

# Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial

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## Summary

**Background** Diabetic foot infections are a common and serious problem, yet few randomised trials of adequate quality have compared the efficacy of the various antibiotic regimens available for their treatment. Our aim was to assess the efficacy and safety of ertapenem versus piperacillin/tazobactam for foot infections.

**Methods** We did a randomised, double-blinded, multicentre trial in adults (n=586) with diabetes and a foot infection classified as moderate-to-severe and requiring intravenous antibiotics. We assigned patients intravenous ertapenem (1 g daily; n=295) or piperacillin/tazobactam (3·375 g every 6 h; n=291) given for a minimum of 5 days, after which oral amoxicillin/clavulanic acid (875/125 mg every 12 h) could be given for up to 23 days. Investigators retained the option to administer vancomycin to patients in either group to ensure adequate coverage for potentially antibiotic resistant *Enterococcus* spp and methicillin-resistant *Staphylococcus aureus* (MRSA). Our primary outcome was the proportion of patients with a favourable clinical response (cure or improvement) on the day that intravenous antibiotic was discontinued. Analyses were by an evaluable-patient only approach. This study is registered with ClinicalTrials.gov, number NCT00229112.

**Findings** Of the 576 patients treated, 445 were available for assessment at the end of intravenous therapy. Both baseline characteristics and favourable clinical response rates were similar for the 226 who received ertapenem and the 219 who received piperacillin/tazobactam (94% vs 92%, respectively; between treatment difference 1·9%, 95% CI -2·9 to 6·9). Rates of favourable microbiological responses (eradication rates and clinical outcomes, by pathogen) and adverse events did not differ between groups.

**Interpretation** Clinical and microbiological outcomes for patients treated with ertapenem were equivalent to those for patients treated with piperacillin/tazobactam, suggesting that this once-daily antibiotic should be considered for parenteral therapy of diabetic foot infections, when deemed appropriate.

## Introduction

Foot infections in patients with diabetes are common and difficult to treat.<sup>1</sup> Along with ulcerations, they are the most frequent diabetes-related cause of admission in the USA, accounting for almost half of all days spent in hospital, and in developed countries they are the leading cause of lower-extremity amputations.<sup>2-4</sup> Although much is known about the prevention<sup>5</sup> and treatment<sup>6,7</sup> of foot ulcerations in people with diabetes, few prospective studies have been done to assess treatment of diabetic foot infections.<sup>1,8</sup> Yet even where general medical and foot care is easily accessible, the yearly rate of foot infections is 36·5 per 1000 people with diabetes.<sup>9</sup> Infections most often originate in skin ulcers then spread to the soft tissues and bone. Guidelines<sup>10,11</sup> for the treatment of these complex infections note that successful outcomes depend on proper wound care, early and repeated consideration of surgical interventions, and appropriate antibiotic therapy.

The antibiotic regimen selected should ideally depend on the known or suspected pathogens associated with the infection. In outpatients with acute wounds who have not recently received antibiotics, the causative organisms are predominately aerobic gram-positive cocci.<sup>12</sup> In other patients, however, a polymicrobial infection, involving

gram-negative and obligate anaerobic organisms, is likely.<sup>1,13-15</sup> Most mild infections can be treated with oral agents with a fairly narrow spectrum. However, many moderate and almost all severe infections require treatment with parenteral, broad-spectrum antibiotics<sup>1,14,16</sup> administered as multiple daily doses or in combination regimens. How broad-spectrum the regimen must be—ie, whether or not all potential pathogens should be covered—is unclear. Several antibiotics are potentially effective against diabetic foot infections, but most of the clinical trials done to assess them were of poor design and included only small numbers of patients.<sup>1</sup>

Ertapenem is a once-daily, parenteral group 1 carbapenem antibiotic used to treat complicated skin and skin-structure infections.<sup>17,18</sup> Its range of activity covers most of the pathogens implicated in diabetic foot infections, including methicillin-susceptible *Staphylococcus aureus*, streptococci, *Enterobacteriaceae*, and anaerobes, but not most *Enterococcus* or *Pseudomonas* spp. Our aim was to compare the efficacy and safety of ertapenem versus piperacillin/tazobactam—an aminopenicillin/β lactamase inhibitor combination agent with a slightly wider antibacterial range<sup>19</sup>—for diabetic foot infections.

