Cefoperazone Compared with Ampicillin plus Tobramycin for Severe Biliary Tract Infections

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In a prospective, randomized, multicenter study, the efficacy and safety of cefoperazone and the combination ampicillin-tobramycin as initial therapy for patients with severe acute biliary tract infections were compared. Of 77 patients initially entered in the study, definite severe biliary tract infection was confirmed in 67. Sixty-four patients completed treatment. At the end of treatment, 35 of 36 (97%) patients given cefoperazone and 23 of 28 (82%) given ampicillin-tobramycin were cured of their infection (P = 0.07). Pathogens were recovered from the bile in 32 patients; microbiological cures were observed in 18 of 19 (94%) patients receiving cefoperazone and 8 of 13 (62%) receiving ampicillin-tobramycin (P = 0.03). Thirteen patients had septicemia. None (0%) of the eight septicemic patients from the cefoperazone group, but two of five (40%) from the ampicillin-tobramycin group, were clinical failures. Of the isolated pathogens, 51% were resistant to ampicillin, while the resistance rate was 4% for tobramycin and 1% for cefoperazone (P < 0.001). Biliary concentrations of cefoperazone were maintained at high levels—236 ± 87 μg/ml up to 12 h after administration. Even in the presence of severe obstruction, cefoperazone levels in the bile and gallbladder wall were above MICs for most pathogens. Cefoperazone may be considered as an excellent alternative in the therapy of severe biliary tract infections.

The ideal drug for the treatment of biliary tract infection should have excellent in vitro activity against potential biliary pathogens and should easily penetrate and concentrate within the biliary tree (9, 15). Cefoperazone is a broad-spectrum cephalosporin which is active in vitro against most aerobic gram-positive bacteria except enterococci and most aerobic gram-negative bacilli including Pseudomonas aeruginosa (17). It has little activity against anaerobes of Bacteroides fragilis groups. Moreover, cefoperazone, a cephalosporin which contains a methylthio tetrazole group, is excreted in large part in the bile where it can achieve concentrations of more than 6,000 μg/ml (6, 23, 24, 28). The unique biliary pharmacokinetics of cefoperazone combined with its excellent in vitro activity against most commonly isolated biliary pathogens led us to undertake an open, prospective, randomized, multicenter comparative study to evaluate the efficacy and safety of cefoperazone compared with that of the combination of ampicillin and tobramycin when used for initial therapy of patients with severe acute biliary tract infection.

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MATERIALS AND METHODS

Adult males or females between the ages of 18 and 90 years with severe acute infections of the biliary tract who were hospitalized in seven different Canadian centers were eligible for the study. Fifteen of the patients were more than 75 years old. For a patient to be eligible, the diagnosis had to be confirmed within 5 days of admission by either biliary tract pathology in patients undergoing surgery or, in patients who did not undergo surgery, by (i) evidence of biliary tract obstruction by invasive or noninvasive techniques, e.g. ultrasonography, intravenous cholangiography, endoscopic retrograde cholangiography, percutaneous transhepatic cholangiography, hepatobiliary imaging with technetium 99m-labeled dimethyl acetylenedicarboxylic acid, or computed axial tomography scan; (ii) one or more of the following signs: right upper quadrant pain or tenderness, hyperbilirubinemia, palpable gallbladder; and (iii) one or more of the following: pyrexia, chills, leukocytosis of >12,000/mm³, and/or septicemia. To be defined as suffering from cholangitis, patients had to present with the triad of Charcot: striking fever with chills, jaundice, and pain in the right upper quadrant. Furthermore, obstruction and inflammation of bile ducts had to be confirmed at surgery.

Reasons for exclusion included patients who were terminally ill or those whose condition precluded evaluation of a therapeutic response, pregnant or nursing women, those with a known or suspected allergy to the penicillin, cephalosporin, or aminoglycoside groups of antibiotics, patients who had been receiving an antibiotic within the preceding 4 days or who required the use of other antibiotic therapy for infections outside the biliary tract, subjects who had an infection outside the biliary tract, patients with significant renal impairment (serum creatinine, >2.5 mg/dl) or with hematological dysfunction (hemoglobin, <9.0 g/dl; leukocyte count, <3,000/mm³; platelets, <75,000/mm³).

