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Clinical and Economic Effects of Mupirocin Calcium on Preventing *Staphylococcus aureus* Infection in Hemodialysis Patients: A Decision Analysis

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● This study was performed to determine the clinical and economic consequences of alternative strategies of preventing *Staphylococcus aureus* infection in chronic hemodialysis patients by use of intranasal mupirocin calcium to clear nasal carriage of *S aureus*. Decision analysis evaluated clinical outcomes and cost-effectiveness of three likely management strategies to address *S aureus* nasal carriage and prevent subsequent infection in chronic ambulatory hemodialysis patients: (1) screen for *S aureus* nasal carriage every 3 months and treat those with a positive test result with mupirocin calcium; (2) treat all patients weekly with mupirocin calcium; or (3) no prevention strategy, treat infection only. Rates of nasal carriage of *S aureus*, *S aureus* infection rates, proportion of infections attributable to nasal carriage, efficacy of mupirocin, natural history of infection, and patient management strategies were derived from the published literature and supplemented by a panel of experts. Actual payments for medical services were obtained from Medicare parts A and B. Incremental cost-effectiveness was calculated from the perspective of Medicare and subjected to sensitivity analyses. Assuming that 75% of *S aureus* infections are attributable to nasal carriage in hemodialysis patients, eliminating nasal carriage of *S aureus* with mupirocin calcium (with or without screening) markedly reduces the number of infections (45% to 55%) and also reduces health care expenditures relative to treating infections when they occur. Annual savings to Medicare are \$784,000 to \$1,117,000 per 1,000 hemodialysis patients, depending on the prevention strategy. Preventing *S aureus* infection by eradicating nasal carriage in chronic hemodialysis patients reduces morbidity while simultaneously reducing medical care costs. The decision to eliminate nasal carriage on a regular basis or use a screening test to guide antibiotic therapy is dependent on the tradeoff between improved short-term clinical and cost benefits and the potential for bacterial resistance that may arise from widespread use of mupirocin calcium.
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INDEX WORDS: Infection control; dialysis; *Staphylococcus aureus*; cost-effectiveness.

APPROXIMATELY 140,000 people are on long-term renal dialysis in the United States,¹⁻³ approximately 85% on hemodialysis and 15% on continuous ambulatory peritoneal dialysis.² Medicare, the primary payer for such patients, spends approximately \$6 billion annually on their dialysis and related care.¹⁻³

Long-term renal dialysis patients are at relatively high risk of adverse events from their disease and treatment, including *Staphylococcus aureus* infection. *S aureus* is ubiquitous and particularly dangerous to these patients.⁴ Approximately half of all chronic renal dialysis patients have a positive nasal culture for *S aureus* during a year, and approximately half with a positive nasal culture (35,000) get *S aureus* infection.⁴⁻¹⁷ A large proportion of these infections are related to the access site, and they can progress to life-threatening bacteremia.

Although the relationship between *S aureus* nasal carriage and infection is not completely elucidated, there is increasing evidence that a link exists and eliminating nasal carriage reduces the risk of infection.⁴⁻¹⁰ Clinical sequelae of infection often entail additional medical care, including hospitalizations and operations for shunt

revision or replacement and reduced quality of life and normal activities beyond those caused by long-term renal disease and dialysis.

The main strategy for preventing *S aureus* infection in long-term renal dialysis patients is education on personal hygiene, that is, frequent cleansing of the skin site. Usual clinical management is to administer an appropriate antibiotic regimen after infection occurs. Mupirocin calcium is the first topical medication proven by randomized controlled trials to eliminate nasal

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carriage of *S aureus*.⁶⁻¹⁰ Given the link of nasal carriage and subsequent infection, reduction in patient morbidity and resource use likely flows from eradicating the organism. Accordingly, the objectives of this cost-effectiveness analysis were to examine the clinical and economic effects of clearing nasal carriage of *S aureus* with mupirocin calcium compared with a strategy of no prevention and treatment after infection occurs, and to determine the most cost-effective intervention strategy.