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## Methods

### Patients

Between April, 2001, and April, 2004, we did a prospective, randomised, double-blinded, multicentre trial, to which we enrolled adults with diabetes mellitus (type 1 or type 2, controlled by diet or medications) who had a foot infection that did not extend above the knee. Signs and symptoms required to diagnose infection were purulent drainage (pus) or three or more of the following: fever ( $\geq 38^{\circ}\text{C}$ ) or hypothermia ( $\leq 36^{\circ}\text{C}$ ); peripheral white blood cell count  $> 10\,000/\text{mm}^3$  with  $\geq 5\%$  band neutrophils; localised periwound oedema, erythema, tenderness, pain, fluctuance, warmth, or induration; or lymphangitis. We excluded patients who had infections that were: mild and did not require parenteral antibiotic therapy; known at entry to be caused by pathogens resistant to either study drug; predominantly caused by thermal burns; categorised as necrotising fasciitis; known or suspected to be associated with underlying osteomyelitis, unless all the infected bone was removed within 48 h after initiating study therapy; complicated by indwelling foreign or prosthetic material; or associated with gangrenous tissue that could not be adequately removed by surgical debridement. We also excluded women who were pregnant, nursing, or fertile and not using contraception, as well as patients with: a history of a serious reaction to any  $\beta$  lactam antibiotic; a need for any additional concomitant systemic antibacterial agent other than the study drug(s) or vancomycin; diabetes or impaired glucose tolerance that was secondary; arterial perfusion insufficiency of the affected limb, requiring a revascularisation procedure; any rapidly progressive or terminal illness; a requirement for dialysis; immunosuppression of any cause; or receiving corticosteroid therapy ( $\geq 40$  mg prednisone daily or its equivalent). Laboratory variables for which patients were excluded were: markedly abnormal liver function tests; haematocrit of less than 25%, haemoglobin of less than 8 g/L, platelet count of less than  $75\,000/\text{mm}^3$ ; or coagulation test results more than 1.5 times the upper limit of normal (unless on anticoagulant therapy). Finally, we excluded patients who had been treated for more than 24 h with systemic antibiotic therapy likely to be effective for their infection within the 72 h before study screening, unless there was clinical evidence of treatment failure with an associated deep-tissue culture that yielded pathogen(s).

All patients provided written informed consent before they were enrolled, and each of the 89 sites involved obtained approval for the study protocol from their local institutional review board. The study was done in accordance with the International Conference on Harmonization Good Clinical Practice guidelines.<sup>20</sup>

### Procedures

Merck and Co provided blocks of computer-generated allocation numbers and open-label study drug to an unblinded pharmacist at every site. The pharmacist was

responsible for randomising patients (1:1 ratio), and prepared intravenous therapy to be administered by clinical personnel (unaware of treatment allocation). Patients received daily treatment for 5–28 days with either intravenous ertapenem (1 g bolus, followed by a saline placebo every 6 h for three additional doses) or intravenous piperacillin/tazobactam (3.375 g every 6 h). This dose of piperacillin/tazobactam is that used in the USA, although in other countries 4.5 g every 8 h is often given. The first dose of study drug was administered in a hospital or at an outpatient clinic, but subsequent doses could be administered in a home-care setting. To ensure adequate antibiotic coverage for potentially antibiotic resistant *Enterococcus* spp and methicillin-resistant *S aureus* (MRSA), investigators could administer vancomycin to patients in either treatment group if these organisms were known or suspected pathogens. We considered patients who received vancomycin in analyses only if at least one vancomycin-resistant pathogen—ie, an aerobic gram-negative or anaerobic organism—was also isolated on culture. After 5 days of intravenous therapy the investigator could elect to switch patients in either group to oral antibiotic therapy with amoxicillin/clavulanic acid (875/125 mg every 12 h) if they met the following prespecified criteria: no fever for at least 24 h; white blood cell count less than 10 000 with no more than 5% band neutrophils; able to tolerate oral feeding; and most signs and symptoms of diabetic foot infection had improved (and none had worsened). The total duration of study therapy could not exceed 28 days. At baseline, we stratified patients with the University of Texas Diabetic Wound Classification.<sup>21,22</sup> Stratum I patients had a relatively superficial wound with or without ischaemia (grade 0 or 1, stages B or D), and stratum II patients had a deeper wound (grades 2 or 3, stages B or D).

Before enrolling any patients, all investigators and study coordinators attended a centralised training meeting (or viewed videotapes of the lectures) to teach them about diabetic foot infections, to ensure they understood the protocol, and to verify that they could properly do all required procedures. At eligibility screening, the investigator obtained a medical history, did an extensive clinical assessment that included a complete physical examination, a study-specified neurological and vascular assessment of the lower extremities, and wound exploration with a metal probe, and specified chemistry, haematology, and urinalysis studies. The investigator also did a standardised detailed wound assessment at each visit, noting the presence and intensity of every sign and symptom of infection. Every patient had plain radiographs of the affected extremity to assess for the presence of any foreign material, tissue gas, or signs of osteomyelitis. Investigators could order any additional studies for patients with suspected osteomyelitis at their discretion, but a patient with investigator-diagnosed osteomyelitis could only be enrolled if all the infected bone was removed within 48 h

after initiation of study therapy and there was residual soft-tissue infection, requiring intravenous antibiotic therapy for 5–28 days. We asked investigators to sharply debride any wounds that had callus or devitalised tissue at baseline, and whenever necessary during the study. Patients could not receive any adjunct therapies, such as topical antimicrobials, hyperbaric oxygen therapy, or granulocyte-colony stimulating factors.

