A case of *Corynebacterium striatum* endocarditis successfully treated with an early switch to oral antimicrobial therapy

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SUMMARY

Patients with *Corynebacterium striatum* endocarditis are usually managed with long-term intravenous antibiotic therapy and hospitalization. Here we describe a case of a 76-year-old woman with hepatitis C virus (HCV) related cirrhosis who developed endocarditis due to *Corynebacterium striatum* associated with severe aortic regurgitation. To our knowledge, this is the first case to be successfully treated with an early switch to oral linezolid after three weeks of vancomycin. We performed a literature review using the PubMed database and found 27 cases which showed the enhanced virulence of this pathogen especially for long-term hospitalized patients with a frequent need of surgical treatment (44.4%) and long course of parenteral antimicrobial therapy, with vancomycin as drug of choice. There are no studies confirming the possibility of using oral treatment in non-diphtheritic Corynebacteria infective endocarditis. This case report provides us with the evidence that once the patient is in a stable condition, the efficacy and safety of linezolid might be similar to vancomycin administration. New trials and prospective studies are needed to confirm the opportunity of an early switch to oral therapy in this specific setting.

Keywords: *Corynebacterium striatum*, endocarditis, linezolid, oral therapy.

INTRODUCTION

Infective Endocarditis (IE) is a potentially life-threatening disease, still characterized by increased morbidity and mortality which requires prolonged hospitalization.

We here report a case of native aortic valve endocarditis due to *Corynebacterium striatum* and review the literature about the therapeutic approach and outcomes of endocarditis caused by this emerging pathogen.

As far as we know, this is the first case report of *C. striatum* endocarditis successfully treated conservatively with an early switch to oral antibiotic therapy. Although the option of oral antibiotic therapy in treating infective endocarditis has been widely hinted at, its role is still not fully understood especially for multidrug-resistant bacteria as Corynebacteria.

CASE PRESENTATION

A 76-year-old woman presented to the Emergency Department due to lethargy and right lower limb erysipelas. She lived in a residential care home for the elderly and her medical comorbidities included Hepatitis C Virus (HCV) related cirrhosis (Model for End-Stage Liver Disease score 11), peripheral vascular disease with chronic venous

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stasis in the lower extremities and severe aortic regurgitation.

Physical examination revealed an axillary body temperature of 37.7°C, a pulse rate of 87 beats/minute, a blood arterial pressure of 115/50 mmHg, and a normal oxygen saturation breathing room air. The patient was lethargic but responsive to verbal stimuli. She had a previously unknown grade III holosystolic ejection murmur, best heard at the second right intercostal space. The patient's lungs were clear on auscultation and no peripheral stigmata of endocarditis were found.

Laboratory evaluation showed anemia (hemoglobin 9.8 g/dL) and thrombocytopenia (platelet count 90,000/µL) with a normal leukocyte count of 7,400 µL. Further testing revealed liver enzymes within normal limits, but elevated blood ammonia levels (153 µg/dL) and slightly increased inflammatory markers (C-Reactive Protein 5.48 mg/dl, procalcitonin 1.15 ng/ml). The chest and abdominal X-ray and Computed Tomography (CT) scan of the brain were unremarkable. Following blood cultures, an empiric antimicrobial treatment with amoxicillin/clavulanic acid 875/125 mg every 8 hours and trimethoprim/sulfamethoxazole 160/800 mg every 12 hours was promptly started. After 22 hours, blood cultures turned positive for *Corynebacterium striatum*. Blood samples for cultures were collected in BD BACTEC culture aerobic/anaerobic vials and were incubated into BACTEC FX automated blood culture system (Becton, Dickinson and Company, Franklin Lakes, New Jersey, United States), according to the manufacturer's instructions. Positive blood cultures were subjected to Gram-staining and sub-cultured into aerobic sheep blood agar plates, chocolate agar plates, selective plates and into Schaedler agar and 5% sheep blood plates (bioMérieux SA, Marcy-L'Étoile, France) anaerobically and incubated at 37 °C overnight: the organisms were identified by Matrix-Assisted Laser Desorption Ionization time-of-flight (MALDI-TOF) (Bruker Daltonics GmbH, Bremen, Germany, Bruker Biotyper 3.1 database). Sensitivity tests for *Corynebacterium striatum* were performed using the Kirby Bauer method, according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints (version 9.0). The isolate resulted only susceptible to linezolid and vancomycin and, accordingly, vancomycin 1000 mg every 12 hours by intravenous route was started. After 48 hours, surveillance blood cultures were repeated and returned negative.

