Short-course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit

A Proposed Solution for Indiscriminate Antibiotic Prescription

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Inappropriate antibiotic use for pulmonary infiltrates is common in the intensive care unit (ICU). We sought to devise an approach that would minimize unnecessary antibiotic use, recognizing that a gold standard for the diagnosis of nosocomial pneumonia does not exist. In a randomized trial, clinical pulmonary infection score (CPIS) (Pugin, J., R. Auckenthaler, N. Mili, J. P. Janssens, R. D. Lew, and P. M. Suter. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am. Rev. Respir. Dis.* 1991;143: 1121–1129) was used as operational criteria for decision-making regarding antibiotic therapy. Patients with CPIS ⩽ 6 (implying low likelihood of pneumonia) were randomized to receive either standard therapy (choice and duration of antibiotics at the discretion of physicians) or ciprofloxacin monotherapy with reevaluation at 3 d; ciprofloxacin was discontinued if CPIS remained ⩽ 6 at 3 d. Antibiotics were continued beyond 3 d in 90% (38 of 42) of the patients in the standard as therapy compared with 28% (11 of 39) in the experimental therapy group ($p = 0.0001$). In patients in whom CPIS remained ⩽ 6 at the 3 d evaluation point, antibiotics were still continued in 96% (24 of 25) in the standard therapy group but in 0% (0 of 25) of the patients in the experimental therapy group ($p = 0.0001$). Mortality and length of ICU stay did not differ despite a shorter duration ($p = 0.0001$) and lower cost ($p = 0.003$) of antimicrobial therapy in the experimental as compared with the standard therapy arm. Antimicrobial resistance, or superinfections, or both, developed in 15% (5 of 37) of the patients in the experimental versus 35% (14 of 37) of the patients in the standard therapy group ($p = 0.017$). Thus, overtreatment with antibiotics is widely prevalent, but unnecessary in most patients with pulmonary infiltrates in the ICU. The operational criteria used, regardless of the precise definition of pneumonia, accurately identified patients with pulmonary infiltrates for whom monotherapy with a short course of antibiotics was appropriate. Such an approach led to significantly lower antimicrobial therapy costs, antimicrobial resistance, and superinfections without adversely affecting the length of stay or mortality.

Inappropriate use of antibiotics for the treatment of suspected pneumonia is widely prevalent in the intensive care unit (ICU) with implications for the emergence of drug-resistant organisms so grave that a Bayesian analysis recently suggested that fewer patients would die if antibiotics were withheld rather than prescribed for the treatment of clinically suspected ventilator-associated pneumonia (1, 2). Ironically, most antibiotic use in the ICU, in fact, occurs in patients in whom pulmonary infiltrates are not caused by pneumonia but by pulmonary edema or atelectasis. Respiratory tract infections accounted for 49% of all antibiotics prescribed in the ICU; 63% of the antibiotics used, however, were for clinically suspected and not proven respiratory tract infections (3). Other studies have documented empiric antibiotic use for ICU patients with pulmonary infiltrates without pneumonia, ranging from 34 to 74% (3–6). Thus, attempts to curtail antibiotic usage in the ICU has greatest relevance in this subset of patients.

A major problem with the studies of nosocomial pneumonia is the fact that accurate diagnostic criteria that can reliably distinguish pneumonia from other causes of pulmonary infiltrates do not exist. Even invasive diagnostic procedures have numerous and serious limitations and have not met with total acceptance (7). Sampling techniques and threshold for positivity remain unstandardized. Routine performance of such invasive tests is neither feasible nor cost-effective.

A major factor contributing to the "spiraling empiricism" in antibiotic usage is that physicians are unwilling to risk missing a treatable infection. Because nosocomial pneumonia in the ICU has substantial attributable mortality, there is justification, albeit unwarranted at times, to use antibiotics for patients with pulmonary infiltrates, despite a low likelihood of infection.

In this study, we proposed to minimize excessive use of antibacterial agent therapy, yet allow the clinicians the flexibility in managing patients with a perceived treatable infection. Our goal was to devise an operational approach involving patients with possible nosocomial pneumonia, recognizing that a gold standard for this diagnosis has not been definitively established. Our study design allowed the clinicians to initiate empiric therapy when faced with uncertainty in accurately diagnosing a pulmonary infiltrate as pneumonia. However, by limiting the number and duration of antibiotics in those with low likelihood of pneumonia, we hypothesized that the emergence of antimicrobial resistance would be reduced.