At baseline, the investigator obtained a wound specimen from every patient, and sent it to the local microbiology laboratory for culture and susceptibility testing. Acceptable culture specimens included skin biopsy, curettage of the wound base after debridement, tissue or bone biopsy, aspiration of purulent secretions, or a leading-edge needle aspiration for patients with cellulitis; we strongly discouraged swabbing of the wound. We asked investigators to obtain blood cultures when clinically indicated; if positive, they were repeated until negative. At subsequent scheduled study visits the investigator obtained a specimen for wound culture only if there were on-going clinical signs of infection and an appropriate sample was available. Local laboratories did all aerobic cultures and susceptibility testing, and a duplicate specimen was sent for anaerobic culture and susceptibility testing to a specialised laboratory (RM Alden Research Laboratory, Santa Monica, CA, USA). The microbiology laboratory identified all isolates and determined their susceptibility to antibiotics, including ertapenem and piperacillin/tazobactam, in accordance with the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS).<sup>23–25</sup> Patients with cultures that yielded pathogens resistant to either study drug could remain in the study at the discretion of the investigator, provided they were clinically improving.

Investigators assessed the clinical response to treatment based on the changes in signs and symptoms of infection on day 5 of intravenous therapy, at the time of discontinuation of intravenous therapy (DCIV), at the time of discontinuation of any subsequent oral antibiotic therapy, and at the follow-up assessment (FUA) 10 days after the last dose of study antibiotic therapy (intravenous or oral). They designated infections as showing cure or improvement if there was resolution of all or most (respectively) pretherapy signs and symptoms of infection (and specifically of fever, lymphangitis, and purulent drainage), and if the patient had no need for additional intravenous antibiotic therapy (at the DCIV assessment) or any antibiotic therapy (at the 10-day FUA). The clinical outcome was unfavourable if one of the following arose: persistence or progression of most or all pretherapy signs and symptoms while on therapy, called failure; or a worsening of signs and symptoms after discontinuation of therapy in a patient with a previously favourable response, called relapse. We judged the treatment of infection a clinical failure if patients required either additional systemic antibiotic therapy for any reason, or unplanned, non-routine, surgical or other adjuvant

therapies because their foot infection had not improved or had worsened after 48 h of study therapy.

Our primary endpoint was the proportion of patients with a favourable clinical response (defined as cure or improvement) at the DCIV assessment. A secondary clinical endpoint was the proportion of patients who had a favourable clinical response at the FUA assessment. In view of the consistency between the DCIV and FUA assessment values, and for clarity of presentation, we primarily present the clinically more important FUA assessment data here.

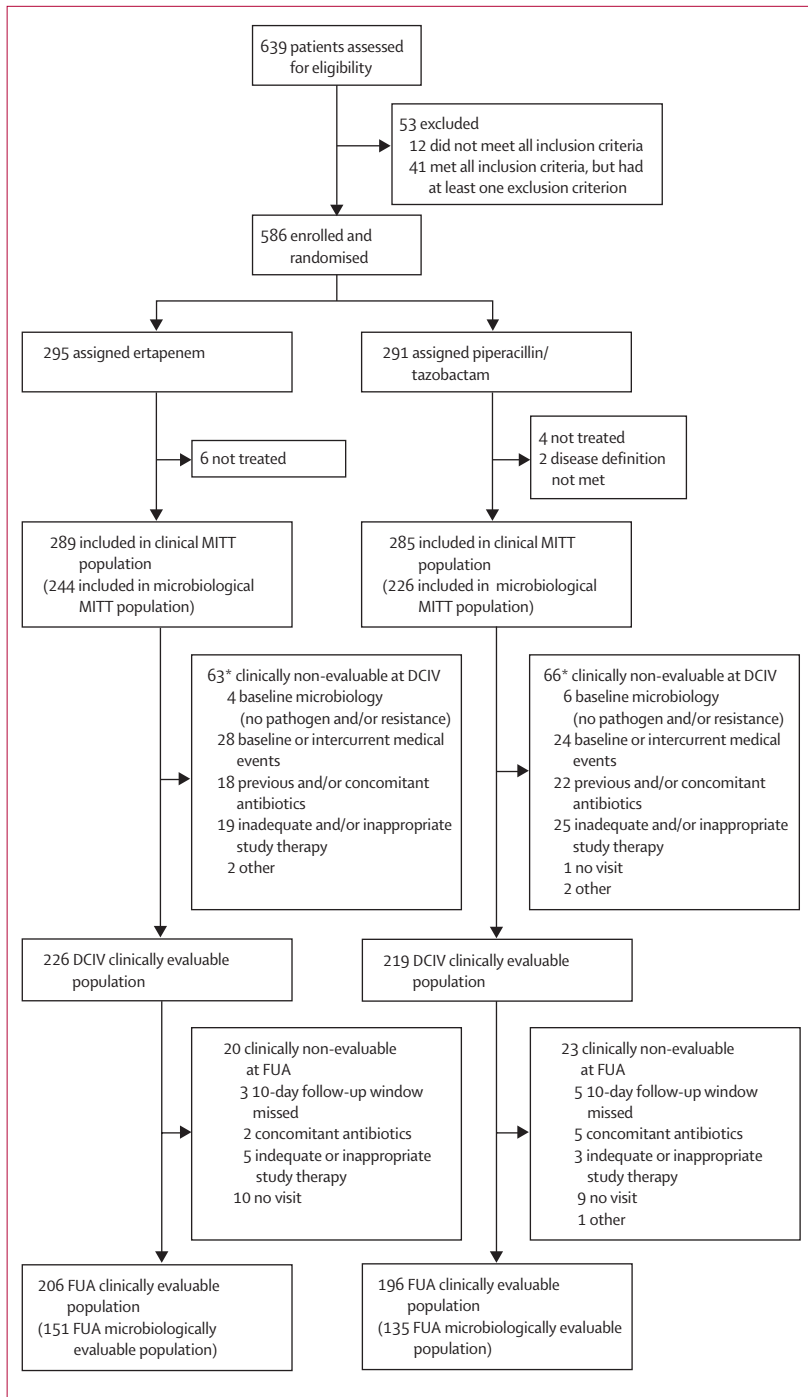
We assessed the microbiological response before unblinding for each identified baseline pathogen. A favourable microbiological response was called eradication when the follow-up culture did not yield the pathogen, or presumptive eradication when a patient with a favourable clinical response had no appropriate material available for culture at the infection site. We considered coagulase-negative staphylococci and *Corynebacterium* spp to be contaminants unless they were the sole isolate from an appropriately obtained specimen. For patients with a polymicrobial infection who received vancomycin, we ascertained per-pathogen outcomes only for gram-negative and anaerobic organisms; we designated gram-positive organisms to have an indeterminate outcome. We considered emergent pathogens separately from baseline pathogens.

