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 8/125 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
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-
Vancomycin-resistant enterococcal species acquired during therapy were both Vancomycin-resistant enterococcus species acquired during 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. There were 122 patients assessable for resistant gram-negative target organisms in each treatment group.

For the eight piperacillin-tazobactam 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. Piperacillin-tazobactam 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-

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**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**

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Ertapenem</th>
<th>Piperacillin-tazobactam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of therapy</td>
</tr>
<tr>
<td></td>
<td>(no. %)</td>
<td>(no. %)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam-resistant Enterobacteriaceae</td>
<td>1 (0.8)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Ertapenem-resistant Enterobacteriaceae</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>ESBL-producing E. coli or Klebsiella species</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Imipenem-resistant P. aeruginosa</td>
<td>0 (0.0)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam-resistant P. aeruginosa</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*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. The number of patients assessable for vancomycin-resistant enterococci was 125 for the ertapenem treatment group and 123 for the piperacillin-tazobactam treatment group.

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

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Ertapenem</th>
<th>Piperacillin-tazobactam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of therapy</td>
</tr>
<tr>
<td></td>
<td>(no. %)</td>
<td>(no. %)</td>
</tr>
<tr>
<td>Vancomycin-resistant E. faecalis</td>
<td>0 (0.0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Vancomycin-resistant E. faecium</td>
<td>1 (0.8)</td>
<td>8 (6.4)</td>
</tr>
</tbody>
</table>

*a* The number of assessable patients with vancomycin-resistant enterococci is given.
pents 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-lactamas 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 Enterococcus faecalis and E. faecium significantly increased from baseline to the end of therapy in ertapenem-treated patients. The lower acquisition rates of resistant Enterobacteriaceae in etrapenem 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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