SUPPLEMENT ARTICLE

# The Efficacy and Safety of Tigecycline for the Treatment of Complicated Intra-Abdominal Infections: Analysis of Pooled Clinical Trial Data

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**This pooled analysis includes 2 phase 3, double-blind trials designed to evaluate the safety and efficacy of tigecycline, versus that of imipenem-cilastatin, in 1642 adults with complicated intra-abdominal infections. Patients were randomized to receive either tigecycline (initial dose of 100 mg, followed by 50 mg intravenously every 12 h) or imipenem-cilastatin (500/500 mg intravenously every 6 h) for 5–14 days. The primary end point was the clinical response at the test-of-cure visit (12–42 days after therapy) in the co-primary end point microbiologically evaluable and microbiological modified intent-to-treat populations. For the microbiologically evaluable group, clinical cure rates were 86.1% (441/512) for tigecycline, versus 86.2% (442/513) for imipenem-cilastatin (95% confidence interval for the difference, −4.5% to 4.4%; $P < .0001$ for noninferiority). Clinical cure rates in the microbiological modified intent-to-treat population were 80.2% (506/631) for tigecycline, versus 81.5% (514/631) for imipenem-cilastatin (95% confidence interval for the difference, −5.8% to 3.2%; $P < .0001$ for noninferiority). Nausea (24.4% tigecycline, 19.0% imipenem-cilastatin [$P = .01$]), vomiting (19.2% tigecycline, 14.3% imipenem-cilastatin [$P = .008$]), and diarrhea (13.8% tigecycline, 13.2% imipenem-cilastatin [$P = .719$]) were the most frequently reported adverse events. This pooled analysis demonstrates that tigecycline was efficacious and well tolerated in the treatment of patients with complicated intra-abdominal infections.**

Intra-abdominal infections are infections that extend beyond a hollow viscus within the abdomen to produce peritonitis or abscess [1]. Complicated intra-abdominal infections are those that require a combination of appropriate and timely surgical source control and broad-spectrum antimicrobial therapy for satisfactory clinical outcomes. Nearly all intra-abdominal infections are caused by multiple microorganisms that constitute the intestinal flora; these include aerobes and facultative and obligate anaerobes, with Enterobacteriaceae (e.g., *Escherichia coli* and *Klebsiella pneumoniae*), enterococci, and *Bacteroides fragilis* isolated most frequently [1–4]. The increased realization that commonly isolated gastrointestinal flora may possess multiple resistance factors that express antimicrobial resistance (e.g., extended-spectrum $\beta$-lactamases [ESBLs]) mandates that empirical antimicrobial therapy for complicated intra-abdominal infections have activity against these difficult-to-treat isolates [5].

The initial selection of empirical antimicrobial therapy for the treatment of intra-abdominal infections is challenging and requires careful consideration, because inappropriate antimicrobial therapy may delay clinical resolution and increase the duration of hospital stay and the risk of mortality [6, 7]. The choice of antimicrobial therapy for intra-abdominal infection depends on the severity of the illness, whether the infec-

Presented in part: 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 30 October to 2 November 2004 (abstract 3841, control number L-992c); 15th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, 4 April 2005 (poster P1317).

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**Clinical Infectious Diseases 2005; 41:S354–66**



1058-4838/2005/4105S5-0007$15.00

tion was community- or hospital-acquired, and the history of bacterial resistance in the hospital and community [1]. Historically, combination antibiotic therapy has been the standard of care for treatment of these mixed infections [1]. Recently updated guidelines of the Infectious Diseases Society of America suggest that broad-spectrum single-agent or combination therapy (e.g., carbapenem monotherapy, piperacillin-tazobactam, third- or fourth-generation cephalosporins, or fluoroquinolones plus metronidazole) be used for high-risk patients with severe or postoperative nosocomial intra-abdominal infections, wherein polymicrobial infection and/or resistant flora are more prevalent [1]. A complex multidrug regimen is advocated, however, when very resistant bacteria are suspected (e.g., vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus,* and *Pseudomonas aeruginosa*) [1]. The rapid and continuing emergence of bacterial resistance over the last decade emphasizes the need for new treatment options for complicated intra-abdominal infections.

The glycylcycline family of antibiotics, which act to inhibit protein synthesis at the level of the bacterial ribosome, are being evaluated in phase 3 trials for the treatment of patients with serious infections. Tigecycline is a novel, first-in-class glycylcycline with expanded broad-spectrum in vitro activity against bacteria commonly recovered from patients with intra-abdominal infections. Notably, the spectrum of activity of tigecycline includes aerobic and facultative gram-positive and gram-negative bacteria and anaerobic bacteria [8–11]. Because of its distinct mechanism of action (i.e., it overcomes 2 types of genetic mechanisms responsible for tetracycline resistance), tigecycline is active in vitro against both susceptible bacteria and multidrug-resistant bacteria, including methicillin-resistant *S. aureus,* vancomycin-resistant *Enterococcus* species, and ESBL-producing *E. coli* and *K. pneumoniae* [8–16]. These characteristics suggest that tigecycline is a promising agent for the treatment of intra-abdominal infections, especially in the current era of antibiotic resistance.

The pooled analysis summarized here reports the findings of 2 phase 3, multicenter, double-blind, randomized trials that compared the clinical efficacy and safety of tigecycline monotherapy with that of imipenem-cilastatin therapy in patients with complicated intra-abdominal infections [17, 18].

## POPULATION AND METHODS

***Study design.*** Two phase 3, randomized, double-blind (third-party-unblinded) trials were conducted among hospitalized adult patients who were candidates for or had undergone a laparotomy, laparoscopy, or percutaneous drainage of an intra-abdominal abscess and had a known or suspected diagnosis of complicated intra-abdominal infections. The studies were conducted from November 2002 to May 2004. The 301 study was conducted in 96 centers in 17 countries in the United States, Canada, Europe, Latin America, India, and Asia, whereas the worldwide 306 study was conducted in 94 centers in 27 countries in Europe, South Africa, and Asia. The protocols were reviewed and approved by the institutional review board or ethical review committee at each participating center. Written informed consent was obtained from each patient or his or her guardian before commencement of any study procedure according to the guidelines of each institution. The trials were conducted in accordance with the Declaration of Helsinki and its amendments. Both trials used a similar study design and methodology and are included in the pooled analysis. Before the pooled analyses were done on the primary efficacy variable, the appropriateness of pooling the data was examined by using a generalized linear model (for adjusted differences) with the following factors: APACHE II score, protocol, geographic region, and treatment. An interaction model examined protocol-by-treatment interaction and geographic region–by-treatment interaction. The results showed that the protocol-by-treatment interaction and the geographic region–by-treatment interaction for clinical response were not significant ($P > .10$) at the test-of-cure assessment, suggesting the appropriateness of the pooling of data from these studies. Similar results were observed when examining interaction effects for treatment group by protocol on microbiological response for the microbiologically evaluable population.

