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Original Research

CRITICAL CARE

Health-care-Associated Bloodstream Infections at Admission to the ICU

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Background: **Infections occurring among outpatients having recent contact with the health-care system have been recently classified as health-care-associated infections to distinguish them from hospital- and community-acquired infections. Patients with bloodstream infections (BSIs) were studied to assess health-care-associated infections at admission in the ICU.**

Methods: **This work was a multicenter, prospective, observational study of all adult patients with BSI at ICU admission at 27 Spanish hospitals and one Argentine hospital. Cases of BSI were classified as community-acquired BSI (CAB), health-care-associated BSI (HCAB), or hospital-acquired BSI (HAB), and their characteristics were compared.**

Results: **Of 726 BSIs, 343 (47.2%) were CABs, 252 (34.7%) were HABs, and 131 (18.0%) were HCABs. Potentially antibiotic-resistant pathogens were more frequently isolated in HABs (34.8%) and HCABs (27.6%) than in CABs (10.3%) ($P < .001$). Logistic regression analysis revealed that HABs (OR, 4.6; 95% CI, 2.9-7.3), HCABs (OR, 3.1; 95% CI, 1.8-5.4), and BSIs of unknown origin (OR, 1.7; 95% CI, 1.0-2.8) were independently associated with the isolation of potentially antibiotic-resistant pathogens. The incidence of inappropriate treatment was significantly higher in HABs (OR, 3.4; 95% CI, 2.1-5.3) and in HCABs (OR, 1.8; 95% CI, 1.0-3.2) than in CABs.**

Conclusions: **One in five BSIs diagnosed at ICU admission is health-care-associated. The incidence of potentially drug-resistant pathogens in HCABs is more similar to that of HABs, and they should be treated as such until culture data are available.** ***CHEST 2011; 139(4):810–815***

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; BSI = bloodstream infection; CAB = community-acquired bloodstream infection; HAB = hospital-acquired bloodstream infection; HCAB = health-care-associated bloodstream infection; MRSA = methicillin-resistant *Staphylococcus aureus*; PARP = potential antibiotic-resistant pathogen

Bloodstream infection (BSI) continues to be a severe condition.[1-8] The cause of death in patients with BSI who are admitted to the ICU is often the severity of systemic response, but at same time a delay in appropriate antibiotic administration can lead to progressive deterioration. The correlation between survival and delay in getting appropriate antibiotic treatment has been demonstrated in patients with community-acquired BSI (CAB) who are admitted to the ICU.[3]

Infections were traditionally classified as either nosocomial or community acquired.[9,10] However, changes in health-care systems have shifted health-care services from hospitals to different outpatient facilities. For this reason, a new classification scheme for BSIs has been proposed to distinguish between infections occurring among outpatients having recurrent or recent contact with the health-care system, patients with community-acquired infections, and inpatients with hospital-acquired infections.[11,12] According to this classification, 40% to 50% of patients admitted to the hospital with what are traditionally defined as CABs should be classified as having health-care-associated BSIs (HCABs).[11-13]

To our knowledge, no prospective studies have examined the importance of HCABs in patients in the ICU. We aimed to analyze the characteristics of HCABs in the ICU and their impact on the

effectiveness of initial antibiotic therapy and outcome. We hypothesized that a substantial proportion of patients admitted to the ICU from the community actually have HCABs, with microbiologic characteristics, appropriate treatments, and outcomes that are different from those of patients with CABs.

Materials and Methods

Study Design

This prospective, observational, multicenter study was performed in 28 ICUs (27 Spanish hospitals and 1 Argentine hospital) of urban teaching hospitals. All consecutive adult patients (>18 years of age) admitted between January 1, 2007, and December 31, 2007, who presented with at least one positive blood culture in the first 48 h after admission to the ICU were included in the study. Data for patients were recorded using a standardized worksheet and stored in a computer database. We excluded all episodes of BSI diagnosed >48 h after admission to the ICU. The ethics committees waived the requirement for informed consent since confidentiality was guaranteed and no interventions were performed.

Data Collection

We collected data on demographic characteristics, comorbidities, microbiologic characteristics, susceptibility testing and appropriateness of empirical antibiotic treatment, and systemic response. Underlying diseases and severity at admission were classified according to the APACHE (Acute Physiology and Chronic Health Evaluation) II score.[14] Crude mortality data included all patients who died in the ICU.

