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Sequential Intravenous-Oral Administration of Ciprofloxacin vs Ceftazidime in Serious Bacterial Respiratory Tract Infections*

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The efficacy and safety of sequential intravenous/oral ciprofloxacin in moderate to severe respiratory tract infections (RTI) were compared with those of ceftazidime in a prospective clinical trial. Sixty-six patients received IV ciprofloxacin (200 to 300 mg twice daily), followed by oral ciprofloxacin (500 mg twice daily). Fifty-six patients received intravenous ceftazidime (1 to 2 g two to three times daily). Ciprofloxacin was as effective as ceftazidime and produced a 91 percent clinical cure rate. Significantly more pretreatment bacterial isolates were susceptible to ciprofloxacin, and ciprofloxacin had a significantly higher rate of sputum bacterial eradication than did ceftazidime. Ciprofloxacin showed broad *in vitro* antibacterial activity with particularly low minimal inhibitory concentrations for Gram-negative organisms. Ciprofloxacin was well tolerated; there were few adverse effects. Ciprofloxacin was an effective and well-tolerated treatment for severe RTI that had the advantages of broad *in vitro* antibacterial activity, twice-daily dosing, and sequential availability in an intravenous and oral formulation. *(Chest 1989; 96:528-37)*

RTI = respiratory tract infections; MIC = minimal inhibitory concentration

The recent introduction of potent 4-quinolones represents a major advance in the development of antibiotics, allowing for the first time effective oral therapy of serious infections caused by multiply resistant bacteria.

Four fluoroquinolones, as follow, are in various stages of approval and clinical investigation in the United States: norfloxacin, ciprofloxacin, enoxacin, and ofloxacin.[1] Of the compounds currently available under investigation, ciprofloxacin is among the most attractive in terms of its potency, rapidity of bacterial killing

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and pharmacokinetics. *In vitro* studies have shown that ciprofloxacin is active against Gram-positive, Gram-negative, and multi-drug-resistant bacteria, as well as organisms such as Chlamydia, Mycobacteria, and Legionella.[2-5] We have previously reported on the results of a prospective, double-blind, clinical trial to assess the safety and efficacy of oral ciprofloxacin in comparison with those of ampicillin in the treatment of mild to moderate respiratory tract infections.[6] In this study, we report our results with the comparison of sequential intravenous/oral ciprofloxacin with intravenous ceftazidime in the treatment of hospitalized patients with lower respiratory tract infections.

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Patients and Methods

Patients hospitalized at Nassau County Medical Center between January 1987 and June 1988 for community-acquired, nursing-home-acquired, hospital-acquired (more than 72 hours of hospitalization) bacterial respiratory tract infections were enrolled in the study. Bacterial lower respiratory tract infection was defined as presumed if patients had compatible clinical features which included fever over 37.2°C, total white blood cell count over 10,000/cu mm, and productive cough with purulent sputum, or proven if patients had, in addition, a positive sputum culture from a sputum which on Gram stain had less than 25 squamous epithelial cells and 25 or more neutrophils per low-power field. All these patients were considered to be suitable for intravenous antimicrobial treatment. Eleven of the 140 patients had normal chest roentgenogram; the remaining 129 patients had roentgenographic findings ranging from bronchopneumonia to multilobar pneumonia. All patients gave written informed consent. Those patients who had compatible clinical features (fever, cough, abnormal x-ray findings) and an unsatisfactory sputum Gram stain result were included in the presumed group. Patients were excluded if they were under 18 years of age, pregnant, serum creatinine value was more than 2 mg/dl, allergic to quinolones, and if their condition was hemodynamically unstable or they had psychiatric disease.

Antibiotic Administration

Antibiotics were administered in a sequential manner with a computer-generated, randomized code. One group received intravenous ciprofloxacin, 200 mg twice a day, except for five patients who received 300 mg twice a day; and the control group received ceftazidime, 1 to 2 g two to three times a day intravenously. A minimum of five days of therapy was required for evaluation. No patient received other antibiotics concomitantly. Ceftazidime was chosen as the control drug because its *in vitro* spectrum closely matched that of ciprofloxacin. In addition, it was the most commonly prescribed parenteral antimicrobial agent for the treatment of both community-acquired and hospital-acquired lower respiratory tract infections.

Clinical Monitoring

Laboratory tests, including liver and renal function tests and complete blood cell count, were performed before and after therapy.

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Pre-enrollment and follow-up chest x-ray films were done on all patients. Serum theophylline levels were monitored in 21 patients receiving that drug. All patients were monitored daily for adverse drug reaction; and a daily record of the physical examination and of fever, cough, and sputum production was maintained.

