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ORIGINAL ARTICLE

Measuring Acceptable Treatment Failure Rates for Community-Acquired Pneumonia: Potential for Reducing Duration of Treatment and Antimicrobial Resistance

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OBJECTIVE.   This study was designed to establish the rates of treatment failure for community-acquired pneumonia that are acceptable to knowledgeable and experienced physicians, in order to facilitate the interpretation of existing studies and the design of new studies aimed at optimizing the duration of antibiotic therapy. Reducing the duration of antibiotic therapy is one strategy for reducing antibiotic exposure and thereby minimizing the potential for the emergence of antimicrobial resistance.

DESIGN.   Survey soliciting the acceptable failure rate for treatment given to an adult patient with uncomplicated community-acquired pneumonia treated with standard-of-care therapy in the outpatient setting. Analysis was performed using a modification of established methods of contingent valuation analysis.

PARTICIPANTS.   Six hundred eighty infectious diseases physicians in North America who were also members of the Emerging Infections Network of the Infectious Diseases Society of America.

RESULTS.   Three hundred seventy-five (55.1%) of 680 physicians responded to the survey. The median acceptable failure rate for treatment was 13.5%. Five hundred ten respondents (75.0%) found a failure rate of 7.3% acceptable, and 170 respondents (25.0%) found a failure rate of 19.8% acceptable.

CONCLUSIONS.   This study identified the failure rates for treatment of community-acquired pneumonia that were acceptable to infectious disease physicians. This range of acceptable treatment failure rates may facilitate the design of studies aimed at optimizing the duration of antimicrobial therapy for community-acquired pneumonia.

Infect Control Hosp Epidemiol 2008; 29:137-142

Community-acquired pneumonia is one of the most commonly treated infections in the United States. It is responsible for 4.5 million outpatient physician visits annually in the United States, and the total cost of care is $8.4 billion, 8% of which is spent on antibiotics.[1] Despite the frequency with which this infection occurs, the optimal duration of antibiotic therapy has not been well established in clinical trials. Although some guidelines suggest that selected patients with community-acquired pneumonia may be treated with antibiotics for as little as 5 days, most patients are treated for 7-10 days or longer.[2] Uncertainty about the optimal duration leads many physicians to prescribe unnecessarily long courses of antibiotic therapy to patients with community-acquired pneumonia. Recent clinical trials have begun to evaluate shorter courses of treatment.[3-5]

Several authors have proposed that a reduction in the du-

ration of antibiotic therapy may result in a decrease in the emergence and spread of antimicrobial resistance.[6-8] In *Streptococcus pneumoniae,* the emergence and spread of resistance to penicillin, cephalosporins, and most recently, fluoroquinolones, have been linked to levels of antibiotic use, both in individuals and in communities.[9-11] In addition, shorter durations of treatment for community-acquired pneumonia are associated with improved patient compliance wit therapy,[4,12,13] lower drug costs,[14] fewer adverse drug-related events,[15] improved patient satisfaction, and patient perception of greater treatment efficacy.[16]

Studies of therapy for community-acquired pneumonia typically use treatment failure as an endpoint and rarely examine the emergence and spread of antimicrobial resistance, cost, patient satisfaction, and/or compliance. Future investigations of shorter durations of therapy for community-ac-

quired pneumonia would benefit from a clear understanding of the treatment failure rates that are acceptable to knowledgeable, experienced physicians. To our knowledge, no prior study has attempted to identify acceptable treatment failure rates for this common infection. In a survey of infectious diseases physicians who were members of the Infectious Diseases Society of America's Emerging Infections Network, we sought to establish what failure rate for treatment given to patients with mild to moderate community-acquired pneumonia would be acceptable to infectious diseases physicians.

METHODS

Pilot Study

We performed a pilot study to develop a range of treatment failure rates. In the pilot study, we asked 55 infectious diseases physicians to estimate an acceptable failure rate for treatment given to a patient with uncomplicated community-acquired pneumonia who met the criteria for outpatient treatment. Approximately half of the respondents received the question in an open-ended format; the other half received a multiple-choice question that provided a range of rates as response options. We defined treatment failure as "the persistence of symptoms after the first week following the office visit, necessitating hospitalization related to persistent and/or worsening pneumonia." We used the results to determine the contingent valuation choices (ie, the possible acceptable failure rates) to be offered in the study questionnaire.

