Reemergence of Gram-negative Health Care–Associated Bloodstream Infections

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Background: Primary health care–associated bloodstream infections (PHA-BSIs) affect as many as 350,000 patients in the United States annually. Whereas gram-negative organisms were the leading cause before the 1970s, gram-positive organisms have been the predominant microbial isolates since then.

Methods: We identified all PHA-BSIs among adult inpatients in a 625-bed quaternary care hospital from January 1, 1996, through December 31, 2003, and evaluated trends in the microbial etiology, geographic distribution within the institution, and antimicrobial susceptibilities.

Results: A total of 3662 PHA-BSIs caused by 4349 bacterial and fungal isolates were identified. From 1999 to 2003, the proportion of PHA-BSIs due to gram-negative organisms increased from 15.9% to 24.1% (P < .001 for trend). This trend was not significantly different across various units of the hospital, and no specific gram-negative species contributed disproportionately to the increase. With few exceptions, there were no significant increases in antimicrobial resistance. The increase in gram-negative organisms was accompanied by a decline in the proportion of PHA-BSIs from coagulase-negative staphylococci (from 33.5% in 1999 to 29.9% in 2003, P = .007) and from Staphylococcus aureus (from 18.8% in 1999 to 11.8% in 2003, P = .004). The proportion of PHA-BSIs from Candida species almost doubled from 5.8% in 1999 to 11.3% in 2003 (P = .002).

Conclusions: To our knowledge, this is the first US study to report a reemergence of gram-negative organisms as a cause of PHA-BSIs. This finding does not seem to be related to changes in specific gram-negative organisms or to antimicrobial resistance. If this trend continues, it will have important implications for the management of bloodstream infections.

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The microbial etiology of PHA-BSIs has important implications for empirical antimicrobial therapy, antimicrobial resistance, patient outcomes, and other patient care and infection control practices. Infection control surveillance data at our institution suggested an increase in gram-negative PHA-BSIs in recent years. Therefore, we chose to characterize the microbial etiology of PHA-BSIs among adult inpatients at our institution from 1996 to 2003, focusing specifically on the latter 5 years.

METHODS

STUDY DESIGN

This study was conducted at the 625-bed quaternary care Hospital of the University of Pennsylvania. All bacterial and fungal isolates from adult inpatients from January 1, 1996, through December 31, 2003, that met the Centers for Disease Control and Prevention definition for nosocomial primary BSIs \(^{12}\) were included in the study. Secondary BSIs (bloodstream infections related to infections at another site) and community-acquired BSIs (infections present or incubating at the time of admission) were not included in the analysis. Repeat isolates (same organism isolated from the same patient) were included only once unless the infection was considered a new episode. For polymicrobial BSIs, each organism was considered a separate isolate in the analysis.

A central microbiology laboratory processes and cultures all clinical isolates from inpatients at the Hospital of the University of Pennsylvania. All organisms were classified broadly as gram-negative organisms, gram-positive organisms, or yeast. \(^{13}\) Organisms not fitting any of these categories (eg, mycobacteria) were grouped as other organisms. The continuous monitoring Bacter 9240 System (Becton Dickinson Diagnostic Instrument Systems, Sparks, Md) was instituted in 1995, and there has been no change in the protocol since that time. Blood cultures were typically drawn by physicians or nurses, although a program using a dedicated blood culture drawing team was instituted on July 1, 2003. Antimicrobial susceptibility testing for all bacterial isolates was performed using the MicroScan WalkAway (Dade Behring, Sacramento, Calif) or the Vitrek2 system (bioMerieux, Inc, Durham, NC). Susceptible and resistant results were determined using the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) break-point values. \(^{14,15}\)

All data were collected by infection control practitioners. Data collected on all BSIs included the following: (1) microbial etiology, (2) polymicrobial or monomicrobial status of the BSI episode, (3) location of the patient within the hospital at the onset of infection, (4) number of days from admission to the onset of infection, (5) central or peripheral catheter use at the onset of infection, (6) catheter types in place at the onset of infection, and (7) clinical or laboratory evidence of catheter infection. A PHA-BSI episode was considered catheter-related if a catheter tip grew more than 15 colony-forming units of the same organism that was isolated in blood culture or if there was evidence of local infection, such as purulent drainage at the catheter site. Bloodstream infections that occurred while a CVC was in place but that did not meet criteria for catheter-related infections were considered catheter-associated BSIs. Catheter-associated and catheter-related infections were combined as catheter-associated episodes in the final analysis.

