Early Antibiotic Treatment for Severe Acute Necrotizing Pancreatitis

A Randomized, Double-Blind, Placebo-Controlled Study

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Background & Aims: In patients with severe, necrotizing pancreatitis, it is common to administer early, broad-spectrum antibiotics, often a carbapenem, in the hope of reducing the incidence of pancreatic and peripancreatic infections, although the benefits of doing so have not been proved.

Methods: A multicenter, prospective, double-blind, placebo-controlled randomized study set in 32 centers within North America and Europe. *Participants*: One hundred patients with clinically severe, confirmed necrotizing pancreatitis: 50 received meropenem and 50 received placebo. *Interventions*: Meropenem (1 g intravenously every 8 hours) or placebo within 5 days of the onset of symptoms for 7 to 21 days. *Main Outcome Measures*: Primary endpoint: development of pancreatic or peripancreatic infection within 42 days following randomization. Other endpoints: time between onset of pancreatitis and the development of pancreatic or peripancreatic infection; all-cause mortality; requirement for surgical intervention; development of nonpancreatic infections within 42 days following randomization.

Results: Pancreatic or peripancreatic infections developed in 18% (9 of 50) of patients in the meropenem group compared with 12% (6 of 50) in the placebo group ($P = 0.401$). Overall mortality rate was 20% (10 of 50) in the meropenem group and 18% (9 of 50) in the placebo group ($P = 0.799$). Surgical intervention was required in 26% (13 of 50) and 20% (10 of 50) of the meropenem and placebo groups, respectively ($P = 0.476$).

Conclusions: This study demonstrated no statistically significant difference between the treatment groups for pancreatic or peripancreatic infection, mortality, or requirement for surgical intervention, and did not support early prophylactic antimicrobial use in patients with severe acute necrotizing pancreatitis.

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Acute necrotizing pancreatitis develops in about 15% of patients with pancreatitis and is a formidable clinical problem with mortality rates of 12% to 35%.[1–3] Much of the morbidity and mortality accompanying this disease are due to pancreatic and peripancreatic infection with reported rates as high as 40% to 70%.[4,5] Infections occurring early (<3 weeks) in the course of the illness appear to be associated with a higher mortality rate than infections that occur later.[6] Infections complicating necrotizing pancreatitis are often polymicrobial and involve both aerobic and anaerobic bacteria. The causative organisms most commonly originate from the gastrointestinal tract and include Escherichia coli, *Klebsiella* spp*, Enterobacter* spp*, Proteus* spp*, Pseudomonas aeruginosa*, Bacteroides spp, and *Clostridium* spp, and the enterococci.[7–13] Consequently, patients with severe necrotizing pancreatitis are often administered prophylactic broad-spectrum antimicrobial agents with the aim of reducing the incidence of pancreatic and peripancreatic infections, and even reducing mortality. As antimicrobial treatment is empirical, the choice of an appropriate regimen is based on expected pathogens and

their predicted susceptibilities. However, the benefits of prophylactic antimicrobial therapy in necrotizing pancreatitis have not been demonstrated consistently. Recently, *Candida* species and Gram-positive organisms have been isolated in greater numbers, which may possibly be linked to the widespread use of prophylactic antimicrobial agents.[14,15] While different clinical evaluations of the efficacy of various antibiotics in preventing/delaying infection associated with necrotizing pancreatitis show conflicting and contradictory outcomes,[16] 4 meta-analyses have suggested a decrease in infection-related morbidity, although their authors have reached differing conclusions.[17–20]

Because of the inconclusive nature and weaknesses of existing studies and because of the potential risk of early, long-term use of antibiotics in this high-risk patient population, we deemed it appropriate and necessary to conduct a clinical trial in the patients at highest risk for infectious complications. We also designed the trial to be prospective and double-blind to address some of the problems in earlier trials. Because the first trial to show a benefit to early antibiotics in patients with necrotizing pancreatitis used imipenem-cilastatin,[1] because meropenem is similar in pharmacokinetics and antimicrobial spectrum to imipenem-cilastatin, and because at least one trial[21] showed equivalent outcomes for patients treated with imipenem-cilastatin and meropenem, we chose meropenem as the active antibiotic in this trial.

Study Aim

The primary aim of this double-blind, placebo-controlled, randomized study was to evaluate the effectiveness of prophylactic intravenous meropenem in preventing/delaying pancreatic or peripancreatic infection in patients with noninfected necrotizing pancreatitis when compared with placebo. In addition, the effects of prophylactic meropenem therapy upon the requirement for operative debridement, overall mortality rate, and time to death were assessed as secondary end points.

MATERIALS AND METHODS

Patients

Male or female patients ≥18 years of age were enrolled with a confirmed diagnosis of necrotizing pancreatitis within 120 hours of the onset of symptoms. Patients with ≥30% necrosis of the pancreas confirmed by contrast-enhanced computerized tomography (CT) were eligible for inclusion into the study. Alternatively, patients who were unsuitable for a contrast-enhanced CT scan in the judgment of the investigator, and who had noncontrast scans with extensive or multiple peripancreatic fluid collections and pancreatic edema (Balthazar grade E),[22] and had either C-reactive protein (CRP) >120 mg/L or a multiple organ dysfunction (MOD) score[23] >2, were also eligible. In addition, for study inclusion, randomization and receipt of first dose of study treatment was required within 120 hours of the onset of symptoms.