Study Subjects

The Infectious Diseases Society of America's Emerging Infections Network includes infectious diseases physicians who belong to either the Infectious Diseases Society of America or the Pediatric Infectious Diseases Society; these physicians regularly engage in clinical activity and participate in network activities. Ninety-five percent of Emerging Infections Network members practice in North America. This survey targeted all 680 Emerging Infections Network members who treat adult patients in North America.

Questionnaire

In May 2003, the Emerging Infections Network distributed the survey via facsimile and e-mail to 680 physicians. Subjects who did not respond to the first survey received a second facsimile 2 weeks later, and a third 4 weeks later. A total of 300 respondents were anticipated on the basis of response rates to previous surveys conducted in this network.[17-19]

The survey included a 1-page introduction and a case-based questionnaire entitled "Failure Rates for Treatment of Community-acquired Pneumonia Patients" (Appendix, Figure). The questionnaire described a 35-year-old patient with uncomplicated community-acquired pneumonia who received standard-of-care oral antibiotic therapy in the out-patient setting. The definition of treatment failure was the same as the definition used in the pilot study. The physicians surveyed were asked, "Given the standard treatment scenario described above, do you feel that the treatment failure rate listed below would be acceptable (i.e. is the rate listed below less than or equal to a reasonable estimate of the percent of patients that you would expect to fail appropriate therapy)?"

A single failure rate was provided, with check boxes marked "yes" and "no" for the physician's response. The specific failure rates that were sent to the physicians being surveyed were based on the results of the pilot study. During the pilot study, physicians who answered the open-ended question reported a median acceptable failure rate of 5.0% (range, 0.2%-20%), and those who answered the multiple-choice question reported a median acceptable failure rate between 2% and 5% (range, 0.1%-10%). Therefore, the following 10 choices of acceptable failure rates were distributed to the physicians in the study questionnaire: 0.1%, 1%, 2%, 3%, 5%, 7%, 10%, 15%, 20%, and 30%. Each Emerging Infections Network member practicing in North America received a questionnaire that included 1 of these choices, which were randomly distributed on a regional basis.

This approach to eliciting the respondent's willingness to accept certain rates of treatment failure is closely related to the contingent valuation methodology used in studies of willingness to pay or willingness to accept payment.[20] The median value for the acceptable rate of treatment failure is the summary measurement of the willingness of the population of respondents to accept the outcome. The "take it or leave it" approach (ie, offering respondents a single failure rate) described above was used to minimize the potential for framing effects and anchoring biases (ie, the sensitivity of subject responses to opening bids and the phrasing of questions), which can occur when open-ended questions are used to elicit preferences in contingent valuation analysis.

TABLE 1. Geographic Distribution of Respondents in Regions Delineated by the Centers for Disease Control and Prevention

Region	No. of respondents
New England	29
Mid-Atlantic	58
East North Central	50
West North Central	22
South Atlantic	80
East South Central	13
West South Central	35
Mountain	23
Pacific	59
US Territory	2
Canada	4
Total	375

TABLE 2.   Proportions of Infectious Diseases Physicians Who Accepted Specified Failure Rates for the Treatment of Community-Acquired Pneumonia

Failure rate specified, %	Proportion (%) of respondents who accepted
0.1	29/30 (96.7)
1	31/34 (91.2)
2	35/38 (92.1)
3	36/41 (87.8)
5	25/32 (78.1)
7	33/40 (82.5)
10	17/31 (54.8)
15	9/30 (30.0)
20	7/39 (18.0)
30	7/54 (13.0)
Total	229/369

Statistical analysis

Statistical analyses were performed using SAS, version 8.2 (SAS Institute), and Excel 2000 (Microsoft). For each failure rate presented to the subjects, the proportion of respondents who found the rate acceptable was calculated. The distribution of the values of acceptable failure rates was examined, and the median and interquartile ranges were determined. The relationship between the willingness to accept a rate and the rate offered to the subject in the questionnaire was evaluated by use of logistic regression. In addition, bivariable and multivariable logistic regression were used to evaluate whether the subjects' number of years in practice might have influenced their willingness to accept a certain rate of treatment failure.

RESULTS

Of 680 physicians surveyed, 375 (55.1%) responded to the survey. A total of 6 respondents failed to provide interpretable data and their questionnaires were excluded, which meant that responses from 369 infectious disease physicians were available for analysis. Three hundred sixty-three subjects were from the United States, 4 subjects were from Canada, and 2 were from a US territory. Subjects in the United States came from all regions of the country (Table 1). The mean duration of clinical practice ($\pm$ SD) among respondents was 16.2 $\pm$ 9.0 years (range, 3 months–41 years).