METHODS

The study was conducted in the surgical and medical ICUs of a tertiary care university-affiliated Veterans Affairs Medical Center. The critical care rounding attendings and the teams were acquainted with the conduct of the study and notified one of the investigators when a patient with new-onset pulmonary infiltrate, suspected of having pneumonia, was identified. In addition, one of the investigators conducted daily rounds in the ICU to identify potential enrollees.

Clinical pulmonary infection score (CPIS), proposed by Pugin and coworkers, was calculated by one of the investigators (N.S., P.R., or C.W.A.) for patients thus identified (8). CPIS incorporates six readily accessible clinical variables to determine the "likelihood" that any given patient's clinical findings are due to pneumonia (8). The temperature used to calculate CPIS was the reading obtained at the time of evaluation of pulmonary infiltrate, i.e., upon entry into the study. The purulence of the tracheal secretions was assessed based on gross examination. The initial chest radiographic interpretation that triggered enrollment was that of the critical care team. However, as part of the protocol, the investigator reviewed each radiograph independently and consulted with the radiologist when differences in interpretation existed. All of the presumed infiltrates in patients enrolled in this study were ultimately confirmed by radiology.

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CPIS criteria, regardless of whether they could truly define a patient population with pneumonia, were used for decision-making regarding antibiotic therapy. Patients with CPIS > 6 were treated as having pneumonia and were not part of the study. In a pilot study from our institution, CPIS > 6 virtually excluded acute lung injury, pulmonary edema, atelectasis, or contusion as causes of pulmonary infiltrates in ICU patients (4).

Patients with CPIS ≤ 6 (APPENDIX), i.e., those in whom pneumonia was considered unlikely, were included in the study. The decision to initiate antibiotics rested solely with the critical care team or primary service caring for the patient. Exclusion criteria included: (*1*) patients with human immunodeficiency virus (HIV) infection, (*2*) patients with cytotoxic chemotherapy–induced neutropenia, (*3*) patients less than 18 y of age, (*4*) use of antibiotics other than those employed for surgical prophylaxis, and (*5*) allergy to fluoroquinolones. Both ventilated and nonventilated patients in the ICU developing a new-onset pulmonary infiltrate were eligible for inclusion.

Patients with CPIS ≤ 6 were randomized to either the control or experimental group. Randomization was conducted in groups of four with no more than two in a row assigned to one group. Patients in the control group received the current standard therapy, i.e., the choice, number, and duration of antibiotics was at the discretion of the care providers. These patients were merely followed in an observational fashion with no interventions from the investigators. This group shall be referred to as the standard therapy group throughout this article.

Patients randomized to the experimental group received ciprofloxacin 400 mg intravenously every 8 h for 3 d. Addition of other antibiotics was not allowed in the ciprofloxacin monotherapy arm. Patients assigned to the ciprofloxacin arm were reevaluated and CPIS was recalculated at 3 d. The CPIS at 3 d took into account whether or not the pulmonary infiltrate had progressed, and the result of Gram stain and semiquantitative cultures of the tracheal secretions (APPENDIX). Gram stains were performed and interpreted by the microbiology laboratory. Plate quantitation for semiquantitative cultures was derived from a four-quadrant streak using the following criteria: fewer than 10 colonies, very rare; between 10 and 100 colonies, rare; greater than 100 colonies in the first, second, and third streaks were light, moderate and heavy, respectively (9). Ciprofloxacin was discontinued if the CPIS remained ≤ 6 at 3 d (implying low likelihood of pneumonias). Patients with CPIS > 6 at 3 d were treated as pneumonia, either by continuation of ciprofloxacin or the therapy was modified based on the culture and sensitivity results at the discretion of the primary care team. Patients in the experimental therapy group with documented extrapulmonary infection or bacteremia likewise had the antibiotic therapy appropriately altered depending upon the pathogen isolated and susceptibility data. The flow chart outlining the study design is shown in Figure 1.

Follow-up respiratory cultures or cultures from clinical specimens performed 7 to 28 d after initiation of antibiotics were evaluated to assess the emergence of antimicrobial resistance or superinfections. Emergence of resistance was defined as the detection of new antimicrobial resistance pattern in the old or previously isolated organism (10). Superinfection was defined as the detection of the following organisms not present at study entry (10): *Acinetobacter* species, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Enterobacter* species, *Citrobacter* species, methicillin-resistant *Staphylococcus aureus* (*MRSA*), *Enterococcus* species, and *Candida* species. Resolution of pulmonary infiltrate was assessed 5 to 7 d after antimicrobial therapy. Primary endpoints were mortality, length of ICU stay, emergence of antimicrobial resistance or superinfections, and antimicrobial therapy cost. The study was approved by the institutional review board, and all patients or next of kin gave written informed consent.

