



ronidazole on the course and outcome of patients with predicted severe acute pancreatitis.

## Patients and Methods

### Selection of Patients

In this double-blind, randomized, multicenter trial, patients with a predicted severe attack of acute pancreatitis were included. Acute pancreatitis was defined as abdominal pain in combination with a 3-fold elevation of serum amylase and/or lipase. From the criteria of our current classification of severe acute pancreatitis,<sup>22</sup> a serum C-reactive protein (CRP) exceeding 150 mg/L<sup>23,24</sup> and/or presence of pancreatic necrosis on contrast-enhanced CT scanning<sup>25–27</sup> (CECT) were chosen to define severity for this study. Study inclusion had to be performed within 72 hours after the onset of upper abdominal pain. The study protocol was reviewed and approved by the ethical committees of the participating hospitals.

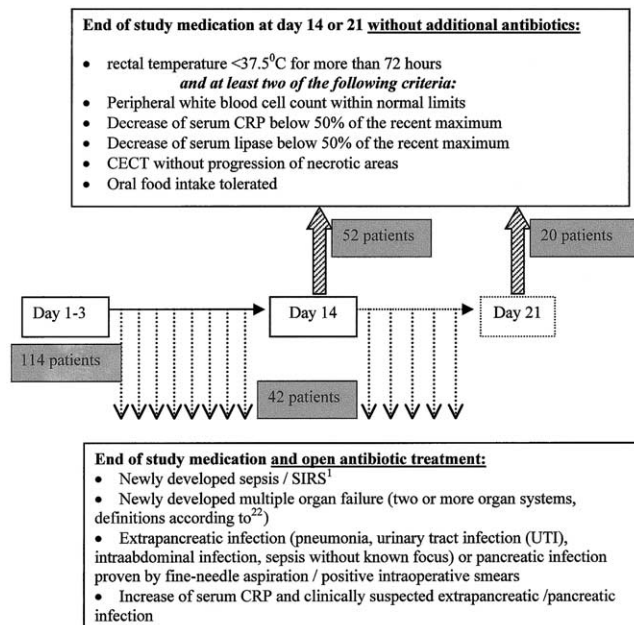
### Study Medication

Prior to initiation of the study, a stratified randomization plan was generated by the Department of Biometry and Medical Documentation, University of Ulm, Ulm, Germany, for each participating center using a block size of 4 patients. Study medication for each patient (verum or placebo) was packed in identical vials and labeled with consecutive patient numbers according to the randomization sequence. After informed written consent, patients were consecutively enrolled. Ciprofloxacin and the corresponding placebo vials were provided by Bayer Vital, Leverkusen, Germany; Metronidazole and its placebo were provided by Ratiopharm, Ulm, Germany.

All persons participating in the study (patients as well as medical staff and physicians) were blinded to assignment of treatment. Study medication was initiated immediately following study inclusion. Patients received either ciprofloxacin 2 × 400 mg/day intravenously (IV) in combination with metronidazole 2 × 500 mg/day (IV), or placebo.

Study medication was planned to be given until day 21 after onset of pancreatitis. From inclusion until day 21, patients were closely monitored and underwent daily reevaluation of their clinical parameters. Physical examination was performed daily during the study period. The study protocol requested discontinuation of the study medication with open antibiotic treatment when the patient fulfilled the criteria given in Figure 1. Briefly, these were cases with progressive pancreatitis characterized by clinical deterioration and/or cases with proven or strongly suspected pancreatic or extrapancreatic infection. In patients that were switched to open antibiotic treatment, the choice of antibiotic regime was the investigator's discretion; the recommendation of the study protocol was to use Imipenem, possibly in combination with Vancomycin.

Patients not qualifying for open antibiotic treatment received study medication at least until day 14 after the onset of symptoms. At day 14, study medication could be stopped without further antibiotic treatment if patients met the criteria given in Figure 1. If these criteria were not fulfilled, study



**Figure 1.** Patient flow and criteria for discontinuation of study medication or change to an open antibiotic treatment. <sup>1</sup>Definitions are according to Bauer and Köhne.<sup>29</sup>

medication was continued, and evaluation was repeated on day 21 after the onset of the disease. At day 21, study medication had to be stopped. Patients not qualifying for discontinuation without further antibiotics were put on an open antibiotic regime.