There was a mean of 36.9 respondents for each numerical failure rate option, with a minimum of 30 and a maximum of 54 respondents for each option (Table 2). In general, the number of respondents who identified a particular failure rate as acceptable declined as the proposed failure rate increased. Twenty-nine (96.7%) of 30 respondents found a failure rate of 0.1% acceptable, whereas only 7 (13.0%) of 54 respondents found a failure rate of 30% acceptable (Table 2).

In the bivariable logistic regression model, with failure rate as the predictor for the binary outcome "accepted" (ie, the failure rate was acceptable) or "not accepted" (ie, the failure rate was not acceptable), the odds that a respondent would find a proposed failure rate acceptable decreased by 0.84 for each 1% increase in the proposed failure rate (95% confidence interval [CI], 0.81-0.87; $P < .001$). Thus, if the failure rate presented in the questionnaire increased from 1% to 2%, the odds that respondents would accept this higher failure rate would fall by a factor of 0.84. Similarly, if the failure rate increased from 5% to 10%, the odds that the 10% rate would be identified as acceptable (relative to the 5% rate) would fall by a factor of 0.84 (ie, 0.42).[5]

Figure 1 shows a fitted logistic curve that illustrates the proportion of respondents who were willing to accept a certain failure rate across the range of proposed failure rates. The estimated median failure rate was 13.5%. Thus, if all subjects were presented with a proposed failure rate of 13.5%, half of them would have been expected to accept that failure rate. Three-quarters of all subjects would have accepted a failure rate of 7.3%, and one-quarter would have accepted a failure rate of 19.8%.

In a logistic regression model adjusting for the effect of years in practice, there was no change in the odds ratio (OR) for likelihood to accept a certain failure rate. The number of years in practice was not a significant independent predictor of whether a respondent would accept a given failure rate (OR, 1.02 [95% CI, 0.99-1.06]; $P = .16$).

DISCUSSION

This study reports physicians' judgments about acceptable failure rates for treatment administered for uncomplicated community-acquired pneumonia in an otherwise healthy 35-
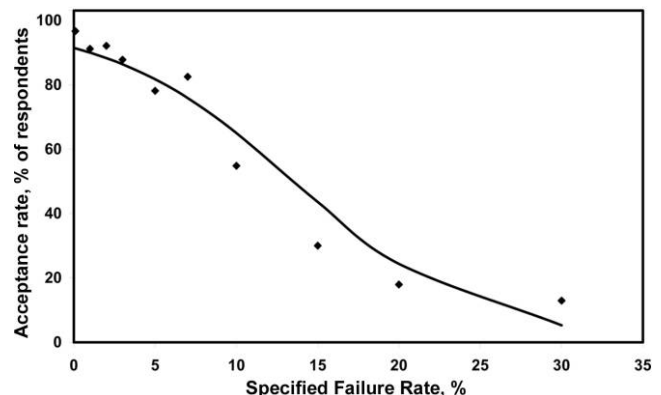

FIGURE 1.   Relationship between the treatment failure rate given on the survey and the percentage of respondents willing to accept that failure rate. *Diamonds,* 30-54 subjects. *Line,* fitted curve that uses all data describing the expected percentage willing to accept each failure rate.

year-old treated in the outpatient setting. The median acceptable treatment failure rate reported in our study, 13.5%, is similar to failure rates reported in recent clinical trials evaluating therapy for community-acquired pneumonia. In a systematic review of prospective, randomized clinical trials of therapy involving adult patients with community-acquired pneumonia from 1990 to 1997, a total of 16 trials with 33 treatment arms had a median failure rate of 15.5% (range, 0%-34%).[21]

Our results will facilitate the design of future clinical trials of treatment of community-acquired pneumonia. Antimicrobial therapy of long duration might improve therapeutic efficacy, but may also increase the emergence and spread of antimicrobial resistance, as well as increase costs, the incidence of adverse events, and rates of noncompliance with therapy; it may also decrease patient satisfaction and perceived treatment efficacy. Therefore, a rational target for treatment efficacy is needed. Our results suggest that a treatment failure rate of 13.5% or less for uncomplicated community-acquired pneumonia is acceptable to at least 50% of physician experts. Thus, investigators might choose to shorten the duration of therapy for a given antibiotic regimen, as long as failure rates do not exceed 13.5%.

