Rapidly Destructive *Staphylococcus epidermidis* Endocarditis

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Abstract

A 29-year-old man with rapidly destructive *Staphylococcus epidermidis* endocarditis after mitral valve reconstruction is presented. Resistance to rifampin and teicoplanin occurred during antibiotic treatment resulting in clinical failure and valve destruction. Subsequently, the patient was successfully treated, by combining valve replacement with antibiotic therapy including quinupristin/dalfopristin, levofloxacin, and vancomycin. In conclusion, *S. epidermidis* can cause rapid valve destruction with large vegetations, and combination of surgery and antibiotic therapy may be necessary.

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Introduction

Coagulase-negative staphylococci (CoNS) are part of normal human skin flora. Defining their clinical relevance in clinical samples poses a major diagnostic challenge. Notably, CoNS such as *Staphylococcus epidermidis* have emerged as a major cause of infection, particularly in hospitalized patients with prosthetic heart valves, joint prostheses or indwelling catheters.

CoNS have the unique property to attach to matrix proteins formed on polymer surfaces of foreign bodies. CoNS may generate a biofilm resulting eventually in multilayered biofilms. The importance of CoNS in foreign body infections is highlighted by the fact that they are responsible for over 50% of all cases of prosthetic valve endocarditis. Only 1–5% of all native valve endocarditis are caused by CoNS [1]. The low virulence of CoNS may explain the typically subacute or even chronic course of infection. So far *Staphylococcus lugdunensis* was thought to be the only CoNS species known to cause rapidly progressive endocarditis [2]. Here, we report a case with *S. epidermidis* endocarditis with a fulminant course causing major therapeutic problems because of emerging resistance to antibiotic therapy.

Case Report

A previously healthy 29-year-old man was admitted to our hospital for elective cardiac surgery of a myxoma located on the anterior mitral leaflet. The mitral valve was reconstructed using xenopercardium as well as an anuloplasty ring. On the 5th postoperative day the patient developed fever up to 39.5 °C and a nonproductive cough. A transesophageal echocardiography (TEE) revealed no vegetations. After blood cultures were drawn, assuming a pneumonia, cefepime 2 g bid intravenously (iv) was started on the 5th postoperative day. No catheter had been in place at the time of the first fever episode. Teicoplanin 800 mg qd iv was added to cefepime on the 6th postoperative day when CoNS grew in the blood cultures. A second set of blood cultures drawn prior to teicoplanin grew CoNS again raising the suspicion of postoperative endocarditis. The resistance patterns of the first and second CoNS were different (Table 1). All CoNS isolates were identified as *S. epidermidis*. Therefore, the antibiotic therapy was switched to vancomycin 1 g bid iv and rifampin 450 mg bid po according to susceptibility testing on the 11th postoperative day. No growth was reported in subsequently drawn blood cultures.

Over the following days, despite adequate vancomycin trough levels (8.9–10.1 mg/l), the patient showed progressive heart failure. TEE was repeated on day 21 after surgery and revealed multiple vegetations and a perforation of the anterior mitral valve leaflet. Because of rapidly progressive heart failure, immediate reoperation was necessary. The vegetations and the anuloplasty ring were removed and the mitral valve was again reconstructed. CoNS could be isolated from the tissue samples and were identified as *S. epidermidis*. Notably, using pulsed-field gel electrophoresis [3], the banding pattern of all isolates (i.e. from blood and tissue samples) was identical pointing to their genetic relatedness. Strikingly, susceptibility testing performed by disk diffusion on Mueller-Hinton agar at 35 °C according to the National Committee for Clinical Laboratory Standards (NCCLS) revealed new rifampin resistance (Table 1). In addition, minimal inhibitory concentrations (MIC) were determined by Etest® (AB Biodisk, Solna, Sweden) according to the manufacturer's instructions. Antibiotic therapy was changed to vancomycin 1 g bid iv, quinupris-

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Table 1
Minimal inhibitory concentrations (MIC) of the three *S. epidermidis* strains (E-test).

Isolates	Vancomycin MIC	Teicoplanin MIC	Rifampin MIC	Oxacillin MIC	Gentamicin MIC	Levofloxacin MIC	Linezolid MIC	Quinupristin/ dalfopristin MIC
	S_1: ≤ 4 mg/l I_2: 8-16 mg/l R_3: ≥ 32 mg/l	S: ≤ 8 mg/l I: 16 mg/l R: ≥ 32 mg/l	S: ≤ 1 mg/l I: 2 mg/l R: ≥ 4 mg/l	S: 0.25 mg/l R: 0.5 mg/l	S: ≤ 4 mg/l I: 8 mg/l R: ≥ 16 mg/l	S: ≤ 2 mg/l I: 4 mg/l R: ≥ 8 mg/l	S: ≤ 4 mg/l	S: ≤ 1 mg/l I: 2 mg/l R: ≥ 4 mg/l
A_4	2	6	≤ 0.016	128	0.5	0.38	2	
B_5	3	12	≤ 0.016	> 256	> 256	0.125	1.5	
C_6	3	32	> 256	32	> 256	0.125	1	0.19

S_1: sensitive against the tested drug; I_2: intermediate resistance against the tested drug; R_3: resistance against the tested drug; strain A_4: blood culture 5th postoperative day; strain B_5: blood culture 6th postoperative day; strain C_6: valve tissue sample

tinum/dalfopristinum 500 mg tid iv and levofloxacin 500 mg bid po for additional 6 weeks. The remainder of the clinical course was favorable.

