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# Results of a Randomized Trial Comparing Sequential Intravenous/ Oral Treatment with Ciprofloxacin Plus Metronidazole to Imipenem/ Cilastatin for Intra-Abdominal Infections

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## Objective

In a randomized, double-blind, multicenter trial, ciprofloxacin/metronidazole was compared with imipenem/cilastatin for treatment of complicated intra-abdominal infections. A secondary objective was to demonstrate the ability to switch responding patients from intravenous (IV) to oral (PO) therapy.

## Summary Background Data

Intra-abdominal infections result in substantial morbidity, mortality, and cost. Antimicrobial therapy often includes a 7- to 10-day intravenous course. The use of oral antimicrobials is a recent advance due to the availability of agents with good tissue pharmacokinetics and potent aerobic gram-negative activity.

## Methods

Patients were randomized to either ciprofloxacin plus metronidazole intravenously (CIP/MTZ IV) or imipenem intravenously (IMI IV) throughout their treatment course, or ciprofloxacin plus metronidazole intravenously and treatment with oral ciprofloxacin plus metronidazole when oral feeding was resumed (CIP/MTZ IV/PO).

## Results

Among 671 patients who constituted the intent-to-treat population, overall success rates were as follows: 82% for the group treated with CIP/MTZ IV; 84% for the CIP/MTZ IV/PO group; and 82%

for the IMI IV group. For 330 valid patients, treatment success occurred in 84% of patients treated with CIP/MTZ IV, 86% of those treated with CIP/MTZ IV/PO, and 81% of the patients treated with IMI IV. Analysis of microbiology in the 30 patients undergoing intervention after treatment failure suggested that persistence of gram-negative organisms was more common in the IMI IV-treated patients who subsequently failed. Of 46 CIP/MTZ IV/PO patients (active oral arm), treatment success occurred in 96%, compared with 89% for those treated with CIP/MTZ IV and 89% for those receiving IMI IV. Patients who received intravenous/oral therapy were treated, overall, for an average of 8.6 ± 3.6 days, with an average of 4.0 ± 3.0 days of oral treatment.

**Conclusions**

These results demonstrate statistical equivalence between CIP/MTZ IV and IMI IV in both the intent-to-treat and valid populations. Conversion to oral therapy with CIP/MTZ appears as effective as continued intravenous therapy in patients able to tolerate oral feedings.

Intra-abdominal infections requiring either operative or percutaneous intervention are common and result in substantial morbidity, mortality, and cost. Antimicrobial therapy for such infections is intended to prevent recurrent intra-abdominal infection, reduce surgical wound complications, and control bacteremia. Such therapy, usually administered intravenously, has traditionally involved empiric use of agents directed at gram-negative facultative and obligate anaerobes. Such therapy is continued until patients are afebrile, have resolved their infections based on physical examination, and have normalized leukocyte counts.[1] Common regimens include either an aminoglycoside or a cephalosporin combined with an antianaerobic agent, certain cephalosporins alone, carbapenems, or β-lactam/β-lactamase inhibitor combinations.[2]

Ciprofloxacin is a 6-fluoroquinolone with considerable activity against the gram-negative facultative and aerobic organisms commonly encountered in intra-abdominal infections.[3–5] This agent has a large volume of distribution and penetrates well into most tissue compartments, including the peritoneal cavity.[6,7] Ciprofloxacin has little activity against *Bacteroides fragilis* and would need to be combined with an antianaerobic agent for empiric treatment of intra-abdominal infections. Recent *in vitro* and animal studies have explored the activity of a quinolone-based regimen for intra-abdominal infections,[8,9] and intravenous (IV) ciprofloxacin therapy has been found clinically effective for other serious gram-negative infections.[10]

One potential advantage of quinolone-based regimens is the prospect of conversion of initially successful IV therapy to oral (*per os* [PO]) treatment. Orally administered ciprofloxacin achieves plasma levels similar to those seen after IV administration.[11] Efforts to minimize treatment costs have led to efforts to limit the use of IV therapy through early conversion to PO treatment for certain infections.[11–14] However, sequential IV/PO therapy for complicated intra-abdominal infection has not been studied previously in a comparative clinical trial.

The purpose of this study was to evaluate the efficacy of IV ciprofloxacin plus metronidazole for complicated intra-abdominal infections. Imipenem/cilastatin was chosen as the control regimen because of the extensive experience with this agent in clinical trials for intra-abdominal infections.[2,15–17] A secondary goal of this trial was to determine whether bioequivalent doses of PO ciprofloxacin and metronidazole would provide equivalent efficacy to continued IV therapy for patients able to tolerate PO intake in the early postoperative period.

The primary result of this study was demonstration of the equivalence of IV ciprofloxacin plus metronidazole and imipenem/cilastatin. Furthermore, our data suggest that PO therapy is efficacious in selected patients tolerating PO intake and after an initial treatment response to IV therapy.

## METHODS

This prospective, multicenter, randomized, double-blind trial was conducted as part of a supplemental new drug application for the use of ciprofloxacin plus metronidazole in complicated intra-abdominal infections. Patients were eligible for inclusion if they were 18 years of age or older, if signs and symptoms of intra-abdominal infection were present, if operative or percutaneous drainage appeared necessary, and if the patient had not been enrolled previously in this trial. Patients were excluded for Acute Physiology and Chronic Health Evaluation (APACHE) II score > 30; acute renal insufficiency, manifested either by need for dialysis or by a serum cre-

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atinine level > 2.5 mg/dL after volume resuscitation; neutropenia less than 1000 leukocytes/mL; or a history of anaphylactoid reactions to metronidazole or β-lactam or quinolone anti-infective agents. Patients known to require treatment with antibacterial agents not specified in the protocol also were excluded. Pregnant women or those who were breast-feeding were excluded. Patients undergoing laparotomy within 12 hours of traumatic visceral perforation were excluded from study entry, as were patients with presumed primary peritonitis or diffuse necrotizing pancreatitis.

