‘TAVR Infected Pseudomonas Endocarditis’: a case report

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Abstract: Pseudomonas aeruginosa (P. aeruginosa) rarely causes infective endocarditis (IE), previously reported for approximately 3% of all patients with IE.¹ Most commonly, the infection occurs in intravenous drug users (IVDU) as right-sided endocarditis, noting presentations of P. aeruginosa IE without history of intravenous drug to be extremely rare, finding only a few cases reported in the literature. However there are increasing reports of cardiovascular implantable electronic device–related and prosthetic heart valve infections caused by this pathogen in non-IVDUs.² This report will focus on the clinical presentation, management, and outcome of P. aeruginosa endocarditis in an 89-year-old patient with a transcatheter aortic valve replacement (TAVR). Medical management was pursued due to the patient’s underlying comorbidities. Long-term suppressive antibiotic therapy with delafloxacin was successful in maintaining negative blood cultures, despite an allergy to levofloxacin and ciprofloxacin.

Plain Language Summary

An 89-year-old male was admitted to our hospital after he was diagnosed with a blood stream infection. The initial identification noted gram-negative organisms consistent with Pseudomonas Aeruginosa so the patient was started on intravenous (IV) antibiotics. He improved after the antibiotics started and was discharged to a nursing facility to complete his antibiotics course. While at the facility, after he had finished his antibiotics, he started to become ill again. He was brought back to the hospital to be evaluated. His repeat blood cultures again grew P. Aeruginosa. This suggested that his infection had not been cleared the first time and most likely he had a source of bacterial growth. A few years prior, a transcatheter aortic valve replacement (TAVR) had been performed for the patient. This was suspected as the source of continued infection and so a transthoracic echocardiogram was obtained, which revealed vegetation on the TAVR. We also obtained a magnetic resonance imaging (MRI) of the brain, which demonstrated infarcts of several portions of the brain consistent with emboli. Due to his age and additional medical issues, the patient was not a candidate for surgical valve replacement. We decided to try medical therapy with a fluoroquinolone antibiotic since the bacteria was susceptible to it. Unfortunately, he had demonstrated allergies to the usual choices to include Levaquin and ciprofloxacin. Therefore, we elected to start him on a new fluoroquinolone agent that had recently been FDA approved and obtained by our facility called delafloxacin. The patient tolerated this well and his repeat blood cultures remain clear. After discussion with the infectious disease specialist, he requires a lifelong suppression with the medication since the TAVR cannot be removed. This case is meant to illustrate the effectiveness of medical therapy when surgical options are not available.

Keywords: infective endocarditis, non-IV drug user, Pseudomonas aeruginosa, TAVR

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Case report

An 89-year-old man was admitted to this hospital initially with findings suggestive of aspiration pneumonia and associated *Pseudomonas aeruginosa* (*P. aeruginosa*) bloodstream infection.

The patient presented with a known history of chronic obstructive pulmonary disease (COPD), stage 3 chronic kidney disease, congestive heart failure with preserved ejection fraction, and severe aortic stenosis treated 2 years prior with transcatheter aortic valve replacement. He described an episode of nausea with meal regurgitation two days prior to presentation after which he developed shortness of breath. His vital signs were: temperature 37.1, heart rate 88, blood pressure 94/60, oxygen saturation 96% on room air. Computed tomography (CT) of his chest was notable for frothy material in trachea, filling defect in minor subsegmental bronchus, and patchy bibasilar reticular and consolidative opacities suggestive of aspiration pneumonia. No murmurs were detected. He had decreased breath sounds bilaterally with crackles in the right base. Upon recognition of a gram-negative bacillus bloodstream infection, carbapenem therapy was initiated and the patient subsequently demonstrated clinical improvement. The blood culture pathogen was identified as *P. aeruginosa*, susceptible to cefepime and there was no additional pathogen recovery from blood culture at 72h, nor identified complicating features. He was able to discharge to skilled nursing for continued cefepime dosing, planned for 10 days from the date of negative surveillance blood cultures.