Afterwards, a trans-thoracic echocardiogram was performed and showed a small aortic valve vegetation of 4 mm with an associated severe aortic regurgitation. Due to the diagnosis of infective endocarditis, a total body Computed Tomography (CT) scan was also performed, showing no septic embolisms of the brain, thorax and abdomen.

After a total of 3 weeks of intravenous vancomycin, considering the significant improvement of the health conditions, the patient was discharged with an indication to continue linezolid 600 mg every 12 hours orally for an additional 7 days. One week after the discontinuation of the entire cycle of antimicrobial therapy, a trans-esophageal echocardiogram was performed and showed the disappearance of aortic valve vegetation with a residual structural alteration of the valve leaflets. She did not report any adverse effect to the medication. At 7 months follow-up, she was in good health condition, afebrile with no relapse.

MATERIALS AND METHODS

With the aim to better delving into outcomes and treatment options of *C. striatum* endocarditis we conducted a literature review of all published cases in the last 25 years. We performed a research in PubMed database using the terms "*Corynebacterium striatum* endocarditis" and "*Corynebacterium striatum* heart infection" excluding the studies involving patients <18 years. The search was limited to papers published in English only. In the articles examined, the bibliographical references were explored in order to report other cases that might have escaped the original query.

RESULTS

The review of the medical literature revealed 26 studies describing a total amount of 27 cases [2-27]. *C. striatum* endocarditis was reported more frequently in men (59.3%, 16 of 27), the average patients' age was 61.8 years. Just one patient had no co-morbidities, confirming the enhanced virulence of this pathogen especially for long-term hospitalized patients with underlying disease [1]. Eight patients of 27 (29%) were diabetics, 6 pa-

tients (22.2%) suffered from chronic renal disease with 2 of 6 who underwent hemodialysis. Seven of 27 (25.9%) had a prosthetic valve, 2 a pacemaker and 1 a ventriculo-atrial shunt for a congenital hydrocephalus. Two patients' past history was not reported.

The most affected valve was the mitral valve (51.8%, 14 of 27) followed by aortic valve (29.6%, 8 of 27). Six valves involved were prosthetic and in 2 cases there were found vegetations on pacemaker leads. Being a life threatening infection, among patients with a reported outcome, 24% (6 of 25) died and 76% (19 of 25) were discharged from the hospital. A high percentage of *C. striatum* endocarditis required surgical treatment (44.4%), 9 of 27 needed valve replacement and 3 of 27 underwent a procedure of leads or whole pacemaker removal.

Fourteen cases over 27 (51.9%) were treated with vancomycin for 4 or 6 weeks. One case has been switched after 4 weeks of vancomycin to oral linezolid for a further 28 days [2] (Table 1).

Table 1 - Twenty-seven cases of Corynebacterium striatum endocarditis reported in literature.

Article	*N. of patients*	*Age/sex*	*Comorbidities*	*Affected valve*	*Antibiotic Treatment*	*Surgery*	*Outcome*
Muñoz P, *Clin Microbiol Infect.* 2007 [2]	1	57/F	Bone marrow transplantation	Atrial wall	VAN+CFT IV for 4 weeks then oral LNZ for 4 weeks	No	Discharged, asymptomatic at 13 months
Naqvi SY, *BMJ Case Reports* 2018 [3]	1	69/M	AVR, CKD stage 3, DM, obesity	AV (prosthetic)	VAN 6 weeks	Valve-in-valve TAVR after 3 weeks	Discharged. Asymptomatic at 12 months
Lee JY, *Korean Circ J.* 2018 [4]	1	54/M	CKD (hemodialysis)	MV, AV, TV	Unknown	Three valves replacement	Unknown
Syed MA, *Cureus.* 2019 [5]	1	65/F	DM, heart failure, CAD and AVR	negative	SAM and DAP	No	ICU, Death
Jagadeeshan N, *Indian Heart J.* 2016 [6]	1	27/M	Rheumatic heart disease, congenital lymphedema	MV	CXM 6 weeks	No	Discharged
Hong HL, *Infect Chemother.* 2016 [7]	1	55/M	Traumatic subdural hemorrhage	MV	VAN 6 weeks	MVR	Discharged. Asymptomatic at 12 months
Rasmussen M, *Eur J Clin Microbiol Infect Dis.* 2020 [8]	1	66/M	Unknown comorbidities, AVR	AV (biological prosthesis)	Unknown	AVR	Death
Xu J, *BMC Infect Dis.* 2017 [9]	1	63/M	Hypertension and atrial fibrillation	AV, MV, left atrial mass	LNZ IV then, after surgery, DAP IV for 4 weeks and LNZ oral for 3 weeks	Mass removal then double valve replacement	Discharged
Fernández Guerrero ML, *Int J Antimicrob Agents.* 2012 [10]	1	78/M	DM, CKD, PM	TV	DAP for 7 weeks	Electrode wires removed and re-implantation	Discharged
Oliva A, *J Clin Microbiol.* 2010 [11]	1	71/F	PM	Intracardiac PM lead	DAP	PM removal and reimplantation	Discharged. Asymptomatic at 1 month.
Tran TT, *Antimicrob Agents Chemother.* 2012 [12]	1	56/M	DM, CKD, MRSA infection and osteomyelitis	MV	TLV	MVR	Death
Mizoguchi H, *Surg Today.* 2014 [13]	1	53/F	None	AV	SAM and GEN IV	AVR	Discharged

