Cost-effectiveness Analysis Of Five Different Antibiotic Regimens For The Treatment Of Uncomplicated *Chlamydia Trachomatis* Cervicitis

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Background: The new Centers for Disease Control and Prevention treatment guidelines for Chlamydia trachomatis include two recently available drugs, azithromycin and ofloxacin. The best choice for initial therapy remains controversial.

Objectives: We wanted to perform a cost-effectiveness analysis of five different antibiotic regimens for the treatment of uncomplicated Chlamydia trachomatis cervicitis.

Methods: Using information gathered from a MEDLINE search of the English language literature from 1966 to 1994, employing the key words "cervicitis," "C. trachomatis," "erythromycin," "tetracycline," "doxycycline," "ofloxacin," and "azithromycin," we developed a decision analysis model specific for a nonpregnant woman with uncomplicated Chlamydia trachomatis cervicitis. Options in this model included an initially cured infection, a failed initial cure resulting in persistent cervicitis, or pelvic inflammatory disease treated either on an inpatient or outpatient basis. Probability estimates for each option were derived from previously published reports. A cost-effectiveness analysis was performed for three end points: cost per cure with initial therapy, cost per case of pelvic inflammatory disease averted, and cost per hospitalization averted. Sensitivity analyses were done by varying the cure rates for each antibiotic and the complication rates for failed therapy. The costs incurred for treatment were also varied.

Results: Using the high estimate for initial cure rates, doxycycline and tetracycline were the most cost-effective agents. Azithromycin was the next most cost-effective agent, followed by ofloxacin and erythromycin. To achieve an equivalent final cost, the probability of initial cure with azithromycin must exceed that of doxycycline by 3 percentage points. As the cost of azithromycin decreases, the difference in initial cure rates between the two drugs to achieve an equivalent final cost becomes smaller.

Conclusions: Doxycycline remains the drug of choice in the treatment of Chlamydia trachomatis cervicitis. The results favor the use of azithromycin rather than doxycycline when there is concern for compliance to the standard doxycycline regimen. A lower cost for azithromycin could favor its use as the drug of choice. (J Am Board Fam Pract 1995; 8:7-16.)

Chlamydia trachomatis infection is one of the most frequently encountered sexually transmitted diseases. Each year more than 4.6 million persons in the United States are infected.[1,2] The standard antibiotics for the treatment of this disease have been doxycycline, tetracycline, and erythromycin.[3] The Centers for Disease Control and Prevention (CDC) recently updated their treatment guidelines for *C. trachomatis*. The guidelines include two newly available drugs, azithromycin and ofloxacin.[4] These drugs provide distinct advantages over the previously used medications: single-dose therapy (for azithromycin) and the potential for improved efficacy and fewer adverse gastrointestinal side effects (for both agents).[5-9] Unfortunately, both new agents cost substantially more than the previously established therapies available in generic formulations.

For nonpregnant women failure to treat adequately *C. trachomatis* cervicitis can result in pelvic inflammatory disease, ectopic pregnancy, and infertility.[10] The costs of treating these complications are substantial.[11-13] Given the concerns with compliance to the standard antichlamydial drugs[14] and the higher costs of the two new agents, we analyzed each of the therapeutic options for treatment of *C. trachomatis* cervicitis through a formal

Submitted, revised, 2 August 1994.

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decision analysis model and designed a cost-effectiveness analysis to determine which of the five antibiotic choices is the most desirable.

Methods

Decision Tree

Figure 1 displays the decision model used in this analysis. The model was specific for a nonpregnant woman with uncomplicated *C. trachomatis* cervicitis. The strategy involves the comparison of erythromycin, tetracycline, doxycycline, ofloxacin, or azithromycin for initial therapy. A cost-effectiveness analysis was performed for three end points: cost per cure with initial therapy, cost per case of pelvic inflammatory disease (PID) averted, and cost per hospitalization averted. We used the software package Decision Maker to carry out the calculations of the model.[15] This package, developed by Sonnenberg and Pauker, allows for the construction, evaluation, and modification of decision trees. Specific programming is provided for cost-effectiveness analysis.