Exclusions

Patients diagnosed with concurrent pancreatic or peripancreatic infection were excluded from the study, as were patients who had received an investigational drug <30 days prior to enrollment, antimicrobial therapy for >48 hours prior to randomization, or who had an allergy to beta-lactam antimicrobial agents. In addition, patients who received or were likely to require probenicid or who had progressing underlying disease, neutropenia, or cirrhosis (Child-Pugh class C), and pregnant or lactating females were also excluded.

Study Design

This was a prospective, multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy of meropenem versus placebo as prophylaxis for the prevention of pancreatic or peripancreatic infections in patients with acute necrotizing pancreatitis. The study was conducted at 32 sites within North America and Europe. The treatment given to each patient was determined by a random scheme prepared by the Biostatistics group at AstraZeneca (Wilmington, DE), using computer software that incorporates a standard procedure for generating random numbers. A randomization schedule was prepared for each center in balanced blocks to ensure that approximately equal numbers of patients were assigned to each treatment arm across the total study population. The random numbers were kept in sealed envelopes by the pharmacy at each site and used sequentially as patients were enrolled. The pharmacy dispensed study drug following patient enrollment. Blinding was maintained until all data collection and data queries were complete and the database was locked.

Meropenem (AstraZeneca) 1 g powder reconstituted in infusion fluid or dose- and administration-matched placebo (supplied by the onsite pharmacy) were administered by intravenous infusion over 15 to 30 minutes, every 8 hours. Opaque zip-lock covers were placed over the infusion bags, and transparent yellow adhesive tape was affixed to the drip regulators such that the study drug solution was color-obscured, but the fluid level could be viewed, to ensure blinding of the study drug during infusion. Patients received randomized trial therapy for a minimum of 7 days (21 doses) and a maximum of 21 days (63 doses), with a recommended duration of 14 days. The use of nonprotocol antibiotics during this time was discouraged but could not be prohibited in these seriously ill patients. If other antibiotics were given, they were documented and the reason for their use was recorded. The protocol recommended stopping study drug when the patient was able to tolerate an oral diet and had a MOD score ≤2, or if pancreatic infection occurred. We attempted to standardize operative debridement which was to be performed only where pancreatic or peripancreatic infection was proven; however, final judgment on operation was left to the individual investigator. Follow-up evaluations and procedures were performed after cessation of study treatment up to and including study day 43; however, for patients still in the hospital on day 43, follow-up continued. To be fully evaluable, a patient had to be followed for at least 35 days.

Sample Size Calculation

A recent review of clinical trials[24] just before the beginning of this study indicated that infection rates in

subjects receiving no antibiotic (control) or prophylactic antibiotic are approximately 40% and 20%, respectively. Based on these figures, it was calculated that approximately 120 subjects per group (240 subjects in all) would be required to detect a reduction of pancreatic infection rates by meropenem compared with placebo from 40% to 20% with 90% power and a 5% significance level (2-sided), based on a two-group χ^2 test (continuity corrected). This calculation is based on an intention-to-treat population.

Ethics

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Regulations, and applicable regulatory requirements. Institutional Review Board or Independent Ethics Committee approval was obtained at each study center, and written informed consent was obtained from all patients prior to enrollment. A data safety monitor reviewed in a blinded fashion all serious adverse events, all deaths with particular attention to any deaths not attributed to pancreatitis, and all nonpancreatic infections. A process was provided to notify the principal investigators if any concerning trends were identified.

Efficacy Measurements

Prior to randomization, patients underwent the following clinical evaluations to record disease severity: Ranson score[25] (completed from measurements taken within 48 hours of primary admission), Glasgow score[26] (completed from measurements taken within 48 hours of primary admission), APACHE II[27] score, including Glasgow Coma Scale (completed on receipt of laboratory and physiological examination results), and MOD score. In addition, baseline clinical status and routine hematology and biochemistry procedures, including CRP measurement and blood gas analysis, were performed. Contrast-enhanced CT scans were done unless contraindicated by the patient's clinical condition; the degree of necrosis and a CT Severity Index (CTSI)[28] were determined for each patient.

While receiving study treatment (days 2–22), patients underwent daily MOD score determinations and monitoring of highest and lowest temperature and enteral or parenteral nutrition administration. Hematology and biochemistry analysis of blood samples were performed on days 7 and 14, and when clinically indicated. In addition, Gram stain and aerobic and anaerobic culture and sensitivity testing of bacterial isolates were performed when infection was suspected in tissue or fluid samples obtained by percutaneous aspirate or operative procedures.

Follow-up evaluations after cessation of study treatment were performed up to and including study day 43. MOD scores were determined when signs of pancreatic or peripancreatic infection were observed or if the patient showed signs of clinical deterioration. Routine hematology and biochemistry evaluations were performed when indicated clinically and microbiologic evaluation was performed if infection was suspected.