Microbiologic Methods

Spontaneously expectorated sputum or sputum obtained by tracheal-bronchial suction was obtained from all patients. Gram stain smears were performed on all expectorated sputum specimens. Only specimens containing less than 25 squamous epithelial cells and 25 or more neutrophils per low-power field were accepted for culture analysis.[7,8]

Specimens were inoculated onto trypticase soy agar supplemented with 5 percent sheep blood, chocolate agar, and MacConkey agar and incubated at 35°C in 5 percent carbon dioxide for 18 to 24 hours. Isolates were identified by previously described methods.[9,10] Disk diffusion susceptibility testing for ceftazidime was performed on all isolates, using the Kirby-Bauer technique.[11] Standard interpretive zone criteria for ceftazidime were used.[12] Interpretive zone size criteria for ciprofloxacin were resistant 15 mm or less, intermediate, 16 to 20 mm, and susceptible, 21 mm or more.

Minimal inhibitory concentrations (MICs) of antibiotics were determined by the agar dilution technique as outlined by the National Committee for Clinical Laboratory Standards, and with the use of twofold dilutions of the antibiotics.[13] Plates were inoculated with a multipoint replicator designed to deliver a 1 μl inoculum containing approximately 10^4 organisms. The plates were read at 24 and 48 hours. A control plate without antibiotics was inoculated before and after each antibiotic series, and appropriate quality control bacteria were included in each series of antibiotic plates. The MIC value was defined as the lowest concentration of antibiotic at which there was no evidence of visible growth. Ciprofloxacin was supplied as a laboratory standard powder. The tentative MIC breakpoints for systemic therapy with ciprofloxacin were 1.0 μg/ml or less for susceptible isolates and more than 2.0 μg/ml for resistant isolates. Strains for which MIC values were more than 1.0 μg/ml but less than or equal to 2.0 μg/ml were considered intermediate in susceptibility. The MIC breakpoints and interpretive criteria as detailed by the National Committee on Clinical Laboratory Standards were used to categorize the susceptibility of isolates to ceftazidime.[13]

Evaluation of Antibiotic Therapy

A clinical cure was defined as the disappearance of previously documented signs and symptoms of infection. Clinical failure was defined as the continuation of signs and symptoms of infection or

Table 1—In Vitro *Bacterial Testing—Ciprofloxacin and Ceftazidime*

		CIPRO Antibiotic Sensitivity (Kirby-Bauer)			MIC	MIC (μg/ml)		CEFT Antibiotic Sensitivity (Kirby-Bauer)			MIC (μg/ml) Minimum Inhibitory Concentration by Agar Diffusion	
	No. of Isolates	S	I	R	No. of Strains	Range	Mean	S	I	R	Range	Mean
Hemophilus sp	38	38	—	—	26	.008-.5	(.059)	38	—	—	.06-8	(.804)
Ps aeruginosa	25	23	1	1	17	.06-1	(.378)	23	1	1	.06-8	(3.4)
Ps maltophilia	5	3	2	—	4	1-2	(1.67)	2	—	3	4-64	(49)
Kleb pneumoniae	13	12	—	—	9	.015-.125	(.057)	12	—	—	.06-.5	(.257)
E Coli	6	6	—	—	3	.008-.03	(.018)	6	—	—	.006-.125	(.103)
Enterobacter sp	9	9	—	—	5	.015-.125	(.04)	5	—	4	.25-32	(7.3)
Citrobacter sp	5	5	—	—	2	.015-.25	(.133)	4	—	1	.06-4	(2.03)
Staph aureus	22	22	—	—	15	.25-1	(.55)	11	9	2	8-64	(21.33)
Strep pneumoniae	12	9	3	—	10	.5-2	(1.75)	12	—	—	.006-1	(.238)
β-Hemolytic strep sp	12	5	6	1	10	.25-2	(1.1)	10	2	—	.125-2	(.475)
Proteus mirabilis	5	5	—	—	4	.015-1	(.269)	5	—	—	.06-1	(.405)
Providencia stuarti	4	4	—	—	2	.03-.06	(.045)	4	—	—	.5	(.5)
Acinetobacter anitratus	3	2	—	1	3	.25-4	(1.58)	3	—	—	4-8	(6.67)
Serratia marceseus	2	2	—	—	2	.03-.125	(.076)	1	—	1	.125-64	(32.06)
Morganella morgani	2	2	—	—	2	.008-.125	(.067)	1	—	1	1-32	(16.5)
Pseudomonas stutzeri	2	2	—	—	1	.25	(.25)	2	—	—	16	(16)
*Other Gram-negatives	5	4	—	—	3	.06-4	(1.52)	5	—	1	8-16	(13.33)
	170*				118†							

*Total number of isolates.

