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Acquisition of Resistant Bowel Flora during a Double-Blind Randomized Clinical Trial of Ertapenem versus Piperacillin-Tazobactam Therapy for Intraabdominal Infections

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Bowel colonization with resistant bacteria can develop in patients receiving broad-spectrum antimicrobial therapy. We compared the impact of two antimicrobial regimens often used to treat intraabdominal infections on susceptibility patterns of bowel flora at the end of therapy. In a double-blind clinical trial, adults with complicated intraabdominal infection requiring surgery were randomized to receive piperacillin-tazobactam (3.375 g every 6 h) or ertapenem (1 g once a day) for 4 to 14 days. Rectal swabs were obtained at baseline and at the end of study therapy to determine the acquisition rates of *Enterobacteriaceae* resistant to the study drug, extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* or *Klebsiella* species, *Pseudomonas aeruginosa* resistant to imipenem or piperacillin-tazobactam, and vancomycin-resistant *Enterococcus faecalis* or *Enterococcus faecium*. Treated patients were assessable for the acquisition of resistant bacteria if appropriate specimens were obtained at both time points. *Enterobacteriaceae* resistant to the treatment received were acquired during study therapy by 8/122 assessable piperacillin-tazobactam recipients (6.6%) compared to 0/122 assessable ertapenem recipients ($P = 0.007$). Neither ESBL-producing *E. coli* or *Klebsiella* species nor *P. aeruginosa* resistant to piperacillin-tazobactam was isolated from patients in either treatment group. Imipenem-resistant *P. aeruginosa* was acquired by two of the ertapenem recipients (1.6%) versus zero of the piperacillin-tazobactam recipients ($P = 0.50$). Vancomycin-resistant enterococci were acquired during therapy by 8/125 assessable ertapenem recipients (6.4%) versus 2/123 assessable piperacillin-tazobactam recipients (1.6%; $P = 0.10$). In this study, the acquisition of resistant *Enterobacteriaceae* occurred significantly more often in patients treated with piperacillin-tazobactam than in those treated with ertapenem.

Treatment with antimicrobial agents broadly active against enteric bacteria has the potential to select for bowel colonization with resistant organisms during therapy (23). In turn, bowel flora may provide an important reservoir for the spread of resistant bacteria (4, 5, 9, 18). The acquisition of resistant bowel flora by patients during treatment may provide early evidence of emerging resistance (4).

Ertapenem is a carbapenem used increasingly as monotherapy for certain mixed aerobic-anaerobic infections (24). In two blinded randomized clinical trials (14, 25), the efficacy of ertapenem was comparable to that of piperacillin-tazobactam for complicated intraabdominal infections. In the more recent study (14), serial rectal cultures were obtained from participants at the beginning and end of study therapy. These data offer an opportunity to assess the relative impact of ertapenem versus piperacillin-tazobactam therapy on the acquisition of resistant aerobic gram-negative bacilli and vancomycin-resistant enterococci.

MATERIALS AND METHODS

Primary study design. Adults with intraabdominal infections requiring surgery were eligible for a double-blind (with laboratory blinding) randomized trial (14) comparing ertapenem (1 g once daily) with piperacillin-tazobactam (3.375 g every 6 h). The recommended duration of study therapy was 4 to 14 days. Patients who had received preoperative nonstudy antimicrobial therapy for >24 h or >2 doses of an antimicrobial regimen postoperatively were ineligible for the study unless they were failing treatment. Nonstudy antimicrobial drugs were prohibited after the first day of the study except for the use of vancomycin for patients with microbiologically documented methicillin-resistant *Staphylococcus aureus* or enterococcal infections.