***Entry criteria.*** Both men and women were eligible for entry into the study if they were ⩾18 years old and required a surgical procedure to treat a complicated intra-abdominal infection. Complicated intra-abdominal infections included such conditions intra-abdominal abscess (including liver and spleen) that developed in a patient following surgery after receiving standard antibacterial therapy (i.e., antibiotics for at least 48 h but not more than 5 days); appendicitis complicated by perforation and/or a periappendiceal abscess; perforated diverticulitis complicated by abscess formation or fecal contamination; complicated cholecystitis with evidence of perforation, empyema, or gangrene; perforation of a gastric or duodenal ulcer with symptoms exceeding 24 h in duration; purulent peritonitis or peritonitis associated with fecal contamination; or perforation of the large or small intestine with abscess or fecal contamination. In addition, patients could not have received >1 dose of an antibiotic (single broad-spectrum agent or 1 dose of each antibiotic in a combination regimen such as metronidazole, ampicillin, and gentamicin) after the baseline sample for culture was obtained from the infected site.

***Exclusion criteria.*** Patients were not enrolled in the study if they had any concomitant condition that precluded evaluation of a response or made it unlikely that the planned course of therapy could be completed. Other reasons for exclusion

were as follows: preoperative suspicion of a diagnosis of spontaneous bacterial peritonitis, simple cholecystitis, gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, pancreatic abscess, or infected necrotizing pancreatitis; APACHE II score of >30; active or treated leukemia or systemic malignancy within the prior 3 months or metastatic malignancy to the abdomen within the prior 6 months; known AIDS; presence of any uncontrolled CNS disease; pregnancy or breast-feeding among women; known or suspected hypersensitivity to either study drug or to related compounds; concomitant ganciclovir therapy; significant hepatic disease (i.e., aspartate aminotransferase or alanine aminotransferase level >10 times the upper limit of normal or total bilirubin value >3 times the upper limit of normal) or acute hepatic failure or acute decompensation of chronic hepatic failure; significant renal disease (i.e., calculated creatinine clearance of <41 mL/min/1.73 $m^2$ after adequate hydration); neutropenia with absolute neutrophil count of <1000 cells/$mm^3$, with counts as low as 500 cells/$mm^3$ permitted if they were a result of the acute infectious process; current intra-abdominal infection known to be caused by ⩾1 bacterial isolates not susceptible to either of the study drugs (e.g., *P. aeruginosa* and *Proteus mirabilis*); surgical procedure requiring that fascia or deep muscular layers be left open or expectation of planned abdominal reexploration either in or out of the operating room; and administration of intraoperative antibacterial irrigants or peritoneal antibacterial agents (e.g., irrigants or antibiotic-impregnated sponges). Any patient requiring additional systemic antibacterial therapy, for any reason, was not allowed to participate in the trial.

***Treatment regimens.*** Patients who satisfied the entry criteria were stratified by randomization into 2 groups on the basis of their APACHE II scores: ⩽15, or >15 but <31. In a 1:1 ratio, patients were randomly assigned to receive either tigecycline (initial 100-mg dose given by intravenous infusion over a 30-minute period, followed by 50 mg intravenously every 12 h) or intravenous imipenem-cilastatin (500 mg/500 mg every 6 h or dose-adjusted on the basis of weight and creatinine clearance or according to local data sheet). Patients randomly assigned to tigecycline received a 100-mL normal saline intravenous infusion 6 h after each dose of active drug in order to maintain the blind. The duration of study drug therapy ranged from 5 to 14 days, unless the patient experienced clinical failure (see definition below).

Study drug was administered only when there was a strong suspicion (i.e., elevated WBC count, elevated band cell counts [i.e., evidence of a "shift to the left"], fever, or highly suggestive radiographic findings) or a confirmed diagnosis of an intra-abdominal infection (presence of pus within the abdominal cavity), and a baseline culture sample was obtained from the site of infection. Patients could be enrolled before drainage of the intra-abdominal infection and may have received up to 2 doses of study drug before the baseline culture samples were obtained. Patients did not receive >1 dose (or combination) of parenteral nonstudy antibacterial drugs after the baseline intra-abdominal culture samples were obtained. Wound irrigation solutions of sterile water or normal saline and topical antiseptics were permitted throughout the course of the study.

***Clinical assessments and definitions.*** The clinical status of the intra-abdominal infection was assessed at serial visits during each study by the presence or absence of the following signs and symptoms: fever, localized or diffuse abdominal wall rigidity or involuntary guarding, abdominal tenderness or pain, ileus or hypoactive bowel sounds, and nausea or vomiting. The clinical response to study drug was determined by the investigator.

At the test-of-cure visit (12–42 days after therapy), each patient's response was categorized as cure, failure, or indeterminate. The responses were defined as follows: cure, the course of study drug and the initial intervention (operative and/or radiologically guided drainage procedure) resolved the intra-abdominal infectious process; failure, the patient required additional antibacterial therapy other than the study drug, the patient required additional surgical or radiological intervention to cure the infection, death due to infection occurred after 48 h of therapy, the patient received an extended course of study drug (i.e., >120% of the planned number of doses), or the patient was prematurely discontinued from study drug because of an adverse event and required additional antibiotic therapy or surgical intervention; and indeterminate, the patient was lost to follow-up, died within 48 h after the first dose of study drug for any reason, or died after 48 h because of non–infectious-related reasons (as judged by the investigator).

***Microbiological assessments and definitions.*** Pretherapy samples were obtained from the primary intra-abdominal site of infection and were cultured for aerobic and anaerobic organisms, and 2 sets of blood samples for culture were obtained within 24 h of the first dose of study drug. All aerobic and anaerobic bacterial isolates, regardless of the source of cultured material, were identified and tested at a central laboratory (Covance Central Laboratory Services, Indianapolis or Geneva) by a standard procedure approved by the NCCLS Subcommittee on Antimicrobial Susceptibility Testing [19–21]. For tigecycline, provisional MIC break points were used (susceptible, ⩽2 $\mu$g/mL; intermediate, 4 $\mu$g/mL; resistant, ⩾8 $\mu$g/mL).

