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A Unique Case of *Burkholderia cepacia* Prosthetic Mitral Valve Endocarditis and Literature Review

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Abstract

Burkholderia cepacia prosthetic valve endocarditis (PVE) is extremely rare, with few cases in the literature. A report of a patient with PVE is described, followed by a literature review on *B. cepacia* PVE. A 38 year old man with poor dentition and a history of intravenous drug use (IVDU) and mitral valve replacement was found to have a mitral valve vegetation. Five sets of blood cultures on different days grew *B. cepacia*. Individual sets of blood cultures on different dates also isolated *S. viridans* (outside hospital culture), methicillin-resistant *S. epidermidis* (hospital day 1), and *Bacillus spp.* (hospital day 6). He was successfully treated with ceftazidime and levofloxacin as dual therapy for *B. cepacia* PVE, in addition to vancomycin for gram positive coverage. This case report and review highlights the possibility of *B. cepacia* PVE in immunocompetent patients with poor dentition, with the potential for a successful outcome following combination antimicrobial therapy.

Keywords

Burkholderia cepacia; *Pseudomonas cepacia*; prosthetic valve; infective endocarditis; PVE; ceftazidime; levofloxacin

Background:

Prosthetic valve endocarditis (PVE) accounts for 1% to 5% of all cases of infective endocarditis, and is associated with mortality rates as high as 22.8%[1]. *Staphylococcus aureus* is the most commonly isolated pathogen, but coagulase-negative *Staphylococcus*, *Enterococcus*, and *Streptococcus* are also common causes[1]. *Burkholderia cepacia* PVE is extremely rare, with a limited number of case reports in English-language literature

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previously describing this entity[2–13]. Here we present a case of mitral PVE caused by *B. cepacia* and review the existing literature on this uncommon infection.

Report of a Case:

A 38 year old man with a medical history of poor dentition, intravenous drug use (IVDU), and chronic hepatitis C was admitted for dyspnea. Approximately 6 months prior to presentation, he was diagnosed with native mitral valve endocarditis caused by *Pseudomonas aeruginosa* and *S. viridans*. He underwent mitral valve replacement with a 3 mm St. Jude Epic porcine bioprosthetic valve (St Jude Medical, Inc, St Paul, Minn) and was treated with 6 weeks of intravenous (IV) cefepime and gentamicin. After completing antibiotics, he was re-admitted approximately 4 months prior to the present episode and found to have a mobile mass on his bioprosthetic mitral valve. Blood cultures were negative, but considering his recent history of *Pseudomonas* endocarditis, he was treated empirically with 6 weeks of IV vancomycin and meropenem.

Upon current presentation, he complained of dyspnea for 3 days. He denied recent IVDU, ill contacts, or recent travel. Human immunodeficiency virus (HIV) testing was negative. Toxicology screen was positive for benzodiazepines and oxymorphone. Transthoracic echocardiogram (TTE) showed a mobile mass on the bioprosthetic mitral valve, measuring 3.2 cm x 2.2 cm, with associated mitral stenosis. There was also a possible vegetation on the native aortic valve. Subsequent TEE confirmed a large vegetation encompassing multiple leaflets of the bioprosthetic mitral valve and a highly mobile mass attached to the ventricular side of the left cusp of the aortic valve. Initial antibiotic treatment included vancomycin, ciprofloxacin 400 mg IV every 8 hours, and cefepime 2 g IV every 8 hours. On hospital day 4, therapy was changed to vancomycin and meropenem 2 g IV every 8 hours. Levofloxacin 750 mg PO daily was added to meropenem and vancomycin 4 days after initial treatment. Four separate sets of blood cultures on different days (hospital days 1, 3, 4, 8) grew *B. cepacia*, susceptible to ceftazidime, levofloxacin, and trimethoprim/sulfamethoxazole. One blood culture performed at an outside hospital also grew *B. cepacia*, sensitive to meropenem, ceftazidime, and levofloxacin, and resistant to amikacin, cefepime, ceftriaxone, and gentamicin. Individual sets of blood cultures also isolated *S. viridans* (outside hospital culture), methicillin-resistant *S. epidermidis* (hospital day 1), and *Bacillus spp.* (hospital day 6).