Estimates of Outcome Probabilities

We analyzed the efficacy of each treatment option in curing an uncomplicated *C. trachomatis* cervicitis infection and in preventing subsequent PID. Probability estimates for each treatment option were derived from previously published reports. To obtain these estimates, we performed a MEDLINE search of studies published in English from 1966 to 1994 using the following key words: "cervicitis," "*C. trachomatis*," "erythromycin," "tetracycline," "doxycycline," "ofloxacin," and "azithromycin." Eligible studies included all published randomized controlled reports of nonduplicated data in which a study antibiotic was used to treat *C. trachomatis* at a dose consistent with current CDC guidelines. Noneligible studies included uncontrolled clinical trials, case series, and interim studies with data included in a later report. The reference list of each retrieved report was scanned for potential additional reports. A manual search of *Index Medicus* was performed as well. Twenty-one reports were selected using this search strategy.[6-8,16-33] From these eligible articles we retrieved the following information:

1. The probability of resolution of the *C. trachomatis* cervicitis infection with each therapeutic agent.
2. The probability of major and minor adverse side effects with each agent.

Probability estimates for the consequences for failing to respond to initial therapy were also derived from previously published reports. The specific probabilities included whether PID would develop in a woman who failed initial therapy and whether treatment would require inpatient or outpatient management. Estimates of probabilities were based on published literature obtained from a MEDLINE search for all articles reporting epidemiologic data on acute pelvic inflammatory disease in the United States including information on hospitalizations. Six reports were selected using this search strategy.[13,34-38]

Sensitivity Analysis for Probability Estimates

For each probability estimate on response to and consequences for failing to respond to initial therapy, we used the information extracted from the literature to estimate a plausible range of probability. We used this range to determine the impact of the high and low values for these probabilities on the study conclusions. The probabilities used in our sensitivity analysis for varying cure rates are listed in Table 1. For the probability that PID would develop in women who failed therapy, we chose 25 percent as the most likely estimate and varied this figure from 10 to 50 percent. In a similar manner, we estimated the probability of a patient with PID requiring hospitalization as 25 percent and varied this figure from 10 to 30 percent in the sensitivity analysis.

Estimates of Costs

Only direct medical costs were included in our analysis, including the costs for the following: treatment of the primary infection, treatment of persistent cervicitis, and treatment of PID as an outpatient and as an inpatient. The charges for each of the antibiotic regimens were based on the mean retail price from three Sacramento pharmacies (Table 1). Estimates of costs for both inpatient and outpatient treatments were obtained in the following ways: in 1991 Washington and Katz[12] reported the costs for the treatment of PID, including trends and projections. Their estimates included data from hospital records and from statewide hospital discharge data compiled by the California Office of Statewide Health