Statistical Analysis

Patient demographics (age, sex, etc.) and laboratory data were entered into PROPHET Statistics (Version 5.0; BBN Systems and Technologies, Cambridge, MA). The chi-square or Fisher test was used to compare categorical variables (presence or absence of an underlying condition). Continuous variables (age, Acute Physiology and Chronic Health Evaluation [APACHE] score, etc.) were compared using the *t* test or the Mann-Whitney test. A logistic regression model was used to evaluate the effects of several factors on outcome.

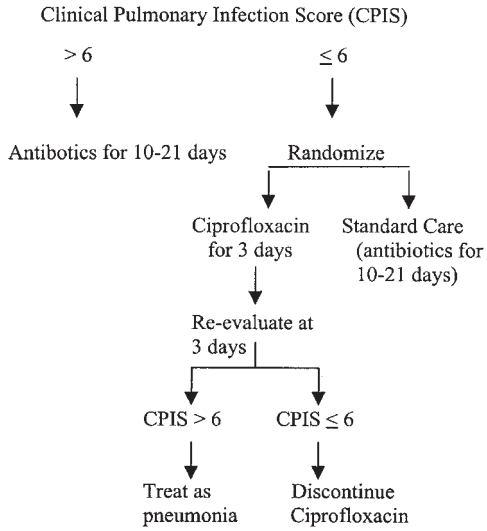

Figure 1. Flow chart representing the study design.

Sample Size

Assuming that the patients in the experimental therapy group would have 10% worse outcome than patients in the standard therapy arm, a sample size of 200 patients (100 in each arm) would detect a difference at 0.05 and power 0.5. Assuming a 20% incidence of development of resistance in the standard therapy group and 5% in the experimental group, a sample size of 176 patients (88 in each group) would be needed for significance at 0.05 and power 0.8.

RESULTS

Of 81 consecutive patients with pulmonary infiltrates and CPIS ≤ 6 that comprised the study population, 58% (47 of 81) were receiving mechanical ventilation. The mean length of ICU stay before the development of pulmonary infiltrate was 9 d. Overall, 79% (64 of 81) of the patients were postsurgical; 38% (31 of 81) had undergone cardiothoracic, 18% (15 of 81) abdominal surgery, 11% (9 of 81) head and neck surgery, 7% (6 of 81) had undergone orthopedic surgery, and 4% (3 of 81) were liver transplant recipients. The admitting diagnosis was nonsurgical in 21% (17 of 81); this included respiratory failure in 7% (6 of 81), coronary artery disease in 5% (3 of 81), end-stage liver disease in 5% (4 of 81), and nonsurgical neurological disorder in 4% (3 of 81). Of 81 patients enrolled, 39 were randomized to the experimental and 42 to the standard therapy arm. The two groups were similar at entry, including APACHE III score, duration of prior ICU stay, number receiving mechanical ventilation, and comorbid illness (Table 1). Patients in the experimental group, however, were somewhat older ($p = 0.06$) and were significantly more tachypneic ($p = 0.02$, Table 1).

Antimicrobial Agents

The experimental group received ciprofloxacin monotherapy for 3 d in accordance with the protocol. For the standard therapy group, 42 patients received 18 different antimicrobial agents, either singly (15) or in combination (27). The four most common antibacterial classes were β-lactam/β-lactamase inhibitors, 23 patients; quinolones 12 patients; aminoglycosides, 10 patients; and vancomycin, 10 patients. For 27 patients who received combination antibiotics, 14 received two antibacterial agents, one received one antibacterial agent plus fluconazole, six received three antibacterial agents simultaneously, five received four antibacterial agents simultaneously, and one