Due to severe periodontal disease, tooth extraction was performed. The patient underwent an embolectomy of the aortoiliac artery for complete occlusion of the distal aorta and bilateral common iliac arteries. The prosthetic mitral valve was replaced while the aortic valve was inspected but left intact. Tissue pathology from the aortoiliac and aortic embolectomy identified gram-positive cocci on gram stain. Additionally, tissue pathology of the explanted bioprosthetic valve was consistent with infective endocarditis and showed cocciform organisms on silver stain that were not identified on Gram stain, likely due to prior antibiotic therapy. *B. cepacia* was the only organism isolated from tissue culture of the explanted bioprosthetic valve, as well as the aortic valve embolectomy.

The patient was treated for *B. cepacia* and *S. viridans* endocarditis. The *Bacillus spp.* in the blood culture of hospital day 6 was also covered by the same agent used to treat *S. viridans*.

Although the patient was initially treated with cefepime and ciprofloxacin, the decision was made to switch to meropenem 2 g IV q8h after three sets of positive blood cultures. After valve replacement, embolectomy, and repeated negative blood cultures, meropenem was changed to ceftazidime to provide a more targeted therapy and decrease unwarranted carbapenem exposure. A single lumen peripherally inserted central catheter was placed after blood cultures were negative. The patient was discharged on ceftazidime 6 g IV continuous infusion daily with oral levofloxacin 750 mg daily for double coverage of *B. cepacia*, and vancomycin for gram positive coverage. The decision to utilize double-coverage for *B. cepacia* was based on the severity and burden of infection, duration of positive blood cultures, and guideline recommendations from the Infectious Diseases Society of America (IDSA), which encourage clinicians to use double gram-negative coverage when treating patients with endocarditis due to non-HACEK gram-negative bacilli[14]. Furthermore, *in vitro* data suggest potential synergy between beta-lactam or carbapenem antibiotics (meropenem or ceftazidime) and fluoroquinolones in the treatment of *B. cepacia*[15]. In a recent study describing the treatment and outcomes of 248 patients over a 17 year period with *B. cepacia* bacteremia, combination therapy was utilized in 29% of cases, most commonly with fluoroquinolone containing regimens (59%)[16]. While *B. cepacia* was the most likely primary pathogen responsible for PVE, this patient's high-risk situation with second valve placement, as well as the gram positive cocci seen on aortic thrombus tissue Gram stain, resulted in the use of vancomycin to cover methicillin-resistant *S. epidermidis*, *Bacillus spp.*, and *S. viridans*.

The patient completed a 6 week course of IV antibiotics. Blood cultures following prosthetic mitral valve replacement were negative. Blood cultures continued to remain negative when checked two weeks after completion of the antibiotic course. Four months later, he was re-admitted for mitral valve endocarditis and multiple brain abscesses, with blood cultures growing *S. viridans* and *Candida albicans*.

Search Strategy:

A review of the existing English-language literature of *B. cepacia* PVE was conducted. All articles yielded by the search terms "*Burkholderia cepacia* endocarditis" and "*Pseudomonas cepacia* endocarditis" using PubMed (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD, USA) were reviewed and included if they focused on PVE. Additionally, Google Scholar was used with the search term "*Burkholderia cepacia* endocarditis." In order to confirm that all journals were discovered, Google Search engine was used for a final search using the terms "prosthetic valve endocarditis burkholderia." References in all relevant articles were reviewed to yield additional articles. Previous reports of *B. cepacia* PVE are summarized in Table 1. For the article Aggarwal, *et al*. only the abstract was available, therefore data appearing in the Literature Review Table are only from the abstract[7]. This literature review is current through August 18, 2018.

Review of Existing Literature:

The *B. cepacia* complex (Bcc) contains at least nine species of Gram negative bacilli. *Burkholderia* species were first described in 1949, as the cause of the maceration, or soft rot, of onion tissue and was originally referred to as *Pseudomonas cepacia*[17]. As a human

pathogen, *Burkholderia* causes respiratory infections in immunocompromised patients, especially those with cystic fibrosis and chronic granulomatous disease[17]. Transmission occurs by aerosol droplet, or by direct physical contact with infected individuals or contaminated surfaces and solutions[17].