†Total number of MICs.

One strain of each of the following: CDC-M6, *Achromobacter xylosoxidans*, *Pseudomonas pseudoalcaligenes*, *Bordetella bronchosepta*, *Serratia liquifaciens*.

Interpretation:

1. Three strains showed *in vitro* resistance to Cipro (1.77%) compared to 14 strains in the Ceft group (8.24%).
2. The MIC's of Cipro for Gram negatives, in general, were lower than those for Gram positive bacteria.
3. Eight out of ten strains of pneumococci tested were of intermediate sensitivity to Cipro (MIC of 2 μg/ml).
4. Three out of four strains of *Pseudomonas maltophilia* tested were resistant to Ceft (MIC more than 64).
5. Four out of five strains of *enterobacter aerogenes* were resistant to Ceft.
6. Two strains of *Staph aureus* were resistant to Ceft (MIC more than 64) and nine strains were of intermediate sensitivity (MIC 16).

S = sensitive; I = intermediate; R = resistant.

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Table 2—*Characteristics of Patients with Pneumonia in Whom Ciprofloxacin Regimen Failed*

Patient No.	Age/Sex	Diagnosis	Underlying Disease	Severity of Infection	Infecting Organisms	Cipro MIC μg/ml	Cipro, Dose, Route and Duration	Comments
38	55/M	Pneumonia	Chronic schizophrenia	Severe	No pathogens isolated	Not done	200 mg IV ×2×3 ½ days	Continuing fever, and respiratory symptoms. Outcome: responded to benzyl penicillin.
46	43/M	Pneumonia	Alcohol abuse, intravenous drug addiction, HIV+ in '85, cryptococcal meningitis in '85	Moderate	*Staph aureus*	.5/S	200 mg IV ×2×3 days	Worsening of clinical signs of infection and switched to Bactrim, erythromycin, nafacillin and amphotericin B Outcome: died.
128	73/F	Pneumonia	Recurrent episodes of pneumonia, CVA, seizure disorder, urinary tract infection	Severe	*Enterobacter aerogenes, P aeruginosa*	.03/S .25/S	200 μg IV ×2×3 ½ days	Patient deteriorated and WBC increased to 28.9; switched to mezlocillin and gentamycin. Outcome: patient died on 4th day of therapy.
133	34/M	Pneumonia	. . .	Severe	No pathogens isolated	Not done	200 μg IV ×2×5 days	Persistence of signs and symptoms of infection. *Pneumocystis carnii* pneumonia diagnosed by bronchoscopy and switched to IV Bactrim. No risk factors for AIDS. Outcome: recovered.

worsening of signs and symptoms. Bacteriologic eradication was defined as the elimination of pretreatment pathogens from sputum. Bacteriologic failure was defined as persistence of the original pathogen and/or isolation of a new pathogen on posttreatment sputum cultures. The chi-square test was used in the statistical analysis, and a p value of less than 0.05 was considered statistically significant.

Results

Of the 140 patients treated, 122 were evaluable and 87 of these patients produced 170 bacterial isolates as listed in Table 1. The 18 patients (eight in the ciprofloxacin group and ten in the ceftazidime group) who were not evaluable were eliminated for the following reasons: failure to take the drug for at least five days (14), confirmation of other diagnosis—tuberculosis (two), endocarditis (one), meningitis (one). Thus, this report is based on the remaining 122 patients with documented respiratory tract infections. There were 68 men and 54 women with a mean age of 58 years (range 21 to 95 years). Sixty-six patients received ciprofloxacin and 56 patients received ceftazidime for a mean duration of six days of intravenous and five days of oral ciprofloxacin, and seven days of intravenous ceftazidime, respectively. There was no significant difference between these two patient groups in age, gender, admission diagnosis, or length of antibiotic therapy. In the 11 patients with acute bronchitis, seven in ciprofloxacin and four in the ceftazidime group, the bacterial isolates were comparable and included *Hemophilus influenza* in five, *Pseudomonas* species in two, *Staphylococcus aureus* in one and no pathogens were isolated in three patients. Similar pattern of bacterial isolates was found in the patients with pneumonia.