Following discharge, the patient was presumed to have completed his prescribed antibiotic course; however, had a decline in his health status within 2 weeks after scheduled completion, prompting return for admission. Upon re-hospitalization, the patient was reported to have increasing shortness of breath and lethargy. Vital signs upon second presentation were: temperature 36.9, heart rate 91, blood pressure 109/57, and oxygen saturation 96% on room air. Physical exam was notable for physiologic splitting of S2, grade 3/4 diastolic murmur at the left sternal border, grade 3/4 systolic murmur. No abnormal breath sounds. Review of blood culture results from the previous admission found that his final surveillance cultures returned positive at 113h. Blood cultures were repeated and again returned with the same *Pseudomonas* isolate as prior. With the previous prolonged positivity of blood cultures and current suspicion for prolonged bacteremia in the absence of continued antibiotic therapy, transthoracic echocardiography (TTE) was sought and demonstrated a large mobile mass on the mitral valve and moderate–severe paravalvular prosthetic aortic regurgitation, both of which were concerning for infective endocarditis in context of persistent bacteremia (Figure 1). CT of the brain or head demonstrated an evolving, subacute right posterior cerebral artery territory infarction and follow-up magnetic resonance imaging of the brain found multiple small foci of restricted diffusion suggestive of emboli (Figure 2). No emboli were found on CT of the chest, abdomen, or pelvis.

The organism susceptibility profile demonstrated expected coverage by all-antipseudomonal therapies with exception of ciprofloxacin having a minimum inhibitory concentration (MIC) of $\leq 1 \mu g/mL$, reported as intermediate susceptibility by the 2019 Clinical and Laboratory Standards Institute (CLSI) Guidelines. In addition, the patient had a remote reported history of ‘tongue swelling’ following levofloxacin use, thus considered a high-risk allergy. The patient was started on piperacillin/tazobactam, dosed for renal function at 3.375g via extended infusion every 8h, and gentamicin per traditional dosing. He was determined by multiple cardiothoracic surgeons to be a poor surgical candidate, thus medical therapy alone was pursued. Surveillance blood cultures cleared within 48h and dual antibiotic therapy continued for another 6 weeks. TTE was repeated, demonstrating persistence of the mitral valve vegetation, with limited visualization of the aortic valve. By that time, subsequent susceptibility testing against delafloxacin had been completed showing an MIC of 0.5µg/mL, consistent with susceptibility. The patient tolerated dosing of this agent despite his reported levofloxacin allergy. He was initially placed in hospice, but graduated after 6 months. After 7 months, the patient was admitted to an outside hospital with hypoxia and altered mental status. He was treated for sepsis with broad antibiotic coverage, including delafloxacin. After several days of treatment without improvement, the patient was again transitioned to hospice, but expired prior to being discharged. Blood cultures remained negative throughout.

Discussion

*P. aeruginosa* is a deadly opportunistic microbe with a high mortality rate.\(^1,2\) This bacterium was first isolated by Gessard from green pus in 1882
Figure 1. Axial diffusion weighted imaging (DWI) demonstrated multiple punctate, T2 hyperintense foci within the centrum semiovale bilaterally, as well as the subcortical white matter of the right frontal lobe. Corresponding hypointense foci on apparent diffusion coefficient mapping (ADC, not shown) confirmed restricted diffusion. In the context of the patient’s known endocarditis, these findings were concerning for septic emboli. (a) PSAX view of aortic valve with what would be classically called moderate paravalvular regurgitation (10–20% of circumference), (b) apical two-chamber view of oscillating mitral valve mass, (c) apical four-chamber view showing mobile mass on mitral valve with mitral annular calcification, and (d) two distinct paravalvular regurgitant jets on apical windows.

Figure 2. Axial gradient recall echo (GRE) imaging demonstrated multiple punctate foci of magnetic susceptibility consistent with microhemorrhages, likely reflecting additional sequela of small emboli.
and then documented in the literature in 1899 by Reyes et al.\(^1\) It is an opportunistic pathogen with a wide range of clinical presentations from major burn wound infections to bacteremia and infective endocarditis.\(^{1,2}\) Our case of prosthetic valve Pseudomonas endocarditis demonstrates the difficulty managing a highly virulent organism in a frail elderly patient and describes our approach utilizing medical therapy alone.

