

Cost-Analysis of Prophylactic Antibiotics in Spontaneous Bacterial Peritonitis

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Background & Aims: Antibiotic prophylaxis has been shown to decrease the incidence of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis and ascites. The aim of this study was to test whether antibiotic prophylaxis for SBP is cost-effective and to compare the costs associated with different patient groups and treatment strategies. **Methods:** A cost-effectiveness analysis was performed using a Markov chain model. The costs incurred during 1-year treatment with prophylactic antibiotics vs. no prophylaxis in patients with cirrhosis and ascites were calculated. The incidence rates of primary and recurrent SBP and the mortality rate of SBP were obtained from the literature. Total direct costs of SBP treatment were determined from the wholesale price of drugs and from disbursements by the Health Care Financing Administration. **Results:** Norfloxacin prophylaxis resulted in savings between \$2216 and \$8545 per patient per year, depending on the patient group studied. Trimethoprim-sulfamethoxazole prophylaxis resulted in savings between \$2934 and \$9251 per patient per year. The groups that benefited most from prophylaxis were patients with an ascitic fluid total protein concentration of ≤ 1 g/dL and those with a previous history of SBP. **Conclusions:** The use of prophylactic antibiotics to decrease the incidence of SBP is a cost-saving strategy in patients with cirrhosis and ascites.

Spontaneous bacterial peritonitis (SBP) is a frequent and severe complication in cirrhotic patients with ascites. The hospital mortality rate of patients diagnosed with SBP ranges from 30% to 50%.¹⁻⁴ Additionally, patients who suffer an episode of SBP and recover are at even higher risk of recurrent episodes.² Certain other subgroups of patients have been identified as having a higher risk of developing SBP. These include patients with low ascitic fluid total protein concentrations or low ascitic fluid opsonic activity.⁵⁻⁸ The majority of organisms that cause SBP are gram-negative bacilli that are present in the intestine,⁹ and the likely mechanism of SBP formation involves transient bacteremia with subsequent seeding of ascitic fluid.^{9,10} Exploiting this route of infection, several studies have shown the utility of

prophylactic orally administered antibiotics to selectively decontaminate the intestine and decrease the incidence of SBP in patients with cirrhosis and ascites.¹¹⁻¹⁴ These studies showed a significant decrease in the frequency of SBP with prophylactically administered norfloxacin, ciprofloxacin, or trimethoprim-sulfamethoxazole. Controversy remains, however, concerning the cost-effectiveness of prophylactic antibiotic therapy to prevent SBP.¹⁵ This study compares the direct costs of SBP incurred during 1-year treatment with and without antibiotic prophylaxis. Our aim was to determine whether antibiotic prophylaxis would decrease the overall cost of therapy in SBP in patients with cirrhosis and ascites.

Materials and Methods

Model

A Markov chain was developed to model the events leading to SBP in patients with cirrhosis and ascites (Figure 1). Seven states were shown, three of which constituted the entry points of separate analyses: patients without a previous history of SBP, patients without a history of SBP but an ascitic fluid total protein concentration of ≤ 1 g/dL, and patients with previous episodes of SBP. After entry into the model, patients were distributed among the remaining four states: the first episode of SBP (primary SBP), resolution of SBP, recurrent SBP, and death. A patient with cirrhosis and ascites was considered to be in one of the three entry states or four subsequent states.

The transition between states was governed by the probabilities of sustaining a first episode of SBP, resolving each episode of SBP, experiencing recurrent SBP, and death attributed to SBP. Once a patient suffered an episode of SBP (primary or recurrent), that patient was assumed to either die, the probability being determined by the mortality rate from SBP, or recover. The mortality rate associated with SBP was taken from the literature. In the baseline model, the mortality rate was 31%² and was subsequently varied in a sensitivity analysis from 20% to 40%.¹⁻⁴ Patients who had not had an episode

Abbreviations used in this paper: CPT, current procedure terminology; DRG, diagnosis-related group; HCFA, Health Care Financing Administration; SBP, spontaneous bacterial peritonitis.

