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AUTHOR REPLY

Reply to Cabrera et al., "Outcomes of Patients with Bloodstream Infections Caused by Ampicillin-Susceptible but Penicillin-Resistant *Enterococcus faecalis*: Caution in Interpreting the Results"

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We thank Cabrera et al. (1) for their interest in our study (2) and for the valuable comments regarding (i) the reliability of *in vitro* ampicillin susceptibility as a surrogate marker for piperacillin-tazobactam (TZP), (ii) the clinical prognoses of patients with bloodstream infections (BSIs) caused by ampicillin-susceptible but penicillin-resistant (ASPR) *Enterococcus faecalis* when treated with TZP, and (iii) the efficacy of combination antimicrobial therapy in patients with high-inoculum BSIs caused by *E. faecalis*.

The Clinical and Laboratory Standards Institute guidelines described that *in vitro* ampicillin susceptibility may predict TZP susceptibility in non-beta-lactamase-producing enterococci (3); however, as a discrepancy from the rule, ASPR *E. faecalis* clinical isolates for which the MICs of piperacillin and/or TZP are high have been reported repeatedly (4, 5). In our study (2), the MICs of piperacillin for all but two (97.0%, 65/67) ASPR isolates were high, ranging from 32 to 128 μg/ml (MIC_{50} = 64 μg/ml; MIC_{90} = 128 μg/ml) by broth microdilution methods. The 65 ASPR *E. faecalis* isolates for which MICs of piperacillin were high belonged to clonal complex 28 (CC28), and they had mutations in the *pbp4* gene as well as in the promoter sequences. The other two ASPR isolates for which piperacillin MICs were 8 μg/ml belonged to CC507 and had mutations neither in the coding sequences of PBP4 nor in the promoter sequences.

Among the 67 patients with ASPR *E. faecalis* BSIs, 16 were treated with TZP-containing regimens and one was treated with ampicillin and ceftriaxone, and both regimens were devoid of glycopeptides (Table 1). Corresponding to the *in vitro* susceptibility results, the TZP-containing regimens resulted in a high 30-day mortality rate (43.8%, 7/16) of the patients with ASPR *E. faecalis* BSIs, which was much worse than that of the glycopeptide-containing regimens (28.6%, 8/28), though the difference in survival was not significant statistically ($P = 0.337$) due to the limited number of cases (Fig. 1). The patient treated with ampicillin and ceftriaxone improved.

Combination antimicrobial regimens have been recommended for serious high-inoculum enterococcal infections (6). Of the 295 *E. faecalis* BSIs that we studied, a total

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TABLE 1 Characteristics of the 17 patients with ASPR *E. faecalis* BSIs treated with ampicillin- or piperacillin-tazobactam-containing regimens[a]

Case	Age (yr)	Origin of BSI	CCI	Initial SOFA score	Antimicrobial regimen		Outcome (day of death after initial blood culture)	Strain type	MIC (μg/ml) of:			
					Beta-lactam	Second agent			AMP	PEN	IMP	PIP
A0017EF0011	66	UNK	7	5	TZP	None	Improved	CC28	8	32	8	64
A16EFA0007	48	UNK	8	15	TZP	CRO	Died (13)	CC28	4	32	8	64
B0017EF0006	76	Urinary tract	8	1	TZP	CRO	Died (26)	CC28	8	32	16	64
B0017EF0018	74	Respiratory tract	3	16	TZP	None	Died (4)	CC28	8	32	16	128
B0017EF0019	80	UNK	3	4	TZP	None	Improved	CC28	8	32	32	128
B0018EF0005	83	Respiratory tract	1	11	TZP	None	Died (16)	CC507	1	16	8	8
B16EFA0004	83	UNK	3	9	TZP	None	Improved	CC28	4	32	8	64
C0017EF0013	56	UNK	0	5	TZP	None	Improved	CC28	4	32	8	64
D0018EF0001	57	UNK	4	8	TZP	None	Died (2)	CC28	4	32	16	64
D0018EF0004	66	UNK	4	6	TZP	None	Died (4)	CC28	4	32	16	64
E0017EF0016	0	UNK	0	2	AMP	CRO	Improved	CC28	8	32	16	64
E0017EF0049	43	UNK	1	5	TZP	None	Improved	CC28	8	16	8	64
E0017EF0054	78	UNK	2	3	TZP	None	Improved	CC28	8	16	8	32
E0018EF0003	49	Peritoneal cavity	4	4	TZP	CRO	Improved	CC507	4	16	8	8
F0017EF0019	74	UNK	4	4	TZP	None	Improved	CC28	8	16	8	64
F16EFA0001	75	UNK	6	7	TZP	None	Died (1)	CC28	8	32	16	128
F16EFA0023	63	UNK	3	2	TZP	None	Improved	CC28	4	16	8	64

