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Efficacy of a β-Lactamase Inhibitor Combination for Serious Intra-abdominal Infections

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A double-blind trial was conducted in 385 patients with suspected bacterial intra-abdominal infections to compare the efficacy and safety of ampicillin-sulbactam with cefoxitin. Patients were randomized to receive either 3 g ampicillin-sulbactam (2 g ampicillin–1 g sulbactam), or 2 g cefoxitin, every 6 hours. To be evaluable, patients had to demonstrate positive culture evidence of peritoneal infection at the time of operation. A total of 197 patients were evaluable for clinical efficacy. The two treatment groups were comparable in demographic features and in the presence of risk factors for infection. Clinical success (absence of infection and of adverse drug reaction) was observed in 86% of patients in the ampicillin-sulbactam group and 78% in the cefoxitin group. Eradication of infection occurred in 88% of the ampicillin-sulbactam group and 79% of the cefoxitin group. There were no differences in the nature or frequency of side effects observed in the two groups. Ampicillin-sulbactam demonstrated no difference in safety or efficacy when compared with cefoxitin in the treatment of serious intra-abdominal infections of bacterial origin.

Antibiotic therapy is an important adjunct to surgical management of serious intra-abdominal infections. Broad-spectrum antibiotic therapy is required, usually on an empiric basis, because of the potential presence of a mixed anaerobic/aerobic infection. The organisms involved usually include a wide variety of gram-positive and gram-negative pathogens.[1,2] Consequently, combinations of an aminoglycoside and an anti-anaerobic agent, such as clindamycin or metronidazole, emerged in the 1980s as the standard treatment for intra-abdominal infections.[3,4] Such combinations are no longer considered ideal from a practical perspective, however, because of the need to administer some drugs separately to avoid incompatibility and the need to perform pharmacokinetic monitoring to achieve an adequate serum concentration and to prevent drug-related toxicity.

The inconveniences associated with combinations of separate drugs has prompted evaluation of broad-spectrum antibiotics as therapeutic agents in the setting of abdominal infection. Cefoxitin, a second-generation

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cephalosporin with anti-anaerobic activity, has been extensively investigated in patients with intra-abdominal infections. It appears to be as effective as aminoglycoside-containing regimens with less potential for toxicity.[5,6] Another alternative having broad-spectrum antibacterial activity is a combination of a β-lactam antibiotic plus a β-lactamase inhibitor. Available parenteral regimens include ampicillin plus sulbactam and ticarcillin plus clavulanate. Both appear to be suitable for the treatment of intra-abdominal infections on the basis of their antimicrobial spectrum.

In the ampicillin-sulbactam combination, sulbactam prevents inactivation of ampicillin by bacterial β-lactamases. This results in activity against β-lactamase–producing Enterobacteriaceae and anaerobes.[7,8] At the same time, ampicillin retains its activity against ampicillin-susceptible pathogens, such as enterococci, that typically are resistant to cephalosporins and imipenem.

The efficacy of ampicillin-sulbactam[9–11] and of ticarcillin-clavulanate[12,13] has been demonstrated previously only in uncontrolled studies or in comparative trials involving only small numbers of patients with intra-abdominal infections. We now report the results of a large, double-blind, randomized, prospective, multicenter trial designed to examine the efficacy and safety of ampicillin-sulbactam in patients with intra-abdominal infections. Cefoxitin was selected as the control drug because it is widely used and is of demonstrated efficacy in this setting. Patients with renal impairment possibly due to their sepsis were included in this trial unless their creatinine clearance was less than 15 mL/minute/1.73 m^2.

MATERIALS AND METHODS

A double-blind, randomized, prospective, multicenter study of parallel design was conducted between August 1987 and October 1990. Informed consent was obtained from all patients. The protocol was reviewed and approved by the Institutional Review Board at each of the five participating institutions.

Hospitalized adults at least 18 years of age suspected of having intra-abdominal infections of bacterial origin and requiring an urgent operation were eligible for the study. Patients had to have visible serosal inflammation and a positive culture of peritoneal exudate at operation to be evaluable. Patients were excluded if any of the following were present: hypersensitivity to penicillins or cephalosporins; concomitant antibiotic administration (including peritoneal irrigation); previous (within 4 days) successful antibiotic therapy; enrollment in another study; other major active infection; terminal illness; immune deficiency or neutropenia (< 1500 neutrophils/mm^3); severe renal failure (creatinine clearance < 15 mL/minute/1.73 m^2); pregnancy, or breast-feeding. On enrollment, each patient underwent a complete physical examination and a series of laboratory tests, which were repeated at appropriate intervals during treatment. All adverse experiences were recorded with regard to duration, severity, action taken, outcome, and possible relationship to treatment.

