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CASE REPORTS

Vancomycin-Resistant *Enterococcus faecalis* Endocarditis: Linezolid Failure and Strain Characterization of Virulence Factors▽

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Infective endocarditis due to vancomycin-resistant (VR) *Enterococcus faecalis* has only rarely been reported. We report a case of VR *E. faecalis* endocarditis that failed to respond to linezolid therapy, outline the virulence traits of the isolate, and review previously published cases of VR *E. faecalis* endocarditis.

CASE REPORT

A 37-year-old female was transferred to our institution for hemodialysis access and sustained vancomycin-resistant (VR) *Enterococcus faecalis* bacteremia. Her medical history was significant for medullary cystic kidney disease diagnosed at age 7, and she had required hemodialysis since age 10. She had four failed renal allografts, the first transplant having been performed at age 11. In addition, she had multiple failed arteriovenous grafts and fistulas, requiring placement of bilateral subclavian subcutaneous hemodialysis ports (LifeSite Hemodialysis Access System) 3 years prior to admission.

Seven months prior to admission, she developed methicillin-resistant *Staphylococcus aureus* bacteremia secondary to infection of her hemodialysis ports and was treated with 4 weeks of intravenous vancomycin. Two months prior to admission, she developed VR *E. faecalis* bacteremia secondary to hemodialysis port infection. The VR *E. faecalis* blood isolate was sensitive to penicillin, ampicillin, linezolid, high-level streptomycin (MIC, <1,000 μg/ml), and rifampin and resistant to high-level gentamicin (MIC, >500 μg/ml), erythromycin, and tetracycline. Due to a history of penicillin allergy, oral linezolid was given for 4 weeks. The hemodialysis ports were not removed at that time due to difficulty with obtaining additional vascular access. No valvular or catheter-associated vegetations were demonstrated on transesophageal echocardiography.

She was subsequently admitted to another institution for evaluation of fever and chills. Two sets of blood cultures grew VR *E. faecalis* with a susceptibility pattern similar to that of the previous VR *E. faecalis* blood isolate obtained 2 months prior. Linezolid, given 600 mg intravenously every 12 h, was initiated. Blood cultures remained positive for VR *E. faecalis* on hospitalization day 2. Both subclavian subcutaneous hemodialysis ports were removed on hospitalization day 3, and bacterial culture of the catheter tips grew VR *E. faecalis*.

The patient was transferred to our institution on hospitalization day 5. At hospital admission, her body temperature was 35.7°C, her blood pressure was 80/48 mmHg, and her heart rate was 101 beats/min. Physical examination did not reveal a cardiac murmur or peripheral stigmata of endocarditis. Laboratory testing showed a peripheral leukocyte count of 12,300/mm^3. Two sets of blood cultures grew VR *E. faecalis* within 24 h; the blood isolate was sensitive to penicillin, ampicillin, linezolid, and daptomycin and resistant to quinupristin-dalfopristin and erythromycin. The isolate was resistant to high-level gentamicin (MIC, >500 μg/ml), although it lacked high-level resistance to streptomycin (MIC, <2,000 μg/ml). In addition, the isolate contained the *vanA* gene by PCR analysis.

Additional blood cultures taken on hospitalization days 7 and 9 were positive for VR *E. faecalis*, despite continued therapy with linezolid. A transesophageal echocardiogram on hospitalization day 7 showed mobile aortic valve vegetations (8-mm and 4-mm vegetations), a mobile mitral valve vegetation (10 by 8 mm), new mitral valve regurgitation, and new moderate-to-severe aortic valve regurgitation. She had more than 10 reported allergies, including penicillin, amoxicillin, cefazolin, tetracycline, and ciprofloxacin. Skin testing for penicillins and cephalosporins was performed and was negative. Antibiotic therapy was changed from intravenous linezolid to aqueous crystalline penicillin G sodium, 3×10^6 U given intravenously every 6 h, plus streptomycin, 300 mg given intravenously three times weekly, after each hemodialysis. Streptomycin levels were monitored. She improved clinically, and follow-up blood cultures performed on hospitalization day 15 were negative. She received 6 weeks of combined treatment with intravenous penicillin G and streptomycin. Relapsing VR *E. faecalis* bacteremia did not occur over the 9 months following the completion of antibiotic therapy.

