Bartonella species as a cause of culture-negative endocarditis in South Africa

Alfonso (AJK) Pecoraro 1 · Philip (PG) Herbst 1 · Colette (C) Pienaar 2 · Jantjie (JJT) Taljaard 3 · Hans (HW) Prozesky 3 · Jacques (JT) Janson 4 · Anton (AF) Doubell 1

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Abstract

Previous reports have highlighted the high prevalence of blood culture negative endocarditis (BCNE) in South Africa. The Tygerberg Endocarditis Cohort (TEC) study is an ongoing prospective cohort study of patients with confirmed or suspected IE presenting to Tygerberg Academic Hospital, Cape Town, South Africa. Current analysis includes patients that presented between November 2019 and August 2020. Forty four (44) patients have been included in this ongoing study. Fourteen of the 44 patients (31.8%) had BCNE. Further analysis of the patients with BCNE identified Bartonella species as the most common causative organism (n=6; 43%). Other causes included Mycoplasma species (n=2). No cause could be identified in 4 of the 44 patients (9%). Bartonella quintana was identified with PCR of valvular tissue as the causative organism in 4 of the 5 patients that underwent urgent surgery. The patients with Bartonella IE (n=6) had an average age of 39 years with equal gender distribution. The common clinical features were clubbing (n=5; 83%), anemia (n=4; 66.6%), haematuria (n=3; 50%), acute on chronic severe regurgitant lesion (n=3; 50%) and acute severe regurgitant lesion (n=2; 33.3%). The aortic valve was involved in 5 of 6 patients. During a mean follow-up period of 251 days after diagnosis, no major adverse events occurred. Bartonella-associated IE is an important cause of BCNE in the Western Cape of South Africa. Imaging findings (in patients with BCNE) of significant valvular destruction with large vegetations on the aortic valve not affected by congenital or rheumatic valve disease should raise the suspicion of Bartonella-associated IE.

Keywords Infective endocarditis · Blood culture negative endocarditis · Bartonella quintana · Bartonella henselae

Background

Infective endocarditis (IE) is defined as an infection involving the endocardial surface of the heart. This can primarily affect native heart valves (native valve endocarditis or NVE), prosthetic heart valves (prosthetic valve endocarditis—or PVE), non-valvular endocardial surfaces (such as IE affecting ventricular septal defects) or any cardiac prosthetic devices [1, 2]. The characteristics of IE have evolved in developed nations with a doubling of patient age, an increase in the prevalence of patients with IE due to Staphylococcus aureus in the setting of normal or non-rheumatic valves and a decrease in the prevalence of blood culture–negative endocarditis (BCNE) [2, 3]. Data regarding the causes and epidemiology of IE in the developing world and specifically South Africa are limited. Current reports from South Africa suggest IE is still a disease of young patients with underlying rheumatic heart disease, predominantly caused by the viridans group of streptococci and with a high rate of BCNE [1, 4]. The postulated reason for the high rate of BCNE in the published South African literature has been the high rate of antibiotic use prior to blood culture sampling [4]. Data from the developed world would suggest that organisms that are difficult to culture and/or identify with standard laboratory methods are the commonest cause of BCNE. These organisms vary according
to region, with developed countries reporting mostly *Coxiella burnetii* as a causative organism in cases of IE previously considered as BCNE [1]. Limited data is available for South Africa, but reports from Algeria (a developing country) suggest *Bartonella* species is a more common cause of BCNE than *C. burnetii* [7]. BCNE is associated with a higher rate of in-hospital adverse events, although recent publications have suggested similar long-term outcomes when compared to blood culture–positive patients [8, 9].

*Bartonella* species are small Gram-negative bacilli that are generally transmitted by arthropod vectors. These fastidious intracellular bacteria cause various clinical syndromes and diagnosis is challenging due to difficulties isolating the organism using traditional culture methods [10]. *Bartonella quintana* is mostly associated with trench fever, IE and bacillary angiomatosis whereas *Bartonella henselae* is associated with cat scratch disease, bacillary angiomatosis and, less commonly, with IE. *B. quintana* infection is often reported in homeless persons infested with body lice as compared to *B. henselae* infection which is usually associated with contact with cats. Single cases of other *Bartonella* species causing IE have been reported [10, 11].

The Tygerberg Endocarditis Cohort (TEC) study is a prospective cohort study of patients with definite or suspected IE according to the European Society of Cardiology (ESC) criteria [2]. All patients included are managed by an Endocarditis Heart Team with a set protocol to detect the causative organism as per the current ESC guidelines [2]. Tygerberg Academic Hospital is a public sector tertiary referral centre for a network of 17 hospitals and serves a population of approximately 2.4 million people [12].