METHODS

Structure of the Decision Tree

Decision analysis was used to estimate clinical and economic consequences of likely alternative clinical approaches to preventing and treating infections attributable to *S aureus*. The primary outcomes were number of cases of *S aureus* infection prevented or treated and resources attributable to these events. The model tested three management strategies in chronic ambulatory hemodialysis patient populations:

Strategy 1: Screen for nasal carriage of *S aureus* every 3 months and treat those with a positive culture with intranasal mupirocin calcium for 5 consecutive days

Strategy 2: Administer intranasal mupirocin calcium to all dialysis patients at weekly intervals without testing for *S aureus* carriage

Strategy 3: No prevention; treat infection only if it occurs with a standard antibiotic regimen

A cohort of 1,000 patients in each strategy was followed for 1 year. The decision model was developed after a critical review of the literature, and in concert with three experts, to ensure accuracy, validity and reality.

The basic decision tree (Fig 1) incorporates the sensitivity and specificity of a screening culture for determining nasal carriage of *S aureus*, an estimate of compliance with mupirocin, the probability of nasal carriage, and the probability of *S aureus* infection with true-positive and false-negative results of nasal culture. The probabilities of access site infections were partially conditional on positive nasal carriage. Given that access site *S aureus* infections are not all related to nasal carriage, 25% of *S aureus* infections were independent of nasal carriage.⁴ Those with false-positive nasal cultures experienced no infections but incurred the costs of therapy and follow-up.

All infections in the terminal branch of Fig 1 were assumed to present initially with an access site infection. Fig 2 demonstrates the cascade of events after infection in hemodialysis patients. Probabilities of access site and systemic infection, hospital and ambulatory treatment, and loss of shunt and effects on direct medical costs were quantified and incorporated into the decision model.

Eradication Regimens

Eradication regimens used in the prevention strategies were the same as those tested in the clinical trials of intranasal

mupirocin calcium.⁶⁻¹⁰ The regimen in the "screen and treat" cohort (strategy 1) was based on a single nasal culture for *S aureus* carriage every 3 months. If the culture was positive, treatment was with intranasal mupirocin calcium twice a day for 5 consecutive days. Among hemodialysis patients in the "treat all" cohort (strategy 2), mupirocin calcium was used twice a day for 3 consecutive days every week for 52 weeks. Treatment in the "no prevention, treat infection" hemodialysis cohort (strategy 3) was a standard antibiotic regimen after the infection was diagnosed on clinical grounds.

Data Sources

We obtained data for this study from three sources. First, a critical review of the medical literature provided probability estimates of incidence and clinical outcomes of *S aureus* nasal carriage and infection in hemodialysis patients. Data were obtained from studies with the most appropriate design, and with relevant populations and results that would be applicable to our study. Second, an independent expert panel reviewed and reconciled conflicting data and supplemented published estimates of probabilities, events, outcomes, and patient management. Last, payment (cost) data for dialysis and all care related to treatment of infection were obtained on end-stage renal disease patients from the Health Care Financing Administration.

Model Inputs

Clinical parameters. Table 1 shows clinical, epidemiologic, and cost input values used in the decision analytic model. Sensitivity and specificity of the culture for nasal carriage was assumed at 0.98.¹⁸ It was assumed that 50% of hemodialysis patients were nasal carriers of *S aureus* at any given time.⁹ The risk of *S aureus* infection for carriers was estimated to be 50%/year; for those without nasal carriage, it was assumed to be 12.5%/year (nonattributable infections/year [25%] × [50%] noncarrier rate = 12.5% infections/year). Because mupirocin calcium was provided in the main by dialysis unit staff, 100% compliance was assumed. Efficacy of mupirocin calcium was defined as clearing nasal carriage of *S aureus* as determined from published trials of hemodialysis patients.⁶⁻¹⁰

Epidemiological parameters. Table 1 also shows the input values used in the base case analysis. Rates of *S aureus* nasal carriage and infection per patient-year were determined from the literature for chronic hemodialysis populations.^{4,17} Rates of *S aureus* shunt site infection, and bacteremia after site infection, were also from the literature.¹¹⁻¹⁷ In this population, *S aureus* access site infection was assumed to be linked in 75% of cases to *S aureus* nasal carriage.⁴ Hospitalization after site or systemic infection¹²⁻¹⁷ and frequency of shunt loss and revision were estimated from the literature and supplemented by the expert panel.^{9,17} Although a likely event in the infected patients, we did not measure death attributable to *S aureus* infection. Inclusion of this outcome would further favor both prevention strategies.

