Antibiotic-Impregnated Catheters Associated With Significant Decrease in Nosocomial and Multidrug-Resistant Bacteremias in Critically Ill Patients*

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Objective: To evaluate the impact of using central venous catheters (CVCs) impregnated with the combination of minocycline and rifampin on nosocomial bloodstream infections (BSIs), morbidity, and mortality in cancer patients in the ICU.

Design: Prospective surveillance study consisting of the following two time periods: September 1997 through August 1998 (ie, fiscal year [FY] 1998); and from September 1998 through August 1999 (ie, FY 1999).

Setting: ICUs of a tertiary care hospital in Houston, TX.

Patients: Cancer patients in the medical ICU (MICU) and surgical ICU (SICU).

Interventions: ICUs started using CVCs impregnated with the minocycline-rifampin combination at the beginning of FY 1999.

Measurements and main results: The rates of nosocomial BSIs and other patients’ characteristics were compared for the two study periods to determine the impact of using the impregnated catheters in the ICU. Patients’ characteristics, including antibiotic use, were comparable for the two study periods in both the MICU and the SICU. The rate of nosocomial BSIs in the MICU unit decreased from 8.3 to 3.5 per 1,000 patient-days (p < 0.01), and decreased in the SICU from 4.8 to 1.3 per 1,000 patient-days (p < 0.01) in FY 1999. Nosocomial vancomycin-resistant enterococcus (VRE) bacteremia also decreased significantly (p = 0.004). Length of stay in the MICU and SICU significantly decreased in FY 1999 (p < 0.01 and p = 0.03, respectively). The rate of catheter-related infections decreased from 3.1 to 0.7 per 1,000 patient-days in FY 1999 (p = 0.02). The decrease in infections resulted in net savings of at least $1,450,000 for FY 1999.

Conclusions: The use of antibiotic-impregnated CVCs in the MICU and SICU was associated with a significant decrease in nosocomial BSIs, including VRE bacteremia, catheter-related infections, and lengths of hospital and ICU stays. (CHEST 2003; 124:1030–1038)

Key words: antibiotic-impregnated central venous catheter; central venous catheters; ICU; minocycline; nosocomial bloodstream infections; rifampin

Abbreviations: AIC = antibiotic-impregnated catheter; APACHE = acute physiology and chronic health evaluation; BSI = bloodstream infection; CR-BSI = catheter-related bloodstream infection; ĈVC = central venous catheter; FY = fiscal year; MIC = minimal inhibitory concentration; MICU = medical ICU; SICU = surgical ICU; VRE = vancomycin-resistant enterococcus, enterococci

Nosocomial bloodstream infections (BSIs) have been shown1,2 to be associated with high morbidity in critically ill patients. However, its association with increased mortality has been debatable. DiGiovine et al3 were unable to detect an association between primary nosocomial BSIs and increased ICU mortality, after matching for severity of illness, but they found an increase in ICU length of stay and cost. Pittet et al3 demonstrated that nosocomial BSI in critically ill patients is associated with an attributable mortality rate of 35%, an excess length of stay in the ICU of 8 days, and extra costs attributable to the infection averaging $40,000 per survivor. In a prospective cohort study, Renaud and Brun-Buisson4 assessed the incidence and outcomes of primary catheter-related infections and secondary nosocomial BSIs. Nosocomial BSI was found to be associated with an attributable mortality rate of 35%.
However, when the authors performed a pairwise (ie, 1:1) case control analysis, the excess mortality was found to be 11.5% in patients with catheter-related BSIs (CR-BSIs), 20% in patients with primary bacteremia, and 55% in patients with secondary bacteremia.