Clinical Efficacy

A clinical cure was achieved in 42 of the 46 patients in the proven group (91 percent) with patients receiving ciprofloxacin and 18 of the 20 in the presumed group (90 percent). This was not statistically significant

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Table 3—*Characteristics of Patients with Pneumonia in Whom Ceftazidime Regimen Failed*

Patient No.	Age/Sex	Diagnosis	Underlying Disease	Severity of Infection	Infecting Organisms	Ceft MIC μg/ml	Ceft, Dose, Route and Duration	Comments
14	34/M	Pneumonia	None	Severe	*Strep pneumoniae*	.25/S	1g×3×1 day	Worsening fever and constitutional and chest symptoms. Outcome: responded to erythromycin.
23	36/M	Pneumonia	Seizure disorder, IVDA, alcohol abuse	Severe	No pathogens isolated		2g×3×6 days	Persistence of fever and signs and symptoms of chest infection. Responded to penicillin and gentamycin.
58	95/M	Pneumonia	COPD, colon cancer, Alzheimer's disease, partial colectomy	Severe	*Strep pneumoniae*, *Staph aureus* superinfection	.25/S	1g×3× 10 days	Worsening of clinical signs and symptoms with increasing WBC; changed to penicillin and gentamycin. Outcome: pneumonia resolved.
139	79/F	Pneumonia	Recurrent UTI with indwelling catheter, Alzheimer's disease, dementia, breast cancer with mastectomy in '77	Severe	*Ps aeruginosa*	8/S	1g IV×3× 14 days	After initial response to 14 days of ceftazidime, she deteriorated clinically and was switched to naficillin, mezlocillin and gentamycin. Outcome: She died 2 days later.
140	86/M	Pneumonia	Colonic polyps with colonoscopy and polypectomy diverticulosis by barium enema	Severe	*Hemophilus influenzae*	.125/S	1g IV×3×6 days	Worsening signs and symptoms with fever, increased WBC and worsening chest x-ray. Died while on protocol. Presumed cause of death: acute myocardial infarction.

from the clinical cure rate obtained with ceftazidime—38 out of 42 in the proven group (90 percent) and 12 out of 14 in the presumed group (85 percent). All 122 of the patients enrolled were adult patients referred to a tertiary care county hospital for treatment of respiratory tract infection considered to be of a severity necessitating hospitalization and parenteral antibiotic therapy. A majority of the patients were elderly who also had significant comorbidities—diabetes, hypertension, ethanol abuse, etc. A clinical and bacteriologic response of over 90 percent in both ciprofloxacin and ceftazidime treated patients in this group of patients is impressive. Tables 2 and 3 summarizes the clinical and bacteriologic features of the patients in whom either regimen failed. Four out of a total of 66 patients in the ciprofloxacin-treated group failed therapy. Two patients (46 and 133) had respiratory infection in a background of HIV disease. One patient (128) was a failure. This 73-year-old man had seizure disorder, recurrent episodes of pneumonia, and a polymicrobial Gram-negative respiratory infection. A fourth patient (38) had no pathogens and he responded to penicillin therapy. Five of the 56 patients in the ceftazidime group failed therapy. Two patients (14 and 58) had *S pneumonia* which responded to penicillin. One (23) had no pathogens and he re-

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sponded to alternate therapy. Two patients (139 and 140), both elderly with multiple medical problems, failed ceftazidime therapy.

Bacteriologic Susceptibility

A total of 170 bacterial isolates were recovered from pretreatment sputum cultures. All these isolates showed *in vitro* sensitivity to ciprofloxacin, except for four isolates (one *Pseudomonas aeruginosa*, one *Acinetobacter*, one *Achromobacter xylosoxidans* and one β-hemolytic strep sp which was resistant by disc diffusion, but was sensitive by the MIC method). All the isolates, except for 13, showed sensitivity to ceftazidime (three *Pseudomonas maltophilia*, one *Pseudomonas aeruginosa*, four *Enterobacter aerogenes*, two *S aureus*, one *Morganella morganii*, one *S marcescens*, one *Citrobacter diversus*). Twenty-two patients in the ciprofloxacin and 18 patients in the ceftazidime treatment group had more than one isolate in their pretreatment sputum culture. This did not appear to influence the sterilization of sputums in either group.

Microbiologic Results

Table 1 summarizes the type and number of isolates recovered in the 87 patients, as well as the disk susceptibility for these isolates and the available MIC values of 118 isolates. Significantly more isolates were susceptible to ciprofloxacin than to ceftazidime as determined by the diffusion technique. The MIC values reveal that ciprofloxacin was more active *in vitro* than ceftazidime against the strains of Gram-negative bacteria tested. All nine of the *Enterobacter* isolates were susceptible to ciprofloxacin at a concentration equal to or less than 0.06 μg/ml, while four of these nine isolates were resistant to ceftazidime. The MIC values of ciprofloxacin for the *Pseudomonas aeruginosa* species range from .06 to 1.0 μg/ml. Ciprofloxacin was more active than ceftazidime against isolates of *Hemophilus influenzae*. All the isolates were susceptible to ciprofloxacin (MIC less than 1 μg/ml), with an MIC range equal to or less than .008 μg/ml to 0.5 μg/ml. The isolates of *Staphylococcus aureus* tested were sensitive to ciprofloxacin. Ceftazidime was more effective than ciprofloxacin against the 12 isolates of *Streptococcus pneumoniae*, with 12 of 12 of the isolates susceptible to ceftazidime and nine of 12 susceptible to ciprofloxacin. Three of the 46 patients in the ciprofloxacin group and three of the 41 patients in the ceftazidime group had organisms persisting at the end of the treatment.

