PAPER

A Trial of Ciprofloxacin and Metronidazole vs Gentamicin and Metronidazole for Penetrating Abdominal Trauma

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Objectives: To determine whether a combination of ciprofloxacin hydrochloride and metronidazole hydrochloride would be as effective or more effective than a combination of gentamicin sulfate and metronidazole hydrochloride for preventing infection in patients with penetrating abdominal trauma, to evaluate the factors associated with increased risk of infection, and to determine the serum peak and trough levels of gentamicin with the dosage regimen of 2.5 mg/kg every 12 hours.

Design: Randomized double-blind study.

Setting: Level I trauma center.

Patients: Eighty-four patients with penetrating intra-abdominal injuries (gunshot wound, 69; stab wound, 15) thought to require laparotomy.

Interventions: The patients were randomized during treatment in the emergency department to be given a combination of ciprofloxacin hydrochloride, 400 mg every 12 hours, and metronidazole hydrochloride, 500 mg every 6 hours, or a combination of gentamicin sulfate, 2.5 mg/kg every 12 hours, and metronidazole hydrochloride, 500 mg every 6 hours.

Results: Of 68 patients with intra-abdominal injuries who could be observed for at least 48 hours after laparotomy, posttraumatic infections developed in 12 (18%), and nosocomial infections developed in 6 (9%). The incidence of posttraumatic infections in patients who were given gentamicin and metronidazole (5/33 [15%]) was not significantly lower than the incidence in patients who were given ciprofloxacin and metronidazole (7 of 35 [20%]; $P = .75$). The presence of any infection increased the mean ± SD length of hospital stay from 8.7 ± 3.5 days to 23.3 ± 10.9 days and increased the mean ± SD hospital charges from \$24 507 ± \$9860 to \$104 920 ± \$49 083 ($P < .001$). Univariate analysis showed the factors most significantly associated with infection were as follows: (1) the use of blood transfusions ($P < .001$), (2) the penetrating abdominal trauma index of 35 or more ($P < .002$), (3) injury to the colon requiring a colostomy ($P = .004$), and (4) a trauma score of less than 12 ($P < .02$). Multivariate analysis showed the only significant factor was the receipt of blood transfusions ($F = 10.165$; $P < .005$).

Conclusions: Ciprofloxacin and gentamicin, each in combination with metronidazole, were equivalent in their ability to prevent infections after penetrating abdominal trauma; other factors, especially the receipt of blood transfusions, had much more effect on the incidence of infection. Infection greatly increases the length of hospital stay and hospital charges. The use of an increased dosing regimen of 2.5 mg/kg every 12 hours of gentamicin sulfate was effective at obtaining a therapeutic peak serum concentration.

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INFECTION IS the leading cause of morbidity and mortality in patients who survive at least 48 hours after a penetrating wound of the abdomen.[1-12] Current therapeutic approaches to reduce the incidence of infection in patients with penetrating abdominal injuries include prompt surgical intervention and empirical antibiotic therapy to prevent or minimize the growth of enteric gram-negative aerobes and anaerobes. However, the optimal antibiotics to be used and the optimal duration of therapy continue to be controversial. Although gentamicin is inexpensive and frequently is used to prevent infection by gram-negative aerobes in patients with abdominal injuries or who are undergoing surgery, it can have many adverse effects, especially with prolonged use of high doses, and obtaining optimal peak and trough levels at the usual dose of 1.5 mg/kg every 8 hours can be difficult. Ciprofloxacin, on the other hand, seems to be safer and has a spectrum of activity that adequately overlaps that of the aminoglycosides. Metronidazole is effective against enteric anaerobes, safe, and inexpensive.

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PATIENTS AND METHODS

Patients were eligible for inclusion in the study if they could give informed consent and had a penetrating abdominal injury that required surgical intervention. Patients were excluded from the study if they could not provide informed consent, were younger than 18 years, were pregnant, had a history of hypersensitivity reactions to any of the medications, or had a history of renal failure that required dialysis. The study format was approved by the Wayne State University (Detroit, Mich) Human and Animal Investigation Committee.

During their initial treatment in the emergency department, 84 patients with penetrating abdominal trauma initially thought to require an emergency laparotomy were enrolled in the study. The penetrating injuries were due to gunshot wounds in 69 patients (82%) and stab wounds in 15 patients (18%). For the 84 patients, the mean ± SD age was 30 ± 12 years, and the mean ± SD initial findings included a systolic blood pressure of 121 ± 26 mm Hg, a trauma score of 11.7 ± 0.8, a revised trauma score of 7.6 ± 0.7, and a penetrating abdominal trauma index (PATI), which quantifies the number and severity of the various abdominal organs injured, of 20 ± 14.