TABLE 1

CHARACTERISTICS OF THE STUDY GROUPS AT ENROLLMENT*

Variable	Experimental Group (*n* = 39)	Standard Therapy Group (*n* = 42)
Age, yr (mean ± SEM)	69 ± 1.4	64.5 ± 1.7
Comorbid illnesses		
Diabetes mellitus	18% (7/39)	26% (11/42)
Chronic obstructive pulmonary disease	26% (10/39)	29% (12/42)
Renal failure (creatinine > 2.0 mg/dl)	18% (7/39)	24% (10/42)
Malignancy	33% (13/39)	24% (10/42)
Liver disease	13% (5/39)	17% (7/42)
Transplantation	5% (2/39)	5% (2/42)
Postsurgical	85% (33/39)	74% (31/42)
Cardiac	46% (18/39)	31% (13/42)
Abdominal	20% (8/39)	17% (7/42)
Head and neck	8% (3/39)	14% (6/42)
Orthopedics	8% (3/39)	7% (3/42)
Transplant	3% (1/39)	5% (2/42)
Mechanical ventilation	59% (23/39)	57% (24/42)
APACHE III score, mean ± SEM	42.7 ± 2.2	41.0 ± 2.9
Prior length of ICU stay, d, mean	7.8	9.8
Duration of mechanical ventilation, d, mean	10.3	5.0
Vital signs†		
Abnormal temperature	39% (15/39)	48% (20/42)
Abnormal respiration	92% (36/39)	71% (30/42)
Abnormal blood pressure	49% (19/39)	38% (16/42)
Abnormal pulse	49% (19/39)	48% (20/42)
Clinical pulmonary infection score, mean	4.8 ± 1.6	4.9 ± 1.8
Temperature points	0.2	0.4
Leukocyte points	0.5	0.7
Tracheal secretions	1.0	0.8
Oxygenation	1.6	1.6
Radiography	1.5	1.4

* None of the variables differed significantly between the two groups except the patients in the experimental group were more likely to have tachypnea ($p = 0.016$).

† Abnormal temperature > 37.7° C or 35.5° C, abnormal pulse < 60 or > 100/min, abnormal respiration < 8 or > 16/min or < 6 or > 12 if ventilated, abnormal blood pressure, systolic < 80 or > 160 mm Hg or diastolic < 60 or > 90 mm Hg (4).

received five antibacterial agents simultaneously. The most common antibiotics used were various combinations of β-lactam/β-lactamase inhibitors or cephalosporins combined with an aminoglycoside.

Outcome Measures

Mortality, extrapulmonary infections, and the number of patients who developed CPIS > 6 at 3 d (implying increased likelihood of bacterial pneumonia) did not differ significantly between the standard therapy and experimental therapy groups (Table 2). However, antibiotics were continued beyond 3 d in a significantly greater number of patients in the standard therapy group (97%, 34 of 39) compared with the experimental group (28%, 11 of 39, $p = 0.0001$) (Table 2). Even though CPIS ⩽ 6 implies a low likelihood for bacterial pneumonia, in patients whose CPIS remained ⩽ 6 at the 3-d evaluation point, antibiotics were still continued beyond 3 d in 96% (24 of 25) of the patients in the standard therapy group but in 0% (0 of 25)

TABLE 2

ANTIBIOTIC USAGE, DURATION, AND COST IN THE EXPERIMENTAL AND STANDARD THERAPY GROUPS

Variable	Experimental (*n* = 39)	Standard Therapy (*n* = 42)	p Value
Deaths at 3 d	0% (0/39)	7% (3/42)	NS*
CPIS > 6 at 3 d	21% (8/39)	23% (9/39)	NS
Extrapulmonary infections†	18% (7/39)	15% (6/39)	NS
Antibiotic continuation > 3 d	28% (11/39)	97% (38/39)	0.0001
Antibiotics in patients with CPIS ⩽ 6 and no extrapulmonary infection			
Continuation < 3 d	0% (0/25)	96% (24/25)	0.0001
Duration of antibiotics, d, mean (range)	3 (3)	9.8 (4–20)	0.0001
Cost, mean	$259	$640	0.0001
Total	$6,482	$16,004	

* NS = not significant, $p > 0.05$.

† One patient with extrapulmonary infection in each study group also had CPIS > 6 at 3 d.

in the experimental group ($p = 0.0001$, Table 2). In accordance with the protocol, antibiotics in patients with CPIS ≤ 6 at 3 d were continued only if an extrapulmonary infection was documented. The duration of antibiotics in patients with CPIS ≤ 6 and no other documented infection, therefore, was 3 d in the experimental as compared with 9.8 d (range 4 to 20 d) in the standard therapy arm ($p = 0.0001$, Table 2). The mean number of antibiotics received by the latter patients was 1.7 and ranged from 1 to 4. Extrapulmonary infections documented in the study patients are outlined in Table 3.

Among patients who survived at least 3 d, 22% (17 of 78) developed CPIS > 6 at the 3-d evaluation point; these included 21% (8 of 39) of the patients in the experimental and 21% (9 of 39) in the standard therapy groups. These patients, in accordance with the protocol (in both arms of the study), were treated presumably as pneumonia with the choice of antibiotics at the discretion of the ICU care providers. Microorganisms detected in respiratory cultures in these 17 patients included gram-negative bacteria in 47% (8 of 17; *P. aeruginosa* 2, *S. marcescens* 2, *Haemophilus influenzae* 3, and *Klebsiella pneumoniae* 1), *S. aureus* in 29% (5 of 17) and *Aspergillus fumigatus* in 6% (1 of 17); 18% had normal flora in cultures. These microorganisms were equally distributed in both groups.