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0016-5085/97/\$3.00

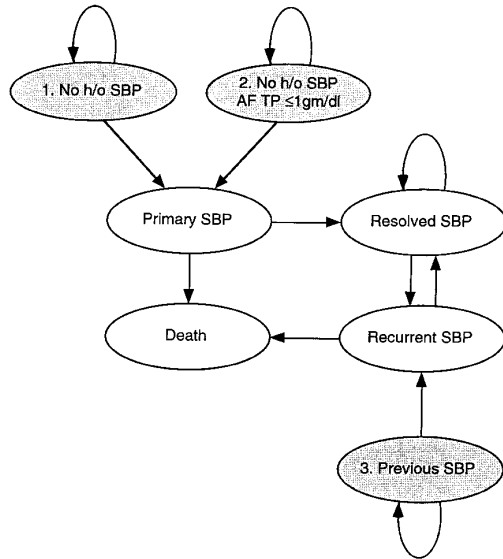


Figure 1. Markov chain modeling patients with cirrhosis and ascites. The three numbered states indicate the entry points into the model. The arrows indicate the possible transitions between states that occur with each successive interval. AF TP, ascitic fluid total protein; h/o, history of.

of SBP remained in the two entry states labeled 1 and 2 of the model. The probability of remaining in these states was 1 minus the probability of developing primary SBP. Similarly, patients with resolved or previous SBP remained in their corresponding states unless they developed recurrent SBP. The probability of maintaining these states was 1 minus the probability of recurrent SBP.

Bacterial peritonitis is not the only cause of death in patients with SBP, and other factors associated with chronic liver disease may contribute to mortality. The influence of these other factors on mortality is encompassed by the overall death rate of patients with SBP used in the present study. However, death related to age or causes other than chronic liver disease were not considered in the model for two reasons. First, their contribution to mortality pales in comparison to the strong influence of SBP-related death. Second, death rates from causes other than chronic liver disease and SBP are not affected by antibiotic therapy and, therefore, would have no influence on the comparison of different management strategies.

The analyses were begun with a hypothetical group of 100 patients with ascites and cirrhosis. Every 5 days (the recommended inpatient treatment duration for confirmed SBP), the patients were redistributed among the seven states according to the probabilities shown in Table 1, which were derived from existing literature. The rates of transition from state to state were assumed to remain constant throughout the year. The rates were taken only from studies with a prospective design and in which the outcome of antibiotic prophylaxis had been tested in a randomized clinical fashion. The model assessed the influence of norfloxacin and trimethoprim-sulfamethoxazole prophylaxis because these two antibiotics comprised the two regimens for which the majority of such data

existed. Published studies showed a difference in the efficacy of SBP prevention between the two antibiotic regimens; however, the study populations differed in the proportion of patients with previous SBP or in the protein concentration of the patients' ascitic fluid. For this analysis, the efficacy of the two antibiotic regimens was assumed to be equivalent within the same patient population. For example, the annual probability of recurrent SBP in patients with a history of SBP treated with prophylactic norfloxacin is 20%.¹¹ No such data for trimethoprim-sulfamethoxazole prophylaxis exists; therefore, the SBP recurrence rate was assumed to be equivalent to the norfloxacin rate. A sensitivity analysis then varied the efficacy rates to account for possible differences between the antibiotics. The proportion of patients in each state was determined, and the direct costs of treatment that arose from drugs and hospitalization were accumulated every 5 days for a duration of 1 year.

Costs

All analyses were performed from the perspective of the third-party payer, specifically the Health Care Financing Administration (HCFA). Direct costs were determined by wholesale prices of norfloxacin (\$2.72 per 400-mg tablet) and trimethoprim-sulfamethoxazole (\$1.00 per double-strength tablet) and from the charges covered by HCFA for treatment of SBP. Norfloxacin (400 mg daily) was used in two prospective trials,^{11,12} trimethoprim-sulfamethoxazole (160 mg/800 mg 5 days per week) was used in a third trial,¹³ and ciprofloxacin (750 mg weekly) was used in a fourth trial,¹⁴ although ciprofloxacin therapy was not modeled in the present study. Patients treated with prophylactic antibiotics were assumed to take the medication on a continuous basis except for episodes of SBP, whereupon intravenous antibiotics would be instituted and prophylactic antibiotic use would be suspended.