The microbiologic evaluations of tissue or fluid samples, obtained from the pancreas or peripancreatic area either by CT-guided fine needle aspiration (FNA) or during operation, were used to determine the primary endpoint of the development of pancreatic or peripancreatic infection within 42 days following randomization. In addition, the data provided evaluation of the secondary endpoints of time interval between onset of pancreatitis and development of pancreatic or peripancreatic infection, change in MOD score, requirement of operative intervention, development of nonpancreatic infections with 42 days of randomization, and mortality.

Safety and Tolerability

Adverse events and clinical laboratory values were monitored and recorded during the course of the study. Adverse events were assessed by severity and by relationship to study treatment according to the judgment of the blinded investigator. Treatment relationship was determined with a reasonable possibility that the event might have been caused by treatment. In addition, a periodic review of deaths and serious adverse events was performed during the course of the study to identify any unexpected risks and allow determination of appropriate actions.

Statistical Analysis

The χ^2 test was used to determine whether prophylactic meropenem therapy prevented the development of pancreatic/peripancreatic infection in patients with noninfected necrotizing pancreatitis and reduced mortality or the requirement for operation/intervention; mortality (time to death) was analyzed using a proportional hazards regression model including 95% confidence interval and P value. The remaining secondary endpoints (time to onset of pancreatic/peripancreatic infection, changes in organ dysfunction, and incidence of nonpancreatic infections) and safety data were summarized with informal descriptive analyses.

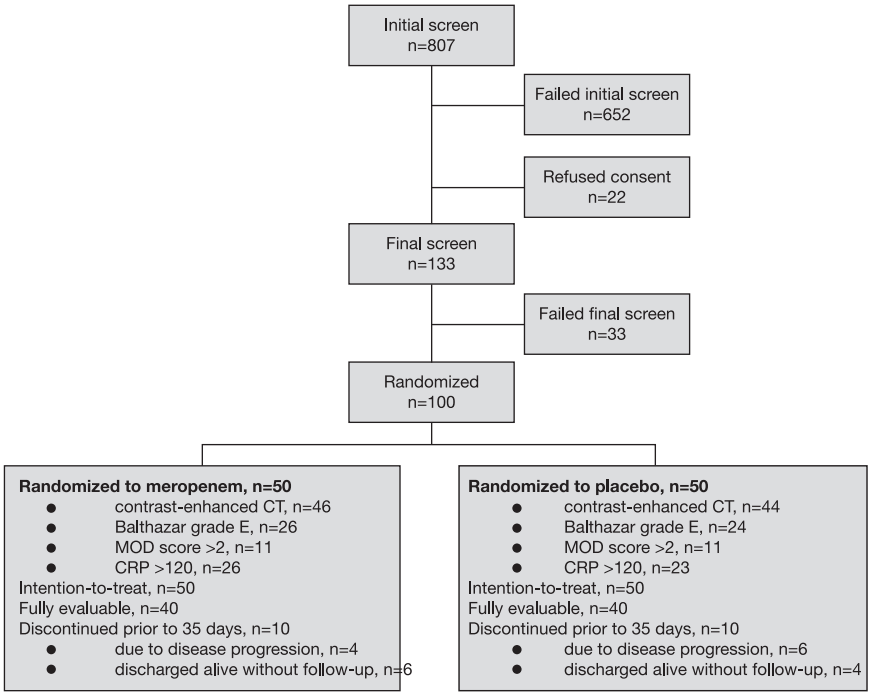
All analyses were based on all patients randomized into the study (intention-to-treat population) and were performed using the SAS system analysis package, version 8.02 (SAS Institute, Cary, NC).

The study was registered at ClinicalTrials.gov on May 27, 2003 and had the identifier: NCT00061438.

RESULTS

Patients

A total of 807 patients were screened for entry into the study. A total of 674 patients were found not to be eligible, including 22 who refused consent. Of the 133 patients who were entered initially at baseline, 33 additional patients failed the final screen at baseline and were dropped. One hundred patients with clinically severe confirmed necrotizing pancreatitis were enrolled and received study drugs: 50 received meropenem and 50 received placebo (Fig. 1). Study enrollment and follow-up occurred between February 2003 and December 2004. Twenty patients were listed as nonevaluable due to follow-up of less than 35 days, including 10 patients in the meropenem group and 10 in the placebo group, owing to early death from disease progression (4 meropenem; 6 placebo on study days 3–24) and discharge to home/self care without further follow-up (5 meropenem; 4 placebo on study days 7–34) (Fig. 1). One meropenem patient was transferred



CT, computerized tomography; CRP, C-reactive protein; MOD, multiple organ dysfunction

FIGURE 1. Disposition of screened and randomized patients.

to another hospital on study day 6 without further follow-up. None of these 20 patients had evidence for pancreatic infection at the time of death or loss to follow-up.

