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Bowel colonization with vancomycin-resistant enterococci after antimicrobial therapy for intra-abdominal infections: observations from 2 randomized comparative clinical trials of ertapenem therapy☆

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Abstract

The impact of different antimicrobial regimens for intra-abdominal infections on the frequency of bowel colonization with vancomycin-resistant enterococci (VRE) was examined in 2 randomized open-label trials of intra-abdominal infection comparing piperacillin–tazobactam or ceftriaxone/metronidazole with ertapenem. In these short-term studies, overall rates of bowel colonization with VRE were generally comparable after treatment with piperacillin–tazobactam, ceftriaxone/metronidazole, or ertapenem.

Keywords: Vancomycin-resistant enterococci; Bowel flora; Intra-abdominal infection; OASIS; Ertapenem

Broad-spectrum antimicrobial therapy may predispose to colonization with resistant organisms (Safdar and Maki, 2002; Paterson, 2004; Donskey et al., 2000; Donskey, 2004). In 2 double-blind randomized clinical trials examining treatment of complicated intra-abdominal infections, the efficacy of ertapenem was comparable with that of piperacillin–tazobactam (Solomkin et al., 2003) and ceftriaxone/metronidazole (Yellin et al., 2002). Subsequently, 2 open-label randomized studies (Optimizing Intra-Abdominal Surgery with Invanz Studies [OASIS]) confirmed the efficacy of ertapenem in treating intra-abdominal infections (Dela Pena et al., 2006; Navarro et al., 2005). Serial rectal cultures were obtained from participants enrolled in OASIS I and II, allowing assessment of the relative impact of therapy with ertapenem, piperacillin–tazobactam, and ceftriaxone/metronidazole on bowel colonization by vancomycin-resistant enterococci (VRE).

Adults with intra-abdominal infections requiring surgery were eligible to enter open-label randomized trials comparing ertapenem 1 g once a day with either piperacillin–tazobactam 13.5 g/day in 3 to 4 divided doses (OASIS I) (Dela Pena et al., 2006) or ceftriaxone 2 g/day in 1 to 2 divided doses plus metronidazole 30 mg/kg a day in 2 to 4 divided doses (OASIS II) (Navarro et al., 2005). Patients receiving antimicrobial therapy for >24 h preoperatively were excluded unless failing the treatment. The recommended duration of study therapy was 4 to 14 days. If enterococci or methicillin-resistant *Staphylococcus aureus* were isolated, open-label vancomycin could be added at the investigator's discretion. Other nonstudy antimicrobial drugs were prohibited after the first study day.

Patients from whom rectal swabs for VRE were appropriately collected and processed at baseline and either of the later points were assessable for the present analysis. The clinical microbiology laboratory was blinded to treatment

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allocation. Cultures were to be obtained using rayon-tipped swabs (BBL CultureSwab, Becton Dickinson, Franklin Lalees, NJ) before the start of study therapy (baseline), at the end of study therapy, and 2 weeks after stopping study therapy. Rectal swabs were immediately placed in Stuart's liquid transport media, refrigerated on-site, and transported to a central Merck laboratory within 1 week. Specimens were plated on Enterococcosel agar (BBL Microbiology Systems, Cockeysville, MD) containing 8 μg of vancomycin/mL to screen for VRE. If growth was detected, identification and susceptibility testing were performed using the MicroScan Walkaway 96 SI system (Dade Behring, Sacramento, CA). Only confirmed enterococcal isolates with a vancomycin MIC ≥32 μg/mL determined by MicroScan were included as VRE in this analysis.

Frequencies of colonization with VRE within a treatment group between baseline and a later point were compared using exact McNemar tests for paired-response data. Acquisition rates of VRE between treatment groups were compared using Fisher exact tests. No adjustment was made for multiple comparisons.

Baseline characteristics, duration of study therapy, and nonstudy antimicrobial drug use were generally similar in the ertapenem and corresponding comparator groups (Table 1). Appendicitis accounted for most cases in both studies. Most participants received antimicrobial treatment before entry, although concomitant use of nonstudy antibacterial agents (including vancomycin) during study treatment after the first day was infrequent.