Written informed consent was obtained, and each patient was randomly assigned to receive either cefoperazone or the combination ampicillin-tobramycin. This was an open study. The dosage of cefoperazone (Pfizer Canada Inc.) was 2 g every 12 h by intravenous (i.v.) infusion over 0.5 to 1 h. The ampicillin (Ayerst) dosage was 1 g every 4 h by i.v. infusion.

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over 0.5 to 1 h. The dosage of tobramycin included a loading dose of 2 mg/kg of lean body weight and a maintenance dose of 1.5 mg/kg 8 h following the loading dose and every 8 h thereafter. This dosage was also adjusted according to the renal function of the patient and by the judicious use of serum tobramycin levels. These were determined on days 1 and 3 and twice a week thereafter, and peaks of 6 and 10 µg/ml and a trough of <2 µg/ml were obtained in patients treated with aminoglycosides. The drug was infused as described above. The duration of therapy was determined by the investigator by evaluation of the response of the patient. To be evaluable, a patient had to be treated for a minimum of 72 h. Patients were evaluated by the investigator for clinical response and signs of toxicity at the end of each day while on i.v. therapy, on the last day of i.v. therapy, and at 4 to 6 weeks following the end of therapy. A telephone evaluation of each patient was made 2 weeks following therapy. Clinical outcome was determined at the end of i.v. therapy and at the 4- to 6-week follow-up visit.

A clinical cure was defined as the disappearance of all base-line signs and symptoms relevant to the acute episode of infection. Improvement meant that clinical signs did not completely disappear during therapy. If no significant improvement in clinical signs and symptoms was observed, treatment was considered a failure. Relapse was defined as the recurrence of signs and symptoms within 4 to 6 weeks after an initial apparent cure.

Cultures of blood, urine, bile, and wound (as applicable) were performed at the initial evaluation period, at the time of surgery, and at various times during i.v. therapy in patients who had T-tubes, or at the end of i.v. therapy. In patients in whom pathogens were isolated either from blood or from the biliary tract, bacteriological outcome was defined as a cure if the pathogen(s) was eliminated or as a failure if the initial pathogen(s) persisted. Colonization was defined as the isolation of a new pathogen in the presence of active infection while the patient received therapy. Disk susceptibility testing for aerobic isolates and broth dilution methods for anaerobic bacteria were done according to the 1984 recommendation of the National Committee for Clinical Laboratory Standards (29).

Antibiotic toxicity was evaluated in all patients who received either antibiotic regimen for at least 72 h. Routine measurements including complete blood count with differential, erythrocyte sedimentation rate, platelet estimation, serum creatinine, blood urea nitrogen, serum glutamic oxalacetic transaminase, alkaline phosphatase, serum amylase, prothrombin time, Coomb’s test, and urinalysis were performed at the initial evaluation, at least twice weekly during i.v. therapy, and at the end of i.v. therapy. Impairment of renal function was defined as a rise in serum creatinine of at least 0.5 mg/dl over the base line during therapy. Levels of tobramycin in serum were monitored in patients who were treated with tobramycin. The levels of cefoperazone in serum, bile, and gallbladder wall were determined over a period of 12 h in 10 patients on the day of surgery and 4 days postsurgery. Cefoperazone concentrations were determined by biological assay with Bacillus subtilis as the indicator microorganism (20).

Statistical analysis. The data in Table 1 were analyzed by using a 2 × 2 contingency table with Yates’ corrections for continuity. The chi-square test of independence between proportions with the Yates’ correction was performed on the data in Tables 4 and 5.

In Table 2, the interaction of medical and surgical treatment versus the effect of the two drug regimens on the outcome was evaluated by a log linear model (8, 34). The overall outcome was analyzed by the likelihood ratio chi-square test (G²).

In Table 3, the comparison of the three drugs for resistance of bacteria was done by using row-by-column contingency tables with G² test values.