Patient demographics and baseline characteristics were well matched between treatment groups, with a similar number in both groups having ≥30% necrosis (26 meropenem; 31 placebo) (Table 1). Pancreatic necrosis of ≥30% was observed in 57% (57 of 100) of patients, while 25% (25 of 100) of patients had some but <30% pancreatic necrosis and 18% (18 of 100) were not recorded, usually due to performance of noncontrast CT scans in critically ill patients with impaired renal function (Table 1). Mean and median highest prerandomization CRP values in patients with necrosis >30% were 255 and 275, in patients with necrosis <30% were 269 and 271, respectively, and in patients without contrast-enhanced CT scans (and thus necrosis not recorded) were 286 and 263. For these same 3 patient groups, the mean prerandomization APACHE II scores were 10, 11, and 17, respectively. MOD scores for patients with necrosis not recorded were a mean of 4.7 and a median of 3.0, on average more than a unit greater than the average for all patients. The mean patient age (standard deviation [SD]; range) was 54.4 years (17 years; 18–83 years) in the meropenem group and 49.6 years (18.8 years; 18–84 years) in the placebo group. However, more patients in the placebo group had alcohol as an etiology, while the meropenem group had more patients with pancreatitis of biliary origin ($P = 0.20$, Table 1). None of the differences between groups was significant.

Nutritional Support

Most patients received nutritional support, and the incidence of support was not different between the meropenem and the placebo arms of the study. Parenteral nutrition alone was given to 19% of the patients (9 meropenem and 10 placebo) while 42% of patients received enteral nutrition alone (24 meropenem and 19 placebo) and 27% of patients received both parenteral and enteral nutrition (16 meropenem and 21 placebo). Only 2% of patients did not receive nutritional support (1 in each group). The mean and median days of initiating nutritional support relative to study enrollment were 1.8 and 1, respectively, with a range of −1 to 7. There were no significant differences between study arms or between infected and uninfected patients in the type of nutrition or time of initiation. The mean duration of nutritional support was 8.9 days with a range of 0 to 21 days.

Administration of Study Drug

Study drug administration began at randomization and continued for a mean and median of 9.9 and 8.5 days, respectively, in the meropenem arm and 10.6 and 9.0 days, respectively, in the placebo with a range from 1 to 21 days in both study arms. Duration of study drug administration was not different between the groups. Forty-seven patients in each study group received study drug for 7 or more days as specified in the protocol. There were 31 patients in the meropenem group and 32 in the placebo group who received study drug for a duration of less than 14 days. The majority of these were stopped because the patient's physician diagnosed an infection and started nonstudy antibiotics or took the patient to the operating room (11 meropenem and 10 placebo) or regarded the patient as recovered from pancreatitis (5 meropenem and 2 placebo), the patient died (2 meropenem and 4 placebo), or the patient refused further drug (1 meropenem). Hospitalization occurred a mean of 1.02 (range, −4 to 4) days after symptom onset in the meropenem group and a mean of 1.12 (range, −2 to 6) days in the placebo group.

TABLE 1. Summary of Patient Population, Demographics and Baseline Characteristics

Demographic or Baseline Characteristic	Treatment Group: Meropenem (n = 50) n	%	Placebo (n = 50) n	%
Sex				
Male	32	64	38	76
Female	18	36	12	24
Age (yr)				
18–64	34	68	34	68
65–74	9	18	9	18
>75	7	14	7	14
Race				
White	49	98	49	98
Black	1	2	1	2
Alcohol use	29	58	33	66
Primary cause of pancreatitis				
Biliary	22	44	12	24
Alcohol	18	36	26	52
Other	10	20	12	24
% necrosis by contrast-enhanced CT				
<30%	15	30	10	20
≥30%	26	52	31	62
Not recorded	9	18	9	18
		Range		Range
Interval, symptom onset to first dose of study drug	3 days	1–6	3 days	1–8
Ranson score (mean/median)	4.5/4	1–8	3.8/3.8	0–8
Modified Glasgow score (mean/median)	4.2/4	1–8	3.4/3	0–7
APACHE II (mean/median)	12.7/12	2–30	11.5/9	0–39
CTSI (mean/median)	7.1/7	6–10	7.7/8	6–10
MOD (mean/median)	3.7/3	0–13	2.8/2	0–12
CRP (mean/median)	274/270	120–456	262/270	50–661

CT indicates computed tomography; CTSI, computed tomography severity index; APACHE, acute physiology and chronic health evaluation. All comparisons not significant.

Randomization and study drug administration occurred a mean of 2 days after hospital admission in both the meropenem group and the placebo group, and the first dose of study drug was administered a mean of 3 days (range, 1–6 days) after symptom onset in the meropenem group and after a mean of 3.3 days (range, 1–8 days) in the placebo group.