Costs inputs. Actual payments (the cost definition used in this study) as of May 1994 by service for hemodialysis patients, hospital inpatient, and ambulatory care were from Medicare part A; to these were added actual physician pay-

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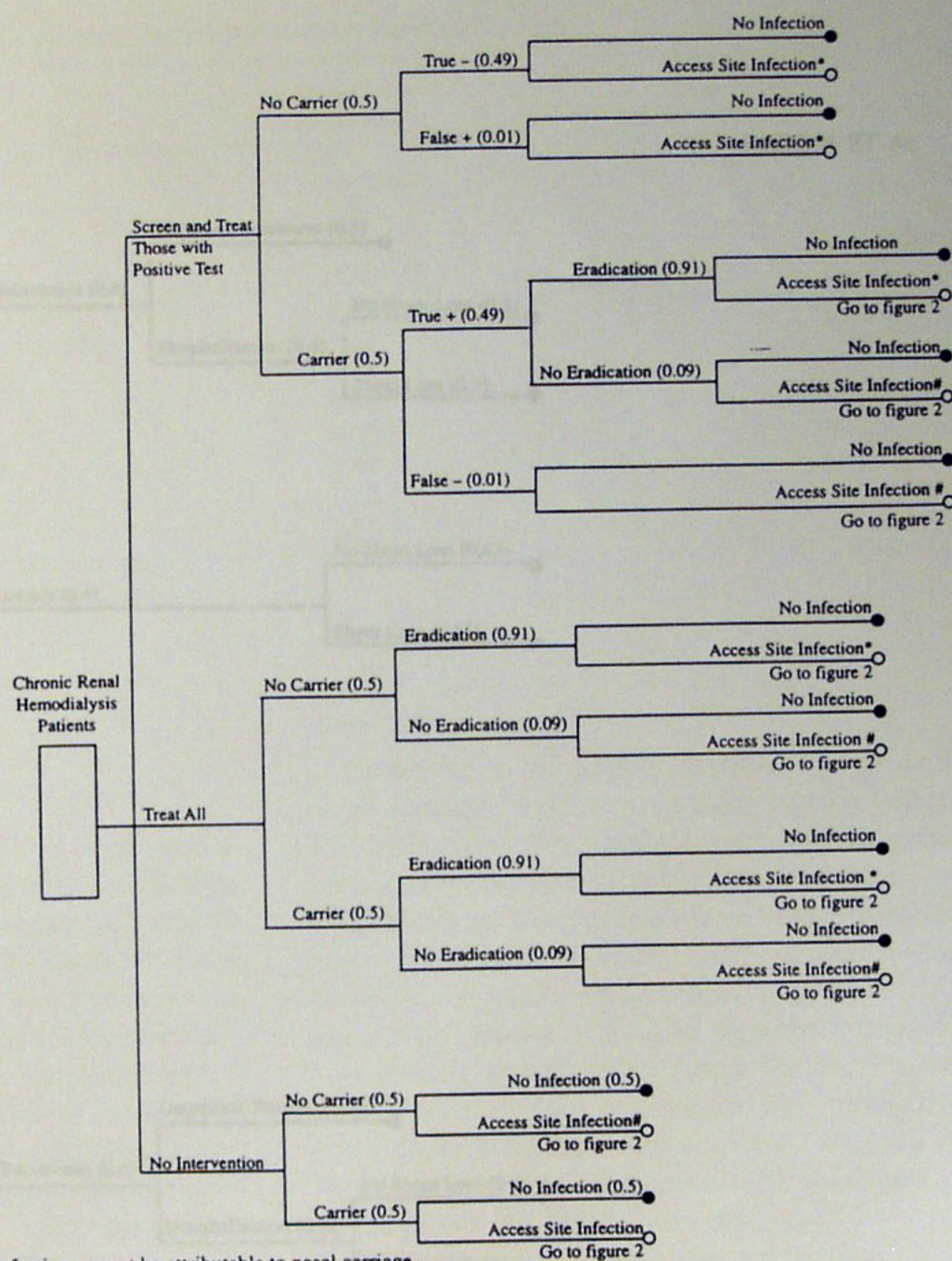


Fig 1. Decision tree of management strategies.

* infection cannot be attributable to nasal carriage
 # infection may be attributable to nasal carriage

ments from Medicare Part B. Payment for the screening culture (\$25) was obtained from a typical private pathology laboratory in Philadelphia, PA, and from the University of Pennsylvania Medical Center. Standard antibiotic cost for outpatient treatment for those with infection (\$30 for hemodialysis patients) was obtained from a survey of eight pharmacies in the greater Philadelphia area. Mupirocin calcium is not approved in the United States for intranasal eradication of *S aureus*, so we constructed its cost (\$7 per day of use) from costs in other countries and from our estimate of the highest likely cost that would be paid in the United States.