In the United States, the incidence of IE increased steadily from 11 to 15 per 100,000 population and the proportion attributed to gram-negatve bacteria increased from 5.3% to 8.2%.\(^2,3\) Prosthetic valve endocarditis (PVE) accounts for about 10% of all IE cases with Pseudomonas IE becoming increasingly common.\(^2\) Halabi et al.\(^4\) and Alabdelly et al.\(^5\) both reported a rare fulminant case of P. stutzeri PVE resulting in early mortality. Casalta et al.\(^6\) reported a case of PVE caused by P. luteola after cardiac surgery leading to replacement of the aortic bioprosthetic valve. Similar reports of other Pseudomonas species prosthetic valve infections,\(^7-11\) as shown in Table 1, have been reported in the literature with a noted common theme of increased morbidity and mortality. While Pseudomonas species are rarely implicated as a cause, P. aeruginosa is the most common isolated pathogen.\(^2,4-11\)

About 90–95% of patients with P. aeruginosa IE are intravenous drug users; however, rarely we can see this in non-IV drug users. Recent literature has shifted toward demonstration of nosocomial or health-care associated infections as a cause of the increasing rates of infection. A cohort study conducted by Morpeth et al. noted that of non-HACEK IE, only 4% were due to IV drug use.\(^1,4\) A subsequent Italian study noted that the most frequent source of IE for gram-negative bacteria was due to a genitourinary source.\(^2\) Lin et al. in their cohort study reported that 56% of patients with P. aeruginosa IE had a history of invasive procedures and noted a higher rate of relapse and mortality among patients who were initially diagnosed with P. aeruginosa IE.

In the case of our patient, we suspect initial bacteremia occurred secondary to frequent aspiration in a patient with multiple prior health-care exposures, with the recurrent bacteremia secondary to endocarditis. In addition, it has been recognized that certain risk factors may increase the rate of relapsed IE and include male sex and older age, both of which apply to our patient. Other risk factors include intravenous drug use, congenital and rheumatic heart disease, prior episodes of endocarditis, and dialysis.\(^1\)

The clinical presentation and diagnosis of infective endocarditis can be difficult but even more so for infections with P. aeruginosa. The early stages of infective endocarditis often lack distinct clinical findings and patients often present with generalized non-specific symptoms.\(^3\) The classical findings of the Duke criteria to include fever, new murmurs or worsening known murmur, and cutaneous manifestations are almost absent in some patients.\(^3\) Echocardiography (transthoracic and transesophageal) remains the first-line imaging modality to evaluate for infective endocarditis given wide availability and ability to simultaneously evaluate for both visible evidence of infective endocarditis (vegetation, abscess, prosthetic valve dehiscence) and to evaluate for hemodynamic sequel of infective endocarditis that have implications on need for surgical management. Leukocyte-labeled SPECT/CT and 18-fluorodeoxyglucose positron emission tomography/CT (\(^18\)FDG-PET/CT) are becoming increasingly utilized in patients where there is diagnostic uncertainty by echocardiography alone, particularly in those patients with implantable cardiac devices (pacemakers, defibrillators, and prosthetic valves) and possible infective endocarditis by modified Duke criteria. Pizzi et al. demonstrated that \(^18\)FDG-PET/CT was able to reclassify 90% of cases initially labeled as possible IE with Duke criteria alone and provide a conclusive diagnosis (definite/rejected) in 95% of cases. Utilization of \(^18\)FDG-PET/CT angiography rather than \(^18\)FDG-PET/non-enhanced CT provided further diagnostic clarity and allowed for simultaneous detection of anatomic lesions.\(^12\) In patients with PVE, \(^18\)FDG-PET/CT also has prognostic implications in patients with PVE with increased composite in-hospital death, 1-year death, recurrence of IE, acute valvular insufficiency, symptomatic embolic events on antibiotic therapy, and rehospitalization for cardiovascular indication in those patients with moderate–intense FDG uptake compared with those with negative-low FDG uptake.\(^13\)