STATISTICAL ANALYSIS

We first determined the annual incidence of PHA-BSIs, the annual percentage of polymicrobial BSIs, and the annual number of bacterial and fungal isolates. We then calculated the annual proportion of PHA-BSIs accounted for by each of the 10 most common bacterial and fungal organisms, as well as the annual proportion of PHA-BSIs accounted for by the following specific organisms or organism groups: S aureus, CNS, enterococci, gram-negative organisms, and Candida species. We evaluated trends in the annual proportion for these 3 organisms or groups using the Cochran-Armitage trend test \( (\chi^2 \text{ test for trend}) \). \(^{16}\)

Preliminary data from the infection control practitioner surveillance indicated that there was a potential change in the microbial etiology of PHA-BSIs starting in 1999; therefore, we focused our analyses on 1999 to 2003. Because our initial analysis showed an increase in the proportion of PHA-BSIs due to gram-negative organisms, a Spearman rank correlation coefficient was calculated to evaluate the relationship between the yearly proportion of PHA-BSIs due to gram-negative organisms and the annual hospitalwide use of specific antibiotics or antibiotic classes. The hospitalwide use of the following specific agents or classes was documented: vancomycin, cefepime, quinolones, aminoglycosides, clindamycin, and metronidazole. Antibiotic use was described as defined daily doses per 1000 patient-days.

To identify the effect of hospital location on temporal trends in the microbial etiology of BSIs, we used a logistic regression analysis with organism prevalence as the dependent variable and with calendar year and hospital location as the independent variable. Hospital floors and units were categorized as medical ICUs, surgical ICUs, oncology, and general medical or surgical floors.

We evaluated the annual proportions and trends for the 4 most common gram-negative organisms \( (\text{Klebsiella species, Escherichia coli, Pseudomonas species, and Enterobacter species}) \), aerobic gram-negative organisms, and all other gram-negative organisms combined. We used the Cochran-Armitage trend test for analysis. \(^{16}\)

To further elucidate our findings, we performed a subanalysis in which we repeated the aforementioned analyses but focused only on the subset of CVC-associated PHA-BSIs. In another subanalysis, we investigated the potential relationship between CVC type \( (\text{specifically triple-lumen catheters and peripherally inserted central catheters (PICCs)}) \) and trends in the microbial etiology of PHA-BSIs. In this subanalysis, we compared temporal trends in gram-negative PHA-BSIs among patients who had a triple-lumen catheter with those who did not have a triple-lumen catheter \( (\text{ie, no central access or any other type of central access}) \). Similarly, we compared temporal trends in gram-negative PHA-BSIs among patients who had a PICC with those who did not have a PICC.

We subsequently evaluated whether the increasing trend in the prevalence of gram-negative PHA-BSIs was related to an increase in antimicrobial resistance among gram-negative organisms. We evaluated hospitalwide susceptibilities of the 4 most commonly isolated gram-negative organisms \( (\text{Klebsiella pneumoniae, E coli, Pseudomonas aeruginosa, and Enterobacter cloacae}) \) from 1999 to 2003. These data were obtained from the annual antibiogram of the microbiology laboratory and included susceptibility results for all inpatient bloodstream isolates \( (\text{ie, including community-acquired and secondary BSI isolates}) \). We evaluated the following organism-antibiotic combinations in our analysis: \text{K pneumoniae}: amoxicillin-sulbactam, trimethoprim-sulfamethoxazole, levofloxacin, gentamicin sulfate, and cefazidime; \text{E coli}: trimethoprim-sulfamethoxazole, levofloxacin, gentamicin, and cefazidime; \text{P aeruginosa}: ceftazidime, cefepime, levofloxacin, aztreonam, imipenem, gentamicin, tobramycin, and amikacin; and \text{E cloacae}: aztreonam, cefazidime, cefepime, gentamicin, trimethoprim-sulfamethoxazole, and levofloxacin.

We then assessed trends in susceptibility for PHA-BSI isolates of the same 4 gram-negative organisms during the same period. In this analysis, only the specific organisms from the
list of PHA-BSI episodes were included. We evaluated the same organism-antibiotic combinations as in the hospitalwide analysis except for ceftazidime susceptibilities, which were not tested for most isolates, and for *P. aeruginosa* susceptibilities to amikacin, which were tested in only a few isolates. We used the Cochran-Armitage trend test for both analyses.16

A significance level of *P* = .05 (2-sided) was used for all statistical tests. Statistical analysis was performed using standard programs in STATA version 8.0 (StataCorp LP, College Station, Tex) and StatXact 4.0 (Cytel Software Corporation, Cambridge, Mass). This study was reviewed and approved by the Committee on Studies Involving Human Beings of the University of Pennsylvania School of Medicine.

