Control of Endemic Methicillin-Resistant Staphylococcus aureus: A Cost-Benefit Analysis in an Intensive Care Unit

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METHICILLIN-RESISTANT Staphylococcus aureus (MRSA) has become endemic worldwide over the past 2 decades,1-3 and is now a major nosocomial pathogen in many hospitals.3,4 There are wide variations among countries and hospitals. In Europe, recent surveys indicate that the proportion of MRSA varies from 30% to 40% in southern countries to less than 1% in some northern countries,2 in which sustained MRSA control programs have been implemented early.5,6 High-risk units, such as intensive care units (ICUs), are most affected. In 1992, MRSA accounted for 57% of all ICU-acquired S aureus infections recorded in the European Prevalence of Infection in Intensive Care study.7

Despite encouraging results,3,6,8,9 debate persists on the costs vs benefits of implementing MRSA control programs in hospitals in which MRSA is endemic.10,11 Three major objections to control program implementation are: (1) their efficacy is poorly documented (except for recent epidemics),10 (2) their costs are substantial, and suspected to obviate their potential benefits, and (3) infections caused by MRSA do not appear to incur higher morbidity than those caused by methicillin-susceptible strains.

Context Despite the success of some countries in controlling endemic methicillin-resistant Staphylococcus aureus (MRSA), such programs have not been implemented for some hospitals with endemic infection because of concerns that these programs would be costly and of limited benefit.

Objective To compare the costs and benefits of an MRSA control program in an endemic setting.

Design and Setting Case-control study conducted at a medical intensive care unit (ICU) of a French university hospital with a 4% prevalence of MRSA carriage at ICU admission.

Patients Twenty-seven randomly selected patients who had ICU-acquired MRSA infection between January 1993 and June 1997, matched to 27 controls hospitalized during the same period without MRSA infection.

Main Outcome Measures Intensive care unit costs attributable to MRSA infection, computed from excess therapeutic intensity in cases using estimates from a cost model derived in the same ICU, were compared with costs of the control program, derived from time-motion study of nurses and physicians. The threshold for MRSA carriage that would make the control strategy dominant was determined; sensitivity analyses varied rates of MRSA transmission and ratio of infection to transmission, length of ICU stay, and costs of isolation precautions.

Results The mean cost attributable to MRSA infection was US $9275 (median, $5885; interquartile range, $1400-$16 720). Total costs of the control program ranged from $340 to $1480 per patient. A 14% reduction in MRSA infection rate resulted in the control program being beneficial. In sensitivity analyses, the control strategy was dominant for a prevalence of MRSA carriage on ICU admission ranging from 1% to 7%, depending on costs of control measures and MRSA transmission, for infection rates greater than 50% following transmission.

Conclusions In this example of a hospital with endemic MRSA infection, selective screening and isolation of carriers on ICU admission are beneficial compared with no isolation.
COST-BENEFIT OF MRSA CONTROL

mented in 1992.13 This program includes selective screening of potential MRSA carriers in selected high-risk areas, and isolation of all patients with MRSA. Four years after implementation, we found a 30% reduction in the incidence of MRSA.12 This was apparent in high-risk units such as the ICUs, despite an unchanged 4% MRSA carriage rate on ICU admission.13

We estimated the costs incurred by the MRSA control program in our medical ICU and compared these with the costs of MRSA infections averted. Our objective was to determine the rate of prevalence of MRSA carriage on admission that made the preventive strategy dominant in comparison with no prevention. When the prevalence of MRSA carriage reaches this threshold, the control program becomes beneficial, while ICU-acquired MRSA infections are reduced. We also performed sensitivity analyses to examine the potential benefits of the MRSA control program under various assumptions.