The patients were randomized, by the dispensing pharmacist who used a previously prepared randomization schedule, to be given a combination of ciprofloxacin hydrochloride, 400 mg every 12 hours, and metronidazole hydrochloride, 500 mg every 6 hours, or a combination of gentamicin sulfate, 2.5 mg/kg every 12 hours, and metronidazole hydrochloride, 500 mg every 6 hours. (The gentamicin-metronidazole and ciprofloxacin-metronidazole combinations are referred to as gentamicin and ciprofloxacin, respectively, in the remainder of the article.) All treatment regimens were prepared in 100 mL of isotonic sodium chloride and administered over a 60-minute period. The pharmacists dispensing the antibiotics were the only individuals who know which drug was being given. Surgery was performed within 4 hours of the initial antibiotic administration. Patients with colon injuries were treated for 96 hours, and patients with stomach or small bowel injuries were treated for 24 hours. Patients with other injuries were given only 1 dose of antibiotics. This dosing schedule was established based on the relative concentration of bacterial contamination predicated by the organ injured.

Owing to the double-blinding, all patients receiving antibiotics for more than 24 hours (colon injuries) underwent pharmacokinetic studies. Thirty minutes before the fourth dose of the antibiotic and 30 minutes after the infusion of the fourth dose was completed, blood specimens were drawn for determination of trough and peak levels, respectively. The dosages were then adjusted as needed to obtain peak levels of 10 to 15 µmol/L (5-7 µg/mL) and trough levels of less than 4 µmol/L (2 µg/mL).

Data were obtained prospectively, and differences were evaluated by analysis of variance, the Fisher exact test, and χ^2 analysis. A multivariate analysis of variance also was performed on all factors thought to be factors in the development of infection. Data are reported as mean ± SD unless otherwise noted.

The diagnosis of pneumonia was made when a new infiltrate was evident on a chest radiograph *and* a Gram stain of sputum showed numerous polymorphonuclear lymphocytes with a predominance of 1 type of bacteria *and* the core body temperature was 38.6°C or more or the white blood cell count was abnormal or showed a shift to the left. That is, the radiological and sputum findings needed to be associated with some sign of systemic infection for the diagnosis of pneumonia to be made.

Wound infections were diagnosed by the presence of cellulitis and purulent drainage. Intra-abdominal infections were defined as intra-abdominal abscesses that were drained surgically or with radiological guidance. Patients were observed throughout the hospital stay and in the outpatient clinic. All patients were evaluated at least once after discharge.

The present study was designed to determine whether a combination of ciprofloxacin and metronidazole would be as effective or more effective than a combination of gentamicin and metronidazole for preventing infection in patients with penetrating abdominal trauma, to evaluate the factors associated with increased risk of infection, and to determine the serum peak and trough levels of gentamicin with the dosage regimen of 2.5 mg/kg every 12 hours.

RESULTS

INFECTION AND MORTALITY RATES

Of the 84 patients enrolled in the study, 3 did not undergo surgery because additional studies indicated that abdominal penetration had not occurred; this was confirmed on later follow-up. Eleven patients had "negative" laparotomies in which no organ injuries were found, and 2 died of their injuries within 24 hours of the operation. Therefore, 68 patients were available for complete evaluation.

Of the 68 remaining patients who underwent a laparotomy for intra-abdominal injuries and survived at least 48 hours, infections developed in 18 (26%) while they were in the hospital; 12 patients (18%) had infections directly related to trauma (abdominal infection, 7; wound infection, 5), and 10 (15%) had nosocomial infections (pneumonia, 7; urinary tract infection, 5); 1 patient had an infection at the intravenous catheter site. Four patients had more than 1 type of infection. No infections developed during the 30 days after discharge.

Of the 18 patients in whom infections developed, multiple organ failure developed in 3 (17%), and they died. One 21-year-old man died on day 12 of pneumonia and multiple organ failure after a gunshot wound to the bladder and iliac arteries causing severe prolonged hypotension that required transfusion of 28 units of blood in the operating room. A 47-year-old man died on day 32 of multiple organ failure due to intra-abdominal infection, pneumonia, and a urinary tract infection after a gunshot wound involving the liver, diaphragm, spleen, and pancreas that required intraoperative transfusion of 19 units of blood. The third death (due to intra-abdominal infection and multiple organ failure), on day 36, was a 50-year-old man with a gunshot wound of the chest causing a hemopneumothorax and injuries to the

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Table 1. Characteristics of Patients Treated With Gentamicin or Ciprofloxacin*

Characteristic	Gentamicin (n = 33)	Ciprofloxacin (n = 35)	Total (N = 68)
Age, y	31 ± 14	29 ± 10	30 ± 12
Trauma score	11.7 ± 0.7	11.7 ± 0.7	11.7 ± 0.7
Revised trauma score	7.5 ± 0.7	7.6 ± 0.5	7.5 ± 0.6
Injury severity score	15 ± 7	15 ± 7	15 ± 7
Systolic blood pressure, mm Hg	119 ± 26	122 ± 31	121 ± 28
Penetrating abdominal trauma index	22 ± 14	23 ± 11	23 ± 12
No. of organs injured	2.4 ± 1.1	2.2 ± 0.9	2.3 ± 1.0
No. (%) of patients requiring blood transfusions	13 (39)	12 (34)	25 (37)
Operating room time, min	185 ± 58	181 ± 84	183 ± 70
Units of blood given	3.7 ± 5.6	3.3 ± 4.2	3.5 ± 4.9
Infection rate, %	30	23	26
Length of hospital stay, d†	12 ± 9	12 ± 8	12 ± 8
Mortality rate, %	6	3	4

*Gentamicin sulfate and ciprofloxacin hydrochloride each were given in combination with metronidazole hydrochloride. Data are given as mean ± SD unless otherwise noted.

