IDCases 19 (2020) e00726

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

Successful treatment of relapsed enterococcal endocarditis with amoxicillin/clavulanate: A case report

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ARTICLE INFO

Article history:
Received 14 February 2020
Received in revised form 19 February 2020
Accepted 19 February 2020

Keywords:
Enterococcus
Endocarditis
Oral
Augmentin
Amoxicillin-clavulanate
Prosthetic
Valve
Relapse
Case report

ABSTRACT

Enterococcus is considered to be a common cause of endocarditis with unfavorable outcomes. We report a case of successful treatment of relapsed prosthetic valve *Enterococcus faecalis* endocarditis with oral amoxicillin/clavulanate. Enterococcal endocarditis is associated with a high relapse rate, even with the recommended treatment duration by the guidelines. Oral therapy is increasingly considered as part of the management of such serious infections.

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Introduction

Enterococci are reportedly the second or third most common etiology of endocarditis. We present a case report of a successful treatment of relapsed Enterococcal endocarditis with oral amoxicillin-clavulanate after the failure of 6 weeks of intravenous therapy of ampicillin and ceftriaxone.

Case presentation

A 65-year-old male known to have hypertension, dyslipidemia, chronic kidney disease, ischemic and valvular heart disease underwent coronary artery bypass grafting and bioprosthetic aortic valve replacement in April 2015 for bicuspid aortic valve and aortic regurgitation. He presented in July 2018 with a sudden onset of dizziness, slurred speech, and right-sided weakness that lasted for one hour and then resolved. This was preceded by 20 days history of undocumented fever and chills. Upon examination, he was conscious, alert and oriented, blood pressure was 93/51 mmHg, heart rate was 58 bpm, temperature was 37 °C, respiratory rate was 18 breath/min, and saturating 98 % breathing ambient air. His jugular venous pressure (JVP) was not raised; a precordial examination was significant for an audible first and second heart sound with a soft systolic murmur heard at the aortic area. Auscultation of the chest revealed bilateral equal vesicular breathing. No signs of heart failure were appreciated. His speech was fluent. Cranial nerve examination was unremarkable apart from reduced sensation on the right side of his face; he had normal power and reflexes in all limbs.

Blood investigations showed a normal complete blood count (CBC) and coagulation profile. Serum creatinine was 1.7 mg/dL, with an estimated glomerular filtration rate (eGFR) of 44 mL/min, which was unchanged from his baseline renal function. His erythrocyte sedimentation rate and C-reactive protein(CRP) were elevated (67 mm/hr and 87 mg/L, respectively). Three sets of peripheral blood cultures were positive in all six vials for *Enterococcus faecalis* susceptible to ampicillin with high-level aminoglycoside resistance. Radiological studies done included transesophageal echocardiography (TEE), which showed a mobile mass (0.9 × 0.4 cm) on one of the bioprosthetic aortic valve leaflets that most likely represented a vegetation (Fig. 1). Brain magnetic resonance imaging revealed right parietal and left acute pontine infarctions, consistent with an embolic event.

Abbreviations: JVP, jugular venous pressure; CBC, complete blood count; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TEE, transesophageal echocardiography; IE, infective endocarditis; POET, The Partial Oral Treatment of Endocarditis Trial.