Patients were stratified before randomization based on APACHE II scores >20 or ≥20 and were assigned to treatment from separate randomization lists for each stratum. This procedure was used to ensure proper randomization of the relatively few more seriously ill patients. Patients could be randomized and receive study therapy either preoperatively or after operative confirmation of infection. Patients were not excluded if they received antibiotics other than study-driven treatment before and up to 24 hours after retrieval of a culture from an intra-abdominal focus of infection by an operative or percutaneous drainage procedure. Informed consent was obtained according to each participating institution's guidelines.

To perform a randomized, double-blind study including patients treated with IV agents and patients treated with sequential IV/PO agents, three randomization groups were created. All three groups initially received IV therapy: two received ciprofloxacin plus metronidazole (ClP/MTZ IV and ClP/MTZ IV/PO), and the other group received imipenem/cilastatin (IMI IV). Intravenous ciprofloxacin was administered at a dosage of 400 mg every 12 hours along with metronidazole 500 mg every 6 hours. Imipenem/cilastatin was administered at a dosage of 500 mg every 6 hours. Patients receiving imipenem/cilastatin also received a placebo infusion every 12 hours.

Physicians were encouraged to initiate PO therapy for all three treatment groups between 3 and 8 days after beginning IV therapy. The criteria for providing patients with PO treatment were restoration of PO intake and an initially favorable clinical response. Patients randomized to the groups referred to as ClP/MTZ IV or IMI IV received ciprofloxacin plus metronidazole or IV imipenem/cilastatin intravenously, respectively. If selected for PO therapy, these patients received PO placebo and continued active IV therapy. Patients randomized to the group referred to as CIP/MTZ IV/PO initially received ciprofloxacin plus metronidazole intravenously, followed by PO ciprofloxacin plus PO metronidazole and IV placebo if selected for PO treatment. Oral ciprofloxacin was given at a dosage of 500 mg every 12 hours, and PO metronidazole was administered 500 mg every 6 hours. A depiction of the study randomization is provided in Figure 1.

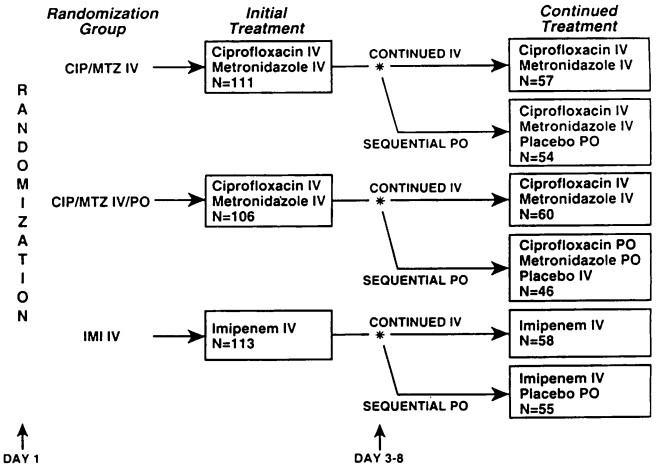


**Figure 1.** Randomization groups and treatment assignments. *Decision to switch patient to oral therapy occurred during days 3 to 8 and was at the physician's discretion.

Aerobic and anaerobic cultures for isolation, identification, and standardized susceptibility testing of organisms were obtained by operative or percutaneous procedures within 72 hours of enrollment.[18–20] Susceptibility testing was performed in each hospital's clinical microbiology laboratory. Blood and other cultures were obtained at the discretion of the investigator. The minimum inhibitory concentration breakpoint for ciprofloxacin resistance was ≥4 μg/mL and for IMI resistance was ≥16 μg/mL.

The choice of operative or percutaneous procedures was not defined by the protocol and was determined by the attending surgeon. Antibiotic lavage was not permitted. Wound closure also was determined by the operating surgeon. For treatment failures, the adequacy of intervention was determined by review of the case report form and any necessary supplemental information. Cases considered to have had inadequate intervention were reviewed by the outcomes committee (J.S., H.R., E.D., J.B., O.R., H.S., S.V., R.E.), which made the final determination.

## Validity and Outcome Assignments

Because the purpose of this study was to evaluate antibacterial drug activity, an *efficacy valid* population was defined as one consisting of patients who underwent either an appropriate operative or percutaneous procedure that identified an intra-abdominal infectious process, had cultures from the abdomen or blood cultures positive for pathogenic bacteria, and survived more than 48 hours. *Streptococcus viridans* and various diphtheroids

were not considered pathogens. Patients had to receive six or more doses of the q12h regimen to be considered valid failures or ten or more doses of the q12h regimen to be considered valid successes. Otherwise valid patients with appendicitis remained so if they received six or more doses of the q12h regimen. The protocol allowed concomitant antifungal therapy as well as vancomycin for suspected methicillin-resistant *Staphylococcus aureus* or enterococcal infections.

Patients who had acute cholecystitis without positive cultures outside of the gallbladder were considered invalid for efficacy analysis, as were patients found to have spontaneous perforations of the stomach or duodenum operated on within 24 hours of symptoms. Patients who received subsequent treatment for extra-abdominal nosocomial infections were considered valid. Patients without a 4- to 6-week follow-up were considered invalid if they were considered cured at the end of therapy.

For the valid population, outcome was based on events occurring while patients received study therapy and during a 4- to 6-week follow-up period. For other patients, the follow-up period was variable, and events occurring during study therapy and until the last available follow-up were used to determine outcome. All patients who received study therapy were assigned an outcome of either success or failure. Failure was defined as death related to abdominal infection at any time point, persisting or recurrent infection within the abdomen documented by the findings at reintervention either percutaneously or operatively, or postsurgical wound infection. Patients who received poststudy treatment with additional antibiotics for undocumented intra-abdominal infection also were considered failures. All other patients were considered successes.