Development of Pancreatic or Peripancreatic Infection

Pancreatic infections were diagnosed by image-guided FNA or by inspection and culture at open operation. Thirty-seven patients underwent FNA for diagnosis, and 11 of these had a total of 26 additional FNAs for further diagnosis. By intention-to-treat analysis, pancreatic or peripancreatic infections developed in 18% (9 of 50) of patients in the meropenem group compared with 12% (6 of 50) in the placebo group ($P = 0.401$) (Table 2). Eighty patients (40 in each group) had follow-up for more than 34 days and were evaluable for the primary outcome of pancreatic or peripancreatic infection within 42 days following randomization; among these 80, pancreatic or peripancreatic infections developed in 23% (9 of 40) of patients in the meropenem group compared with 15% (6 of 40) in the placebo group ($P = 0.390$). Among the 9 infected meropenem patients, 21 separate organisms were isolated and designated as pathogens by the investigators. Of these, 6 bacterial isolates were tested for antimicrobial susceptibility and 5 were recorded as resistant to meropenem, and another 2 isolates were *Candida albicans*. Among the 6 infected placebo patients, there were 9 separate organisms isolated and designated as pathogens; 5 were tested for antimicrobial susceptibility with 2 being resistant to meropenem and another was *C. albicans*. The pathogens isolated from pancreatic infections are listed in Table 3. Furthermore, the overall pancreatic or peripancreatic infection rate was higher in those patients with a greater degree of necrosis: 18% (10 of 57; n = 6, meropenem group; n = 4, placebo group) in patients with ≥30% necrosis versus 12% (3

TABLE 2. Development and Time to Onset of Pancreatic or Peripancreatic Infection From Symptom Onset

	Treatment Group: Meropenem (n = 50) n	%	Placebo (n = 50) n	%
Patients with pancreatic or peripancreatic infection	9	18	6	12
Patients with resistant pancreatic or peripancreatic infection	4	8	3	6
Mean (range) no. of days to diagnosis of infection	21.3 (5–35)	—	20.8 (11–25)	

TABLE 3. Pathogens Isolated From 15 Patients With Pancreatic or Peripancreatic Infections

Organism	Meropenem [no. isolated]	Placebo [no. isolated]	Total [no. isolated]
Enterococcus spp	6	1	7
Coagulase-negative staphylococcus	3	1	4
S. aureus	0	3	3
Proteus spp	2	1	3
P. aeruginosa	3	0	3
C. albicans	2	1	3
E. coli	1	1	2
A. baumannii	2	0	2
Enterobacter spp	1	0	1
S. viridans	1	0	1
Bacillus spp	0	1	1

of 25; n = 2, meropenem group; n = 1, placebo group) in patients with <30% necrosis. Eleven percent (2 of 18; n = 1 meropenem group; n = 1, placebo group) were infected in the "not recorded" group.

Time to Onset of Pancreatic/Peripancreatic Infection

The mean time between onset of pancreatitis and the development of pancreatic or peripancreatic infection was 21 days (range, 5–35 days) in patients in the meropenem group and 21 days (range, 11–25 days) in the placebo group (Table 2). Meropenem treatment did not delay the time to onset of infection compared with placebo.

Operative Interventions

There was no significant difference between treatment groups in number of operative interventions required. Operative or percutaneous intervention for treatment of pancreatitis with or without infection was performed within 42 days following the day of randomization in 26% (13 of 50) and 20% (10 of 50) of meropenem- and placebo-treated patients, respectively ($P = 0.476$). Of the 23 interventions, 9 were necrosectomies, 9 were laparotomy and drainage, 4 were percutaneous drainage only, and 1 was a pancreaticoduodenectomy. Nine patients (7 infected and 2 not) had 14 additional interventions after the first. Time to intervention was a mean and median of 21 and 19 days (range, 1–69 days), respectively, in the meropenem group and 21 and 20 days (range, 4–42 days), respectively, in the placebo group. Of the 10 patients who were operated on for pancreatic necrosis or infection and subsequently died, the mean and median interval between operation and death was 3 and 5 days, respectively, with a range from 0 to 36. In addition, 4 patients in the meropenem group and 2 in the placebo group had a cholecystectomy while on the study and one meropenem patient required a tracheostomy. Only 8 (62%) of the operated meropenem patients and 6 (60%) of the operated placebo patients proved to have pancreatic infections. One additional meropenem patient was diagnosed as infected by percutaneous aspiration but recovered without operation.

Incidence of Nonpancreatic Infections

Development of nonpancreatic nosocomial infections within 42 days following randomization occurred in 32% (16 of 50) and 48% (24 of 50) of patients in the meropenem and placebo groups, respectively ($P < 0.20$), with 19 isolates and 33 isolates in the meropenem and placebo arms, respectively. In total, there were 16 bloodstream infections, 10 lower respiratory tract infections, 8 surgical site infections, and 6 urinary tract infections. The mean and median times to onset of nonpancreatic infection in the meropenem group were 12 and 11 days, versus 10 and 8 days in the placebo group. Thirteen of the 15 patients with pancreatic infection also had a nonpancreatic infection. In 5 of these the nonpancreatic, infection occurred 2 to 28 days before the pancreatic infection, and in 3 (bloodstream, urinary, and lower respiratory tract infections, respectively), the pathogens were the same. In 3, the pancreatic infection occurred 2 to 12 days before the nonpancreatic infection, and all of these had differing pathogens. Five patients had the 2 infections diagnosed within 1 day, 4 with the same organism and 3 bloodstream infections that were probably secondary to the pancreatic infection. The incidence of nonpancreatic infection in both groups was higher in patients with ≥30% necrosis. There was no patient in the study with documented *C. difficile* infection.