RESULTS

Patient population. Seventy-seven subjects (39 randomly assigned to receive cefoperazone and 38 to receive ampicillin-tobramycin) were initially included in the study. Eight patients receiving ampicillin-tobramycin and two receiving cefoperazone were excluded because the diagnosis was not subsequently confirmed. Sixty-seven patients could be analyzed; 37 with a mean age of 64 years received cefoperazone therapy, and 30 with a mean age of 63 years received the combination ampicillin-tobramycin. The distribution of age, sex, weight, number of underlying diseases, and duration of illness was similar in both groups. A total of 73% and 63% of the patients receiving either cefoperazone or the combination therapy, respectively, were experiencing their first biliary tract infection. The mean duration of illness before diagnosis was 4.9 and 3.7 days in the cefoperazone and ampicillin-tobramycin groups, respectively. A total of 78% and 68% of patients receiving cefoperazone or ampicillin-tobramycin, respectively, underwent surgery. Some patients (24 for the cefoperazone group and 17 for the ampicillin-tobramycin group) received antibiotics for 0 to 2 days before they underwent surgery, while 4 and 2 patients from each group, respectively, began to receive antibiotics 24 to 48 h after surgery. The types of biliary tract infections and surgical interventions, complications, and associated diseases are shown in Table 1. There was no significant difference in the types of pathology, complications, interventions, and associated diseases observed in the two groups. The mean duration of therapy (7.2 days for cefoperazone and 6.8 days for ampicillin-tobramycin) was similar in both arms of the study.

| TABLE 1. Types of biliary tract infections, complications, intervention, and associated diseases observed in patients receiving either of the antibiotic regimens |
|-------------------------------------------------|-----------------|-----------------|
| Description                                      | Cefoperazone (36 patients) | Ampicillin-tobramycin (28 patients) |
| Pathology                                        | No. (%) of patients     | No. (%) of patients     |
| Cholangitis                                      | 11 (31)              | 5 (18)              |
| Necrotizing cholecystitis                        | 7 (19)               | 4 (14)              |
| Cholecystitis                                    | 18 (50)              | 19 (68)             |
| Complications                                    | 8 (22)               | 5 (18)              |
| Septicemia                                       | 15 (42)              | 11* (39)            |
| Biliary tract obstruction                        |                      |                    |
| Surgical intervention                            | 28 (78)              | 19 (68)             |
| Cholecystectomy and choledoctomy (T-tube)        | 15 (42)              | 8 (29)              |
| Cholecystectomy                                  | 13* (36)             | 11* (39)            |
| Surgery while on antibiotics                     | 24 (66)              | 17 (61)             |
| Medical treatment alone                          | 8 (22)               | 9 (32)              |
| Associated diseases                              |                      |                    |
| Adenocarcinoma of the gallbladder                | 2 (6)                | 0 (0)               |
| Cancer of the pancreas                           | 1 (3)                | 2 (7)               |

* Two of these cholecystectomies were done after cessation of antibiotics.

* Four of these cholecystectomies were done after cessation of antibiotics.
Clinical efficacy. Of the 67 patients confirmed to have definite severe biliary tract infections, 64 completed treatment. Thus, 36 patients receiving cefoperazone and 28 patients receiving ampicillin-tobramycin were evaluable for clinical efficacy. Clinical response is shown in Table 2. Clinical efficacy was not evaluable in one patient receiving cefoperazone and two patients receiving ampicillin-tobramycin because of discontinuation of therapy. In the cefoperazone-treated patient, therapy was stopped owing to severe phlebitis, and in the ampicillin-tobramycin group, one patient developed a rash and the other had a pulmonary embolism and died.

Cure was achieved in 35 of 36 (97%) cefoperazone-treated patients. Cure rates were identical whether or not patients had surgery. The patient who failed had a cholecystectomy for cholecystitis. All 36 patients receiving cefoperazone were evaluable clinically after therapy. Of the 36, 35 (97%) were judged as clinically cured; in one patient who was cured at the end of therapy, symptoms recurred 4 weeks after therapy. The other patient was considered to have a clinical failure at the end of therapy.

A cure was achieved in 23 of 28 (83%) ampicillin-tobramycin-treated patients (Table 2). A satisfactory clinical response (cure or improvement) was observed in 25 (88%). Of the 28 ampicillin-tobramycin-treated patients, 27 were evaluated after therapy. Of the three patients considered to have clinical failures at the end of therapy, two had to be given cefoperazone and cefamandole as alternative therapy and were cured at follow-up. The third one was unavailable for follow-up. Of the patients initially cured or improved, none had any recurrence and all were well at follow-up.