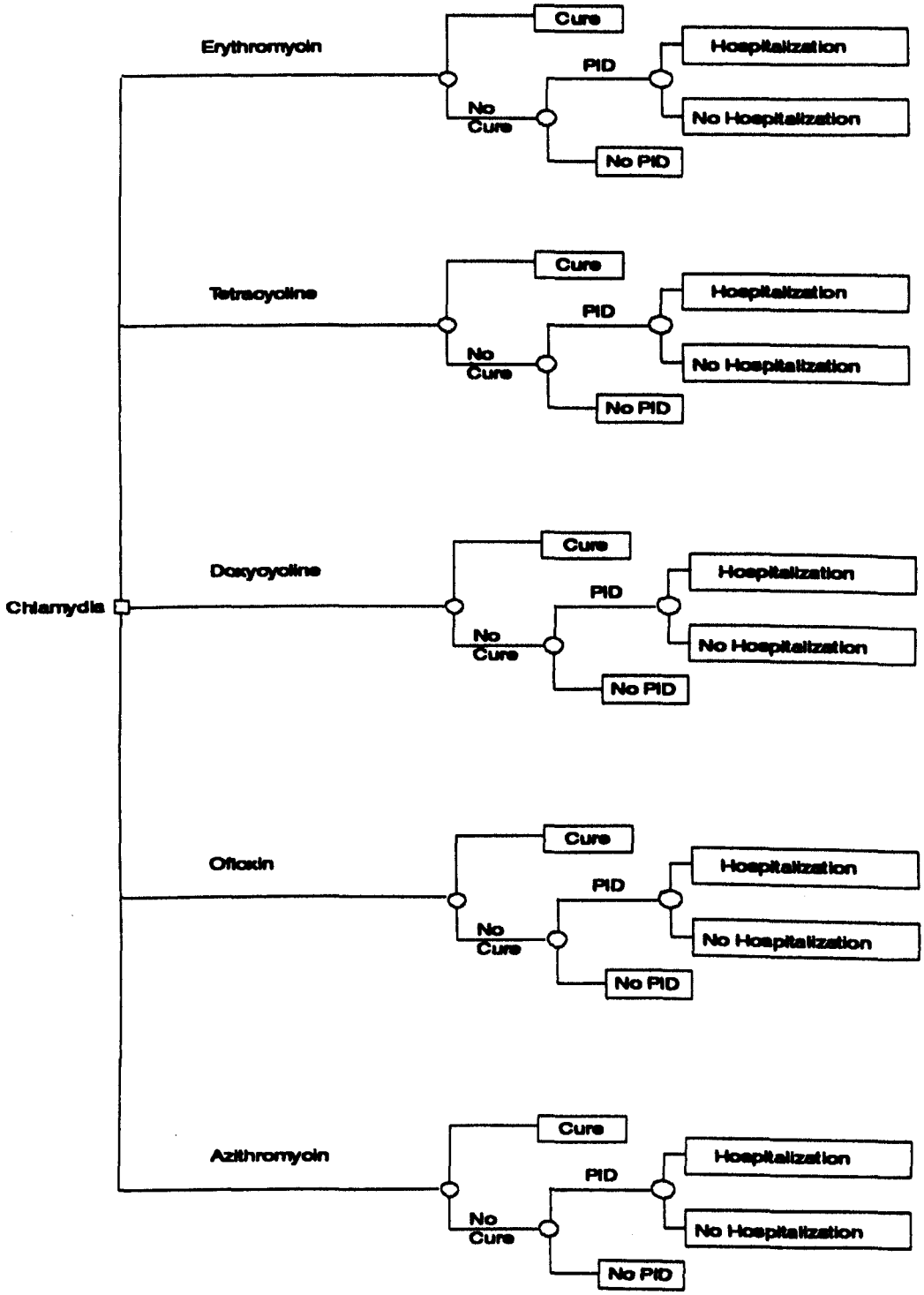

Figure 1. Decision tree comparing five different antibiotics for the treatment of Chlamydia trachomatis cervicitis. The square indicates a decision node; circles, chance nodes; and rectangles, outcomes.

Planning, and Development. To corroborate these estimates, we obtained 1993 data on mean payments for medical services (laboratory tests, physicians' services, hospital care, and hospital medications) from California Blue Shield. From these information sources the costs selected for our analysis were as follows: the cost to treat PID requiring hospitalization was $9,252, and the cost to treat outpatient PID was $195. Given the potential impact of each of these costs on the conclusions, we conducted a sensitivity analysis for costs by varying each cost estimate across a plau-

Table 1. Range of Efficacy and Cost for Each Antibiotic Option.

Drug	Probability of Cure	Cost Estimate	References
Azithromycin	0.88–0.99	$36.05	16–18
Doxycycline	0.82–0.99	$13.17	7, 16–20, 24, 26–28, 33
Erythromycin	0.77–0.91	$11.39	22, 28–31
Ofloxacin	0.93–0.99	$50.45	6–8, 24, 25
Tetracycline	0.79–0.98	$8.10	20–23, 31–33

sible range. Specifically, on the cost for hospitalization we chose a range from $5,000 to $15,000. Finally, a three-way sensitivity analysis was done to elucidate further the effect of varying the cost of azithromycin and the initial cure probabilities for azithromycin and doxycycline.