### Methods

All patients referred to the Division of Cardiology, Department of Medicine at Tygerberg Hospital in Cape Town, South Africa, with definite or suspected IE from November 2019 to August 2020 were included in this ongoing study. All patients underwent standard transthoracic echocardiography (TTE) with the majority also undergoing transoesophageal echocardiography (TEE) in the absence of identifiable contra-indications to TEE [13, 14].

A minimum of three sets of blood cultures (BacT/ALERT, bioMérieux, Marcy l’Etoile, France), including one aerobic and one anaerobic bottle per set, were required, with repeated cultures if clinical features of infection persisted. All blood culture bottles were loaded into an automated blood culture instrument (BacT/ALERT, bioMérieux, Marcy l’Etoile, France) for 5 days. If growth was detected by the instrument, the signal-positive bottles were removed from the instrument and a Gram stain performed on the blood culture broth. Based on the Gram stain findings, the broth was sub-cultured onto appropriate agar-based culture media and incubated at the required temperature and atmosphere to optimize the growth of the organism observed. After 18–24 h of incubation, the agar plates were examined for growth. The cultured organism was identified by standard laboratory methods such as manual and automated biochemical assays, and upon failure of these, mass spectrometry (Vitek MS, bioMérieux, Marcy l’Etoile, France) was performed by a referral laboratory. Antimicrobial susceptibility testing (AST) was performed on all isolates using disk-diffusion (Kirby-Bauer), the Vitek 2 automated AST system (bioMérieux, Marcy l’Etoile, France) and/or Etest (bioMérieux, Marcy l’Etoile, France). A stepwise protocol for organism detection was utilised to identify the common causative organisms of IE and to minimize the incidence of BCNE (Fig. 1). Patients without an identified organism using standard culture techniques after 5 days were defined as having BCNE.

All BCNE patients underwent further venous blood analysis for further testing, including:

- Serology for detection of IgM and IgG antibodies to *Bartonella* species, *Brucella* species, *C. burnetii*, *Legionella pneumophila* and *Mycoplasma pneumoniae*
- Antibody testing for antinuclear antibodies (ANF) and anti-cardiolipin antibodies (ACLA)
- Direct polymerase chain reaction (PCR) was performed on negative blood culture bottles for detection of the universal bacterial 16S RNA and fungal 18S rRNA genes, followed by sequencing to identify the amplified DNA product.

A sample of heart valve tissue was collected from all patients who required surgery and this was submitted for:

- Bacterial and fungal culture
- 16S and 18S PCR followed by sequencing
- Histopathologic examination to detect bacteria and fungi, as well histopathological features of IE.

All patients were treated by an Endocarditis Team according to the current ESC guidelines [2]. Patients with BCNE were treated with empirical intravenous therapy for native valve endocarditis comprising of penicillin G 5 million units 6 hourly (42 days), cloxacinil 3 grams 6 hourly (42 days) and gentamycin 240 milligrams daily (14 days) [2]. Doxycycline 100mg twice daily (for *Bartonella* associated IE) was added as results of serology and/or PCR became available and continued for a minimum of 6 weeks.

### Results

Forty four (44) patients have been included in this ongoing study. Fourteen of the 44 patients (31.8%) had BCNE.
analysis of the patients with BCNE identified Bartonella species as the most common causative organism (n=6; 43%). Other causes included Mycoplasma species (n=2). No cause could be identified in 4 of the 44 patients (9%). Two of the 4 patients had suspected Mycobacterium tuberculosis–associated IE based on typical clinical and echocardiographic features, but without microbiological confirmation [1].

The patients with Bartonella-associated IE (n=6) had an average age of 39 years with equal gender distribution (Table 1). Two patients lived in informal housing, with one patient homeless prior to admission. None of the patients had a history of intravenous drug abuse, although two patients reported previous use Marijuana. Five of the six (83.3%) reported the onset of fever and dyspnoea more than 2 weeks prior to presentation. The common clinical features were clubbing (n=5; 83%), anemia (n=4; 66.6%), haematuria (n=3; 50%), acute on chronic severe regurgitant lesion (n=3; 50%) and acute severe regurgitant lesion (n=2; 33.3%). No features of bites or infestation of lice were observed in the patients.