Adverse Reactions

Both antibiotic regimens were generally well-tolerated by both patient groups. The common side effects encountered were skin rash in five of the 66 patients who received ciprofloxacin, necessitating discontinuation of the drug in one patient; another patient developed transient abdominal cramps and diarrhea while receiving ciprofloxacin. Of the 56 patients who received ceftazidime, the following adverse effects were noted: seizures (one), hallucinations (one), progressive decrease in WBC (one). Ceftazidime was not discontinued in any of these three patients. We did not observe any clinically significant interaction between ciprofloxacin and theophylline in the 21 patients who received both drugs in this therapy.

Superinfections

Three of 66 patients in the ciprofloxacin group developed superinfection. All three patients had multiple underlying medical problems and two of the three eventually died from the superinfection. Six of the 56 patients in the ceftazidime group developed superinfection; one died from this superinfection and the remaining five recovered. The highlights of these patients are summarized in Tables 4 and 5.

Discussion

Oral ciprofloxacin has been found to be quite effective in the treatment of various forms of respiratory tract infection.[14,15] Contrary to the favorable results found by Gleedhill et al and Kobayashi,[14,15] Davies,[16] in his study of oral ciprofloxacin for respiratory tract infection, reported several problems; most of the problems were due to resistance or recurrence of streptococcal pneumonia infection or failure to eradicate *Pseudomonas*. We also reported on a large, prospective, double-blind, randomized study where we compared ciprofloxacin, 750 mg twice a day, with ampicillin in the treatment of bacterial respiratory tract infection.[17] Eight-seven patients received either ciprofloxacin or oral ampicillin. Ciprofloxacin was as effective as ampicillin and produced a 98 percent clinical cure rate. Significantly more pretreatment bacterial isolates were susceptible to ciprofloxacin (p value of less than 0.05), and ciprofloxacin had a significantly higher rate of sputum bacterial eradication than ampicillin (p values of less than 0.05). Ciprofloxacin showed broad *in vitro* antibacterial activity with particularly low minimal inhibitory concentrations for Gram-negative organisms. Ciprofloxacin was well tolerated; there were few adverse effects, and patients had a significantly lower incidence of diarrhea with ciprofloxacin than with ampicillin (p value of less than 0.05). We felt that ciprofloxacin was an effective and well tolerated treatment for bacterial bronchitis that had the advantage of broad *in vitro* antibacterial activity and twice daily dosing.[6] In the study of oral ciprofloxacin, we did encounter interaction between ciprofloxacin and theophylline, and this was particularly seen in elderly patients who had been on long-term theophylline, and who received the total dose of

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Table 4—*Characteristics of Patients with Pneumonia on Ceftazidime Who Developed Superinfection*

Patient No.	Age/Sex	Diagnosis	Underlying Disease	Severity of Infection	Infecting Organisms	Ceft MIC μg/ml	Ceft, Dose, Route and Duration	Comments
43	86/F	Pneumonia	Carcinoma of uterus, hysterectomy in 1965, anemia, chronic diarrhea of unknown etiology	Severe	*Staph aureus, P aeruginosa*	8/S 2/S	1g IVQ8 10 days	Developed bacteremic *Strep fecalis* superinfection. Outcome: died.
41	66/M	Acute exacerbation of COPD	Chronic bronchitis, emphysema	Severe	*H parainfluenzae*	.03/S	1g IVPBQ8 8 days	Improvement. Developed superinfection with *Pseudomonas aeruginosa, Ps maltophila*. Outcome: recovered.
48	23/M	Pneumonia	None	Severe	No pathogens	—	2g IVPBQ8 5 days	Improvement. Developed superinfection with *H influenzae*. Outcome: recovered.
52	56/M	Pneumonia	S/P aortofemoral bypass graft, alcohol abuse	Moderate	No pathogens	—	1g IVPQ8 6 days	Improvement. Superinfection with *E coli*. Outcome: recovered.
32	47/F	Pneumonia	Sarcoidosis diagnosed during current admission for pneumonia	Moderate	*H Parainfluenzae*	.008/S	1g IVPBQ8 4 days	Improvement. *Candida albicans* superinfection.
58	95/M	Pneumonia	COPD, colon cancer with right hemicolectomy, Alzheimer's disease	Severe	*Strep pneumonia*	10 days	1g IVPBQ6	Worsening of clinical signs and symptoms with increased WBC, *Staph aureus* superinfection in sputum. Switched to penicillin and gentamycin. Outcome: pneumonia resolved.