The cost (total payments) of each clinical outcome was determined by aggregating the individual cost elements (e.g., hospital, physician, testing, pharmaceuticals) into a gross amount (Table 1) and applying the probability estimates.² For example, mean Medicare parts A and B hospitalization payments for hemodialysis patients without shunt loss was \$5,602; if shunt loss occurred, the total inpatient payment

was \$13,128. The model included only direct medical costs; indirect costs, such as those associated with time away from normal activities, were excluded. The study perspective was that of Medicare, the primary payer of care for hemodialysis patients, and all medical care costs were assumed attributable to Medicare. Thus, this analysis presents conservative cost-effectiveness estimates of the alternative strategies examined; for example, the substantial patient and family out-of-pocket expenses related to the episode of illness attributable to infection are not included. Because the length of the analysis was limited to 1 year, discounting of costs and benefits was not necessary.

Incremental Cost-Effectiveness

Number of *S aureus* infections and cost per 1,000 patients were calculated for each strategy. Incremental cost-effectiveness (the extra cost to prevent one additional infection) of

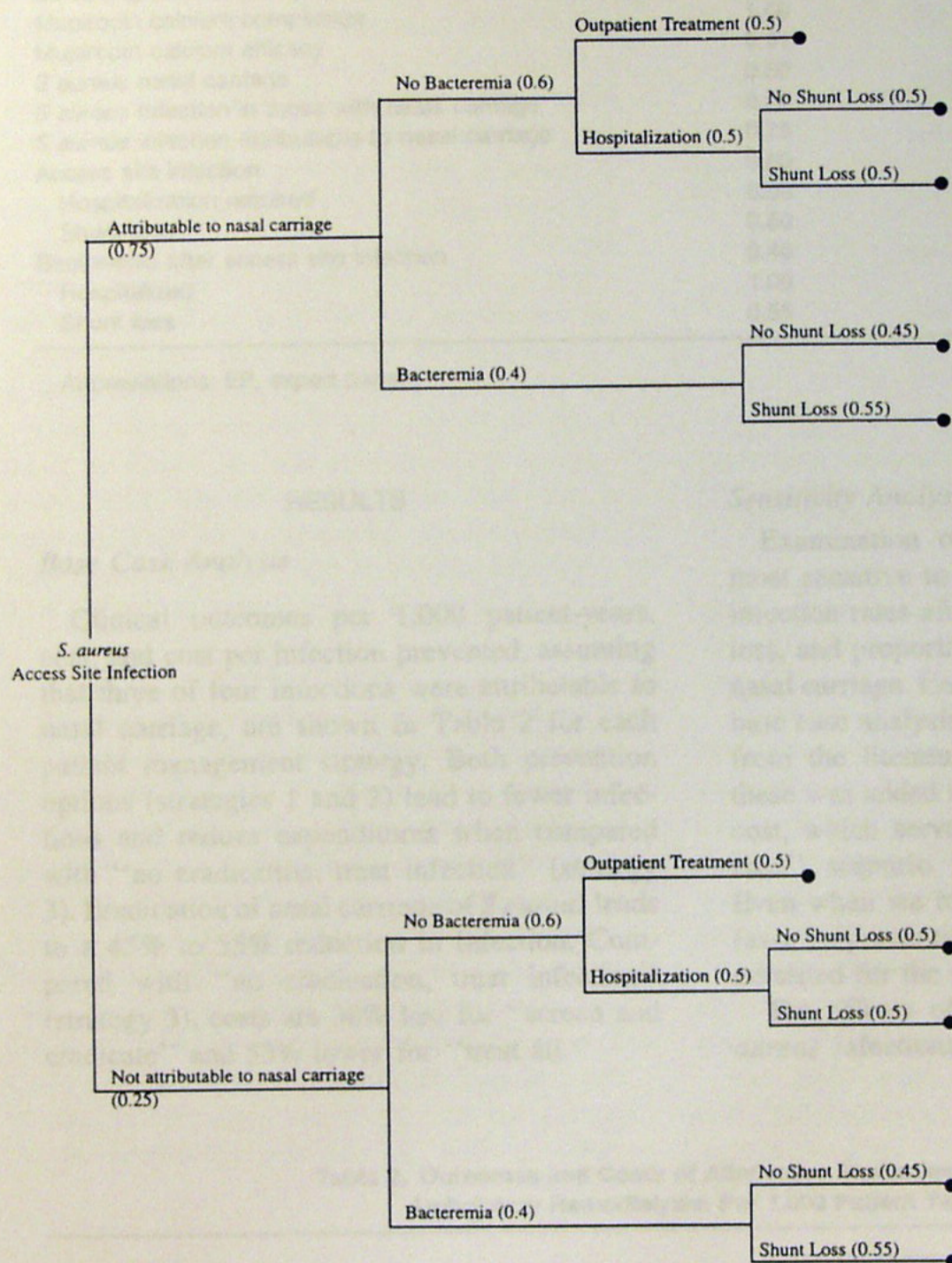


Fig 2. Outcomes of access site infection.

each nasal carriage eradication alternative was compared with a patient management strategy of "no eradication, treat infection only" (strategy 3). The difference was expressed as cost per infection prevented. Incremental cost-effectiveness was not calculated when one strategy was dominant over another (ie, fewer infections occurred *and* costs were lower).

Sensitivity Analyses

Using decision analytic models always entails uncertainty. For example, results from published studies showed variability of *S aureus* nasal carriage and subsequent infection rates. Sensitivity analyses were performed on all variables with important variation to test robustness, that is, the effect of that input variable on number of infections, cost, and cost-effectiveness. A worst case scenario also was tested for each

alternative, simultaneously using the lowest rate of nasal carriage and infection, lowest rate of access loss, and highest cost of mupirocin calcium. For example, in the worst case scenario, the nasal carriage rate was reduced to 0.23 per patient-year,¹⁰ less than half that used in the base case.⁶⁻⁹