A cure was thus achieved in 97% of patients receiving cefoperazone versus 83% of patients receiving ampicillin-tobramycin therapy \( (P = 0.07) \). The analysis of the data revealed that surgery, the severity of the infection, the presence of underlying disease, or biliary tract obstruction did not influence the outcome of therapy, whether cefoperazone or ampicillin-tobramycin was administered.

The bacteriological response was evaluated according to the base-line pathogens isolated prior to or within the first 2 days of therapy. Pathogens were isolated from bile, blood, or both from 19 of 24 cefoperazone-treated patients and 13 of 17 ampicillin-tobramycin-treated patients who were operated on while receiving antibiotics and completed therapy. The main pathogens were Escherichia coli (24%), Klebsiella species (19%), Enterobacter spp. and Citrobacter spp. (13%), and enterococcus (9%). There were four infections with Clostridium perfringens and three with Pseudomonas spp. recovered from patients with cancer. These latter pathogens were often associated with the primary pathogens E. coli (59%) and Klebsiella spp. (12%). These two bacteria were also the most commonly recovered pathogens in the blood. B. fragilis, C. perfringens, and Citrobacter freundii were associated with E. coli in the three episodes of mixed septicemia. B. fragilis was isolated in only one patient who had cancer of the pancreas and obstruction of the biliary tree.

In vitro testing of 27 initial isolates from the bile of cefoperazone-treated patients demonstrated that all were susceptible to cefoperazone (Table 3). A total of 12 of 23 (52%) initial isolates from the group receiving combination treatment were susceptible to ampicillin, and 22 of 23 (96%) were susceptible to tobramycin. Pathogens isolated from blood were also highly resistant to ampicillin (57%) \( (P < 0.001) \), while 0 and 12% of these bacteria were resistant to cefoperazone and tobramycin, respectively. The overall susceptibility of all pathogens isolated during the study is also shown in Table 3. Similar patterns of susceptibility were observed. At total of 26% of E. coli were resistant to ampicillin.

### Table 2. Medical, surgical, and overall outcome at the end of therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Total no. of patients</th>
<th>Medical treatment alone</th>
<th>Medical treatment and surgery</th>
<th>Overall outcome (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>Cured</td>
<td>Improved</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>36</td>
<td>8</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Ampicillin-tobramycin</td>
<td>28</td>
<td>7</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Statistical analysis between the cefoperazone and ampicillin-tobramycin groups was done by using a log linear model and was not significant.

### Table 3. Resistance of bacterial strains isolated initially from bile and blood and overall susceptibility of all microorganisms isolated during the study

<table>
<thead>
<tr>
<th>Isolates</th>
<th>Cefoperazone</th>
<th>Ampicillin</th>
<th>Tobramycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reistant initial isolates from bile</td>
<td>0/27 (0)</td>
<td>12/23 (52)</td>
<td>1/23 (4)</td>
</tr>
<tr>
<td>Resistant initial isolates from blood</td>
<td>0/9 (0)</td>
<td>4/7 (57)</td>
<td>1/8 (12)</td>
</tr>
<tr>
<td>Overall resistance of bacteria isolated throughout the study</td>
<td>1/76 (1)</td>
<td>48/93 (51)</td>
<td>3/69 (4)</td>
</tr>
<tr>
<td>Resistance of most commonly isolated bacteria from the biliary tract</td>
<td>0/31</td>
<td>10/39</td>
<td>0/27</td>
</tr>
<tr>
<td><strong>E. coli</strong></td>
<td>0/5</td>
<td>3/3</td>
<td>0/5</td>
</tr>
<tr>
<td><strong>Klebsiella sp.</strong></td>
<td>0/15</td>
<td>18/18</td>
<td>0/10</td>
</tr>
<tr>
<td><strong>Citrobacter sp.</strong></td>
<td>0/5</td>
<td>6/6</td>
<td>0/6</td>
</tr>
<tr>
<td><strong>Enterobacter sp.</strong></td>
<td>0/3</td>
<td>4/4</td>
<td>1/3</td>
</tr>
<tr>
<td><strong>Pseudomonas sp.</strong></td>
<td>0/3</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td><strong>B. fragilis</strong></td>
<td>1/3</td>
<td>1/9</td>
<td>1/3</td>
</tr>
<tr>
<td><strong>S. faecalis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominators vary since not all strains were tested for susceptibility to the three antibiotics.