1,500 mg ciprofloxacin a day.[18] We have also reported on the effectiveness of oral ciprofloxacin in the treatment of 14 adult patients with bacterial pneumonia. These 14 patients received 750 mg of ciprofloxacin for a duration of 11.5 days. Thirteen had underlying lung disease, and 12 of the 14 (86 percent) were cured. All the isolates, which included streptococcal pneumonia in five, Hemophilus in four, were sensitive to ciprofloxacin and only two pathogens persisted in this group.[19] Ernst et al[20] also reported on the effectiveness of 750 mg twice a day in 25 patients with pneumonia, of whom 19 had bacterial isolates from sputum or blood, and all patients improved in this study.

Based on an analysis of the reported studies, it is evident that oral ciprofloxacin is effective in the treatment of bacterial respiratory tract infection, both bronchitis as well as pneumonia.

Cystic Fibrosis

A number of studies have reported on the effectiveness of oral ciprofloxacin in the treatment of bacterial infection in cystic fibrosis.[21-25]

Oral ciprofloxacin is of special interest in the treatment of patients with cystic fibrosis in view of ciprofloxacin's special activity against *Pseudomonas aeruginosa*, *S aureus*, and *Hemophilus influenzae*, the three pathogens which, not uncommonly, cause exacerbations in patients with cystic fibrosis. The attraction lies in safety, oral bioavailability, and possible outpatient use. Some studies show the emergence of

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Table 5—*Characteristics of Patients with Pneumonia on Ciprofloxacin Who Developed Superinfection*

Patient No.	Age/Sex	Diagnosis	Underlying Disease	Severity of Infection	Infecting Organisms	Cipro MIC μg/ml	Cipro, Dose, Route and Duration	Comments
137	25/M	Pneumonia	Posttraumatic brain hemorrhage, ventriculoperitoneal shunt, feeding gastrostomy tube, permanent tracheostomy	Severe	*Proteus mirabilis*, *Providencia stuarti*	.125/S .06/S	IV 13 dys PO 2 dys	*Pseudomonas aeruginosa*, *Ps maltophilia*, *Citrobacter* sp superinfection. Outcome: Initial response to gentamycin and ceftazidime; subsequently died from recurrent pneumonia.
94	88/F	Pneumonia	Diabetes mellitus, congestive heart failure, multiple decubiti, anemia, hyperosmolar coma	Severe	*Pseudomonas aeruginosa*, *Enterbacter* sp, *H parainfluenzae*	.5/S .03/S	IV 2 dys PO 15 dys	*Strep fecalis* bacteremia superinfection. Outcome: died.
53	60/F	Pneumonia	Congestive heart failure, cardiac arrhythmias, Sarcoidosis Stage III, insulin-requiring diabetes, alcoholism, chronic liver disease	Severe	*H influenzae*, *Bordetella bronchosepta*, *Staph aureus*	.015/S .5/S 1/S	IV 7 dys PO 7 dys	Superinfection with *Strep pneumonia*; treated with IV Zincef and PO Ceclar. Outcome: recovered.

resistance. Interestingly, this resistance does not predict clinical failure. Ciprofloxacin might be useful for prolonged chemotherapy following maximum suppression of *Pseudomonas aeruginosa* by parenteral agents. Most authors recommend that ciprofloxacin should be used intermittently in the management of the recurrent pulmonary exacerbations of bacterial infections in patients with cystic fibrosis. Thus, it is evident that oral ciprofloxacin is a useful additional antimicrobial agent for the treatment of both acute and chronic bacterial respiratory tract infections.

Therefore, the results of our clinical study in serious bacterial respiratory tract infection using intravenous ciprofloxacin is of special interest. Intravenous ciprofloxacin was highly effective for the treatment of bacterial respiratory tract infections. We observed comparable high clinical cure rates with both ciprofloxacin and ceftazidime. Forty-two of the 46 patients in the proven group and 18 of 20 in the presumed group were cured of the infection in the ciprofloxacin group for an overall cure rate of 91 percent, while in the ceftazidime group, 38 of 42 in the proven group and 12 of 14 in the presumed group were cured with an overall cure rate of 89 percent. In addition, a significantly higher number of isolates showed resistance to ceftazidime, (8 percent), while only three isolates were resistant to ciprofloxacin (1.7 percent). The patients who failed to respond to ciprofloxacin and ceftazidime are summarized in Table 2. The overall bacterial eradication rates were similar in both groups, three of 46 in ciprofloxacin (7 percent) and three of 41 (10 percent) in the ceftazidime group had persistent organisms at the end of the therapy.