The study complied with published guidelines to minimize bias in economic analyses funded by pharmaceutical firms.¹⁹ Because we wanted to recommend a prevention strategy only if we could do so convincingly on both clinical and economic grounds, the study made conservative assumptions on model input values that would favor a strategy of no prevention, treat infection only. To address this point, we performed worst-case scenarios, chose and worked closely with members of the expert panel, developed the model, performed all analyses, and interpreted the results with all biases favoring an expectant management approach.

Table 1. Base Case Input Values: Per Patient-Year

	Base Case Probability	Reference	Cost (\$)
Screening test sensitivity/specificity	0.98/0.98	18, EP	25
Mupirocin calcium compliance	1.00	EP	30
Mupirocin calcium efficacy	0.91	6-10	7/day
<i>S aureus</i> nasal carriage	0.50	9, EP	
<i>S aureus</i> infection in those with nasal carriage	0.50	4-10	
<i>S aureus</i> infection attributable to nasal carriage	0.75	4	
Access site infection	0.80	12-17	110
Hospitalization required	0.50	12-17, EP	5,602
Shunt loss	0.50	11-17	13,128
Bacteremia after access site infection	0.40	4.13	
Hospitalized	1.00	EP	5,602
Shunt loss	0.55	11-14	13,128

Abbreviations: EP, expert panel.

RESULTS

Base Case Analysis

Clinical outcomes per 1,000 patient-years, cost, and cost per infection prevented, assuming that three of four infections were attributable to nasal carriage, are shown in Table 2 for each patient management strategy. Both prevention options (strategies 1 and 2) lead to fewer infections and reduce expenditures when compared with "no eradication, treat infection" (strategy 3). Eradication of nasal carriage of *S aureus* leads to a 45% to 55% reduction in infection. Compared with "no eradication, treat infection" (strategy 3), costs are 38% less for "screen and eradicate" and 53% lower for "treat all."

Sensitivity Analysis

Examination of input variables found four most sensitive to change—nasal carriage rates, infection rates after nasal carriage, rate of shunt loss, and proportion of infections attributable to nasal carriage. Each of these was varied from the base case analysis to reflect lower reported rates from the literature in hemodialysis.^{4,6,7,11,12} To these was added a tripling of mupirocin calcium cost, which served as the basis for the "worst case" scenario for the prevention strategies. Even when we maximally biased the models to favor no prevention, the cost-effective advantage persisted for the prevention strategies.