Results

The cost per case cured with initial therapy when varying the initial cure rate for each agent is depicted in Figure 2. These results are based on the previously described cost assumptions. There is no substantive cost difference between doxycycline, tetracycline, and erythromycin when their initial cure rates are similar. To achieve an equivalent final cost for doxycycline and azithromycin, the probability of initial cure with azithromycin must exceed that of doxycycline by 3 percentage points. For ofloxacin the probability of initial cure must exceed that of doxycycline by 4.5 percentage points to achieve an equivalent final cost per cure. If the probability of initial cure with doxycycline is equal to or greater than 95 percent, both azithromycin and ofloxacin must have near perfect initial cure rates to achieve an equivalent final cost per cure with initial therapy. Varying the cost of hospitalization for PID did not change the relative cost effectiveness of the drug regimens. At the low cost estimate for hospitalization ($5,000), azithromycin and ofloxacin must exceed the probability of initial cure with doxycycline by an additional percentage point to achieve an equivalent final cost. Conversely, at the high cost estimate for hospitalization ($15,000), azithromycin and ofloxacin must exceed the probability of initial cure with doxycycline by one less percentage point.

The results of varying the range of initial cure for each of the study drugs from the highest to the lowest value derived from our search of the literature are seen in Figures 3 and 4. Doxycycline and tetracycline were the most cost-effective agents when their initial cure rates were the highest. Azithromycin was the next most cost-effective agent followed by ofloxacin and erythromycin (Figure 3). In comparing the five drugs at their low estimate for initial cure, ofloxacin was the most cost-effective agent, followed by azithromycin, doxycycline, tetracycline, and erythromycin, respectively (Figure 4). This relation held when either the probability of developing PID or the probability of hospitalization was varied. As the probability of PID or of hospitalization increased, the cost differences between the drugs widened.

The results of the three-way sensitivity analysis are presented in Table 2. We fixed the probability of initial cure with either doxycycline or azithromycin and then varied the cost of azithromycin from $35 to $20 in $5 increments. When the probability of initial cure with doxycycline is set at 95 percent and the cost of azithromycin is decreased from $35 to $20, the difference in initial cure rates between the two drugs to achieve an equivalent final cost narrows

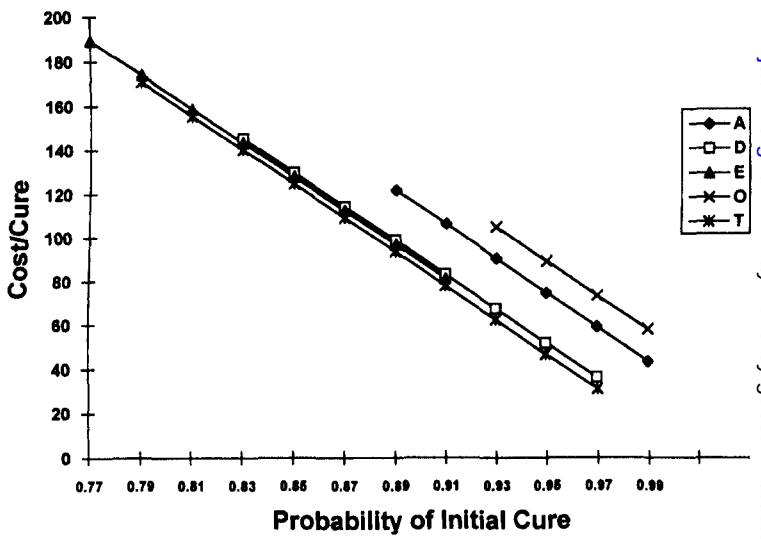

Figure 2. The cost per case cured with initial therapy for each antibiotic agent (A = azithromycin, D = doxycycline, E = erythromycin, O = ofloxacin, T = tetracycline).

