

The Role of Ertapenem for the Treatment of Complicated Intra-abdominal Infections With a Positive Culture for *Enterococcus faecalis*

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Controversy remains as to whether *Enterococcus faecalis* recovered from intra-abdominal infections (IAIs) requires targeted therapy. In a multicenter study comparing patients with IAIs from which *E. faecalis* was identified in intra-abdominal cultures, no difference in clinical outcomes was observed between patients receiving ertapenem vs those receiving piperacillin/tazobactam.

Keywords. *Enterococcus faecalis*; ertapenem; intra-abdominal infection.

Enterococcus faecalis is isolated in up to 30% of intra-abdominal infections (IAIs) [1–3]. However, its pathogenicity in mixed infections remains unclear. Ertapenem is a broad-spectrum antibiotic with activity against a range of gram-positive, gram-negative, and anaerobic gastrointestinal organisms but with limited activity against *E. faecalis* [4, 5]. Previous studies have shown that ertapenem is equally effective as piperacillin-tazobactam (PTZ) for the treatment of complicated IAIs (cIAIs) [3, 6–8], supporting the notion that targeted enterococcal therapy may not be necessary in polymicrobial infections. However, these studies included small numbers of patients with confirmed *E. faecalis*. We conducted a multicenter observational study comparing the clinical outcomes of patients with cIAIs and adequate source control with intra-abdominal cultures growing *E. faecalis* who received ertapenem or PTZ.

METHODS

Patients 13 years of age and older admitted with cIAIs who underwent appropriate source control measures through surgery or percutaneous drainage and had an intra-abdominal fluid culture positive for *E. faecalis* between 2012 and 2017 were included. cIAI was defined as an IAI extending into the peritoneal space and associated with either peritonitis or abscess formation. Participating hospitals included The Johns Hopkins Hospital (1194 beds), Bayview Medical Center (560 beds), Sibley Memorial Hospital (318 beds), Howard County General Hospital (264 beds), and Suburban Hospital (222 beds), all part of the Johns Hopkins Health System (JHHS).

Patients were excluded if any of the following criteria were met: (1) receipt of an agent with in vitro coverage of *E. faecalis* (with the exception of PTZ if assigned to the PTZ group) for more than 24 hours (ie, ampicillin, imipenem-cilastatin, meropenem, vancomycin, linezolid, or daptomycin); (2) receipt of <4 calendar days [9] of the prescribed antibiotic (ertapenem or PTZ); (3) sequential receipt of both ertapenem and PTZ; (4) lack of adequate source control within 4 days of presentation, as determined by 2 physicians; or (5) recovery of additional organisms from intra-abdominal fluid that were not susceptible to the prescribed antibiotic (eg, *Pseudomonas aeruginosa*, carbapenem-resistant *Enterobacteriaceae*).

Clinical data were manually collected from electronic health records for all patients. An immunocompromised state was defined by any of the following: chemotherapy within 6 months before presentation, hematologic stem cell transplantation within 12 months before presentation, absolute neutrophil count <500/μL, HIV with CD4 cell count <200/mm³, or ≥10 mg/d of corticosteroids or immunomodulators for greater than 2 weeks. The following were collected as proxies for severity of illness, all within 72 hours of the surgical procedure: intensive care unit admission for reasons other than routine postoperative care, highest APACHE 2 score achieved, vasopressor requirement for >1 calendar day, and mechanical ventilation for >1 calendar day. IAIs were classified as community-acquired if there was no previous intra-abdominal intervention related to the current infection within 90 days before the current hospital admission.

Outcomes

The primary outcome was clinical failure within 30 days of presentation, which was a composite outcome (adjudicated by 2 physicians and discussed with a third if there was disagreement), including (1) an unplanned subsequent intra-abdominal intervention, (2) additional unplanned antibiotic courses related to the original IAI, or (3) death [9]. JHHS outpatient records and the Epic Care Everywhere network were reviewed for all patients

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to identify relevant postdischarge data as this network provides access to clinical information from a large number of health care facilities using Epic electronic health records throughout the United States. The study was approved by the Johns Hopkins Institutional Review Board with a waiver of informed consent.