Article	*N. of patients*	*Age/sex*	*Comorbidities*	*Affected valve*	*Antibiotic Treatment*	*Surgery*	*Outcome*
Bhat Y, *Int J Infect Dis.* 2008 [14]	1	83/M	Metastatic prostate cancer, intracerebral bleed	MV	PEN and GEN then DAP IV	No	Death
Marull J, *Cases J.* 2008 [15]	1	73/F	Hypertension, CKD, heart failure and DM.	MV	VAN IV for 6 weeks	No	Discharged
Rufael DW, *Clin Infect Dis.* 1994 [16]	1	54/M	Hypertension	AV	VAN IV for 6 weeks	AVR	Discharged
Boltin D, *Eur J Intern Med.* 2009 [17]	1	71/M	DM, bedridden and cognitive impairment	MV	VAN IV for 6 weeks	No	Death, blood cultures negative
Shah M, *Ann Pharmacother.* 2005 [18]	1	46/F	CKD (hemodialysis)	TV	LNZ IV switched to DAP and RIF for 6 weeks	No	Discharged. Asymptomatic at 3 months.
Juurlink DN, *Eur J Clin Microbiol Infect Dis.* 1996 [19]	1	68/M	DM, hypertension, congestive heart failure, COPD.	MV	VAN then PEN IV for 6 weeks	No	Unknown
Elshibly S, *Br J Biomed Sci.* 2006 [20]	1	77/F	Unknown	MV	Antibiotic treatment for seven weeks	No	Discharged
Mashavi M, *J Infect. 2006* [21]	1	68/M	CVA, atrial fibrillation, congestive heart failure. AVR, MVR	MV (prosthetic)	VAN IV for 6 weeks	No	Discharged, asymptomatic at 2 months.
Stoddart B, *Rheumatology (Oxford).* 2005 [22]	2	72/F	Rheumatic fever, MVR	MV (prosthetic)	VAN and RIF IV for 6 weeks	No	Discharged
		61/F	Rheumatic fever, LES, multiple pulmonary emboli, hypothyroidism and CAD	MV	VAN IV for 4 weeks and GEN IV for 1 week	No	Discharged
Melero-Bascones M, *Clin Infect Dis.* 1996 [23]	1	73/M	PM implantation 6 years previously	PM electrode wire and TV	VAN IV for 4 weeks after electrode wire removal	electrode wire was removed	Discharged
de Arriba JJ, *J Infect.* 2002 [24]	1	72/F	hypertension, DM, CAD, AVR with a metallic prosthesis	MV, AV (prosthetic)	VAN and GEN IV	No	Death
Tattevin P, *Clin Infect Dis.* 1996 [25]	1	24/M	Congenital hydrocephalus, ventriculoatrial shunt	PV close to ventriculoatrial shunt catheter	AMX, netilmicin and TEC IV 12 weeks then oral AMX 2 weeks	No	Discharged, asymptomatic at 10 months
Houghton T, *Postgrad Med J.* 2002 [26]	1	62/F	Bioprosthetic AVR	negative	VAN IV for 6 weeks	No	Discharged, asymptomatic at 12 months
Kocazeybek B, *Chemotherapy.* 2002 [27]	1	50/M	Operated for a mycotic aneurysm	AV	Coinfection C.striatum and MRSE. VAN, GEN IV and DOX os	AVR	Discharged, no fever at follow up