Direct costs of SBP were determined using payments allocated by HCFA for treatment of SBP during fiscal year 1994 (Table 2). Hospital disbursements were determined by diagnosis-related group (DRG) codes, whereas physician services were added according to payments made by HCFA by current procedure terminology (CPT) code. No indirect costs were included in the analyses. DRG category 202 is designated for use with patients admitted for cirrhosis or alcoholic hepatitis. CPT codes were added to reflect the physician charges associated with hospitalization for SBP, including a limited ultrasound examination of the abdomen, initial and follow-up paracenteses with appropriate microbiology and microscopic examination of fluid, and hospital care for 5 days. It should be noted that charges and costs are not necessarily the same. The HCFA data used in this analysis relate to payment for services provided to patients covered by Medicare. Depending on the type of service, the reimbursement rate from HCFA to the health provider may be only 50% of the allowable charges.

The results of our analysis pertain to three different patient groups: (1) patients without a history of SBP, (2) patients with an ascitic fluid total protein concentration of ≤ 1 g/dL, and (3) patients with a previous history of SBP. These groups varied by their incidence rates of primary and recurrent SBP. The

Table 1. Transition Rates Between Disease States Involving SBP

Transition	Annual SBP rate without antibiotics (%)	SBP rate with antibiotic prophylaxis (%)	Rates with antibiotic in sensitivity analysis (%)
Incidence of SBP in			
Patients without previous history of SBP	28	12	0-20
Patients with ascitic fluid protein of ≤ 1 g/dL	41	16	12-20
Patients with previous SBP	69	20	12-35

analysis was performed both with and without the use of prophylactic antibiotics in each patient group.

Sensitivity Analysis

To test the robustness of the model, we performed a sensitivity analysis. The incidence rates of SBP and the mortality rates of SBP were varied in separate, one-way analyses. The impact on the cost of SBP treatment with varying rates of SBP was evaluated. Rates found in the literature that were both higher and lower than the baseline SBP rate with antibiotic prophylaxis were used and are shown in Table 1.¹⁰⁻¹³ The effect of varying the baseline SBP mortality rate from 20% to 40%¹¹⁻¹⁴ was also determined, and the results were expressed as the cost of prophylactic antibiotics per year-life saved. Two threshold analyses were also performed: one to examine the impact of varying the cost of inpatient treatment of SBP and the other to evaluate various rates of primary SBP. To determine the threshold cost of SBP treatment, the point at which costs of treatment strategies both with and without antibiotics were equal was determined. Below this threshold, antibiotic prophylaxis would not provide an economic benefit. In an analysis of patients without a history of SBP, the rate of primary SBP was varied to determine the rate at which the costs of treatment strategies with and without antibiotics were equal. In this manner, the minimum rate at which antibiotic prophylaxis still resulted in lower costs was determined.

Table 2. HCFA Hospital Reimbursements for Inpatient Treatment of SBP

Service	Code	HCFA Payments
Cirrhosis/alcoholic hepatitis	DRG 202	\$12,124
Paracentesis, initial	CPT 49080	\$75
Paracentesis, subsequent	CPT 49081	\$70
Ultrasonography, limited	CPT 76705	\$47
Emergency room evaluation, moderate complexity	CPT 99284	\$76
Initial hospital care	CPT 99222	\$92
Hospital care, subsequent 3 days	CPT 99231	\$90
Hospital discharge	CPT 99238	\$49
Fluid culture	CPT 87070	\$13
Fluid smear, twice	CPT 87205	\$12
Cell count with differential, twice	CPT 89051	\$16
HCFA reimbursements for inpatient treatment of SBP		\$12,664

NOTE. The source of the data is HCFA, 1994.