Discussion

This case report shows that similar to *S. lugdunensis*, *S. epidermidis* can also cause rapidly progressive and destructive endocarditis, requiring surgery and antibiotics for successful treatment. Despite adequate antibiotic therapy, resistance in CoNS may emerge and lead to treatment failure. Recently, seven cases of native valve endocarditis due to *S. epidermidis* were reported of which three showed an acute course [4]. All seven patients needed cardiac surgery with valve replacement. Microscopic examinations of the valves showed gram-positive cocci and six of seven tissue specimens grew *S. epidermidis*. Similar to our case, eradication was found to be difficult and required a combination of surgery and antibiotics. However, in contrast to our experience, antibiotic resistance did not emerge in that case series [4]. Recently, a report on 99 patients with native valve endocarditis due to CoNS was published [5]. Patients with native valve endocarditis due to CoNS had rates of heart failure and mortality similar to patients with native valve endocarditis due to *Staphylococcus aureus*. The proportion of patients requiring cardiac surgery was higher for native valve endocarditis due to CoNS compared to *S. aureus*. The frequent need for surgery had already been noted previously in a series of 21 patients with native valve endocarditis due to CoNS [6].

S. epidermidis is capable of forming thick and multilayered biofilms, especially in the presence of foreign bodies. Bacteria in biofilms show much slower growth rates than in their planktonic form [7]. These physiological factors render antibiotics, such as β-lactam antibiotics and glycopeptides, which target metabolically active bacteria, much less active. The biofilm also hinders the immune system to display its full armamentarium by limiting access of phagocytic cells to pathogenic bacteria [8, 9].

Optimal antibiotic therapy of infections caused by CoNS is further complicated by the difficulty to precisely determine the susceptibility of these bacteria to glycopeptides by agar disk diffusion assays. The large glycopeptide molecules diffuse only poorly in agar. Thus the relevant zones of inhibition in disk assays remain small and difficult to interpret [10]. The poor correlation between the obtained zone diameters and the MIC often leads to incorrect interpretation [11]. Therefore, determination of MIC of glycopeptides against CoNS is recommended in patients with complicated CoNS bacteremia. The isolate in our case initially was considered susceptible to vancomycin and teicoplanin based on MIC determinations. After prolonged glycopeptide therapy, the isolates showed a higher MIC for teicoplanin. It is well known that isolates with decreased susceptibility to glycopeptides (especially to teicoplanin) can be selected *in vitro* and *in vivo* by exposure to glycopeptides [12].

Nevertheless, even the MICs for glycopeptides must be interpreted cautiously since strains considered susceptible according to the NCCLS may de facto be resistant to glycopeptide therapy. *Peck* et al. [13] reported *S. epidermidis* strains, which were susceptible to vancomycin in the planktonic form (MIC: 3.1 mg/l; MBC 6.3 mg/l) but showed tolerance when tested sessile in a biofilm (MIC: 3.1 mg/l; MBC > 400 mg/l), indicating that vancomycin may not efficiently kill the sessile bacteria in biofilms even at concentrations far above the MIC [13, 14].

Rifampin is the single most active agent against biofilm-producing *S. epidermidis*, but resistant mutants can be readily selected with monotherapy. Mutations within rpoB (which encodes the β-subunit of the RNA polymerase) can arise at frequencies of around 10^{-8} and may result in different levels of resistance to rifampin in the studied bacterial populations [15]. The whole population of susceptible bacteria will be replaced by a resistant subpopulation following exposure to rifampin. Since only approximately 10^6 cfu/ml are used for conventional MIC

determinations, this method may not detect the naturally occurring resistant variants in a population. On the other hand, high cell densities exceeding 10^8 cfu/ml may be found in biofilms [16], raising the possibility that rifampin-resistant bacteria may already be present in this situation at the onset of treatment.

In our case, the relatively high MICs for glycopeptide antibiotics taken together with the diminished efficiency of these antibiotics in biofilms, and the high bacterial load in endocarditis may have contributed to treatment failure with the documented development of rifampicin resistance. The banding pattern of all isolated *S. epidermidis* isolates was indistinguishable in pulsed-field gel electrophoresis (PFGE), indicating that they were identical despite the different antibiotic resistance patterns found. The differences in aminoglycoside resistance are most likely due to changes in plasmid content as described previously [17].

In the presented case, treatment consisting of quinupristin/dalfopristin, levofloxacin, and vancomycin after surgical removal of the vegetations and the anuloplasty ring proved to be successful. Quinupristin/dalfopristin is the first semisynthetic injectable streptogramin antibiotic available and a promising alternative to glycopeptides for the treatment of many multiresistant gram-positive bacteria. Quinupristin/dalfopristin has a greater bactericidal effect on CoNS in biofilms than flucloxacillin, glycopeptides, erythromycin, and ciprofloxacin [18].

In conclusion, *S. epidermidis* can cause rapid valve destruction resulting in heart failure and a combination of surgery and antibiotic therapy may be necessary. In our case, the surgical removal of the infected tissue alone might have been sufficient for the favorable outcome. Blood cultures positive for *S. epidermidis* must be interpreted carefully in high-risk patients, endocarditis should be excluded and adequate resistance testing performed. Combination therapy with vancomycin and rifampin must be used with caution because high bacterial loads in endocarditis together with low efficiency of antibiotics within biofilms may readily select for rifampin-resistant clones.

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