Doxycycline Is a Cost-effective Therapy for Hospitalized Patients With Community-Acquired Pneumonia

Reba K. Ailani, MD; Gautami Agastya, MD; Rajesh K. Ailani, MD; Beejadi N. Mukunda, MD; Raja Shekar, MD

Background: Doxycycline has a high degree of activity against many common respiratory pathogens and has been used in the outpatient management of lower respiratory tract infections, including pneumonia.

Objective: To evaluate the efficacy of intravenous doxycycline as empirical treatment in hospitalized patients with mild to moderately severe community-acquired pneumonia.

Patients and Methods: We conducted a randomized prospective trial to compare the efficacy of intravenous doxycycline with other routinely used antibiotic regimens in 87 patients admitted with the diagnosis of community-acquired pneumonia. Forty-three patients were randomized to receive 100 mg of doxycycline intravenously every 12 hours while 44 patients received other antibiotic(s) (control group). The 2 patient groups were comparable in their clinical and laboratory profiles.

Results: The mean ± SD interval between starting an antibiotic and the clinical response was 2.21 ± 2.61 days in the doxycycline group compared with 3.84 ± 6.39 days in the control group ($P = .001$). The mean ± SD length of hospitalization was 4.14 ± 3.08 days in the doxycycline group compared with 6.14 ± 6.65 days in the control group ($P = .04$). The median cost of hospitalization was $5126 in the doxycycline group compared with $6528 in the control group ($P = .04$). The median cost of antibiotic therapy in the doxycycline-treated patients ($33) was significantly lower than in the control group ($170.90) ($P<.001$). Doxycycline was as efficacious as the other regimens chosen for the treatment of community-acquired pneumonia.

Conclusion: Doxycycline is an effective and inexpensive therapy for the empirical treatment of hospitalized patients with mild to moderately severe community-acquired pneumonia.

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From the Department of Medicine, Meridia Huron Hospital, Cleveland, Ohio.

PNEUMONIA IS the sixth leading cause of death in the United States and is the most common cause of infection-related mortality.[1] The cost of treating the illness in United States is estimated to be $23 billion per year.[2]

In patients hospitalized with the diagnosis of community-acquired pneumonia (CAP), antibiotics are usually chosen empirically to treat the most likely causative organisms until a microbiologic cause is established. However, a definitive cause is not usually established; and if there is a good clinical response, the course of therapy is completed with the initially chosen antibiotic. Combinations of antibiotics are often used and these regimens can be expensive.

Considerations in choosing antibiotics should include the following: antibacterial spectrum, efficacy, adverse effects, ease of administration, and cost.

In various studies from the literature, percentage of cases where no definitive cause for CAP was established ranged from 32.9%[3] to 63.3%.[4] The most commonly detected organism was *Streptococcus pneumoniae*, ranging from 8.5%[5] to 37.6%.[4] Atypical pneumonias caused by *Legionella*, *Chlamydia*, and *Mycoplasma* together accounted for 8% to 20% of the cases.[3-6]

Doxycycline has a high degree of activity against many common respiratory pathogens including *S pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, anaerobes such as *Bacteroides* and anaerobic/microaerophilic streptococci and atypical agents like *Legionella*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.[7] Doxycycline has been used as oral therapy in the outpatient management of lower respiratory tract infections (including pneumonia), where it has been compared with ofloxacin and spiramycin, and has been found to be comparable.[8-10] Doxycycline is an attractive alternative for hos-

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PATIENTS, MATERIALS, AND METHODS

The study was conducted in a 371-bed community teaching hospital from August 1995 to December 1997. Patients were eligible for the study if they had a clinical and radiological diagnosis of pneumonia acquired in the community before admission to the hospital. Patients were excluded if any of the following were present: younger than 18 years, pregnant or lactating women, history of allergic reaction to the use of tetracycline or doxycycline, severe hepatic or renal dysfunction, human immunodeficiency virus infection, immunocompromised state, clinical sepsis, patients requiring intubation, and patients from a nursing home or a long-term care facility. Patients were enrolled in the emergency department or soon after admission to the hospital.

During the study period there were a total of 356 patients admitted with the diagnosis of pneumonia. Of these 356 patients, 136 were from long-term care facilities. Forty-six patients required intubation in the emergency department. Thirty-eight had 1 of the exclusion criteria including immunocompromised state, renal or hepatic failure, or pregnancy. Another 22 patients received antibiotics before enrollment. In 27 patients who were not enrolled in the study, consent could not be obtained. Eighty-seven patients hospitalized with CAP were randomly assigned to receive either doxycycline or 1 or more antibiotics selected by the patient's physician.