Intravascular catheters are the main source of BSIs in critically ill patients. In a 25-year study involving 486 episodes of nosocomial BSIs in an adult ICU, 62% of the BSIs were associated with catheter colonization or were infections that suggested the catheter to be the source.2

Central venous catheters (CVCs) impregnated with minocycline and rifampin in combination were shown in vitro, ex vivo, and in animal studies to be efficacious in preventing the catheter infections, and were significantly more active against bacterial organisms when compared with catheters coated with chlorhexidine/silver sulfadiazine.5,6 Prospective, randomized multicenter clinical studies7,8 have shown that such catheters are efficacious in preventing CR-BSIs in critically ill patients and were 12 times less likely to be associated with CR-BSIs than were catheters coated with chlorhexidine/silver sulfadiazine. There has been concern that the use of these antibiotic-impregnated catheters (AICs) might increase the risk of multidrug-resistant organisms9 such as vancomycin-resistant enterococci (VRE). In this study, we attempted to evaluate the impact of the use of such catheters on nosocomial BSIs, VRE bacteremia, morbidity, and related mortality in critically ill cancer patients, and we performed a cost analysis.

**Materials and Methods**

**Patients**

This study was conducted between September 1997 and August 1999 as part of an infection control surveillance in the ICUs (ie, both the surgical ICU [SICU] and the medical ICU [MICU]) of The University of Texas MD Anderson Cancer Center. The study consisted of two phases. The first phase was the period from September 1997 through August 1998 (ie, fiscal year [FY] 1998), during which most of the CVCs that were used were uncoated. The second phase was the period between September 1998 and August 1999 (ie, FY 1999), during which most of the catheters that were used were impregnated with the combination of minocycline and rifampin (ie, minocycline-rifampin). The MICU consisted of a 16-bed unit. The SICU consisted of an 18-bed unit. In January 1999, patients were moved to a new 42-bed ICU, with patients designated to MICU or SICU according to the hospital admitting service in the new hospital. Blood cultures were obtained for patients who had fever (ie, core temperatures ≥ 38.3°C) that could not be explained by a noninfectious etiology such as an underlying tumor or the use of a cytokine. Patients with positive blood culture findings were evaluated through appropriate investigative means, such as radiographs, BAL, and cultures of suspected infected sites, for the potential source of BSIs such as nosocomial pneumonia, urinary tract infection, soft-tissue infection, surgical wound infection, or catheter infection.

Patients admitted to the MICU and SICU during each of the two FY periods (ie, FY 1998 and FY 1999) were compared in terms of age, gender, race, duration of ventilation, duration of catheter placement, duration of neutropenia, peak creatinine levels, albumin, hyperalimentation through the CVC, and the frequency of using AICs. In addition, patients in the MICU were evaluated using the ICU cancer mortality model score, which was shown to be a better predictor of severity of illness than the APACHE (acute physiology and chronic health evaluation) II score in immunocompromised cancer patients.10,11 Outcome was evaluated in terms of the following parameters: (1) nosocomial BSIs (including nosocomial VRE BSIs); (2) catheter-related infections (including local catheter site infection); (3) duration of ICU and hospital stays; and (4) mortality during the ICU stay related to the BSI.

**Catheters**

During FY 1998, uncoated, 7F, 20 cm and 25 cm long, noncuffed, double-lumen and triple-lumen polyurethane CVCs (Arrow International; Reading, PA) were used. In August 1998, the same type of catheters impregnated with minocycline-rifampin (Cook Spectrum; Cook Critical Care; Bloomington, IN) were introduced and were heavily used in the MICU and the SICU. The catheters that were coated with minocycline-rifampin provided antimicrobial activity on both the external and the internal surfaces, and they were also 20 and 25 cm long, noncuffed, double-lumen and triple-lumen polyurethane. During the study period, all catheters were inserted using maximum sterile barrier precautions. At the time of catheter insertion and at each subsequent dressing change, the insertion site was disinfected with 10% povidone-iodine. Dressings at the insertion sites were changed every 3 days. The decision to remove and/or culture the catheter was made solely by the primary physician. A catheter was removed and cultured if a patient had either a local catheter site inflammation with purulent discharge or a fever, with or without a positive blood culture finding, that had been persistent for 48 h after the initiation of appropriate antibiotic therapy, and in the absence of another source for the infection other than the catheter. The decision to remove and/or culture the catheter tip was made solely by the primary physician.