P. aeruginosa is a virulent pathogen with the ability to express a number of toxic factors that results in deleterious effects. The treatment of Pseudomonas endocarditis can be very difficult for a multitude of reasons to include the ability to form biofilm, evade antimicrobial agents, and develop resistance to
Table 1. Summary of prior case reports.

| Cases                                                                 | Country   | Year of publication | Valve                     | Antibiotics used                                                                                       | Outcome                          | Source of infection            | Time after cardiac surgery |
|----------------------------------------------------------------------|-----------|---------------------|---------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------|-------------------------------|---------------------------|
| Multidrug-resistant *Pseudomonas aeruginosa* causing prosthetic valve endocarditis: a genetic-based chronicle of evolving antibiotic resistance | USA       | 2016                | Prosthetic aortic         | Meropenem, ceftazidime, amikacin, pipercillin/tazobactam, colistin, rifampin, doxycycline             | AV replaced, survived           | Not identified                | 24 h                      |
| Convexity subarachnoid hemorrhage, *Pseudomonas Aeruginosa* (PA) infective endocarditis and left atrial appendage occluder (LAAO) device infection | France    | 2017                | LAAO                      | Cefotaxime, ciprofloxacin, amikacin                                                                   | Cured, died 3 days after discharge | Not identified                | 30 months                 |
| Prosthetic valve endocarditis caused by *Pseudomonas aeruginosa* with variable antibacterial resistance profiles: a diagnostic challenge | Switzerland | 2019                | TAVR                      | Ceftriaxone, amoxicillin-clavulanate, piperacillin-tazobactam, ceftazidime, meropenem, gentamicin, cefepime, tobramycin, ciprofloxacin | Valve replaced, cured           | Not identified, possible CAUTI | 1 year                    |
| 18 F-FDG PET-CT for diagnosing prosthetic device–related infection in an infant with CHD | Japan     | 2021                | RV–PA conduit             | Cefozopran, ceftazidime                                                                               | Replaced conduit, cured         | Surgical infection, mediastinitis | 4 days                    |
| Combined computed tomography and fluorodeoxyglucose positron emission tomography in the diagnosis of prosthetic valve endocarditis: a case series | Italy     | 2014                | Prosthetic aortic         | Clindamycin, meropenem, levofloxacin, meropenem, ciprofloxacin                                       | Replaced, cured, chronic suppression | Not identified, CAP           | 1 month 1 year            |
| Relapsing tricuspid valve endocarditis by multidrug-resistant *Pseudomonas aeruginosa* in 11 years: tricuspid valve replacement with an aortic valve homograft | South Korea | 2015                | Native tricuspid, prosthetic tricuspid twice | Meropenem, colistin, ciprofloxacin, rifampin, ceftazidime                                             | Valve replaced, cured           | Not identified                | 10 years, 10 months       |
| Prosthetic valve endocarditis caused by *Pseudomonas luteola*         | France    | 2005                | Prosthetic aortic         | Ticarcillin/clavulanic acid, gentamicin                                                             | Valve replaced, recovered       | Unknown                       | 16 months                 |
| *Pseudomonas stutzeri* prosthetic valve endocarditis: A case report and review of the literature | Lebanon   | 2018                | Prosthetic aortic valve, native tricuspid | Amoxicillin/clavulanate, gentamicin, vancomycin, rifampin, ceftazidime                                 | Died after surgical valve replacement | Renal calculus                | N/A                      |
| A relapsed *Pseudomonas stutzeri* prosthetic valve endocarditis: a case report and review of the literature | Saudi Arabia | 2021                | Bioprosthetic mitral valve | Zosyn, ciprofloxacin, ceftazidime,                                                                  | Cured after valvular replacement | Unknown                       | 1 month                   |
| Expect the unexpected: a rare case of *Pseudomonas aeruginosa* endocarditis | USA       | 2020                | Aortic                    | Zosyn, ciprofloxacin, cefepime, tobramycin                                                           | Recovered with indefinite antibiotic therapy, lost to follow-up | UTI calculus                  | N/A                      |