In our center, the most common bacteria identified during exacerbations of chronic lung disease or nosocomial infection are Hemophilus, *Pseudomonas aeruginosa*, Klebsiella, and *Staphylococcus aureus*. These organisms, as well as other Gram-negative and Gram-positive organisms tested, were highly susceptible to ciprofloxacin with MICs of 1 μg/ml or less in all cases. Thus, ciprofloxacin can be expected to be effective in hospitalized patients with nosocomial, Gram-negative infections or elderly patients who have a higher incidence of *Staphylococcus aureus* infection.[26] The adverse reactions to ciprofloxacin were generally mild and self-limiting, the most common being skin rash; and in one of the patients, the drug therapy was discontinued because of the skin rash. Contrary to our earlier experience where we encountered significant interaction between ciprofloxacin and theophylline when 750 mg was used twice a day,[17] in this study, we encountered no interaction between ciprofloxacin and theophylline in the 21 patients who received both drugs. In another study where we compared the effectiveness of oral 250 mg *bid vs* ampicillin in the treatment of mild respiratory infection, we also did

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not encounter any interaction between ciprofloxacin and theophylline. We now feel that this interaction is dose-related and encountered only when more than 1,000 mg of ciprofloxacin is used.

The superinfection observed in the three patients in the ciprofloxacin group and the six patients in the ceftazidime group is not surprising. Potent antimicrobial therapy in elderly, debilitated, sick people has been associated with superinfection with various organisms, and the present study also confirms this finding.[27]

The role of ciprofloxacin and the treatment of infections by Gram-positive bacteria, particularly Streptococcus pneumonia, had not been fully established, the doubt arising from the laboratory observation of high MICs. We have also observed high MICs in our previous study and the study being reported here. However, our clinical results in the seven patients who received ciprofloxacin indicated that the high MICs did not interfere with the action of the drug. The reasons for this interesting observation are perhaps related to the unique property of the ciprofloxacin in penetrating tissue compartments. The four quinolones, enoxacin, pefloxacin, ciprofloxacin, ofloxacin, have unique properties of penetrating into the bronchial lining and achieving high concentrations in the lung, in the bronchial mucosa, and in the sputum. Bergogne et al[28] studied 21 patients who received a single *oral* dose of 500 mg ciprofloxacin. Ten successive samples of the sputum were collected over a 12-hour period. The serum levels peaked at 2.2 ± 1.3 mg/L at two hours and decreased slowly to $.6 \pm 0.4$ mg/L at six hours. The corresponding bronchial levels were .5 mg/L at two hours and they stayed stable until six hours with a range of 0.5 to 0.8 mg/L. The ratio of serum to bronchial fluid levels at two hours was 0.19 to 0.95 at six hours. In another study, the same author reported on the penetration of ciprofloxacin into the lung parenchymal tissue. Intravenous 100 mg ciprofloxacin was given and surgical samples of the lung were obtained. The lung tissue level exceeded the corresponding serum level with a distribution ratio of 300 to 900 percent. Ciprofloxacin also achieved a high concentration in the pleural fluid with a peaked pleural level six to nine hours after administration of ciprofloxacin and averages 0.9 μg/ml after 24 hours.[29] Schlenkhoff et al[30] reported on 14 patients who had been premedicated with 100 mg intravenous ciprofloxacin prior to thoracic surgery. Four groups received injections one, two, three, and four hours before tissue sampling and the results showed that the penetration of ciprofloxacin into the lung tissue is marked with the tissue level significantly exceeding the corresponding serum concentration. These authors found a lung-serum ratio of 195 to 753 percent at one hour, 545 to 1044 percent in two hours, 675 percent in three hours, and 800 to 1000 percent in four hours. Honeybourne et al[31] studied the bronchial level in 15 patients who had received 500 mg ciprofloxacin twice daily for four days. The bronchial biopsy samples were assayed for the levels. Timed biopsies and venipunctures were done after the final dose. In the 15 patients, the serum levels ranged from 1 to 9 μg/L while the bronchial levels ranged between 1.1 to 17.32 mg/g. The average penetration of the drug into bronchial mucosa was 161 percent but was found to be quite variable. Although the sputum levels are low, the bronchial mucosa levels are very high. Marlin et al[32] studied the distribution ratio of enoxacin between plasma and bronchial mucosa in patients after distribution equilibrium was established. They also compared the absolute bronchial mucosal concentration achieved with the *in vitro* bacterial activity of enoxacin. Eighteen patients received enoxacin, 400 mg twice daily, for four days; on the fifth morning, a 500 mg dose of enoxacin was given to all 18 patients. Bronchial mucosal biopsies and plasma samples were obtained at three, four, or five hours in six patients each, and the samples were assayed for enoxacin by high-pressure liquid chromatography. Marlin et al[32] concluded that equilibrium between bronchial mucosa and plasma is achieved within three hours of dose. The mean bronchial mucosal concentration for all patients was 117 (47.8 μg/g); the mean plasma concentration was 3.1 (1.1 μg/ml), and the mean ratio was 46.8. These data suggest the possibility of active transport into the bronchial mucosa, and avid tissue binding to the tissue macromolecules may account for the extensive accumulation of the quinolones in the bronchial respiratory tract. These findings support the use of ciprofloxacin in severe chest infections and help to dispel the earlier apprehension about the use of the medication, particularly in patients who have streptococcal pneumonia infections.