Although echocardiography identified significant valvular destruction in all patients, no underlying structural valve disease (rheumatic valve disease or congenital abnormalities) was identified. The aortic valve was involved in 5 of 6 patients. Acute severe aortic regurgitation was confirmed in 2 patients, acute on chronic severe aortic regurgitation in 2 patients, chronic severe aortic regurgitation in one patient and acute severe mitral regurgitation in one patient.

Vegetation size ranged from 10 to 15mm on linear measurement with an average circumference of 28mm. Only one patient had a raised white cell count (WCC). C-reactive protein (CRP) levels were mildly raised with only one value above 50. Two of our 6 patients were HIV-positive; one was on antiretroviral treatment with undetectable viral load and one had a CD4 count of more than 1000 per microliter of blood. Four patients (66%) had low complement levels (Table 2).

*B. quintana* and *B. henselae* IgG and IgM were detected by an immunofluorescence assay (IFA). IgG was positive in all patients with titres ranging from 1:256 to 1:512, while IgM was positive in 5 of the 6 patients. The 16S and 18S PCRs performed on blood cultures were negative in all patients. Both patients with acute severe aortic regurgitation underwent emergency valve replacement, and 3 of the other 4 patients underwent urgent/inpatient valve replacement. Valve repair was not possible in one patient. Sequencing of the 16S PCR product from valve tissue identified *B. quintana* in 4 of the 5 patients who had surgery. The patients who underwent surgery survived their hospital stay and were discharged home on oral doxycycline. One patient declined surgery but successfully completed 3 months of oral doxycycline. During a mean follow-up period of 251 days after diagnosis, no major adverse events (death, embolic events, renal failure requiring dialysis or rehospitalization) occurred.

**Discussion**

This is the first study that identifies Bartonella species as an important cause of BCNE in the Western Cape province of
South Africa. Previous cohort studies of patients with IE in the Western Cape and South Africa overall have not reported *Bartonella* species as a cause of IE [4–6, 15]. The first case was described in 1993 and another case was reported recently [16, 17]. Our findings are in keeping with data from other developing countries where *Bartonella* species are the most common cause of BCNE contrasting with developed countries that report *C. burnetii* as the commonest cause of BCNE [7, 11, 18]. The reasons for the lack of reporting of *Bartonella* species as a cause of BCNE in South Africa are probably multifactorial. We postulate that our systematic approach to organism detection, including serology and newer diagnostic modalities such as PCR performed on valves, explains this new finding, rather than the emergence of *Bartonella* species as a new cause of BCNE in South Africa. Should this be the case, it follows that a large group of patients previously labelled as BCNE were not adequately treated for Bartonella associated IE and this may have contributed to the adverse outcome of these

### Table 1 Demographic information, clinical and imaging findings

| Demographic information | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Age (years)             | 39        | 26        | 36        | 41        | 57        | 37        |
| Sex                     | Male      | Female    | Female    | Male      | Male      | Female    |
| Rural/urban             | Rural     | Urban     | Urban     | Rural     | Urban     | Rural     |
| Housing                 | Informal  | Formal    | Homeless  | Formal    | Formal    | Informal  |
| Clinical and imaging features |          |           |           |           |           |           |
| Clubbing                | Yes       | Yes       | Yes       | No        | Yes       | Yes       |
| Anemia                  | Yes       | No        | No        | Yes       | Yes       | No        |
| Hematuria               | No        | No        | No        | Yes       | Yes       | Yes       |
| Valve involvement       | Aortic    | Aortic    | Mitral    | Aortic    | Aortic    | Aortic    |
| Hemodynamic lesion      | Acute     | Acute on chronic | Acute on chronic | Chronic    | Acute     | Acute on chronic |
| Vegetation length (mm)  | 15        | 12        | 10        | 11        | 10        | 10        |
| Vegetation circumference (mm) | 47  | 29        | 22        | 25        | 25        | 22        |
| Vegetation number       | Multiple  | Multiple  | Single    | Multiple  | Multiple  | Multiple  |
| Pre-existing valvular structure | Normal   | Normal    | Normal    | Normal    | Normal    | Normal    |