METHODS

Study Design

The reference strategy used for cost comparisons was the absence of screening for MRSA and standard precautions. The costs to the hospital and medical benefits to patients of the strategy to prevent cross-transmission of MRSA were compared with costs of the reference strategy, assuming that the potential medical benefits of isolation were represented only by MRSA infections averted. The control program included screening for MRSA at ICU admission in patients at risk of carriage, as previously described13 and weekly in patients staying in the ICU for 7 days or more, and assigning all patients colonized or infected with MRSA to specific contact isolation precautions. The latter included placing patients in a single room, wearing gloves and a disposable gown or plastic apron for all contacts with patients or their potentially contaminated environment, handwashing with an antiseptic solution, and wearing a mask in case of respiratory infection or extensive wound and/or skin colonization. Contact isolation was maintained until hospital discharge or documented eradication of MRSA colonization.

This study included 3 parts. First, we performed a matched retrospective case-control study to determine the excess length of stay and costs attributable to nosocomial infection caused by MRSA. Second, we observed isolation practices to estimate the excess workload and cost of supplies attributable to isolation precautions. Third, we performed sensitivity analyses, exploring the effect of variation in isolation costs, in isolation efficacy, and risk of infection after MRSA transmission, to assess under various assumptions the threshold for MRSA carriage rate at admission for which the control strategy was dominant (i.e., benefits exceeded costs).

All costs were computed from the viewpoint of the hospital. Production costs after discharge from the ICU were not included.14 The costs for MSRA screening, isolation, and infection were derived from our patient population. Since the time horizon was the duration of the ICU admission, no discounting was necessary. The reference year for all cost computations was 1997. Costs were converted to US dollars at a one-fifth rate.

Setting

The study was conducted at the medical ICU of Henri Mondor hospital in France, a 1000-bed referral university hospital with 108 ICU beds. The medical ICU has 26 beds, including an acute care and a step-down unit of 13 beds each. The acute care unit includes a special care subunit with 5 single-bedded rooms, 2 of which are equipped with anteroom for isolation purposes. An average of 950 patients are admitted to the medical ICU each year, of which approximately 4% are MRSA carriers.13

Outcomes

To estimate morbidity and costs associated with MRSA, we performed a retrospective case-control study, comparing patients having ICU-acquired MRSA infection with matched controls. The number of cases and controls (25 for each group) was predetermined to detect an expected difference in length of ICU stay of 6 days or more.

Using a random number table, cases were selected from the database of the infection control unit among patients diagnosed as having had ICU-acquired MRSA infection (acquired ≥72 hours following ICU admission) between January 1993 and June 1997. Severely neutropenic patients were excluded. A control was defined as a patient similar to a case, but without infection or colonization caused by MRSA during the hospital stay. The ICU admission database was searched for potential controls hospitalized during the same period. Four variables recorded on ICU admission were used for matching cases and controls: age (±5 years); severity of underlying disease classification, using the risk stratification proposed by McCabe and Jackson as rapidly fatal (death expected within 1 year), ultimately fatal (death expected within 5 years), or nonfatal (or no underlying disease);15 the simplified acute physiology score (±3 points)16; and number of organ system failures at ICU admission. To ensure the same duration of exposure to risk in cases and controls, the controls had to have an ICU length of stay greater than or equal to the duration of stay of the corresponding case before infection with MRSA was diagnosed. When several potential controls were found, the control with the nearest age and date of admission to the case was selected.

The following was also recorded: sex, duration of ICU stay, organ system failures recorded at ICU admission (pulmonary failure, cardiovascular failure or shock, renal failure, neurological failure or coma, metabolic disturbances), and the site of Staphylococcus aureus infection, whether bacteremia (including catheter-related bacteremia), lower respiratory tract, urinary tract, or wound infection.

Derivation of Costs

We recorded the intensity of therapeutic activity for cases and controls using the omega score, a workload scoring system similar to the Therapeutic Intervention Scoring System,17 and cur-
Currently used in cost evaluation of French medical ICUs. The omega score includes 47 different diagnostic or therapeutic procedures classified into 3 categories: (1) procedures recorded only once during the ICU stay (omega 1), (2) procedures recorded each time they are performed (omega 2), and (3) procedures recorded daily (including continuous monitoring) throughout the ICU stay (omega 3), which indirectly reflects the ICU length of stay. The total omega score is calculated on the last ICU day. Surgical or interventional radiological procedures performed during the ICU stay were also recorded.