The investigator assessed the microbiological response at the patient level and at the isolate level on the basis of results of the pretherapy intra-abdominal cultures, the susceptibilities of identified organisms, and the clinical outcome of the patient. Microbiological response by patient was categorized at the test-of-cure visit as eradication, persistence, or superinfection (i.e., the emergence of a new isolate was documented at the site of infection with worsening signs and symptoms of infection). The microbiological response for each pretherapy isolate at the

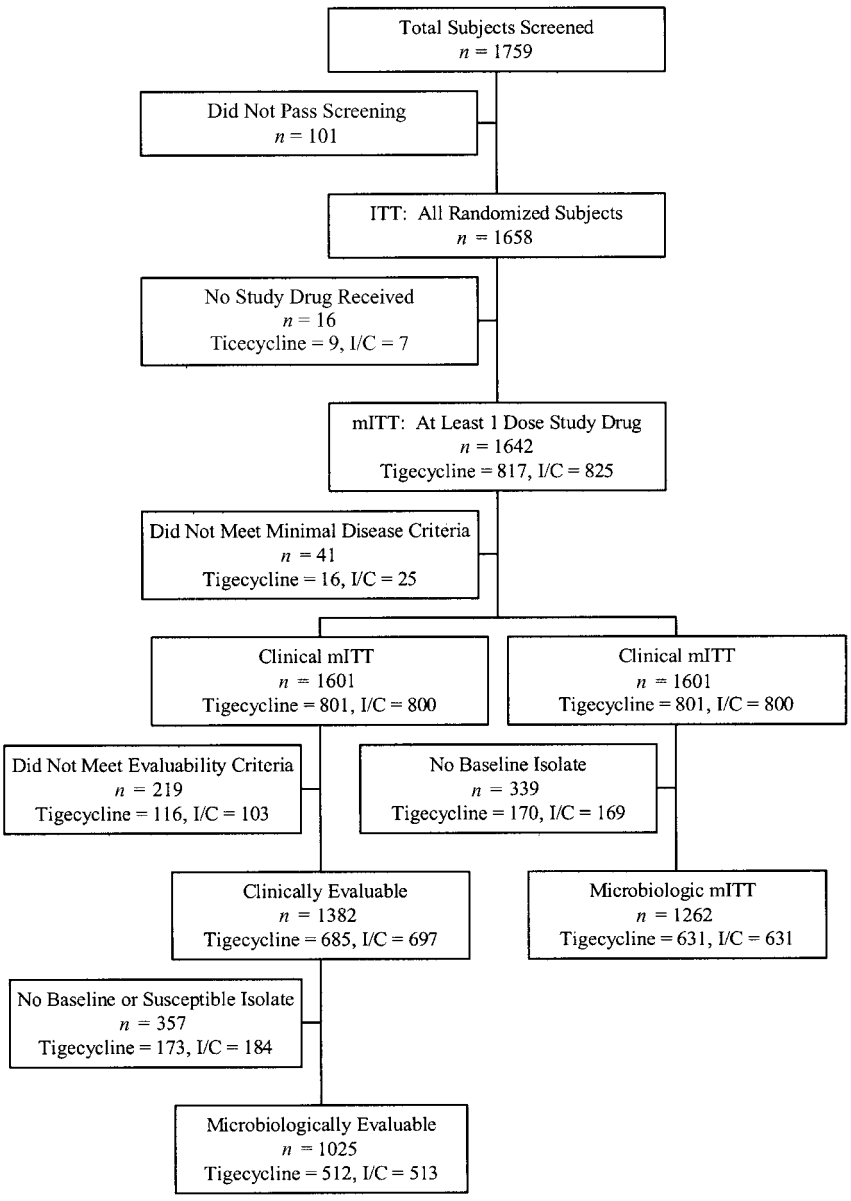


**Figure 1.** Disposition of patients in studies of tigecycline versus imipenem-cilastatin (I/C) in the treatment of complicated intra-abdominal infections. ITT, intent-to-treat; mITT, modified intent-to-treat.

test-of-cure visit was described as eradication, persistence, or indeterminate. Many microbiological responses, at both the patient and isolate level, were categorized as either presumed eradication or presumed persistence because the majority of patients did not have follow-up samples obtained for culture.

***Safety and tolerability assessments.*** Each patient who received at least 1 dose of study drug was evaluated for safety (modified intent-to-treat [mITT] population) on the basis of serial medical history and physical examinations, reports of clinical adverse events, and findings from routine electrocardiography and serum chemistry, hematology, coagulation, and urinalysis tests. Adverse events were recorded throughout the study period, up to and including the test-of-cure visit. Before unblinding, the investigator categorized the severity of each adverse event and the potential for relationship to study drug. Serious adverse events (i.e., those that were life threatening, led to prolongation of the existing hospitalization, or caused persistent or significant disability, incapacity, or death) were also recorded. Treatment-emergent adverse events were defined as those that appeared or worsened 5 days after the last day of drug therapy.

***Statistical analysis.*** Because both trials used a similar study design and methodology, the integrated pooled analysis is justified. In addition, treatment group–by-protocol and treatment

**Table 1. Demographic and baseline medical characteristics of the pooled microbiologic modified intent-to-treat population with complicated intra-abdominal infections.**

| Characteristic | Tigecycline ($n$ = 631) | Imipenem-cilastatin ($n$ = 631) |
|---|---|---|
| Age, mean ± SD, years | 47.1 ± 18.6 | 46.8 ± 18.2 |
| Sex, no. (%) of male patients | 401 (63.5) | 393 (62.3) |
| Ethnic origin, no. (%) of patients | | |
| White | 416 (65.9) | 413 (65.5) |
| Black | 28 (4.4) | 37 (5.9) |
| Asian | 58 (9.2) | 53 (8.4) |
| Hispanic | 60 (9.5) | 55 (8.7) |
| Other | 69 (10.9) | 73 (11.6) |
| Weight, mean ± SD, kg | 72.0 ± 15.2 | 72.0 ± 16.0 |
| Creatinine clearance, mean ± SD, mL/min | 93.0 ± 32.3 | 92.7 ± 30.9 |
| Duration of therapy, mean ± SD, days | 7.7 ± 2.8 | 7.7 ± 2.7 |
| APACHE II score, mean | 6.3 | 6.0 |
| Primary intra-abdominal diagnosis, no. (%) of patients | | |
| Complicated appendicitis | 319 (50.6) | 307 (48.7) |
| Complicated cholecystitis | 81 (12.8) | 95 (15.1) |
| Intra-abdominal abscess | 68 (10.8) | 58 (9.2) |
| Perforation of intestine | 67 (10.6) | 59 (9.4) |
| Complicated diverticulitis | 39 (6.2) | 49 (7.8) |
| Gastric/duodenal perforation | 33 (5.2) | 36 (5.7) |
| Peritonitis | 21 (3.3) | 22 (3.5) |
| Other[a] | 3 (0.5) | 5 (0.8) |

[a] Other diagnoses included infected hematoma, pelvic inflammatory disease, acute abdomen subocclusion, acute inflammatory abdomen, disease pelvic infectious, tubo-ovarian abscess, right tubal abscess, infected left subphrenic hematoma, complicated salpingitis, pyosalpinx, peritonitis due to left pyoovarium (local abscess), right and left purulent salpingitis, perforated suppurative left ovary cyst, intra abdominal abscess after ovarian cystectomy, acute salpingitis with purulent peritonitis, and septic incomplete abortion with traumatized uterus and perforation.

group–by–geographic region interaction effects were tested at the .10 level of significance, and no significant interactions were detected.