†Given only for those who survived for at least 48 hours.

colon, small bowel, spleen, and mesentery. Thus, the mortality rate for nosocomial pneumonia was 28% (2 of 7 patients), and for intra-abdominal infection, it was 14% (1 of 7).

INFECTING MICROORGANISMS

The cultures from the infections produced 16 aerobic gram-positive cocci (*Staphylococcus epidermidis,* 7; *Enterococcus* species, 5; and *Streptococcus* species, 4). The 10 aerobic gram-negative bacilli cultured included the following: *Acinetobacter* species, 4; *Escherichia coli,* 2; *Klebsiella* species and *Proteus* species, 2; *Enterobacter* species, 1; and *Pseudomonas* species, 1. *Candida* organisms were recovered from 6 infections, but only 1 anaerobic genus (*Bacteroides*) was found.

Because the organisms obtained from the various infections were so variable, no patterns were discernible except for 4 *Candida* species found in 6 abdominal infections. The sputum specimens for patients with pneumonia produced 6 additional gram-negative aerobes, 2 organisms considered normal flora, and 1 *Candida* species.

GENTAMICIN VS CIPROFLOXACIN

Demographics

Of the 68 patients with abdominal injuries who survived at least 48 hours, 33 were given gentamicin, and 35 were given ciprofloxacin. The demographics for these 2 groups were similar (**Table 1**).

Incidence of Infection

The incidence of infection (posttraumatic and nosocomial) was almost the same for the patients who were given gentamicin as for the patients who were given ciprofloxacin. There was no difference in the incidence of trauma or nosocomial infections between the gentamicin- and ciprofloxacin-treated patients, but there was a tendency for a higher incidence of pneumonia in the gentamicin-treated patients (**Table 2**).

Table 2. Types of Infections in Patients Treated With Gentamicin or Ciprofloxacin*

Type of Infection	Gentamicin (n = 33)	Ciprofloxacin (n = 35)	Total (N = 68)	*P*
Posttraumatic	5 (15)	7 (20)	**12** (18)	.75
Wound	2 (6)	3 (8)	5 (7)	. . .
Abdominal	3 (9)	4 (11)	7 (10)	. . .
Nosocomial	7 (21)	3 (8)	**10** (15)	.18
Pneumonia	6 (18)	1 (3)	7 (10)	.05
Urinary tract	3 (9)	2 (6)	5 (7)	. . .
Phlebitis	. . .	1 (3)	1 (2)	. . .
Total†	10 (30)	8 (23)	**18** (26)	.59

*Gentamicin sulfate and ciprofloxacin hydrochloride each were given in combination with metronidazole hydrochloride. Data are given as number (percentage). Ellipses indicate not applicable.

†Two gentamicin-treated patients and 2 ciprofloxacin-treated patients had posttraumatic and nosocomial infections.

Table 3. Number of Microorganisms Present in Patients With Infections*

	Gentamicin	Ciprofloxacin	Total
Gram-positive cocci	7	9	**16**
Staphylococcus epidermidis	2	5	7
Enterococcus species	2	3	5
Streptococcus species	3	1	4
Gram-negative aerobes	3	7	**10**
Acinetobacter species	0	4	4
Escherichia coli	1	1	2
Klebsiella species and *Proteus* species	2	0	2
Enterobacter species	0	1	1
Pseudomonas species	0	1	1
Candida species	0	6	**6**
Bacteroides species	0	1	**1**
Total	**10**	**23**	**33**

*Gentamicin sulfate and ciprofloxacin hydrochloride each were given in combination with metronidazole hydrochloride.

Organisms Recovered

The types of organisms recovered from the patients with infections were extremely variable. More organisms overall were obtained from patients treated with ciprofloxacin than from patients treated with gentamicin (**Table 3**). The incidence of gram-positive cocci was similar in both groups; however, the incidence of gram-negative aerobes and *Candida* species, tended to be higher for ciprofloxacin-treated patients than for gentamicin-treated patients. The only organisms seen more frequently in gentamicin-treated patients were *Streptococcus* species and *Klebsiella* and *Proteus* species. Many of the organisms found in the ciprofloxacin-treated patients tended to be antibiotic-resistant species (*Candida* species, 6; *Acinetobacter* species, 4; *Enterococcus* species, 3; and *Pseudomonas* species, 1).

