Central venous catheters are essential in caring for many hospitalized patients who are critically ill and those requiring repeated venous access. Despite the advantages of their use, such as the ability to administer medications and large fluid volumes, central venous catheters are associated with mechanical and significant infectious complications. Catheter-related bloodstream infection (CR-BSI) occurs with 3% to 7% of catheters and affects more than 200,000 patients per year in the United States. The attributable mortality of CR-BSI ranges from approximately 10% to 25%, and CR-BSI has been associated with significant increases in the length of hospitalization and medical care costs.

Strategies have been evaluated to decrease the incidence of CR-BSI, including the use of transparent dressings, strict adherence to proper aseptic technique and handwashing, silver-impregnated catheter cuffs, topical antiseptic solutions, and routine catheter changes. Some of these interventions have shown promise, but CR-BSI remains a significant cause of morbidity and mortality in hospitalized patients.

A novel strategy for the prevention of CR-BSI is the use of central venous catheters impregnated with the antiseptic combination of chlorhexidine and silver sulfadiazine (antiseptic-impregnated catheters). These catheters are designed to reduce the incidence of CR-BSI by inhibiting bacterial colonization of the catheter surface.

Almost all of the randomized controlled trials evaluating these catheters have shown promise, but CR-BSI remains a significant cause of morbidity and mortality in hospitalized patients.

Context A recent randomized controlled trial and meta-analysis indicated that central venous catheters impregnated with an antiseptic combination of chlorhexidine and silver sulfadiazine are efficacious in reducing the incidence of catheter-related bloodstream infection (CR-BSI); however, the ultimate clinical and economic consequences of their use have not been formally evaluated.

Objective To estimate the incremental clinical and economic outcomes associated with the use of antiseptic-impregnated vs standard catheters.

Design Decision analytic model using data from randomized controlled trials, meta-analyses, and case-control studies, as well as safety data from the US Food and Drug Administration.

Setting and Patients A hypothetical cohort of hospitalized patients at high risk for catheter-related infections (eg, patients in intensive care units, immunosuppressed patients, and patients receiving total parenteral nutrition) requiring use of a central venous catheter.

Intervention Short-term use (2-10 days) of chlorhexidine-silver sulfadiazine-impregnated multilumen central venous catheters and nonimpregnated catheters.

Main Outcome Measures Expected incidence of CR-BSI and death attributable to antiseptic-impregnated and standard catheter use; direct medical costs for both types of catheters.

Results In the base-case analysis, use of antiseptic-impregnated catheters resulted in a decrease in the incidence of CR-BSI of 2.2% (5.2% for standard vs 3.0% for antiseptic-impregnated catheters), a decrease in the incidence of death of 0.33% (0.78% for standard vs 0.45% for antiseptic-impregnated), and a decrease in costs of $196 per catheter used ($532 for standard vs $336 for antiseptic-impregnated). The decrease in CR-BSI ranged from 1.2% to 3.4%, the decrease in death ranged from 0.09% to 0.78%, and the costs saved ranged from $68 to $391 in a multivariate sensitivity analysis.

Conclusion Our analyses suggest that use of chlorhexidine-silver sulfadiazine-impregnated central venous catheters in patients at high risk for catheter-related infections reduces the incidence of CR-BSI and death and provides significant saving in costs. Use of these catheters should be considered as part of a comprehensive nosocomial infection control program.
catheters have reported reductions in the incidence of CR-BSI, but there has been some uncertainty regarding their efficacy because only 1 of these trials reported a statistically significant reduction. However, a recent meta-analysis of these studies found a statistically significant reduction in the incidence of CR-BSI, and suggests that the majority of previous trials were underpowered to evaluate CR-BSI incidence.

The clinical and economic effects of using antiseptic-impregnated central venous catheters have not been formally evaluated. Given the results of the recent meta-analysis summarizing the evidence from randomized controlled trials, new reports of hypersensitivity reactions to these catheters in Japan and the current interest in their use, a cost-effectiveness analysis is warranted to assist decision making regarding adoption of this new technology.