### Table 2 Special investigations and surgical outcome

| Special investigations | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| *B. quintana* IgG      | Positive  | Positive  | Positive  | Positive  | Positive  | Positive  |
| Titre                  | 1:256     | 1:256     | 1:512     | 1:256     | 1:512     | 1:256     |
| *B. quintana* IgM      | Negative  | Positive  | Positive  | Positive  | Positive  | Positive  |
| Titre                  | 1:256     | 1:256     | 1:64      | 1:128     | 1:512     | 1:64      |
| *B. henselae* IgG      | Positive  | Positive  | Positive  | Positive  | Positive  | Positive  |
| Titre                  | 1:256     | 1:256     | 1:512     | 1:512     | 1:512     | 1:256     |
| *B. henselae* IgM      | Negative  | Positive  | Positive  | Positive  | Positive  | Positive  |
| Titre                  | 1:64      | 1:64      | 1:64      | 1:512     | 1:512     | 1:128     |
| 16S PCR on valve tissue | *B. quintana* | Not done | Negative | *B. quintana* | *B. quintana* | *B. quintana* |
| 16S PCR on blood cultures | Negative | Negative | Negative | Negative | Negative | Negative |
| HIV status             | Positive  | Positive  | Negative  | Negative  | Negative  | Negative  |
| CRP                    | 50        | 37        | 209       | 22        | 33        | 12        |
| WCC (per microliter)   | 7700      | 10000     | 27600     | 7300      | 3150      | 8800      |
| Complement level       | Normal    | Low       | Normal    | Low       | Low       | Low       |
| Valve replaced          | Aortic    | Refused   | Mitral    | Aortic    | Aortic    | Aortic    |
| In-hospital mortality   | No        | No        | No        | No        | No        | No        |
| Current follow-up period (days) | 369 | 128       | 352       | 306       | 226       | 130       |
B. quintana

IE, the IgG titres for

ogy [20], in our series of 4 patients with PCR-confirmed the likely causative organism will have higher titers by serol-

ogy. In our series, we identified B. quintana as the causative species in 4 of the 5 patients who underwent surgery. Of the 30 patients with culture-positive endocarditis, 18 underwent valve surgery. None of these cases were PCR positive for Bartonella species on their valve tissue.

Two patients were diagnosed with Bartonella associated IE without PCR confirmation on blood or heart valve. The decision was made by the Endocarditis Team on the basis of the typical clinical features, elevated serology titres and the absence of another cause in spite of a set protocol for organism detection. Currently, criteria are lacking for the diagnosis of Bartonella associated IE if PCR on both the blood and heart valves is negative or unavailable in the setting of typical clinical and imaging findings and suggestive serology. Different serological cut-offs for the diagnosis of Bartonella associated IE has been suggested [11], with higher titers of IgG increasing the positive predictive value of serology assays. Serum samples of healthy volunteers typically have IgG titres by IFA of less than 1:128 and IgM titres less than 1:20, with no IgG titres above 1:256 [20]. An IgM titre of more than 1:20 with an IgG titre of more than 1:128 suggests active Bartonella infection. We suggest that elevated Bartonella antibody titres in the setting of a typical clinical and imaging profile in the absence of another cause (after a set protocol for organism detection was followed) be utilised for the diagnosis (and thus initiation of therapy) of Bartonella associated IE.

Seroogy for B. henselae and B. quintana is not very useful in distinguishing between species due to the high rate of cross-reactivity between the assays [11]. Although it is reported that the likely causative organism will have higher titers by serology [20], in our series of 4 patients with PCR-confirmed B. quintana IE, the IgG titres for B. quintana was either equal or lower than the IgG titres for B. henselae, while the B. quintana IgM titres were either similar, higher or lower than B. henselae IgM titres, suggesting that it is less helpful in distinguishing between Bartonella species.

Previous case reports from South Africa and a case series from the USA also identified B. quintana as the causative species in BCNE [16, 17, 21]. A case series from Japan identified B. henselae as the causative species in five cases of BCNE [19]. B. henselae has been detected on blood PCR in up to 10% of HIV-positive patients in South Africa whereas no cases were detected in the non-HIV-infected control cohort. No cases of IE due to B. henselae from South Africa have been published. The treatment for the different species of Bartonella is similar and currently no evidence is available to suggest the outcome of Bartonella associated IE is influenced by the specific causative species.

The cross-reactivity of the serological tests for the different Bartonella species extend to patients with other causes of BCNE, including C. burnetii, Brucella and Mycoplasma species [22]. One of our patients with confirmed Mycoplasma hominis IE also had positive serology for B. henselae, although the IgG titre was less than 1:256. This finding puts into perspective the importance of performing PCR on both blood and valve tissue to confirm the causative organism in patients with BCNE, even if serology is positive for Bartonella, Brucella, Coxiella or Mycoplasma. Although the 16S PCR on blood was negative in all our patients, it remains important to detect organisms associated with BCNE (e.g. Mycoplasma) that might cause false-positive serology.