### Study End Points

The study was designed to demonstrate that prophylactic intravenous ciprofloxacin/metronidazole is efficacious in reducing the incidence of infected pancreatic necrosis (primary end point). Infected pancreatic necrosis was defined as the presence of bacteria in intraoperative smears taken from the pancreas or assumed if computed tomography-guided or ultrasound-guided, fine-needle aspiration from necrotic area revealed bacterial infection.

Other criteria for evaluation of the efficacy of ciprofloxacin/metronidazole (secondary end points) were death, extrapancreatic infection, surgical treatment for necrotizing pancreatitis, duration of stay in the intensive care unit, and hospitalization as well as systemic complications of the disease. The magnitude of systemic complications was assessed by a clinical severity score (CSS), which comprised the following variables: development of SIRS (definition according to American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference<sup>28</sup>), shock, pulmonary insufficiency, and renal insufficiency (definitions according to Bradley<sup>22</sup>). Fulfillment of each of these criteria was scored with 1 point, and the maximum score was calculated at the end of hospital stay.

### Statistical Analysis

Sample size calculations were based on the assumption that antibiotic prophylaxis would reduce the incidence of

**Table 1.** Baseline Characteristics of Patients Enrolled in the Intention-to-Treat Analysis and Patients With Necrotizing Pancreatitis

	Intention-to-treat analysis 114 patients		Necrotizing pancreatitis 76 patients	
	Ciprofloxacin/ metronidazole 58 patients	Placebo 56 patients	Ciprofloxacin/ metronidazole 41 patients	Placebo 35 patients
Male/Female	43/15	44/12	31/10	25/10
Age, yr (median, minimum-maximum)	47.9 (25.1–72.5)	45.6 (21.9–78.4)	49.4 (27.5–72.5)	46.5 (21.9–78.4)
Etiology (%)				
Alcohol	n = 32 (55)	n = 34 (60)	n = 24 (59)	n = 20 (57)
Biliary	n = 13 (22)	n = 9 (16)	n = 8 (19)	n = 8 (23)
Others	n = 13 (22)	n = 13 (24)	n = 9 (22)	n = 7 (20)
Ranson 48 h points (median, minimum-maximum)	2.5 (0–6)	2 (0–7) <sup>a</sup>	3 (0–6)	2 (0–7) <sup>b</sup>
Serum CRP at inclusion, mg/L (median, minimum-maximum)	175 (1–790)	176 (0–492) <sup>a</sup>	184 (8–790)	179 (0–492) <sup>b</sup>
Study inclusion after onset of symptoms, hr (median, minimum-maximum)	52 (4–84) <sup>c</sup>	41 (11–89) <sup>a</sup>	53.6 (4–84) <sup>d</sup>	42 (14–89) <sup>b</sup>

<sup>a</sup>Data from 54 patients.<sup>b</sup>Data from 34 patients.<sup>c</sup>Data from 57 patients.<sup>d</sup>Data from 40 patients.

infected pancreatic necrosis from 40% in the placebo group to 20% in the verum group. These assumptions were based on the experiences of recent studies on this topic<sup>10,11</sup> showing a baseline incidence of about 40%, which could be expected to be reduced by about 20 points of percentage if patients were treated prophylactically with antibiotics. Assuming a 1-sided significance level of 5% and a power of 90%, a sample size of 100 patients in each group would be necessary to demonstrate this effect.

An adaptive interim analysis (according to Bauer and Köhne with  $\alpha_0 = 0.5^{29}$ ) was performed for the primary end point “infected pancreatic necrosis” after 105 patients had been enrolled. At that time, the incidence of infected pancreatic necrosis was 7 of 53 in the verum group and 5 of 52 in the placebo group ( $\chi^2$  test, 1-sided,  $P = 0.719$ ). Consequently, recruitment was stopped because the trend in the incidences was in the opposite direction and a final analysis of the study data was performed.