Prior and Concomitant Antibiotic Therapy

Six patients in the meropenem arm of the study and 10 placebo patients received an average of 1.0 and 1.2 days of 6 different nonstudy antibiotics prior to randomization, respectively. After enrollment in the study, 25 meropenem patients and 27 placebo patients received additional antibiotics other than study drug for clinical indications. The mean and median start days were day 19 and 17 for the meropenem group, and day 17 and 14 for the placebo group, respectively. Ten patients in each group had their nonstudy antibiotics begun during the first 7 days on study. Of these, 4 meropenem and 1 placebo patient subsequently proved to have a pancreatic infection. The mean and median duration of nonstudy, "open" antibiotic administration were 7 and 5 days in both arms.

Patient Mortality

The overall mortality rate was 20% (10 of 50) in the meropenem group and 18% (9 of 50) in the placebo group. The median time from onset of symptoms to death in the meropenem group was 28 days compared with 18 days in the placebo group ($P = 0.972$, by proportional hazards regression). Four deaths occurred within 7 days, 4 between 8 and 14 days, and 11 between 21 and 71 days after symptom onset. All deaths in both groups were due to disease progression, usually with progressive organ failure, either with or without pancreatic infection. None of the 8 deaths within 14 days of symptom onset was attributed to pancreatic infection, but 3 were diagnosed with nonpancreatic infection while 5 had no infection at all. Six (40%) of 15 patients with pancreatic infection died (4 patients and 2 patients in the meropenem and placebo groups, respectively) compared with 13 (15%) of 85 without pancreatic infection (6 patients and 7 patients in the meropenem and placebo groups, respectively). Forty patients had nonpancreatic infections (including 13 who also had pancreatic infections) and 11 (28%) of these died. Of the 58 patients with neither pancreatic nor nonpancreatic infections 7 (12%) died. There were 15 patients in the meropenem arm and 13 in the placebo arm who had pancreatic infection, died, or both ($P = 0.656$). Among patients with <30% necrosis 1 of 25 (4%) died, compared with 11 of 58 (19%) in patients with >30% necrosis and 7 of 18 (39%) with degree of necrosis not recorded.

Safety and Tolerability

All randomized patients who received at least one dose of study treatment were included in the population safety analysis. As expected by the severe nature of illness in this trial, a high proportion of patients in both groups (74%) were reported to have adverse events. Meropenem was generally well tolerated with fewer serious adverse events or discontinuations due to adverse events than the placebo group (Table 4). The most frequently reported (>10%) adverse

TABLE 4. Overview of Adverse Events and Number (%) of Patients With Most Commonly Reported (>10%) Treatment-Related Events

	Treatment Group	
Event*	**Meropenem† (n (%))**	**Placebo† (n (%))**
Patients		
With at least one AE	32 (64)	42 (84)
Discontinued due to an AE	0 (0)	4 (8)
With serious AEs	6 (12)	9 (18)
With serious treatment-related AEs	2 (4)	0 (0)
Most common AEs		
Anemia	1 (2)	6 (12)
Abdominal pain	5 (10)	0 (0)
Diarrhea	2 (4)	5 (10)
Fever	5 (10)	9 (18)
Bronchospasm	5 (10)	2 (4)
Insomnia	5 (10)	7 (14)
Anxiety	2 (4)	7 (14)
Rash	6 (12)	1 (2)

*A patient may be counted in more than one category.
†n = 50.
N indicates number of patients assessed in each treatment group; n, number of patients in each category of adverse event; AE, adverse event.

events were pyrexia (meropenem, 10%; placebo, 18%), anemia (meropenem, 2%; placebo, 12%), diarrhea (meropenem, 4%; placebo, 10%) and abdominal pain (meropenem, 10%; placebo, 0%). Six patients treated with meropenem experienced serious adverse events: leukopenia, thrombocytopenia, coronary artery stenosis, myocardial infarction, pneumonia, septic shock, myoglobinuria, and hypovolemic shock. The investigators considered the serious adverse events in 2 patients (leukopenia with thrombocytopenia and myoglobinuria) to be treatment-related. Nine patients who received the placebo experienced serious adverse events: colonic fistula, pancreatic pseudocyst, pneumonia, septic shock, procedural hypotension, cerebrovascular accident, hypoxia, hypovolemic shock, phlebothrombosis, or vena cava thrombosis. None was considered treatment related.

DISCUSSION

The results of this study demonstrated similar rates of infection, operation, and death between the treatment groups receiving meropenem or placebo. Meropenem was generally well tolerated with fewer serious adverse events, or discontinuations due to an adverse event, than the placebo group. Previously published trials of early prophylactic antimicrobial administration in patients with severe, necrotizing pancreatitis claim to demonstrate a benefit of prophylactic antimicrobial administration to patients with severe, necrotizing pancreatitis when compared with patients not receiving early antimicrobial treatment.[1–3,21,29–32] Several early studies[33–35] enrolled only low-risk patients and lacked the discriminatory power to identify important differences in subgroups of patients according to the severity of pancreatitis. In addition, these studies have been questioned because the antimicrobial tested lacked sufficient penetration into pancreatic tissue.[36,37] More recent studies have largely suggested a possible benefit associated with prophylaxis; however, the true picture remains unclear. A comparison study of imipenem-cilastatin to nontreatment in patients with necrotizing pancreatitis (n = 74) demonstrated a significant reduction in the incidence of pancreatic infection with treatment but no difference for operations or mortality.[1] Another study noted a reduction in both infections and mortality in patients with necrotizing pancreatitis (n = 60) receiving prophylactic cefuroxime compared with the nontreatment group, in a study flawed by apparent problems with intravenous catheter infections and by a unique method for counting infections.[3]