The clinical features of the patients with Bartonella associated IE had significant overlap with the known features of IE caused by the usual organisms, with clubbing, anaemia and haematuria being the most common [4]. In all but one of the patients, the aortic valve was involved, which is in keeping with previous reports [16, 21]. All patients had hemodynamically severe incompetence of either the aortic (n=5) or mitral (n=1) valve with clinical features of acute (n=2), acute on chronic (n=3) or chronic (n=1) incompetence. Historically, acute IE and acute valvular incompetence is associated with S. aureus IE and these patients often do not demonstrate the classical findings of clubbing and anaemia as these features take time to develop [23]. In our series, patients with acute valve lesions had both clubbing and anaemia; clubbing was also present in all of the patients with acute on chronic valve lesions. This would suggest a significant time from infection/bacteraemia to presentation, even though patients present with acute or acute on chronic valve incompetence. We postulate that patients with Bartonella IE has an early phase with minimal symptoms and low-grade underlying bacteraemia during which time the patient develops clubbing and anaemia of chronic disease. Patients only seek medical attention at the time of significant valvular destruction with the associated sequelae of dyspnea and hemodynamic compromise.

The majority of patients had severe destruction of the aortic valve with no evidence of underlying congenital heart/valve disease (e.g. bicuspid aortic valve, ventricular septal defect) or rheumatic valve disease (Fig. 2). The propensity of Bartonella species to involve the aortic valve is well documented, although no clear explanation exists for this finding [18].

Maximum vegetation length by two-dimensional echocardiography of 10mm or more in patients with left-sided IE is associated with an increased risk of embolic events. Although large vegetations were observed in all our patients, no embolic events occurred [24]. In contrast to other causes of IE of the
aortic valve, no peri-annular extension, e.g. peri-aortic abscess formation was noted. The fact that most patients underwent surgery early and were on appropriate antimicrobial therapy may have contributed to this finding. Due to the severe destruction of the aortic valve, 4 of 5 patients underwent aortic valve replacement with a mechanical valve. Mitral valve repair was attempted in the single patient with severe mitral regurgitation, but was converted intra-operatively to mitral valve replacement due to extensive tissue destruction. It would be difficult to draw meaningful conclusions from this small number of patients, but it seems that patients with Bartonella IE have a reasonably good short-term outcome in spite of the significant valvular destruction and large vegetations observed with echocardiography.

Conclusion

*Bartonella species* is an important cause of BCNE in the Western Cape of South Africa. A systematic approach to organism detection in patients with suspected or confirmed IE is essential for the diagnosis of the causative organism in patients with BCNE. Imaging findings (in patients with BCNE) of significant valvular destruction with large vegetations on the aortic valve not affected by congenital or rheumatic valve disease should raise the suspicion of Bartonella-associated IE. Early initiation of appropriate antimicrobial therapy combined with early surgery seems to provide a good in-hospital and short-term outcome.

Availability of data and material All data is securely stored on a digital database that is password protected. Data is available for review.

Declarations

Ethics approval Ethics approval was obtained from the committee for Human Research of the Faculty of Medicine, Stellenbosch University, Cape Town (ID 10660).

Consent to participate All patients provided written, informed consent.
Consent for publication  The authors consent to publication of the data if accepted. Patients consented to the publication of the data and images.

Conflict of interest  The authors declare that they have no competing interests.

References

1. Pecoraro AJ, Doullb AF (2020) Infective endocarditis in South Africa. Cardiovasc Diagn Ther 10(2):252–261 Apr [cited 2020 Jun 2]; Available from: http://cdn.amegroups.com/article/view/20995/50160

2. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, del Zotti F et al (2015) 2015 ESC Guidelines for the management of infective endocarditis. Euro Heart J 36(44):3075–3128 Available from: https://academic.oup.com/euheartj/article-lookup doi/10.1093/eurheartj/ehv319

3. Cahill TJ, Prendergast BD (2015) Current controversies in infective endocarditis. F1000Research 4:1287

4. Koegelenberg CFN, Doullb AF, Orth H, Reuter H (2003) Infective endocarditis in the Western Cape Province of South Africa: a three-year prospective study. QJM [Internet] 96(3):217–225 Available from: https://academic.oup.com/qjmed/article-lookup/doi/10.1093/qjmed/hcg028

5. Koshy J, Engel M, Human P, Carrara H, Brink J, Zilla P (2018) Long term outcome and EuroSCORE II validation in native valve surgery for active infective endocarditis in a South African cohort. SA Heart 15(2):116–126