The following statistical tests were used for exploratory data analysis. For dichotomous end points, treatment groups were compared by applying a  $\chi^2$  test, and a Wilcoxon Mann-Whitney test was used for quantitative end points. All  $P$  values presented are 2-sided.

## Results

### Baseline Characteristics of the Patients

A total of 119 patients from 19 participating hospitals were enrolled in this study between January 1999 and June 2002. Three patients were lost to follow-up, and 2 were withdrawn from the study prior to receiving study medication; thus, 114 patients were included in the intention-to-treat (ITT) analysis.

Fifty-one patients were recruited on the basis of an elevated serum CRP in combination with pancreatic necrosis on CECT. Nine of the patients developed infected necrosis, and 6 of them died. Nineteen patients were recruited with pancreatic necrosis on CECT but serum CRP <150 mg/L. Three of them developed infected necrosis; none of them died. Forty-four patients were recruited on the basis of an elevated serum CRP. In this group, there were no pancreatic infections and 1 death. Six patients of this group developed pancreatic necrosis during the latter course. Thus, a total of 76 patients of this study suffered from necrotizing pancreatitis (41 in the verum group, 35 in the placebo group).

The baseline characteristics were similar for verum and placebo in both the ITT population as well as in the subgroup of patients with necrotizing pancreatitis (Table 1).

### Study Medication

Study medication was given for 3–23 days (median 14 days) after onset of symptoms in the verum group and 2–19 days (median 12 days) in the placebo group. Forty-two patients of the ITT population were switched to open antibiotic treatment (verum: 16 of 58 patients; placebo: 26 of 56 patients;  $P = 0.037$ ). Switch over was performed after a median of 11.5 days (range, 3–22 days) in the verum group and after a median of 5 days (range, 2–15 days) in the placebo group.

In patients with necrotizing pancreatitis, study medication was discontinued after 3–23 days following the onset of pancreatitis (median 14 days) in the verum group and after 2–19 days (median 9 days) in those

**Table 2.** Indications for Discontinuation of Study Medication With Subsequent Antibiotic Treatment in 114 Patients of the Intention-to-Treat Analysis

	CIP/MET 58 patients (%)	Placebo 56 patients (%)
Total switch overs	n = 16 (28)	n = 26 (46)
Reasons for switch over		
Newly developed SIRS	n = 4 (7)	n = 5 (9)
Newly developed multiple organ failure	n = 3 (5)	n = 6 (11)
Infected pancreatic necrosis	n = 5 (9)	n = 3 (5)
Extrapancreatic infection	n = 4 (7)	n = 14 (25)
Pneumonia	n = 0	n = 7 (13)
UTI	n = 0	n = 2 (4)
Sepsis of unknown origin	n = 3 (5)	n = 2 (4)
Unspecified	n = 1 (2)	n = 3 (5)
Increase in serum CRP and suspected bacterial infection	n = 5 (9)	n = 4 (7)

NOTE. In 5 patients of the CIP/MET group and 6 patients of the placebo groups, more than 1 complication was the reason for a switch over to open antibiotic treatment.

receiving placebo. In the subgroup with necrotizing pancreatitis, 35 of the 76 patients received open antibiotics: 15 of 41 patients of the verum group and 20 of 35 patients of the placebo group ( $P = 0.073$ ).

The reasons for discontinuation of study medication with subsequent open antibiotic treatment are given in Table 2. After discontinuation of study medication, 96 different antibiotic regimes were given in the placebo group and 68 regimes in the verum group. Thirty-one percent of these regimes contained a carbapenem, 13% other  $\beta$ -Lactamantibiotics, 15% Vancomycin, 10% quinolones, and 9% antifungal agents. There was a total of 4 study-drug related side effects: 1 in the verum (central-nervous reaction) and 3 (2 patients with exanthema and 1 with a central-nervous reaction) in the placebo drug.

### Bacterial Infection

A total of 39 bacterial infections were observed in 35 patients of the ITT analysis during hospital stay. All but 2 infections (1 central line infection in the verum group and 1 pneumonia in the placebo group) were found in patients with necrotizing pancreatitis.