VRE were recovered from none of 51 assessable piperacillin–tazobactam recipients at baseline or at the end of therapy, and from 1 (*Enterococcus faecium*) of 43 assessable ertapenem recipients at the end of therapy compared with none at baseline ($P = 0.32$) (Table 2). Two weeks after stopping study therapy, VRE were recovered from 1 (*E. faecium*) of 42 assessable piperacillin/tazobactam recipients compared with none at baseline ($P = 0.32$), and from 1 (*E. faecium*) of 37 assessable ertapenem recipients compared with none at baseline ($P = 0.32$). Overall, among assessable recipients in OASIS I, VRE were acquired by 1 ertapenem recipient (2.3%) versus 0 piperacillin/tazobactam recipients (0%) during therapy ($P = 0.46$), and by 1 ertapenem recipient (2.7%) and 1 piperacillin/tazobactam recipient (2.4%) during the study ($P = 1.00$).

VRE were recovered from 3 (all *E. faecium*) of 85 assessable ceftriaxone/metronidazole recipients at the end of therapy compared with 0 at baseline ($P = 0.08$), and from 3 (all *E. faecium*) of 89 assessable ertapenem recipients at the end of therapy compared with 2 at baseline ($P = 0.32$). Two weeks after stopping study therapy, VRE were recovered from 2 (1 *Enterococcus faecalis* and 1 *E. faecium*) of 73 assessable ceftriaxone–metronidazole recipients compared with none at baseline ($P = 0.16$), and 3 (1 *Enterococcus casseliflavus* and 2 *E. faecium*) of 81 assessable ertapenem

Table 1
Baseline characteristics in assessable patients[a] by treatment group

	OASIS I		OASIS II	
	Ertapenem, $n = 51$	Piperacillin–tazobactam, $n = 57$	Ertapenem, $n = 95$	Ceftriaxone/metronidazole, $n = 87$
Age (years)				
Mean (SD)	48 (18)	49 (19)	45 (18)	46 (20)
Median (range)	44 (20–85)	47 (18–84)	45 (18–85)	42 (18–88)
Female, *n* (%)	16 (31%)	19 (33%)	25 (26%)	26 (30%)
Geographic origin, *n* (%)				
Asia[b]	7 (14%)	7 (12%)	37 (39%)	29 (33%)
Mexico			6 (6%)	
South America			15 (16%)	20 (23%)
Europe	32 (63%)	36 (63%)	28 (29%)	32 (37%)
South Africa	8 (16%)	8 (14%)	4 (4%)	4 (5%)
Middle East	4 (8%)	6 (11%)	5 (5%)	2 (2%)
Type of intra-abdominal infection, *n* (%)				
Postoperative	4 (8%)	2 (4%)	2 (2%)	2 (2%)
Spontaneous	43 (84%)	54 (95%)	91 (96%)	91 (96%)
Posttraumatic	4 (8%)	1 (2%)	2 (2%)	2 (2%)
Prior antibacterial therapy, *n* (%)	38 (75%)	39 (68%)	57 (60%)	62 (71%)
For >24 h before study therapy	5 (10%)	3 (5%)	7 (7%)	7 (8%)
For >48 h before study therapy	4 (8%)	2 (4%)	4 (4%)	7 (8%)
Duration of study therapy (days)				
Mean (SD)	6 (1.9)	7 (2.5)	7 (2.6)	7 (2.5)
Median (range)	6 (4–14)	6 (4–17)	6 (4–16)	6 (4–14)
Concomitant use of vancomycin				
Frequency, *n* (%)	0	1 (2)	2 (2)	0
Median duration (days)	–	1	7	–

[a] For the purposes of this tabulation, assessable patients included any patient who received at least 1 dose of study drug and had rectal cultures appropriately processed at baseline and at either or both of the subsequent visits.

[b] Excluding the Middle East.