AV, aortic valve; CAP, community-acquired pneumonia; CAUTI, catheter-associated urinary tract infection; CHD, congenital heart defect; FDG, fluorodeoxyglucose; N/A, not available; PA, *Pseudomonas aeruginosa*; PET, positron emission tomography; RV–PA, right ventricle to pulmonary artery; TAVR, transcatheter aortic valve replacement; UTI, urinary tract infection.
multiple classes of antibiotics before and during the course of treatments. The ability to form resistance to antibiotics can be postulated to be due to plasmid exchange with acquisition of genetic data or select mutations under exquisite pressure with expression of new chromosomal DNA. Further complicating the utility of beta-lactams, certain strains producing a metallo-beta-lactamase have been demonstrated as reported by Kato et al. Due to the diagnostic challenges of multiple strains, molecular mechanisms such as whole genome sequencing are becoming necessary to assist in epidemiology, course of the disease, and identify resistance patterns. In the case of our patient, the cultured strain demonstrated a favorable susceptibility profile, maintaining susceptibility to all antipseudomonal agents throughout subsequent cultures with exception of ciprofloxacin, for which an intermediate interpretation persisted.

Understanding that our patient was unlikely to achieve cure with medical therapy alone and was not a surgical candidate, long-term antibiotic suppression therapy was considered, but oral options were limited owing to the patient’s reported allergy and the susceptibility result for ciprofloxacin. At this time, there remain no reliable oral antibiotic treatment options for P. aeruginosa outside of the fluoroquinolone class.

Delafloxacin is a novel anionic fluoroquinolone approved for the treatment of both acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia in adult patients. The unique structure of delafloxacin allows for increased intracellular and biofilm penetration as well as increased potency in acidic environments making it a promising agent for infections due to abscesses and/or high biofilm burden. Unlike other fluoroquinolones, delafloxacin has equal affinity for both DNA gyrase and topoisomerase IV contributing to its broad-spectrum of activity against gram-positive and gram-negative bacteria including P. aeruginosa. This dual-targeted mechanism may reduce the selection of resistant organisms. Gram-negative bacteria resistant to other fluoroquinolones have been shown to retain susceptibility to delafloxacin.

Fluoroquinolone cross-reactivity data remains inconclusive and is limited to case reports. There are currently four generations of fluoroquinolones and this classification is based on chemical structure, spectrum of activity, and pharmacokinetic properties. Ciprofloxacin, levofloxacin, and delafloxacin belong to second, third, and fourth generation, respectively. The cross-reactivity of fluoroquinolones could potentially be attributed to similar structure of the core ring and side chains at N1, C7, and C8 positions. Delafloxacin has three key structural differences compared with other fluoroquinolones and these include a heteroaromatic substitution at the N-1 position, lack of a strong basic group at the C-7 position, and addition of a chlorine at the C-8 position. Although data are conflicting, it may be prudent to use delafloxacin in patients reporting an allergy to a second- or third-generation fluoroquinolone when alternatives are lacking.

This case represents an uncommon, but increasingly recognized infection syndrome that is complicated by low probability of cure, limited antibiotic treatment options with high potential for resistance, and high rates of mortality. Our patient presented with multiple risk factors predisposing to infective endocarditis as well as increased mortality risk. Though he did not demonstrate the typically associated urinary colonization with P. aeruginosa as his predisposing infection risk, the patient’s recurrent aspiration set him up for pulmonary infection of this water-associated pathogen. With low expectation of cure in a patient who is not a candidate for cardiac valve surgery, indefinite oral antibiotic suppression following the standard treatment course is often considered. Owing to the availability of a novel fluoroquinolone, we were able to provide a suppression course despite the increased MIC to ciprofloxacin and reported allergy history.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Verbal and written informed consent was obtained from the patient for the publication of this case report and accompanying images.
Author contributions
Francis Essien: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.
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Timothy Wall: Investigation; Writing – original draft; Writing – review & editing.
John Madden: Investigation; Methodology; Writing – review & editing.
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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supplemental material
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