**RESULTS**

From January 1, 1996, through December 31, 2003, a total of 3662 episodes of PHA-BSIs occurred in adults (2.42 BSIs per 1000 patient-days). The annual incidence of PHA-BSIs did not change significantly during the study period (range, 1.96-3.12 BSIs per 1000 patient-days). Approximately 16% of all episodes were polymicrobial, resulting in 4349 bacterial and fungal isolates. The annual proportion of PHA-BSIs that was polymicrobial did not change significantly during the study period (mean, 15.7% [range, 11.6%-18.8%]). There was a mean±SD of 21.5±2.4 days from admission to the onset of PHA-BSIs, and this did not vary significantly during the study period (annual mean range, 19-25 days [total range, 0-351 days]).

The annual proportion of PHA-BSIs accounted for by *S. aureus*, CNS, gram-negative organisms, and *Candida* species changed markedly during the study period (**Figure 1**). From 1999 to 2003, the proportion of PHA-BSIs due to gram-negative organisms increased from 15.9% in 1999 to 24.1% in 2003 (**P** < .001 for trend). During this same period, CNS decreased to 29.9% in 2003 from 33.5% in 1999 (**P** = .007). Similarly, *S. aureus* decreased to 11.8% in 2003 from 18.8% in 1999 (**P** = .004). The proportion of PHA-BSIs due to *Candida* species almost doubled from 5.8% in 1999 to 11.3% in 2003 (**P** = .002). In 1999, gram-negative organisms ranked fourth after CNS, enterococci, and *S. aureus*, but by 2003, gram-negative organisms surpassed enterococci and *S. aureus* to rank second only to CNS as a cause of PHA-BSIs. Furthermore, the proportion of PHA-BSIs in 2003 caused by *Candida* species (11.3%) approximately equals the proportion due to *S. aureus* (11.9%). There were no significant trends for any of the others among the 10 most commonly isolated organisms (data not shown).

Neither the rate of PHA-BSIs due to gram-negative organisms at any given time nor the trend over time differed significantly by hospital location (**Figure 2**). There was a significant correlation of the annual proportion of PHA-BSIs due to gram-negative organisms with the annual hospitalwide use of levofloxacin (**P** = < .001) but not with the use of any other antibiotic assessed.

The specific microbial etiology among gram-negative organisms did not change significantly during the study period, and no particular organism contributed disproportionately to the rise in PHA-BSIs from gram-negative organisms. For the study period, the following 4 species accounted for more than 70% of all PHA-BSIs due to gram-negative organisms: *Klebsiella* species (24.3%), *E. coli* (19.0%), *Pseudomonas* species (14.8% [>99% *P. aeruginosa*]), and *Enterobacter* species (14.8%). There were no significant trends over time in the proportion of PHA-BSIs caused by these organisms (**Figure 3**).

Between 85% and 92% of all PHA-BSIs each year were associated with the use of a CVC, and these proportions did not vary significantly across study years. When analyzing only CVC-associated infections, the results were not substantially different from those in the primary analysis (data not shown). Of 2898 PHA-BSIs from 1999 to 2003, a total of 2620 (90.4%) were associated with a CVC. Of these, 1119 (42.7%) involved a triple-lumen catheter, while 712 (27.2%) involved a PICC. Temporal trends in PHA-BSIs due to gram-negative organisms from 1999 to 2003 did not differ significantly when comparing patients who had and those who did not have a triple-lumen catheter (**P** = .94) or when comparing patients who had and those who did not have a PICC (**P** = .78).

Among hospitalwide inpatient bloodstream isolates of *K. pneumoniae*, *E. coli*, and *P. aeruginosa*, there was no increase in resistance for any of the organism-antibiotic com-

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**Figure 1.** Trends in the etiology of primary health care–associated bloodstream infections. *P* values indicate *P* for trend from 1999 to 2003.

**Figure 2.** Gram-negative primary health care–associated bloodstream infection trends by hospital location. *P* values indicate *P* for trend from 1999 to 2003 (overall *P* = .38). ICU indicates intensive care unit.