Thirteen extrapancreatic infections were found in 13 of 58 patients (22%) of the CIP/MET group compared with 14 extrapancreatic infections in 13 of 56 patients (23%) of the placebo group. Eight central line infections and 2 pneumonia infections were observed in the antibiotic group compared with 5 central line infections and 5 pneumonia infections in the placebo group. In addition, 2 urinary tract infections were found in patients of

the placebo group. Five bacterial infections (3 CIP/MET, 2 placebo) were due to other reasons.

Among the 76 patients with necrotizing pancreatitis, 7 patients (17%) of the verum group and 5 patients (14%) of the group receiving placebo developed infection of pancreatic necrosis.

### Bacteriology

Gram-positive bacteria were predominantly found in this study, with 56% of the isolated strains in the antibiotic group and 61% in the placebo group. Gram-negative bacteria accounted for 28% of the strains in the verum group and for 33% of those in the placebo group (Table 3). In infected pancreatic necrosis, *Escherichia coli* and coagulase-negative Staphylococci were the predominant germs.

Antibiotic susceptibility testing, which was performed at the participating hospitals according to the local standards, was available for 23 bacterial strains isolated from patients receiving verum and for 28 strains isolated from patients receiving placebo. Bacterial isolates from the antibiotic group were more frequently resistant to Ciprofloxacin (18 of 23 isolates vs. 6 of 28 isolates,  $P < 0.0001$ ).

### Systemic Complications and Outcome of Acute Pancreatitis

The course of acute pancreatitis, assessed by the clinical severity score (CSS), did not differ between ciprofloxacin/metronidazole and placebo. Median CSS in the

**Table 3.** Bacterial Isolates from 114 Patients

	CIP/MET 25 strains	Placebo 36 strains
<i>Staphylococcus epidermidis</i>		
coagulase negative	10 (2)	9 (3)
Enterococci	2 (1)	4 (1)
<i>Staphylococcus aureus</i>	2 (1)	5 (1)
<i>Staphylococcus</i> spp.		2
Streptococci		2
<i>Escherichia coli</i>	3 (3)	5 (3)
Pseudomonas	1	
Enterobacter	1 (1)	
Klebsiella	2	2
<i>Proteus mirabilis</i>		1
<i>Haemophilus influenza</i>		1
<i>Lactobacillus</i> spp.		1 (1)
<i>Neisseria</i> spp.		1
<i>Moraxella catharalis</i>		1
<i>Bacillus</i> spp.	1	
Peptostreptococci	1	
<i>Candida albicans</i>	2 (1)	
<i>Candida glabrata/tropicalis</i>		1 (1)/1

NOTE. Figures in brackets indicate bacteria isolated from infected pancreatic necrosis.

**Table 4.** Complications and Hospital Course of 114 Patients With Predicted Severe Acute Pancreatitis and 76 Patients With Necrotizing Pancreatitis

	Intention-to-treat analysis, 114 patients		Necrotizing pancreatitis, 76 patients	
	Ciprofloxacin/metronidazole, 58 patients	Placebo, 56 patients	Ciprofloxacin/metronidazole, 41 patients	Placebo, 35 patients
Pulmonary insufficiency (%)	n = 26 (45)	n = 25 (45) <sup>a</sup>	n = 21 (51)	n = 21 (60)
Renal insufficiency (%)	n = 7 (12)	n = 8 (14) <sup>a</sup>	n = 7 (17)	n = 7 (20)
Shock (%)	n = 5 (9)	n = 7 (13) <sup>a</sup>	n = 5 (12)	n = 7 (20)
SIRS (%)	n = 31 (53)	n = 24 (43) <sup>a</sup>	n = 24 (59)	n = 18 (51)
Clinical Severity Score, <i>points</i> (median, minimum-maximum)	1 (0–4)	1 (0–4) <sup>a</sup>	1 (0–4)	2 (0–4)
Mortality (%)	n = 3 (5)	n = 4 (7)	n = 3 (7)	n = 4 (11)
Surgical treatment (%)	n = 10 (17)	n = 6 (11)	n = 10 (24)	n = 6 (19)
ICU stay, <i>days</i> (median, minimum-maximum)	8 (0–103)	6 (0–80) <sup>a</sup>	10 (0–103)	7 (0–80)
Hospitalization, <i>days</i> (median, minimum-maximum)	21 (7–237)	18 (3–129)	22 (10–237)	23 (3–129)
Extrapancreatic infections (%)	n = 13 (22)	n = 13 (23)	n = 12 (29)	n = 12 (34)
Infected pancreatic necrosis (%)	n = 7 (12)	n = 5 (9)	n = 7 (17)	n = 5 (14)

<sup>a</sup>Data from 55 patients.