All French public hospitals receive an annual budget to cover all services, including physicians' salaries. Hospitals do not use a cost-to-charges ratio and accounting systems do not collect resources used on a patient basis. A per diem cost is computed, but this cost does not accurately reflect actual expenses.

The newly implemented diagnosis related groups cost system allows estimation of global cost per admission but not a valid identification of the specific cost associated with the days in the ICU as part of an admission.

To estimate the costs of medical interventions for individual patients, we used a model we developed that relates costs to the intensity of interventions in each ICU patient. The model was tested on a random cohort of 99 patients hospitalized in the same medical ICU during the years 1996 to 1997, using actual costing at individual patient level. Total medical costs (Cm) are estimated, excluding salaries and overhead costs, for a given patient were made by the equation: Cm (US$) = 451 + 1 062i + 163i + 4703K + 191 in which subscripts 1, 2, and 3 are the 3 components of the therapeutic activity score omega, and K is a binary variable (scored as 0 or 1), indicating whether a surgical or invasive radiological therapeutic procedure was performed during the ICU stay.

Per diem costs of personnel and overhead were derived from the hospital's cost accounting system. These costs were added, according to length of ICU stay of patients, to medical costs to derive total hospital costs. Costs attributable to S aureus infection were then derived from the difference in costs between cases and controls.

The additional costs of isolation precautions compared with the reference strategy were estimated through an observational time-motion study, recording additional items and time required because of isolation precautions. Unobtrusive observations were performed during January and March 1997 on selected patients admitted to the acute care unit by comparing patients isolated vs not isolated requiring the same level of care. We estimated only medical costs to the ICU, including all costs of supplies and products that could be attributed to contact isolation of a patient. The cost of supplies was the purchase prices from manufacturers. The average nurse's gross hospital salary is $46 000 for 1700 hours, or $27 per hour. The extra costs of nursing were estimated by multiplying the average time spent per day for contact isolation by the average wage (plus social charge) of registered nurses, multiplied by the length of stay. Physicians' labor costs were computed similarly. The medical staff in French university hospitals is paid a salary (half by the hospital, the other half by the university). The average physician's gross hospital salary is $70 000 for 1700 hours, or $41 per hour. The estimated additional time spent by physicians because of control measures was estimated at 10 min/day so we added a fixed $10 per day to the cost of control measures. We did not weigh labor costs according to the severity of the patients. The overall costs of isolation per patient at our institution was then estimated from adding medical, labor, and overhead costs (represented 25% of total operating costs). Isolation costs were computed over the duration of patients' stay in the ICU. The isolation room cost was estimated by the cost of building an isolation room, assuming a depreciation over 10 years. We used this overall isolation cost in the sensitivity analyses, to allow cost modeling for institutions that do not have isolation rooms.

In sensitivity analyses, we varied the probability of MRSA transmission in patients isolated vs not isolated, and probability for ICU patients of becoming infected following MRSA cross-transmission. Figure 1 illustrates the strategy of screening and isolation vs no isolation and the hypotheses tested and range of values applied. Given these assumptions, we explored the ranges of probabilities of being an MRSA carrier at ICU admission that would make the strategy of targeted screening and isolation dominant.

**Statistical Analysis**

Data are reported as median with interquartile range, unless indicated otherwise. Data were analyzed using statistical software programs for the decision tree analysis. Qualitative variables were compared using the chi-square test or Fisher exact test, and median values were compared using the Wilcoxon rank sum test. P<.05 was considered statistically significant. All tests of significance were 2-tailed. Because the distribution of costs was skewed, we computed medians for comparisons and means to compute the average benefit expected from preventive measures.