Colony lysates of the VR *E. faecalis* blood isolate from hospitalization day 5 (TX2853) were prepared by previously described methods (29) and hybridized with probes represent-

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TABLE 1. Potential virulence- and PAI-associated genes

Locus	Gene name/function	TX2853 HS hybridization	Reference(s)
Virulence associated			
ef1091	*ebpA*/endocarditis- and biofilm-associated pili	+	16
ef1092	*ebpB*/endocarditis- and biofilm-associated pili	+	16
ef1818	*gelE*/protease	+	22
ef1824	Glycosyl hydrolase, family 31/fibronectin type III domain protein with Ig-like fold-containing putative surface adhesin	−	15, 27
ef3023	*hylA*/putative hyaluronidase	+	15, 27
ef1896	Cell wall surface anchor family protein with Ig-like fold-containing putative surface adhesin	+	Sillanpää et al., unpublished
ef2347	Cell wall surface anchor family protein with Ig-like fold-containing putative surface adhesin	−	Sillanpää et al., unpublished
ef2505	Cell wall surface anchor family protein with Ig-like fold-containing putative surface adhesin	+	Sillanpää et al., unpublished
ef0818	*hylB*/putative hyaluronidase	−	15
ef1099	*ace*/collagen adhesin protein	+	17, 18
PAI associated			
ef0482	Hypothetical protein	+	15
ef0521	*cbh*/putative choloylglycine hydrolase family protein	−	15, 24
ef0527	*cylM*/cytolysin	−	15, 24
esp[a]	*esp*/enterococcal surface protein	+	15, 24, 25
ef0556	*xylA*/putative xylose isomerase	+	15, 24
ef0571	Putative DNA-binding response regulator	−	15, 24
ef0604	*gls24*-like gene	−	15, 24

[a] The DNA probe for the *esp* gene was amplified from strain MMH594, and those for all other genes were amplified from V583 (19).

ing 17 genes that encode proven or suspect virulence determinants. These included the gelatinase gene (22, 26, 28, 30); recently described pilus-encoding genes (16); genes encoding putative MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) with predicted immunoglobulin (Ig)-like folds (17, 18, 27; J. Sillanpää, S. R. Nallapareddy, and B. E. Murray, unpublished data); genes, including *esp* (33), in a predicted pathogenicity island (PAI) (15); and an acquired gene that contributes to biofilm formation (32) (Table 1). The strain was examined for phenotypic production of gelatinase (22), hemolytic activity on Bacto Tryptic Soy Agar (Becton Dickinson and Company, Sparks, MD) plus 5% human blood agar plates, and biofilm formation (14). DNA was extracted with a DNeasy tissue kit (QIAGEN Sciences, Maryland) by following the manufacturer's instructions and tested by PCR as previously described to determine if the conserved junction of the PAI with chromosomal DNA was present (15). Pulsed-field gel electrophoresis and multilocus sequence typing of internal regions of five housekeeping genes were performed to determine if TX2853 belonged to the previously described beta-lactamase, vancomycin-resistant, endocarditis clone (15).

TX2853 produced gelatinase; it also contained five of seven putative adhesin genes (including the *ebpA* and *ebpB* genes, which are related to pilus formation), one of two predicted hyaluronidase genes, *esp*, and two of six other PAI genes. The common PAI-chromosome junction point previously described (15) was also present. TX2853 tested negative by PCR for the *bee* (biofilm enhancer in enterococcus) locus (32). By pulsed-field gel electrophoresis and multilocus sequence typing, this strain did not belong to the beta-lactamase, vancomycin-resistant, endocarditis clone (or to one of the sequence types we have previously classified by this system). Biofilm assay showed that the strain was a medium biofilm producer (33). TX2853 tested negative for hemolytic activity on blood agar plates, which is consistent with *cylM* probe negative results.

Vancomycin-resistant enterococci have emerged as a well-defined cause of health care-associated and nosocomial infections (5, 8). Despite the increasing prevalence of vancomycin-resistant enterococci in most tertiary-care and other health care settings, infective endocarditis due to these organisms has been reported in only a limited number of cases (31). Moreover, endocarditis due to VR *E. faecalis* isolates is extremely rare. We performed a review of the PubMed database (English language) through the end of September 2006 with the search terms "vancomycin resistant enterococcus endocarditis" and "glycopeptide resistant enterococcus endocarditis." An article was included in our review if it described a case of VR *E. faecalis* infective endocarditis that fulfilled the modified Duke criteria for definite or possible infective endocarditis (13). There were only six previously reported cases of infective endocarditis caused by VR *E. faecalis* that met our criteria (Table 2). Two cases met criteria for definite infective endocarditis (patients 1 and 3), and four cases met criteria for possible infective endocarditis (patients 2, 4, 5, and 6). In the majority of previously reported cases of VR *E. faecalis* infective endocarditis in our review, the mitral or aortic valve was affected; our case report represents the first description of bivalvular endocarditis due to VR *E. faecalis*. Only one of seven isolates was resistant to ampicillin, which is consistent with the rates of ampicillin resistance (between 0.9 and 2.7%) observed in *E. faecalis* isolates in the United States (5, 8). The mechanism of resistance to ampicillin in the isolate from patient 5 (Table 2) was not mentioned in the case report (7). Most patients were

treated with either ampicillin or penicillin, and synergistic bactericidal combination therapy with an aminoglycoside was given to four patients. There were two deaths, and two patients required valve replacement.