AVR: Aortic Valve Replacement; MVR: Mitral Valve Replacement; CAD: Coronary artery disease; CKD: Chronic Kidney disease; CVA: Cerebrovascular Accident; DM: Diabetes mellitus; ICU: Intensive Care Unit; MRSA: Methicillin-Resistant Staphylococcus Aureus; MRSE: Methicillin-Resistant Staphylococcus Epidermidis; PM: Pacemaker; TAVR: Transcatheter aortic valve replacement; AMX: Amoxicillin; CFT: Ceftriaxone; CXM: Cefuroxime; DAP: Daptomycin, DOX: Doxycycline; GEN: Gentamicin; LNZ: Linezolid; PEN: Penicillin; RIF: Rifampicin; SAM: Ampicillin-sulbactam; TEC: Teicoplanin, TLV: Telavancin; VAN: Vancomycin.

DISCUSSION

Intravenous vancomycin is currently the drug of choice as empiric treatment for *C. striatum* endocarditis. Hence, although *C. striatum* isolates are frequently susceptible to many antimicrobial drugs, resistance to penicillin, cephalosporins, ciprofloxacin, meropenem, tetracycline, and clindamycin has been recently reported [28-30]. Multidrug-resistant *C. striatum* outbreaks have occurred among patients with prolonged hospitalization and exposure to broad-spectrum antibiotics, in carriers of intracardiac or endovascular devices or immunocompromised individuals. Recently, several cases of patient-to-patient transmission in Intensive Care Unit have been described [31, 32]. In vitro resistance to vancomycin has not been reported yet in any of the Corynebacterium species [33, 34]. Daptomycin may be an alternative with a favorable side effect profile but rapid development of resistance has been described among a large sampling of isolates by McMullen et al. and the failure of a prolonged therapy with this antibiotic has been documented in case reports [35, 36].

According to Hahn *et al.* infections due to *C. striatum* are associated with a longer course of parenteral antimicrobial drugs compared to coagulase-negative staphylococci's infections [33]. Nevertheless, an oral treatment option for multidrug-resistant *C. striatum* could be feasible with linezolid as drug of choice. Hence, a strain resistant to linezolid has never been reported [28, 37].

In the present review of the literature we found just one case treated with oral linezolid after 4 weeks of vancomycin. The therapy was continued for a long time, for further 28 days, which determined bone marrow toxicity differently from our case [2].

Emerging data suggest the potential benefit of oral switch strategy as an alternative to standard intravenous therapy in low-risk patients with uncomplicated Gram positive blood stream infection and endocarditis [38-41].

Linezolid has more than 99% of oral bioavailability and 30% of serum protein binding rate. It has activity against a wide range of antibiotic-susceptible and resistant Gram-positive bacteria and, due to its novel mechanism of action, it lacks cross-resistance with other antimicrobial therapies [42, 43].

Several studies have demonstrated that switching clinically stable patients to appropriate oral antibiotics is safe and effective and helps to reduce time of hospitalization and the consequent risk of acquiring nosocomial infections [44-47].

Choosing oral rather than parenteral therapy might be a key strategy in the struggle to decrease antimicrobial resistance. The reduction of length of stay associated with the use of oral linezolid, indeed, could diminish the reservoir of resistant Gram-positive infected patients from the hospital population and the potential transmission to non-infected patients. Secondly, limiting the utilization of vancomycin would decrease selective pressure for resistant organisms such as Vancomycin-Resistant Enterococci (VRE).

Evidence is lacking for oral treatment in Corynebacteria endocarditis and blood stream infections as streptococci and *Staphylococcus aureus* are the predominant microorganisms studied. The available trials which showed non-inferiority of partial oral therapy to intravenous therapy in endocarditis (POET) and bone and joint infections (OVIVA), have the important limitation that they include few multidrug resistant bacteria [41, 48].

In conclusion, the present is the first case report of endocarditis due to *C. striatum* which has been managed with an early switch to oral linezolid after 3 weeks of vancomycin with a good outcome and absence of relapse or reinfection at 7-months follow up. The review of the literature showed that *C. striatum* endocarditis is usually managed with a long course of parenteral antimicrobial drugs and studies are lacking about the opportunity to reduce hospital length of stay and duration of intravenous therapy using linezolid.

Once the patient is in stable condition, efficacy and safety of an oral effective treatment could be similar to vancomycin administration but new trials and prospective studies are needed to confirm this therapeutic strategy.

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Conflict of interest
The authors report no conflict of interest.

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