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Table 4. Factors Associated With Risk of Infection*

	Patients With Infection (n = 18)	Patients Without Infection (n = 50)	F	*P*
Units of blood given	10.1 ± 9.8	1.1 ± 3.0	34.120	<.001
Penetrating abdominal trauma index	31.8 ± 11.9	19.4 ± 12.0	14.198	<.001
Trauma score	11.1 ± 1.5	11.9 ± 0.4	12.130	<.001
Operating room time, min	225 ± 76	166 ± 67	9.56	.003
Injury severity score	18.9 ± 8.7	13.5 ± 6.3	7.88	.007
Revised trauma score	7.1 ± 1.5	7.7 ± 0.3	7.37	.008
No. of organs injured	2.83 ± 1.15	2.09 ± 0.95	7.17	.009
Initial systolic blood pressure†	107 ± 30	126 ± 27	6.18	.02
Age	32.1 ± 14.1	30.3 ± 10.6	0.32	.57
Length of hospital stay‡	23.3 ± 10.9	8.7 ± 3.5	71.07	<.001

*Data are given as mean ± SD.
†Initial reading on admission to the emergency department.
‡For patients who survived throughout hospitalization.

Pharmacokinetic Studies

It is generally believed that to be most effective and safe, the peak serum level for gentamicin should be at least 10 µmol/L (5 µg/mL), and the trough level should be less than 4 µmol/L (<2 µg/mL). The pharmacokinetic studies performed after the fourth dose of gentamicin (which was given at 2.5 mg/kg every 12 hours) revealed a peak level of 16.8 ± 5.5 µmol/L (8.0 ± 2.6 µg/mL) and a trough level of 1.3 ± 1.0 µmol/L (0.6 ± 0.5 µg/mL). The volume of distribution was 0.35 ± 0.11 L/kg (normal, 0.24 ± 0.08 L/kg). The dose of gentamicin had to be adjusted for only 2 of the patients to obtain a peak level of at least 10 µmol/L (5 µg/mL).

FACTORS ASSOCIATED WITH AN INCREASED RISK OF INFECTION

The biggest differences between the 18 patients with infections and the 50 patients without infections were the average number of units of blood transfused (**Table 4**) and the incidence of blood transfusions (83% [15 of 18 patients] vs 20% [10 of 50 patients]) (*P*<.001). Other major differences between the patients with infections and the patients without infections included the PATI, the trauma score, operating room (OR) time, and the injury severity score (ISS).

Blood Transfusions

The receipt of any blood transfusion during the first 24 hours after admission to the hospital was associated with a significant increase in the infection rate (15 of 25 patients [60%] vs 3 of 43 [7%], *P*<.001). Even with only 1 to 4 units of blood, the infection rate was 45% (5 of 11 patients). The infection rate was particularly high in the patients who received massive transfusions (10 or more units of blood during the first 24 hours after admission to the hospital; **Table 5**). Multivariate analysis of variance showed that this was the only factor that significantly correlated with an increased incidence of infection (F = 10.165, *P*<.001).

Table 5. Association of Blood Transfusions and PATI With Incidence of Infection*

	No Infection	Infection	Total	Infection Rate, %
Units of blood given†				
0	40	3	**43**	7
1-4	6	5	**11**	45
5-9	3	3	**6**	50
≥10	1	7	**8**	88
PATI‡				
1-19	27	1	**28**	4
20-34	18	11	**29**	38
≥35	5	6	**11**	54

*PATI indicates penetrating abdominal trauma index.
†χ^2 = 27.448, P<.001.
‡χ^2 = 13.955, P<.001.

Penetrating Abdominal Trauma Index

An elevated PATI of 19 or less was associated with an infection rate of only 4% (1 of 28 patients). However, a PATI of 35 or more was associated with an infection rate of 54% (6 of 11, *P* = .001) (Table 5).

Trauma Score

The 56 patients with a normal trauma score and a normal revised trauma score had an infection rate of 20% (11 of 56 patients). In contrast, any physiological abnormality causing the trauma score or revised trauma score to be abnormal increased the infection rate to 58% (7 of 12 patients, *P* = .011).

OR Time

As the OR time increased from less than 2 hours, to 2 to 4 hours, and to 4 hours or more, the infection rate rose from 8% (1 of 13 patients) to 22% (9 of 41) to 57% (8 of 14), respectively. A longer OR time, especially if more than 4 hours, also was associated with increases of the ISS, PATI, number of blood transfusions, infection rate, and length of hospital stay (LOS). As might be expected, the PATI was particularly apt to be higher in the patients with an OR time exceeding 4 hours (vs an OR time <2 hours; 33 ± 11 vs 11 ± 9, *P*<.001).

Organs Injured

The incidence of infection tended to rise with the number and type of organs injured (**Table 6**). The infection rate in patients with only 1 injured organ (2 of 16 patients [12%]) tended to be lower than in those with 2 injured organs (6 of 28 [21%]) and than in those with 3 or more injured organs (10 of 24 [42%], *P* = .09).