The effects of altering the percentage of *S aureus* infections attributable to nasal carriage

Table 2. Outcomes and Costs of Alternative Strategies in Chronic Ambulatory Hemodialysis: Per 1,000 Patient Years

	Patient Management Strategies		
	Screen & Treat	Treat All	No Prevention, Treat Infection
Infections*	173	142	313
Infections prevented	140	171	N/A
Access site	84	103	N/A
Bacteremia	56	68	N/A
Strategy cost	\$1,324,460	\$991,941	\$2,109,313
Savings/strategy	(\$784,853)	(\$1,117,372)	N/A
Cost/infection prevented	Savings	Savings	N/A

* 75% of *S aureus* infections attributable to nasal carriage.

over a range of 1.0 (all attributable) to 0.0 (never attributable) on annual cost per 1,000 patients is shown in Fig 3. Even if only 25% of infections are attributable to nasal carriage, implementation of either prevention strategy would save money when compared with expectant management. Fig 4 shows the number of infections per 1,000 patients per year at varying rates of infection attributable to nasal carriage. As the association between carriage and infection is reduced, the clinical benefit of both prevention strategies decreases almost linearly. If only half of the infections are linked to nasal carriage (50% attributable), both prevention strategies still led to marked reduction in the annual number of infections per 1,000 (78/1,000 reduction strategy 1, 114/1,000 reduction strategy 2.)

DISCUSSION

Patients on long-term renal dialysis have a high frequency of *S aureus* nasal carriage and related infection. Unfortunately, there is considerable morbidity of untoward events and reduced quality of life and daily function associated with infection. Education on cleanliness, watchful waiting, diagnosing *S aureus* infection, and treating with sensitive antibiotics are the standard of care. In addition to the undesirable health outcomes of infection, *S aureus* infection treatment costs Medicare over \$200 million annually. Although not yet approved for use in the United States, mupirocin calcium, as well as other

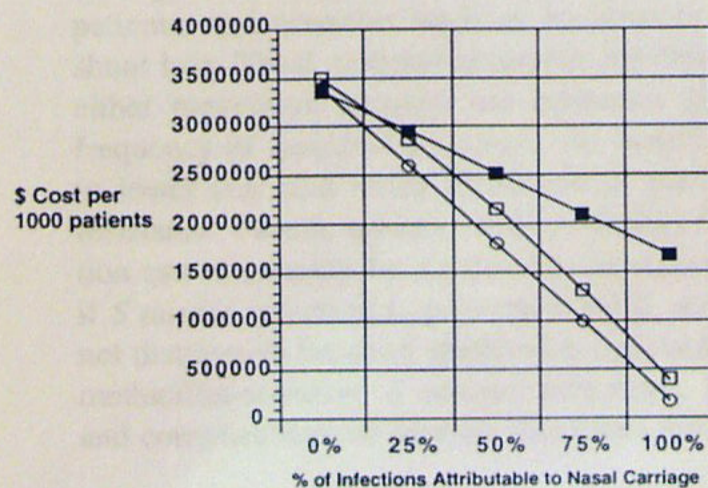


Fig 3. Sensitivity analysis: Percentage of *S aureus* infections attributable to nasal carriage on the cost per 1,000 patients, by management strategy. (□) Screen and treat; (○) treat all; (■) no prevention.

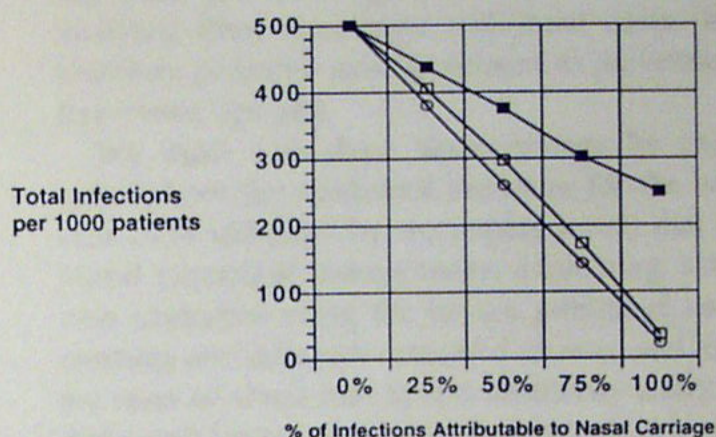


Fig 4. Sensitivity analysis: Percentage of *S aureus* infections attributable to nasal carriage on total infections, by management strategy. (□) Screen and treat; (○) treat all; (■) no prevention.

agents, have been shown in prospective trials to interrupt the nasal carriage-to-infection relationship.^{4,6-10}

The decision analytic model compared the current strategy of expectant management with two prevention options based on an intervention recently proven efficacious in clearing nasal carriage of *S aureus*. If as few as 15% of infections are attributable to nasal carriage, both prevention strategies reduce infection rates and save money. This is not often the case in new medical innovation; introduction of a intervention usually improves clinical outcome at increased cost.