We used decision-analytic techniques to evaluate the incremental clinical and economic outcomes associated with the use of antiseptic-impregnated vs standard central venous catheters in hospitalized patients.

METHODS
Decision Model
A decision model was created to evaluate the outcomes associated with the use of antiseptic-impregnated catheters vs standard catheters (FIGURE 1). The time horizon for the analysis was the period of hospitalization and the perspective was that of the health care payer. In the decision model, either an antiseptic-impregnated or standard catheter could be used in a patient requiring a central venous catheter. The use of either catheter type could lead to (1) CR-BSI (defined as an identical organism isolated from a peripheral blood culture and a venous catheter), (2) catheter colonization without bloodstream infection, or (3) no infectious complications. We assumed that some colonized catheters (without bloodstream infection) would be associated with signs of local infection such as purulence or erythema at the insertion site and thus require replacement; we did not include this outcome for catheters that were not colonized based on preliminary calculations indicating the incremental effect was small. Hypersensitivity reaction was included as a potential adverse event associated with antiseptic-impregnated catheters. The final outcome for all patients was life or death.

The hypothetical patient cohort in the model consisted of hospitalized patients at high risk for catheter-related infections requiring the short-term use (2 to 10 days) of multilumen central venous catheters. We chose this cohort because the majority of patients in the clinical trials evaluating antiseptic-impregnated catheters were from high-risk populations such as patients in intensive care units (ICUs), immunosuppressed patients, and patients receiving total parenteral nutrition. and these patients are the primary recipients of central venous catheters in clinical practice. The majority (99%) of patients in the trials received multilumen catheters. A duration of catheterization of 2 to 10 days was chosen because some trials excluded catheters in place for less than 1 day, the mean duration of catheterization in the trials was 7.9 days, and the efficacy of these catheters beyond 10 days has not been well studied.

Table 1. Likelihood of Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR-BSI</td>
<td>0.0046</td>
</tr>
<tr>
<td>No CR-BSI</td>
<td>0.9954</td>
</tr>
<tr>
<td>Local Infection</td>
<td>0.0110</td>
</tr>
<tr>
<td>No Local Infection</td>
<td>0.9890</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0.0080</td>
</tr>
<tr>
<td>No Hypersensitivity</td>
<td>0.9920</td>
</tr>
<tr>
<td>Catheter Colonization</td>
<td>0.0164</td>
</tr>
<tr>
<td>No Catheter Colonization</td>
<td>0.9836</td>
</tr>
<tr>
<td>Antiseptic-Impregnated Catheter Colonization</td>
<td>0.0164</td>
</tr>
<tr>
<td>No Antiseptic-Impregnated Catheter Colonization</td>
<td>0.9836</td>
</tr>
</tbody>
</table>