Clinical, microbiological, and safety outcomes were assessed in several key subpopulations of patients. The intent-to-treat (ITT) population included those patients who satisfied the inclusion and exclusion criteria, whereas the mITT population was the subset of patients who received at least 1 dose of study drug. The microbiological mITT (m-mITT) population included those patients in the mITT population who had clinical evidence of a complicated intra-abdominal infection, by meeting the minimal disease criteria, and had a confirmed baseline isolate. From this latter group, the microbiologically evaluable population was defined as those who met all inclusion and exclusion criteria, received therapy for at least 5 days, did not receive concomitant antibiotics after the pretherapy intra-abdominal culture was obtained through the test-of-cure visit, had a test-of-cure visit 12–42 days after the first dose of study drug, and had a pretherapy intra-abdominal culture containing at least 1 causative isolate that was susceptible to both study drugs. If these criteria were not satisfied at any time during the study, the patient was declared to be nonevaluable, and the outcome of cure, failure, or indeterminate was analyzed within the m-mITT population. Patients were considered to be nonevaluable for inclusion in the microbiologically evaluable population if death occurred or if they withdrew from the study <48 h after the first dose of study drug.

The primary end point of the study was the clinical response at the test-of-cure visit (12–42 days after therapy) for the m-mITT and microbiologically evaluable populations. Secondary analyses included bacteriologic response at the test-of-cure visit by patient and isolate, as well as clinical response rates stratified as monomicrobial versus polymicrobial and stratified by isolate.

Statistical analysis was done by the Clinical Biostatistics department of Wyeth Research (Collegeville, PA). Categorical baseline demographic and medical variables were analyzed by Fisher's exact test. Continuous variables were compared by a one-way analysis of variance model with treatment as a factor. Between-group comparisons of adverse events were analyzed by Fisher's exact test. For laboratory tests, vital signs, and elec-

**Table 2. Clinical cure rates, by study population, at the test-of-cure visit.**

| Population | Tigecycline | | Imipenem-cilastatin | | Difference (tigecycline − imipenem-cilastatin), % (95% CI) | Test for noninferiority, *P* | Test for differences |
|---|---|---|---|---|---|---|---|
| | No. of patients/total | Percentage of patients (95% CI) | No. of patients/total | Percentage of patients (95% CI) | | | |
| Clinically evaluable | 594/685 | 86.7 (83.9–89.2) | 607/697 | 87.1 (84.4–89.5) | −0.4 (−4.1 to 3.3) | <.0001 | 0.9003 |
| Overall | | | | | | | −0.3 (−3.8 to 3.3)[a] |
| c-mITT | 639/801 | 79.8 (76.8–82.5) | 656/800 | 82.0 (79.2–84.6) | −2.2 (−6.2 to 1.8) | <.0001 | 0.2851 |
| Overall | | | | | | | −2.0 (−5.9 to 1.8) |
| Microbiologically evaluable | 441/512 | 86.1 (82.8–89.0) | 442/513 | 86.2 (82.9–89.0) | 0.0 (−4.5 to 4.4) | <.0001 | 1.0000 |
| Monomicrobial | 166/180 | 92.2 (87.3–95.7) | 175/194 | 90.2 (85.1–94.0) | 2.0 (−4.3 to 8.3) | | |
| Polymicrobial | 275/332 | 82.8 (78.3–86.7) | 267/319 | 83.7 (79.2–87.6) | −0.9 (−6.8 to 5.1) | | |
| Overall | | | | | | | 0.6 (−3.5 to 4.6)[a] |
| m-mITT | 506/631 | 80.2 (76.9–83.2) | 514/631 | 81.5 (78.2–84.4) | −1.3 (−5.8 to 3.2) | <.0001 | 0.6167 |
| Monomicrobial | 204/241 | 84.6 (79.5–89.0) | 211/247 | 85.4 (80.4–89.6) | −0.8 (−7.5 to 5.9) | | |
| Polymicrobial | 302/390 | 77.4 (73.0–81.5) | 303/384 | 78.9 (74.5–82.9) | −1.5 (−7.5 to 4.5) | | |
| Overall | | | | | | | −1.2 (−5.4 to 3.1)[a] |

**NOTE.** c-mITT, clinical modified intent-to-treat population; m-mITT, microbiological modified intent-to-treat population.

[a] Adjusted difference and its 95% CI were calculated from a generalized linear model with a binomial probability function and an identity link.

trocardiographic results, within-group changes from baseline were analyzed with a paired *t* test, and between-group comparisons were made by analysis of covariance, adjusting for baseline value. The difference between treatment groups in the percentage of premature withdrawal from study drug was evaluated by a 2-sided Fisher's exact test.

The noninferiority of the efficacy of tigecycline, compared with that of imipenem-cilastatin, was evaluated for clinical and microbiological responses by using a 2-sided 95% CI for the true difference in efficacy (tigecycline minus imipenem-cilastatin) adjusted for the stratification variable APACHE II score and corrected for continuity. Noninferiority was concluded if the lower limit of the 2-sided 95% CI was greater than or equal to −15%. For all subpopulation analyses (e.g., monomicrobial versus polymicrobial infection), an adjusted difference between treatment groups with its 95% CI was calculated from a generalized linear model with a binomial probability function and an identity link (Proc GENMOD). Interaction effects were tested at the .10 level of significance.

## RESULTS

A total of 1759 patients were screened for study participation, of whom 1658 were randomly assigned to receive either tigecycline or imipenem-cilastatin (figure 1). Sixteen patients did not receive study drug; therefore, 1642 patients (817 treated with tigecycline, and 825 treated with imipenem-cilastatin) made up the mITT population. Of this latter group, 41 patients did not meet the criteria for the severity of infection, such that 1601 patients (801 treated with tigecycline, and 800 treated with imipenem-cilastatin) constituted the clinical mITT population. The clinically evaluable population contained 1382 patients, of whom 1262 had a pretherapy isolate recovered and thus made up the m-mITT population. A total of 1025 patients (512