The randomization process was done by a predetermined numbered sequence. As the patients were enrolled into the study, they were assigned to either the doxycycline group or the control group depending on the number to which they were assigned.

The Institutional Research and Review Committee of the hospital approved the study protocol. All patients were informed about the study and a written consent was obtained.

PATIENTS

After enrollment, patients were interviewed and information was recorded on a standard data collection form. Data included demographic information, history, physical examination, and admission laboratory findings. All patients had baseline investigations that included a chest radiograph, complete blood cell count with differential, serum electrolytes, serum urea nitrogen, serum glucose, pulse oximetry or arterial blood gases, sputum Gram stain and culture, and blood cultures. All patients were examined daily for their complete blood cell counts and electrolyte levels. Additional tests such as sputum, acid-fast stains, serology for *Chlamydia*, *Mycoplasma*, and *Legionella* were performed when clinically indicated, at the discretion of the patient's physician.

COMORBID CONDITIONS

Conditions such as chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, neoplastic disease, diabetes mellitus, chronic renal failure, alcoholism, and smoking were recorded.

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pitalized patients with mild to moderately severe CAP. The objective of this study was to evaluate the efficacy of intravenous doxycycline as empirical treatment in hospitalized patients with mild to moderately severe CAP.

RESULTS

A total of 87 patients were enrolled into the study. Forty-three were randomized to receive doxycycline, and 44 were assigned to the control group. The clinical and laboratory features between the 2 groups of patients were not significantly different, as shown in **Table 1** and **Table 2**.

The ages of the patients in the doxycycline and control groups ranged from 18 to 84 years, and 23 to 81 years, respectively (Table 1). However, only 20 (23%) of the 87 patients were older than 60 years. Twenty-seven patients (63%) in the doxycycline group and 21 (48%) in the control group were women. The average number of comorbid conditions between the 2 groups were not statistically significant ($P = .18$). In both groups, 40% of the patients had documented underlying lung disease.

The median cost of antibiotic(s) during hospitalization for the doxycycline group was $33, compared with $170.9 in the control group ($P<.001$) (**Table 3**). The median cost of hospitalization in the doxycycline group was $5126, compared with $6528 in the control group ($P = .04$) (Table 3). The mean ± SD time to respond to treatment was 2.21 ± 2.61 days in the doxycycline group, compared with 3.84 ± 6.39 days in the control group ($P = .001$) (Table 3). The mean ± SD length of hospitalization was 4.14 ± 3.08 days in the doxycycline group, compared with 6.14 ± 6.65 days in the control group ($P = .04$) (Table 3). The mean ± SD number of antibiotics used, including the one given on discharge, was significantly lower in the doxycycline group than in the control group: 1.16 ± 1.04 in the doxycycline group vs 2.43 ± 1.59 in the control group ($P<.001$) (Table 3).

In the doxycycline group, 6 patients developed adverse effects, but none required a change of antibiotic because of the adverse effects. In the control group, 11 patients had adverse effects ($P = .19$) and 3 of these 11 required a change of antibiotic. Two patients had diarrhea with the use of clindamycin and 1 patient had severe vomiting with the use of erythromycin; hence, their antibiotics were changed.

Three patients in the doxycycline group required a change in antibiotic because of a lack of response. Two patients failed to respond to the use of doxycycline. One patient was misdiagnosed and had tuberculosis on the basis of a strongly positive tuberculin skin test and a persistent infiltrate on chest radiograph. This was not confirmed by cultures; however, the patient improved with antituberculous treatment.

Eight patients in the control group required a change in the antibiotic regimen, 3 because of adverse

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TREATMENT

Doxycycline (100 mg) was given intravenously every 12 hours in patients randomized to the study group. In patients randomized to the control group, the physician taking care of the patient chose antibiotics without restrictions. All patients were monitored daily by one of us for improvement or deterioration while receiving therapy and were also monitored for any adverse drug effects.