**Microbiological Testing**

Four-centimeter segments from the tips of catheters that had been removed from patients with suspected infection were
Aseptically cut and cultured by the roll plate method, as described by Maki et al. \(^\text{12}\) Organisms recovered from the catheter tips or blood cultures were identified by standard microbiological methods. Minimal inhibitory concentrations (MICs) of minocycline-rifampin were tested for VRE organisms that had been isolated from blood and catheter tip cultures using standard broth microdilution assays. In addition, the antimicrobial activity of AICs against VRE was investigated by using the modified Kirby-Bauer technique, \(^\text{5,6}\) determining the zones of inhibition of these catheters against VRE organisms.

Definitions

We adopted the definitions for nosocomial BSIs, CR-BSIs, local catheter infections, and catheter colonizations as proposed by Pittet et al. \(^\text{1}\) the Centers for Disease Control and Prevention, \(^\text{13}\) and the Infectious Disease Society of America guidelines on intravascular catheter-related infections. \(^\text{14}\) Nosocomial primary BSIs were defined as a positive blood culture finding (ie, at least two blood cultures that were positive for skin organisms such as coagulase-negative staphylococci and one blood culture positive for a known pathogen such as *Staphylococcus aureus*, Gram-negative bacilli, and Candida species) in critically ill patients occurring 48 h after admission to the ICU that was associated with clinical manifestations of infection such as fever and chills, and with no other source for the BSI (such as pneumonia, urinary tract infection, or surgical site infection) except for the catheter. Documented CR-BSI was defined as a nosocomial BSI in a patient with no other apparent source for the infection, except the catheter, in whom the organism that was isolated from a peripheral blood culture is of the same species with identical antimicrobial susceptibility as the organism isolated from a catheter colonized with \(\geq 15\) colony-forming units. Local catheter site infection was defined as the presence of inflammation (ie, erythema, induration, or tenderness) or the occurrence of purulence at the catheter exit site. Catheter-related infection was considered as the summation of CR-BSIs and local catheter site infections. Colonization was defined as the isolation of \(\geq 15\) colony-forming units of any organism from a 4-cm catheter tip segment.

### Table 1—Characteristics of Patients in the ICU for the FYs 1998 and 1999\(^*\)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MICU FY 1998 (n = 653)</th>
<th>MICU FY 1999 (n = 764)</th>
<th>p Value</th>
<th>SICU FY 1998 (n = 1,128)</th>
<th>SICU FY 1999 (n = 1,285)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57 (11–94)</td>
<td>57 (2–90)</td>
<td>0.7</td>
<td>60 (2–95)</td>
<td>58 (3–92)</td>
<td>0.07</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>347 (53)</td>
<td>458 (60)</td>
<td>0.01</td>
<td>666 (59)</td>
<td>935 (59)</td>
<td>1.0</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>94 (14.4)</td>
<td>106 (13.9)</td>
<td>0.8</td>
<td>6 (0.5%)</td>
<td>7 (0.4%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Leukemia</td>
<td>191 (29.2)</td>
<td>194 (25.4)</td>
<td>0.1</td>
<td>5 (0.4%)</td>
<td>16 (1%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Ventilator time &gt; 96 h, %</td>
<td>121 (62)</td>
<td>109 (58)</td>
<td>0.4</td>
<td>102 (51)</td>
<td>80 (56)</td>
<td>0.4</td>
</tr>
<tr>
<td>Duration of CVC, d</td>
<td>20 (1–45)</td>
<td>32 (1–46)</td>
<td>0.01</td>
<td>8 (1–24)</td>
<td>12 (1–34)</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration of neutropenia, d</td>
<td>8 (1–64)</td>
<td>9 (1–65)</td>
<td>0.3</td>
<td>7 (4–30)</td>
<td>7 (1–16)</td>
<td>0.5</td>
</tr>
<tr>
<td>Peak creatinine level, mg/dL</td>
<td>1.6 (0.4–13.4)</td>
<td>1.5 (0.4–8)</td>
<td>0.4</td>
<td>1.5 (0.4–10.8)</td>
<td>1.4 (0.4–7.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>2.9 (0.6–4.5)</td>
<td>2.8 (0.9–4.6)</td>
<td>0.1</td>
<td>2.5 (0.4–4.9)</td>
<td>2.5 (0.4–4.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>ICU cancer mortality model</td>
<td>0.4 (0.002–0.98)</td>
<td>0.27 (0.03–0.98)</td>
<td>0.9</td>
<td>0.38 (0.06–0.99)</td>
<td>0.39 (0.06–0.99)</td>
<td>0.64</td>
</tr>
<tr>
<td>Hyperalimentation</td>
<td>166 (25)</td>
<td>188 (25)</td>
<td>0.7</td>
<td>73 (6)</td>
<td>128 (8)</td>
<td>0.1</td>
</tr>
<tr>
<td>Frequency of AIC use, %</td>
<td>2/99 (1)</td>
<td>226/236 (96)</td>
<td>&lt; 0.001</td>
<td>12/286 (4)</td>
<td>242/338 (72)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