Figure 1. Decision Tree Used to Evaluate Antiseptic-Impregnated Central Venous Catheters
duced a summary measure with no statistical evidence of heterogeneity (P = .10) or publication bias was used. The probability of CR-BSI with standard catheters (the baseline risk) was derived by statistically pooling the proportion of standard catheters associated with CR-BSI. The probability of catheter colonization with standard catheters was derived in a similar fashion. The probability of CR-BSI with antiseptic-impregnated catheters was determined by multiplying the RR for CR-BSI with antiseptic-impregnated catheters by the probability of CR-BSI with standard catheters (Table 1). The probability of catheter colonization with antiseptic-impregnated catheters was derived similarly. We estimated that half of colonized catheters were associated with signs of local infection. The probability of death attributable to CR-BSI was based on previous reports. A matched case-control study by Pittet et al of 86 cases of bloodstream infection in a surgical ICU found an attributable mortality of 35% (95% CI, 25%-45%). However, attributable mortality in a subset of 20 patients with bloodstream infection associated with central venous catheters was 25%. Patients’’ to 10% to 25% for patients hospitalized. We used a 13% attributable mortality for the base-case scenario and explored a range from 5% to 25% in sensitivity analyses. Although there have been no reports of hypersensitivity reactions to chlorhexidine–silver sulfadiazine–impregnated central venous catheters in the United States (P. Johnson, Arrow International, written communication, March 18, 1999), 13 cases of immediate hypersensitivity reaction were reported in Japan, including 1 potentially associated death. There were 117 000 antiseptic-impregnated catheters sold in Japan before their use was halted because of these cases. Assuming that all reported cases were caused by antiseptic-impregnated catheters, the approximate incidence in Japan per catheter sold was 11.1 cases per 100 000. We used this estimate in our base-case analysis to ensure that potential risks from antiseptic-impregnated catheters were adequately captured (Table 1). The probability of death due to a hypersensitivity reaction was based on the 1 death in 13 cases in Japan. High and low estimates were obtained by doubling and halving the probability, respectively. We assumed the incidence of mechanical complications was the same for both catheter types. Costs Pittet et al reported an average additional charge for patients with nosocomial bacteremia in the ICU in 1990 of $33 268 and an excess hospital stay of 8 days in the ICU and 6 days in the general ward. The excess ICU stay for patients with CR-BSI who survived was 6.5 days, and their average additional charge was $28 690. We chose to estimate the current attributable cost of CR-BSI by multiplying the excess hospital stay for these patients by current per diem hospital costs. The costs at the University of Washington Medical Center for a day in the ICU and a day in the ward ($1152 and $375, respectively) were estimated by multiplying the per diem room charges by the appropriate cost-to-charge ratio (0.631). These per diem costs do not include procedural costs or professional fees. The per diem hospital costs, multiplied by the additional days of stay (6.5 ICU days, 6 ward days), give a total additional cost for CR-BSI of $5738, which was used in the base-case analysis (Table 1). The low estimate for the cost of CR-BSI, $4869, was obtained by halving the base-case cost, and is similar to an inflation-adjusted cost estimate for CR-BSI of $6005 in hospital-wide patients reported by Arnow and colleagues. The high estimate, $19 476, is double the base-case cost, and is significantly less than Pittet and Wenzel’s estimate converted to cost and adjusted for inflation ($44 864).

The additional cost of an antiseptic-impregnated catheter compared with a standard catheter for an averaged-sized hospital is approximately $25. We estimated that a hypersensitivity reaction would require subcutaneous epinephrine and intravenous corticosteroids, diphenhydramine, and cimetidine. The treatment costs for these items at the University of Washington Medical Center is approximately $40. We assumed that 1 additional day in the ICU would be required for a total cost of $1192. High and low estimates were derived by doubling and halving the treatment cost for the base case. It was assumed that a locally infected catheter insertion site

<table>
<thead>
<tr>
<th>Table 1. Parameters Used in Decision Analysis Model†</th>
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<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>CR-BSI</td>
</tr>
<tr>
<td>Standard catheter, %</td>
</tr>
<tr>
<td>Risk ratio†</td>
</tr>
<tr>
<td>Catheter colonization</td>
</tr>
<tr>
<td>Standard catheter, %</td>
</tr>
<tr>
<td>Risk ratio†</td>
</tr>
<tr>
<td>Death attributable to CR-BSI, %</td>
</tr>
<tr>
<td>Hypersensitivity reaction, %†</td>
</tr>
<tr>
<td>Death from hypersensitivity reaction, %</td>
</tr>
<tr>
<td>Local infection if colonization, %</td>
</tr>
</tbody>
</table>

| Costs for 1998, $                                  |                             |              |
| Additional cost of antiseptic catheter            | 25 (20-30)                  | 23, 29, 47   |
| CR-BSI§                                           | 9738 (4869-19 476)          | 6, 44        |
| Hypersensitivity reaction                          | 1192 (596-2384)             | . . . .       |
| Cost of managing local infection                  | 210 (105-315)               | 47           |

*CR-BSI indicates catheter-related bloodstream infection.
†Probability for antiseptic-impregnated catheters was calculated by multiplying the RR by the probability for standard catheters.
‡Based on incidence in Japan.
§|Six and a half days in the intensive care unit ($1152/d) and 6 ward days ($375/d).
|See “Methods” section.