Of the organ injuries associated with infection, the most prominent were colon injuries requiring a colostomy, and of 12 patients with such injuries, infections

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Table 6. Infection Rates and Organs Injured*

Organ Injured	Gentamicin	Ciprofloxacin	Total
Colon, colostomy performed	2/2 (100)	7/10 (70)	**9/12** (75)
Pancreas	2/4 (50)	1/2 (50)	**3/6** (50)
Bladder	1/3 (33)	1/1 (100)	**2/4** (50)
Major vessel	2/2 (100)	2/7 (28)	**4/9** (44)
Stomach	4/9 (44)	2/5 (40)	**6/14** (43)
Mesentery	1/2 (50)	1/3 (33)	**2/5** (40)
Kidney	1/2 (50)	1/3 (33)	**2/5** (40)
Lung (HPTX)	2/3 (67)	0/3 (0)	**2/6** (33)
Small bowel	4/13 (31)	4/13 (31)	**8/26** (31)
Spleen	3/5 (60)	0/6 (0)	**3/11** (27)
Diaphragm	2/8 (25)	0/5 (0)	**2/13** (15)
Liver	1/9 (11)	1/5 (20)	**2/14** (14)
Colon, no colostomy performed	1/10 (10)	0/8 (0)	**1/18** (6)
Rectum, colostomy performed	0/3 (0)	0/1 (0)	**0/4** (0)

*Gentamicin sulfate and ciprofloxacin hydrochloride each were given in combination with metronidazole hydrochloride. Data are given as number of patients with infection/number of patients with the injury (percentage). HPTX indicates hemopneumothorax.

developed in 9 (75%). In contrast, of 18 patients with colon injuries not requiring a colostomy, an infection developed in only 1 (6%), and of 4 patients with rectal injuries (all underwent colostomy), no infections developed. We could discern no relevant pattern to the combinations of organs injured, other than the greater the number injured, the higher the risk of infection.

Length of Hospital Stay

The LOS for the 68 patients who had intra-abdominal injuries was 12.4 ± 8.3 days. The major cause of a prolonged LOS was the presence of an infection. The 18 patients with infections (vs the 50 without infections) had an LOS of 23.3 ± 10.9 days (vs 8.7 ± 3.5 days, $P<.001$). When correlation coefficients were calculated for the LOS vs all the other factors studied, the most significant correlations were the presence of an infection ($r = 0.76$), the use of blood transfusions ($r = 0.67$), the trauma score ($r = 0.50$), and the PATI ($r = 0.47$). Even the receipt of only 1 to 4 units of blood increased the LOS to 13.6 ± 9.3 (vs 9.2 ± 2.9 in those not receiving blood, $P = .01$). Multivariate analysis showed that the only significant factors correlating with the LOS were the presence of infection ($F = 25.67$; $P<.001$) and use of blood ($F = 9.01$; $P = .0039$).

Hospital Charges

The hospital charges for the 68 patients with abdominal injuries surviving at least 48 hours were $45 793 ± $6507. For the 18 patients in whom infections developed, the charges were $104 920 ± $49 083, and for the 50 without infections, the charges were $24 507 ± $9860 ($P<.001$). The charge per day also was higher in the patients with infections ($4503 ± $1728 vs $2817 ± $591) ($P<.001$). A wound infection increased hospital charges to $71 673 ± $10 138, while an intra-abdominal infection increased hospital charges to $120 519 ± $34 990.

COMMENT

POSTTRAUMATIC INFECTION RATES

A number of randomized double-blind studies have been performed to determine whether selected antibiotics are more effective for reducing the incidence of infection in patients with penetrating wounds of the abdomen.[1-12] In these studies, the incidence of posttraumatic infections involving the abdominal cavity or abdominal wall has ranged from 7.0%[9] to 20.6%.[2,7]

In 3 articles describing patients having only colon or small bowel injuries,[8,10,12] the cumulative posttraumatic infection rate was 16.8% (56 of 334 patients). In 9 articles that included all intra-abdominal injuries (colon, small bowel, and other), the cumulative posttraumatic infection rate was 13.8% (224 of 1618).[1-7,9,11] In the present study, the posttraumatic infection rate was 18% (12 of 68), and for injuries involving the colon or small bowel, the infection rate was 22% (11 of 51). For other injuries, the posttraumatic infection rate was 6% (1 of 17). In the present study, the higher posttraumatic infection rate associated with colon and small bowel injuries may be related to the relatively large number of colostomies performed (12 of 30 patients [40%]) owing to the colon injuries.

NOSOCOMIAL INFECTION RATES

Although many reports have not included nosocomial infections in their statistics, such infections can have profound effects on outcome. Indeed, in 2 of the 3 deaths after 48 hours of hospitalization in the present study, nosocomial pneumonia was an important factor. Of the 6 patients who had only nosocomial infections, 1 patient died, and the mean LOS in the 5 survivors was 22 ± 10 days. The hospital charges for these 5 patients averaged $105 000 each, which is almost $80 000 more per hospitalization than the charges for the patients without infections.

MORTALITY RATES

Overall, 5 (7%) of 70 patients with proved intra-abdominal injuries in the present study died. Two died of massive injuries with prolonged shock within 24 hours of admission to the hospital and were excluded from the study, and 3 died later (on days 12, 32, and 36) of sepsis with multiple organ failure related to severe intra-abdominal infections, pneumonia, or both. The injuries in the 3 patients who died later were considered severe (mean ISS, 21; mean PATI, 33), and the number of units of blood given during the first 24 hours to the 5 patients who died was 25 ± 16; no errors in management were found on review of the medical records.