Patients were assigned to treatment groups in a 1:1 ratio by a computer-generated randomization code. Patients were given 3 g ampicillin-sulbactam (Unasyn, Roerig, New York, NY; 2 g ampicillin—1 g sulbactam) or 2 g cefoxitin (Mefoxin, Merck Sharp & Dohme, West Point, PA), intravenously every 6 hours. For patients with moderate renal impairment (creatinine clearance 15 to 40 mL/minute/1.73 m^2), the dosing interval was increased to 8 to 12 hours. If creatinine clearance decreased to below 15 mL/minute while on study, the drug dose was shifted to 1.0 g every 24 hours. Patients were *not* dropped from the study if renal failure appeared during treatment.

The minimum duration of therapy for evaluation for efficacy was 4 days; the maximum was determined by the investigator and was based on patient response. Treatment was stopped if there was no response after 48 hours or if a significant adverse drug experience was observed (both defined as failure). Because of the advanced nature of the abdominal infection in many of our patients, primary closure of the skin and subcutaneous tissues was not a requirement in our protocol. If the surgeon chose to close the skin primarily and a wound infection developed, however, such patients were classed as failures.

Specimens were taken from infected sites for culture and susceptibility testing within 2 hours after initiation of antibiotic therapy. All pathogens were tested by nitrocefin disk for β-lactamase production as well as for susceptibility to ampicillin, ampicillin-sulbactam, and cefoxitin by broth dilution or disk diffusion methods using NCCLS (National Committee for Clinical Laboratory Standards) standards and procedures.[14]

Clinical outcomes were determined blindly on completion of therapy. The clinical response was considered a success if there was no evidence of infection at completion of treatment and no adverse drug reaction had occurred that necessitated termination of therapy. All other outcomes, including those patients whose abdominal infection resolved but who developed a new infection outside the abdomen that required treatment, were considered clinical failures.

Patients whose cultures were negative, or whose causative pathogens were resistant to ampicillin-sulbactam or cefoxitin, were not bacteriologically evaluable. At the end of therapy, bacteriologic response was categorized by organism as eradication (elimination of pathogen or disappearance of culturable material), persistence, su-

Table 1. REASONS FOR EXCLUSION

Reason	No. of Patients		
	Ampicillin-Sulbactam (n = 194)	Cefoxitin (n = 191)	Total (N = 385)
Culture documentation of infection absent	67	60	127
Minimum treatment (4 days) not achieved, although infection clinically controlled	12	14	26
Operation not performed	10	2	12
Protocol violation	6	13	19
Other reasons	3	1	4
Total no. excluded	98	90	188
No. evaluable	96	101	197

perinfection (emergence of new pathogen), or indeterminate.

The sample size was selected to detect a 50% difference in treatment outcome, assuming a failure rate (one-sided) of approximately 25% in the worst outcome group, with $\alpha = 0.05$ and $\beta = 0.20$.[15,16] Approximately 90 evaluable cases would be needed in each treatment group. We predicted a 50% nonevaluability rate and chose an enrollment population size of 400 patients. Appropriate tests were performed on continuous and categorical variables, both within each study site and across all study sites. The following tests were performed: for demographic and baseline variables (continuous measures), two-sample Wilcoxon rank sum tests (within each study site) and two-way factorial analysis of variance (across study sites); for categorical variables, Fisher's exact and chi square tests (within each study site), and Cochran-Mantel-Haenszel tests (across study sites); for global efficacy assessments, chi square tests for trend (ordered categorical for clinical response) or for independence (for bacteriologic response) within study sites and Cochran-Mantel-Haenszel tests (across study sites).

RESULTS

Patient Data

A total of 385 patients from five institutions were enrolled. One hundred eighty-eight patients were excluded from analysis for clinical efficacy (Table 1), most commonly because evidence of infection at operation was lacking. Among the 197 clinically evaluable patients, there were no important between-group demographic or treatment differences within or across study sites; pertinent data are recorded in Table 2. The most common primary diagnoses were perforated gastric/duodenal ulcer (n = 67), appendicitis with peritonitis (n = 50), small bowel perforation (n = 16), and perforated appendicitis (n = 11). Patients with perforated bowel had cultures taken intraoperatively from fluid collections away from the site of perforation; to be evaluable, these cultures had to be positive for accepted pathogens.