Design of nested bowel colonization study. Rectal cultures were to be obtained from all participants at the initiation and discontinuation of study therapy using cotton-tipped swabs placed in buffered glycerol saline (Remel, Lenexa, KS) and rayon-tipped swabs placed in Stuart's medium (Becton Dickinson, Sparks, MD). Baseline specimens could be obtained from 2 days before until 1 day after the first day of study therapy. End-of-therapy specimens could be obtained from the day before until 3 days after the discontinuation of study therapy. Culture specimens were refrigerated until they were transported to the central Merck microbiology laboratory.

MacConkey agar plates with ertapenem (0.5 μg/ml), piperacillin (5 μg/ml)-tazobactam (μg/ml), or ceftazidime (1 μg/ml) were inoculated from swabs in buffered glycerol saline vials. Identification and susceptibility testing were performed on all unique colony types growing on the selective medium by using a MicroScan system (Dade MicroScan, Sacramento, CA). MICs of ertapenem and piperacillin-tazobactam for resistant *Enterobacteriaceae* were confirmed by the epsilometric test (Etest; AB Biodisk, Culver City, CA). Susceptibility results were interpreted according to National Committee for Clinical Laboratory Standards breakpoints (15).

Escherichia coli and *Klebsiella* species growing on ceftazidime-supplemented MacConkey agar were tested for extended-spectrum β-lactamase (ESBL) production by the double-disk test. ESBL production was defined as a ≥5-mm increase in zone diameter for ceftazidime or cefotaxime tested with clavulanic acid compared to the zone diameter when tested alone (15). *Pseudomonas*

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aeruginosa recovered from antibiotic-containing plates was tested for susceptibility to imipenem and piperacillin-tazobactam.

Specimens in Stuart's medium were plated on Enterococcosel agar (BBL Microbiology Systems, Cockeysville, MD) containing 8 μg of vancomycin/ml to screen for vancomycin-resistant enterococci. If growth was detected, identification and susceptibility testing of the isolate by MicroScan was routinely confirmed with conventional methods. Only confirmed *Enterococcus faecalis* and *Enterococcus faecium* with a vancomycin MIC of ≥32 μg/ml by Etest were counted as vancomycin-resistant enterococci in this analysis.

Statistical methods. The primary objective of this study was to compare acquisition rates of resistant target organisms during study therapy between treatment groups. The prevalences of resistant target organisms within each treatment group between baseline and the end of study therapy were also compared. Participants who received at least one dose of the study drug and from whom rectal swabs were obtained at baseline and at the end of therapy could be assessed for the acquisition of resistant bowel flora during study therapy. The assessable population for each target organism included all treated patients from whom appropriate specimens for the specific target organism were obtained at baseline and at the end of study therapy. Since specimens for different target organisms were processed separately, the assessable population could differ depending on target organism. The prevalence of resistance at baseline or at the end of therapy was expressed as the number of patients with any resistant *Enterobacteriaceae*, imipenem- or piperacillin-tazobactam-resistant *P. aeruginosa*, or vancomycin-resistant enterococci divided by the total number of patients assessable for the specified target organism. For an individual patient, resistant bacteria present at the end of therapy were considered to have been acquired during therapy if resistance in that species had not been detected at baseline, whereas resistant bacteria were presumed to have persisted during therapy if the same resistant species isolated at baseline was again recovered at the end of therapy.

Comparisons of frequencies of resistant target organisms within a treatment group between baseline and end of therapy were made by exact McNemar tests for paired-response data. Acquisition rates between treatment groups were compared by Fisher exact tests. No adjustment was made for multiplicity.

RESULTS

There were 251 patients randomized to ertapenem and 249 patients randomized to piperacillin-tazobactam, of whom 247 in each group were treated with the study drug (14). Fifty-three percent of randomized patients in each treatment group were assessable for the acquisition of one or more resistant target organisms during study therapy; the others were excluded from the analysis because of missing or inadequate specimens at baseline and/or the end of therapy. Baseline characteristics and nonstudy antimicrobial use for assessable patients are shown by treatment group in Table 1. Assessable patients were comparable in baseline characteristics to the entire randomized population.