Mortality at 14 d (2 of 8 versus 3 of 9) or at 30 d (3 of 8 versus 5 of 9) did not differ for the experimental as compared with the standard therapy arm patients who developed CPIS > 6 at 3 d. Two of the five deaths in the standard therapy group and one of three in the experimental group were considered attributable to the pulmonary infiltrates. These included one patient with invasive aspergillosis and another with *S. aureus* pneumonia in the standard therapy arm. The patient in the experimental group fulfilled the criteria for acute respiratory distress syndrome (ARDS) at 3 d; no infection (extrapulmonary or pulmonary) was documented despite aggressive diagnostic testing, including bronchoscopy, in this patient. However, mortality at 30 d was significantly higher in patients who developed CPIS > 6 at 3 d, as compared with those in whom CPIS remained ≤ 6 at 3 d (47% [8 of 17] versus 16% [10 of 64], $p = 0.018$).

The length of ICU stay was significantly shorter in the experimental (mean 9.4 d, range 1 to 47 d) as compared with the standard therapy group (mean 14.7, range 1 to 91 d, $p = 0.04$) (Table 4). Excluding patients who died, the mean length of ICU stay was 8.7 d for patients in the experimental as compared with 14.7 d for those in the standard therapy arm ($p = 0.11$).

Mortality at 3 d, 14 d, or 30 d did not differ significantly between the patients in the experimental as compared with the standard therapy group (Table 4). When APACHE III score, CPIS > 6 at 3 d, and study regimen were entered into a multivariate model, only APACHE III score was significantly predictive of 14-d mortality. However, for 30-d mortality, all three variables were significant, with experimental treatment being protective and CPIS > 6 being 5.5 times more likely to be associated with mortality. The resolution of pulmonary infiltrates did not differ significantly for the two study groups (Table 4).

TABLE 3

EXTRAPULMONARY INFECTIONS IN THE STUDY GROUP

Infection	Experimental Group	Standard Therapy Group
Bacterial	18% (7/39)	24% (6/42)
Bacteremia	8% (3/39)	7% (3/42)
Enterococcus faecalis	1	1
Methicillin-sensitive *Staphylococcus aureus*	1	0
Morganella morganii	1	0
MRSA	0	2
Mediastinitis	1	1*
Abdominal abscess	1	0
Urinary tract infection	1	2
Clostridium difficile colitis	1	0
Fungal (invasive aspergillosis)	3% (1/39)	2% (1/42)

* The patient also had bacteremia.

TABLE 4

OUTCOME ENDPOINTS IN THE TWO STUDY GROUPS

Variable	Experimental	Standard Therapy	p Value
Length of ICU stay, d			
Mean/median	9.4/4	14.7/9	0.04
Range	1–47	1–91	
Mortality, d			
3	0% (0/39)	7% (3/42)	NS*
14	8% (3/39)	21% (9/42)	NS
30	13% (5/39)	31% (13/42)	NS (0.06)
Resolution of pulmonary infiltrate			NS
Complete resolution	41% (16/39)	21% (9/42)	
Partial resolution	18% (7/39)	14% (6/42)	
Unchanged	18% (7/39)	36% (15/42)	
Worsening	0/39	10% (4/42)	
No follow-up films	23% (9/39)	19% (8/42)	

* NS = not significant, $p > 0.05$.

Antimicrobial Resistance

Patients surviving at least 7 d after the initiation of antibiotics were considered evaluable for the assessment of antimicrobial resistance. Antimicrobial resistance and/or superinfections were documented in 15% (5 of 37) of the patients in the experimental and 35% (14 of 37) of the patients in the control group ($p = 0.017$, Table 5). Microorganisms associated with superinfections or resistance are outlined in Table 5. In all study patients, including those who died prior to 7 d, antimicrobial resistance and/or superinfections occurred in 13% (5 of 39) of the patients in the experimental and 33% (14 of 42) in the standard therapy group ($p = 0.025$).

