Oral Bacitracin: A Consideration for Suppression of Intestinal Vancomycin-Resistant Enterococci (VRE) and for VRE Bacteremia From an Apparent Gastrointestinal Tract Source

To the Editor—Intestinal colonization with vancomycin-resistant *Enterococcus faecium* (VRE) is considered the major risk factor for VRE infection and transmission. Bacitracin was previously shown to decrease VRE colonization burden during its administration. Here, we describe a neutropenic patient with VRE bacteremia, which persisted despite multiple combination therapies until decolonization was initiated with oral bacitracin.

A 25-year-old patient with leukemia and neutropenia after chemotherapy presented with *Klebsiella pneumoniae* and *Escherichia coli* bacteremia, successfully treated with doripenem. Subsequently, VRE resistant to ampicillin and daptomycin (minimum inhibitory concentration [MIC], 12 μg/mL) but susceptible to linezolid and quinupristin-dalfopristin were isolated from the patient's blood. Catheters were changed multiple times, but blood cultures continued to grow VRE despite combinations of tigecycline, rifampin, quinupristin-dalfopristin, linezolid, and ampicillin; transthoracic echocardiography was normal and an indium white blood cell scan revealed uptake consistent with focal pericecal colitis. A perirectal swab grew VRE. Based on previous reports [1–5], oral bacitracin 25 000 U/125 mL 4 times a day was begun. Forty-eight hours later, stool cultures were negative for VRE as were blood cultures for the first time in 17 days. Unfortunately, the patient later died from other causes.

Intestinal domination by VRE has been reported to precede bloodstream infections in patients with neutropenia after hematopoietic stem cell transplant [6, 7]. Recent attempts to decrease VRE bacteremia in neutropenic patients report the use of parenteral daptomycin or of

Table 1. Strains of Enterococci and Susceptibility to Bacitracin and Daptomycin

Isolate	*Enterococcus* Species	MIC, μg/mL		Reference for Strain
		BAC	DAP	
Clinical origin				
AR01/138	*E. faecium*	32	2	[11]
AR99/1107	*E. faecalis*	≥256	2	[11]
AR99/107	*E. faecalis*	≥256	2	[11]
AR96/360	*E. faecalis*	≥256	1	[11]
AR99/84	*E. faecalis*	≥256	3	[11]
AR00/128	*E. faecalis*	32	2	[11]
AR00/36	*E. faecalis*	≥256	2	[11]
AR01/215	*E. faecalis*	3	0.064	[11]
S447[a]	*E. faecium*	16	3	[12]
R446[a]	*E. faecium*	8	16	[12]
DO (TX16)	*E. faecium*	48	2	[10]
Laboratory derivative				
DO-BAC[b]	*E. faecium*	≥256	2	This study
JH2-2	*E. faecalis*	24	2	[11]
JH2-2/pAMBcr1	*E. faecalis*	≥256	2	[11]
Chicken broiler				
10-2A	*E. faecium*	≥256	2	[13]
12-5VP	*E. faecium*	≥256	2	[13]
7/12/1968	*E. faecalis*	≥256	2	[13]
13-9VP	*E. faecalis*	≥256	2	[13]
13-1VP	*E. faecalis*	≥256	2	[13]
1/13/2009	*E. faecalis*	≥256	2	[13]

Abbreviations: BAC, bacitracin; DAP, daptomycin; MIC, minimum inhibitory concentration.

[a] Clinical strain-pair isolated from patient before and after daptomycin therapy.

[b] Strain DO (TX16) serially passaged to obtain a BAC resistant derivative.

combined oral linezolid/daptomycin [8, 9]. We are concerned that the routine use of these agents for prophylaxis will increase resistance, as seen in an alarming increase in daptomycin-resistant VRE reported from one such hospital [9], and would prefer a nonabsorbed, nontherapeutic agent [1–5].

Bacitracin was previously reported to consistently decrease VRE gastrointestinal (GI) burden during its administration, although recurrence was common after bacitracin discontinuation [1–3]. For example, O'Donovan et al reported that oral bacitracin eradicated VRE from the GI tract of 8 of 8 patients (25% later recurred) [3], and Chia et al eradicated VRE in 6 of 8 patients [2]. McGeer et al reported that bacitracin eradicated VRE from 76% of patients by day 7, and that 50 000 U 4 times daily was more rapid and more effective than a lower dose [5]. Similarly, oral bacitracin plus doxycycline resulted in an early approximate 3 $\log_{10}$/g reduction in VRE and, by the end of therapy, rectal swabs of 15 of 15 patients were VRE negative [4].

To investigate if bacitracin resistance resulted in cross-resistance to daptomycin, we serially passaged an *E. faecium* endocarditis isolate [10] (bacitracin MIC, 48 μg/mL) in increasing bacitracin concentrations and obtained a derivative with bacitracin MIC ≥256 μg/mL but an unchanged daptomycin MIC (Table 1). We also found that bacitracin-resistant enterococci from animals and humans and an isogenic pair of *Enterococcus faecalis* with and without plasmid-mediated *bcr* operon, which confers bacitracin resistance [11, 13], were all daptomycin susceptible (Table 1). In turn, a clinical strain-pair of daptomycin-susceptible and resistant VRE that emerged during daptomycin therapy [12] had similarly low bacitracin MICs (Table 1).

In summary, we present results that suggest a benefit, by decreasing the intestinal VRE burden, of oral bacitracin therapy as an adjunctive therapy for VRE bacteremia that failed to respond to systemic antibiotics. Neither exposure of *E. faecium* to bacitracin that resulted in resistance nor the presence of plasmid-mediated bacitracin resistance resulted in resistance to daptomycin. Thus, we suggest that clinicians consider oral bacitracin as a VRE GI suppression strategy in patients with VRE intestinal domination [6, 7], in other VRE-colonized patients considered at high risk for VRE bacteremia [14, 15], or in patients with persistent VRE bacteremia potentially from the GI tract, and we recommend that linezolid and daptomycin be reserved for therapeutic, as opposed to prophylactic, use.

Notes

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