Definitions

HCAB was defined by a positive blood culture test result obtained within 48 h of ICU admission if the patient fulfilled any of the following criteria[11]: residence in a nursing home or long-term-care facility during the past 30 days; hospitalization for at least 48 h during the past 90 days; hemodialysis or IV chemotherapy during the past 30 days; IV therapy, wound care, enteric nutrition, or health care at home during the past 30 days. CAB was defined by a positive blood culture test result obtained within 48 h of ICU admission from a patient who did not fit the criteria for a health-care-associated infection. Hospital-acquired BSI (HAB) at admission to the ICU was defined by a positive blood culture test result obtained from a patient proceeding from another ward of the same hospital who had been hospitalized for 48 h or longer.

The source of infection was classified as one of the following: lower respiratory tract, intraabdominal (including biliary infections), catheter related, genitourinary tract, skin and soft tissue, or other, when the microorganism isolated in the blood culture coincided with a culture from a distal source. Episodes in which there was no documented distal source were defined as BSIs of unknown origin.

Information about comorbidities was obtained through a medical record review. Patients were considered to have received immunosuppressive treatment, chemotherapy, or a corticosteroid if they had been receiving therapy within the 4 weeks before the BSI. Patients who had organ transplants and patients who were HIV-positive were also considered to be immunocompromised.

Therapy for the BSI was considered appropriate when at least one effective drug was included in the empirical antibiotic treatment within the first 24 h after the blood sample test result was obtained.[15] In practice, this involves targeting therapy to the desired pathogens as well as using the appropriate drug, optimal dose, and correct route of administration.[16]

Microbiologic Techniques

All isolates from patients were identified using standard microbiologic techniques. Antimicrobial susceptibility testing was carried out in accordance with the standards of the Clinical and Laboratory Standards Institute.[17] The microorganisms *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* sp (known as ESKAPE microorganisms)[18,19] were considered to be potential antibiotic-resistant pathogens (PARPs). Cases in which more than one microorganism was isolated were defined as polymicrobial BSIs.

Statistical Analysis

Descriptive statistical analysis included frequencies and percentages for categorical variables and means and SDs for continuous variables. Means were compared using the analysis of variance test. Proportions were compared using the χ^2 test or Fisher exact test. Moreover, post hoc pair-wise comparisons were conducted (CAB vs HCAB, CAB vs HAB, and HCAB vs HAB) as usual. To take into account multiple comparisons, these analyses were repeated applying Bonferroni adjustments. The ORs and 95% CIs were calculated according to standard methods.[20] Multivariate logistic regression analysis was performed to assess which factors were associated with the isolation of PARPs to the blood culture, inappropriate treatment, and mortality. In the multivariate analysis, variables were selected for entry into the logistic regression model if they were significantly associated with mortality at a P value < 0.1 in the univariate analysis or if we considered that the variable had clinical significance. Statistical significance was defined as $P < .05$. Statistical analysis was done using SPSS software, version 15.0 (SPSS Inc; Chicago, Illinois).

Results

During the study period, 19,785 patients were admitted, and BSIs were present at ICU admission in

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726 patients (mean APACHE II score, 21 ± 8; mean age, 61 ± 15 years). BSIs were classified as CABs in 47.2% of patients (343 of 726), as HABs in 34.7% (252 of 726), and as HCABs in 18% (131 of 726).

Clinical characteristics were different among the BSI subgroups (Table 1). Among patients with HCABs, 51% had been hospitalized in an acute-care hospital before the BSI, 25.2% had attended dialysis or received IV chemotherapy, 22.1% had received health care at home, and 9.2% had resided in a nursing home or long-term-care facility. Some patients presented with more than one factor defining the condition of HCAB.

Globally, the most common sources of BSI were lower respiratory tract infections and intraabdominal infections (Table 2). Respiratory tract infection was the most frequent source in CABs, whereas abdominal infection was the most frequent source in HCABs and HABs.

The distribution of pathogens was significantly different among the BSI subgroups (Table 3). PARPs (ESKAPE microorganisms) were more frequent in HABs (34.8%) and HCABs (27.6%) than in CABs (10.3%) ($P < .001$). To identify the risk factors independently associated with the isolation of PARPs, we fitted a multivariate logistic regression model, including as covariates age, sex, and APACHE II score at admission, to address cases with more than two comorbidities, systemic response, source, and origin of BSI. The significantly associated factors were: unknown origin as source of BSI (OR, 1.7; 95% CI, 1.0-2.8), HCAB (OR, 3.1; 95% CI, 1.8-5.4), and HAB (OR, 4.6; 95% CI, 2.9-7.3). Among patients with HCABs, PARPs were more frequent in patients receiving health care at home (33%) and in patients hospitalized in an acute-care hospital before the BSI (25.4%) or residing in a nursing home or long-term-care facility (25%).