We considered a patient clinically evaluable if there were data to assess the patient's clinical response and no confounding factors interfering with an assessment. In addition to meeting disease and previous antimicrobial therapy definitions, patients had to have received at least 48 h of intravenous study antibiotic therapy to be considered an evaluable failure, and at least 80% of their intended doses of study therapy to be considered an evaluable success. A clinically evaluable patient was also microbiologically evaluable if we could identify the microbiological response at the DCIV and 10-day FUA visits, and there were appropriate eligibility screening cultures obtained within 48 h before the first dose of study drug, and a pathogen isolated from a prestudy culture that was susceptible to both ertapenem and piperacillin/tazobactam.

The safety assessment included all patients who received at least one dose of study drug. The investigators monitored for adverse events, including abnormal laboratory values and the occurrence of any infusion-site reaction(s), every day during study therapy and for 14 days thereafter. The investigators rated the likelihood that any adverse event was possibly, probably, or definitely causally related to the study drug.

#### Statistical analysis

Ours was a non-inferiority trial done to ascertain whether the clinical effectiveness of treating diabetic foot infections was as good with ertapenem as with piperacillin/tazobactam. As such, a two-sided 95% CI for



**Figure: Trial profile**

\*Patients might have more than one reason for being non-evaluable, but are counted only once in this category.

the difference in response rates between the two treatment groups needed to contain zero and have a lower range of greater than -15%. We stratified the analysis by baseline severity (stratum) of the primary infection.

We calculated the required sample size with the Blackwelder approach to assessing a non-zero

difference.<sup>26</sup> We set the  $\alpha$  level at 0.05 (two-sided) and the response rate for each treatment group at 70%,<sup>27-29</sup> assuming a  $\delta$  (lower limit of the 95% CI on the difference in response rates) of -15 for the power and sample-size calculations. As such, we needed 200 clinically evaluable patients per group.

We analysed the efficacy variables, using an evaluable-patients only approach as the primary method for all study hypotheses, as well as with a modified-intention-to-treat (MITT) approach. The two populations containing only evaluable patients were: 1) patients clinically evaluable up to and including the DCIV assessment (used to address the primary hypothesis); and 2) patients clinically evaluable up to and including the 10-day post-antibiotic therapy FUA (used for all other analyses).

At every timepoint, we did a test of treatment by baseline severity interaction (Breslow-Day test of homogeneity of odds ratios).<sup>30</sup> If the p value of the test was more than 0.10, we concluded that the odds ratios were similar across the baseline severity strata and that the strata could be combined. In such instances, we display results combined over strata within each group. We compared the two treatment groups for efficacy variables at every relevant timepoint and calculated the differences in proportions, along with corresponding 95% CIs. We based the estimated CIs for the difference between treatment groups, accounting for baseline severity, on Cochran-Mantel-Haenszel weights, using a method proposed by Miettinen and Nurminen.<sup>31</sup> Where results were pooled over strata for observed proportions and analyses with a small sample size, we calculated exact CIs based on the binomial distribution, if the sample size upon which an individual proportion is based was at least ten. This study is registered with ClinicalTrials.gov, number NCT00229112.

**Role of the funding source**

The sponsor of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

The figure shows the trial profile and table 1 the baseline characteristics—including details of peripheral neuropathy, palpable pedal pulses, and wound severity—of those randomised, which were similar between groups. We assigned 295 patients to ertapenem and 291 to piperacillin/tazobactam. Of these, 445 were clinically evaluable at the DCIV assessment and 402 at the 10-day FUA assessment. Of those evaluable for the FUA assessment, the infection was at or below the ankle in 355 (88%) and above the ankle but not past the knee in the rest (table 2); most infections involved the forefoot and toes.