Relatively few studies included the mortality rates in published reports. The overall mortality rate in the present study for patients with proved abdominal injuries (5 of 70 patients [7%]) is comparable to that in other series, such as the series of Sims et al[4] (6.1%); however, 41% of the patients in that series had stab wounds, and the mor-

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tality rate with stab wounds usually is low; in the present study, none of the 12 patients with stab wounds died.

GENTAMICIN VS CIPROFLOXACIN

Incidence of Infection

The combined incidence of posttraumatic infections and nosocomial infections in the patients treated with gentamicin (30%) was not significantly higher than the incidence in patients treated with ciprofloxacin (23%). In addition, the demographics and organ injuries for the 2 groups were almost identical.

Infecting Microorganisms

The microorganisms found in the present study were so extremely varied that it was difficult to draw any conclusions about them. There were, however, 4 peritoneal cultures of *Candida* species from patients with abdominal infections. In addition, for 6 of 8 cases of pneumonia, the cultures showed gram-negative bacilli, and no specific gram-positive organisms, except normal flora, were found in sputum. Interestingly, there were more organisms per infection in ciprofloxacin-treated patients than in gentamicin-treated patients (2.08 ± 0.64 vs 1.00 ± 0.47, $P < .001$).

Pharmacokinetic Studies

In almost all previous studies of gentamicin sulfate, the dosage used has been 1.5 mg/kg every 8 hours (sometimes associated with an initial dose of 2 mg/kg), and in such studies, it has been difficult to obtain the peak levels of 13 to 17 µmol/L that generally are considered to be effective. Fabian et al[1] noted that gentamicin sulfate in dosages of 2 mg/kg initially and then 1.5 mg/kg every 8 hours resulted in 48% of the patients having peak levels less than 13 µmol/L. Indeed, 6 of the 7 therapeutic failures (intra-abdominal infection, wound infection, or necrotizing fasciitis) in their study occurred in patients treated with a combination of gentamicin and clindamycin, and subtherapeutic levels of gentamicin were found in 3 of the 6 patients who experienced therapeutic failure. Reed et al[13] noted similar problems, especially a decrease in therapeutic half-lives with amikacin in the patients they studied. In light of this, we dosed the gentamicin sulfate for the present study at 2.5 mg/kg every 12 hours.

Based on the pharmacokinetic studies performed in the present study, the peak levels that would have been obtained if the gentamicin sulfate had been given at 1.5 mg/kg every 8 hours would have been only 9 µmol/L. The peak levels obtained in the present study were therapeutic (16.8 ± 5.5 µmol/L) with the regimen of 2.5 mg/kg every 12 hours.

Since severely injured patients tend to have higher volumes of distribution for most drugs, they also would tend to have the lowest blood levels, further reducing the likelihood that gentamicin sulfate in doses of 1.5 mg/kg every 8 hours would be effective. It also would seem prudent to readminister the antibiotics to patients who have experienced major blood loss, once the bleeding has been controlled. Indeed, virtually all of the studies in which gentamicin sulfate or tobramycin sulfate have been used in doses of 1.5 mg/kg every 8 hours should probably be viewed with some skepticism.

FACTORS INCREASING THE RISK OF INFECTION

Few studies have reviewed all of the factors thought to increase the risk of infection in abdominal trauma. In the study by Nichols et al,[14] the use of blood or blood products was not as important as a critical condition on admission to the hospital, an operation lasting more than 4 hours, 3 or more injured organs, colon injury, or an age of 45 years or older. When correlation coefficients were determined for all of the factors that might be associated with infection in patients in the present study, the highest correlations were seen with the use of blood transfusions ($r = 0.58$) and the PATI ($r = 0.43$).

Blood Transfusions

It is generally assumed that there is an increased risk of infection after allogeneic blood transfusions,[15,16] particularly massive transfusions.[17,18] It has been shown that allogeneic blood transfusions cause immunosuppression by increasing numbers of suppressor T cells and by altering cytokine production and the function of monocytes and natural killer cells.[19] There also is an obvious association between the need for blood transfusions and shock. However, the incidence of infection in patients with an initial systolic blood pressure of 90 mm Hg or more was 7% (3 of 42 patients) if no blood was transfused and 62% (10 of 16) if blood was transfused. For an initial systolic blood pressure of less than 90 mm Hg, no infection occurred in the 1 patient who received no transfusions, but the infection rate was 56% (5 of 9) in the patients who received blood transfusions. Multivariate analysis showed the need for blood transfusion was the only significant factor predicting infections in the present study.

Penetrating Abdominal Trauma Index

In an attempt to better quantify injuries and the risk of complications after abdominal trauma, Moore et al[20] described the PATI in 1981. In calculating the PATI, each abdominal organ is given a risk factor of 1 to 5, and the severity of each organ injury also is graded on a scale of 1 to 5. Thus, the PATI for each abdominal organ injury may range from 1 to 25, but if multiple organs are injured, the PATI may be much higher.