<sup>b</sup> E. coli \( (n = 1) \), Klebsiella sp. \( (n = 2) \), B. fragilis \( (n = 1) \).

<sup>c</sup> B. fragilis.
As shown in Table 4, 18 of 19 (94%) microbiologically evaluable cefoperazone-treated patients were assessed as having microbiological cures, while 8 of the 13 (62%) ampicillin-tobramycin-treated patients were considered to have microbiological cures \((P = 0.03)\). The bacteriological outcome was similar whether patients had multiple pathogens or a single pathogen. In the cefoperazone-treated patients, one patient had a microbiological failure owing to persistent infection with \(E.\ coli\) and colonization with \(Klebsiella\ oxytoca\) and enterococcus. In another patient, \(Salmonella\) species was isolated from bile a few days after the initial bile culture had shown \(E.\ coli\). We believe that the \(Salmonella\) species was missed on the initial culture and that it was a mixed infection with \(E.\ coli\) and \(Salmonella\) species.

In three of the patients receiving ampicillin-tobramycin, treatment failed to eradicate the original pathogens from the bile (two \(E.\ coli\), one \(P.\ aeruginosa\)), and in one case \(B.\ fragilis\) was isolated in the blood of the patient on day 3 of therapy. On day 4, the patient was switched to cefoperazone and did well. The fifth patient with microbiological failure had ampicillin-resistant \(Klebsiella\ pneumoniae\) isolated from blood and, although sensitive to tobramycin and cefoperazone, was switched to cefamandole. Two patients were colonized with \(Serratia\) spp. Most pathogens involved in the failures were susceptible to either cefoperazone or tobramycin but resistant to ampicillin. We did not find any difference in the ampicillin plus tobramycin or cefoperazone group in the type of biliary pathology or underlying diseases.

Three of the ampicillin-tobramycin-treated patients having microbiological failure were septicemic, and two of these had clinical failures. None of the septicemic patients receiving cefoperazone had clinical failures, but one had a microbiological failure. Most patients with septicemia were initially obstructed, and the incidence of septicemia in obstructed biliary tract disease was not significantly different in both groups.

Minor drug-related side effects including rash, diarrhea, and phlebitis occurred in seven cefoperazone- and five ampicillin-tobramycin-treated patients. No significant laboratory abnormality was detected which necessitated discontinuation of treatment. In one apparently normal patient with common bile duct obstruction treated with cefoperazone, a prothrombin time prolongation was observed during therapy without any adverse consequence. It was corrected with vitamin \(K\) administration at the end of therapy. An increase in serum creatinine was noted in three patients receiving ampicillin-tobramycin, while it was observed in only one patient receiving cefoperazone. The creatinine rises were, respectively, 1.3, 1.3, and 1.99 mg. The level returned to normal as treatment with tobramycin ceased.

In the 10 patients in whom levels of cefoperazone were evaluated, the respective serum levels (micrograms per milliliter ± standard deviation) at 1.5, 4, 8, and 12 h were 157 ± 16, 84 ± 9, 35 ± 3, and 26 ± 4. Biliary levels peaked at 464 ± 151 \(\mu\)g/ml between 2 and 4 h after the dose and were maintained at high levels (236 ± 87 \(\mu\)g/ml) up to 12 h after administration. Of these 10 patients, 4 had severe obstruction of their biliary tracts. The levels of cefoperazone were still several times above the MIC for the pathogens involved (Table 5). As observed in two patients in whom biliary levels were determined again 3 days after the obstruction was released, the levels increased considerably. Levels in gallbladder walls were lower than those in the bile.

### DISCUSSION

Despite the fact that severe biliary infection is a common clinical problem associated with high morbidity and mortality, there is no standardized approach to the therapy of these infections. The proper choice of a therapeutic regimen should be based on the severity of the disease process, the suspected biliary pathogens, and the in vitro activity and biliary pharmacology of potentially effective antimicrobial agents.