CRITERIA FOR RESPONSE

The time to respond to treatment was defined as the number of days between the day of randomization (day 1) and the day on which the last of the following parameters was met: (1) oral temperature of 37.9°C or lower over 3 consecutive 8-hour periods; (2) beginning of a decrease in total white blood cell counts, ie, the day the count showed a tendency toward normal in patients who had leukocytosis; (3) subjective improvement of symptoms for which the patient was admitted to the hospital. This was decided by the primary physician's clinical notes and interview of the patient by one of us; and (4) in patients with no underlying disease like chronic obstructive pulmonary disease, congestive heart failure, and who were hypoxic on admission, resolution of hypoxia.

Patients who showed any sign of deterioration or who were not responding to therapy or who developed serious adverse effects had their antibiotic regimen changed at the discretion of the physician taking care of them. Patients who improved while receiving therapy were switched to an oral regimen, which in the study group was 100 mg of doxycycline orally every 12 hours. The attending physician determined the time of discharge.

STUDY CRITERIA

The 2 patient groups were then compared on the following parameters: (1) time to resolution of morbidity, (2) length of hospital stay, (3) cost of antibiotics during hospitalization, (4) cost of hospitalization, (5) adverse effects from the use of antibiotics, and (6) number of antibiotics used per patient, including the antibiotic on discharge. The time to respond to treatment was calculated as described earlier. The length of hospital stay was calculated by subtracting the admission date from the discharge date. The cost of antibiotics used during hospitalization was obtained from the number of antibiotic doses times the cost of each dose. The cost of each dose of antibiotic was obtained from the miniformulary of the pharmacy department of the hospital and was the amount charged to the patient. The mean cost of antibiotic in the doxycycline and the control groups included the antibiotics that were used even when the patient failed while receiving initial therapy. The cost of hospitalization was obtained from the computer records of the hospital bill and not the actual payment made.

STATISTICAL ANALYSIS

Comparison of patient age was done by Student 2-sample *t* test. All other variables were analyzed by Wilcoxon rank sum test rather than the Student *t* test, because of violation of the distributional normality assumption. Because of nonnormal distributions exhibited by most of these variables, medians along with the means and SDs were calculated. The adverse effects were compared by the χ^2 test. $P<.05$ was considered to indicate statistical significance.

effect (as described earlier) and 5 because of a lack of response.

Of the 87 patients enrolled in the study, 7 were found to have pneumococcal bacteremia. Three of these 7 patients received doxycycline and 4 received other antibiotics. The pneumococci were sensitive to the use of penicillin in 6 of the 7 patients. One patient had intermediate-level resistance to penicillin and he had been randomized to the control group. All these isolates were susceptible to the use of tetracycline. All 7 patients recovered and were discharged from the hospital.

From January to June 1997 in our hospital system, 10% of *S pneumoniae* isolates had high-level resistance to penicillin (minimal inhibitory concentration, ≥2 µg/mL) and another 10% had intermediate-level resistance to penicillin (minimal inhibitory concentration, 0.1-1.0 µg/mL). Resistance to tetracycline was 6.5%. Of the penicillin-resistant pneumococci, 16.6% were resistant to tetracycline (B.N.M., written communication, May 18, 1998).

COMMENT

Doxycycline has a good activity against most of the common pathogens causing CAP.[7,11] In this study, we have shown that doxycycline is an effective option for the treatment of patients admitted to the hospital with mild to moderately severe CAP. Doxycycline was more cost-effective than other antibiotic options chosen for the empirical treatment of CAP. The cost of hospitalization, time to respond to treatment, and the length of hospitalization were significantly lower in the doxycycline group than in the control group. Besides being inexpensive and effective, the number of patients with adverse effects in the doxycycline group was less than in the control group. This was probably because many patients in the control group received complex regimens involving 2 or more antibiotics.

The empirical treatment of CAP has many options. Some of the options involve the use of 2 agents to cover the common respiratory pathogens like *S pneumoniae, H influenzae*, as well as organisms that cause atypical pneumonia. According to the recommendations of the Infectious Diseases Society of America,[12] the empirical treatment for patients hospitalized to the general wards includes a β-lactam antibiotic with or without a macrolide or a quinolone.[12] Doxycycline has been recommended only in the empirical treatment of outpatients with CAP.[12] Even in the recommendations of the American Thoracic Society,[13] tetracycline has been recommended only as an outpatient treatment of CAP.