\(^*\)Values given as median (range) or No. (%), unless otherwise indicated.

\(^\dagger\)Absolute neutrophil count of < 500 cells/mm³.

### Statistical Analysis

The significance of differences between study groups was determined through the use of the Student *t* test or the Mann-Whitney test for continuous variables, and the Fisher exact test or the Chi² test for categoric variables. All *p* values were based on two-tailed tests of significance. Whenever multiple comparisons were made, *p* values were adjusted using the Bonferroni correction (eg, infection rates in the MICU and SICU were determined separately and also by combining Gram-positive and Gram-negative bacteremia rates). A *p* value of \(\leq 0.05\) was considered significant. All computations were performed with a statistical software package (SPSS, version 10.0 for Windows; SPSS, Inc.; Chicago, IL). The severity of illness in the MICU was assessed in terms of the ICU cancer mortality model.

### Results

#### Characteristics of Patients

As shown in Table 1, most of the patient characteristics that could have had an impact on outcome for FY 1998 and FY 1999 were comparable in the MICU and SICU. For the MICU, there were 653 patients admitted during FY 1998 and 764 admitted in FY 1999. The two groups were comparable in terms of age, underlying disease, frequency of intubation for \(> 96\) h, duration of catheter placement, duration of neutropenia, peak creatinine level, albumin, and duration of neutropenia. The MICU cancer mortality model was defined as the occurrence of inflammation (ie, erythema, induration, or tenderness) or the occurrence of purulence at the catheter exit site. Catheter-related infection was considered as the summation of CR-BSIs and local catheter site infections. Colonization was defined as the isolation of \(\geq 15\) colony-forming units of any organism from a 4-cm catheter tip segment.
min level, ICU cancer mortality model score, and hyperalimentation administered through the CVC. There was, however, a higher frequency of male gender for FY 1999 among the MICU patients. For the SICU, there were 1,128 patients admitted during FY 1998 compared with 1,585 admitted during FY 1999. The two groups were comparable in terms of gender, underlying disease, intubation for > 96 h, duration of neutropenia, peak creatinine level, albumin level, and hyperalimentation given through the CVC. There was a trend for older age in the SICU patients for FY 1998 compared to FY 1999; however, the difference was not statistically significant (p = 0.07). The use of AICs in both ICUs increased significantly from FY 1998 to FY 1999. In the MICU, AICs were used at a frequency of 1% in FY 1998, which increased to 96% in FY 1999 (p < 0.001). Similarly, in the SICU the frequency of using the AIC was increased from 4% in FY 1998 to 72% in FY 1999 (p < 0.001). Table 2 shows that antibiotic usage in the ICU in terms of grams per 1,000 patient-days was comparable for FY 1998 and FY 1999. First-generation cephalosporins were used as prophylactic agents in surgical patients, and oral quinolones were used as prophylactic agents in MICU patients with leukemia and in those who had undergone bone marrow transplantation. Of particular interest is that these prophylactic agents were used more frequently in FY 1998 than in FY 1999 (Table 2).