58 patients receiving antibiotics was 1 point (0–4 points) compared with 1 point (0–4) in the 56 patients of the placebo group. The incidence of systemic complications is shown in Table 4. Nine patients underwent surgical necrosectomy for infected pancreatic necrosis.

In patients with necrotizing pancreatitis, no differences between both treatment groups were observed with regard to primary and secondary study end points (Table 4). Median CSS in patients with necrotizing pancreatitis was 1 point (0–4 points) for the CIP/MET group and 1.5 points (0–4 points) for placebo.

Outcome was also similar if data were analyzed only for the subgroup of patients with Ranson scores of 3 or more points and/or an APACHE-II score of 8 or more points: Infected necrosis were found in 5 of 40 of the placebo patients and in 7 of 40 of the verum patients. Mortality was 10% for placebo (4 of 40 patients) and 7.5% for verum (3 of 40 patients).

**Stratification According to the Extent of Necrotic Pancreatic Necrosis**

A substratification of patients according to the extent of pancreatic necrosis was done because patients

with extended pancreatic necrosis generally represent the subgroup with the most severe clinical outcome.<sup>30</sup> Information about the extent of necrotic pancreatic parenchyma was available from the contrast-enhanced CT scans in 58 patients. In 34 patients, the amount of necrosis was less than 30% of the gland’s parenchyma; in the remaining 24 patients, 30% or more of the tissue revealed necrosis. No differences between both treatment arms were noted in the subgroup of patients with necrosis exceeding more than 30% of the gland (Table 5).

**Discussion**

Antibiotic prophylaxis in severe acute pancreatitis has been a matter of discussion during the past years.<sup>7,31,32</sup> Recent clinical studies seem to support the notion that early administration of broad-spectrum antibiotics is capable of reducing the incidence of infected pancreatic necrosis.<sup>10,14,15</sup> However, none of these series was conducted in a double-blind fashion, which would provide the highest level of evidence. Therefore, the aim of our study was to evaluate the role of antibiotic prophylaxis in predicted severe acute pancreatitis in a dou-

**Table 5.** Extent of Necrotic Parenchyma on CECT Scan and Incidence of Complications

	Extent <30%, 34 patients			Extent 30% or more, 24 patients		
	CIP/MET, 20 patients (%)	Placebo, 14 patients (%)	<i>P</i> value	CIP/MET, 13 patients (%)	Placebo, 11 patients (%)	<i>P</i> value
Infected necrosis	n = 2 (10)	n = 1 (7)	0.77	n = 4 (31)	n = 3 (27)	0.85
SIRS	n = 11 (55)	n = 6 (43)	0.48	n = 6 (46)	n = 9 (82)	0.07
Shock	n = 0	n = 0		n = 1 (8)	n = 4 (36)	0.08
Pulmonary failure	n = 8 (40)	n = 6 (43)	0.86	n = 8 (62)	n = 7 (64)	0.91
Renal failure	n = 1 (5)	n = 0	0.39	n = 3 (23)	n = 3 (27)	0.81

ble-blind, placebo-controlled trial. Moreover, the number of included patients should clearly exceed the study population of former series, which ranged from 23 to 74 evaluable patients.<sup>10-13,33,34</sup>

Imipenem (Merck & Co., Inc., Whitehouse Station, NJ) is commonly recommended as a prophylactic antibiotic drug in severe acute pancreatitis<sup>7,9,35</sup> because this drug has been used in the majority of clinical trials.<sup>10,33,34</sup> We have chosen ciprofloxacin and metronidazole for antibiotic prophylaxis because both drugs show favorable pharmacokinetics in human pancreatic tissue<sup>36</sup> and have proven effectiveness in severe intraabdominal infection.<sup>37</sup> In an experimental model of necrotizing pancreatitis, the effectiveness of ciprofloxacin/metronidazole in reducing the incidence of infected pancreatic necrosis has been clearly demonstrated.<sup>38</sup>