Antimicrobial Cost

The average wholesale price of the antibiotics (*Drug Topics Red Book*, Montvale Medical Economics Company, Mont-

TABLE 5

ANTIMICROBIAL RESISTANCE AND SUPERINFECTIONS IN THE EXPERIMENTAL AND STANDARD THERAPY GROUPS

Variable	Experimental	Standard Therapy	p Value
Antimicrobial resistance and/or superinfections*	14% (5/37)	38% (14/37)	$p = 0.017$
Microorganisms†			
Pseudomonas aeruginosa	8% (3/37)	16% (6/37)	
Enterobacter cloacae	—	5% (2/37)	
MRSA	5% (2/37)	14% (5/37)	
Pseudomonas cepacia	3% (1/37)	—	
Citrobacter freundii	—	3% (1/37)	
Pseudomonas stutzeri	—	3% (1/37)	
Enterococcus species	3% (1/37)	11% (4/37)	
E. faecalis	1	3	
Vancomycin-resistant *E. faecium*	0	1	
Candida species	8% (3/37)	14% (5/37)	
C. albicans	3	3	
C. glabrata	0	2	

* Patients who died < 7 d after study entry were excluded for this analysis.
† Patients who may have more than one microorganism.

vale, NJ, 1998), was used to calculate the cost of acquisition of antimicrobial agents based on the dosages and duration of antibiotic therapy used. Among patients with CPIS ⩽ 6 and no extrapulmonary infection, only ciprofloxacin monotherapy was employed for 3 d. Antibiotics used in the standard therapy arm for the similar group of patients included vancomycin, piperacillin–tazobactam, ampicillin–sulbactam, ticarcillin–clavulanic acid, ciprofloxacin, ofloxacin, gentamicin, erythromycin, amoxicillin, clindamycin, piperacillin, ceftazidine, and aztreonam; the mean number of antibiotics used was 1.7. The total cost of antibiotics for the patients with CPIS ⩽ 6 at 3 d and no extrapulmonary infections was $6,484 in the experimental and $16,004 in the standard therapy arm (Table 2).

Study Termination

Because the study was not blinded, physicians and care providers could see the results. We observed a trend toward physicians prescribing fewer antibiotics for shorter duration in patients randomized to standard therapy as the study progressed. When 24 patients in the standard therapy arm, who had CPIS ⩽ 6, no extrapulmonary infection, and who survived at least 3 d, were divided into four equal groups of six patients each over time, the duration of antibiotic use was significantly shorter in Group 4 (last six patients) compared with those in Groups 2 and 3 (Patients 7 to 12 and 13 to 18, respectively) and tended to be shorter compared with those in Group 1 (first six patients). Overall, the duration of antibiotics was significantly shorter in Group 4 as compared with all other groups ($p = 0.0001$). After interviewing the investigators and attending physicians and reviewing the results, the protocol was terminated because the institutional review board determined that it was unethical to continue to study.

DISCUSSION

This study documents that overprescription of antibiotics was widely prevalent for patients with pulmonary infiltrates in our ICU. Antibiotics once initiated, were invariably continued for 4 to 20 d (average 10 d), regardless of the likelihood of pneumonia and in the absence of an extrapulmonary infection. Although pneumonia could arguably have been present despite the clinical criteria suggesting otherwise, the outcome of these patients was similar to those in whom antibiotics were discontinued after 3 d, implying thereby that prolonged antibiotic usage in the former group of patients was unnecessary and even inappropriate.

Although the escalating trend in indiscriminate and inappropriate prescription of antibiotics has been decried by academicians, widespread antibiotic usage continues (11). One factor contributing to this worrisome practice is the fact that a gold standard for the diagnosis of nosocomial pneumonia has not been clearly established. The role of invasive procedures for the diagnosis of pneumonia remains a contentious topic in ICU pulmonary medicine. The proponents of such an approach argue that clinical criteria are unreliable and overestimate the incidence of pneumonia (12–14). Although a lower mortality and decreased antibiotic use was reported in a study with invasive as compared with noninvasive management strategy, these results remain to be verified in future studies (15). Sanchez-Nieto and coworkers have documented that invasive diagnostic procedures merely led to more frequent antibiotic modification with no change in mortality (16). Furthermore, in patients suspected of having pneumonia, physicians invariably continued antibiotics, regardless of the results of bronchoscopy, thereby nullifying any potential benefit of the invasive procedure (15). These data have led some experts to conclude that instead of relying on microbiologic tests, the management of nosocomial pneumonia should focus on approaches that are intended to affect clinically relevant outcomes, for example, mortality, antimicrobial resistance, and cost (8, 17, 18).

Thus, physicians caring for ICU patients continue to struggle with the optimal management of possible nosocomial pneumonia. Withholding antibiotics when faced with uncertainty in diagnosing a potentially treatable infection is a simplistic and a largely unrealistic approach toward curtailing antibiotic use. Indeed, empiric antibiotic prescription is often a reflex decision when new pulmonary infiltrates are observed in an ICU patient.