Only a few published studies have compared the efficacy of using different durations of therapy involving the same drug for the treatment of community-acquired pneumonia. Recent studies have reported similar rates of treatment failure among hospitalized patients who received different durations of azithromycin therapy for the treatment of atypical pneumonia[5] and among children who received different durations of amoxicillin therapy for treatment of nonsevere community-acquired pneumonia.[4] Dunbar et al.[3] recently reported the results of a study involving adults with mild to severe community-acquired pneumonia. A total of 528 patients were randomized to receive either levofloxacin therapy for 5 days (750 mg per day) or levofloxacin therapy for 10 days (500 mg per day). At a follow-up visit 7-14 days after the initiation of treatment, similar rates of clinical failure were observed in the 5-day group and the 10-day group (7.6% vs 8.9%).[3]

There were limitations to this study. The response rate to the survey was 55.1%. This response rate is similar to other published surveys and questionnaires distributed by the Emerging Infections Network, and the percentage of respondents was consistent between regions of North America.[17-19] It is unlikely that nonparticipation would be associated with different preferences with respect to acceptable treatment failure rates. Additionally, the survey included only 1 scenario, that of an otherwise healthy 35-year-old man. Our estimate of an acceptable treatment failure rate should not be extrapolated beyond such a clinical situation. Patient perceptions were not measured, and decisions about treatment are often shared between physician and patient.[22] Our findings provide new information regarding physicians' perceptions of acceptable failure rates, which is an important step in developing effective shared decision-making models. Future studies might focus on acceptable failure rate thresholds as reported by patients. Finally, only infectious diseases specialists were surveyed. Additional studies including the opinions of different specialists would be of interest.

The questionnaire methodology, which used an approach similar to economic contingent valuation, is a strength of this study. This approach has been used to generate monetary values for abstract quantities, such as water quality, to evaluate preferences for health products,[23-27] to evaluate societal preferences for health states,[28] and to determine acceptable rates of treatment failure for diabetic foot osteomyelitis.[19] The "take it or leave it" strategy that we used may better approximate real-life decision making,[29] and it may be less prone to framing and anchoring biases,[19,20,30] compared with open-ended strategies.

Estimates of the treatment failure rates that are acceptable to knowledgeable and experienced physicians can be used to establish targets for therapeutic efficacy in the design of studies that aim to reduce excess antibiotic use. Decreasing overall antibiotic exposure will likely slow the emergence and spread of antimicrobial resistance, reduce medical costs and the incidence of adverse events, and improve patient compliance with antibiotic therapy. The estimate of an acceptable treatment failure rate for community-acquired pneumonia reported in this study provides a formalized frame of reference for both the interpretation and design of clinical trials for treatment of mild to moderate community-acquired pneumonia. Ongoing studies of acceptable treatment failure rates for community-acquired pneumonia as well as other infectious diseases will help guide the implementation of new methods of antibiotic therapy, such as short-course therapy, while also helping to improve communication and facilitate shared decision making between physicians and patients.

EMERGING INFECTIONS NETWORK QUERY SHEET

Name: _____   # of Years in Practice: _____

Failure Rates for Treatment of Community-acquired Pneumonia Patients

A 35-year old male presents to your office with complaints of cough productive of yellow-green sputum and fever for 48 hours. He also complains of occasional shaking chills and decreased appetite. He has no co-morbid conditions and has never had an overnight hospital stay. He has no HIV risk factors, and had a negative serum HIV antibody for insurance screening 2 months ago.

On exam, he is non-toxic appearing. Temperature (oral) = 101° F, heart rate = 100, respiratory rate = 23, oxygen saturation 96% and blood pressure = 120/80. He is not orthostatic. On pulmonary exam, he has dullness to percussion, crackles, and bronchial breath sounds at his left base. His other lung fields are normal.

Chest radiograph reveals partial consolidation of his left lower lobe suggestive of and consistent with pneumonia. There are no pleural effusions, no cavitary components and no involvement of other lobes of the lungs.

You feel that the patient's clinical presentation is consistent with community-acquired pneumonia. Since the patient is stable and meets IDSA guidelines for treatment as an outpatient you decide to treat him accordingly. You prescribe one of the recommended oral agents for outpatient therapy for a standard treatment duration (as recommended by IDSA and American Thoracic Society guidelines).

For the purposes of this case, treatment failure is defined as the persistence of symptoms after the first week following the office visit, necessitating hospitalization related to persistent and/or worsening pneumonia.

Given the standard treatment scenario described above, do you feel that the treatment failure rate listed below would be acceptable (i.e. is the rate listed below less than or equal to a reasonable estimate of the percent of patients that you would expect to fail appropriate therapy)?

Failure rate = x%   (*Check only one*)   ☐ **Yes**

                                                     ☐ **No**

FIGURE.   Questionnaire distributed to Emerging Infections Network members

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