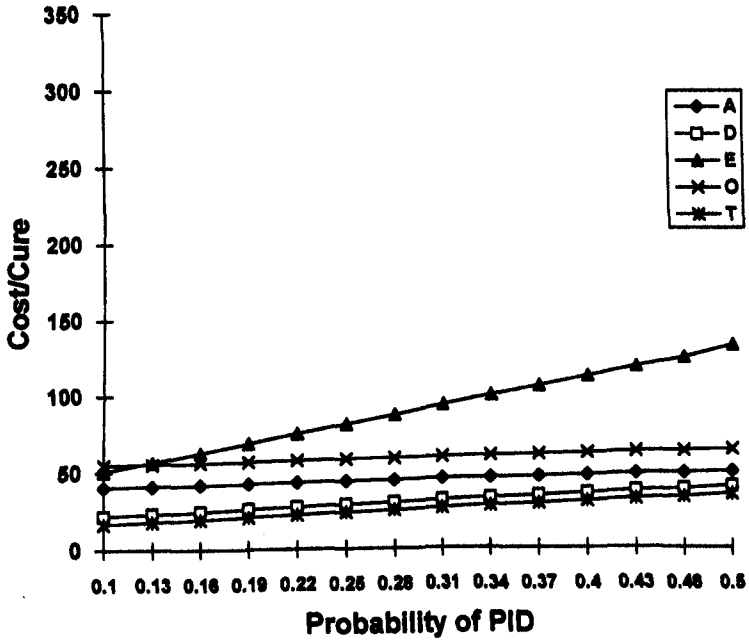

Figure 3. The cost per case cured with initial therapy for the high range estimates for each antibiotic (A = azithromycin, D = doxycycline, E = erythromycin, O = ofloxacin, T = tetracycline).

(from 2.8 percentage points to 1.5). When the probability of initial cure with azithromycin is set at 95 percent, the same pattern is seen. Across all ranges for drug costs and cure rates, azithromycin must have a higher initial cure rate to achieve equivalent cost effectiveness with doxycycline.

There was no consistency among the eligible reports on presenting the incidence of adverse side effects to the study medications. The reports ranged from having no accounting of adverse reactions to documenting the frequency of specific adverse side effects and categorizing these as either mild, moderate, or severe. Three reports gave the most precise data for adverse side effects. Martin, et al.[16] compared single-dose azithromycin with doxycycline for the treatment of chlamydial cervicitis. Twenty percent of the patients on doxycycline (n = 125) and 17 percent of the patients on azithromycin (n = 141) had any adverse side effect. Only 1 doxycycline-treated patient was withdrawn from treatment; withdrawal was due to nausea and vomiting. The most common treatment-related side effect in both involved the gastrointestinal tract. Diarrhea was more common in azithromycin-treated patients (6 percent), whereas nausea and vomiting were more common among those taking doxycycline (11 percent). All side effects were judged to be mild or moderate in severity except for 1 patient. Hammerschlag, et al.[17] compared single-dose azithromycin with doxycycline for the treatment of genital chlamydial infections in 46 adolescents. They found that 19.6 percent of the patients who received azithromycin and 33.3 percent who received doxycycline had gastrointestinal side effects, including nausea, vomiting, abdominal cramps, or diarrhea. In the study group 1 patient receiving doxycycline discontinued treatment for 2 days because of protracted nausea and vomiting. Romanowski, et al.[19] studied