**Table 3. Clinical cure rate, by baseline diagnosis, (microbiologically evaluable population) at test-of-cure visit.**

| Clinical diagnosis | Tigecycline | | Imipenem-cilastatin | | Difference (tigecycline − imipenem-cilastatin), % (95% CI) |
|---|---|---|---|---|---|
| | No. of patients/total | Percentage of patients (95% CI) | No. of patients/total | Percentage of patients (95% CI) | |
| Complicated appendicitis | 232/263 | 88.2 (83.7–91.8) | 234/262 | 89.3 (84.9–92.8) | −1.1 (6.8 to 4.6) |
| Complicated cholecystitis | 67/69 | 97.1 (89.9–99.6) | 70/74 | 94.6 (86.7–98.5) | 2.5 (−6.4 to 11.4) |
| Intra-abdominal abscess | 40/51 | 78.4 (64.7–88.7) | 35/45 | 77.8 (62.9–88.8) | 0.7 (−17.0 to 18.8) |
| Perforation of the intestines | 38/51 | 74.5 (60.4–85.7) | 29/40 | 72.5 (56.1–85.4) | 2.0 (−17.0 to 21.8) |
| Complicated diverticulitis | 23/32 | 71.9 (53.3–86.3) | 30/42 | 71.4 (55.4–84.3) | 0.4 (−22.1 to 21.7) |
| Gastric and abdominal perforations | 23/25 | 92.0 (74.0–99.0) | 23/25 | 92.0 (74.0–99.0) | 0.0 (−20.6 to 20.6) |
| Peritonitis | 16/18 | 88.9 (65.3–98.6) | 18/20 | 90.0 (68.3–98.8) | −1.1 (−27.4 to 23.8) |
| Other | 2/3 | 66.7 (9.4–99.2) | 3/5 | 60.0 (14.7–94.7) | 6.7 (−56.6 to 60.0) |
| Concomitant bacteremia | 33/40 | 82.5 (67.2–92.7) | 40/50 | 80.0 (66.3–90.0) | 2.5 (−16.0 to 19.6) |

**Table 4. Microbiological response at the patient level (microbiologically evaluable population) at the test-of-cure visit.**

| Response | Tigecycline | | Imipenem-cilastatin | | Difference (tigecycline−imipenem-cilastatin), % (95% CI) | Test for noninferiority, *P* | Test for differences |
|---|---|---|---|---|---|---|---|
| | No. of patients/total | Percentage of patients (95% CI) | No. of patients/total | Percentage of patients (95% CI) | | | |
| Eradication | 441/512 | 86.1 (82.8–89.0) | 442/513 | 86.2 (82.9–89.0) | 0.0 (−4.5 to 4.4) | <.0001 | 1.0000 |
| Monomicrobial | 167/180 | 92.8 (88.0–96.1) | 175/194 | 90.2 (85.1–94.0) | 2.6 (−3.7 to 8.7) | | |
| Polymicrobial | 274/332 | 82.5 (78.0–86.5) | 267/319 | 83.7 (79.2–87.6) | −1.2 (−7.1 to 4.8) | | |
| Persistence | 60/512 | 11.7 (9.1–14.8) | 68/513 | 13.3 (10.4–16.5) | | | |
| Monomicrobial | 11/180 | 6.1 (3.1–10.7) | 17/194 | 8.8 (5.2–13.7) | | | |
| Polymicrobial | 49/332 | 14.8 (11.1–19.0) | 51/319 | 16.0 (12.1–20.5) | | | |
| Superinfection | 11/512 | 2.1 (1.1–3.8) | 3/513 | 0.6 (0.1–1.7) | | | |
| Monomicrobial | 2/180 | 1.1 (0.1–4.0) | 2/194 | 1.0 (0.1–3.7) | | | |
| Polymicrobial | 9/332 | 2.7 (1.2–5.1) | 1/319 | 0.3 (0.0–1.7) | | | |
| Overall | | | | | −0.4 (−3.8 to 4.6)[a] | | |

[a] Adjusted difference and its 95% CI were calculated from a generalized linear model with a binomial probability function and an identity link.

treated with tigecycline, and 513 treated with imipenem-cilastatin) met clinical evaluability criteria and had a pretherapy isolate (microbiologically evaluable population). The primary reasons for exclusion from the clinically evaluable population were no clinical evaluation at the test-of-cure visit ($n = 80$); entry criteria not met ($n = 59$); blind broken ($n = 40$); and receipt of >1 dose of prior antibiotic after the pretherapy culture sample was obtained ($n = 14$). The rates of the reasons for exclusion were generally similar between treatment groups.

***Demographic and medical characteristics at baseline.*** The demographic characteristics for the 1262 m-mITT patients were comparable between the 2 treatment groups (table 1). The study population was mostly white (66%) and male (63%) and had a mean age of 47 years. Complicated appendicitis (50%) was the most common intra-abdominal infection diagnosis, followed by complicated cholecystitis (14%). No significant differences between treatment groups were observed in the number or types of infections diagnosed at baseline. The severity of intra-abdominal illness was similar in each treatment group (mean APACHE II score, ~6.3). A small proportion of patients had an APACHE II score of >15 (22 [3.5%] patients treated with tigecycline vs. 13 [2.1%] patients treated with imipenem-cilastatin). The initial surgical assessment based on the operating physician's observations revealed that abscess was present in approximately two-thirds of patients in each treatment group, of whom ~30% had an abscess size of >100 mL at clinical presentation. Multiple abscesses were noted in 10.4% of patients treated with tigecycline and in 11.0% of patients treated with imipenem-cilastatin. In addition, ~20% of patients in each treatment group had fecal contamination at clinical presentation, and >75% presented with peritonitis.

***Clinical efficacy.*** For the microbiologically evaluable population, clinical cure rates were virtually identical between treatment groups (86.1% for tigecycline and 86.2% for imipenem-cilastatin; 95% CI for the difference, −4.5% to 4.4% [$P <$ .0001 for noninferiority]; table 2). Corresponding clinical cure rates for the m-mITT population were 80.2% and 81.5% (95% CI for the difference, −5.8% to 3.2%; $P <$ .0001 for noninferiority), respectively. For both the microbiologically evaluable and m-mITT populations, tigecycline was efficacious and statistically noninferior to imipenem-cilastatin. Multiple subgroup analyses of clinical responses (e.g., age, sex, and race) found consistently efficacious clinical responses between the treatment groups. No significant treatment differences in clinical response were observed between treatment groups when patients were stratified by the number of organisms isolated at baseline (table 2). However, in both treatment groups, patients with monomicrobial infections tended to have higher rates of clinical cure than did those with polymicrobial infections. For the microbiologically evaluable population, tigecycline had a 92.2% clinical cure rate at the test-of-cure visit for monomicrobial infections and a 82.8% clinical cure rate for polymicrobial infections. Similar rates were observed for patients treated with imipenem-cilastatin (90.2% and 83.7%, respectively).

For complicated appendicitis, the most frequent diagnosis, the clinical cure rate at the test-of-cure visit was 88.2% for tigecycline and 89.3% for imipenem-cilastatin (table 3). In both treatment groups, lower clinical cure rates (≤78%) were observed in patients who had intra-abdominal abscess, complicated diverticulitis, or intestinal perforation (table 3). Overall, there were no significant differences in clinical cure rates between tigecycline and imipenem-cilastatin on the basis of primary intra-abdominal diagnosis. A total of 40 patients treated with tigecycline and 50 treated with imipenem-cilastatin in the microbiologically evaluable population had positive pretherapy blood culture results. Clinical cure in patients with bacteremia was reported for 82.5% and 80.0% of patients treated with tigecycline and imipenem-cilastatin, respectively.