The systemic response was similar in all three groups, although in patients with CABs, the infection clinically manifested more frequently as sepsis than

Table 1—*Patient Demographics and Clinical Characteristics by Type of BSI*

Characteristic	CAB (n = 343)	HCAB (n = 131)	HAB (n = 252)
Demographics			
Age, y, mean (SD)	60 (16)	64 (13)[a]	62 (14)
Male, %	62.7	69.5	72.6[a]
APACHE II score, mean (SD)	19 (9)	23 (9)[b]	21 (9)
Comorbidities, %			
Cardiovascular disease	12.8	21.4[a]	15.5
Diabetes mellitus	21.6	25.2	18.7
COPD	12.8	16.8	14.3
Chronic hepatic failure	9.6	7.6	10.3
Cancer	7.6	31.3[c]	34.5[c]
Chronic renal failure	5.8	13.0[a]	9.1
Immunosuppression	6.1	29.0[c]	17.9[c]
HIV infection	5.0	3.1	1.2[a]
Comorbidities, No.			
0, %	32.7	13.7[c]	20.6[b]
≥ 2, %	33.5	56.5[c]	50.4[c]

APACHE = Acute Physiology and Chronic Health Evaluation; BSI = bloodstream infection; CAB = community-acquired bloodstream infection; HAB = hospital-acquired bloodstream infection; HCAB = healthcare-associated bloodstream infection.
[a]$P < .05$, compared with CAB.
[b]$P < .01$, compared with CAB.
[c]$P < .001$, compared with CAB.

Table 2—*Distribution of Sources by Type of BSI*

Source	CAB (n = 343)	HCAB (n = 131)	HAB (n = 252)
Secondary BSI, %			
Lower respiratory tract	25.4	20.6	15.4[a]
Intraabdominal	24.9	22.1	33.3[b]
Genitourinary tract	11.8	17.6	6.5[b]
Catheter	0	7.6[c]	14.6[c]
Other, %	20.7	16	11[a]
Unknown origin of BSI, %	17.2	16	19.1

See Table 1 for expansion of abbreviations.
[a]$P < .01$, compared with CAB.
[b]$P < .05$, compared with CAB.
[c]$P < .001$, compared with CAB.

Table 3—*Distribution of Pathogens by Type of BSI*

Pathogen, %	CAB (n = 341)	HCAB (n = 130)	HAB (n = 249)
Gram-positive bacteria	50.1	38.5[a]	34.1[b]
Staphylococcus aureus, all	10.3	13.8	9.6
MSSA	10	10	4.4[a]
MRSA	0.3	3.8[c]	5.2[b]
CNS	3.5	6.2	10.8[c]
Streptococcus, all	30.5	15.4[c]	11.2[b]
Streptococcus pneumoniae	21.4	4.6[b]	1.6[b]
Enterococcus sp	1.5	4.6[a]	8.4[b]
Other streptococci	7.6	6.2	1.2[b]
Other gram-positive bacteria	3.2	0.8	0.8
Gram-negative bacteria	36.1	50.8[c]	42.2
Escherichia coli	20.5	26.9	18.5
Klebsiella sp	4.1	4.6	6.0
Pseudomonas sp	1.8	4.6	6.4[c]
Enterobacter sp	2.3	6.9[a]	3.6
Other gram-negative bacteria	7.3	7.7	7.6
Anaerobes	3.2	1.5	1.6
Candida sp	1.5	3.8	8.4[b]
Polymicrobial	9.1	5.4	13.7

We excluded from the analysis of microorganisms six episodes of bloodstream infections, corresponding to two in the CAB group, one in the HCAB group, and three in the HAB group. There were three fungus infections (two *Cryptococcus neophormans* and one *Geotrichum candidum*) and three infections in which identification of the microorganisms was not possible. MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *S aureus*; CNS = coagulase-negative staphylococci. See Table 1 for expansion of other abbreviations.
[a]$P < .05$, compared with CAB.
[b]$P < .001$, compared with CAB.
[c]$P < .01$, compared with CAB.