Because of the multiple factors that affect clinical outcome, bacteriologic responses were determined separately to examine the antimicrobial activity of study therapy. These responses were classified as eradication, presumed eradication, persistence, and indeterminate, and were determined by events up to poststudy day 7. The following definitions were employed: *eradication,* the absence of all causative organisms; *presumed eradication,* repeat cultures were not obtained because of the absence of material to culture in a patient who had responded clinically to treatment; *persistence,* any valid causative organism present at the end of therapy from a culture of intra-abdominal abscess, peritonitis, or surgical wound infection; *presumed persistence,* repeat cultures were not obtained because of the absence of material to culture in a patient who was given additional antibiotic treatment for abdominal infection; and *indeterminate,* entry cultures either not obtained or no growth, or assessment not possible because of protocol violation.

Validity and clinical outcome assessments were made by the study site and reviewed by two attending physicians (J.S. and H.R.). Complex cases and discrepant assignments were referred to the outcomes committee, which established decision rules. All validity and outcome assignments were made before the treatment code was unblinded.

## Statistical Methods

The primary comparison was between patients randomized to CIP/MTZ IV and those randomized to IMI IV. The secondary comparison was between the subset of CIP/MTZ IV/PO patients who were given active PO treatment and the subset of patients randomized to IMI IV who were given placebo PO treatment. Sample size calculations were based on an intent to demonstrate treatment equivalence, defined as a maximum tolerable difference in bacterial eradication rates between treatments of 10%, and a two-tailed equivalence test at the 0.05 level. The sample size requirement was 150 patients in each treatment group. Assuming a bacterial eradication rate of 90%, the study had 80% power to detect a treatment difference.

To test for equivalence, 95% confidence intervals were constructed for the differences in observed success rates between the groups in the comparison. The difference in success rates was constructed by subtracting the success rate for IMI IV from the success rate for ClP/MTZ IV. To account for the multicenter nature of the study, a Mantel-Haenszel weighting scheme was used to compute confidence intervals. For the secondary comparison, the difference in success rates was constructed by subtracting the success rate for IMI IV from the success rate for CIP/MTZ IV/PC, employing only patients who received PO therapy. An exact method was used to construct intervals for this comparison.

To test for overall comparability and adjust for the multicenter nature of the study, Cochran-Mantel-Haenszel tests were performed for categorical values. Tests were performed on the intent-to-treat population and the efficacy valid population. Analysis of variance was used to test continuous variables, with treatment and center included as factors.

## RESULTS

Twenty-two medical centers in the United States and Canada participated in this trial and enrolled 691 patients from September 1990 to March 1993. Nineteen patients did not receive the study drug either by pharmacy error or withdrawn consent. Insufficient data were reported on these cases to assess infection or clinical outcome, and they were not considered further. One patient

was entered in this trial twice. His outcome from his second enrollment was considered indeterminate. Six hundred seventy-one patients received the study drug and were considered the intent-to-treat population. Of these patients, 330 were valid for efficacy assessment.

## Adequacy of Randomization

No differences were identified for the intent-to-treat population or for the valid population for the categorical variables sex, race, etiology of infection, whether the infection was hospital acquired, the presence of accompanying diseases, and the administration of previous, concomitant, and post-therapy antimicrobials. For the continuous variables of age, APACHE II score, and duration of therapy, there were no differences identified in the intent-to-treat population.

## Characteristics of the Intent to Treat Population

There were no demographic differences between treatment groups. Three hundred forty-one patients were invalid for efficacy analysis. There were no apparent differences between treatment groups in this regard. The most common reason for exclusion was absence of infection documented by cultures from operation or percutaneous drainage in the presence of intraperitoneal inflammatory disease. The diagnoses for patients without positive cultures primarily included acute appendicitis (n = 47), acutely perforated gastroduodenal ulcers (n = 35), bowel obstruction (n = 34), acute diverticulitis without abscess (n = 27), pancreatitis (n = 23), and no inflammatory disease identified (n = 23). Six patients were considered to have inadequate initial operations for the following reasons: unrecognized enterotomy at first operation led to peritonitis and the need for an additional operation in one patient; two patients underwent percutaneous drainage of pathology requiring operative intervention, including one lesser sac abscess: pancreatitis in one patient with multiple abscesses, only one of which was percutaneously drained; and two patients with diffuse peritonitis were treated with percutaneous drainage only because of poor general health, both of whom died.

Of the 691 patients entered in this trial, 72 died within 30 days of the start of the study. Among the invalid patients, death occurred in 15 patients treated with CIP/MTZ IV (12 failures), 16 treated with CIP/MTZIV/PO (11 failures), and 14 treated with IMI IV (12 failures). The distribution of deaths among valid patients is presented in Table 1. Ten invalid and six valid patients who died were considered cured. In each case, resolution of intra-abdominal infection had occurred and the patient survived for 7 or more days without further antibiotic treatment. Death was due to progression of metastatic malignancy. There were no imbalances among treatment groups. The mean APACHE II score at study entry for nonsurvivors was 17.4 ± 6.0 *versus* 10.5 ± 6.1 for survivors (p = 0.0004).

## Characteristics of Valid Patients

Table 1 presents demographic data on the valid patients. Age was the only variable different between the valid treatment groups, with IMI IV-treated patients being the oldest (CIP/MTZ IV: 49.7 ± 9.7 years of age; CIP/MTZ IV/PO: 52.3 ± 18.3 years; IMI IV: 56.1 ± 20.2 years; p = 0.033). Mean APACHE II scores analyzed by treatment are presented in Figure 2. The mean APACHE II scores were as follows: CIP/MTZ IV: 9.2 ± 5.3; CIP/MTZ IV/PO: 9.2 ± 5.7; and IMI IV: 10.5 ± 6.3 (p = 0.09). This lack of difference in physiologic severity between the primary treatment groups was confirmed by analysis of the acute physiology scores for these groups, which were 6.9 ± 4.6 for the CIP/MTZ IV group, 6.7 ± 4.5 for the CIP/MTZ IV/PO group, and 7.4 ± 5.2 for the IMI IV group (p = 0.32). Figure 3 depicts the relationship between APACHE II scores, survival, and infection outcome.