Croce et al,[21] in a review of 592 patients with penetrating trauma, found that as the PATI rose from 1 to 10, to 11 to 15, to 16 to 25, and 26 or more, the incidence of abdominal septic complications rose from 2% to 4% to 7% to 27%, respectively. Thus, a PATI of 26 or more was a strong predictor of infection. In the present study, a PATI of 20 or more was associated with a total infection rate of 42% (17 of 40 patients) vs 4% (1 of 28) in patients with a lower PATI, and the abdominal infection rate was 18% (7 of 40). All 7 of the patients in the present study with intra-abdominal infections had a PATI of 26 or more.

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OR Time

Nichols et al[14] noted that as the OR time increased from less than 2 hours, to 2 to 4 hours, to 4 or more hours, the total infection rate rose from 12% to 33% to 38%, respectively. In the present study, the total infection rate for the same OR durations was 8% (1 of 13 patients), 22% (9 of 41) and 57% (8 of 14). However, many factors affect the OR time, particularly the number of organs injured and the severity of the injuries, and this would be reflected in the PATI and ISS.

Organs Injured

Nichols et al[14] noted that as the number of organs injured increased from 1 to 3 or more, the infection rate also increased from 20% to 46%. In the present study, the total infection rate also rose as the number of organs injured increased: 12% (2 of 16 patients), 21% (6 of 28), and 42% (10 of 24), respectively for 1, 2, and 3 or more organs injured.

Fabian et al[1] found that posttraumatic infection rates with bowel injuries were 24% (4 of 17 patients) for colon injuries, 18% (2 of 11) for stomach injuries, and 6% (2 of 35) for small bowel injuries. In the present study, the incidence of abdominal infections was 33% (2 of 6 patients) for pancreatic injuries, 21% (3 of 14) for stomach injuries, 15% (4 of 26) for small bowel injuries, and 13% (4 of 30) for colon injuries. If the colon injuries were divided according to their severity, the abdominal infection rate was 33% (4 of 12) in those having a colostomy and 0% (0 of 18) in those who underwent primary repair of colon injuries.

Length of Hospital Stay

The LOS is not mentioned in many reports of penetrating abdominal trauma. Nichols et al,[14] however, reported a mean LOS of 13.9 days compared with the overall LOS of 12.4 days in the present study; the LOS was 8.7 ± 3.5 days for the 50 patients without infections and 23.3 ± 10.9 days for the 18 patients with infections.

Hospital Charges

There is virtually no information in the literature about the cost of infections after trauma. It is clear, however, that any factor, especially infection, that increases LOS greatly increases the cost of medical care. Not only did infection increase the LOS, but it also increased the cost per day by about 60%. In the present study, the development of an infection, on the average, increased hospital charges more than 4-fold. It also should be emphasized that the hospital charges given in the present article do not include charges for professional care.

CONCLUSION

The incidence of infection (18% posttraumatic and 9% nosocomial) after penetrating abdominal trauma was almost identical in the patients receiving gentamicin or ciprofloxacin. Gentamicin in dosages of 2.5 mg/kg every 12 hours produced much better peak levels than would have been expected with previously reported doses of 1.5 mg/kg every 8 hours. The most significant factor associated with an increased risk of infection was the use of blood transfusions. The presence of infection increased the LOS almost 3-fold (23.3 vs 8.7 days) and increased hospital charges more than 4-fold ($104,920 for patients with an infection vs $24,507 for patients with no infection).

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DISCUSSION

John M. Davis, MD, Neptune, NJ: I would like to compliment the authors on a thoughtful and thought-provoking study. I appreciate their submitting the manuscript to me in advance of the meeting. The study shows a number of risk factors contributing to posttraumatic infection as part of a double-blinded prospective randomized trial. These factors include number of transfusions, OR time, shock, the number of organs injured, and a number of different injury severity scores. I would like to ask the authors a number of questions. First of all, I consider cefoxitin, or single-agent therapy, as the standard, and I think a lot of trauma surgeons around the country do, so I wonder if you could comment on the cost of combination therapy vs single-agent therapy in management of trauma patients.

The second issue is that there are a number of recent studies, Patch probably publishing the first, and Fabian and Kudsk, a more recent study, advocating a single-day, 24-hour antibiotic coverage vs prolonged therapy, even for colon injuries, and showing no significant difference with a shorter course of therapy. And so I would like to ask the authors to justify their prolonged use, and as a tail to that question, to perhaps comment on infections that they saw in the colon-injured patients, what kind of organisms they saw, resistance patterns, and so on, with prolonged antibiotic use.

The study compared ciprofloxacin with gentamicin, and I know there are a number of reasons why I don't like using gentamicin. The pharmacodynamics and pharmacokinetic studies are costly. There is the risk of toxicity; recently I saw in the *JAMA* a description of vestibular toxic effects. So could you comment on the risk of aminoglycoside use in these patients?

Finally, I for a long time viewed with interest the studies documenting the risk of infection associated with large blood transfusions, but I have never known how to use that information. In mortally injured trauma patients, you have got to give them blood. I wonder if you could comment on how you recommend us to interpret it. Is this a marker, do you watch these patients more closely, or how do you use that information?