**Outcome Related to Infections**

As shown in Table 3, in the MICU the rate of nosocomial BSIs decreased from 8.3 per 1,000 patient-days in FY 1998 to 3.5 per 1,000 patient-days in FY 1999 (p < 0.01), despite a longer duration of central venous catheterization (p = 0.01) [Table 1]. Similarly, in the SICU the rate of nosocomial BSIs decreased from 4.8 per 1,000 patient-days in FY 1998 to 1.3 per 1,000 patient-days in FY 1999 (p < 0.01). Associated with a decrease in the nosocomial BSI rates in both the MICU and SICU was a concurrent decrease in morbidity as measured by the ICU and hospital lengths of stay. The lengths of stay in both the MICU and SICU were significantly decreased from FY 1998 to FY 1999 (p ≤ 0.01 and p = 0.03, respectively) [Table 2]. The hospital length of stay was significantly decreased in the SICU (p < 0.01), and there was a definite trend for decrease in the MICU (p = 0.06; Table 2). Mortality that was related to or attributed to nosocomial BSI was slightly decreased in the SICU and the MICU (Table 3). However, the difference was not statistically significant, possibly because of the small numbers of fatal episodes.

As shown in Figure 1, the rate of nosocomial BSIs (in the MICU and SICU combined) decreased from 6.3 per 1,000 patient-days in FY 1998 to 2.2 per 1,000 patient-days in FY 1999 (p = 0.02). Associated with this decrease in nosocomial BSIs was a more than fourfold decrease in catheter-related infections from a rate of 3.2 per 1,000 patient-days in FY 1998 to 0.6 per 1,000 patient-days in FY 1999 (p < 0.001). The rate of CR-BSI separately dropped from 1.4 per 1,000 patient-days to 0.46 per 1,000 patient-days (p = 0.044). Local catheter site infections also decreased significantly from 1.8 per 1,000 patient-days to 0.12 per 1,000 patient-days (p < 0.001).

**Other Factors**

On January 1, 1999, all adult critically ill patients were moved to new and larger SICU and MICU facilities. The rate of nosocomial infections was calculated before and after the introduction of the AIC as an intervention for the time periods that preceded the move. On August 1, 1998, the AICs were introduced to the MICU and SICU. In the old unit, the rate of nosocomial BSIs decreased from 6.8 per 1,000 patient-days prior to the introduction of the AICs (ie, September 1, 1997, to July 31, 1998) to 1.9 per 1,000 patient-days after their introduction (ie, August 1 to December 31, 1998) [p < 0.001]. Similarly, the rate of documented catheter-related infections decreased from 3.4 per 1,000 patient days to 0.2 per 1,000 patient-days (p = 0.003) during the two time periods described above. In addition, the rate of nosocomial Gram-positive BSIs significantly decreased during the same time periods (p < 0.01).

### Table 2—Antibiotic Usage in the ICU Before and After Intervention

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>FY 1998</th>
<th>FY 1999</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First generation</td>
<td>2.67</td>
<td>2.20</td>
<td>NS</td>
</tr>
<tr>
<td>Third and fourth</td>
<td>8.58</td>
<td>8.33</td>
<td>NS</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>6.00</td>
<td>5.36</td>
<td>NS</td>
</tr>
<tr>
<td>Quinolones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>7.47</td>
<td>6.05</td>
<td>NS</td>
</tr>
<tr>
<td>Total (oral + IV)</td>
<td>8.15</td>
<td>7.54</td>
<td>NS</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.28</td>
<td>0.52</td>
<td>NS</td>
</tr>
</tbody>
</table>

*The total number of patient-days for FY 1998 was 8,348, and for FY 1999 was 8,627. Third-generation cephalosporins included ceftaxone and ceftazidime, while fourth-generation cephalosporins consisted of cefepime. Carbapenems include imipenem and meropenem. Quinolones include ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, and norfloxacin. NS = nonsignificant.