	Ertapenem (n=289)	Piperacillin/ tazobactam (n=287)
<b>Demographic characteristics</b>		
Male	176 (61%)	194 (68%)
Age (median, range) (years)	59 (25–90)	57 (22–94)
Ethnic origin		
White	195 (67%)	194 (68%)
Hispanic	66 (23%)	64 (22%)
Black	25 (9%)	26 (9%)
Other	3 (1%)	3 (1%)
<b>Stratum and wound classification</b>		
Moderate	196 (68%)	188 (66%)
Grade 0 stage B	4 (1%)	6 (2%)
Grade 0 stage D	0	1 (<1%)
Grade 1 stage B	181 (63%)	173 (60%)
Grade 1 stage D	11 (4%)	8 (3%)
Severe	93 (32%)	99 (34%)
Grade 2 stage B	66 (23%)	67 (23%)
Grade 2 stage D	4 (1%)	5 (2%)
Grade 3 stage B	20 (7%)	19 (7%)
Grade 3 stage D	3 (1%)	8 (3%)
<b>Dorsalis pedis pulse*</b>		
0–2	106 (37%)	102 (36%)
2–3	119 (41%)	129 (45%)
3–41	60 (21%)	52 (18%)
<b>Posterior tibial pulse*</b>		
0–2	128 (44%)	136 (47%)
2–3	102 (35%)	102 (36%)
3–41	55 (19%)	45 (16%)
<b>Monofilament test†</b>		
0–1*	63 (22%)	61 (21%)
2–3	33 (11%)	35 (12%)
≥4	186 (64%)	187 (65%)

Data are number (%) unless otherwise indicated. \*0=not palpable; 1=barely palpable; 2=normal; 3–41=bounding. †Number of sites (out of 10) with loss of sensation.

**Table 1: Baseline characteristics of treated patients**

Most clinically evaluable patients in the FUA assessment (84% [173 of 206] in the ertapenem group and 77% [151 of 196] in the piperacillin/tazobactam group) had at least one pathogen isolated from a wound culture at baseline. Infections were polymicrobial in 47% (187 of 402) of evaluable patients, with 9% (37 of 402) of patients having both gram-positive and gram-negative aerobic organisms on culture. Infections were exclusively aerobic in 36% (146 of 402) of positive cultures, exclusively anaerobic in 8% (33 of 402), and mixed in 27% (108 of 402) of evaluable patients. The most commonly isolated pathogen was *S aureus* (169 isolates), identified in 44% (90 of 206) of patients treated with ertapenem and 40% (79 of 196) of those on piperacillin/tazobactam. Nearly 80% (135 of 169) of *S aureus* isolates were methicillin-sensitive; the proportion of MRSA isolates did not differ greatly between groups (ertapenem: 20% [18 of 90]; piperacillin/tazobactam 19% [15 of 79]). Other common isolates were *Peptostreptococcus* spp (114 isolates), *Prevotella*-*Porphyrmonas* group (75 isolates), *Enterobacteriaceae* (75 isolates), *Enterococcus* spp (64 isolates), *Streptococcus agalactiae* (47 isolates), *Bacteroides fragilis* group (36 isolates), and *Pseudomonas aeruginosa* (28 isolates). Investigators obtained baseline blood cultures from only

	Number (%)
Lower extremity	46 (11%)
Foot (unspecified)	15 (4%)
Ankle	19 (5%)
Hindfoot	17 (4%)
Midfoot	40 (10%)
Forefoot	95 (24%)
Hallux	87 (32%)
Toes (lesser digits)	82 (20%)

**Table 2: Sites affected in 402 patients for whom information was available (FUA assessment)**

16 patients, three of which were positive (one each with methicillin-sensitive *S aureus*, *S agalactiae*, and *Streptococcus pyogenes*). The antibiotic susceptibility patterns of the baseline pathogens were similar in the two groups, with two exceptions: among species of *Enterococcus*, 16% (9 of 58) of isolates were susceptible to ertapenem compared with 93% (54 of 58) to piperacillin/tazobactam; and among *P aeruginosa* isolates, corresponding figures were 46% (13 of 28) and 93% (26 of 28).

At the DCIV timepoint, 226 ertapenem-treated and 219 piperacillin/tazobactam-treated patients were clinically evaluable. The mean duration of intravenous therapy in the FUA clinically evaluable population was 11.1 days for ertapenem and 11.3 days for piperacillin/tazobactam. 67% (137 of 206) of patients in the ertapenem group and 68% (134 of 196) of those in the piperacillin/tazobactam group completed therapy with an oral antibiotic agent. Of those who received oral antibiotics, 96% (261 of 271) received amoxicillin/clavulanic acid; alternative oral agents (ciprofloxacin, clindamycin, dicloxacillin, levofloxacin, or moxifloxacin) were permitted in cases of documented pathogen resistance or patient intolerance to amoxicillin/clavulanic acid. The mean duration of oral antibiotic therapy (in those so treated) was 9.7 days (range 4.0–23.0), for a total mean duration of antibiotic therapy of 17.4 days (3.0–37.0).

The proportion of patients with a favourable clinical response at the DCIV timepoint, adjusted for baseline severity, was 94% (213 of 226) for the ertapenem group and 92% (202 of 219) for the piperacillin/tazobactam group. At the 10-day FUA timepoint, the clinical response rate, adjusted for baseline severity, was 87% (180 of 206) in the ertapenem group and 83% (162 of 196) in the piperacillin/tazobactam group. Among the 574 patients in the more conservative MITT analysis (those who received at least one dose of study drug, with patients with missing or indeterminate outcomes considered treatment failures), the proportion with a favourable clinical response at the 10-day FUA was 71% (206 of 289) and 66% (188 of 285), respectively (treatment difference 5%, 95% CI –2.6 to 12.5). None of these differences between treatment groups is significant.

