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Uncertainty of Treatment of *Serratia marcescens* Endocarditis

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Authors' contributions

This work was carried out in collaboration among all authors. Authors MG and JK identified and analyzed the patient cases and wrote the first draft of the manuscript. Authors MS and KML managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aim: To discuss two patient cases of *Serratia marcescens* endocarditis and the paucity of literature regarding treatment options.

Presentation of Case: Patient 1 was a 29-year old male who presented with native mitral valve *Serratia marcescens* endocarditis presumed secondary to intravenous drug use. He was empirically treated with vancomycin and piperacillin/tazobactam then transitioned to meropenem and gentamicin 1 mg/kg every 8 hours. He was maintained on vancomycin monotherapy for days 4-14. Gentamicin was restarted on hospital day 14 at 7 mg/kg every 36 hours for 6 weeks. He underwent mitral valve replacement on hospital day 20. He was readmitted on day 42 with splenic lesions and enlarging mycotic aneurysms. Patient 2 was a 38-year old male with native aortic valve *Serratia marcescens* endocarditis with septic emboli presumed secondary to intravenous drug use. He was treated with vancomycin and cefepime then was transitioned to ceftriaxone and levofloxacin. The patient underwent aortic valve replacement on hospital day 3 and was transitioned to meropenem and levofloxacin for 6 weeks.

Discussion: The treatment strategies for both patients demonstrates that the optimal treatment strategy for *Serratia marcescens* endocarditis remains unclear. The gentamicin dosing for patient 1 demonstrates "synergy" and extended-interval dosing. Despite both dosing strategies being used, the patient continued to exhibit complications of the infection. Patient 2 demonstrates successful

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treatment of the infection with surgical intervention and a carbapenem/fluoroquinolone regimen.
Conclusion: These cases demonstrates that much remains unclear in the treatment of *Serratia marcescens* endocarditis and more studies and case reports are needed.

Keywords: Serratia; endocarditis; mycotic aneurysms.

1. INTRODUCTION

Bartolomeo Bizio, a pharmacist, first cultivated and reported a reddish coloration from a microorganism on fresh polenta in 1819. He named the discovered bacteria *Serratia marcescens*. *Serratia spp.* are a group of gram-negative bacilli and a part of the Enterobacterales group. Readily found in the environment, *S. marcescens* frequently resides in soil and water and is also associated with plants, insects, and animals [1]. It is also considered to be a human pathogen which was originally thought to be opportunistic, nosocomial, and related to intravenous drug abuse [1,2]. *S. marcescens* has been isolated in human wounds, urinary tracts, central nervous systems, respiratory tracts, bloodstreams, and heart valves. However, it is only associated with ocular infections as a primary bacterium [1,3]. *S. marcescens* is an intrinsically resistant bacterium which can potentially produce AmpC beta-lactamase and extended-spectrum beta-lactamase leading to a lack of potential treatment options [1,4,10]. Treatment regimens are guided by known susceptibilities, inducible resistance patterns, and penetration of antibiotic into the targeted infection site. Current guidelines for non-HACEK infective endocarditis recommend combination antibiotic therapy with a beta-lactam and either an aminoglycoside or fluoroquinolone although they address the lack of data considering the rarity of this infection (Table 1). Additionally, they do not have recommendations specifically for *Serratia spp* [4]. Given the morbidity and mortality of S*erratia spp*. endocarditis and the intrinsic resistance and virulence of *Serratia spp.,* more clinical data regarding dosing regimens and attaining their pharmacokinetic and pharmacodynamic goals is needed. This article presents two patient cases of *Serratia marcescens* infective endocarditis treated at a tertiary academic medical center.

2. PATIENT CASE 1

A 29-year old male with past medical history significant for intravenous drug use presented from an outside hospital with native mitral valve endocarditis for consideration of mitral valve replacement. Before presentation, he was noted to be confused and fatigued with dysuria and poor oral intake. Upon presentation, he was afebrile, tachycardic, and mildly hypotensive with systolic blood pressure ranging from 90-100 mmHg. His physical exam was otherwise unremarkable. Blood cultures at the outside hospital grew *Serratia marcescens* in three of four bottles and were reported to be susceptible to meropenem, ciprofloxacin, and levofloxacin. A CT head scan showed possible septic emboli in the cerebellum while a CT abdomen and pelvis showed bilateral pyelonephritis. TTE showed a 14x10 mm vegetation on the anterior mitral leaflet with severe posterior mitral regurgitation.