Our approach accepts the realities of empiric prescription of antibiotics. Our focus was, instead, to limit the number and duration of antibiotic use. We used the CPIS proposed by Pugin and coworkers to determine the "likelihood" of pneumonia (8); CPIS ⩽ 6 implied that the patient was unlikely to have bacterial pneumonia. The CPIS was used, not as a diagnostic tool as originally proposed by Pugin and coworkers, but as a screen for decision-making regarding antibiotic therapy. It should be noted that we did not attempt to define pneumonia nor determine with precision whether the patient truly had a pneumonia. Indeed, we accepted that clinical criteria, including CPIS, may be unreliable for the diagnosis of pneumonia. CPIS, therefore, was not used to discern whether the patient did or did not have pneumonia, but rather to identify patients for whom a shorter course of antibiotic therapy would suffice.

Microbial ecology and the predominant bacterial flora can have wide institutional variation. Ciprofloxacin was selected as empiric antibiotic based on the fact that gram-negative bacteria (enteric gram-negative bacilli, *P. aeruginosa*, and *H. influenzae*) have been identified as the predominant microbial causes of nosocomial pneumonia at our institution (4). Additionally, 12% and 5% of the nosocomial pneumonias in the ICU have been attributed to MRSA and *Legionella* respectively (4). Ciprofloxacin has *in vitro* antimicrobial activity against all of these bacteria. Furthermore, ciprofloxacin is less likely to lead to extended-spectrum β-lactamase production in gram-negative bacteria and was shown to be efficacious as monotherapy for nosocomial pneumonia in a randomized, controlled trial (19).

Thirteen patients in the standard therapy arm also received a quinolone as antibiotic therapy according to the primary care providers (ofloxacin, eight; ciprofloxacin, five). We, however, emphasize that the overall approach, and not utilization of a particular antibiotic regimen identifies the essence of our strategy. A 3-d duration for empiric ciprofloxacin monotherapy was selected because this time period would allow microbiologic culture data to be available for assessing the need to continue antibiotics. Furthermore, antibiotic therapy for as short as 3 d has been documented to sterilize the lung in patients with ventilator-associated pneumonia (20).

Patients with a CPIS ⩽ 6 who received experimental therapy had a significantly lower duration of antibiotic use (3 d versus 9.8 d, $p = 0.0001$) and a lower total antimicrobial therapy cost ($6,482 versus $16,004) when compared with standard therapy. Despite the shorter duration with monotherapy, the length of ICU stay or survival was not affected adversely. Our study showed that in 79% (64 of 81) of the study patients, CPIS remained ⩽ 6 at 3 d, implying that antibiotics can be safely discontinued in the majority of ICU patients, provided no extrapulmonary infections were documented. Most importantly, however, we documented a significantly lower rate of the emergence of antimicrobial resistance and superinfections in the experimental therapy group as compared with the standard therapy group.

Even in patients in whom the CPIS increased to > 6 at the 3-d evaluation point, implying development of pneumonia, the

experimental therapy group had an outcome similar to the standard therapy. In 21% (8 of 39) and 21% (9 of 42)of the patients in the experimental and standard therapy arms, respectively, the CPIS increased to > 6 at 3 d. Potentially pathogenic microorganisms were documented in respiratory cultures of 82% of these patients and included gram-negative bacteria in 47%, *S. aureus* in 29%, and *A. fumigatus* in 6%. Mortality at 14 d or 30 d did not differ between the patients with CPIS > 6 who initially received monotherapy, as compared with standard therapy.

Possible reasons that could account for the success of the experimental therapy include the fact that patients with CPIS ≤ 6 indeed did not have a nosocomial pneumonia and thus CPIS accurately ruled out an infection. It is also conceivable that a proportion of patients with CPIS ≤ 6 had a mild infection, e.g., tracheobronchitis or minimal pneumonitis, that was treatable with 3 d of monotherapy. Regardless of the precise explanation, the CPIS criteria were documented to be efficacious in minimizing antibiotic usage without compromising the clinical outcome.

Our study, however, has weaknesses that deserve to be acknowledged. The study was conducted in a Veterans Affairs hospital with its predominance of elderly men with chronic underlying diseases. We are unconvinced that this is a major weakness because the presence of chronic illness is typical of ICU patients everywhere; we doubt that the preponderance of male sex would have affected the validity of these conclusions. Furthermore, the problem of overprescription of antibiotics is not unique to the Veterans Affairs hospital (3, 5, 6, 21).