Results from this study examining clinical and economic outcomes of likely management alternatives show that "screen and eradicate" (strategy 1), relative to "treat infection only" (strategy 3) for hemodialysis patients, would have saved Medicare over \$90 million in direct medical costs in 1994, and would have led to a 45% reduction in *S aureus* infections. This is a savings of over \$750,000 annually for every 1,000 hemodialysis patients. The "treat all" option (strategy 2) would have further reduced infection (by 55%) and led to even greater savings to Medicare, approximately \$130 million, or approximately \$1 million annually per 1,000 chronic dialysis patients. Secondary to this dramatic reduction in infections, both eradication strategies prevent deaths and improve quality of life in those patients whose infections were prevented, attributes not heretofore measured in completed trials, and ones that increase savings beyond those measured in this study.

Which Prevention Strategy is Better?

How best to achieve the benefits of prevention of *S aureus* infections by way of nasal carriage eradication in the long run is an important issue. Periodic screening to guide antibiotic use is slightly more expensive and less effective than a strategy that treats all patients on a regular basis. An important additional advantage of the test-and-treat strategy over treating all patients is that it minimizes antibiotic use and theoretically reduces the potential development of resistance by *S aureus* to mupirocin calcium²⁰—an important issue of use in clinical practice.

Concerns of inappropriate antibiotic use and potential decreased effectiveness over time are important issues. Any low-risk, high-benefit, easy-to-use and relatively inexpensive treatment may be used more widely than strict clinical criteria will allow. The lack of data did not allow us to test *S aureus* resistance over time to mupirocin. There are but a few years' clinical data on use of mupirocin calcium, and thus breadth and depth of resistance are unknown.^{6,21} Although appreciable resistance has not been found, sporadic resistance in small and unique populations has been reported.²² Most importantly, future levels and populations affected remain unknown.²³

As with any decision analytic model, a number of cautionary notes need to be considered. First, there is still uncertainty about the role of *S aureus* nasal carriage and subsequent infection. We conservatively assumed that three of four infections were attributable to nasal carriage. As this rate approaches 1.0, as found in prospective clinical trials,⁴ the clinical and economic advantages of prevention are strengthened. Second, there are differences of reported rates of *S aureus* nasal carriage and infection in chronic hemodialysis patients, and sequelae such as bacteremia and shunt loss. Third, optimal treatment regimens in either prevention strategy are unknown; lower frequency of mupirocin calcium use would lead to lower cost and lower likelihood of bacterial resistance. Fourth, quality of life and daily function can reasonably be expected to be improved if *S aureus* infection is prevented. Fifth, we did not distinguish between methicillin-resistant and methicillin-sensitive *S aureus* infections. Cost and complications of treating infections attribut-

able to the former are greater than treating the latter; cost of eradication is the same for both. Lastly, cost of death and other costs borne by the patient and family, such as time from work and pain and suffering, are not included in the analysis; thus, significant additional costs (and therefore potential savings related to prevention) have been ignored.

We dealt with these shortcomings by using values from the published literature for the base case (and validated by the expert panel) that favored expectant management, evaluating worst case scenarios using the lowest published nasal carriage and infection rates of *S aureus*, and lowest rates of shunt loss in the sensitivity analysis, and a cost for mupirocin calcium threefold higher than realistically expected.

Last, we devised a 1-year model knowing that the problem lasts a lifetime for patients on long-term renal dialysis. Rather few published data extend beyond 1 year for any aspect of this study. To conform to the best available published data, we thus kept the study to 1 year. Whether the clinical and economic impact of each strategy would persist over time must be left to long-term follow-up studies. Until the long-term impact of widespread use of mupirocin calcium is known, the tradeoff between a small short-term advantage in terms of infections avoided and increased likelihood of the potential resistance must be recognized.

Deciding between two effective and cost-reducing disease management strategies is a luxury in a health care system that can boast few medical interventions that improve health outcomes and simultaneously reduce costs. This interesting dilemma should not diminish the main finding of our analysis: regardless of how implemented, prevention of related infections by eradicating nasal carriage of *S aureus* in long-term renal dialysis patients should be aggressively pursued when available. This recommendation is strongly backed on both clinical and economic grounds.

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