**Table 5. Microbiological eradication at the isolate level: selected baseline isolates at test-of-cure visit (microbiologically evaluable population).**

| Isolate | Tigecycline | | Imipenem-cilastatin | |
|---|---|---|---|---|
| | No. of patients/total | Percentage of patients (95% CI) | No. of patients/total | Percentage of patients (95% CI) |
| *Bacteroides fragilis* | 68/87 | 78.2 (68.0–86.3) | 59/73 | 80.8 (69.9–89.1) |
| *Citrobacter freundii* | 12/16 | 75.0 (47.6–92.7) | 3/4 | 75.0 (19.4–99.4) |
| *Clostridium perfringens* | 18/19 | 94.7 (74.0–99.9) | 20/22 | 90.9 (70.8–98.9) |
| *Enterobacter cloacae* | 14/16 | 87.5 (61.7–98.4) | 16/17 | 94.1 (71.3–99.9) |
| *Enterococcus faecalis* (non–vancomycin resistant) | 26/33 | 78.8 (61.1–91.0) | 35/47 | 74.5 (59.7–86.1) |
| *Escherichia coli* | 280/325 | 86.2 (81.9–89.7) | 296/340 | 87.1 (83.0–90.4) |
| *Klebsiella oxytoca* | 19/20 | 95.0 (75.1–99.9) | 17/19 | 89.5 (66.9–98.7) |
| *Klebsiella pneumoniae* | 46/52 | 88.5 (76.6–95.6) | 54/60 | 90.0 (79.5–96.2) |
| *Peptostreptococcus micros* | 13/17 | 76.5 (50.1–93.2) | 8/11 | 72.7 (39.0–94.0) |
| *Pseudomonas aeruginosa* | 33/39 | 84.6 (69.5–94.1) | 31/36 | 86.1 (70.5–95.3) |
| *Staphylococcus aureus* | | | | |
| Methicillin resistant | 3/4 | 75.0 (19.4–99.4) | 1/3 | 33.3 (0.8–90.6) |
| Non–methicillin resistant | 26/28 | 92.9 (76.5–99.1) | 22/24 | 91.7 (73.0–99.0) |
| *Streptococcus anginosus* | 103/119 | 86.6 (ND) | 60/79 | 75.9 (ND) |

**NOTE.** ND, not determined.

[a] The *Streptococcus anginosus* category includes *S. anginosus, S. intermedius,* and *S. constellatus.*

***Microbiological efficacy.*** For the microbiologically evaluable population, eradication of intra-abdominal isolates at the patient level mirrored the clinical cure rates: 86.1% for the tigecycline group and 86.2% for the imipenem-cilastatin group (95% CI for the difference, −4.5% to 4.4%; $P < .0001$ for noninferiority), indicating that tigecycline was efficacious and statistically noninferior to imipenem-cilastatin (table 4). No significant differences between treatment groups were found when eradication rates were stratified by monomicrobial versus polymicrobial infection (table 4).

In general, eradication rates at the test-of-cure visit for the most commonly isolated intra-abdominal organisms were similar between treatment groups (table 5). For *E. coli,* the most commonly isolated aerobe, eradication rates were 86.2% for tigecycline, versus 87.1% for imipenem-cilastatin. Corresponding eradication rates for *K. pneumoniae,* the second-most-frequently isolated gram-negative aerobe, were 88.5% and 90.0%, respectively. Both treatments were effective at eradicating pretherapy methicillin-susceptible *S. aureus* isolates (92.9% for tigecycline, vs. 91.7% for imipenem-cilastatin). Bacterial eradication for patients with methicillin-resistant *S. aureus* was 75% (3 of 4 patients) for tigecycline, compared with only 33% (1 of 3 patients) for imipenem-cilastatin. One tigecycline-treated patient with vancomycin-resistant enterococci recovered from a pretherapy intra-abdominal source (microbiologically evaluable population) achieved bacterial eradication. Tigecycline

**Table 6. MIC range and $MIC_{50}$ and $MIC_{90}$ values for selected primary baseline isolates (microbiologically evaluable population).**

| Isolate | No. | Tigecycline | | | Imipenem-cilastatin | | |
|---|---|---|---|---|---|---|---|
| | | MIC range | $MIC_{50}$ | $MIC_{90}$ | MIC range | $MIC_{50}$ | $MIC_{90}$ |
| *Bacteroides fragilis* | 160 | 0.06–16.0 | 1.0 | 2.0 | 0.12–4.0 | 0.25 | 0.5 |
| *Clostridium perfringens* | 41 | 0.06–2.0 | 0.12 | 1.0 | 0.12–0.25 | 0.12 | 0.25 |
| *Enterococcus faecalis* (non–vancomycin resistant) | 77 | 0.06–0.25 | 0.12 | 0.25 | 0.5–8.0 | 1.0 | 4.0 |
| *Escherichia coli* | 665 | 0.06–1.0 | 0.25 | 0.5 | 0.12–1.0 | 0.12 | 0.25 |
| *Klebsiella pneumoniae* | 111 | 0.25–4.0 | 0.5 | 1.0 | 0.12–0.5 | 0.25 | 0.25 |
| *Staphylococcus aureus* (non–methicillin resistant) | 52 | 0.06–0.5 | 0.12 | 0.25 | 0.12–4.0 | 0.12 | 0.12 |
| *Streptococcus anginosus*[a] | 195 | 0.008–1.0 | ND | ND | 0.06–0.5 | ND | ND |

**NOTE.** MICs are given in micrograms per milliliter. ND, not determined.

[a] The *Streptococcus anginosus* category includes *S. anginosus, S. intermedius,* and *S. constellatus.*