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Outcome Assessment and Sensitivity Analyses

The following primary outcome measures were calculated for each catheter type: incidence of CR-BSI, incidence of death attributable to CR-BSI and/or hypersensitivity reaction, and direct medical costs. The incremental value for each of these measures was determined by subtracting the result for standard catheters from that for antiseptic-impregnated catheters. Local infection associated with catheter colonization was also determined.

We performed a series of sensitivity analyses to evaluate the uncertainty in our analysis. To evaluate the impact of the uncertainty in all of the parameters in the model, we performed a multivariate sensitivity analysis by conducting a Monte Carlo simulation. Such a calculation provides an estimate of the overall uncertainty by simulating the use of multiple catheters in which the clinical probabilities and costs are randomly drawn from probability distributions that represent the uncertainty of each of the parameters. The probability distributions for the parameters were fit so that the means were similar to the base case and the central ranges corresponded with the ranges in Table 1. In general, logistic normal distributions were used to model clinical probabilities and gamma distributions were used to model costs. The use of 10,000 catheters was simulated, and the mean and the central range containing 95% of the values for the incremental costs, incidence of CR-BSI, and incidence of death were determined.

We also conducted a series of 1-way sensitivity analyses to evaluate the effect of varying individual probabilities and costs. These analyses were performed by varying 1 parameter at a time while holding the others fixed. Finally, to test further the robustness of the results, we set all parameters in the model to favor standard catheters more than antiseptic-impregnated catheters in a worst-case scenario.

RESULTS

Costs and Outcomes

In the base-case analysis, use of an antiseptic-impregnated catheter compared with a standard catheter resulted in an expected saving of costs of $196 per catheter (TABLE 2). The expected incidence of CR-BSI decreased from 5.2% for standard catheters to 3.0% for antiseptic-impregnated catheters, an absolute decrease of 2.2% and a relative decrease of 42%. The expected incidence of death attributable to the combination of CR-BSI and/or hypersensitivity reaction decreased from 0.78% to 0.45%, an absolute decrease of 0.33% and a relative decrease of 42%. The incidence of local infections decreased from 12.4% to 7.5%. The calculation of an incremental cost-effectiveness ratio (eg, cost per death avoided) was not conducted because the intervention is dominant: greater efficacy and lower costs.

Sensitivity Analyses

Antiseptic-impregnated catheters remained the dominant strategy (decreased costs and increased efficacy) over the central range of values calculated in the multivariate sensitivity analysis (Table 2). These results held for the worst-case scenario, in which antiseptic catheters resulted in equal costs (incremental cost of $0), decreases in the incidence of CR-BSI (0.6%) and death (0.03%).

The impact on the incremental cost of the most influential individual parameters is shown in a series of 1-way sensitivity analyses in FIGURE 2. The greatest variation in the results was associated with the cost of CR-BSI; the results ranged from $−408 to $−91. The threshold value for the cost of CR-BSI was $687. In other words, in the base-case scenario, antiseptic-impregnated catheters would save costs as long as the attributable cost of an episode of CR-BSI is more than $687. The other most influential variables were the RR for CR-BSI and the incidence of CR-BSI. The additional cost of an antiseptic-impregnated catheter had only a small impact on the incremental cost; the threshold value was $221 in the base-case scenario and $30 in the worst-case scenario. When the RR for CR-BSI was set to 1.0 but the RR for catheter colonization remained unchanged, use of an antiseptic-impregnated catheter resulted in an expected cost $15 higher than for a standard catheter.