[a]Abbreviations: BSI, bloodstream infection; CCI, Charlson comorbidity index; SOFA, sepsis-related organ failure assessment; AMP, ampicillin; PEN, penicillin; IMP, imipenem; PIP, piperacillin; CRO, ceftriaxone; TZP, piperacillin-tazobactam; UNK, unknown; CC, clonal complex.

of 257 cases were preselected by excluding 38 cases with lower-risk sources of BSIs (urinary tract infection, $n = 33$; central-line infection, $n = 5$) to compare the clinical prognoses of monotherapy and combination therapy. Among them, 61 patients were treated with antimicrobial regimens containing either ampicillin or TZP without glycopeptides, and 8 of the 45 patients (17.8%) who received monotherapy and 3 of the 16 patients (18.8%) who received combination therapy (9 cases with ceftriaxone and 7 cases with aminoglycosides) died within 30 days (Fig. 2). In sum, no significant difference in survival between monotherapy and combination therapy was observed ($P = 0.998$). Among 56 patients treated with regimens containing glycopeptides, none was treated with aminoglycoside combination therapy.

In conclusion, most ASPR *E. faecalis* blood isolates exhibited piperacillin MICs of $\geq$32 μg/ml, which means that *in vitro* susceptibility to penicillin in non-beta-lactamase-producing enterococci is a better surrogate marker for piperacillin susceptibility than that to ampicillin. Antimicrobial treatment using TZP-containing regimens for the

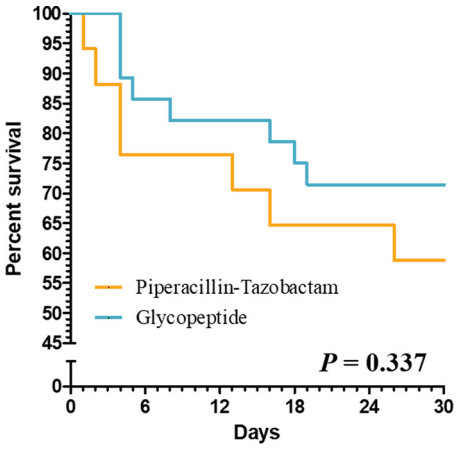

FIG 1 Survival analysis of the patients with ASPR *E. faecalis* BSIs according to antimicrobial regimens, using the log rank test. Piperacillin-tazobactam-containing regimens were without glycopeptides. The line labeled "Glycopeptide" indicates results with glycopeptide-containing regimens.

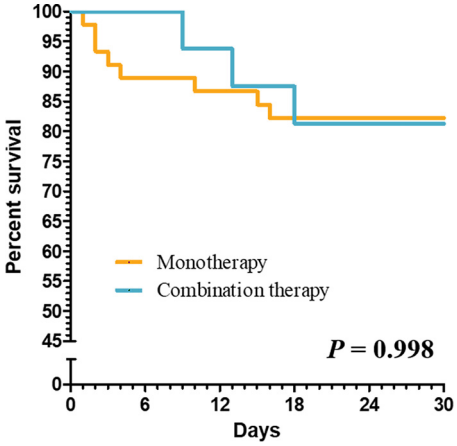

FIG 2 Survival analysis of the patients with *E. faecalis* BSIs treated with ampicillin- or piperacillin-containing regimens without glycopeptides, according to monotherapy and combination therapy, using the log rank test.

patients with BSIs caused by ASPR *E. faecalis* may result in a worse prognosis. For the usefulness of the combination antimicrobial therapy, further study is needed with a high-enough number of clinical cases.

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