardiology training in Queensland, Australia and Adult Congenital Heart Disease fellowship at University Hospital Southampton NHS Foundation Trust before taking on her current role as a locum adult congenital cardiologist. Her clinical and research interests in adult congenital heart disease include imaging, pregnancy, and pulmonary hypertension. She aims to pursue a formal research degree in adult congenital heart disease.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE Guidance.

Conflict of interest: None declared.

Funding: None declared.

References

1. Michel PL, Acar J. Native cardiac disease predisposing to infective endocarditis. Eur Heart J 1995;16:2–6.
2. De Gevigney G, Pop C, Delahaye JP. The risk of infective endocarditis after cardiac surgical and interventional procedures. Eur Heart J 1995;16:7–14.
3. Rader BL, Wandall DA, Esparren F, Frimodt-Møller N, Shihpej P, Rosdahl VT. Neurologic manifestations in Staphylococcus aureus endocarditis: a review of 260 bacteremic cases in nondrug addicts. Am J Med 1997;102:379–386.
4. Ishiwada N, Niwa K, Tateno S, Yoshimaga M, Terai M, Nakazawa M, Japanese Society of Pediatric Cardiology and Cardiac Surgery Joint Working Group for Guidelines for Prophylaxis, Diagnosis and Management of Infective Endocarditis in Patients With Congenital Heart Disease. Causative organism influences clinical profile and outcome of infective endocarditis in pediatric patients and adults with congenital heart disease. Circ J 2005;69:1266–1270.
5. Knirsch W, Haas NA, Uhtemann F, Dietz K, Lange PE. Clinical course and complications of infective endocarditis in patients growing up with congenital heart disease. Int J Cardiol 2005;101:285–291.
6. Takeda S, Nakashishi T, Nakazawa M. A 28-year trend of infective endocarditis associated with congenital heart diseases: a single institute experience. Pediatr Int 2005;47:393–396.
7. Zuberbühler JR. The changing face of infectious endocarditis. Cardiol Young 1997; 7:129–130.
8. Knirsch W, Nadal D. Infective endocarditis in congenital heart disease. Eur J Pediatr 2011;170:1111–1127.
9. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F et al. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075–3128.
10. Tattewicz P, Watt G, Revest M, Arvieux C, Fournier P-E. Update on blood culture-negative infective endocarditis. Med Mal Infect 2015;45:1–8.
11. Lamas CC, Eley KN. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years. Heart 2003;89:258–262.
12. Okaro U, Addisu A, Casanas B, Anderson B. Bartonella species, an emerging cause of blood-culture-negative endocarditis. Clin Microbiol Rev 2017;30:709–746.
13. Houptkian P, Raoult D. Blood culture-negative endocarditis in a reference center: etiologic diagnosis of 348 cases. Medicine (Baltimore) 2005;84:162–173.
14. Subek S, Jennings Z, Chen SC-A. Laboratory approach to the diagnosis of culture-negative infective endocarditis. Heart Lung Circ 2017;26:763–771.
15. Liesman RM, Print BS, Maleszewska JJ, Patel R. Laboratory diagnosis of infective endocarditis. Kraft CS, editor. J Clin Microbiol 2017;55:2599–2608.
16. Harris KA, Yam T, Jaliil S, Williams OM, Alishah K, Gouloumis T et al. Service evaluation to establish the sensitivity, specificity and additional value of broad-range 16S rDNA PCR for the diagnosis of infective endocarditis from resected endocardial material in patients from eight UK and Ireland hospitals. Eur J Clin Microbiol Infect Dis 2014;33:2061–2066.
17. El-Dalati S, Murthy VL, Owczanczyk AL, Fagan C, Riddell J, Cinti S et al. Correlating cardiac F-18 FDG PET/CT with intra-operative findings in infectious endocarditis. J Nucl Cardiol 2021;28:289–294.
18. Abu Jokh Casas E, Pujol Z, Núñez V, Pombo Pasin MDC, Garrido Pumar M, Martinez MA, Abu Jokh Casas C et al. Advantages and limitations of 18-fluorodeoxyglucose positron emission tomography/computed tomography in the diagnosis of infective endocarditis. Rev Port Cardiol 2019;38:573–580.
19. Wahdad AR, Tanis W, Swart LE, Scholten A, Krestin GP, van Meijhem NM et al. Added value of 18F-FDG PET/CT and cardiac CTA in suspected transcatheter aortic valve endocarditis. J Nucl Cardiol 2019;doi:10.1007/s12350-019-01963-x.
20. Roque A, Pizzi MN, Fernández-Hidalgo N, Permanyar E, Cuellar-Calabria H, Romero-Farina G et al. Morpho-metabolic post-surgical patterns of non-infected prosthetic heart valves by [18F]FDG PET/CT: “normality” is a possible diagnosis in endocarditis. Eur Heart J Cardiovasc Imaging 2020;21:24–33.
21. Rouzet F, Iung B, Duval X. 18F-FDG PET/CT in infective endocarditis: new perspectives for improving patient management. J Am Coll Cardiol 2019;74:1041–1043.
22. Gould FK, Denning DW, Elliott TS, Foweraker J, Perry JD, Prendergast BD et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother 2011;67:269–289.