**Table 7. Common treatment-emergent adverse events (⩾3% in either group) in the intent-to-treat population.**

| Body system adverse event[a] | Tigecycline ($n$ = 817) | Imipenem-cilastatin ($n$ = 825) | Fisher's exact $P$[b] |
|---|---|---|---|
| Any | 603 (73.8) | 591 (71.6) | .346 |
| Body as a whole | 289 (35.4) | 260 (31.5) | .105 |
| Abdominal pain | 65 (8.0) | 55 (6.7) | .343 |
| Fever | 74 (9.1) | 99 (12.0) | .054 |
| Headache | 28 (3.4) | 48 (5.8) | .025 |
| Infection | 83 (10.2) | 45 (5.5) | <.001 |
| Cardiovascular system | 121 (14.8) | 151 (18.3) | .063 |
| Hypertension | 49 (6.0) | 51 (6.2) | .918 |
| Phlebitis | 16 (2.0) | 33 (4.0) | .019 |
| Digestive system | 363 (44.4) | 325 (39.4) | .040 |
| Constipation | 21 (2.6) | 29 (3.5) | .315 |
| Diarrhea | 113 (13.8) | 109 (13.2) | .719 |
| Nausea | 199 (24.4) | 157 (19.0) | .010 |
| Vomiting | 157 (19.2) | 118 (14.3) | .008 |
| Hemic and lymphatic system | 123 (15.1) | 124 (15.0) | 1.000 |
| Anemia | 39 (4.8) | 43 (5.2) | .734 |
| Leukocytosis | 36 (4.4) | 20 (2.4) | .030 |
| Thrombocythemia | 49 (6.0) | 53 (6.4) | .760 |
| Metabolic and nutritional | 215 (26.3) | 217 (26.3) | 1.000 |
| Alkaline phosphatase increased | 33 (4.0) | 21 (2.5) | .098 |
| Healing abnormal | 37 (4.5) | 24 (2.9) | .090 |
| Hypokalemia | 19 (2.3) | 26 (3.2) | .365 |
| Hypoproteinemia | 48 (5.9) | 30 (3.6) | .037 |
| Lactate dehydrogenase increased | 38 (4.7) | 37 (4.5) | .906 |
| Peripheral edema | 30 (3.7) | 36 (4.4) | .531 |
| AST increased | 24 (2.9) | 28 (3.4) | .673 |
| ALT increased | 27 (3.3) | 23 (2.8) | .568 |
| Respiratory system | 138 (16.9) | 130 (15.8) | .548 |
| Cough increased | 33 (4.0) | 40 (4.8) | .473 |
| Dyspnea | 30 (3.7) | 23 (2.8) | .331 |
| Pulmonary physical finding | 25 (3.1) | 28 (3.4) | .780 |
| Adverse event associated with miscellaneous factors | 95 (11.6) | 96 (11.6) | 1.000 |
| Local reaction to procedure | 94 (11.5) | 96 (11.6) | .939 |

**NOTE.** Data are no. (%) of patients. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] Body system totals are not necessarily the sum of the individual adverse events, because a subject may report ⩾2 different adverse events in the same body system.

[b] Significant between-group difference at .05 level.

also eradicated common gram-negative isolates confirmed to produce ESBL. Twelve (80%) of 15 patients with either ESBL-producing *E. coli* or *K. pneumoniae* achieved bacterial eradication after receiving tigecycline. Eradication rates for *B. fragilis* were 78.2% for tigecycline and 80.8% for imipenem-cilastatin.

A select number of pretherapy isolates from tigecycline-treated patients (microbiologically evaluable population) were evaluated to compare the in vitro activity and clinical and microbiological responses among isolates carrying specific gene combinations for resistance, including isolates that were known to possess ESBL resistance determinants. Among 117 *E. coli* isolates genotyped, 9 were found to produce ESBL. The tigecycline MIC range did not differ for the ESBL producers (0.25–1 μg/mL) versus non–ESBL producers (0.06–1 μg/mL). Seven (78%) of 9 patients with ESBL-producing *E. coli* achieved clinical cure or eradication after receiving tigecycline. Similar findings were reported for 6 ESBL-producing *K. pneumoniae* isolates, whereas 83% of patients (5/6) had clinical cure or eradication after tigecycline therapy.

Pretherapy in vitro activity against baseline isolates for tigecycline and imipenem-cilastatin are shown in table 6. The mean tigecycline $MIC_{90}$ for the most commonly isolated aerobes

**Table 8. Number (%) of patients in the modified intent-to-treat population who withdrew because of an adverse event.**

| Body system adverse event[a] | Tigecycline ($n$ = 817) | Imipenem-cilastatin ($n$ = 825) | $P$[b] |
|---|---|---|---|
| Any adverse event | 21 (2.6) | 12 (1.5) | .116 |
| Body as a whole | 14 (1.7) | 8 (1.0) | .205 |
| Abdominal pain | 1 (0.1) | 0 | .498 |
| Abscess | 0 | 1 (0.1) | 1.000 |
| Accidental injury | 0 | 1 (0.1) | 1.000 |
| Ascites | 0 | 1 (0.1) | 1.000 |
| Carcinoma | 1 (0.1) | 0 | .498 |
| Chest pain | 0 | 1 (0.1) | 1.000 |
| Fever | 1 (0.1) | 1 (0.1) | 1.000 |
| Headache | 0 | 1 (0.1) | 1.000 |
| Infection | 3 (0.4) | 2 (0.2) | .686 |
| Pain | 1 (0.1) | 0 | .498 |
| Peritonitis | 2 (0.2) | 0 | .247 |
| Sepsis | 3 (0.4) | 1 (0.1) | .372 |
| Septic shock | 3 (0.4) | 0 | .123 |
| Cardiovascular system | 3 (0.4) | 2 (0.2) | .686 |
| Angina pectoris | 0 | 1 (0.1) | 1.000 |
| Heart failure | 1 (0.1) | 0 | .498 |
| Hypotension | 1 (0.1) | 0 | .498 |
| Left heart failure | 0 | 1 (0.1) | 1.000 |
| Shock | 1 (0.1) | 0 | .498 |
| Digestive system | 3 (0.4) | 4 (0.5) | 1.000 |
| Colitis | 0 | 1 (0.1) | 1.000 |
| Liver damage | 1 (0.1) | 0 | .498 |
| Nausea | 2 (0.2) | 3 (0.4) | 1.000 |
| Vomiting | 1 (0.1) | 2 (0.2) | 1.000 |
| Hemic and lymphatic system | 4 (0.5) | 1 (0.1) | .216 |
| Leukocytosis | 4 (0.5) | 1 (0.1) | .216 |
| Metabolic and nutritional | 4 (0.5) | 2 (0.2) | .450 |
| Bilirubinemia | 1 (0.1) | 0 | .498 |
| Healing abnormal | 3 (0.4) | 2 (0.2) | .686 |
| Nervous system | 0 | 2 (0.2) | .500 |
| Paresthesia | 0 | 1 (0.1) | 1.000 |
| Somnolence | 0 | 1 (0.1) | 1.000 |
| Tremor | 0 | 1 (0.1) | 1.000 |
| Respiratory system | 2 (0.2) | 3 (0.4) | 1.000 |
| Dyspnea | 0 | 2 (0.2) | .500 |
| Pneumonia | 1 (0.1) | 0 | .498 |
| Respiratory distress syndrome | 0 | 1 (0.1) | 1.000 |
| Respiratory failure | 1 (0.1) | 0 | .498 |
| Skin and appendages | 1 (0.1) | 0 | .498 |
| Sweating | 1 (0.1) | 0 | .498 |
| Urogenital system | 2 (0.2) | 1 (0.1) | .623 |
| Kidney failure | 0 | 1 (0.1) | 1.000 |
| Kidney function abnormal | 2 (0.2) | 0 | .247 |

[a] Body system totals are not necessarily the sum of the individual adverse events because a subject may report ⩾2 different adverse event in the same body system.