Over 90% of assessable patients had received antimicrobial treatment in the 14 days before entering the study. The type and frequency of prior antimicrobial use in the two treatment arms were generally similar. The most commonly used antibacterial agents prior to study entry included metronidazole, piperacillin-tazobactam, levofloxacin, cefotetan, and cefazolin. The use of nonstudy antibacterial agents concomitantly with the study drug (other than overlap therapy on the first and last day of study treatment) was much less frequent than prestudy use, although almost twice as common in the piperacillin-tazobactam group (20.5%) than in the ertapenem group (10.6%). Vancomycin (as allowed by protocol) was the most frequent concomitant antibacterial drug in both treatment groups, followed by metronidazole. Between the first and last days of study therapy, 5 (3.8%) of the assessable ertapenem recipients and 19 (14.4%) of the assessable piperacillin-tazobactam recipients received vancomycin.

TABLE 1. Participant characteristics and nonstudy therapy in assessable patients by treatment group[a]

Participant characteristic	No. of patients in treatment group indicated	
	Ertapenem (n = 132)	Piperacillin-tazobactam (n = 132)
Age, yr		
Mean (standard deviation)	51.8 (17.6)	50.3 (18.0)
Median (range)	51 (18–86)	49 (18–89)
No. female (%)	51 (38.6)	48 (36.4)
No. with indicated site of infection (%)		
Appendix	57 (43.2)	56 (42.4)
Gallbladder or biliary tract	9 (6.8)	7 (5.3)
Colon	31 (23.5)	26 (19.7)
Stomach or duodenum	14 (10.6)	17 (12.9)
Lower small bowel	9 (6.8)	12 (9.1)
Other	12 (9.1)	14 (10.6)
No. receiving prior antibacterial therapy (%)	123 (93.2)	120 (90.9)
No. receiving a concomitant antibacterial drug (%)[b]	14 (10.6)	27 (20.5)
No. receiving vancomycin therapy (%)		
Prior therapy	7 (5.3)	3 (2.3)
Concomitant therapy	5 (3.8)[c]	19 (14.4)[d]

[a] Assessable patients include all patients assessable for the acquisition of at least one resistant target organism, including *Enterobacteriaceae*, *E. faecalis*, *E. faecium*, and/or *P. aeruginosa*.

[b] Includes all antibacterial treatment other than the study drug administered between the first and last day of study therapy.

[c] All five patients received intravenous vancomycin.

[d] In 4 of these 19 patients, vancomycin was administered orally only; in one other patient, the route of vancomycin administration was not specified.

Enterobacteriaceae resistant to piperacillin-tazobactam were recovered from 9/122 assessable piperacillin-tazobactam recipients (7.4%) at the end of therapy, compared to 1 patient (0.8%) at baseline ($P = 0.008$) (Table 2). No ertapenem-resistant *Enterobacteriaceae* were recovered from the 122 assessable ertapenem recipients at either baseline or the end of therapy. The acquisition of *Enterobacteriaceae* resistant to the treatment received occurred significantly more often during piperacillin-tazobactam treatment (6.6%) than during ertapenem treatment (0.0%) ($P = 0.007$). Nine resistant *Enterobacteriaceae* species were acquired during therapy by eight piperacillin-tazobactam recipients, as follows: *Enterobacter cloacae* (four patients) and *Enterobacter aerogenes*, *Enterobacter asburiae*, *E. coli*, *Klebsiella pneumoniae*, and *Serratia plymuthica* (one patient each). No ESBL-producing *E. coli* or *Klebsiella* species were acquired by either treatment group. Imipenem-resistant *P. aeruginosa* was acquired by two ertapenem recipients (1.6%), compared to zero piperacillin-tazobactam recipients ($P = 0.50$). No isolates of *P. aeruginosa* resistant to piperacillin-tazobactam were recovered at baseline or the end of therapy from either treatment group.