Of the 402 patients in the FUA clinically evaluable population, 257 (64%) were treated as outpatients at baseline, and all but three remained so throughout the

	Ertapenem (n=206)	Piperacillin/tazobactam (n=196)	Observed differences (95% CI)*
Moderate	127/142 (89.4%)	119/135 (88.1%)	1.3 (-6.3 to 9.1)
Severe	53/64 (82.8%)	43/61 (70.5%)	12.3 (-2.6 to 27.1)
Grade 0	2/2 (100.0%)	5/5 (100.0%)	0
Grade 1	125/140 (89.3%)	114/130 (87.7%)	1.6 (-6.2 to 9.6)
Grade 2	43/51 (84.3%)	33/48 (68.8%)	15.6 (-1.2 to 32.1)
Grade 3	10/13 (76.9%)	10/13 (76.9%)	0.0 (-33.3 to 33.3)
Stage B	172/195 (88.2%)	156/187 (83.4%)	4.8 (-2.3 to 12.0)
Stage D	8/11 (72.7%)	6/9 (66.7%)	6.1

Data are number of FUA clinically evaluable patients with favourable assessment/number of FUA clinically evaluable patients assessed (observed response) unless otherwise indicated. \* CIs not calculated for categories in which there were <10 patients in at least one treatment group. Moderate infections include: grade 0 or 1 stage B or D. Severe infections include: grade 2 or 3 stage B or D.

**Table 3: Rate of favourable clinical response at 10-day FUA, by baseline stratum and wound classification**

study. Among the 145 (36%) who were inpatients at baseline, 99 (68%) remained so. There was no significant difference between treatment groups with respect to inpatient versus outpatient status.

Table 3 shows the clinical response at the 10-day FUA timepoint by baseline severity and University of Texas wound score. Clinical cure rates were generally similar between treatment groups for patients with either moderate or severe infections, and for every stage and grade. There was a trend towards lower success rates with deeper wounds (moving from grade 0 to grade 3), and patients with an ischaemic limb (stage D) generally had lower clinical success rates than patients with adequate perfusion (stage B).

Among individuals with a positive wound culture, 358 of 384 (93%) isolates were known or presumed to be eradicated in those in the ertapenem group compared with 271 of 336 (81%) in the piperacillin/tazobactam group (difference 12.5%, 95% CI 7.2–18.8). Eradication rates for each treatment group by pathogen are shown in table 4.

There were no clinically important differences in the clinical response rates in the ertapenem and piperacillin/

tazobactam treatment groups for patients with gram-positive, gram-negative, or anaerobic pathogens (table 5). Among patients from whom methicillin-sensitive *S aureus* were isolated, the clinical response rates were comparable for ertapenem and piperacillin/tazobactam (table 5). Clinical response rates for patients with MRSA isolates were 77.8% in the ertapenem group and 66.7% in the piperacillin/tazobactam group; they were similar irrespective of whether the patient received concomitant vancomycin therapy (71.4% [5 of 7] and 60.0% [3 of 5], respectively) and whether the infections were monomicrobial or polymicrobial (83.3% [10 of 12] and 70.0% [7 of 10], respectively). Of note is that the clinical response rates were similar for ertapenem and piperacillin/tazobactam in patients with isolates of *Enterococcus* spp (86.8% vs 80.8%, respectively) and *P aeruginosa* (83.3% vs 70.0%, respectively), despite the fact that most of these isolates were resistant to the former but not to the latter agent. Most patients from whom enterococci or *P aeruginosa* were isolated had polymicrobial infections (83% [53 of 64] and 71% [20 of 28], respectively).

No patient had documented persistence of a baseline pathogen related to development of antibiotic resistance while enrolled in the study. Emergent pathogens were cultured infrequently, the most common being *P aeruginosa* (four isolates) and enterococci (five isolates) in the ertapenem group, and *S aureus* (five isolates) in the piperacillin/tazobactam group.

Most adverse events were unrelated to the study drugs. 137 (47%) patients on ertapenem and 136 (47%) on piperacillin/tazobactam had at least one adverse event during parenteral therapy. There were no significant differences between treatment groups in drug-related adverse events (n=44 [15%] for ertapenem; n=57 [20%] for piperacillin/tazobactam) or study discontinuations due to drug-related adverse events (n=3 [1%]; n=6 [2%]) during