Clinical Outcome

Infection was cured in 84 of 96 (88%) ampicillin-sulbactam– and 80 of 101 (79%) cefoxitin-treated patients (Table 3). One additional patient in each group experienced an adverse drug reaction leading to termination of treatment. These two cases are classed as failures along with the 12 ampicillin-sulbactam and 21 cefoxitin patients in whom infection persisted or recurred (Table 4). The overall success rates, therefore, were 86% (83/96) of ampicillin-sulbactam– and 78% (79/101) of cefoxitin-treated patients, respectively.

The highest rates of clinical failure occurred in patients with appendicitis (n = 3 and n = 6 in the ampicillin-sulbactam and cefoxitin groups, respectively), small bowel perforation or dead bowel (n = 3 in both groups), and postoperative or other abscess (n = 2 and n = 7) (Table 3). The most common causes of clinical failure were persistent peritonitis (n = 3 and n = 6) and persistent abscess (n = 4 and n = 5) in the ampicillin-sulbactam and cefoxitin groups, respectively.

Table 2. DEMOGRAPHIC AND TREATMENT DATA (Evaluable patients)

Feature	Ampicillin-Sulbactam	Cefoxitin
No. of patients	96	101
Sex (M:F)	79:17	76:25
Age (yr) (mean ± SD)	44 ± 17	46 ± 19
Underlying disease*		
Alcohol/drug abuse	22	27
Cardiovascular disease	24	27
Respiratory disease	6	6
Malignancy	7	8
Diabetes	5	10
Liver disease	2	1
Renal disease	0	1
None	42	41
Primary wound closure	48	52
No. of drug doses (mean ± SD)	23 ± 8	25 ± 10

* Some patients had more than one underlying disease.

Table 3. SOURCE OF INFECTION IN PATIENTS CLASSED AS FAILURES

Source of Infection	No. of Failures/No. Evaluable: Ampicillin-Sulbactam	Cefoxitin
Stomach/duodenum		
Perforated ulcer	1/34	2/33
Appendicitis		
Gangrene	1/3	0/3
Perforation	0/6	0/5
Peritonitis	2/23	6/27
Small bowel		
Perforation	2/10	3/6
Dead bowel	1/3	0/2
Cecum/colon rectum		
Perforation	0/1	1/4
Peritonitis	1/3	1/2
Dead bowel	0/1	1/1
Gallbladder		
Empyema	1/3	0/1
Gangrene	0/3	0/2
Pancreatic abscess	2/3	4/8
Postoperative peritonitis or abscess	1/3	3/7
Total	12/96 (13%)	21/101 (21%)

Despite the contaminated nature of the operations conducted in evaluable cases, 100 patients (48 ampicillin-sulbactam, 52 cefoxitin) had primary closure of the skin and subcutaneous tissues based on the intraoperative judgment of the surgeon. One wound infection in an ampicillin-sulbactam–treated patient ensued.

Microbiologic Outcome

Cultures showed that most of microbiologically evaluable patients (59%) had infections caused by mixed aerobic/anaerobic bacteria. Pure gram-negative or gram-positive aerobic infections were present in 8% and 19% of patients, respectively. The remaining patients had mixed gram-negative/gram-positive aerobic infections (11%) or pure anaerobic infections (4%). β-Lactamases were detected in 29% of all pathogens, including 5% of gram-positive aerobes, 56% of gram-negative aerobes, and 34% of anaerobes.

Ampicillin-sulbactam eradicated 276 of 323 microorganisms (85%); cefoxitin eradicated 316 of 381 microorganisms (83%). There were no between-group differences in eradication rates overall or when pathogens were stratified as gram-negative aerobes, gram-positive aerobes, or anaerobes. Table 5 summarizes the eradication rates for frequently isolated microorganisms.

Candida were recovered in cultures from 14 patients, 7 in each treatment group, at entry or during therapy. These Candida cleared in all of the ampicillin sulbactam and in five of seven cefoxitin-treated patients. At the end of therapy, six patients who were clinical failures had *Candida* species recovered from their final culture. Of these, two cefoxitin-treated patients were *Candida*-positive at entry and had remained persistently positive throughout treatment; four ampicillin-sulbactam–treated patients had the new appearance of Candida noted in the polymicrobic flora obtained at the termination of treatment.