The incremental incidence of death was dependent on the probability of death attributable to CR-BSI (FIGURE 3); the results ranged from −0.54% to −0.11%; the parameter threshold value was 0.2%. The RR for CR-BSI was also influential, producing results from −0.47% to −0.12%. In addition, the baseline risk of CR-BSI had a significant impact, −0.41% to −0.25%. The probability of hypersensitivity reaction, explored over the ranges given in Table 1, had little discernable effect on the incremental incidence of death.
sensitivity reaction would have to occur with 4.2% of antiseptic-impregnated catheters to produce equal incidences of death for both catheter types; this is more than 350 times the base-case value. The equivalent threshold value in the worst-case scenario was 0.2%.

**COMMENT**

We used decision analytic techniques to evaluate the clinical and economic consequences of using antiseptic-impregnated central venous catheters in hospitalized patients at high risk for CR-BSI. Our analysis indicates that the use of antiseptic-impregnated catheters in this patient population results in decreased medical care costs, a reduction in the incidence of CR-BSI, and a decrease in the incidence of death compared with use of standard catheters. These results hold true over a wide range of clinical and economic assumptions. The base-case analysis suggests that for every 300 antiseptic-impregnated catheters used, approximately $59 000 will be saved, 7 cases of CR-BSI avoided, and 1 death prevented.

The analysis presented here differs from previous informal cost estimates of antiseptic-impregnated central venous catheters in several ways. First, we used decision analytic techniques to provide a formal framework for our analysis. Second, we evaluated the incidence of death associated with the use of central venous catheters. Third, the estimates used for the efficacy of antiseptic-impregnated catheters were based on evidence from a series of randomized controlled trials rather than a single study. Fourth, we included hypersensitivity reaction as a potential adverse event associated with antiseptic-impregnated catheters. Finally, a wide range of costs and probabilities were explored in 1-way and multivariate sensitivity analyses. Clinical trials confirming the results reported here are needed but may be costly; for example, a randomized trial with 90% power to detect a statistically significant decrease in mortality would require more than 10 000 patients in each study arm based on the effect size and incidence estimates in this study.

Why do antiseptic-impregnated catheters result in such significant cost saving? The use of these catheters is essentially a disease-prevention strategy. The disease in this case, CR-BSI, has an incidence of about 5% and leads to additional medical care costs of about $10 000. The intervention costs an additional $25, reduces the incidence of disease by about 40%, and unlike many prevention strategies, the benefits of its use are seen almost immediately. An equivalent pharmaceutical intervention would be highly valued. In addition to the costs saved from preventing CR-BSI, there are costs saved because of the decreased need for placing new catheters. In our model, we estimate that the decrease in local infections alone results in a costs saving of approximately $10 per catheter. Although an-

![Figure 2. One-way Sensitivity Analyses for Incremental Cost: Effect of Varying Individual Parameters](image)

Threshold values represent parameter values that result in no difference in cost between catheter types.

![Figure 3. One-way Sensitivity Analyses for Incremental Incidence of Death: Effect of Varying Individual Parameters](image)

Threshold values represent parameter values that result in no difference in the incidence of death between catheter types.
tic impregnated catheters appear to be effective for the primary prevention of CR-BSI, it is critical that proper infection-control practices\(^{19}\) be followed, as in the clinical trials, to observe the expected benefits.

The results of our study are not generalizable to all patients requiring a central venous catheter. The meta-analysis on which our study was based included the results from clinical trials in which the majority of patients were from groups at high risk for catheter-related infections such as patients in the ICU, patients receiving total parenteral nutrition, and immunosuppressed patients. The parameters in our analysis for the baseline risk of CR-BSI and the attributable mortality and costs of CR-BSI are also reflective of this patient population. Therefore, the policy implications of this analysis should be limited to similar patient populations. If the hospital policy were to provide these catheters to all patients requiring central venous catheters, the costs saved may not offset the additional cost of antiseptic-impregnated catheters. Further studies are needed to identify more clearly high-risk patients and the appropriate duration of catheterization for antiseptic-impregnated catheters.