Table 4—*Systemic Response, Inappropriateness of Antibiotic Treatment, and Mortality by Type of BSI*

Variable	CAB (n = 343)	HCAB (n = 131)	HAB (n = 252)
Systemic response			
Sepsis	24.5	15.3[a]	19.8
Severe sepsis	17.5	19.8	19.4
Septic shock	58.0	64.9	60.7
Inappropriate treatment	9.9	16.8[a]	27.4[b]
Crude mortality	29.2	34.4	40.9[c]

See Table 1 for expansion of the abbreviations.
[a]$P < .05$, compared with CAB.
[b]$P < .001$, compared with CAB.
[c]$P < .01$, compared with CAB.

in patients with HCABs or HABs (Table 4). The incidence of inappropriate treatment was different among the BSI subgroups (Table 4). In an unadjusted logistic regression analysis, the incidence of inappropriate treatment was significantly higher in patients with HABs (OR, 3.4; 95% CI, 2.1-5.3) and in patients with HCABs (OR, 1.8; 95% CI, 1.0-3.2) than in those with CABs. When the analysis was adjusted for covariates (sex, age, APACHE II, source, microorganisms, and origin of BSI), unknown origin (OR, 1.9; 95% CI, 1.2-3.0), isolation of PARPs (OR, 3.9; 95% CI, 2.3-6.6), and HABs (OR, 1.7; 95% CI, 1.0-2.9) were independent predictors of inappropriate treatment, and HCABs did not reach significance (OR, 1.39; 95% CI, 0.7-2.6). Among patients with HCAB, inappropriate treatment was more frequent in patients hospitalized in an acute-care hospital before the BSI (17.9%).

The overall crude mortality was 34.2%, and it was significantly higher in patients with HABs than in those with CABs (Table 4). Mortality was also higher in those with HCABs than CABs, but the difference was not significant. In a multivariate analysis, factors independently associated with mortality were severity (based on APACHE II score) at admission (OR, 1.1; 95% CI, 1.0-1.1) and HAB (OR, 1.5; 95% CI, 1.0-2.3). The mean length of stay of survivors was similar for patients with CABs (12.3 ± 21.4 days) and HCABs (12 ± 12.7 days), and neither group's stay was significantly shorter than the length of stay for patients with HABs (16 ± 19.7 days) ($P = 0.09$).

Discussion

Our results indicate that one in five BSIs diagnosed at ICU admission are HCABs. Compared with CABs, HCABs are associated with more comorbidities, more resistant pathogens, higher incidence of inappropriate antibiotic treatment, and a trend to greater mortality. Our findings support the new BSI classification scheme that distinguishes among CAB, HCAB, and HAB, and as suggested in previous studies,[13,21,22] our results support the idea that HCAB represents a transition between CAB and HAB, with a trend toward increasing disease severity from CAB to HAB.

No studies have specifically addressed the importance of HCABs in patients in the ICU; however, data from a recent study carried out in Spain[21] showed that the distribution of the three different types of BSIs was different in the ICU. Whereas HCABs accounted for 24% of BSIs among patients who were hospitalized, only 10% of BSIs diagnosed in patients in the ICU were classified as HCABs. To our knowledge, the present study is the first prospective study that compares the epidemiologic characteristics and outcomes of CABs, HCABs, and HABs in patients who are critically ill. Only 18% of BSIs were HCABs; thus, our results confirm that CABs and HABs acquired in other wards of the hospital account for most BSIs in patients at ICU admission. The high number of comorbidities and worse basal conditions suggest that the lower rates of admission of patients with HCABs to ICUs might be in part the result of therapeutic-effort limitation. In a previous study, the mean Barthel index in patients with HCABs was significantly lower (72 ± 31) than in those with CABs (89 ± 22) and HABs (82 ± 27) ($P < .01$).[14] Our results are also concordant with findings reported in a recent study carried out in patients with bacteremic *Streptococcus pneumoniae* pneumonia.[23] In that study, they reported a lower ICU admission rate and a trend toward lower rates of mechanical ventilation and vasopressor use in patients with HCABs than in patients with CABs, related in part to a significantly higher incidence in therapeutic-effort limitation in the group with HCABs.