6. de Villiers MC, Viljoen CA, Manning K, van der Westhuizen C, Seedat A, Rath M et al (2019) The changing landscape of infective endocarditis in South Africa. S Afr Med J 109(8):592–596

7. Pournier P, Thuny F, Richet H, Lepidi H, Casalta J, Azrouni J et al (2010) Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. Clin Infect Dis 51(2):131–140

8. Zamorano J, Sanz J, Moreno R, Almeria C, Rodrigo JL, Samede M et al (2001) Comparison of outcome in patients with culture-negative versus culture-positive active infective endocarditis. Am J Cardiol 87(12):1423–1425 [cited 2020 Nov 4]; Available from: https://www.ajconline.org/action/showPdf?pii=S0002-9149%2801%2901570-3

9. Trichine A, Foudad H, Bouaguel I, Merghit R (2015) 0175: Reassessment of blood culture-negative endocarditis: its profile is similar to that of blood culture-positive endocarditis. Arch Cardiovasc Dis Suppl 7(1):46–47

10. Lam JC, Fonseca K, Pabbaraju K, Weatherall BL (2019) Case report: Bartonella quintana endocarditis outside of the Europe-African gradient: comprehensive review of cases within North America. Am J Trop Med Hyg 100(5):1125–1129

11. Edouard S, Nabet C, Lepidi H, Fournier P-E, Raoult D (2015) Bartonella, a common cause of endocarditis: a report on 106 cases and review. J Clin Microbiol 53(3):824–9

12. Western Cape Government (2017). City of Cape Town 2017. Available from: https://www.westerncape.gov.za/assets/departments/treasury/Documents/Socio-economic-profiles/2017/city_of_cape_town_2017_socio-economic_profile_sep-lg_-_26_january_2018.pdf. Accessed 01/12/2020

13. Wharton G, Steeds R, Allen J, Phillips H, Jones R, Kanagala P et al (2015) A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. Echo Res Prac 2(1):G9–G24

14. Wheeler R, Steeds R, Rana B, Wharton G, Smith N, Allen J et al (2015) A minimum dataset for a standard transoesophageal echocardiogram: a guideline protocol from the British Society of Echocardiography. Echo Res Prac 2(4):G29–G45

15. Meel R, Essop MR (2018) Striking increase in the incidence of infective endocarditis associated with recreational drug abuse in urban South Africa. S Afr Med J 108(7):585 Available from: http://www.samj.org.za/index.php/samj/article/view/12330

16. Moodley VM, Zeeman MTS, van Greune CHJ, Corcoran C (2016) Culture-negative endocarditis due to Bartonella quintana. S Afr Med J 106(5):470–471 Available from: http://www.scielo.org.za/pdf/samj/v106n5/29.pdf

17. Raoult D, Gouriet F, Casalta J-P, Lepidi H, Chaudet H, Thuny F et al (1996) Diagnosis of 22 new cases of Bartonella endocarditis. Ann Intern Med 125(8):646–652

18. Pachirat O, Prathanee S, Watt G (2018) Echocardiographic features in Bartonella endocarditis: a case series. Cardiol Res 9(2):116–119

19. Nakasu A, Ishimine T, Yasumoto H, Tengan T, Mototake H (2018) Infective endocarditis associated with Bartonella henselae: a case series. IDCases 12:127–129

20. Bartonella Serology interpretation [Internet]. [cited 2020 Nov 10]. Available from: https://www.childrensmon.org/references/Lab/serology/bartonella-antibody.pdf

21. Ghidiey FY, Igbinosoa O, Mills K, Lai L, Woods C, Ruiz ME, et al. Case Series Case series of Bartonella quintana blood culture-negative endocarditis in Washington, DC.

22. Pournier P-E, Gouriet F, Casalta J-P, Lepidi H, Chaudet H, Thuny F, et al. (2020) Blood culture-negative endocarditis improving the diagnostic yield using new diagnostic tools. 2017; Available from: https://doi.org/10.1097/MID.0000000000008392

23. Silverman ME, Upshaw CB (2007) Extracardiac manifestations of infective endocarditis and their historical descriptions. Am J Cardiol 100:1801–1807

24. Berdejo J, Shibayama K, Harada K, Tanaka J, Mihara H, Gurudevan SV et al (2014) Evaluation of vegetation size and its relationship with embolism in infective endocarditis: a real-time 3-dimensional transoesophageal echocardiography study. Circul Cardiovasc Imag 7(1):149–154

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