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https://doi.org/10.1016/j.idcr.2020.e00726
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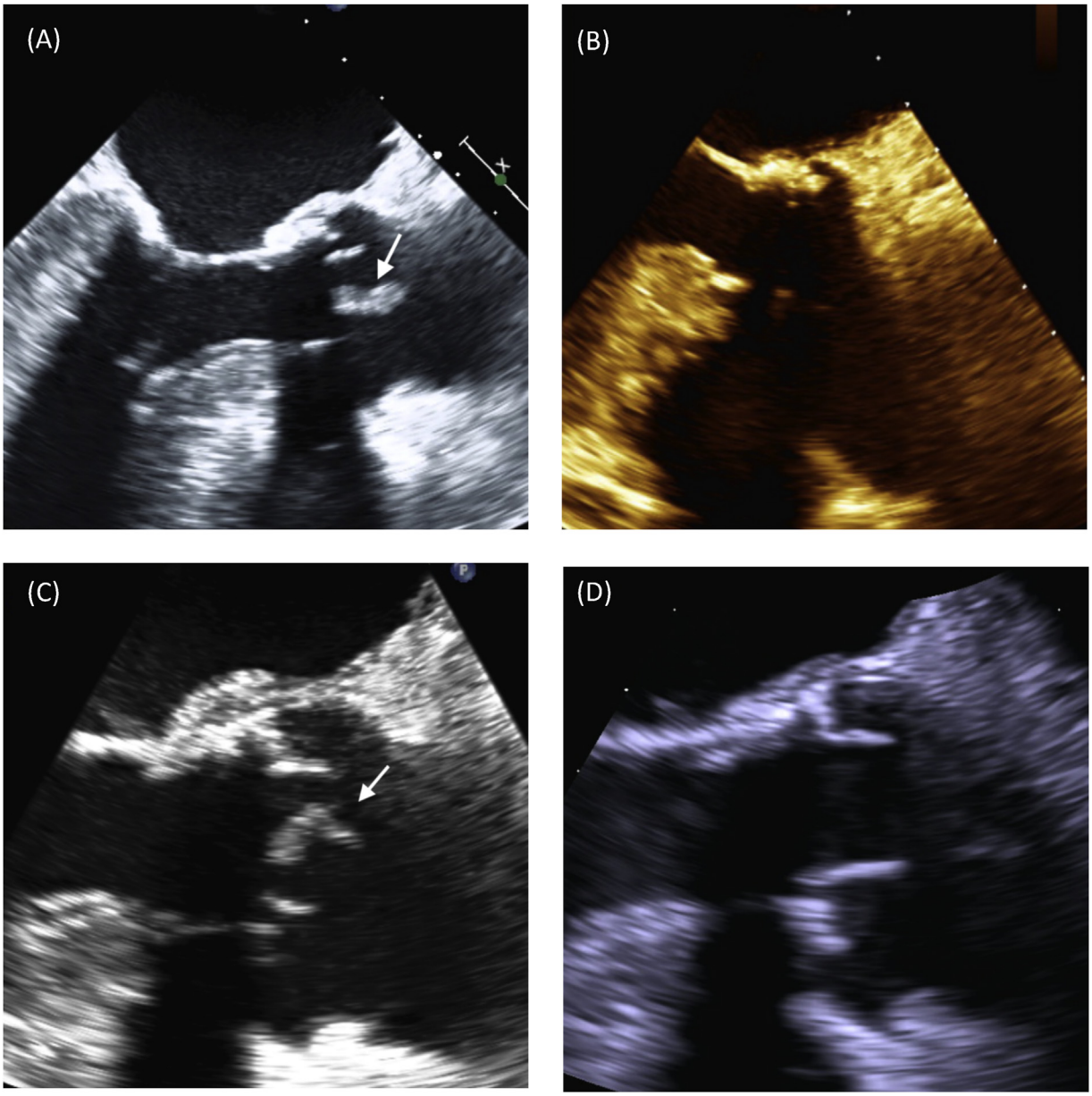

Fig. 1. Transesophageal Echocardiography. (A) Vegetation shown on bioprosthetic aortic valve. (B) Resolution of the vegetation one month later (C) Linear vegetation on bioprosthetic aortic valve 3 months after (D) Complete resolution of the vegetation 12 months after.

Based on the clinical presentation along with echocardiographic findings and blood cultures, the patient was diagnosed as a case of definite *Enterococcus faecalis* bioprosthetic aortic valve endocarditis. He was started on intravenous ampicillin 2 g every 4 h and ceftriaxone 2 g every 12 h. Benefits and risks of surgery, including the hemorrhagic transformation of his brain infarctions, were discussed between the treating team and the patient, who opted for medical therapy with six weeks of intravenous antimicrobials. The patient's clinical status improved, repeat blood cultures were negative, and another TEE was repeated, which showed complete resolution of the previous vegetation (Fig. 1). He was discharged 6 weeks after the admission date in an improved condition without any residual defects.

He presented again a month later with two days history of fever and flu-like symptoms. His blood cultures were positive again in 4 out of 6 vials for *Enterococcus faecalis* susceptible to ampicillin with high-level aminoglycoside resistance. A repeat TEE showed a long linear mass attached to the base of the bioprosthetic aortic valve suggestive of a vegetation (Fig. 1).

He was diagnosed as a case of relapsed enterococcal bioprosthetic aortic valve endocarditis, but the patient refused to be treated or admitted despite counseling from multiple specialties including cardiology and infectious diseases regarding the need of intravenous therapy, assessment for the presence of possible complications, and necessity of surgical evaluation for his relapsed endocarditis. He was discharged against medical advice. Then a month later, he presented for follow-up in the clinic and was counseled again. He refused admission or intravenous therapy but agreed to receive oral therapy. He was started on oral amoxicillin/clavulanate (875 mg/125 mg) twice daily.

During the follow-up a month later, the patient was doing well with no specific complaints. He was compliant with his medications but still refusing intravenous therapy or invasive imaging. Six months later, he presented with a two-day history of

undocumented fever and generalized body aches. He was admitted for further evaluation. Laboratory investigations revealed negative blood cultures. His ESR was 50 mm/hr, and his CRP was 25 mg/L upon admission. A TEE showed thin bioprosthetic aortic valve leaflets with normal movement and no evidence of aortic valvular vegetation (Fig. 1). His symptoms were attributed to an upper respiratory tract infection, and he was discharged to continue on amoxicillin/clavulanate in a stable condition until a further follow-up in the clinic.

He remained well while on therapy and his antibiotics were stopped after completion of one year of treatment, and upon presentation to the most recent follow-up (8 weeks from discontinuation of therapy), he remained clinically well, with negative repeated blood cultures and low inflammatory markers (CRP level of 2 mg/L), consistent with the successful treatment of his relapsed endocarditis.