**RESULTS**

**Patients and Clinical Outcomes**

During the study period, 85 patients developed MRSA infection, of whom 27 were randomly selected to be included in the case-control study. The median interval from admission to diagnosis of nosocomial infection was 8 days (range, 3-17 days). The sites (number) of ICU-acquired MRSA infections recorded in cases were bacteremia (9), catheter-related (2), lower respiratory tract (14), and urinary tract (2) infections. There was no statistically significant difference in the clinical characteristics of cases and their matched controls in terms of age, sex, admission category, severity of underlying disease, simplified acute physiology score, and number and types of organ failures at ICU admission (Table 1). Hospital and ICU mortality were significantly higher in MRSA cases compared with control patients (Table 2). The case patients with MRSA...
stayed a median of 4 days longer in the ICU than matched controls (18 vs 14 days; P = .02); the difference was larger for surviving pairs (n = 8), but did not reach conventional statistical significance (21 vs 12.5 days; P = .08).

**Figure 1.** Costs and Benefits of Isolation Precautions Compared With No Isolation

MRSA indicates methicillin-resistant *Staphylococcus aureus*; MRSA carrier (+), patient colonized or infected with MRSA on admission, thus exposing other patients to cross-transmission; MRSA carrier (−), patient not colonized or infected with MRSA, and not exposing other patients to MRSA cross-transmission. The definitions for probabilities of variables considered are as follows: p1, prevalence of MRSA carriage at intensive care unit admission, varied from 1% to 15%; p2, probability of MRSA cross-transmission from an isolated MRSA carrier to a noncolonized patient, varied from 0.01 to 0.05; p3 and p5 (infection to transmission ratio), probability of MRSA infection in a patient colonized following cross-transmission of MRSA (it was assumed that p3 is equal to p5), varied from 1:4 to 3:4; and p4, probability of MRSA cross-transmission from an MRSA carrier not in isolation precautions, varied from 0.01 to 0.05.

**Table 1.** Clinical Characteristics of Patients With Infection Caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA) and of Matched Controls at Intensive Care Unit Admission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MRSA Cases (n = 27)</th>
<th>Controls (n = 27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (interquartile range), y</td>
<td>66 (24-84)</td>
<td>68 (26-83)</td>
<td>.90</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10</td>
<td>8</td>
<td>.56</td>
</tr>
<tr>
<td>Women</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapidly fatal</td>
<td>17</td>
<td>17</td>
<td>.94</td>
</tr>
<tr>
<td>Ultimately fatal</td>
<td>5</td>
<td>5</td>
<td>.89</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Admission category</td>
<td></td>
<td></td>
<td>.38</td>
</tr>
<tr>
<td>Medical</td>
<td>21</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Surgical (scheduled/unscheduled)</td>
<td>6 (2/4)</td>
<td>2 (1/1)</td>
<td></td>
</tr>
<tr>
<td>Primary organ system dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>8</td>
<td>14</td>
<td>.22</td>
</tr>
<tr>
<td>Coma</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Metabolic failure</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Simplified Acute Physiologic Score II</td>
<td>37 (31-44)</td>
<td>37 (32-45)</td>
<td>.49</td>
</tr>
</tbody>
</table>

**Costs and Benefits**

The MRSA case patients required significantly more therapeutic activity than controls (Table 2). The mean total costs of treating MRSA cases exceeded that of their matched controls by $9275. This result was used to derive benefits expected from a reduction of MRSA infection through control measures. In surviving pairs, the excess medical and total costs incurred by MRSA infection were $4380 and $10 560, respectively.

We computed the costs of isolation precautions, corresponding to the actual practice observed, and to a theoretical 100% compliance to recommended control measures (TABLE 3). The average daily excess nursing time attributed to contact isolation was measured by direct observation at 16 minutes, and would increase to 20 minutes per patient-day if full compliance to isolation precautions were observed. The total extra cost of contact isolation, including supplies and screening for MRSA, was estimated to range from $655 to $705 (≡ $1480 with investment costs) per patient assigned to isolation for an average of 20 days in the ICU.