The most common source of infection at study entry was the colon, followed by the appendix and the small bowel. For all valid patients, 19% of the infections resulting in study entry occurred after operation; excluding patients with appendicitis, that percentage increased to 26%. All valid patients underwent either operative or percutaneous intervention.

Nine patients received vancomycin, equivalently distributed in the treatment arms. There was one treatment failure among these patients, a patient initially harboring enterococci and two gram-negatives. An abscess recurred and the same isolates were recovered at percutaneous drainage.

## Microbiologic Findings

The organisms encountered are listed in Table 2. One or more gram-negative isolates were found in 269 patients, and anaerobes were found in 161 patients. Mixed gram-negative/anaerobic infections were found in 127 patients, and 27 patients had only aerobic gram-positive isolates.

*In vitro* resistance to either regimen was uncommon and was encountered primarily with gram-positive organisms. For ciprofloxacin, one *Alcaligenes faecalis* isolate and one *Pseudomonas aeruginosa* isolate were found to be resistant. Five unspeciated enterococci were resistant, as was one *Enterococcus faecalis* isolate. For imipenem/cilastatin, three *Proteus mirabilis* isolates were found to be resistant, as were one *P. aeruginosa,* one *Enterobacter aerogenes,* and one *Morganella morganii.* Two unspeciated enterococci,

**Table 1. DISTRIBUTION OF VALID INFECTIONS BY ANATOMIC SOURCE AND FINDINGS**

| | CIP/MTZ IV (n = 111) | CIP/MTZ IV/PO (n = 106) | IMI IV (n = 113) |
|---|---|---|---|
| Sex (F:M) | 66:45 | 67:39 | 60:53 |
| Age | 49.7 ± 19.7 | 52.3 ± 18.3 | 56.1 ± 20.2 |
| Mean APACHE II | 9.2 ± 5.3 | 9.2 ± 5.7 | 10.5 ± 6.3 |
| Deaths within 30 days of study start | 5 | 12 | 10 |
| Death associated with failure | 3 | 7 | 5 |
| Source and Anatomy of infection | | | |
| Stomach and duodenum | 2 | 6 | 7 |
| Biliary tract | 6 | 7 | 8 |
| Pancreas* | 5 (2) | 4 (2) | 3 |
| Jejunum/ileum* | 21 (5) | 10 (6) | 13 (4) |
| Appendix | | | |
| Abscess | 12 | 11 | 14 |
| Perforated | 15 | 27 | 14 |
| Colon* | | | |
| Abscess | 22 (8) | 12 (4) | 16 (8) |
| Peritonitis | 23 (3) | 25 (5) | 33 (2) |
| Miscellaneous causes of infection | | | |
| Liver abscess* | 1 | 1 | 1 (1) |
| Abscess of ovaries/uterus | 1 | 1 | 1 |
| Psoas abscess* | 2 | 2 (1) | 1 |
| Abscess after clean operation | 1 | 0 | 2 |

APACHE = Acute Physiology and Chronic Health Evaluation; CIP/MTZ = ciprofloxacin plus metromidazole; IV = intravenously; PO = by mouth (oral); IMI = imipenem.
* Numbers in parentheses indicate postoperative processes where not otherwise stated.

one *E. faecalis,* and two *Enterococcus faecium* isolates were imipenem/cilastatin-resistant. Forty-nine of 315 patients (15%) without resistant isolates failed, compared with 6 of 15 patients (40%) with organisms resistant to the therapy given (p = 0.02).

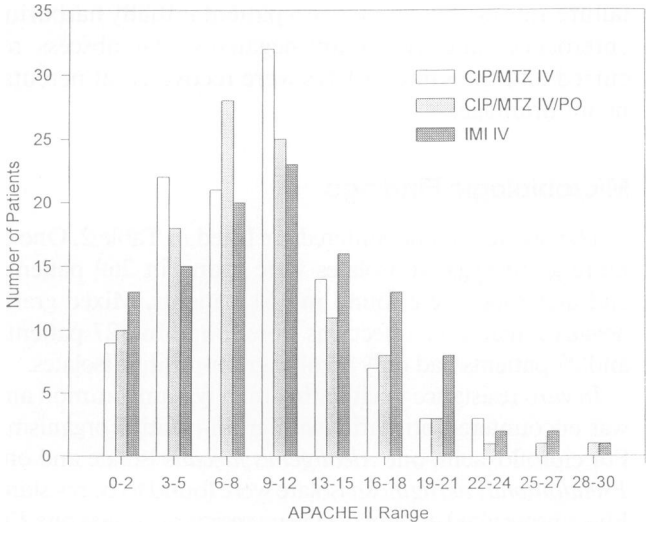


**Figure 2.** Acute Physiology and Chronic Health Evaluation (APACHE) II distributions for valid patients. The mean APACHE II (± standard deviation) for ciprofloxacin plus metronidazole intravenously is 9.2 ± 5.2, for ciprofloxacin plus metronidazole intravenously/orally is 9.2 ± 5.7, and for imipenem intravenously is 10.5 ± 6.3.

## Outcomes

The overall clinical success rates for each arm in the intent-to-treat analysis were 82% (182/222) for CIP/

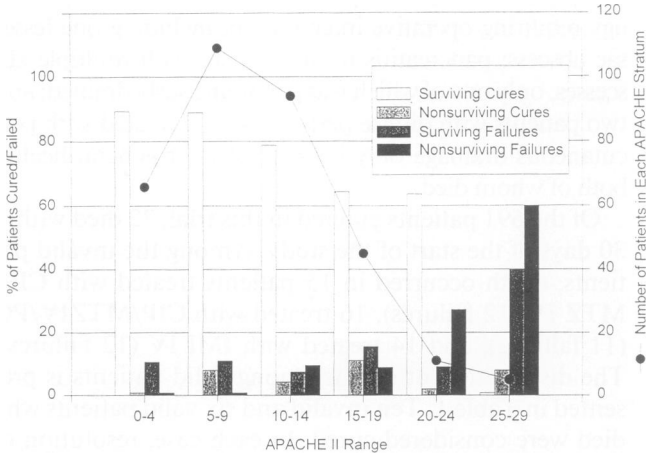


**Figure 3.** The association of Acute Physiology and Chronic Health Evaluation (APACHE) II score with failure and with death is depicted.