	Ertapenem (n=151)*	Piperacillin/tazobactam (n=135)*	Observed differences (95% CI)
Gram-positive aerobic cocci	135/151 (89.4%)	122/146 (83.6%)	5.8 (-2.0 to 13.9)
Enterococcus†	15/18 (83.3%)	8/9 (88.9%)	-5.6
Enterococcus faecalis	10/12 (83.3%)	7/9 (77.8%)	5.6
Staphylococcus aureus	68/77 (88.3%)	57/70 (81.4%)	6.9 (-4.9 to 19.4)
Meticillin resistant	6/8 (75.0%)	4/6 (66.7%)	8.3
Meticillin susceptible	62/69 (89.9%)	53/64 (82.8%)	7.0 (-5.2 to 19.8)
Streptococcus agalactiae	19/21 (90.5%)	21/25 (84.0%)	6.5 (-16.6 to 28.3)
Gram-negative aerobic bacilli	62/67 (92.5%)	40/51 (78.4%)	14.1 (1.5 to 28.5)
Enterobacteriaceae‡	39/41 (95.1%)	26/31 (83.9%)	11.3 (-3.0 to 28.9)
Pseudomonas aeruginosa	10/13 (76.9%)	7/10 (70.0%)	6.9 (-29.2 to 45.7)
Gram-positive anaerobic cocci	72/74 (97.3%)	51/62 (82.3%)	15.0 (5.1 to 27.0)
Peptostreptococcus magnus	37/38 (97.4%)	24/27 (88.9%)	8.5 (-4.5 to 27.0)
Peptostreptococcus asaccharolyticus	11/11 (100.0%)	9/11 (81.8%)	18.2 (-12.1 to 48.3)
Gram-positive anaerobic bacilli§	25/25 (100.0%)	13/17 (76.5%)	23.5 (7.2 to 49.0)
Gram-negative anaerobic bacilli¶	37/40 (92.5%)	30/40 (75.0%)	17.5 (1.1 to 34.7)
Gram-negative anaerobic coccobacilli	25/25 (100.0%)	11/16 (68.8%)	31.3 (12.8 to 56.4)

Data are number of pathogens with associated favourable assessment/number of pathogens assessed (observed response) unless otherwise indicated. \*Number observed calculated by pooling across baseline severity. †No species identified. ‡Includes *Enterobacter* spp, *Escherichia* spp, *Klebsiella* spp, *Morganella* spp, *Proteus* spp, *Providencia* spp, and *Serratia* spp. §Includes *Clostridium* spp, *Eubacterium* spp, and *Propionibacterium* spp. ¶Includes *Porphyromonas* spp and *Prevotella* spp. ||Includes *Bacteroides* spp.

**Table 4: Microbiological eradication rates for species with at least 20 isolates at FUA, by baseline pathogen**

	Ertapenem (n=173)*	Piperacillin/tazobactam (n=151)*	Observed differences (95% CI)
Gram-positive aerobic cocci	149/176 (84.7%)	132/166 (79.5%)	5.1 (-3.1 to 13.6)
Enterococcus†	19/22 (86.4%)	8/9 (88.9%)	-2.5
<i>Enterococcus faecalis</i>	13/15 (86.7%)	12/16 (75.0%)	11.7 (-19.2 to 41.1)
<i>Staphylococcus aureus</i>	75/90 (83.3%)‡	62/79 (78.5%)	4.9 (-7.6 to 17.2)
Meticillin resistant	14/18 (77.8%)	10/15 (66.7%)	11.1 (-19.8 to 42.7)
Meticillin susceptible	60/71 (84.5%)	52/64 (81.3%)	3.3 (-9.9 to 17.1)
<i>Streptococcus agalactiae</i>	15/21 (71.4%)	22/26 (84.6%)	-13.2 (-38.3 to 10.9)
Gram-negative aerobic bacilli	64/73 (87.7%)	43/56 (76.8%)	10.9 (-2.3 to 25.2)
Enterobacteriaceae§	36/42 (85.7%)	26/33 (78.8%)	6.9 (-11.1 to 25.9)
<i>Pseudomonas aeruginosa</i>	15/18 (83.3%)	7/10 (70.0%)	13.3 (-18.2 to 48.7)
Gram-positive anaerobic cocci	66/74 (89.2%)	48/62 (77.4%)	11.8 (-0.8 to 25.2)
<i>Peptostreptococcus magnus</i>	34/38 (89.5%)	24/27 (88.9%)	0.6 (-15.4 to 20.6)
<i>Peptostreptococcus asaccharolyticus</i>	10/11 (90.9%)	7/11 (63.6%)	27.3 (-10.9 to 58.6)
Gram-positive anaerobic bacilli¶	23/26 (88.5%)	12/17 (70.6%)	17.9 (-6.9 to 45.1)
Gram-negative anaerobic bacilli	33/40 (82.5%)	28/40 (70.0%)	12.5 (-7.2 to 31.3)
Gram-negative anaerobic coccobacilli**	21/25 (84.0%)	11/16 (68.8%)	15.3 (-10.8 to 43.3)

Data are number of pathogens with associated favourable assessment/number of pathogens assessed (observed response) unless otherwise indicated. \*Number observed calculated by pooling across baseline severity. †No species identified. ‡Oxacillin susceptibility not provided for one isolate. §Includes *Enterobacter* spp, *Escherichia* spp, *Klebsiella* spp, *Morganella* spp, *Proteus* spp, *Providencia* spp, and *Serratia* spp. ¶Includes *Clostridium* spp, *Eubacterium* spp, and *Propionibacterium* spp. ||Includes *Porphyromonas* spp and *Prevotella* spp. \*\*Includes *Bacteroides* spp.