‡All p values were > 0.1.
and tended to decrease for nosocomial Gram-negative BSIs \( (p = 0.06) \) [Table 4].

**Microbiology of Infections**

As shown in Table 4, most of the nosocomial primary BSIs were caused by Gram-positive organisms. When calculated in terms of 1,000 patient-days, there was a significant decrease in nosocomial Gram-positive BSIs from FY 1998 to FY 1999 (Fig 2). For specific Gram-positive organisms, there was a significant decrease in the rate of nosocomial BSIs independently for VRE infections (Fig 2), coagulase-negative staphylococci, and vancomycin-sensitive enterococci \( (p = 0.05) \). In addition, the rate of nosocomial BSIs caused by Gram-negative bacillary organisms tended to decrease from 1 per 1,000 patient-days in FY 1998 to 0.2 per 1,000 patient-days in FY 1999 \( (p = 0.06) \). Within the limitations of small numbers, there was no significant decrease in the frequency of *Pseudomonas aeruginosa* infections or Candida infections for the two time periods. In three of eight (38%) of the nosocomial VRE bacteraemias diagnosed in FY 1998, the catheter was documented as the source of the BSI.

**VRE Susceptibility**

Seven of the eight VRE isolates were available for susceptibility testing. As shown in Table 5, five of the seven isolates were susceptible to minocycline (MIC, \( \leq 2 \) \( \mu \)g/mL). There were two additional VRE bacteraemic isolates, one of which (isolate 2 in Table 5) was resistant to minocycline (MIC, 8 \( \mu \)g/mL) but was highly susceptible to rifampin (MIC, \( < 0.06 \) \( \mu \)g/mL). The other VRE bacteremic isolate (isolate 4 in Table

![Figure 1. Rate of nosocomial bloodstream infections and documented catheter infections in the ICU.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=data/journals/chest/21998/)


5) had intermediate susceptibility to minocycline (MIC, 4 µg/mL) but was highly resistant to rifampin (MIC, >128 µg/mL). Hence, six of the seven isolates were susceptible either to minocycline or rifampin, and therefore, the catheters impregnated with minocycline and rifampin had a zone of inhibition of ≥11 mm against these same isolates. The one isolate (isolate 4 in Table 5) with intermediate susceptibility to minocycline and resistance to rifampin was associated with a zone of inhibition of 6 mm to the catheter impregnated with minocycline-rifampin.

### Discussion

**Efficacy of AIC**

The data derived from this study show a significant decrease in nosocomial primary BSIs occurring in the SICU and the MICU associated with the introduction of AICs to these units. In addition, the significant decrease in nosocomial BSIs was associated with a significant decrease in catheter-related infections in the ICU (Fig 1) as well as a significant decrease in the nosocomial Gram-positive BSIs. Removed CVCs were cultured by the roll-plate technique, which retrieves organisms on the outer surface of the catheter. However, many of the CVCs were used for long-term therapy (Table 1); and since this method fails to culture intraluminal organisms and, hence, its use may have led to an underestimation of the intraluminal colonization, which predominates for long-term CVCs, thus leading also to an underestimation of the rate of CR-BSI. The significant decrease in nosocomial BSIs was also associated with a decrease in the length of stay in the ICU and in the hospital in general, as well as a >50% reduction in mortality associated with or attributed to nosocomial BSIs in the ICUs. Despite the concern that the use of AICs would lead to an increase in resistant organisms causing BSIs in the ICU, the introduction of catheters impregnated with minocycline-rifampin was associated with a significant decrease in nosocomial primary VRE bacteremia.