Our results confirm that the pathogenic distribution for HCABs is distinct from that for CABs. The frequency of PARPs in patients with HCABs was higher than in patients with CABs and similar to the frequency in those with HABs, which agrees with two other recently published European multicenter study of BSIs, also carried out in Spain,[21,24] which also found a higher incidence of antibiotic-resistant organisms in patients with HCABs compared with patients with CABs. Among patients with HCABs included in our study, PARPs were most frequent in patients hospitalized in an acute-care hospital before the BSI and in those residing in a nursing home or long-term-care facility or receiving health care at home. These findings coincide with those of previous studies that reported the highest incidence of PARPs in patients with previous hospitalization or residing in long-term-care facilities.[25-27] Those studies also confirm that not all patients meeting the criteria for health-care-associated infections have a similar risk of being infected with resistant pathogens.

The incidence of *S aureus* in our study was lower than in previous studies carried out in the United States, where it was the dominant pathogen in all types of BSI.[11,13] This difference was also found in the previous multicenter study carried out in Spain.[14] Differences in patients and characteristics of the health-care system might explain this discrepancy. We found no differences in the global incidence of *S aureus* among the three types of BSIs, although the incidence of MRSA was more frequent in patients with HCABs and HABs than in those with CABs. However, compared with previous studies, our results show a lower incidence in BSIs caused by MRSA in all three groups.[11,13]

We found significant differences in the appropriateness of empirical antibiotic treatment of HCABs and CABs (16.8% vs 9.9%, respectively). These results underline the importance of classifying BSIs in outpatients into HCABs and CABs because each type of infection requires a different type of empirical antibiotic treatment to minimize the rate of inappropriate treatment. A previous study[28] that also analyzed the impact of HCABs on the efficacy of initial antibiotic therapy of patients with BSIs found that HCABs and HABs were independent predictors of ineffective initial antibiotic therapy. In our study, the incidences of inappropriate treatment of patients with CABs and HABs were similar to those reported in that previous study. However, we found a lower incidence of inappropriate antibiotic treatment of patients with HCABs, which was probably related to the lower incidence of MRSA infections in our study (18% vs 3.8%), and in the multivariate analysis, only HAB was independently associated with inappropriate antibiotic treatment.

Patients with HAB at ICU admission showed the highest mortality in our study, and this is related to the higher rate of inappropriate antibiotic treatment and higher incidence of PARPs in this group. The patients in the HCAB group also had more PARPs and a higher incidence of inappropriate treatment than those in the CAB, but although the mortality was higher in the HCAB group than in the CAB group, the difference was not significant, probably because of the relatively small number of patients with HCABs and the lower mortality for patients with HCABs compared with those with HABs. Friedman et al[11] also found significant differences in hospital mortality between patients with HABs and those with the other two types of BSIs, but they found no differences between those with HCABs and those with CABs. Two recent studies in patients who were not in ICUs have reported similar results between those with HCABs and those with CABs.[24,29] They found differences in some aspects, such as comorbidities and antibiotic-resistant pathogens, but not in the incidences of inappropriate treatment and mortality.

Some limitations of our study should be noted. This was an observational study, and the criteria for performing blood cultures were not standardized. This point may have influenced the final incidence of BSIs. In addition, our results may have been biased by local patterns of health care and antimicrobial resistance, which differ from those in other areas of the world. The prevalence of MRSA colonization in nursing homes and long-term-care facilities may be different from that of other countries, and in Spain the incidence of community-acquired MRSA is still sporadic.

Conclusions

Although HCABs are less common than CABs or HABs in patients who are critically ill, HCABs account for one in five BSIs diagnosed at ICU admission. Our results confirm that HCABs show important clinical differences from CABs and that the incidence of PARPs in HCABs is more similar to that of HABs. Therefore, they should be treated as such in the absence of culture data, although the differences in epidemiologic characteristics of drug-resistant pathogens in countries and regions should be taken into account.

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Dr Alvarez-Lerma: collected, analyzed, and interpreted the data; provided important critical revisions of the manuscript; and read and approved the final manuscript.
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Additional information: The e-Appendix can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/139/4/810/suppl/DC1.