We computed a threshold rate for the benefit of isolation as a function of the reduction of MRSA infection, under our baseline hypothesis for costs and efficacy of prevention derived from the above (an extra cost of an MRSA infection of $9275 and costs of isolation precautions, including costs of single room isolation, of $1480 per patient). If the MRSA carriage rate on admission was 4%, and the rate of MRSA transmission and infection was reduced 15-fold by isolation precautions, isolation measures were cost-beneficial if the ICU-acquired MRSA infection rate was reduced by 14%. In that case, screening and isolation dominated the reference strategy of no prevention.

**Sensitivity Analyses**

We explored the threshold for MRSA carriage rate on ICU admission that would make the strategy of targeted screening and isolation dominant, vary-
is less efficient (ie, includes all costs directly attributed to isolation precautions taken when caring for a patient (ie, supplies, nurse and physician labor costs, and overhead costs)). A fixed $10 per day was used for added physician’s costs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Observed Procedures</th>
<th>Full Compliance to Isolation Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average nursing time per day attributable to contact isolation precautions*</td>
<td>16 min</td>
<td>20 min</td>
</tr>
<tr>
<td>Nursing time attributable to contact isolation precautions, per patient stay†</td>
<td>2 h 50 min to 5 h 25 min</td>
<td>3 h 25 min to 6 h 40 min</td>
</tr>
<tr>
<td>Excess physicians’ costs, per patient stay, $</td>
<td>100-200</td>
<td>100-200</td>
</tr>
<tr>
<td>Extra cost attributable to contact isolation, per patient stay,$‡</td>
<td>325-640</td>
<td>350-690</td>
</tr>
<tr>
<td>Cost of screening at ICU admission, per patient, $</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Total cost of contact isolation and screening, per patient, $</td>
<td>340-655</td>
<td>365-705</td>
</tr>
</tbody>
</table>

*Contact isolation precautions consisted of antiseptic handwashing, and wearing a mask, a gown, and gloves. The measurement of daily attributable nursing time was based on observations made during 21 8-hour shift periods, comparing isolated with nonisolated patients. The right column lists theoretical corresponding times and costs for 100% compliance to isolation precautions.
†Mean length of stay of patients colonized or infected with MRSA varied from 10 to 20 days.
‡Includes all costs directly attributable to isolation precautions taken when caring for a patient (ie, supplies, nurse and physician labor costs, and overhead costs). A fixed $10 per day was used for added physician’s costs.

COMMENT

Our study suggests identification of MRSA carriers via selective screening and subsequent isolation in our endemic MRSA environment is a beneficial strategy when compared with no screening and standard precautions. This strategy was dominant (ie, reduced both morbidity and costs) if only a relatively small fraction (14%) of MRSA infections are averted and not substituted by methicillin-susceptible S aureus infection. Varying the MRSA transmission rate and infection to transmission ratio, the control strategy remained dominant when the prevalence of MRSA carriage on ICU admission ranged from 1% to 7%.

The excess length of ICU stay attributable to MRSA infection recorded in our study (4 days overall and 8.5 days in survivors) is lower than expected from reports on several other nosocomial infections and other studies estimating morbidity resulting from infection caused by MRSA. Prior studies have compared patients infected with patients not infected, without controlling for confounding factors reflecting severity of illness or underlying disease. We matched cases and controls on several variables strongly correlated with outcome of ICU patients (age, the severity of underlying disease and of acute illness, and num-

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number of organ failures). This matching procedure, based on several severity of illness criteria, might have resulted in underestimating the consequences of ICU-acquired MRSA infection. Although controls were selected in the absence of *S. aureus* infection, several patients actually had other nosocomial infection that was expected to increase their length of stay and mortality. Our study assessed only the consequences of MRSA infection to the ICU budget and workload, and not on the entire hospital admission, or from a societal perspective. Our approach focused on ICU costs from the hospital’s perspective, which can be useful for comparing different strategies and making infection-control decisions at the local level.