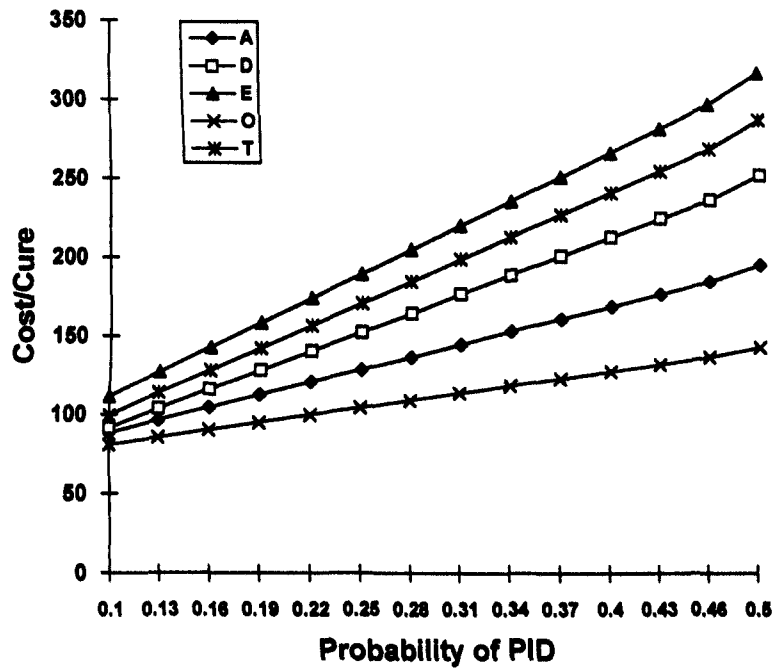

Figure 4. The cost per case cured with initial therapy for the low range estimates for each antibiotic (A = azithromycin, D = doxycycline, E = erythromycin, O = ofloxacin, T = tetracycline).

doxycycline and minocycline in the treatment of 62 women with mucopurulent cervicitis. Of these patients, 62 percent described an adverse reaction (13 percent vomiting, 48 percent any gastrointestinal upset, and 13 percent dizziness). Only 1 patient discontinued doxycycline because of the side effects. In the entire study 77 percent described mild, 14 percent described moderate, and 9 percent described severe adverse side effects.

Discussion

Despite the number of treatment options now available to the patient with *C. trachomatis* infection, complications from failed treatment continue to be a problem. A substantial number of patients with *C. trachomatis* infection fail to respond to therapy. Poor compliance to antibiotic therapy probably accounts for many of these treatment failures.[14] The reasons for poor compliance are diverse and include cost, dosing, and side effects. Those who fail to resolve their initial infection face the risks of complications that are well documented and include the following: (short-term) PID, tubo-ovarian abscess, pyosalpinx, hydrosalpinx, transmission to a newborn, and (long-term) infertility and ectopic pregnancy.[10] All of these complications carry costs to the patient and the health care system. The costs for PID (all causes) were estimated to be $4.2 billion in 1990 and could rise to $10 billion by 2000.[11,12]

The new CDC treatment guidelines offer a wide variety of choices for the treatment of *C. trachomatis*.[4] Each treatment option available has its own particular problems that can impair compliance. Doxycycline is inexpensive; however, adverse side effects are extremely common. Adverse gastrointestinal side effects complicate therapy in up to one-third of patients given doxycycline.[14] Azithromycin offers single-dose therapy with which one would assume excellent compliance, but at a cost of 2.5 to 3 times that of doxycycline. Ofloxacin, with dosing similar to doxycycline, has a lower incidence of adverse side effects, but the cost of ofloxacin is 3 to 5 times that of doxycycline. As noted by Jordan,[33] "what we are looking for is the ideal regimen in terms of providing a safe, effective, and inexpensive treatment."

Our analysis of the treatment of *C. trachomatis* cervicitis indicates that the choice for initial therapy with doxycycline might need to be challenged. Despite the lower cost for the medication, the substantial costs incurred for the treatment of complications might favor the use of the costlier medication under certain conditions. The overriding issue in this debate is that of the true difference between the efficacy and effectiveness of each antibiotic. The relevant factors include compliance, the effect of suboptimal compliance on cure rates, and generalizing the results of controlled trials to the whole population.

The true compliance rate with treatment for sexually transmitted diseases is a controversial subject. Some authors have questioned the high cure rates seen in randomized controlled trials and whether similar cure rates are realized in the setting of a usual practice. As stated by Martin, et al.,[16] "though published studies consistently report high success rates after multiple dose therapy for chlamydia infections, there has always been some doubt that treatment is as effective outside the research setting because of problems with compliance." Stamm[14] has stated that "gastrointestinal and other side effects coupled with the need to use 7 days of drug often result in poor patient compliance. Thus, shorter regimens given in less frequent dosing schedules and with fewer side effects would clearly be of benefit." Other authors have expressed the opinion that patients with sexually transmitted diseases will adhere to a 7-day regimen, particularly if there are accompanying educational interventions.[39]

The studies done on compliance with antibiotic therapy in the treatment of sexually transmitted diseases indicate that in general compli-

Table 2. Results of Three-Way Sensitivity Analysis Varying Cost of Azithromycin and Initial Cure Probabilities for Azithromycin and Doxycycline to Achieve Equivalent Overall Cost.