A controlled trial of selective gut decontamination, which investigated treatment with oral colistin sulfate, amphotericin B, norfloxacin, and intravenous cefotaxime was shown to significantly reduce late mortality (>2 weeks), pancreatic infections, and operative interventions compared with a nontreatment control in a prospective, randomized, multicenter comparative trial (n = 102). However, early deaths (<2 weeks) were the same in both groups, and there was not a significant difference in total mortality between groups.[2] This study is different from all others because of its use of oral and rectal antibiotics but similar in its early administration of parenteral antibiotics to all patients in the treatment group.

A multicenter comparison of pefloxacin and imipenem-cilastatin in patients with necrotizing pancreatitis (n = 60) found a lower incidence of infection with imipenem-cilastatin but no difference between groups in mortality.[29] Two smaller trials (n = 23 and n = 26) also reflect the results of these larger trials.[30,32] Another trial, without a placebo group, showed no additional benefit to continuing imipenem-cilastatin beyond 14 days.[8] More recently, a randomized study conducted in patients with acute necrotizing pancreatitis (n = 58) showed a significant reduction in the *clinical* diagnosis of pancreatic infection without culture or operative confirmation without, however, a reduction in proved infections, actual operations, or mortality rate.[31] Manes et al have reported meropenem to be as effective as imipenem-cilastatin in preventing infectious complications in patients with acute pancreatitis in a randomized, controlled trial (n = 176),[21] but there was no placebo group. The only published double-blind study (n = 114) in acute necrotizing pancreatitis, which had a greatly improved design compared with previous studies, demonstrated no advantage of early antimicrobial (ciprofloxacin and metronidazole) prophylaxis when compared with placebo.[38] In this study, 35 of 76 patients with necrotizing pancreatitis received additional, nonstudy antibiotics (half in the first week) for increasing systemic inflammatory response syndrome or MOD with no significant difference between the antibiotic and the placebo group.

All these studies have substantial weaknesses, such as being underpowered due to insufficient patient numbers, nonblinded, or including subgroups of differing disease severity.[1,30,33] Other problems associated with the published data on prophylaxis include difficulty in interpretation due to

various antimicrobial agents with different application schemes and heterogeneous study endpoints. In addition, the pancreatic tissue to serum concentration ratios diverge among antimicrobials, although carbapenems, metronidazole, and fluoroquinolones have shown some consistency in both normal and infected pancreatic tissue. In addition, the importance of these ratios is unknown because they are measured in living pancreatic tissue while the infections occur in necrotic pancreatic and peripancreatic tissue that is not perfused. Indeed, it is not even known whether penetration into pancreatic tissue is important for prophylaxis designed to prevent infection in and around the pancreas.

Four meta-analyses of published trials of antimicrobial prophylaxis for necrotizing pancreatitis have concluded that prophylaxis reduces associated mortality.[17–20] However, these meta-analyses reached statistical significance only through inclusion of study results, which were biased by a problem with either catheter sepsis or catheter management.[3] These meta-analyses were performed prior to the recent double-blind study by Isenmann et al,[38] as was the Cochrane review, which reported that, despite variations in antimicrobial agent used, degrees of necrosis, and duration of treatment, there was strong evidence that antimicrobial prophylaxis decreased the risk of infection and mortality.[17] If the data from Isenmann et al[38] and this report are added to the data in the Cochrane review, then the comparisons between antibiotic and placebo lose statistical significance both for pancreatic infection and mortality. This trial was initiated before the Isenmann et al results[38] were available, but they lend weight to the conclusions of that paper. It is important to review these data because the early and extensive use of antibiotics in critically ill patients exposes them to change in flora, development of resistant flora and subsequent infections, and ultimately affects the flora of all hospitalized patients. Prophylactic antibiotics should not be used in these patients without compelling evidence for their benefit.

The current study was rigorous, both in the definition of necrotizing pancreatitis and the recruitment criteria with matched groups at baseline. It was designed to include patients at highest risk for pancreatic/peripancreatic infection (those with necrosis $\geq$30%) to afford the best opportunity to demonstrate a benefit for prophylactic antibiotic administration. Unfortunately, some patients did not have contrast-enhanced CT scans and thus did not have documented necrosis. These patients were required to have a Balthazar grade E scan and either elevated CRP or MOD score. These noncontrast CT criteria were chosen because, in the CTSI, a Balthazar grade E and >30% necrosis have the same point score. A patient with Balthazar grade E combined with MOD or an increased CRP was presumed likely to have necrosis. By the objective parameters of CRP, APACHE II score, MOD score, and mortality, these patients were actually considerably more ill than the other patients in the trial. This study, unlike the others, demonstrated equivalent management of nutritional support in the groups, an intervention that is increasingly believed to influence infectious outcomes of pancreatitis.[39] In contrast with the only other placebo-controlled trial, in the present study nonstudy antibiotic use (especially in the placebo group) occurred much later, on average nearly 3 weeks after randomization, enabling us to report with confidence the comparison between treatment and placebo groups for the effect of *early* prophylactic administration of antibiotic.