We found mean excess medical and total costs attributable to nosocomial MRSA infection of about $3500 and $9275, respectively. These data were derived from a cost model we developed and validated on a cohort of ICU patients from the same ICU. Our cost estimations are less accurate than those provided by a prospective cost study. However, similar models based on our workload score have been developed for cost evaluation of ICUs, and have been shown to correlate well with actual direct costs and mean costs of ICU admission. Our model provides a reasonable estimate of costs incurred by patients treated in ICUs with comparable practice patterns.

Conversely, we used direct observation of workload through time-motion studies to compute the costs of isolation. The relatively low cost of isolation precautions may be related to the fact that control measures had been implemented in the ICU for several years at the time of these observations. Isolation procedures were familiar to ICU personnel, which causes more efficient organization of nursing interventions, minimizing constraints associated with their observance. When compared with uninfected patients cared for in identical isolation rooms, the workload attributable to isolation precautions for MRSA patients may have been minimized. Also, the costs of infection control personnel related to implementation and follow-up of the program were not included, since we did not assess the time specifically devoted by this personnel to the MRSA control program. Since our results may not be directly applicable to other units having different structures, we introduced the additional cost of a new isolation room in the sensitivity analysis, which resulted in doubling the costs of isolation precautions.

Rising health care costs have become an increasing concern to consumers, providers, and payers of health care services, and cost-outcome studies are increasingly affecting the allocation of limited health care resources. In this context, it appears useful to assess the costs and benefits of infection-control programs. This particularly holds true for endemic MRSA control programs, in which debate persists on the type and extent of control measures that should be implemented. Accordingly, widely divergent strategies have been advocated in face of the MRSA problem, ranging from complacency to the “search and destroy” strategy. Opponents to control programs for endemic MRSA emphasize that the morbidity and mortality of infection caused by MRSA and methicillin-susceptible strains are similar (making the control of MRSA questionable if substitution of MRSA by methicillin-susceptible strains follows). Building on early experience accumulated from protracted outbreaks, other authors point out that MRSA adds substantially to the burden of nosocomial infections, and that costs of control measures are likely lower than costs averted from prevention of infection. For example, the cost of control measures implemented during 1 outbreak involving 25 patients amounted to less than 10% of the costs of treating infected patients. In addition, most nosocomial infections caused by MRSA result from cross-transmission, and are therefore potentially preventable. Finally, limitation of vancomycin usage in hospitals is an important objective in the context of increasing resistance in enterococci and emerging resistance in

The cost-beneficial (with no investment) threshold for MRSA carriage (see legend to Figure 1) is shown, according to the probability of infection following cross-transmission (infection to transmission ratio, varying from 0.25 [upper curve], to 0.5 [middle curves], and 0.75 [lower curve]), the risk of cross-transmission from non-isolated MRSA carriers (x axis), and that from MRSA carriers on isolation precautions.
Targeted screening for MRSA carriage at admission to high-risk areas helps identify a substantial proportion of colonized patients and contributes to early implementation of contact isolation to reduce the risk of cross-transmission. Compared with no screening, this strategy appears to effectively reduce MRSA rates. Comparing targeted screening with a strategy of universal screening and isolation dominates other strategies over a range of MRSA carriage on admission, efficacy of the control program, and infection rates following transmission.

The threshold rate for MRSA carriage at ICU admission making our MRSA control strategy dominant varies according to the efficacy of prevention of cross-transmission and the rate of infection in patients with ICU-acquired MRSA carriage. In settings in which relative costs are similar to those included in this analysis, our control strategy is dominant when MRSA carriage on admission ranges from 1% to 7%, when the MRSA transmission rate from colonized to isolated patients is at least 5-fold less than to patients not isolated, and when the infection to transmission ratio is greater than 0.25. Our findings may be generalizable to similar ICUs and patients, but not necessarily to settings in which the MRSA transmission rate and/or the infection to transmission ratio could be lower.

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