There is a very limited number of prospective randomized clinical trials on the proper choice of antimicrobial agents in the treatment of biliary tract infections (7, 14, 22). Most studies have been retrospective investigations (21) or non-comparative trials dealing with uncomplicated or severe biliary tract infection (3, 27, 30). Although many therapeutic

### TABLE 5. Biliary and gallbladder wall levels of cefoperazone in four patients with severe biliary obstruction

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time of sampling (h)</th>
<th>Serum bilirubin (mg%)</th>
<th>Alkaline phosphatase (IU)</th>
<th>Cefoperazone levels</th>
<th>Bile ((\mu)g/ml)</th>
<th>Gallbladder wall ((\mu)g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>5.3</td>
<td>286</td>
<td>106</td>
<td>660</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>6.3</td>
<td>410</td>
<td>62</td>
<td>43</td>
<td>1,200</td>
</tr>
<tr>
<td>3</td>
<td>4.0</td>
<td>6.6</td>
<td>354</td>
<td>130</td>
<td>85</td>
<td>603</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>9.9</td>
<td>225</td>
<td>150</td>
<td>31</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Time after first dose.
* Normals are 0 to 1.2 mg%.
* Normals are 30 to 120 IU.
* Samples were taken after the fifth dose of cefoperazone on day 3.
* ND, Not done.
regimens presently used for the therapy of biliary infections have not been proved effective in a comparative fashion, most investigators agree that severe infection, especially acute suppurative cholangitis, should be treated with a penicillin combined with an aminoglycoside. The combination of ampicillin with either gentamicin or tobramycin has been the most commonly recommended regimen (4, 18, 35, 40). In cases of cholangitis, some investigators have suggested the use of clindamycin to treat *B. fragilis* although there is no evidence in the literature for this approach (16). To cover nearly all possible pathogens, a combination of ureidopenicillins or cephalosporins including the broad-spectrum cephalosporins with an aminoglycoside has been suggested as another logical approach to therapy (9). For less severe biliary infections, single therapy with a parenteral cephalosporin or ampicillin has also been found adequate (7, 9, 14), but the use of antibiotics in patients with uncomplicated cholecystitis is still a matter of controversy. In fact, unless cholecystitis occurs in an older patient or is associated with cystic or common bile duct obstruction (1, 10, 36), the incidence of active infection is less than 50% (11, 32).

In the present study, criteria for inclusion were very strict. Only patients with severe biliary tract infection could be included. A total of 25% of our patients had severe cholangitis, 40% had either cystic or common bile duct obstruction, 20% developed septicemia, and 17% had severe necrotizing cholecystitis at the time of operation.

The results of our evaluation suggest that cefoperazone is more effective than ampicillin plus tobramycin in the acute phase of biliary tract infection. Of 36 cefoperazone-treated patients and 28 ampicillin-tobramycin-treated patients, 35 (97%) and 23 (82%), respectively, were cured of their infections ($P = 0.07$). Although the number of evaluable patients was smaller in the ampicillin-tobramycin arm of the study, none of the base-line characteristics of the two groups differed statistically. Measures of association for two-way frequency tables and log linear model were done to assess the influence of surgery, the severity of infection, the presence of underlying disease, or the presence of biliary obstruction on the outcome of therapy. After these factors were taken into account, treatment with cefoperazone was still associated with a higher response rate. In a prospective randomized study in which 119 patients were given either ampicillin or cefamandole as prophylaxis or treatment of biliary tract infections, Levi et al. (22) did not find any difference in the outcome of therapy. Havig and Hertzberg (14), comparing ampicillin, chloramphenicol, and penicillin-chloramphenicol in 77 patients with cholecystitis, and De Ritis and Sciolli (7), comparing ampicillin and hetacillin in 38 patients with either acute or chronic cholecystitis or cholangitis, observed that all these drug regimens were equally effective. In most of these studies, the cure rate varied between 80 and 100%, but in these four randomized trials, the patients studied were not as severely ill as in the present study and the criteria for diagnosis and outcome were poorly defined. In the few noncomparative studies in which either ampicillin or gentamicin was used alone for the treatment of biliary diseases, the cure rate varied between 80 and 88%, but these studies involved small numbers of cases which were not well defined (12, 13, 41). In Japan, noncomparative trials with cefoperazone have revealed an overall success rate of 78% in 116 patients suffering from biliary tract infections (24). The efficacy in 50 cases of cholecystitis was 84%, in 33 patients with cholangitis it was 67%, and in 27 cases identified as biliary tract infections it was 82% (24). Six patients had a liver abscess, and the cure rate was 67% (11). Cristiano et al. (6), in a smaller study involving 25 patients, showed that 21 patients (84%) recovered completely with cefoperazone. In the few patients who failed to recover (16%), one was pancytopenic, one had diabetes mellitus, one had multiple liver abscesses, and the other had gallbladder cancer (6).