Finally, I would like to thank the Society for the opportunity of reviewing this paper.

Dr Tyburski: I would agree with you that a lot of us use single-agent therapy. This study was designed, I think, and again, to quote President Dellinger, there were 2 aspects of the study. The people who produced the drug were trying to get an indication for ciprofloxacin, I think, and we were trying to look at gentamicin dosing and see what other factors would associate with infection.

I would agree a lot of us do use single-agent therapy. I am going to skip down to your third question, the use of gentamicin. If you remember the data presented just a day ago gave a nephrotoxicity rate with gentamicin of 12% to 14%. The average age in that study, if I recall, was around 60 or 62 years of age. The average age here was 30 years. I think in this trauma population the use of gentamicin is exceedingly safe. We know of very little nephrotoxicity in this population. There were 3 mortalities that were over 24 hours; 2 of them did get gentamicin. One who died at 12 days had some renal [problems] throughout that you could maybe extrapolate to the use of gentamicin. The other 2 died long after their gentamicin dosings were over; they died of late sepsis 30 days out. So we didn't see this nephrotoxicity in this population. This is very high GFR, high volume of distribution, basically street-warrior type of a population we are seeing.

I am glad you brought up the length of coverage. Within our own group there is a large debate over how long people should keep people on antibiotics. It seems to be age-specific, not to the patient, actually the prescriber is what I was just referring to. And it seems the people who have been on the service longer like to put patients on longer doses of antibiotics. This is how this protocol was set up. However, it is routine now in our group not to try to allow antibiotics to go longer than 24 to 48 hours at the most in these trauma patients. We did try to stratify that a little bit. If there was no hollow organ injury, we tried to give them only 1 dose.

A comment on the use of transfusion, we agree, there is not a lot you can do. Stop the bleeding, I guess, is my best advice. We do watch them more closely. We have looked at end-tidal CO_2 use in these patients, we have looked at the transfusions, we have looked at their pulmonary vascular resistance, and we do alert ourselves to a higher incidence of infections and mortalities with those patients.

Dietmar H. Wittmann, MD, PhD, Milwaukee, Wis: I have 2 points to make. You did pharmacokinetics on aminoglycosides. My question is why didn't you do it on ciprofloxacin and metronidazole also? If you would have done it on metronidazole, for example, you would have found that metronidazole has an elimination half-life of about 8 hours, which would enable you to give the drug every 24 hours, just like ceftriaxone, for example.

The second point is, you were using antimicrobials in trauma patients. Trauma implies tissue injury, tissue injury implies acidotics as an environment, and aminoglycosides don't work well in an acid environment. Maybe in that group for the aminoglycosides you didn't need any of the aminoglycosides at all.

Dr Tyburski: It is true, Dr Wittmann, we did not look at the levels of either ciprofloxacin or metronidazole. The previous work that had been done that we were part of did look at some of the levels of metronidazole. We didn't find that a significant contribution. Some people have even suggested that the dosage of ciprofloxacin we used was a little bit high. Those are data that are not presented here. We were looking specifically at gentamicin. And as we well know, it is expensive to get levels on these drugs. I think those data would have been valuable additions to the paper, and I think it would have reinforced the increased volume of distribution and increased renal clearance of these drugs in these young trauma populations.

We didn't show the acid-base data here, but hopefully the patients, at least systemically, weren't underresuscitated. Again, we tried to use many markers of that and tried to get them out of an acid environment. But I do think, and I will state again that I do think that the gentamicin in this population, it is a cheap drug, and it seems to be relatively safe, at least in this young, rather healthy, hyperdynamic population.

Charles H. Cook, MD, Columbus, Ohio: I was intrigued by the incidence of *Candida* infection in the ciprofloxacin treatment group. I wondered if you did a Fisher exact or χ^2 to determine whether it was statistically different from the gentamicin treatment group, and if so, or not, how you might explain that finding.

Dr Tyburski: We did look at the statistical significance of that, and it was just barely missed. It was a P value of .09 or something like that. I am not sure what to make of that. In other words, it is a little bit unusual. Most of those patients had perforation of the abdominal viscera, and perhaps with these high-dose antibiotics we did select out, fungus; maybe ciprofloxacin was better at selecting out fungus, but it is pure speculation. The numbers were too small to make any real conclusions on any of the data. We were looking to see if because ciprofloxacin has better gram-positive coverage than gentamicin that we would have had more gram-positive infections with the gentamicin. That wasn't true. Except for that 1 point that was not statistically significant, there was very little I could make out of the microbiological data.

E. Patchen Dellinger, MD, Seattle, Wash: Could I just comment that if you could get your superannuated surgeons to feel confident, a single dose of gentamicin, 7 mg/kg or maybe just 500 mg across the board and a single dose of 1 g of metronidazole would take care of all of your patients very cheaply, very effectively, and very safely.

Dr Tyburski: Our common clinical practice now is to give a single 7 mg/kg dose of gentamicin. We had a hard time getting this through the IRB because it was quite a change at the time in the dosing, but we do routinely use single-dosing antibiotics now.

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