Adverse Drug Experiences

All patients who received at least one dose of study drug were included in the safety analysis. As might be expected in seriously ill patients with intra-abdominal infection, a wide variety of events that may or may not have been drug related were observed. Adverse drug experiences were reported in 33 ampicillin-sulbactam and 32 cefoxitin recipients. Nausea, vomiting, diarrhea, and rash were the most frequently recorded reactions in the two treatment groups. There were no between-group differences in these or any other adverse drug experience.

Treatment was discontinued in one patient in each group because of an adverse event; these patients are classed as treatment failures. Ampicillin-sulbactam was stopped because of fever, which then resolved spontaneously without further treatment. It was unclear whether the fever was caused by the drug or the infection. Cefoxitin was stopped because of rash and hives. The patient was treated with diphenhydramine and recovered without further incident.

DISCUSSION

Ampicillin-sulbactam produced high clinical success (86%) and microbiologic eradication rates (85%) in this

Table 4. PATTERNS OF CLINICAL FAILURE

Reason for Failure	No. of Failures: Ampicillin-Sulbactam	Cefoxitin
Persistent peritonitis	3	6
Persistent abscess	4	5
New intra-abdominal abscess	1	3
Subcutaneous wound infection	1	0
Pneumonia or urinary tract infection	3	7
Adverse drug reaction; treatment stopped	1	1
Total	13 (14%)	22 (22%)

Table 5. MICROBIOLOGIC OUTCOME FOR FREQUENTLY RECOVERED MICROORGANISMS (≥4 isolates)

Microorganism (n)	% of Microorganisms			
	Eradication	Persistence	Superinfection	Indeterminate
Gram-negative aerobes				
E. coli				
Ampicillin-sulbactam (28)	75	7	7	11
Cefoxitin (36)	83	8	3	6
Enterobacter/Klebsiella/Serratia				
Ampicillin-sulbactam (27)	81	4	11	4
Cefoxitin (26)	77	4	15	4
Pseudomonas				
Ampicillin-sulbactam (7)	71	0	29	0
Cefoxitin (16)	75	0	25	0
Others				
Ampicillin-sulbactam (6)	100	0	0	0
Cefoxitin (10)	80	0	10	10
Gram-positive aerobes				
Streptococci				
Ampicillin-sulbactam (62)	94	0	2	5
Cefoxitin (68)	97	0	1	1
Enterococci				
Ampicillin-sulbactam (16)	88	0	12	0
Cefoxitin (28)	71	7	21	0
Staphylococci				
Ampicillin-sulbactam (13)	85	0	15	0
Cefoxitin (24)	79	4	17	0
Anaerobes				
Bacteroides				
Ampicillin-sulbactam (67)	82	3	5	10
Cefoxitin (71)	86	3	7	4
Clostridium and other gram-positive rods				
Ampicillin-sulbactam (59)	88	2	5	5
Cefoxitin (58)	71	2	16	12
Peptostreptococci and other cocci				
Ampicillin-sulbactam (18)	83	0	6	11
Cefoxitin (19)	89	5	5	0
Fusobacterium				
Ampicillin-sulbactam (10)	90	0	0	10
Cefoxitin (12)	100	0	0	0

study of intra-abdominal infection of bacterial origin. These response rates were comparable to the clinical (78%) and microbiologic (83%) response rates in patients randomized to receive cefoxitin.

Our study was double blinded and randomized. The protocol was clearly established at the onset and was followed without deviation at each participating study site. There were no differences in demographic features across the study sites. In contrast to most other studies of antibiotic efficacy in abdominal infections, in which patients with even minor degrees of renal impairment are excluded, patients with renal impairment were excluded in our study only if they had a creatinine clearance of less than 15 mL/minute/1.73 m^2. The criteria for clinical success were rigorous. Patients who improved, but were not cured, and those who developed new infections outside the abdomen that required further treatment were considered to be clinical failures.

Nearly 400 patients were enrolled, but approximately one third were excluded, even though they had clinical signs and symptoms of peritonitis, because of a lack of culture documentation of infection. This is not surprising in view of the difficulty of predicting the actual presence of bacterial infection prior to operation. Both ampicillin-sulbactam and cefoxitin were well tolerated in our study. The frequency and nature of adverse events were similar in the two treatment groups. Only one patient in each treatment group discontinued treatment because of

an adverse event, both of which resolved without further sequelae. Both these patients are considered failures.