The baseline risk of CR-BSI used in our analysis is similar to published rates. The Centers for Disease Control and Prevention reported average CR-BSI rates of 2.8 to 12.8 infections per 1000 catheter-days (median, 1.8-7.1) for all ICU types and average rates of 4.5 to 6.1 infections per 1000 catheter-days (median, 4.6-5.3) for medical/surgical ICUs.\(^{23}\) The range of values for the baseline risk of CR-BSI explored in our analysis was 4.9 to 8.2 infections per 1000 catheter-days. These results suggest that antiseptic-impregnated catheters are likely to save costs in other high-risk, ICU settings. However, hospitals in the Centers for Disease Control and Prevention sample tended to be large teaching hospitals that are not representative of most US hospitals, and the benefits reported in this analysis may not be seen for institutions in which CR-BSI rates for central lines are significantly lower.

The uncertainty in several of the parameters used in our study merits discussion. The attributable cost of CR-BSI has a significant effect on the results of the analysis. Because we based our estimate on the excess ICU stay reported in a study using 1988-1990 data, and because the average length of hospitalization has decreased by 15% to 25% over the past 5 to 10 years,\(^{24}\) this cost could be overestimated, favoring antiseptic-impregnated catheters. However, the per diem hospital costs we used do not include procedure costs or professional fees, and are thus likely conservative enough to compensate for a moderate decrease in the length of hospitalization. We used a conservative estimate for the attributable mortality of CR-BSI (15% vs 25% reported in the study by Pittet and Wenzel\(^{44}\)) and explored a wide range of values to account for the uncertainty in this estimate. The attributable cost and mortality of CR-BSI have not been adequately studied, and a well-designed case-control study that matches patients for length of catheterization in addition to parameters such as disease severity is required. In the meantime, our results suggest that antiseptic-impregnated catheters should save costs for reasonable ranges of CR-BSI attributable costs and mortality found in high-risk patients.

The occurrence of immediate hypersensitivity reaction in association with the use of chlorhexidine–silver sulfadiazine–impregnated catheters is of potential concern. There have been 4 reports of hypersensitivity reactions in Japan, 3 in the United Kingdom, and none in the United States since a Food and Drug Administration warning letter\(^{38}\) was issued in March 1998 (P. Johnson, Arrow International, written communication, March 18, 1999). The higher incidence of hypersensitivity reaction in Japan may be caused by a higher previous exposure of patients in Japan to chlorhexidine or by a genetic predisposition.\(^{38}\) The lack of any recent reports of hypersensitivity reactions in the United States suggests the difference between the United States and Japan is not due to different levels of clinician awareness. Because we used the incidence of hypersensitivity reaction in Japan as our base-case estimate, our results could be considered conservative for patients in the United States.

Finally, our analysis was conducted from the perspective of a health care payer. An analysis from the societal perspective, which might include indirect costs such as patient’s time lost from work, would result in even greater costs saved than reported here. In addition, we limited the time frame of analysis to the period of hospitalization. If this time frame were extended to include medical costs after hospitalization, a decreased incidence of CR-BSI might result in additional costs saving due to decreased health care needs such as home nursing.

The application of advanced catheter technologies such as antiseptic-impregnation and antibiotic-coating\(^{37-39}\) may save costs or be cost-effective for a variety of catheter types and patient populations and warrants research. Importantly, careful patient monitoring is needed to determine the risk factors and frequency of hypersensitivity reactions to chlorhexidine–silver sulfadiazine–impregnated catheters. Also, although there has been no evidence for the development of bacterial resistance,\(^{23}\) the use of antiseptic-impregnated catheters should be monitored for this potentially serious complication that could offset the benefits of their use in the long-term.

Our analysis indicates that the use of antiseptic-impregnated central venous catheters results in both decreased costs and decreased morbidity and mortality in hospitalized patients at high risk for catheter-related infections. This conclusion holds true over a wide range of clinical and economic assumptions. The use of antiseptic-impregnated central venous catheters in high-risk patients should thus be considered as part of a comprehensive nosocomial infection control program.
PREVENTION OF BLOODSTREAM INFECTION

REFERENCES