Although there are some case reports of linezolid efficacy for infective endocarditis due to vancomycin-resistant *Enterococcus faecium* (31), there has been very limited experience with the use of linezolid to treat infective endocarditis due to VR *E. faecalis*. In the six previously reported cases of VR *E. faecalis* in our review, only two of the patients were treated with linezolid (Table 2, patients 5 and 6). Patient 5 was treated with linezolid for 6 weeks because he had an ampicillin-resistant strain of VR *E. faecalis* (7). He had multiple negative surveillance blood cultures during antibiotic therapy, although he died from an unknown cause 1 week after completion of linezolid therapy. Patient 6 was treated with linezolid for 12 weeks plus gentamicin for 6 weeks because of a previous anaphylactic reaction to penicillin (35). Six weeks after discontinuation of linezolid, blood cultures were positive for VR *E. faecalis* although subsequent blood cultures remained negative for 52 months of follow-up time. Our patient had persistent VR *E. faecalis* bacteremia for 9 days while on linezolid therapy but was subsequently cured after starting therapy with aqueous crystalline penicillin G sodium plus streptomycin. Based on the limited and conflicting data in these case reports, further studies are needed to elucidate the role of linezolid in the treatment of infective endocarditis due to VR *E. faecalis*.

Although there are multiple virulence factors that may contribute to the ability of enterococci to cause infective endocarditis, there have been limited studies of virulence traits in VR *E. faecalis* infective endocarditis isolates due to its rarity (Table 2). Our patient's VR *E. faecalis* infective endocarditis strain (TX2853) tested positive for five of seven genes thought to be involved in adhesion (*ebpA*, *ebpB*, *ace*, and two cell surface anchor family proteins with Ig-like fold-containing putative surface adhesin), enterococcal surface protein gene *esp*, gelatinase gene *gelE*, one of two putative hyaluronidase genes (*hylA*), and two of six PAI genes (*xylA*, which encodes a hypothetical protein) (Table 1). In addition, the strain was a medium biofilm producer by biofilm assay and tested negative for hemolytic activity on blood agar plates.

Microbial adherence to host cells is a pivotal stage in infection pathogenesis, regardless of the organism or infection syndrome. *E. faecalis* strains recovered from patients with endocarditis have a greater capacity to adhere to Girardi heart cells than to urinary tract epithelial cells in vitro (6), which suggests that adherence to vascular endothelium may be important. MSCRAMMs mediate binding of bacteria to extracellular matrix proteins and function as adhesins to damaged heart tissue (17, 18, 27). Ace is a specific collagen-binding adhesin of the MSCRAMM family, has been identified in *E. faecalis* endocarditis isolates (17), and mediates attachment of *E. faecalis* to collagen types I and IV and laminin (18). Subsequently, a family of seven genes encoding MSCRAMM-like proteins was found in 100% (nine out of nine) of the *E. faecalis* endocarditis strains tested, and elevated titers of IgG to these MSCRAMM-like proteins were found in the sera of nine patients with *E. faecalis* infections (27). Three of these genes, *ebpA*, *ebpB*, and *ebpC* (*e*ndocarditis- and *b*iofilm-associated *p*ili), control sur-

TABLE 2. Characteristics of patients with infective endocarditis due to VR *E. faecalis*

Patient no., age (yr)/sex[a] (reference)	Predisposing heart condition[b]	Valve(s) involved[b]	Susceptibility data[c]	Vancomycin resistance phenotype[d]	Antibiotic therapy (duration [wk])[e]	Surgical intervention[b]	Outcome	Follow-up[e]
1, 64/M (36)	AV prosthesis	AV	AMP (S), CIP (S), GEN (HLR)	NR	AMP + CIP (2)	No	Death	Death 2 wk after diagnosis of endocarditis
2, 61/M (34)	None	AV	AMP (S), OFX (S), GEN (HLR)	NR	AMP + OFX (6)	AV replacement	Cure	1 mo
3, 68/M (4)	MV prosthesis	MV	AMP (S), GEN (S)	VanA^r	AMP (8) + GEN (6)	MV replacement	Cure	4 mo
4, 68/M (3)	Rheumatic heart disease, AV prosthesis, MV prosthesis	Undefined	PEN (S), AMP (S), GEN (S)	VanA^r	AMP + GEN (6)	No	Cure	3 mo
5, 64/M (7)	None	PV	AMP (R), GEN (R)	NR	LZD (6)	No	Death	Death 1 wk after completion of linezolid
6, 79/F (35)	MV prosthesis	Undefined	AMX (S), GEN (S), LZD (S)	VanA^r	LZD (12) + GEN (6)	No	Cure	52 mo
7, 37/F (this study)	None	AV, MV	PEN (S), AMP (S), STR (S), GEN (HLR), LZD (S), DAP (S)	VanA^r	PEN + STR (6)	No	Cure	9 mo