Discussion and conclusion

Enterococci are normal inhabitants of the gastrointestinal tract and occasionally of the anterior urethra. All enterococci are in Lancefield group D; they are catalase-negative and non-motile, and they may exhibit α-, β-, or γ-hemolysis on blood agar [1]. Enterococci are reportedly the second or third most common group of endocarditis-causing pathogens worldwide [2] and are becoming increasingly prevalent [3,4]. Although there is a scarcity of reporting from our neighboring countries, it was the second most common organism responsible for infective endocarditis (IE) in the two-case series from Saudi Arabia [5,6].

The recommended treatment for prosthetic valve enterococcus endocarditis is six weeks of intravenous therapy. Choices of therapy depend on susceptibility results; the combination of ceftriaxone and ampicillin is recommended for patients with *Enterococcus faecalis* endocarditis with high-level aminoglycoside resistance, while the treatment duration ranges between four weeks for native valve to six weeks for prosthetic valve or prolonged symptoms [7]. However, there are no clear recommendations regarding treatment strategies for relapsed endocarditis.

In a retrospective cohort of 78 patients with enterococcal native and prosthetic valve endocarditis evaluating different combination regimens and duration of therapy, relapse occurred in four of them (5%), three were treated for four weeks, and three also had liver cirrhosis. Combination treatment with ampicillin and aminoglycosides, compared to ampicillin and ceftriaxone, did not show any difference in relapse rate or 1-year mortality [8].

A similar relapse rate was observed in another multi-center cohort study without a difference in treatment strategies [9]. While in The Partial Oral Treatment of Endocarditis (POET) trial [4], enterococcus had a worse outcome with a more aggressive nature; 6/10 of the total relapsed bacteremia was secondary to enterococcus during the follow-up of 6 months, which represents a higher relapse rate compared to *Staphylococcus aureus* endocarditis.

However, the mortality rate of enterococcus reported in the (POET) trial 3/97(3%) was low compared to the other reports from Spain cohorts 26 % and 27 % respectively [8,10]. This might be attributed to the study population in the (POET) trial, as the included patients were in a stable condition and had no evidence of complicated endocarditis with an adequate initial response to intravenous therapy [4]. In our case, the relapse of bacteremia occurred after 30 days of completing the treatment course of 6 weeks of ampicillin and ceftriaxone, which is close to the reported time in one retrospective cohort (46-120-21-42 days, a mean of 57 days) [8], while the median was 37 days in the retrospective cohort comparing ampicillin combination with ceftriaxone versus gentamicin [9].

The idea of non-inferiority of the partial oral regimen to the complete intravenous one is becoming more acceptable with the growing number of trials documenting the efficacy of using partial oral therapy in treating acute infections, i.e., endocarditis or bone and joint infection [4,11].

The success of the treatment in our case is interesting as the relapse of endocarditis may tend to be treated with a more aggressive approach and surgery, particularly in the setting of prosthetic valves, although evidence reporting the optimal management and duration of antibiotics specifically regarding relapsed endocarditis is missing. We have not found previous reports of successful treatment of enterococcal endocarditis with an oral option of amoxicillin/clavulanate. One case reported in 1974 was treated with amoxicillin after two failed courses of intravenous therapy, but that patient underwent surgery [12].

It is interesting that in the POET trial, partial oral therapy was superior to complete intravenous therapy in enterococcal endocarditis. The listed oral options were as follows: 1) amoxicillin and rifampin, 2) amoxicillin and moxifloxacin, 3) linezolid and rifampin, 4) linezolid and moxifloxacin. Managing our patient was difficult as he was not keen to take the medications, and some of the listed options are difficult to tolerate, are inconvenient, or have a higher risk of side effects. The addition of rifampicin is not strongly justified by evidence, similar to the recommendations related to infections caused by staphylococcal organisms. Hence, we selected amoxicillin/clavulanate (875 mg/125 mg) orally twice daily, as an agent with an acceptable safety profile, especially for a prolonged duration of therapy [13]. We thought that a dose of one gram orally twice daily would be appropriate for the patient (70 kg) and mild chronic kidney disease (estimated glomerular filtration rate of 44) [14].

The cure was judged by the clinical, laboratory, and echocardiographic features. The complete resolution of infection is difficult to attribute to the sole effect of oral antibiotics, taking into consideration the previous intravenous therapy given, as well as the longer duration of oral therapy he received compared to the intravenous one. Keeping in mind that partial oral therapy was not associated with a higher relapse rate even after a prolonged follow-up (three and a half years) in the (POET) trial [15], our patient will be followed closely for the possibility of relapse after cessation of antibiotics due to the nature and complexity of his infection.

Our case and the literature are signaling a high relapse rate of enterococcal endocarditis despite giving the recommended duration of intravenous antibiotics. Further studies are needed to evaluate the optimal duration for such infections, taking into consideration the possibility of using partial oral therapy as a therapeutic option.

CRediT authorship contribution statement

Ebrahim Mahmoud: Conceptualization, Writing - original draft, Supervision, Writing - review & editing. **Reem Abanamy:** Conceptualization, Writing - original draft, Writing - review & editing. **Mohammad Bosaeed:** Conceptualization, Writing - review & editing. **Zeinelabdien Elsherif:** Conceptualization, Writing - review & editing.

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