The patient was empirically treated with vancomycin (trough goal 15-20 ug/mL) and piperacillin/tazobactam. Once cultures and susceptibilities resulted, the patient was transitioned to meropenem 2 g intravenously (IV) every 8 hours and gentamicin 1 mg/kg actual body weight IV every 8 hours and was continued on this regimen for days 2-4 when the gentamicin was discontinued. Vancomycin was re-initiated on days 4-14 for empiric Gram positive coverage but was discontinued after a negative MRSA swab [11]. Gentamicin was restarted on day 14 for additional gram-negative coverage at a dose of 7 mg/kg actual body weight IV every 36 hours based on pharmacokinetic optimization calculations. Gentamicin troughs on this regimen were: 0.7, 0.9, <0.5, and <0.5 ug/mL. The patient underwent mitral valve replacement on day 20 of hospitalization and was continued on gentamicin and meropenem for a total duration of 6 weeks.

Intermittent low-grade fevers were present during treatment, however all cultures remained negative after the initial culture. White blood cell counts down-trended from days 5 to 16 and remained stable thereafter. He was discharged to a rehab facility on day 42. He was readmitted 2 days later with splenic lesions and enlarging mycotic aneurysms and underwent embolization. He represented a month later with altered mental status, fever, and tachycardia of unclear origin that rapidly resolved.

Table 1. Publications of *Serratia marcescens* endocarditis

Citation	Presentation	Treatment	Result
Mills J, Drew D. *Serratia marcescens* endocarditis: A regional illness associated with intravenous drug abuse. Ann Intern Med. 1976;84(1):29-35. [5]	• 19 cases observed between 1969-1974 in the San Francisco Bay area • 17/19 patients were used illicit intravenous substances	• Aminoglycoside alone or in combination with ampicillin, carbenicillin, or chloramphenicol • The most successful antibiotic therapies were gentamicin (6 mg/kg per day) combined with carbenicillin (30 g/day) or chloramphenicol (3-4 g/day)	• 6/19 patients survived • 3 patients each survived with combination therapy of gentamicin with carbenicillin or chloramphenicol
Baggish AL, Nadiminti H. Intracranial abscess from embolic *Serratia marcescens* endocarditis. Lancet Infect Dis. 2007;7(9):630. [6]	• 43-year old female with past medical history of a distant splenectomy secondary to mononucleosis presented with headache, fevers, night sweats, gait instability, and a cardiac murmur • MRI showed a 1.9x2.4 cm parietal lobe lesion. TTE showed 1x1x2 cm sessile mass from anterior leaflet of the mitral valve	• Cefepime 1g Q12H for 6 weeks • Gentamicin 80mg Q8H for 2 weeks	• Complete resolution
Hadano Y, Kamiya T, Uenishi N. A fatal case of infective endocarditis caused by an unusual suspect: *Serratia marcescens*. Intern Med. 2012;51(11):1425-8. [7]	• 85-year old women with diabetes mellitus and hypertension admitted for fever and general fatigue • MRI showed multiple acute cerebral infarctions. TEE showed a 20x10 mm floppy vegetation on the mitral valve with severe regurgitation.	• Days 1-2 the patient was treated with ampicillin-sulbactam • Gentamicin was added days 3-7 and stopped for acute renal failure • Ceftazidime administered from day 3-42	• Expired on day 65 due to uncontrolled heart failure
Marvelous but Morbid: Infective endocarditis due to *Serratia marcescens* Phadke et al. Infect Dis Clin Pract (Baltim Md). 2016 May ; 24(3): 143–150. [8]	• 46-year old man with a history of human immunodeficiency virus (HIV), hepatitis C infection, HSV keratitis, chlamydia urethritis, IVDU, and syphilis. • Presented with fever and myalgias. Ten days prior to presentation he sought care at an outpatient clinic for fevers as high as 39.3°C, myalgias, and migratory arthralgias • TEE demonstrated a large 1.7×1.1 cm mobile vegetation on the anterior mitral leaflet/annulus with leaflet perforation, severe mitral regurgitation and a left ventricular ejection fraction of 60%. MRI showed multiple embolic infarctions.	• Started empirically on ceftriaxone and changed to high dose meropenem for treatment of infective endocarditis due to *s. marcescens* with cerebral emboli.	• Expired on day 10 of hospitalization
Meyer CG, Vacek TP, Bansal A, Gurujal R, Parikh A. Dynamic Course of Pulmonic Valve Endocarditis Resulting in Submassive PE and Valve Replacement. J Investig Med High Impact Case Rep. 2018;6:2324709618759128. [9]	• 42-year old male with PMH of IVDU and hepatitis C with 1 month history of fevers, chills and weight loss. The patient was in septic shock on admission • TEE showed a mobile 2.5x2.5 cm vegetation attached to the right ventricular outflow tract and PV leaflet. CT scan showed multiple septic emboli. Repeat TEE showed persistent vegetation 1.5x1.5 cm.	• Empiric therapy with vancomycin 1250 mg Q12H and piperacillin-tazobactam 3.375 g Q8H • PV replacement after repeat TEE • Ceftriaxone 2 g daily for 6 weeks from date of initial positive blood cultures	• Discharged to nursing home for completion of IV antibiotics