**Table 2. MICROORGANISMS ENCOUNTERED IN VALID INFECTIONS**

| | CIP/MTZ IV (n = 111) | CIP/MTZ IV/PO (n = 106) | IMI IV (n = 113) |
|---|---|---|---|
| No. of patients with any *,† | | | |
| Facultative/aerobic gram-negatives | 91 | 84 | 92 |
| Any anaerobes | 50 | 50 | 65 |
| Any gram-positive cocci | 71 | 57 | 72 |
| Gram-negative rods + anaerobes | 37 | 38 | 53 |
| Gram-positive cocci + anaerobes | 58 | 42 | 56 |
| Microorganism | | | |
| *Escherichia coli* | 65 | 61 | 68 |
| *Klebsiella species* | 17 | 22 | 24 |
| *Pseudomonas aeruginosa* | 15 | 11 | 15 |
| *Proteus species* | 6 | 8 | 8 |
| *Enterobacter species* | 6 | 5 | 7 |
| *Citrobacter species* | 7 | 5 | 4 |
| Other gram-negatives‡ | 14 | 13 | 13 |
| *Bacteroides fragilis* | 28 | 30 | 45 |
| Other *Bacteroides* | 10 | 13 | 12 |
| *Clostridium species* | 15 | 11 | 14 |
| Peptostreptococci | 6 | 8 | 17 |
| *Fusobacterium* | 2 | 3 | 3 |
| Other anaerobes | 12 | 14 | 13 |
| *Staphylococcus aureus* | 4 | 4 | 8 |
| Other staphylococci | 6 | 4 | 3 |
| Coagulase-negative staphylococci | 6 | 8 | 5 |
| Streptococci | 16 | 16 | 22 |
| *Streptococcus viridans* | 23 | 16 | 17 |
| Beta-hemolytic streptococci | 4 | 5 | 7 |
| Enterococcus, not speciated | 21 | 12 | 22 |
| Enterococcus faecalis | 3 | 4 | 6 |
| Enterococcus faecium | 2 | 2 | 1 |
| Group D streptococcus | 6 | 4 | 8 |
| *Candida albicans* | 11 | 11 | 9 |
| *Candida* not speciated | 3 | 6 | 3 |
| Other *Candida* | 0 | 5 | 4 |
| Grand total | 310 | 299 | 356 |

CIP/MTX-ciprofloxacin plus metronidazole; IV = intravenously; PO = by mouth (oral); IMI = imipenem.

* Patients with more than one isolate of the same species by colony morphology are counted only once.

† Six patients had Bacillus species isolated.

‡ Other gram-negatives included various species of *Serratia, Salmonella, Acinetobacter, Alcaligenes, Haemophilus, Hafnia, Providencia,* and *Xanthomonas.*

MTZ IV, 84% (183/219) for ClP/MTZ IV/PO, and 82% (189/230) for IMI IV. The 95% confidence interval for the difference between ClP/MTZ IV and IMI IV was −0.074 to 0.067. Bacteriologic eradication rates for the primary comparison (CIP/MTZ IV *vs.* IMI IV) were statistically equivalent, with a 95% confidence interval of −0.059 to 0.103.

The clinical success rates for invalid patients were 80% (89/111), 81% (92/113), and 84% (98/117) for ClP/MTZ IV, CIP/MTZ IV/PO, and IMI IV, respectively. The most common reasons for failure were death due to ongoing sepsis and presence of an initially unrecognized fistula. Eighty-four patients underwent operative or percutaneous interventions and had positive intra-abdominal cultures, yet were considered invalid. Eleven such patients were considered treatment failures. Six patients died of sepsis syndrome without reoperation. Of the four patients undergoing subsequent intervention, all were infected initially only with yeast and at reoperation were found to have persistent *Candida.* One failed with a wound infection.

The success rates for CIP/MTZ IV and IMI IV valid patients were statistically equivalent. Bacterial eradication or presumed eradication occurred in 98 of 111 patients treated with CIP/MTZ IV and in 100 of 113 patients treated with IMI IV (95% confidence interval of −0.050–0.108). The overall clinical success rate for ClP/MTZ IV was 84% (93/111) and for IMI IV was 81% (91/113).

**Table 3. SPECIFIC PROCESSES RESULTING IN FAILURE FOR VALID PATIENTS**

| | CIP/MTZ IV (n = 111) | CIP/MTZ IV/PO (n = 106) | IMI IV (n = 113) |
|---|---|---|---|
| Abscess | 9 (8)* | 6 (5)* | 12 (12)* |
| Diffuse peritonitis | 2 (2)* | 1 (1)* | 2 (2)* |
| Persisting bacteremia | 0 | 0 | 2 |
| Persisting sepsis resulting in death | 2 | 4 | 4 |
| Persisting sepsis not resulting in death | 1 | 1 | 0 |
| Poststudy antibiotics given without documented recurrence | 1 | 1 | 1 |
| Wound infection | 3 | 2 | 1 |
| Totals | 18 (16%) | 15 (14%) | 22 (19%) |

CIP/MTZ = ciproflaxacin plus metronidazole; IV = intravenously; PO = by mouth (oral); IMI = imipenem.

* Numbers in parentheses indicate number of patients undergoing either operative or percutaneous reintervention for treatment failure.

The two patients found to have abscesses but not undergoing treatment succumbed after the abscesses were identified but before intervention was undertaken.

Two patients had both peritonitis and necrotizing fasciitis; one was treated with IMI IV, and one was treated with CIP/MTZ IV.

## Treatment Failure for Valid Patients

Fifty-five of 330 valid patients (17%) were considered treatment failures for reasons detailed in Table 3. Eighteen of these patients died, and 11 died of progressing sepsis without undergoing subsequent intervention. The survival time for this group was 7.9 ± 3.4 days. Five patients underwent laparotomy and then died; two died after percutaneous reintervention.