Vancomycin-resistant enterococci were recovered from 2/123 piperacillin-tazobactam recipients (1.6%) at end of therapy, compared to none at baseline ($P = 0.50$), and from 9/125 ertapenem recipients (7.2%) at end of therapy, compared to 1 patient (0.8%) at baseline ($P = 0.008$) (Table 3). Vancomycin-resistant enterococci were acquired by eight assessable ertapenem recipients (6.4%) versus two assessable piperacillin-ta-

TABLE 2. Frequency of assessable patients with resistant gram-negative bacilli isolated from rectal swabs at different time points during the study by treatment group[a]

Isolate	No. of assessable patients in treatment group and at time point indicated (%)[b]			
	Ertapenem		Piperacillin-tazobactam	
	Baseline	End of therapy	Baseline	End of therapy
Piperacillin-tazobactam-resistant *Enterobacteriaceae*	1 (0.8)	2 (1.6)	1 (0.8)	9 (7.4)
Ertapenem-resistant *Enterobacteriaceae*	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
ESBL-producing *E. coli* or *Klebsiella* species	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imipenem-resistant *P. aeruginosa*	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Piperacillin-tazobactam-resistant *P. aeruginosa*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Assessable patients include those patients who received at least one dose of therapy and had adequate specimens for gram-negative bacilli collected at both baseline and the end of therapy. There were 122 patients assessable for resistant gram-negative target organisms in each treatment group.
[b] The number of assessable patients with resistant gram-negative target organisms is given.

zobactam recipients (1.6%) during therapy ($P = 0.10$). Vancomycin-resistant enterococcal species acquired during therapy were both *E. faecium* in the piperacillin-tazobactam group, and one instance of *E. faecalis* and seven of *E. faecium* in the ertapenem group.

The median duration of study therapy for patients not acquiring resistant target organisms was 6 days for both treatment groups. For the eight piperacillin-tazobactam recipients acquiring resistant *Enterobacteriaceae*, the median duration of piperacillin-tazobactam therapy was 8.5 days (range, 6 to 15 days). Three of these patients received nonstudy antibacterial drugs (2 days of cefazolin, 4 days of vancomycin and 1 day of cefotetan, and 1 day of metronidazole for one patient each) concurrently with piperacillin-tazobactam. The median duration of ertapenem therapy for the eight ertapenem recipients acquiring vancomycin-resistant enterococci was 9 days (range, 7 to 20 days). None of these patients received concomitant antibacterial therapy. The two piperacillin-tazobactam recipients who acquired vancomycin-resistant enterococci received piperacillin-tazobactam for 4 and 12 days. One of these patients received 6 days of ciprofloxacin concurrently with piperacillin-tazobactam.

DISCUSSION

Treatment of patients with broad-spectrum antimicrobial agents predisposes to the emergence of resistant bowel flora during therapy (1, 4, 12, 22, 23, 26, 27). Resistant organisms can emerge through genetic mutation or induction, can be acquired exogenously, or, if already present in undetectably low concentrations, may overgrow under selective pressure. The present analysis prospectively compared the frequency with which the standard use of ertapenem or piperacillin-tazobactam for intraabdominal infections was associated with bowel colonization by resistant *Enterobacteriaceae*, *P. aeruginosa* resistant to imipenem or piperacillin-tazobactam, or vancomycin-resistant enterococci in patients enrolled in a double-blind, randomized, comparative trial (14).

Our analysis has several shortcomings. Approximately half of the enrolled patients could not be assessed for the acquisition of resistant target bacteria. Although our study focused on the effect of the study drug on the acquisition of resistant organisms from baseline to the end of study therapy, many participants in both treatment groups had received antimicrobial agents in the 14 days prior to study entry. However, nonprotocol antibacterial agents were administered much less frequently during study therapy, which constituted the critical interval for our analysis. Only 4 of 18 patients acquiring resistant target organisms received nonstudy antibacterial drugs concomitantly with the study drug. The sensitivity of rectal swabs in identifying resistant bowel flora may be lower than stool cultures for some organisms (3, 11, 29). Given the small sample size, a true difference between treatment groups cannot be confidently excluded on the basis of failure to demonstrate a significantly increased frequency of a resistant target organism at the end of therapy in one group.