Cost of Azithromycin	Probability of Initial Cure with Azithromycin	Probability of Initial Cure with Doxycycline	Difference in Cure Rate
$35	0.978	0.950	0.028
$30	0.973	0.950	0.023
$25	0.969	0.950	0.019
$20	0.965	0.950	0.015
$35	0.950	0.922	0.028
$30	0.950	0.927	0.023
$25	0.950	0.931	0.019
$20	0.950	0.935	0.015

ance is poor. Katz, et al.[40] found that only 63.4 percent of patients complied with a 7-day regimen of doxycycline. This level of compliance has been confirmed by others.[33] Compliance does not appear to be related to such demographic variables as age, sex, educational level, and socioeconomic status.[33,40,41] Educational interventions have not been shown to be effective in improving compliance.[42] Determining an estimate of compliance with doxycycline therapy in the setting of a usual practice is critical in the assessment of the most cost-effective drug for *C. trachomatis*. If compliance with doxycycline therapy is indeed poor, and cure rates are as low as suggested by some authors, then the initial use of azithromycin is justifiable. If, however, the initial cure rate with doxycycline is good even despite suboptimal compliance, then doxycycline remains the drug of choice. Unfortunately, there are no good predictors of compliance, and there are inadequate data to assess the effects of noncompliance in the setting of a usual practice.

It is not clear whether there is a distinct advantage in efficacy among doxycycline, azithromycin, and ofloxacin in achieving an initial cure. Our review of the medical literature was notable for the range in efficacy for each of the drugs and for the excellent efficacy of doxycycline under ideal conditions. Review of the randomized controlled trials shows the cure rate for doxycycline to be consistently high (>95 percent).[6,16-18,26-28] Three randomized controlled trials directly compared doxycycline with azithromycin; in each, the initial cure rate with doxycycline exceeded 95 percent.[16-18] If the probability of initial cure with doxycycline is indeed as good as seen in these three trials, then neither azithromycin nor ofloxacin at their present costs should become the drug of choice. Azithromycin (given an initial cure rate for doxycycline of 95 percent) would need to have a cure rate of greater than 98 percent to become the initial drug of choice.

Our study findings help clarify the relevant cost issues that can be used to determine the initial drug of choice for an infection with *C. trachomatis*. As the cost difference between doxycycline and azithromycin decreases, azithromycin becomes favored at a smaller difference in initial cure rates. For azithromycin to be preferred to doxycycline, the initial cure rate of azithromycin must exceed that of doxycycline. In turn, the initial cure rate with ofloxacin must exceed that of azithromycin. The amount one cure rate must exceed another depends on the costs incurred for treatment of the potential complications. The potential economic impact of a widespread change from doxycycline to azithromycin for initial therapy remains uncertain pending further information. Our analysis found the two critical areas that must be addressed before the most cost-effective therapy for *C. trachomatis* cervicitis can be determined. First, the effectiveness of each drug, that is, the cure rate under the circumstances of usual practice, needs to be better defined. The studies from which the cure rates used in our analysis were derived made extra efforts to encourage patient compliance with the antibiotic regimen. Second, the importance of patient compliance with the full 7-day regimen of doxycycline to achieve a cure for *C. trachomatis* cervicitis is not known. In the case of uncomplicated urinary tract infection, compliance with long-term antibiotic treatment (7- to 10-day course) has been unnecessary.[43]

Several considerations can affect the results of our study, including the following: (1) the difficulty in obtaining a precise estimate for drug-specific initial cure rates, (2) the inability to include a quantitative assessment on the impact of compliance and adverse side effects, and (3) the limitations posed by the cost estimates used in the analysis.