[b] Overall $P$ was based on 2-tailed Fisher's exact test.

and anaerobes was ⩽2.0 μg/mL. Bacterial susceptibilities to tigecycline were consistent with clinical responses. Two pretherapy isolates *(K. pneumoniae* and *Morganella morganii)* were resistant to tigecycline (MIC for each, 8 μg/mL) on the basis of the provisional break points used. Both patients with these isolates experienced clinical failure. Ribotype analysis indicated that all *K. pneumoniae* isolates were identical for the patient with *K. pneumoniae* and all isolates of *M. morganii* were identical for the patient with *M. morganii.*

***Safety and tolerability.*** Data from all 1625 patients in the mITT population who received tigecycline or imipenem-cilastatin treatment for a median of 7–8 days were analyzed for safety. Regardless of study drug causality or severity, the frequency and distribution of treatment-emergent adverse events occurring in at least 3% of patients in either treatment group were similar (table 7). Nausea (24.4% tigecycline, 19.0% imipenem-cilastatin; $P = .010$), vomiting (19.2% tigecycline, 14.3% imipenem-cilastatin; $P = .008$), and diarrhea (13.8% tigecycline, 13.2% imipenem-cilastatin; $P = .719$) were the 3 most frequently reported adverse events in both treatment groups. No tigecycline-treated patient had a positive result of assay for *Clostridium difficile* toxin or developed *C. difficile*–associated diarrhea. There was no statistical difference between tigecycline and imipenem-cilastatin in the number of patients in the mITT population who with withdrew because of an adverse event (table 8).

A total of 41 patients died during the study: 24 in the tigecycline group and 17 in the imipenem-cilastatin treatment group. The majority of patients who died had serious underlying preexisting conditions, tended to be >65 years of age, and had relatively high APACHE II scores (7–9.5). Only one death, after septic shock in the tigecycline group, was considered by the investigators to be possibly related to study drug secondary to an inadequate response to therapy.

## DISCUSSION

This large, pooled multicountry analysis demonstrates that tigecycline monotherapy (100-mg initial dose, followed by 50 mg every 12 h) is effective for the treatment of adult patients with complicated intra-abdominal infections. For >1000 clinically evaluable patients with proven bacterial infections, clinical cure rates were nearly identical for tigecycline (86.1%) and imipenem-cilastatin (86.2%) at the test-of-cure visit, demonstrating that tigecycline met the statistical criteria for noninferiority, compared with the carbapenem regimen. As expected, patients in both treatment groups tended to have higher clinical cure rates with infection with a single isolate (⩾90%) than with polymicrobial infection (⩽83.7%). We also observed that the clinical efficacy of tigecycline and imipenem-cilastatin were similar across the variety of anatomic infections encountered, although rates of cure varied by the type of infection. For

complicated appendicitis, rates of clinical cure were uniformly high in both treatment groups (88%–89%), whereas clinical cure occurred at lower rates for those with intra-abdominal abscess, complicated diverticulosis, or intestinal perforation (71%–79%). Because bacteremia is a frequent complication among patients with these infections, it is encouraging that tigecycline monotherapy provided efficacy similar to that of imipenem-cilastatin (82.5% versus 80.0%).

The clinical and microbiological efficacy of tigecycline monotherapy was also consistent across the different species of commonly encountered aerobic and anaerobic intestinal bacteria. Clinical and microbiological eradication rates by patient were identical, reflecting the fact that many infections were presumed to be eradicated. More than 86% of *E. coli* and *Klebsiella* species (the 2 most frequently isolated gram-negative aerobes) were eradicated by tigecycline and imipenem-cilastatin. Tigecycline also eradicated the majority of *Streptococcus* species, methicillin-susceptible *S. aureus,* non–vancomycin-resistant enterococci, and *B. fragilis* isolates recovered from patients with complicated intra-abdominal infections, supporting in vitro observations that tigecycline has broad-spectrum activity against common isolates found in intra-abdominal infections [8–16].

Although few resistant isolates were recovered in the current trial, tigecycline has in vitro activity against typically resistant organisms (e.g., methicillin-resistant *S. aureus,* vancomycin-resistant enterococci, ESBL-producing *E. coli,* and *Klebsiella* species). Additional studies are recommended to establish efficacy against these isolates [11, 16, 22]. The current pooled analysis also confirmed the in vitro activity of tigecycline against intra-abdominal isolates, with a mean $MIC_{90}$ of $\leqslant 2.0$ $\mu$g/mL against the most commonly isolated aerobes and anaerobes, including ESBL-producing gram-negative bacteria.

Tigecycline and imipenem-cilastatin were well tolerated in the current trial, with a similar frequency and distribution of treatment-emergent adverse events. In general, gastrointestinal-related adverse events were the most frequently reported adverse events in both the tigecycline (44%) and imipenem-cilastatin treatment groups (39%; $P = .04$). Few clinically important or unexpected changes in any routine hematologic or serum chemistry test results, vital signs, or electrocardiographic data were associated with the use of tigecycline (i.e., leukocytosis or hypoproteinemia) or imipenem-cilastatin (i.e., low glucose, potassium, phosphorus, or lymphocyte values). The rates of serious adverse events or the proportion of adverse events that required premature discontinuation of tigecycline or imipenem-cilastatin occurred at similar frequencies between the 2 treatment groups. We also observed that postsurgical wound infection rates after tigecycline (2.8%) and imipenem-cilastatin therapy (1.3%), although significantly different ($P = .038$), were similar to those of previously conducted studies of intra-abdominal infection [1]. Collectively, the adverse event profile after tigecycline therapy in this pooled analysis supports previous safety data from phase 2 and 3 studies [23–26].

Tigecycline is an effective and well-tolerated monotherapy option for the treatment of patients with complicated intra-abdominal infections, with efficacy comparable to that of imipenem-cilastatin. The rise in rates of antibiotic-resistant bacteria, in both the community and hospital settings, sets the stage for tigecycline's potential role in the empirical treatment of these conditions when coverage is needed against both gram-positive and gram-negative aerobic and anaerobic bacteria, including activity against resistant isolates.

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## Acknowledgments

We thank Wyeth Research employee Patricia Bradford for microbiological analysis and Upside Endeavors for professional medical writing services.

***Financial support.*** Wyeth Research.

***Potential conflicts of interest.*** T.B., E.E.-G., N.D., G.M.R., and E.L. are employees of Wyeth.

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