The group of patients selected for study inclusion represents the typical cohort of patients with predicted severe acute pancreatitis. We have chosen serum C-reactive protein and evidence of pancreatic necrosis on CECT as the 2 criteria that define predicted severe acute pancreatitis for this study because they represent powerful markers for patients at risk for bacterial infection.

Following the recommendation that effective antibiotic prophylaxis in acute pancreatitis has to be initiated as early as possible,<sup>7,18</sup> patients were included at a rather early stage of this disease. Sixty-seven percent of the recruited patients developed necrotizing pancreatitis during the later course, representing the subgroup with the highest risk for developing septic complications. Despite the facts that only patients with a predicted severe attack of acute pancreatitis were included and study medication was started during the initial hours after the onset of symptoms, the study failed to demonstrate differences between both treatment groups. This appears to be surprising because our findings are contradictory to the results of most other studies investigating this topic.

We used rather stringent criteria for a switch over from study medication to open antibiotic treatment. Open antibiotics had to be given not only when patients had bacteriologically proven bacterial infection but also in cases of strong suspicion of bacterial infection or beginning of severe inflammatory response syndrome.

The difference in the switch over rates to open antibiotic treatment demonstrate the capability of ciprofloxacin/metronidazole to prevent extrapancreatic infection during application of study medication. Nevertheless, because the infections developing during placebo administration were promptly and adequately treated, this did not result in differences in outcome of our patients. Thus, the recommendation of antibiotic treatment "on demand" at

given indications may be one of the reasons for the comparatively low mortality of predicted severe acute pancreatitis and for the low incidence of infected pancreatic necrosis observed in our series, which is lower than the rate reported from most centers with expertise in necrotizing pancreatitis.<sup>2,6,39</sup>

One limitation of this study is that the sample size was not large enough to detect confidently potential beneficial effects of low magnitude or potential benefits involving infrequent secondary end points (e.g., mortality, pancreatic necrosis, shock, and renal insufficiency). Thus, even though our study was larger than each prior study on this topic, an even larger study would be needed to test conclusively whether prophylactic antibiotics prevent infrequent secondary end points like these.

Because the outcome of both treatment groups did not differ for each study end point, the data from this study support evidence that antibiotic treatment "on demand" might be as effective as antibiotic prophylaxis in our series of patients. This view is supported by recent results from Nordback et al. In their series, on-demand treatment with Imipenem led to a prompt response in a number of patients with necrotizing pancreatitis, fulfilling the criteria for surgical necrosectomy. Nine out of 14 patients with progressive severe pancreatitis resolved after initiation of antibiotic treatment.<sup>34</sup>

Criteria to initiate antibiotic treatment in patients with a predicted severe course of acute pancreatitis can be derived from our study: newly developed sepsis or SIRS, newly developed failure of 2 or more organ systems, proven pancreatic or extrapancreatic infection, and an increase in serum C-reactive protein in combination with evidence of pancreatic or extrapancreatic infection. These criteria could possibly revise the policy of general antibiotic prophylaxis as it has been advocated previously.<sup>7,35</sup>

The strategy of antibiotic treatment on demand in predicted severe acute pancreatitis has economic aspects as well. Based on the calculations for a German university hospital, expenditures for open antibiotic treatment were EURO 34,061.85 in the placebo group and EURO 34,355.75 in the verum group (1 EURO = \$1.05, at that time). A total of 712 days of study medication was given in the verum group, which, theoretically, would have resulted in additional expenditures of Euro 51,799.98 (Euro 893.10 for each patient of this group). Based on our experience from this study, these additional costs can be avoided.

In summary, this double-blind, placebo-controlled study found that prophylactic antibiotics (ciprofloxacin/metronidazole) did not significantly reduce the risk of developing infected pancreatic necrosis.

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