Several prospective randomized studies have demonstrated that catheters impregnated with minocycline-rifampin were associated with a significant decrease in nosocomial CR-BSIs and are significantly more efficacious in the prevention of catheter-related infections than are catheters impregnated only on the external surface with chlorhexidine and silver sulfadiazine. Gilliam et al showed that the introduction of AICs was associated with a significant reduction in nosocomial BSIs per 1,000 patient-days in the burn ICU and pediatric ICU. The rate of nosocomial BSIs in the burn ICU decreased from 17.9 per 1,000 patient-days in 1998 to 4.7 per 1,000 patient-days in 1999. Similarly, the rate of nosocomial BSIs decreased from 17.1 per 1,000 patient-days in 1998 to 3.3 per 1,000 patient-days for the year 1999 in the pediatric ICU. In addition, Dauenhauer et al showed that the introduction of catheters impregnated with minocycline-rifampin was associated with a ninefold decrease compared with uncoated catheters, and at least a sixfold reduction in CR-BSIs compared with catheters coated with chlorhexidine and silver sulfadiazine. Darouiche et al showed in a prospective randomized study that catheters impregnated with minocycline-rifampin were 12 times less likely to be associated with CR-BSIs compared with catheters coated on the external surface with chlorhexidine and silver sulfadiazine. However, in addition to the decrease in nosocomial BSIs and CR-BSIs, this current study uniquely shows that the introduction of AICs also associated with a decrease in multidrug-resistant VRE bacteremia and a significant decrease in ICU length of stay.

### The Effect of Using AICs

The decrease in nosocomial primary BSIs occurred in the two adult ICU units and was associated with the introduction of the AIC and a significant reduction in catheter-related infections. In addition, this decrease in nosocomial BSIs could not be explained by any other factor. The characteristics of the patients in the two units over the two time periods were comparable (Table 1). The only significant difference in terms of characteristics occurred in the MICU, where there was a higher frequency of...
male gender in FY 1999. In a previous prospective randomized study involving catheters impregnated with minocycline-rifampin, male gender was found to be an independent risk factor for catheter colonization, according to a multivariate logistical regression model. Therefore, the increase in the frequency of male gender for FY 1999 should have resulted in increased nosocomial and catheter-related infections rather than the decrease noted in this study. Additionally, the amount of antibiotic usage in the ICU (in grams per 1,000 patient-days) was comparable for FY 1998 and FY 1999, suggesting that systemic antibiotic usage did not contribute to the significant decrease in nosocomial bacteremia or VRE bacteremia that had been noted during the two time periods.

The only potential confounding factor was that in January 1999 the patients were moved to a new ICU. However, a subset analysis comparing the rate of nosocomial BSIs, Gram-positive BSIs, catheter infections, and nosocomial VRE bacteremia for FY 1998 (ie, between September 1997 and August 1998) to the first 4 months of FY 1999 (ie, between September 1, 1998, and December 31, 1998), during which time all patients were in the same unit, showed a significant decrease in all of these infections associated with the introduction of AICs. Therefore, the decrease in nosocomial BSIs, as well as in other types of infections, occurred even before the move to the new ICU.

**Morbidity and Mortality**

The data from this study suggest that the decrease in nosocomial BSIs associated with the introduction of the AIC could have been associated with a significant decrease in morbidity (as measured in terms of length of stay in the ICU and the hospital) and could have contributed to earlier discharge from the unit (Table 3). Pittet et al reported that a single episode of nosocomial BSI would increase the length of hospital stay by an average of 24 days and the length of ICU stay by 8 days. dos Santos et al concluded that the efficacy and impact of new antimicrobial catheters should be assessed in terms

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**Table 5—Activity of Minocycline and Rifampin Against VRE Isolated During FY 1998**

<table>
<thead>
<tr>
<th>Isolate No.</th>
<th>Zone of Inhibition of AICs, mm</th>
<th>MIC of Minocycline, μg/mL</th>
<th>MIC of Rifampin, μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>0.5</td>
<td>8</td>
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of the ability to be associated with earlier discharge from the ICU and decreases in overall morbidity and mortality.