Thirty of the 55 patients considered treatment failures underwent second interventions. Ten of 18 CIP/MTZ IV failures, 6 of 15 CIP/MTZ IV/PO failures, and 14 of 22 IMI IV failures underwent reintervention. This occurred on day 9.8 ± 3.4. Fifteen percutaneous and 15 operative procedures were performed.

Of the 30 patients undergoing intervention for recurrent abscesses or peritonitis, 25 had microbiology results reported. The organisms that were found in failures are described in Table 4. Ten of these patients harbored enterococcal isolates, but in only four patients were these possible persisting isolates because they were the same species found at the initial, on-study intervention.

Thirteen of the 14 IMI IV failures undergoing subsequent intervention with the finding of positive cultures had facultative or aerobic gram-negative isolates, and nine were of the same species found at the study entry procedure. In five of these cases, the organisms were resistant to imipenem. Four of 11 patients treated with CIP/MTZ IV or IV/PO had persisting gram-negative isolates, none of which were resistant to ciprofloxacin. The 95% confidence interval for the treatment group difference between IMI IV and CIP/MTZ IV patients initially found to have gram-negative bacteria and having persisting gram-negatives was 0.03 to 0.21 ($p = 0.003$). The data suggest that persistence of gram-negative organisms was more common in the IMI IV-treated patients. The gram-positive isolates recovered at intervention for failure were not tested for susceptibility to the study agents.

We examined the associations between various microorganisms and treatment outcome. Gram-negative isolates were identified in 269 of 330 valid patients, and there were no differences in treatment success between regimens for these groups (number of failures/number with isolate: CIP/MTZ IV, 13/92 [14%]; CIP/MTZ IV/PO, 15/85[18%]; and IMI IV, 19/92[21%]). Treatment success for patients with gram-negative infections but without *P. aeruginosa* isolated (187/228, 82%) was the same as for those with this organism (35/41, 85%) and did not vary by regimen. Four patients treated with IMI IV had persistence (n = 3) or acquisition of *P. mirabilis,* an organism known not to be highly susceptible to imipenem/cilastatin.

Patients with *P. aeruginosa* isolated were more likely to have a colon-derived infection (86 of 228 [38%] *vs.* 26 of 41 [63%]). The incidence of *P. aeruginosa* in patients with appendicitis was not different than for patients with other infections (22% *vs.* 28%). Similarly, patients enrolled because of postoperative infection had the same incidence of *P. aeruginosa* infection as those with other infectious etiologies (17% *vs.* 19%).

*Bacteroides fragilis* or other *Bacteroides* species were associated with treatment failure in 7 of 35, 6 of 40, and 9 of 51 patients harboring these organisms (for CIP/MTZ IV, CIP/MTZ IV/PO, and IMI IV, respectively) and were not associated with failure rates different than those in patients without these organisms. Patients infected with facultative gram-negative organisms and *Bacteroides* species had treatment failure rates not different than those patients with gram-negative organisms not including *Bacteroides* species.

We identified a significant association between the presence of *Enterococcus* and subsequent treatment failure. For all patients, regardless of treatment, treatment failure occurred in 20 of 71 (28%) patients with enterococci and 35 of 259 (14%) without enterococci ($p = 0.004$). Fifteen of these 20 patients underwent subsequent interventions for either abscess (12) or peritonitis (3). Five were found to still harbor enterococcal isolates. Two of these isolates were known to be *E. faecium,* and the others were not speciated. The incidence of enterococci and treatment failure with enterococcus was not

**Table 4. ISOLATES ENCOUNTERED IN TREATMENT FAILURES FOR PATIENTS UNDERGOING OPERATIVE OR PERCUTANEOUS REINTERVENTION**

| | CIP/MTZ IV | CIP/MTZ IV/PO | IMI IV |
|---|---|---|---|
| No. of valid patients | 111 | 106 | 113 |
| No. of valid failures undergoing reintervention | 10 | 6 | 14 |
| No. of valid failures with positive cultures at intervention for failure* | 6 | 6 | 13 |
| *Escherichia coli* | 1/1 | 1/1 | 6/6 |
| *Klebsiella oxytoca* | 0 | 0 | 1/0 |
| *Proteus mirabillis* | 0 | 0 | 4/3 |
| *Enterobacter aerogenes* | 0 | 0 | 1/1 |
| *Enterobacter cloacae* | 0 | 1/1 | 0 |
| *Morganella morganii* | 0 | 0 | 1/1 |
| *Serratia marsescens* | 1/0 | 0 | 0 |
| *Citrobacter freundii* | 0 | 1/1 | 1/0 |
| *Pseudomonas aeruginosa* | 0 | 0 | 2/1 |
| No. of patients with any gram-negative | 2 | 2 | 13 |
| *Staphylococcus aureus* | 0 | 0 | 2/1 |
| Other staphylococci | 2/1 | 2/0 | 1/0 |
| Coagulase-negative staphylococci | 1/1 | 0 | 4/0 |
| Streptococci | 1/1 | 1/0 | 3/2 |
| *Streptococcus viridans* | 0 | 2/0 | 4/2 |
| Group D streptococci | 0 | 1/0 | 1/0 |
| Enterococci | 3/1 | 4/2 | 3/1 |
| No. of patients with any gram-positives | 5 | 5 | 10 |
| *Bacteroides fragillis* | 1/1 | 0 | 1/0 |
| *Clostridia species* | 1/0 | 0 | 1/0 |
| *Candida albicans* | 1/1 | 0 | 2/0 |
| Other *Candida* | 0 | 1/0 | 2/0 |
| No. of patients with other organisms | 3 | 1 | 4 |
| No. of patients with any persisting organisms | 5 | 3 | 12 |

CIP/MTZ = ciprofloxacin plus metronidazole; IV = intravenously; PO = by mouth (oral); IMI = imipenem.
* In five cases, no cultures were reported at reintervention, but the operative description suggested recurrent or persisting infection.
Numbers indicate number of patients with the particular microorganisms/number of patients in whom the organism persisted from the initial on-study intervention.
The numbers add up to >100% because of multiple isolates from some patients.

different among the treatment groups (number of failures/number with enterococcus: 6/17 CIP/MTZ IV, 7/28 CIP/MTZ IV/PO, and 7/26 IMI IV; p = not significant).