Results

Using a hypothetical population of 100 patients, the model shows that, during the span of 1 year without the use of prophylactic antibiotics, patients with cirrhosis and ascites and no previous history of SBP accumulate a mean cost per patient of \$4765 per year (Figure 2). The

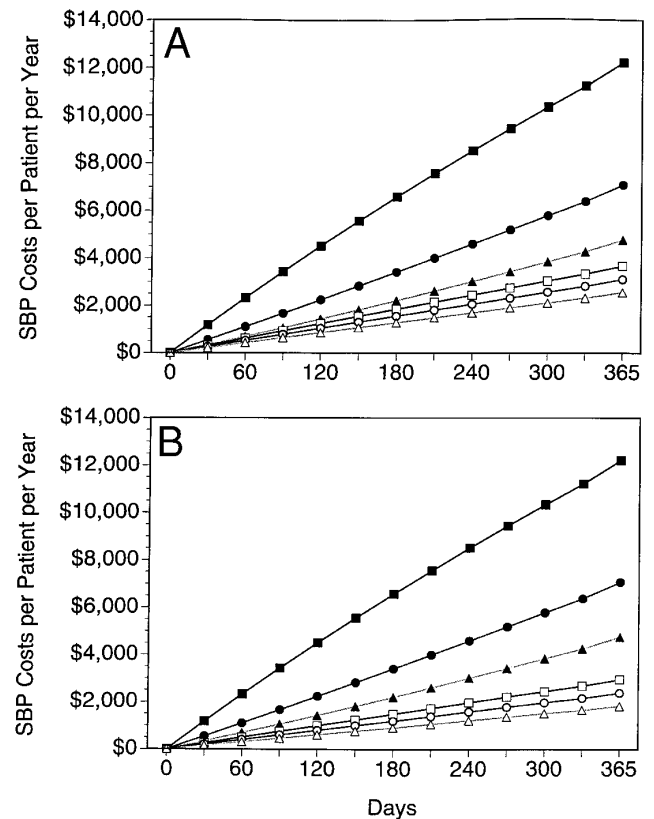


Figure 2. SBP treatment costs per patient accumulated during the course of 1 year according to patient group both with and without antibiotic prophylaxis. The upper three lines in each graph are identical, representing the costs in each patient group without antibiotics. The lower three lines represent the costs accumulated in each patient group using (A) norfloxacin prophylaxis or (B) trimethoprim-sulfamethoxazole prophylaxis. The patient groups consist of the following: (1) previous history of SBP (■ and □); (2) no history of SBP but an ascitic fluid total protein concentration of ≤ 1 g/dL (● and ○); and (3) no history of SBP (▲ and △). The filled symbols represent the scenario without antibiotics, and the open symbols represent the scenario with antibiotics. ■, Previous SBP; ●, AF TP ≤ 1 g/dL; and ▲, no history of SBP.

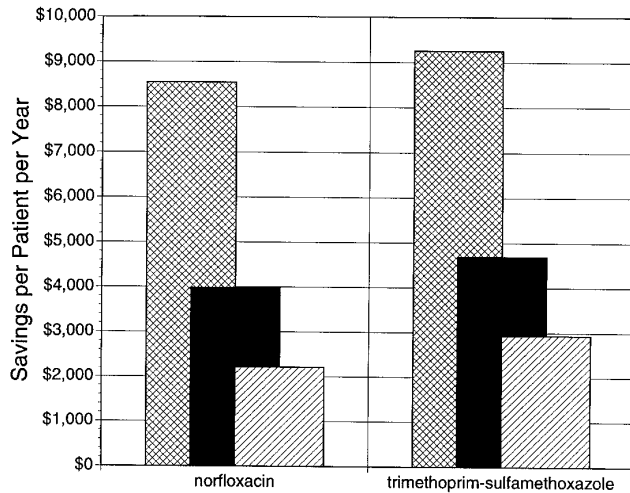


Figure 3. Savings in SBP direct costs per patient per year in each patient group with the use of prophylactic norfloxacin or trimethoprim-sulfamethoxazole. ▨, Previous SBP; ■, AF TP \leq 1 g/dL; and ▩, no history of SBP.

use of prophylactic norfloxacin in this group decreases the cost to \$2549, a savings of \$2216 per patient per year (Figure 3). Use of trimethoprim-sulfamethoxazole decreases the yearly cost per patient to \$1831, a savings of \$2934 per patient per year. Use of prophylactic norfloxacin in the subgroup of patients with an ascitic fluid total protein of \leq 1 g/dL has an even greater impact by decreasing direct costs by \$3980 per patient per year or by \$4692 with trimethoprim-sulfamethoxazole. The most dramatic effect is observed in the population of patients in whom SBP had occurred previously; the model predicts a decrease in the costs per patient per year of \$8545 with norfloxacin and \$9251 with trimethoprim-sulfamethoxazole.