In addition to the excellent clinical response observed in our study, very few microbiological failures were observed in the cefoperazone group. While cefoperazone could not eradicate the pathogens in only 6% of the patients, ampicillin-tobramycin failed to sterilize the bile in 36% of patients ($P = 0.03$). The incidence of positive cultures and the bacterial species recovered from blood and bile were identical to those reported by others (5). The limited eradication rate with ampicillin-tobramycin can most likely be explained by the fact that 51% of the bacteria isolated from the biliary tree were resistant to ampicillin. Although most pathogens (96%) were susceptible to tobramycin, the poor penetration of aminoglycosides into the bile may explain the persistence of pathogens within the bile (19, 31, 39). In contrast, only 1% of the pathogens were resistant to cefoperazone. The three *Pseudomonas* spp. tested were also susceptible to cefoperazone. Of crucial importance was the finding that two of the five patients who had septicemia and were treated with ampicillin-tobramycin failed to recover on this regimen, while all eight septicemic patients treated with cefoperazone were cured of their disease.

The observed increase in clinical and bacteriological cure rate with cefoperazone may also be attributed to its unique biliary pharmacology. In contrast to other cephalosporins which may reach maximum biliary concentrations of less than 364 μg/ml after a 1- or 2-g dose (33), cefoperazone may reach maximal biliary levels of more than 6,000 μg/ml in the common duct bile and 680 μg/ml in gallbladder bile after a 2-g dose (20, 23). Maximum cefoperazone concentrations of 348 μg/g of gallbladder wall have been observed after a 2-g dose (6). In our present study, the mean peak biliary level was 464 μg/ml. All patients including those with severe obstruction had levels above 30 μg/ml in the bile and 3.5 μg/g in the gallbladder. These levels are above the MIC of cefoperazone for most biliary pathogens. After a 500-mg dose of ampicillin, Mortimer et al. (26) have observed levels of 22 μg/ml in the bile from the common bile duct. Maximum levels of 273 μg/ml were observed by Ayliffe and Davis (2). Aminoglycosides penetrate poorly into the bile.

Maximum biliary levels of 3.0 μg/ml were observed after high doses of gentamicin (25, 39). The extremely high biliary levels of cefoperazone, coupled with its excellent in vitro activity, which resulted in a very high concentration over MIC ratio within the infected biliary tree, have certainly played a determinant role in the outcome of therapy in these patients with severe biliary tract infections and were probably responsible for the elimination of the biliary pathogens in 18 of the 19 patients. The limited in vitro activity of ampicillin coupled with the poor penetration of aminoglycosides into the bile may have been responsible for the limited clinical and microbiological outcome with the combination. Cefoperazone, which was effective in vitro against *P. aeruginosa* isolated in this study, sterilized the bile of two patients harboring this agent. As reported previously, *P. aeruginosa* was observed exclusively in patients with cancer (1, 5, 16, 36). Anaerobes were recovered from six patients. With the exception of an episode of *B. fragilis* septicemia which did not respond to ampicillin-tobramycin, all the other anaerobes were eliminated rapidly from the bile. Of interest,
the only patient with *B. fragilis* in the bile also had an underlying cancer. Furthermore, when enterococci were isolated from the bile, all patients responded to therapy. Colonization was observed in only two patients from each of the study arms.

Of the 28 ampicillin-tobramycin-treated patients, 3 did show signs of nephrotoxicity. The incidence of nephrotoxicity observed here was identical to that previously observed by Smith et al. (38). Prolongation of the prothrombin time was observed in one patient receiving cefoperazone (37).

In conclusion, in this study, treatment with cefoperazone, 4 g/day, was at least as effective and probably more effective than the combination of ampicillin plus tobramycin for the treatment of patients with serious biliary tract infections. Cefoperazone appears to be a safe and very promising agent for the treatment of severe biliary tract infections.

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LITERATURE CITED