Unfortunately, the rigor and severity of the entry criteria made patient enrollment very slow, and the trial was stopped short of the original recruitment goal due to restriction of resources to continue the trial. Of the 807 patients screened, only 12% fulfilled all study entry criteria on initial screen and were randomized. Although this may at first raise concern about selective bias in enrollment, this is an appropriate proportion of all patients admitted to a hospital with pancreatitis. Our goal was to test the hypothesis in only the most seriously ill patients who were at highest risk to develop infection. We succeeded in enrolling more patients with necrotizing pancreatitis than any prior prospective randomized trial. The trial was stopped while all investigators were blinded to treatment allocation and results. In addition, the overall pancreatic/peripancreatic infection rate in this study of 15% was lower than anticipated despite the severity of disease. Despite falling short of the enrollment goal, this trial has enrolled the greatest number of patients with confirmed pancreatic necrosis of more than 30% of any trial to date and is only the second published study to be conducted in a double-blind, placebo-controlled manner. Six prior antibiotic studies for necrotizing pancreatitis.[1–3,21,30,38] have had infection rates ranging from 12.5%[21] to 35%,[3] with the median being 17%, suggesting that infection rates may be decreasing with modern care, and placing this study squarely within the mid range of similar reports.

The results of this study differ from previous reports that have suggested a possible benefit associated with early prophylaxis,[1,2,3,21,29–32,40] but they are in agreement with those of the only other double-blind study, which demonstrated no advantage of early antimicrobial prophylaxis.[38] Beger et al believe the inefficacy of prophylactic antimicrobial agents may be in part due to their late usage, that is after the development of necrosis, as in this study.[16] However, the treating clinician never has access to patients with severe pancreatitis prior to the development of necrosis. The majority of patients in this trial had study drug treatment begun within 4 days of symptom onset. Furthermore, these results support the recent international consensus statement issued by experts in the field of pancreatitis and intensive care, which did not favor the routine use of prophylactic antimicrobial agents in pancreatitis.[41]

It is generally considered that patients with biliary pancreatitis have a higher risk of infection than patients with alcohol as an etiology, and there were more patients with biliary pancreatitis in the meropenem arm than in the placebo arm. However, the overall distribution of etiologies (biliary, alcohol, other) was not significantly different between groups (Table 1, $P > 0.1$). In addition, the infection rate was higher in pancreatitis of other etiology (27% than either biliary (15%) or alcohol (9%), and there were more patients with "other" etiology in the placebo group. In addition, there were more patients with necrosis >30% in the placebo group than in the meropenem group, although this difference also was

not statistically significant ($P < 0.5$). As in any randomized study with many variables recorded, there will be some minor imbalances in risk factors. However, none was considered important enough to plan risk adjustment in advance, and none of the differences was statistically significant.

Another weakness of this study and of most prior studies in this field is the high number of patients in both study arms who received nonstudy antibiotics at some time during the trial (25 meropenem, 27 placebo). The numbers who received antibiotics *before* randomization were small, and such treatment was of short duration, and pancreatic infections that did occur tended to occur around 3 weeks, so we do not believe that this affected outcome, nor the validity of our comparison. These patients were very ill at enrollment and, despite study protocol restrictions, it is difficult to prevent clinicians from administering antibiotics empirically to patients who are ill. Nonstudy antibiotics were not administered until patients had been on study for a mean of 17 days and were given for suspected but not proven infection. Thus, this study is consistent with the only other double-blind study by Isenmann et al who concluded that "treatment on demand" is equivalent to early prophylaxis for patients with severe necrotizing pancreatitis, with consequent reductions in antibiotic exposure.[38] Review of the other prospective trials of early antibiotic use for necrotizing pancreatitis that have been cited in this paper reveal that in 4 no information regarding nonstudy antibiotic use is provided.[1,2,21,30] In one unblinded study where both groups received broad-spectrum antibiotics for 14 days, no nonstudy antibiotics were given during that time.[29] In the other 3, nonstudy antibiotics were administered to between 19% and 72% of randomized patients.[3,31,38]

CONCLUSION

This study, containing the largest number of patients to date with verified severe necrotizing pancreatitis, demonstrated no statistically significant difference between the treatment groups for pancreatic or peripancreatic infection, mortality, the combined outcome of infection or mortality, or requirement for surgical intervention, and did not support early prophylactic antimicrobial use in patients with severe acute necrotizing pancreatitis. Although this study standing alone lacks the power to reject a benefit of early antibiotics for patients with necrotizing pancreatitis, when combined with prior studies as noted above, early prophylactic antibiotic use for patients with necrotizing pancreatitis is not supported.

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