It thus appears that the quinolones far exceed all the other known and studied antibiotics in their unique property of tissue penetration, particularly into the respiratory tract. This unique feature helps to understand the apparent paradox in the results obtained with ciprofloxacin in the treatment of *S pneumonia* infection. Almost 100 patients with *S pneumonia* infection have been treated with ciprofloxacin, with a clinical cure rate of over 95 percent in spite of the relatively high MICs in these patients. The very high lung parenchymal and bronchial tissue levels achieved with ciprofloxacin apparently overcome the marginal MIC level against *S pneumonia* and help to explain the excellent results reported by several authors.[6,14,17,20]

Cost Analysis

Intravenous ciprofloxacin or another comparable

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intravenous quinolone has, as yet, not been approved by federal drug agency, and thus, the market cost of the intravenous preparation is not available.

However, comparable cost analysis of oral ciprofloxacin with other conventional therapies is available. In one study, IV cefotaxime was compared with oral ciprofloxacin in the treatment of soft-tissue infections. Thirty-two patients were treated with cefotaxime, 2 g IV every eight hours. Ciprofloxacin was given to 24 patients at a dose of 750 mg orally every 12 hours. The mean duration of therapy in both groups was approximately 11.5 days and the clinical results were comparable in both groups. The daily cost of cefotaxime totaled $59 per day compared to approximately $9.00 per day for ciprofloxacin, and the cost savings of $50/day or $579/total course of therapy could be achieved. If the 32 patients who had received cefotaxime had been treated with ciprofloxacin, a total savings of $18,000 could have been realized without any compromise in clinical efficacy.

In addition to the dollars saved, the "hidden" costs of parenteral therapy would have been saved as well—storage/preparation/administration, supplies (solutions, tubing, etc), complications (phlebitis, etc), and inconvenience (nurse, patient, family).[33]

In our study, the 56 ceftazidime-treated patients received, on an average, seven days of intravenous ceftazidime, followed by various currently available broad spectrum oral antibiotics for a variable period of time. The 66 ciprofloxacin-treated patients, on an average, received six days of intravenous ciprofloxacin, followed by an average of five days of oral ciprofloxacin, 500 mg twice daily. The daily cost of intravenous ceftazidime at Nassau County Medical Center is approximately $78/day while oral 500 mg twice daily ciprofloxacin costs $4/day. Thus, in the ceftazidime group of 56 patients who received one extra day of intravenous ceftazidime, the extra cost was $4,144 (56 patients × $74).

In conclusion, we feel that ciprofloxacin will play a major role in the treatment of various respiratory tract infections in the years to come. The oral ciprofloxacin has been found useful in the treatment of bacterial exacerbations of patients with COPD and cystic fibrosis, and the agent will play a particularly useful role in the treatment of respiratory tract infections in the elderly patients who often have Gram-negative organisms and Staphylococcus respiratory tract infections.[34] Ciprofloxacin would also be of use in the treatment of respiratory tract infections in diabetics and alcohol abusers who have a higher propensity for developing Gram-negative respiratory tract infections than the general population.[35] Ciprofloxacin has *no* use in the treatment of aspiration pneumonia and anaerobic infections. After the intravenous formulation of ciprofloxacin becomes available, it will be an attractive initial antimicrobial therapy for those hospitalized patients who are considered suitable for parenteral antimicrobial therapy, for respiratory tract infection caused by Gram-negative organisms, *S aureus*, and polymicrobial infections. After the clinical condition improves, the patients can be switched over to the oral formulation of the same drug and, thus, this would be the first antimicrobial which would have both a sequential intravenous and an oral formulation available. Our study demonstrates that this type of a regimen works as effectively as a potent third-generation cephalosporin and the regimen costs less. The potential cost savings of this sequential regimen are significant.

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Sequential intravenous-oral administration of ciprofloxacin vs ceftazidime in serious bacterial respiratory tract infections.
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