## Outcome Results: Oral Therapy Group

One hundred fifty-five of the 330 valid patients (47%) received PO treatment as part of the study protocol. Patients initially randomized to the CIP/MTZ IV/PO group received active PO therapy (n = 46). The control group was defined *a priori* as those patients randomized to IMI IV and receiving PO placebo. One hundred seventy-five patients were not given oral treatment, and 39 of these patients were treatment failures. The major reasons patients were not given oral therapy were absent bowel function (n = 126), physician discretion (n = 9) and no improvement (n = 8) (Table 5).

Only 2 of 46 patients who received active PO treatment were considered clinical failures. One failed because of a wound infection identified after discharge, and the other failed because of treatment with nonprotocol therapy at discharge without documented infection. Six

**Table 5. REASONS THAT ORAL TREATMENT WAS NOT GIVEN TO VALID PATIENTS**

| Reason | Cures | Failures |
|---|---|---|
| Death | 0 | 4 |
| Medication error | 2 | 0 |
| No improvement | 6 | 2 |
| Patient discretion | 2 | 0 |
| Physician discretion | 8 | 1 |
| Remains NPO | 9 | 27 |
| Unknown | 19 | 5 |
| Totals | 136 | 39 |

NPO = nothing by mouth.

of 55 IMI IV-treated patients given PO placebo therapy were considered clinical failures. All developed abscesses and underwent either operative (3) or percutaneous (3) drainage. This difference was not statistically significant ($p = 0.2854$).

Six of 54 patients treated with CIP/MTZ IV who received PO placebo and continued CIP/MTZ IV failed. Two developed wound infections, three developed abscesses drained percutaneously, and one received poststudy antibiotic treatment without documented infection. No patients assigned to either active or placebo therapy died.

For all valid patients given oral agents, active or placebo, the average duration of all therapy was $8.6 \pm 3.6$ days, including $4.0 \pm 3.0$ days of PO treatment. For the patients receiving active PO CIP/MTZ, treatment was given intravenously for $5.2 \pm 1.7$ days and orally for $3.8 \pm 3.2$ days, for a total treatment duration of $9.0 \pm 3.8$ days. Examination of the total duration of treatment for groups who received IV/PO therapy and IV therapy alone suggested that duration of treatment was approximately the same for both groups. Patients not converted to PO treatment received an average of $9.67 \pm 4.9$ days of treatment, not significantly different than the group converted to PO therapy.

There were several differences in study entry characteristics that were helpful in predicting patients who would be given PO therapy. Patients chosen to receive PO treatment were, on average, less acutely ill than those who were not given PO treatment. Patients receiving PO therapy had a mean APACHE II score on study entry of $8.1 \pm 4.9$ *versus* a mean of $10.9 \pm 8.1$ for patients not receiving PO treatment ($p < 0.0001$). Age also was considerably different between the two groups. Patients not receiving PO agents had a mean age of $55.46 \pm 10.9$ years *versus* $49.7 \pm 8.1$ years for those given PO therapy ($p = 0.0076$). Finally, the diagnostic mix was considerably different. Forty percent of patients given PO therapy had appendicitis, compared with 17% of those not given PO therapy.

## DISCUSSION

This report details the largest prospective trial of antiinfective therapy for intra-abdominal infections published to date. Additionally, this is the first trial reported to use the recently developed Infectious Diseases Society of America/Food and Drug Administration proposed clinical trial guidelines.[21,22] The sample size was determined by power calculations for a comparison of IV ciprofloxacin plus metronidazole to IV imipenem/cilastatin. The primary finding of the study was the statistical equivalence of these two IV regimens.

### Characteristics of the Study Population

The population enrolled in this trial appears to be representative of the more difficult to treat infections encountered within the abdomen. The severity of illness for this population was described by the mean APACHE II score for valid patients, which was 8.6. One hundred fifty-five patients had scores of 10 or greater. We excluded simple acute cholecystitis or acutely perforated ulcers, infections which have nearly 100% cure rates.[23,24] For appendiceal infections, which were present in 28% of enrolled patients, 40% were abscessed and the others perforated. The complex appendiceal pathology encountered resulted in 9 of 93 treatment failures in this group, 6 of which involved recurrent abscesses treated either percutaneously or operatively.

### Treatment Failure

The large sample size and the inclusion of patients with complicated intra-abdominal infections provided a substantial number of patients who failed with recurrent abscesses or peritonitis that required subsequent intervention. This provided considerable information regarding the microbiology of treatment failure. It was in this area that certain differences between treatment regimens were identified. Perhaps most striking was the high incidence of gram-negative organisms among patients with IMI IV treatment failures who underwent reintervention. One hundred thirteen valid patients were treated with IMI IV, 22 of whom failed.

In a previous comparative trial of imipenem/cilastatin *versus* tobramycin plus clindamycin,[15] a treatment failure rate for imipenem/cilastatin of 12% was found using similar outcome evaluation criteria. Six of 82 patients treated with imipenem/cilastatin in that study[15] had cultures taken of recurrent infection, and gram-negative organisms were identified in four patients. Therefore, the findings of the previous and current trials are consistent.

The basis for the persistence of gram-negative organisms in imipenem/cilastatin treatment failures is unclear. We are concerned that the dose of imipenem/cilastatin employed in the current trial, 500 mg every 6 hours, may be relatively low given the need to achieve effective antibiotic levels in peritoneal fluid. This is supported by the findings of two recent studies performed by the Swedish Multicenter Study Group. In studies using either imipenem/cilastatin or meropenem at 500 mg every 8 hours, even higher failure rates were encountered.[25,26] Penetration of imipenem/cilastatin and of ciprofloxacin into the peritoneal cavity has been studied in patients undergoing elective laparotomy.[27-29] These data show achievement of antibiotic concentrations related to the dose administered and approximating 60% of simulta-

neously studied plasma levels. No data are available regarding penetration of either imipenem/cilastatin or ciprofloxacin into the inflamed peritoneum.