In the group of 100 patients without a history of SBP, a total of 38 episodes of SBP will occur (Table 3). Antibiotic prophylaxis will, according to the model, decrease the number of episodes of SBP in this group by 25. Patients with low ascitic fluid protein concentrations will have 39 fewer SBP episodes with antibiotic prophylaxis. In patients with a prior history of SBP, the number of SBP episodes is reduced by 76 with antibiotic prophylaxis.

Antibiotic prophylaxis results in a decrease in mortality attributable to SBP (Table 3). In a population of 100 patients, antibiotic prophylaxis decreases deaths per year by 8 in patients without previous SBP, by 12 in those with an ascitic fluid total protein of \leq 1 g/dL, and by 23 in those with previous SBP.

Sensitivity analyses were performed to assess the model dependence on a variety of factors. In one analysis, changes in the cost of SBP using varying rates of antibi-

otic efficacy reported in the literature were calculated. In each of the three patient groups studied, increasing the efficacy of antibiotic prophylaxis in preventing SBP increased the savings obtained with antibiotic use. The increased yearly savings per patient ranged from \$3772 in the patients without previous SBP treated with norfloxacin to \$10,380 in patients with previous SBP treated with trimethoprim-sulfamethoxazole. Decreasing the efficacy of antibiotic prophylaxis in preventing SBP decreased yearly savings in SBP cost that ranged from \$1099 in patients without previous SBP treated with norfloxacin to \$6915 in patients with a history of SBP treated with trimethoprim-sulfamethoxazole. Over the broad range of rates used in the sensitivity analyses, antibiotic prophylaxis consistently resulted in lower costs than if no antibiotics were used.

The mortality rate from an episode of SBP was also varied in a one-way sensitivity analysis. The results were calculated as a ratio comparing the drug cost of antibiotic prophylaxis per life-year saved. In the baseline case, norfloxacin prophylaxis resulted in a drug expenditure of \$98,225 for 100 patients without previous SBP during the course of 1 year. Compared with the group not taking prophylaxis, eight fewer deaths associated with SBP occurred; therefore, the antibiotic cost per life-year saved was \$12,278. Decreasing the mortality associated with SBP from 31% to 20% increased the cost per life-year saved to \$16,538, whereas increasing the mortality rate to 40% decreased the cost per life-year saved to \$10,890. As the mortality associated with SBP increased, the cost per life-year saved decreased, and antibiotic prophylaxis became an even greater cost-saving strategy.

Threshold analysis was performed to examine the effect of varying the cost of inpatient treatment of SBP. In the group of patients without a prior history of SBP, use of norfloxacin prophylaxis continued to constitute a cost-saving strategy as long as the inpatient treatment costs of SBP exceeded a threshold of \$3842; if costs of SBP treatment decreased to below this value, prophylaxis

Table 3. Outcomes of Patient Groups During 1-Year Follow-up

Group	No. of SBP episodes	Deaths
No antibiotic prophylaxis		
Patients without history of SBP	38	12
Ascitic fluid protein of \leq 1 g/dL	56	17
Previous history of SBP	97	30
Prophylactic antibiotics		
Patients without history of SBP	13	4
Ascitic fluid protein of \leq 1 g/dL	17	5
Previous history of SBP	21	7

failed to provide economic benefit. Likewise, use of trimethoprim-sulfamethoxazole was cost-saving above a threshold of \$1006 for inpatient treatment costs.

Threshold analysis was also performed to determine the lowest primary SBP rate at which antibiotic prophylaxis would still provide cost benefit. With a primary SBP rate of $\geq 19\%$, antibiotic use resulted in reduced costs; less than this SBP rate, antibiotic prophylaxis failed to constitute a cost-saving strategy.