**Table 5: Favourable clinical response rates, for species with at least 20 isolates at FUA, by baseline pathogen**

parenteral therapy. A serious drug-related adverse event during parenteral therapy arose in one patient (0.3%) in each treatment group. The most commonly occurring adverse events during parenteral therapy were diarrhoea (8% [24 of 289] for ertapenem, 14% [41 of 287] for piperacillin/tazobactam), nausea (6% [16 of 289], 7% [19 of 287]), and headache (4% [10 of 289], 6% [16 of 287]). Adverse laboratory events categorised by the investigator as possibly, probably, or definitely related to the study drug during parenteral therapy arose in 11 (4%) patients in the ertapenem group and in 27 (10%) patients in the piperacillin/tazobactam group (causing discontinuation of the study drug in two patients in the piperacillin/tazobactam group).

## Discussion

Our findings concur with those of previous randomised trials of the treatment of moderate-to-severe diabetic foot infections,<sup>15,28,32,33</sup> and show that ertapenem<sup>14</sup> is as safe and effective as piperacillin/tazobactam. About two-thirds of patients, irrespective of assigned drug, were able to switch to an oral antibiotic within 2 weeks of treatment with intravenous therapy. Furthermore, microbiological response rates did not differ between groups.

Results of previously published studies<sup>34–40</sup> indicate that for patients with moderate-to-severe infections, especially the substantial proportion who have already received antibiotic therapy,<sup>41</sup> the causative organisms almost invariably include aerobic gram-positive cocci, often mixed with gram-negative bacilli and sometimes obligate anaerobes.<sup>34,35,40</sup> The clinical significance of some of these isolates, especially as part of a polymicrobial infection, is often unclear. Additionally, isolates from diabetic foot infections are increasingly antibiotic resistant, even in individuals with community-acquired infections.<sup>42</sup> To ensure that the causative pathogens are treated, most specialists therefore recommend use of broad-spectrum

therapy for moderate-to-severe infections, at least initially.<sup>14,41,43</sup> To help curb antibiotic resistance, however, authorities have urged doctors to avoid long-term use of overly broad-spectrum therapy<sup>144</sup> and to consider narrowing the regimen when culture and sensitivity results are available.

As such, many have attempted to find an antimicrobial agent or regimen with the appropriate spectrum for diabetic foot infections. Ertapenem is a fairly broad-spectrum agent that has the advantage of covering the most common pathogens (except MRSA). Unlike some suggested agents—eg, imipenem/cilastatin or piperacillin/tazobactam—it does not cover most enterococci and *P aeruginosa*. But how important are these organisms in diabetic foot infection?<sup>45</sup> Some<sup>15,46–49</sup> believe that rather than being clinically important pathogens, enterococci simply contaminate or colonise diabetic foot infections. Findings of studies<sup>12,50,51</sup> lend support to this notion, indicating good clinical outcomes despite the use of agents that are not active against enterococci. Several investigators<sup>16,35,52</sup> have expressed similar views about *P aeruginosa*, which is common in the environment. Our findings concur with these observations; we noted similar clinical outcomes for patients from whom these organisms were isolated in both treatment groups.

Our study had several strengths. We enrolled a large number of patients (which enabled us to better define the microbiology, especially of obligate anaerobic organisms, and outcomes of treatment for moderate-to-severe diabetic foot infections than possible in previous studies), and used a multicentre, double-blinded, study design, and newly adopted diabetic foot infection classification guidelines. However, we excluded patients with mild infections (who would not normally require parenteral therapy) and those with possible osteomyelitis (which usually requires long-term antibiotic therapy, often combined with surgical debridement). Furthermore, the

number of patients enrolled at the study sites varied considerably, and the types of investigators included primary-care providers, medical and surgical specialists, and podiatrists. A third limitation was that most of the patients received some oral antibiotic therapy after the parenteral study medication; what role this might have had in resolving the infection is undefined. Fourth, not all sites reliably tracked the minor surgical procedures undertaken—eg, debridement, incision, and drainage—so we were unable to explore the part they played in resolving the infections. Additionally, we counted on the trained investigators and their study coordinators to correctly do the assessments and procedures needed, but did not test inter-rater reliability. Finally, we do not have long-term follow-up data, and cannot therefore define the durability of infection resolution.

Nevertheless, our findings indicate that ertapenem is as effective as piperacillin/tazobactam in the treatment of diabetic foot infections. Although another parenterally administered drug, ertapenem has the advantage of once-daily dosing, making it a convenient alternative in the hospital setting and especially useful in the outpatient setting.<sup>51</sup> When possible, targeted and fairly narrow-spectrum antimicrobial regimens are preferable to empiric broad-spectrum agents. Where MRSA is common, doctors should consider a regimen able to treat this organism,<sup>53–55</sup> irrespective of the fact that in our study and in others<sup>32,33</sup> many patients from whom MRSA was isolated responded to treatment that did not cover the organism. Doctors should also be mindful that the high rate of good outcomes in this and other randomised trials of treatment for diabetic foot infections are attributable not only to effective antibiotic therapy, but also to overall careful attention to the need for surgical procedures and proper wound care.

#### Contributors

All authors helped to draft, review, and edit the report, and approved the final version. B A Lipsky and D G Armstrong developed the study protocol, and B A Lipsky, D G Armstrong, and A D Tice participated in the study as clinical investigators. D M Citron did clinical microbiology work. D E Morgenstern managed and coordinated the study. M A Abramson was the medical monitor and director of the study.

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#### Conflict of interest statement

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