Although *B. cepacia* native valve endocarditis has been reported multiple times[4,18], there are few case reports that describe PVE caused by *B. cepacia* (Table 1)[2–13]. To our knowledge, only 15 patients have been previously reported in the English-language literature suffering from *B. cepacia* PVE. One abstract briefly mentioned two cases of *B. cepacia* PVE, but details about the patient were not described[13]. Three other cases were found in two non-English-language reports[11,12]. One case report described a renal transplant patient with *B. cepacia* endocarditis associated with an intracardiac fragment of a catheter[19]. Patient age, sex, prosthetic valve site, antibiotic therapy, if valve replacement was required, and outcome for 13 prior patient reports are outlined (Table 1). The most common valve affected was the mitral valve. Patient ages ranged from 25–75 years old, and males were affected slightly more often than females. Most treatment regimens included trimethoprim combined with sulfamethoxazole as the mainstay of therapy, with additional agents including penicillins, carbepenems, cephalosporins, kanamycin, and polymyxin B[2–10]. Currently, no specific treatment guidelines exist. Although most case reports described treatment regimens containing trimethoprim/sulfamethoxazole, this patient was treated with ceftazidime and levofloxacin, based on the most current *in vitro* data and IDSA guidelines regarding treatment of endocarditis due to non-HACEK gram-negative bacilli.

Discussion:

This case highlights the possibility of *B. cepacia* PVE in immunocompetent patients. The patient denied IVDU, but the toxicology screen was positive for opiates. IVDU remains the most likely cause of PVE. However, the patient did have a history of impaired tooth enamelization, leading to carious teeth with chronic apical infections and need for multiple extractions. It is speculative that his poor dentition increased his risk for *Burkholderia*, with one study citing the presence of *Burkholderia* on microbiologic characterization of the apical portion of teeth[20]. Another potential etiology in this patient is his distant history of IV drug use, with a previous report of *B. cepacia* endocarditis in five patients after heroin use[4].

Treatment guidelines for *Burkholderia* PVE do not exist. We present a successful outcome with an antibiotic treatment regimen consisting of ceftazidime and oral levofloxacin as dual therapy for *B. cepacia* PVE, in addition to vancomycin for gram positive coverage.

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Table 1.

A Review of the Literature on Prosthetic Valve Endocarditis secondary to *Burkholderia Cepacia*

Patient Age	Patient Sex	Prosthetic Valve	Therapies	Valve Replacement for Treatment	Outcome	Reference
38	M	Mitral	ceftazidime, vancomycin, levofloxacin	Yes	Survival	Present Case
55	M	Mitral	Co-trimoxazole*, kanamycin	No	Death (reportedly unrelated to infection)	2
48	F	Mitral	Co-trimoxazole (10 months), kanamycin	No	Survival	2
38	Unknown	Tricuspid	Trimethoprim, sulfanamide, polymyxin B#	Yes	Death	3
42	M	Aortic	S-T-P^	Yes	Death (10 months post treatment)	4
25	M	Mitral	S-T-P^	Yes	Survival	4
54	F	Mitral	Piperacillin and tazobactam, then 30 days later imipenem and cilastin	No	Death	5
71	M	Aortic	Meropenem	No	Death	5
75	F	Mitral	Cefepime, trimethoprim-sulfamethoxazole	Yes	Survival	6
58	F	Mitral	Trimethoprim-sulfamethoxazole	Unknown	Unknown	7
28	F	Mitral	Trimethoprim-sulfamethoxazole, levofloxacin, ceftazidime	Yes	Survival	8
56	M	Mitral	Imipenem, vancomycin	Yes	Survival	9
47	M	Aortic	Caspofungin, cefepime	No	Survival	10

*co-trimazole: 80mg trimethoprim plus 400mg sulfamethoxazole

#Antibiotic history: chloramphenicol (3 weeks), but fever recurred six months later. Patient was then treated with TMP, sulfisoxazole (4 months). Blood cultures were still positive, and fever recurred. The patient was then treated with chloramphenicol, amphotericin B, and valve replacement. Post-op therapy included polymyxin B, amphotericin B, and chloramphenicol, followed later by polymyxin B and sulfadiazine. Antibiotics were stopped due to signs of an adverse drug reaction, and the valve was again replaced. Postoperative treatment consisted of sulfisoxazole, trimethoprim, and polymyxin B.

^Trimethoprim 960mg; sulfamethoxazole 4.8g; and polymyxin B 2 mg/kilograms daily