Discussion

We find a decrease in direct costs associated with the treatment of SBP with the use of prophylactic antibiotics. The savings are most prominent in patients who have an ascitic fluid total protein of ≤ 1 g/dL and in those who have had a previous episode of SBP, but benefit is also noted in all patients with cirrhosis and ascites. Threshold analysis shows that antibiotic prophylaxis remains beneficial for a wide range of SBP treatment costs. The model also predicts a decrease in the number of deaths attributable to SBP by 8%–23% per year, depending on the type of patient population studied.

Direct costs only were used in this study. Indirect costs, such as income lost as the result of disability or death of patients or complications of antibiotic therapy, were not included in the study. The advantages of using only direct costs are simplification of the model and less influence from data that may not be reliable, such as estimation of the cost of death or the amount of income lost from missed work. The disadvantage of omitting indirect costs is that a major contributing variable may be not accounted for in the analysis. As with any modeling procedure, trade-offs exist between the amount of detail built into the model and its applicability to the general population.

Crucial to the relevance of this study is the assumption that antibiotic prophylaxis remains effective in decreasing the frequency of SBP during the time period of 1 year. The median duration of follow-up was 90 days in the study by Singh et al.,¹³ while mean follow-up in the trial by Ginés et al. was 6.4 months (range, 1–19 months).¹¹ Resistant *Pseudomonas* or *Aeromonas* were isolated from the stool of patients treated with prophylactic norfloxacin in the study by Ginés et al. at 1 and 9 months into therapy¹¹; however, colonization by resistant bacteria was not documented in any patient of their study after a follow-up period of 24 months.¹⁵ Although our model suggests cost-savings for time periods beyond 1 year of prophylaxis, validation of this assumption would require extension of the follow-up period in clinical trials to ensure the continued efficacy of antibiotic prophylaxis.

Substantial savings are observed during a 1-year period

with the use of prophylactic antibiotics in patients with low ascitic fluid total protein concentrations and in patients with a previous history of SBP. The cost benefit is less in patients with high ascitic fluid protein concentrations and without previous SBP. Sensitivity analysis yielded a threshold primary SBP rate of 19%, which is 9% less than the rate reported in the literature. Thus, in this group of patients, the recommendations in favor of or against prophylaxis with norfloxacin depend on the accuracy of the published rate of SBP. With a margin this small, it is difficult to be assured of the cost-savings of antibiotic prophylaxis in patients without low ascitic fluid protein or a history of SBP.

There is a decrease in the mortality from SBP with the use of prophylactic antibiotics. This stems from a decrease in the total number of SBP episodes that occur with prophylaxis, combined with the high mortality rate associated with SBP. Previous clinical trials have not shown significant survival benefit with prophylactic antibiotic use. Singh et al. noted a trend towards survival benefit with the use of trimethoprim-sulfamethoxazole, but this result did not achieve statistical significance.¹³ Survival was not an outcome parameter in the study by Ginés et al.; the variable of interest was recurrence of SBP, and thus, no conclusion was made concerning the survival benefit of prophylactic norfloxacin.¹¹ Although mortality associated with an episode of SBP is high, the actual cause of death is rarely peritonitis. An episode of SBP could reflect the degree of hepatic decompensation present, or the comorbid conditions associated with SBP may result in excess mortality. If either of these is the case, antibiotic prophylaxis would not be expected to provide survival benefit. If, however, SBP causes an otherwise avoidable decompensation of hepatic function or triggers a chain of events that lead to death, antibiotic prophylaxis could improve survival. Further clinical trials will be necessary to determine the true influence of prophylactic antibiotics on the survival of patients with cirrhosis and ascites.

We estimate a decrease in the total direct costs of treatment of SBP with the use of prophylactic antibiotics in patients with cirrhosis and ascites. The benefit is minor in patients without a previous history of SBP. Increased benefit is noted in patients with an ascitic fluid total protein concentration of ≤ 1 g/dL, and the greatest benefit is observed in patients with a previous episode of SBP. The savings are preserved for a large range of hospital costs for treatment of SBP and are seen with the use of either norfloxacin or trimethoprim-sulfamethoxazole.

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Received August 26, 1996. Accepted June 17, 1997.

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