Statistical Analysis

Baseline categorical data were compared using the chi-square or Fisher exact test, as appropriate, and continuous data were compared using the Wilcoxon rank-sum test. Unadjusted odds ratios and 95% confidence intervals were calculated for the analysis of clinical failure within 30 days. Covariates with a *P* value of <.10 on univariable analysis that resulted in a ≥10% change in the parameter estimate of the ertapenem group were retained in the final multivariable logistic regression model. A 2-sided *P* value <.05 was considered statistically significant for all tests. Statistical analysis was completed using STATA, version 13.0 (StataCorp, College Station, TX).

RESULTS

Overall, 754 patients with intra-abdominal fluid cultures positive for *E. faecalis* were evaluated, and 538 were excluded. The primary reasons for exclusion (categories not mutually

exclusive) included treatment with a nonstudy drug (21%), treatment with a study drug for <4 calendar days (18%), or recovery of *Pseudomonas* spp. or multidrug-resistant gram-negative organisms (17%). There were 216 patients who met eligibility criteria, 65 patients (30%) received ertapenem, and 151 patients (70%) received PTZ. Demographic characteristics, severity of illness, immunocompromised status, and preexisting medical conditions were generally similar between the 2 groups (Table 1). Of note, there were no patients meeting eligibility criteria with IAIs with confirmed extended-spectrum beta-lactamases (ESBL) infections. Patients in the PTZ group had a trend toward higher median APACHE 2 scores (9.2 vs 10.5, *P* = .07) and had higher median weights (73 vs 77 kg, *P* = .05).

More than 95% of patients received ertapenem dosed at 1 g intravenously once a day; PTZ was dosed at 3.375 g intravenously every 6 hours over 30 minutes (or its equivalence when accounting for renal function) for all patients who received this agent. There were some differences in the source of IAI between the treatment groups (Table 1). Among patients receiving ertapenem, the small bowel was the source of IAI for 55%, the biliary tree for 32%, and colorectal for 12%. Among patients receiving PTZ, the sources of IAI were as follows: colorectal 59%, biliary 34%, and small bowel or appendix 7%. For both groups,

Table 1. Comparing Baseline Characteristics of Patients With *Enterococcus faecalis* Recovered From Intra-Abdominal Infections Treated With Either Ertapenem or Piperacillin/Tazobactam, With Adequate Source Control

Variables on Day of Initial Surgical Intervention	Ertapenem (n = 65)	Piperacillin/Tazobactam (n = 151)	<i>P</i> Value
Age, y	63 (54–69)	63 (52–69)	.882
Female	31 (47.7)	67 (44.4)	.653
Weight, kg	72.6 (64–83)	77.3 (61.6–89.4)	.054
Caucasian	45 (69.2)	101 (66.9)	.736
Intensive care unit admission	13 (20.0)	41 (27.2)	.266
Vasopressor requirement for >1 calendar d	5 (7.7)	17 (11.3)	.427
Mechanical ventilation >1 calendar d	4 (6.2)	12 (7.9)	.658
APACHE 2 score	9.2 (7–12)	10.5 (7–14)	.067
Preexisting medical conditions			
Diabetes	20 (30.8)	35 (23.2)	.240
End-stage liver disease	3 (4.6)	8 (5.3)	.834
End-stage renal disease requiring dialysis	1 (1.5)	3 (2.0)	.823
Congestive heart failure	11 (16.9)	24 (15.9)	.851
Structural lung disease	5 (7.7)	4 (2.6)	.132
Immunocompromised	35 (53.9)	75 (49.7)	.657
No prior intra-abdominal procedure within 90 d	42 (64.4)	96 (63.6)	1.000
Time from onset of abdominal symptoms until surgical intervention, d	3.0 (1–3)	2.1 (1–3)	.629
Intra-abdominal organ of origin			
Biliary	21 (32.3)	52 (34.4)	.876
Small bowel	36 (55.4)	5 (3.3)	.000
Appendix	0	5 (3.3)	.138
Colon or rectum	8 (12.3)	89 (58.9)	.000
Polymicrobial	47 (72.3)	110 (72.8)	.935
Duration of therapy, d	7 (4–9)	7 (4–11)	.861

Data are median and IQR or frequency (%).