In this study, the prevalence of bowel colonization with *Enterobacteriaceae* resistant to the study drug significantly increased from baseline to the end of therapy in the piperacillin-tazobactam treatment group. The acquisition rate of resistant *Enterobacteriaceae* was significantly higher in participants treated with piperacillin-tazobactam (6.6%) than in partici-

TABLE 3. Proportion of assessable patients with vancomycin-resistant enterococci isolated from rectal swabs at different time points during the study by treatment group[a]

Isolate	No. of assessable patients in treatment group and at time point indicated (%)[b]			
	Ertapenem		Piperacillin-tazobactam	
	Baseline	End of therapy	Baseline	End of therapy
Vancomycin-resistant *E. faecalis*	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Vancomycin-resistant *E. faecium*	1 (0.8)	8 (6.4)	0 (0.0)	2 (1.6)

[a] Assessable patients include those patients who received at least one dose of therapy and from whom adequate specimens for enterococci were collected at both baseline and the end of therapy. The number of patients assessable for vancomycin-resistant enterococci was 125 for the ertapenem treatment group and 123 for the piperacillin-tazobactam treatment group.
[b] The number of assessable patients with vancomycin-resistant enterococci is given.

pants treated with ertapenem (0%). Piperacillin-tazobactam has been in widespread clinical use much longer than the recently introduced ertapenem. Mutations in genes encoding class C or A β-lactamases in *Enterobacteriaceae* would more likely result in piperacillin-tazobactam resistance than ertapenem resistance. The horizontal spread of bacteria already resistant to piperacillin-tazobactam may occur more readily than de novo selection of ertapenem-resistant bacteria.

The prevalence of bowel colonization with vancomycin-resistant *E. faecalis* and *E. faecium* significantly increased from baseline to the end of therapy in ertapenem-treated patients. The difference in acquisition rates for vancomycin-resistant enterococci between the two treatment groups did not reach statistical significance. The frequency of vancomycin use was higher for the piperacillin-tazobactam group than for the ertapenem group, although the importance of intravenous vancomycin in selecting for bowel colonization with vancomycin-resistant enterococci has been challenged (8, 16, 17). In our study, none of the patients who acquired vancomycin-resistant enterococci received vancomycin or cephalosporins concomitantly with the study drug. The sensitivity of our methods for identifying bacteria resistant to antimicrobial agents other than the administered study drug may be diminished when the study drug retains some activity against the resistant target organism (8, 26, 27). Unlike ertapenem, to which almost all enterococci are intrinsically resistant, piperacillin-tazobactam has antienterococcal activity. Piperacillin-tazobactam in the stool may transiently suppress the emergence of vancomycin-resistant enterococci. Colonization with vancomycin-resistant enterococci may become evident shortly after discontinuation of treatment with active antimicrobial agents that are excreted into the bowel (27).

The lower acquisition rates of resistant *Enterobacteriaceae* in ertapenem compared to piperacillin-tazobactam recipients observed in this study are consistent with the findings of two open-label comparative trials in which bowel colonization with resistant *Enterobacteriaceae* was less likely to develop after treatment of intraabdominal infections with ertapenem than with either piperacillin-tazobactam (6) or ceftriaxone/metronidazole (7). The clinical and epidemiological consequences of bowel colonization with resistant bacteria cannot be ascertained from our data, but rectal colonization with resistant microorganisms may portend the nosocomial spread and subsequent development of serious infections with difficult-to-treat bacteria (2, 10, 13, 17, 19, 20, 21, 28).

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