Regarding the probability assumptions for drug-specific initial cure rates, we chose to vary each probability across a plausible range. By this method we were able to determine the impact of the high and low values for these probabilities on the study conclusions. Although the selected range is useful for this task, the ability to assign a precise estimate for each drug-specific initial cure rate would complement the information available from our sensitivity analysis. Unfortunately, a precise estimate for drug-specific initial cure rates in the setting of a usual practice remains unknown. Clinical trials from which we derived our estimates might have yielded overly optimistic treatment values, particularly for such drugs as doxycycline. It is likely that the twice-daily regimen, along with the frequent adverse gastrointestinal side effects, makes the initial cure rate with doxycycline in the setting of a usual practice lower than that reported in the literature. The potential impact of a lower initial cure rate for doxycycline would favor

azithromycin as the drug of choice even at its present cost, as the initial cure rate of azithromycin must only exceed that of doxycycline by 3 percentage points.

Because of the described reporting inconsistencies in the literature, we were unable to make quantitative estimates of compliance and adverse side effects. It is reasonable to assume that compliance with azithromycin therapy is better than with the other drugs because of its single-dose regimen. If compliance could be factored in, it could have considerable impact on the results of this analysis. Given the relatively small difference between doxycycline and azithromycin in initial cure rates to achieve an equivalent cost, poor compliance with doxycycline could make azithromycin the drug of choice under all circumstances. With respect to adverse side effects, available data do not suggest that any of the study drugs had a greater potential for major adverse side effects. It is likely that inclusion of this variable would not have affected the study results.

The final consideration is the effect of the cost estimates on the results. The specific costs used in our calculation were conservative estimates. As with the probability estimates, we varied the costs across a plausible range to determine the impact of the high and low values on the study conclusions. Because a major expense in the treatment of PID is hospitalization costs, we determined the impact of a wide range of these values. In our sensitivity analysis we found that the impact of tripling the cost of hospitalization from $5,000 to $15,000 was to narrow the gap between the initial cure rates needed to achieve equivalent overall cost. In comparing doxycycline and azithromycin, at a hospitalization cost of $5,000, the initial cure rate of azithromycin must exceed that of doxycycline by 4 percentage points; at a hospitalization cost of $15,000, azithromycin must exceed doxycycline by 2 percentage points.

We did not calculate the indirect costs associated with failed treatment (lost wages, lost value of household management, lost value of lifetime earnings from death). It has been estimated that inclusion of these indirect costs will double the overall total costs.[13] The potential impact on the results of the study had these costs been included is as follows: the larger costs for failure to provide an initial cure would have magnified the effect of differences in the initial cure rate between each drug. This point underscores the importance of a precise estimate of that value. As was seen in the assessment of the impact of tripling the cost of hospitalization, it is likely that inclusion of these additional costs would have affected the magnitude of the difference in cost effectiveness between the drugs but not the direction of the results.

How can the practicing physician benefit from the information presented in this cost-effectiveness analysis? We believe a practitioner should be able to conclude:

1. The initial cure rates for azithromycin and doxycycline are high when a patient is able to take the recommended regimen.
2. Compliance with the doxycycline dosing regimen and frequency of adverse side effects are concerns; however, it is difficult to quantify these problems precisely given the stated problems in the medical literature.
3. At the present cost differences between azithromycin and doxycycline, the physician must be confident that there will be an advantage in initial cure rate of at least 3 percentage points for azithromycin to be the drug of choice.
4. The indicators to determine which patients will be compliant with any of the antibiotic regimens are imprecise; nevertheless, patients with a history of failures on doxycycline or intolerance to doxycycline and adolescents would be considered to have a greater chance of poor compliance.[40]
5. The present cost of azithromycin represents a potential barrier to compliance.

Should the manufacturer of azithromycin lower the price, azithromycin could potentially become the drug of choice for all patients with *C. trachomatis* infections.

Summary

We report the results of a cost-effectiveness study comparing five different antibiotic regimens in the treatment of uncomplicated *C. trachomatis* cervicitis in terms of the cost per initial cure. The conclusions favor the use of azithromycin rather than doxycycline when there is concern about compliance with the standard doxycycline regimen. A lower cost for azithromycin could favor its use as the drug of choice.

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