Abbreviation: IQR, interquartile range.

27% of infections were monomicrobial *E. faecalis* infections. Approximately 65% of patients in both groups had community-acquired IAIs. Patients in both groups received a median of 10 days of total antibiotic therapy and a median of 7 days of antibiotic therapy after source control. Similarly, the median time to achieve source control from the onset of abdominal symptoms related to the current infection was 3 days for the ertapenem group and 2 days for the PTZ group ($P = .32$).

Overall, 13 (20%) patients receiving ertapenem and 36 (24%) patients receiving PTZ had the composite outcome which included (1) an unplanned additional intra-abdominal surgical intervention (15% for ertapenem vs 14% for PTZ); (2) readmission requiring antibiotics related to the original surgery (17% for ertapenem vs 16% for PTZ); or (3) mortality (0% for ertapenem vs 5% for PTZ), all within 30 days, with none of these differences reaching statistical significance. There was no difference in the 30-day composite outcome (including patients who achieved any of the aforementioned outcomes) between the ertapenem and PTZ groups (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.39–1.63). The composite outcome remained similar after adjusting for patient weight, APACHE 2 score, and source of infection (adjusted OR, 1.11; 95% CI, 0.44–1.77). Similarly, there were no differences in the composite outcome between patients with monomicrobial vs polymicrobial *E. faecalis* infections (OR, 1.05; 95% CI, 0.49–2.26). There were 3 *Clostridioides difficile* episodes within 30 days (5%) in the ertapenem group and 5 episodes (3.3%) in the PTZ group ($P = .64$).

DISCUSSION

We conducted a multicenter observational study to evaluate the role of ertapenem for the treatment of cIAIs with *E. faecalis* recovered from intra-abdominal fluid cultures in patients with appropriate source control. The cohort was composed of a diverse mix of patients from both community and tertiary care hospitals. Overall, we found no difference in 30-day clinical failure between the groups regardless of whether ertapenem or PTZ was prescribed after adjusting for patient weight, illness severity, and source of infection.

Several randomized controlled trials have concluded that ertapenem is comparable to PTZ for IAIs; however, these studies were not specifically designed to address *E. faecalis* infections and had limited numbers of patients with culture-confirmed *E. faecalis* [3, 5, 7], making it difficult to draw meaningful conclusions about the role of ertapenem in treating cIAIs when *E. faecalis* is identified. The need for empiric or targeted therapy for *E. faecalis* for treatment of cIAIs remains controversial. The Infectious Diseases Society of America (IDSA) and Surgical Infection Society (SIS) guidelines outline recommendations regarding anti-enterococcal therapy [2, 10].

These recommendations were designated a 2 or 3B score (based on expert opinion or studies with small numbers of patients). Despite these existing guidelines, many providers may opt for PTZ over ertapenem for the presumed or confirmed presence of *E. faecalis* in intra-abdominal cultures as ertapenem is unlikely to be have targeted *E. faecalis* activity [4].

Our study is observational and retrospective, so there is the possibility of missing data and lingering confounding by indication. Additionally, our sample size was limited, resulting in the possibility of a type 2 error. Finally, although almost half of the patients meeting eligibility criteria met our definition of immunocompromised, the numbers for any individual group (eg, solid organ transplant, AIDS, etc.) were small. Despite these limitations, our study adds to the published literature on the role of ertapenem for the treatment of cIAIs when *E. faecalis* has been identified. Moreover, we believe our findings support the current IDSA/SIS guidelines, which recognize the role of ertapenem for nonsevere IAIs.

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