Gram-positive organisms were encountered in treatment failures in both treatment regimens. Nine CIP/MTZ-treated and nine IMI IV-treated patients had a range of gram-positive organisms identified at reintervention that were not present at study entry, and most of which commonly are regarded either as nonpathogens (*e.g.*, coagulase-negative staphylococci and *Streptococcus viridans*) or unlikely pathogens (*e.g.*, enterococci).[30] Activity of study therapy against these organisms generally is poor. Four of these 18 patients died.

We identified an association between the presence of enterococci in initial cultures and subsequent treatment failure. Patients with enterococci were different than those without and were more likely to have postoperative infections. Whether treatment of these patients with specific antienterococcal therapy would have altered outcome is unclear, and our data do not provide a rationale for primary empiric treatment with regimens encompassing agents active against enterococci.

## Results of Oral Therapy

In the current trial, patients who had resumed PO intake were eligible for PO antimicrobial treatment. Most of these patients were given PO treatment, indicating considerable physician acceptance of this approach. These criteria appeared quite useful in identifying patients who were likely to survive and who were likely to be treatment successes.

Of the 155 patients who received PO treatment, 11 required reintervention for recurrent abscess. Seven were treated percutaneously. All seven patients were receiving active IV treatment and PO placebo, and therefore, inadequate absorption of antimicrobial cannot explain these findings. We compared various characteristics of this group, including APACHE II score, age, initial source of infection, duration of IV treatment before addition of PO therapy to patients receiving PO treatment, and no recurrent infection. We identified no obvious characteristics that would allow recognition of such failures. Leukocyte counts and temperatures on the day that PO therapy was begun were similarly not helpful.

Conversion of IV to PO therapy, if not associated with an increase in treatment failure, would be of considerable benefit in reducing the incidence of infusion-related complications, allowing earlier hospital discharge for some patients, and reducing drug and drug administration costs. The results of this study would support the efficacy of this approach. The appropriate time point for such conversion was not defined by this study. In the current study, a general requirement was in place in which patients show clinical improvement before addition of PO treatment. It is unknown whether there is an advantage in delaying conversion until clinical response to IV treatment occurs; it would depend on the reliability of PO absorption of the antimicrobials employed.

Certain cautions must be exercised when ciprofloxacin is used as a PO agent. Absorption is impaired by divalent cation-containing medications or tube feedings, and such treatments should be held for 2 hours prior to drug administration.[31,32] Given concerns for the effects of post-infective ileus and antibiotic treatment on bowel function, further studies are needed to confirm adequate absorption of PO agents considered for replacement of parenteral therapy. Certainly, the availability of potent PO agents does not change the indications for antibiotic treatment.

## Infectious Diseases Society of America/ Food and Drug Administration Guidelines

The design of anti-infective clinical trials intended to obtain Food and Drug Administration approval recently has undergone considerable discussion.[33,34] In regard to intra-abdominal infection trials, previous practice dictated that patients not have received anti-infective therapy before study entry. This restriction was intended to examine the activity of study-driven therapy without the possible confounding effects of antecedent treatment. This restriction limited clinical trials, by and large, to appendicitis or to acutely perforated gastroduodenal ulcers, infections with low morbidity and high cure rates.[17,35–37] Carefully performed clinical trials in appendicitis have identified outcome differences based on prominent differences in antimicrobial spectra of activity.[38,39] Bacterial inocula in appendicitis are relatively low, and it is unlikely that this disease model would identify relatively modest differences in antimicrobial efficacy.[40,41] The difficulty with this approach is that patients with important intra-abdominal infectious problems, such as postoperative abscesses, inflammatory bowel disease with abscess, or perforated malignancies with abscess typically receive broad-spectrum antibiotic treatment while diagnostic efforts are pursued and have not been eligible for registration studies for new antimicrobials.

When this trial was designed, the Infectious Diseases Society of America/Food and Drug Administration guidelines were under discussion, and this study incorporated the recommendations ultimately published.[21,22,42] The guidelines detail many variables related to study design, including choice of control agent, randomization techniques, definitions of encountered infections, and outcome analysis. These guidelines are likely to be adopted in Europe[43] and allow patients who have received preoperative treatment with nonstudy medica-

tion to be entered in clinical trials. We examined this issue by cataloging microbial isolates from patients not receiving prior treatment and admitted to the hospital within 48 hours of study start, compared with patients hospitalized more than 48 hours and receiving nonstudy therapy. The primary differences were acquisition of *P. aeruginosa, Enterobacter* and *Citrobacter* species, *P. mirabilis,* and various enterococci. There was no decrease in the incidence of *Escherichia coli, B. fragilis,* or other anaerobes. The appearance of this relatively more resistant infecting flora was anticipated and provided a valuable subset of patients who represent treatment problems with currently available therapeutic regimens. Recognizing that registration trials are intended to examine efficacy in the clinical settings the agent would be employed in if approved, we believe this population to be essential for inclusion in registration studies. We believe the current study validates use of such patients.

The number of patients not valid for efficacy assessment in the current trial is similar to that reported in other trials allowing preoperative patient enrollment (>50%).[15,17] This large number of invalid patients creates difficulties in both interpreting and reporting the results of the trial. One approach to reducing this number would be to randomize patients after operative confirmation of infection.

## CONCLUSIONS

Based on the findings of this study, CIP/MTZ was found to be effective for the treatment of serious and complicated intra-abdominal infections. Sequential IV/PO therapy with CIP/MTZ was efficacious in patients able to tolerate PO intake. The study design employed in this trial provided insight into the consequences of different antimicrobials used for complicated but not uncommon intra-abdominal infections. We recommend continued testing and further development of the guidelines for anti-infective clinical trials proposed by the Infectious Diseases Society of America/Food and Drug Administration.

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