3. PATIENT CASE 2

A 38-year old male with a past medical history significant for intravenous drug use presented from an outside hospital with aortic valve endocarditis. Blood and urine cultures from outside hospital were positive for *Serratia marcescens*. Blood cultures were found to be sensitive to ceftriaxone, cefepime, ciprofloxacin, and sulfamethoxazole/trimethoprim, while resistant to doxycycline. The patient presented with chest pain and altered mental status. Transesophageal echocardiogram showed evidence of severe aortic insufficiency and a large vegetation on the aortic valve. Other initial imaging and physical findings were significant for evidence of an aortic root abscess, cerebral septic emboli, Osler nodes, multiple Janeway lesions of the distal digits of the hands and feet, splenic infarcts, and renal septic emboli. The patient was initially febrile to 100.8 degrees Fahrenheit on day two of hospitalization however remained afebrile for the remainder of the hospitalization. Of note patient's serum creatinine remained relatively stable ranging from 0.9-1.1 mg/dL throughout admission.

The patient was being treated with ciprofloxacin for a urinary tract infection when he presented to the outside hospital and was then transitioned to vancomycin and cefepime; dosing at outside hospital unclear. He was continued on vancomycin (trough goal 15-20 ug/mL) when transferred to the tertiary academic medical center and cefepime was transitioned to ceftazidime 2 g IV every 8 hours. On day 2 of treatment he was transitioned to ceftriaxone 2g IV every 24 hours and levofloxacin 750 mg IV every 24 hours. Patient underwent bioprosthetic aortic valve replacement and aortic route repair on day 3 of hospitalization. He was transitioned to meropenem 2g IV every 8 hours and levofloxacin 750 mg IV every 24 hours post operatively due to large abscess found in the interventricular septum.

Blood, urine, and valve tissue cultures remained negative throughout hospitalization. He remained hemodynamically stable throughout admission with mild post-operative tachycardia up to 110 beats per minute for which he was started on metoprolol. He was discharged to a rehabilitation center on post-op day 12 for continued cardiopulmonary recovery, pain management and suboxone induction. Patient has since been discharged from rehabilitation center and has completed his six-week course of meropenem and levofloxacin with no further complications.

4. DISCUSSION

Serratia marcescens endocarditis can be difficult to eradicate due to its site of infection and potential for empiric antibiotic resistance. This is further complicated by a lack of consensus regarding the most optimal treatment strategy. This is demonstrated in our literature review detailed in Table 1 and also in the two patient cases presented.

Patient 1 demonstrates the uncertainty in the most optimal dose of gentamicin for *Serratia marcescens* endocarditis. This patient was initially started on gentamicin 1 mg/kg actual body weight IV Q8H which is reflective of the synergy dosing utilized for endocarditis with select gram positive organisms. We were unable to ascertain the rationale for this dosing as it was started at the outside hospital. Upon re-initiation of gentamicin, the dose was adjusted to 7 mg/kg to optimize the pharmacokinetic parameters of the high-dose extended-interval regimen for this gram-negative organism. Despite pharmacologic therapy and clear blood cultures, the patient continued to exhibit complication of the infection through splenic lesions, mycotic aneurysms, fever, and altered mental status. Although it is difficult to say with certainty that these sequalae were caused by persistent *Serratia marcescens* endocarditis, the likelihood appears to be high. It is also difficult to determine if the sequelae were due to inadequate optimization of pharmacokinetic parameters with the initial treatment regimen of gentamicin 1 mg/kg or if the gentamicin 7 mg/kg high-dose extended-interval dosing was not effective. The case begs the question if the same outcome would be reached if the extended interval dosing was started initially or even if the discontinuation of gentamicin for 10 days had an impact. It is difficult to assess the efficacy of gentamicin in this patient since two different dosing strategies were utilized – instead it highlights the current uncertainty regarding the best dosing strategy to use for this particular infection.

Patient 2 demonstrated clinical success after surgical intervention and treatment with meropenem 2 g every 8 hours and levofloxacin 750 mg every 24 hours. To our knowledge, previous trials have not specified dosing of carbapenems or fluoroquinolones in the treatment of *Serratia marcescens* endocarditis. It can perhaps be speculated that this dosing strategy is adequate in the treatment of *Serratia* endocarditis.

However, given that this patient had clear cultures upon presentation from outside hospital and surgical intervention, this cannot be said with certainty.

5. CONCLUSION

Serratia marcescens endocarditis remains a relatively uncommon infection and the consensus regarding optimal treatment remains unclear. The intrinsic resistance of the bacterium and site of infection may confer difficulty in eradication. The existing cases, including the two presented here, outlines two very different treatment options of *Serratia marcescens* endocarditis. More studies and case reports are needed to better detail optimal drug treatment and dosing.

CONSENT

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

The authors have no disclosures concerning relationships with entities that may have a direct/indirect interest in the subject matter of this presentation.

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