Given the variable effects on outcome of study design, response criteria, and patient factors, direct comparison of our results in patients with intra-abdominal infection with those in previous reports presents some difficulties. Our patients were seriously ill and had significant intra-abdominal infections, as demonstrated by the diagnoses recorded in Table 3. Most patients also had underlying illness. Nonetheless, the response rates in our trial appear to be comparable to those of others. Severity of illness is an important determinant of outcome.[17–19] Several indices for scoring the severity of intra-abdominal infections are currently available.[20,21] The use of such indices has been recommended to facilitate comparison of the results of different clinical trials.[3,22,23] Severity of illness was not scored in our study because no single system was universally accepted at the time (1986) our study was designed.

The efficacy of cefoxitin in abdominal infections is well established. The efficacy of ampicillin-sulbactam has been evaluated previously in only a limited number of studies. In one blinded, randomized trial involving 83 evaluable adults with intra-abdominal infections,[10] ampicillin-sulbactam resulted in clinical and microbiologic cure rates of 78 and 83%, respectively; these response rates were similar to those in the gentamicin-clindamycin control group (p = not significant). In 26 adults who had intra-abdominal infections and were enrolled in an uncontrolled study,[24] clinical and bacteriologic response rates of 85% were observed that were consistent with our findings.

In another study[25] of 105 evaluable patients with gangrenous and perforated appendicitis, the response rate in the ampicillin-sulbactam group was 88%, a rate comparable to that seen in other studies but lower than the response rate of the concurrent gentamicin-clindamycin control group (100%; $p < 0.05$). Resistant *Pseudomonas* species appeared to play an important role in this study and were recovered from five of eight cases in which treatment with ampicillin-sulbactam failed.

Ticarcillin-clavulanate also has been evaluated in a small number of patients with intra-abdominal infections. In 99 patients with suspected gangrenous or perforated appendicitis, the postoperative complication rates (*i.e.*, wound infection, abscess, or fever) were 14% and 16% in patients randomized to receive ticarcillin-clavulanate or gentamicin-clindamycin, respectively.[12] Corresponding microbiologic eradication rates were 98% and 92% (p = not significant). In another trial comparing ticarcillin-clavulanate with gentamicin-clindamycin, both regimens were effective and well tolerated although the sample size was too small to allow meaningful comparison of efficacy and safety.[13] In an uncontrolled study of 50 consecutive patients with secondary peritonitis, 17 deaths were attributed to failure of the surgical procedure (n = 10) or to ticarcillin-clavulanate (n = 7).[26] In the latter group, persistent microorganisms were *P. aeruginosa, Enterobacter* species, *Citrobacter* species, *Serratia marcescens,* and enterococci.

The efficacy of imipenem in the treatment of abdominal surgical infections has recently been evaluated by Solomkin and colleagues.[27] Their clinical success rate with imipenem was 82%; overall success among all patients studied was 77%. Their experience can be compared with success rates of 86% with ampicillin-sulbactam and 82% overall in our study. Despite the comparable outcomes, there are a number of differences between our study and that of the Solomkin group. In their study, postoperative infections of the abdomen and the abdominal wound were the primary basis for comparing outcomes, whereas we defined success as the absence of any infection at the completion of treatment. The Solomkin group also permitted different treatment regimens at different study sites; we did not permit such a variable. Furthermore, we did not observe fasciitis in any of our patients, which contrasts with eight such cases in 162 evaluable patients (5%) in their study.

Our study meets the major design criteria recommended for antibiotic trials in abdominal infections.[21] We did not find it necessary to stratify patients because we drew our study subjects from a relatively homogenous population, including only those subjects in our evaluation who had documented infection, and found no differences between our two randomized patient groups in those variables likely to affect outcome.

We conclude from our double-blind, randomized study of patients with serious intra-abdominal infections that the efficacy of ampicillin-sulbactam was not demonstrably different from that of cefoxitin on the basis of clinical success in treating infection or in microbiologic eradication rate. Ampicillin-sulbactam was well tolerated and as safe as cefoxitin, and appears in our judgment to be useful in the treatment of a variety of serious surgical infections of the abdomen.

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