References

1. Weinstein MP, Towns ML, Quartey SM, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clin Infect Dis*. 1997;24(4):584-602.
2. Gatell JM, Trilla A, Latorre X, et al. Nosocomial bacteremia in a large Spanish teaching hospital: analysis of factors influencing prognosis. *Rev Infect Dis*. 1988;10(1):203-210.
3. Vallés J, Rello J, Ochagavía A, Garnacho J, Alcalá MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. *Chest*. 2003;123(5):1615-1624.
4. Warren DK, Zack JE, Elward AM, Cox MJ, Fraser VJ. Nosocomial primary bloodstream infections in intensive care unit patients in a nonteaching community medical center: a 21-month prospective study. *Clin Infect Dis*. 2001;33(8):1329-1335.
5. Leibovici L, Konisberger H, Pitlik SD, Samra Z, Drucker M. Bacteremia and fungemia of unknown origin in adults. *Clin Infect Dis*. 1992;14(2):436-443.
6. Uzun O, Akalin HE, Hayran M, Unal S. Factors influencing prognosis in bacteremia due to gram-negative organisms: evaluation of 448 episodes in a Turkish university hospital. *Clin Infect Dis*. 1992;15(5):866-873.
7. Vallés J, León C, Alvarez-Lerma F; Spanish Collaborative Group for Infections in Intensive Care Units of Sociedad Espanola de Medicina Intensiva y Unidades Coronarias (SEMIUC). Nosocomial bacteremia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. *Clin Infect Dis*. 1997;24(3):387-395.
8. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA*. 1994;271(20):1598-1601.
9. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control*. 1988;16(3):128-140.
10. Horan TC, Emori TG. Definitions of key terms used in the NNIS System. *Am J Infect Control*. 1997;25(2):112-116.
11. Friedman ND, Kaye KS, Stout JE, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med*. 2002;137(10):791-797.
12. Siegman-Igra Y, Fourer B, Orni-Wasserlauf R, et al. Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. *Clin Infect Dis*. 2002;34(11):1431-1439.
13. Shorr AF, Tabak YP, Killian AD, Gupta V, Liu LZ, Kollef MH. Healthcare-associated bloodstream infection: a distinct entity? Insights from a large U.S. database. *Crit Care Med*. 2006;34(10):2588-2595.
14. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829.
15. Gross PA, Barrett TL, Dellinger EP, et al; Infectious Diseases Society of America. Quality standard for the treatment of bacteremia. *Clin Infect Dis*. 1994;18(3):428-430.
16. Bell DM. Promoting appropriate antimicrobial drug use: perspective from the Centers for Disease Control and Prevention. *Clin Infect Dis*. 2001;33(Suppl 3):S245-S250.
17. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; Seventeenth Informational Supplement. CLSI Document M100-S20*. Wayne, PA: Clinical and Laboratory Standards Institute; 2007.
18. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis*. 2008;197(8):1079-1081.
19. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(1):1-12.
20. van Belle G, Fisher, LD. *Biostatistics: A Methodology for the Health Sciences*. New York, NY: J.Wiley & Sons; 1993:496-595.
21. Vallés J, Calbo E, Anoro E, et al. Bloodstream infections in adults: importance of healthcare-associated infections. *J Infect*. 2008;56(1):27-34.
22. Venditti M, Falcone M, Corrao S, Licata G, Serra P; Study Group of the Italian Society of Internal Medicine. Outcomes of patients hospitalized with community-acquired, health care-associated, and hospital-acquired pneumonia. *Ann Intern Med*. 2009;150(1):19-26.
23. Rello J, Luján M, Gallego M, et al; PROCORNEU Study Group. Why mortality is increased in health-care-associated pneumonia: lessons from pneumococcal bacteremic pneumonia. *Chest*. 2010;137(5):1138-1144.
24. Rodríguez-Baño J, López-Prieto MD, Portillo MM, et al. Epidemiology and clinical features of community-acquired, healthcare associated and nosocomial bloodstream infections in tertiary and community hospitals. *Clin Microbiol Infec*. 2010;16(9):1408-1413.
25. Smith PW, Seip CW, Schaefer SC, Bell-Dixon C. Microbiologic survey of long-term care facilities. *Am J Infect Control*. 2000;28(1):8-13.
26. Warshawsky B, Hussain Z, Gregson DB, et al. Hospital- and community-based surveillance of methicillin-resistant *Staphylococcus aureus*: previous hospitalization is the major risk factor. *Infect Control Hosp Epidemiol*. 2000;21(11):724-727.
27. Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med*. 2008;168(20):2205-2210.
28. McDonald JR, Friedman ND, Stout JE, Sexton DJ, Kaye KS. Risk factors for ineffective therapy in patients with bloodstream infection. *Arch Intern Med*. 2005;165(3):308-313.
29. Marschall J, Fraser VJ, Doherty J, Warren DK. Between community and hospital: healthcare-associated gram-negative bacteremia among hospitalized patients. *Infect Control Hosp Epidemiol*. 2009;30(11):1050-1056.