Historically, tetracycline is considered inferior to penicillin in the treatment of *S pneumoniae* infections. How-

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Table 1. Clinical Features Comparing the Doxycycline-Treated Patients and Control Patients

Clinical Features	Doxycycline Group (n = 43)	Control Group (n = 44)
Age, y		
Mean ± SD	46.37 ± 16.91	47.86 ± 16.42
<60	34	33
>60	9	11
Sex		
Male	16	23
Female	27	21
History of		
Smoking	33	35
Alcohol abuse	9	15
Drug abuse	11	15
Comorbid diseases (average per patient), mean ± SD	2.34 ± 1.52	1.93 ± 1.35
Underlying lung disease	17	17
Heart disease	22	16
Diabetes mellitus	7	6
No underlying conditions	7	7
Fever		
No fever, temperature <38.0°C	15	10
Temperature, 38.1°C-38.5°C	12	11
Temperature, 38.6°C	16	23

Table 2. Laboratory Features Comparing the Doxycycline and Control Groups*

Laboratory Features	Doxycycline Group (n = 43)	Control Group (n = 44)
Cause, known	13	16
Streptococcus pneumoniae	8	9
Positive blood culture	3	4
Haemophilus influenzae	1	3
Staphylococcus aureus	1	1
Klebsiella	. . .	1
Mycoplasma	1	. . .
Chlamydia	. . .	1
Pseudomonas	1	1
Mixed	1	. . .
Not known	30	28
White blood cell count/μL		
<10 000	20	17
10 000-20 000	15	21
>20 000	8	6
Hypoxia, Pao_2 <60 mm Hg or pulse oximetry <92% on room air		
Present	17	17

*Ellipses indicate not applicable.

ever, in certain places there has been a changing trend, with decreasing tetracycline resistance and increasing penicillin resistance.[14] In the United States, 7.5% of *S pneumoniae* are resistant to tetracycline.[15] Moreover, tetracycline resistance is not the same as doxycycline resistance. In a study of 256 clinical isolates of *S pneumoniae* described by Shea and Cunha,[7] 30% were resistant to penicillin, 20% to tetracycline, and only 5% to doxycycline. Plouffe et al[16] reported antimicrobial susceptibilities on 499 isolates of

Table 3. Response to Treatment: Comparison Between the Doxycycline-Treated Patients and Control Patients*

Results	Doxycycline Group (n = 43)	Control Group (n = 44)	*P*
Time to respond, d			
Mean ± SD	2.21 ± 2.61	3.84 ± 6.39	.001
Median	2.0	3.0	
Length of hospitalization, d			
Mean ± SD	4.14 ± 3.08	6.14 ± 6.65	.04
Median	3.0	5.0	
Cost of hospitalization, $			
Mean ± SD	6518 ± 5701	13 558 ± 36 690	.04
Median	5126.0	6528.1	
No. of antibiotics used per patient			
Mean ± SD	1.16 ± 1.04	2.43 ± 1.59	<.001
Median	1	2	
Cost of antibiotics in hospital, $			
Mean ± SD	51.36 ± 112.34	232.72 ± 209.42	<.001
Median	33.0	170.9	
Adverse effects			
Nausea or vomiting	4	5	
Diarrhea	. . .	5	
Rash	. . .	1	.19
Itching	1	. . .	
Worsening azotemia	1	. . .	
No. of patients requiring a change of antibiotic(s)	3	8	.12

*Ellipses indicate not applicable.

S pneumoniae from Franklin County, Ohio, between 1991 and 1994. Doxycycline was found to have excellent activity against pneumococcus (99.2% isolates susceptible) with no trend toward decreasing susceptibilities. High-level penicillin resistance was found in 5 isolates, and all of them were susceptible to doxycycline. Among isolates with intermediate level of sensitivity to penicillin, only 6% were not susceptible to doxycycline.[16]

Our study shows doxycycline to be effective for the empirical treatment of hospitalized patients with mild to moderately severe CAP.

Some limitations of this study include (1) the study was not blinded, (2) patients with severe disease requiring intubation were excluded, (3) the cause of pneumonia was not established in most of our patients, and (4) we did not perform antibacterial susceptibilities of the organisms isolated against doxycycline.

Doxycycline has activity against the common respiratory pathogens, relatively low toxicity, very low cost, and a convenient twice-daily dosing. It should be considered in the empirical treatment of hospitalized patients with mild to moderately severe CAP.

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Reprints: Raja Shekar, MD, Department of Medicine, Meridia Huron Hospital, 13951 Terrace Rd, East Cleveland, OH 44112.

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