[a] M, male; F, female.
[b] AV, aortic valve; MV, mitral valve; PV, pulmonic valve.
[c] In vitro susceptibility data for VR *E. faecalis* isolates; antibiotic therapy, final antibiotic regimen; S, susceptible; R, resistant; HLR, high-level resistance to gentamicin (MIC, >500 μg/ml); AMP, ampicillin; AMX, amoxicillin; CIP, ciprofloxacin; DAP, daptomycin; GEN, gentamicin; LZD, linezolid; OFX, ofloxacin; PEN, penicillin; STR, streptomycin.
[d] NR, not reported.
[e] Follow-up, follow-up time without relapse after completion of antibiotic therapy, unless otherwise specified.

face pilus formation and may be important in endocarditis pathogenesis (16).

Biofilm formation, which is modulated by many genes, including *esp* and the *fsr* locus, likely serves as an important factor in *E. faecalis* infections (16, 32). In one study, *E. faecalis* endocarditis isolates produced biofilm more often than did *E. faecalis* isolates from nonendocarditis sources and from hospital fecal specimens (14). The *esp* gene, which encodes an enterococcal surface protein (Esp), plays an important role in biofilm formation (33) and has been identified more often among *E. faecalis* isolates that cause endocarditis and other bloodstream infections than in *E. faecalis* fecal isolates (14).

A quorum-sensing *fsr* locus has recently been described that regulates the transcription of a gelatinase gene (*gelE*) and a serine protease gene (*sprE*) and could contribute to *E. faecalis* virulence (22, 26, 28). The *fsr* locus regulates biofilm formation (14, 20). One study showed that 100% (12 out of 12) of the *E. faecalis* endocarditis isolates tested had *fsr* compared to only 53% (10 out of 19) of the fecal isolates tested (21). In contrast, two subsequent studies did not show an increased prevalence of *fsr* in *E. faecalis* endocarditis and bloodstream isolates (11, 23). In a rat endocarditis model, an *E. faecalis* mutant that did not produce gelatinase or serine protease had an endocarditis induction rate that was significantly reduced compared to that of wild-type *E. faecalis* (28). Further investigation is needed to elucidate the role of the *fsr* locus in the pathogenesis of *E. faecalis* infective endocarditis.

There are several other potential virulence traits of enterococci that could be operative in endocarditis pathogenesis. These include aggregation substance (1, 12); multiple genes located in a PAI, including *xylA*, *cbh*, one that encodes a hypothetical protein, and others (15, 24); hyaluronidases (15); extracellular superoxide production (9); and cytolysins-hemolysins (1, 8, 10, 30).

There is only one previous description of pathogen virulence factors in a patient with VR *E. faecalis* infective endocarditis (2, 4) (Table 2, patient 3). That patient's isolate was similar to our strain (TX2853) in that it was positive for *ace*, was a biofilm producer, and did not display hemolytic activity. In contrast to our patient's isolate, that strain was *esp* negative. Although a molecular examination for the gelatinase gene (*gelE*) was not performed, phenotypically, the strain did not produce gelatinase. The strain was positive for the *asa1* (aggregation substance) gene.

In conclusion, we report a case of VR *E. faecalis* endocarditis that failed to respond to linezolid therapy and review previously published cases of VR *E. faecalis* infective endocarditis. More information is needed in order to establish the role of linezolid in the treatment of VR *E. faecalis* endocarditis. In addition, we have also outlined the virulence traits of our patient's isolate. Further studies are needed to identify which virulence factors are operative in the pathogenesis of VR *E. faecalis* infective endocarditis and may lead to potential targets for novel therapeutic agents. Subsequent investigations should also include etiologic and prognostic cohort studies of patients with enterococcal bacteremia and infective endocarditis to identify which virulence traits play a role in the development of endocarditis and which affect outcome.

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