Susceptibility and Reduction of VRE

Some investigators have raised the concern that the use of AICs could lead to the emergence of multidrug-resistant bacteria leading to BSIs in hospitalized patients. However, the introduction of AICs into our ICU was associated with a significant decrease of VRE BSIs in our study (Fig 2). Tambe et al demonstrated that after 10 to 20 passages through subinhibitory concentrations of minocycline and rifampin, a 10-fold to 16-fold decrease in susceptibility of the tested organism to this combination was noted. However, after these repeated passages the Staphylococcus epidermidis organisms tested remained susceptible to minocycline-rifampin at an MIC of 0.25 μg/mL. In addition, Tambe et al demonstrated that minocycline has a protective effect on rifampin resistance, a finding that was previously demonstrated by Yourassowsky et al with respect to methicillin-resistant S. aureus. No resistance to either minocycline or rifampin has been demonstrated clinically after the use of the AICs in clinical trials.

In two independent studies, Gilliam et al and Dauenhauer et al demonstrated that the introduction of AICs to the ICU was associated with a significant decrease in the number of blood cultures performed and a decrease in vancomycin usage. This has been postulated as a mechanism through which the use of catheters impregnated with minocycline-rifampin could result in a decrease in VRE bacteremia in the ICU. In a multicenter study of a large number of adult ICUs in the United States, Fridkin and colleagues demonstrated that CR-BSIs are a major determinant of vancomycin usage and subsequently showed that the use of IV vancomycin was independently associated with an increase in and prevalence of VRE in the ICU. However, in the current study, the decrease in nosocomial VRE bacteremia was not associated with a decrease in vancomycin usage in our adult MICU and SICU. A number of factors may explain this observation. Critically ill patients in the MICU and SICU often receive antibiotics empirically and prophylactically, not only therapeutically. Also, ICU patients who were receiving antibiotics for community-acquired infections were not considered since the study addressed only nosocomial BSIs. In addition, all infections occurring at sites other than the bloodstream and that were treated with antibiotics were also not part of this study.

Of the cases of VRE bacteremia in the current study, 38% were due to documented catheter-related infections, and in the remaining 62% the catheter tip was not cultured, suggesting that the rate of catheter-related VRE bacteremias could have been higher. Beezhold et al demonstrated that VRE could colonize the inguinal and antecubital skin in 86% of patients with VRE bacteremia, suggesting that VRE may be an important cause of catheter-related bacteremia in hospitalized patients. In addition, Bassetti et al demonstrated a correlation between zones of inhibition and the in vitro efficacy of AICs. Since most of the VRE isolates in our unit prior to the introduction of the AICs were susceptible to either minocycline or rifampin, and since the AICs had zones of inhibition against most of the VRE isolates, it is possible that the AIC significantly decreased the risk of catheter-related VRE bacteremia in our ICUs, resulting in a significant decrease in this type of infection.

Cost Savings

Several investigators have demonstrated that the use of the AIC in the ICU was associated with a significant decrease in the cost of medical care through the prevention of CR-BSIs. Pittet et al estimated the extra cost of a single episode of nosocomial BSI to be $40,890 (in 1994 dollars). This could be converted to $44,864 per nosocomial BSI in 1999. The introduction of AICs into our adult ICU resulted in the prevention of at least 33 episodes of nosocomial BSI. This resulted in a cost saving of $1,450,512 for FY 1999. The added cost related to the AIC is $46 per catheter, which would result in a total of $21,528 for the purchase of the 468 AICs used in FY 1999. The net savings for FY 1999 would have been $1,458,984. However, it should be noted that this cost saving estimation did not differentiate between primary BSIs and CR-BSIs.

In conclusion, the introduction of AICs to the adult MICU and SICU was associated with a significant decrease in nosocomial primary Gram-positive and Gram-negative bacteremia. This reduction of nosocomial bacteremia was associated with a significant decrease in catheter-related infections and cases of nosocomial multidrug-resistant VRE bacteremia, as well as a significant decrease in the length of hospital and ICU stay. This significant decrease in nosocomial BSIs resulted in a net savings of at least $1,450,000 during FY 1999.

APPENDIX

The members of the MD Anderson Catheter Study Group are as follows: George Habanbo, MD, D. Edward Supkis, Jr, MD, Gregory H. Botz, MD, and Karen Chen, MD.
REFERENCES