Because the study was not blinded, it became apparent to the physicians that the routine administration of multiple broad-spectrum antibiotic therapy for prolonged duration did not favorably affect outcome nor decrease complications. Instead, the notable number of patients experiencing emergence of resistant microorganisms and superinfection was not only statistically significant, but clinically apparent. Because the standard therapy was unrestricted in the original study protocol, a bias gradually occurred as physicians began to minimize the number of antibiotics prescribed and number of days of administration. We point out that this bias actually favored the standard therapy rather than the experimental therapy; however, the emergence of antibiotic resistance and superinfection was so striking that statistical significance was attained despite the appearance of this bias. After a review of the preliminary findings and discussion with the attending physicians, the institutional review board recommended that the study be terminated.

Because of the aforementioned weaknesses of our study, we recommend that other institutions should neither accept our results nor implement our recommendations without validating our approach in their own unique patient population and hospital. However, we are also recommending that the study be replicated for another reason. The problem of inappropriate antibiotic use has become so pervasive that bureaucratic restrictions are being implemented, including approval by infectious disease physicians and strict pharmacy guidelines. Education has not been uniformly successful in improving physician prescribing habits. During the course of our study, the physicians began to voluntarily modify and curtail their antibiotic prescribing habits, because of the gradual realization that their standard practice not only lacked a detectable benefit, but was causing measurable harm to their patients. Thus, performing a study to validate our conclusions would not only conform to the highest level of evidence-based medicine, but the conduct of such a study would contribute toward physician understanding of the fundamentals of appropriate antibiotic usage. We claim that such insights gained by the practicing physician will be a more powerful and effective deterrent to antibiotic misprescription than imposed regulations.

In summary, most pulmonary infiltrates in the ICU are not pneumonia. Indeed, patients with CPIS ≤ 6 comprise a large subgroup, as we have shown previously; 74% of the patients with pulmonary infiltrates in the ICU had CPIS ≤ 6 (4). Our findings may, therefore, have widespread applicability and significant implications for curtailing antibiotic usage in these patients. CPIS used as operational criteria in the present study, regardless of the precise definition of pneumonia, was accurate in identifying patients with pulmonary infiltrates in the ICU for whom monotherapy with a shorter duration of antibiotics was appropriate.

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APPENDIX

CLINICAL PULMONARY INFECTION SCORE CALCULATION*†

Temperature (°C)
- > or equal to 36.5 and < or equal to 38.4 = 0 point
- > or equal to 38.5 and < or equal to 38.9 = 1 point
- > or equal to 39 and < or equal to 36 = 2 points

Blood leukocytes, mm^3
- > or equal to 4,000 and < or equal to 11,000 = 0 point
- < 4,000 or > 11,000 = 1 point + band forms > equal to 50% = add 1 point

Tracheal secretions
- Absence of tracheal secretions = 0 point
- Presence of nonpurulent tracheal secretions = 1 point
- Presence of purulent tracheal secretions = 2 points

Oxygenation: $Pa_{O_2}/F_{I_{O_2}}$, mm Hg
- > 240 or ARDS (ARDS defined as $Pa_{O_2}/F_{I_{O_2}}$, or equal to 200, pulmonary arterial wedge pressure
- < or equal to 18 mm Hg and acute bilateral infiltrates) = 0 point
- < or equal to 240 and no ARDS = 2 points

Pulmonary radiography
- No infiltrate = 0 point
- Diffuse (or patchy) infiltrate = 1 point
- Localized infiltrate = 2 points

Progression of pulmonary infiltrate
- No radiographic progression = 0 point
- Radiographic progression (after CHF and ARDS excluded) = 2 points

Culture of tracheal aspirate
- Pathogenic bacteria‡ cultured in rare or light quantity or no growth = 0 point
- Pathogenic bacteria cultured in moderate or heavy quantity = 1 point
- Same pathogenic bacteria seen on Gram stain, add 1 point

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CHF = congestive heart failure; $Pa_{O_2}/F_{I_{O_2}}$ = ratio of arterial oxygen pressure to fraction of inspired oxygen.

* Modified from Pugin and coworkers (8).

† CPIS at baseline was assessed on the basis of the first five variables, i.e., temperature, blood leukocyte count, tracheal secretions, oxygenation, and character of pulmonary infiltrate. CPIS at 72 h was calculated based on all seven variables and took into consideration the progression of the infiltrate and culture results of the tracheal aspirate. A score > 6 at baseline or at 72 h was considered suggestive of pneumonia.

‡ Predominant organism in the culture.