***1998 2001***

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We found a significant increase in the proportion of PHA-BSIs caused by gram-negative organisms from 1999 to 2003. By 2003, gram-negative organisms had surpassed S. aureus and ranked second only to CNS as a cause of PHA-BSIs. This increase in gram-negative organisms was observed across all hospital locations, and no particular species contributed disproportionately to the overall increase. With few exceptions, there was no increase in antimicrobial resistance among gram-negative organisms during the study period, and the increase in gram-negative organisms was seen in patients regardless of the use of specific types of CVCs. Finally, the annual incidence of PHA-BSIs did not change significantly during the study period.

Before the onset of these trends in 1999, the frequency of gram-negative organisms as a cause of PHA-BSIs at our institution was similar to that among the NNIS System ICUs during the 1990s. Comparing our data with those of the NNIS System needs to be done cautiously because the NNIS System during the 1990s was limited to ICUs, whereas our analysis is hospitalwide. Furthermore, the NNIS System summary does not report longitudinal trends in the proportion of infections caused by different groups of organisms (eg, gram negative). Although other large prevalence and surveillance studies have been performed in the last 10 years, all of them include secondary BSIs, and some include community-acquired BSIs. As such, E. coli and other gram-negative organisms account for the higher proportions of BSIs in these studies. To our knowledge, ours is the first US study to report an increase in the proportion of PHA-BSIs due to gram-negative organisms in adults. Most other studies have reported consistent increases in health care–associated BSIs due to gram-positive organisms, particularly CNS. The frequency of gram-negative organisms has been constant or declining in these investigations. A study in England and Wales from 1990 to 1998 reported significant annual increases for 7 organisms, 4 of which were gram-negative organisms (Acinetobacter species, Serratia species, Citrobacter species, and Enterobacter species). However, in addition to secondary BSIs, this study included community-acquired infections.

The observed shift in the microbial etiology of PHA-BSIs at our institution suggests that selection of empirical therapy will become increasing complex given the recent increases in antibiotic resistance among gram-negative pathogens. Our observed rise of gram-negative organisms as a cause of PHA-BSIs is particularly concerning given the lack of development of new antimicrobial agents.

In addition to its effect on antimicrobial therapy and resistance, the shift in PHA-BSI organisms has important implications for patient outcomes. Mortality from BSIs varies significantly for different organisms and generally is highest for Candida species and is lowest for CNS. Infections with gram-negative organisms are associated with worse outcomes. In addition, patients with gram-negative infections frequently receive inadequate empirical therapy because of antimicrobial resistance, which in turn is an important predictor of mortality.

We also evaluated the potential role of the use of triple-lumen catheters in the microbial etiology of PHA-BSIs. Our institution introduced triple-lumen catheters that were coated with silver sulfadiazine–chlorhexidine in 2000. Because these coated catheters are believed to more selectively inhibit growth of gram-positive organisms compared with gram-negative organisms and yeast, we hypothesized that this may have played a role in the changing microbial etiology of PHA-BSIs. The increase in the proportion of PHA-BSIs due to gram-negative organisms did not differ significantly among patients who had and those who did not have a triple-lumen catheter, and the substitution of the coated catheters in our institution is an unlikely explanation for the observed trends.

Other possible explanations for the observed microbial trends include differences in patient populations over time and changes in CVC use other than the use of coated catheters. Differences in patient populations could not directly be evaluated but are unlikely to account for the observed trends because the changes were seen hospitalwide among all patient groups. Other potential changes in the practice of CVC use, such as line location or catheter type (other than triple-lumen catheters), were not formally examined. However, we do not have any reason to believe that line location practices or types of catheters (other than coated catheters) changed significantly.
cantly during these 5 years. The observed trends were similar among patients who had and those who did not have a CVC. However, because most PHA-BSIs occurred in patients who had a CVC, differences among patients who had and those who did not have a CVC may have been difficult to detect given the few patients who did not have a CVC.

We found a significant correlation between the annual hospitalwide use of levofloxacin therapy and the proportion of PHA-BSIs due to gram-negative organisms. However, the ecologic nature of these analyses limits the degree to which causal inferences can be made. In addition, we did not find significant increases in resistance as a possible explanation for increases in PHA-BSIs due to gram-negative organisms.

Our study has several potential limitations. It is possible that a small percentage of BSI episodes each year were misclassified as to health care–associated vs community acquired, primary vs secondary, or infection vs colonization or contaminant. However, it is unlikely that the number of misclassifications each year varied significantly over time because data were collected by the same infection control practitioner staff according to the same protocols and definitions. Therefore, any potential misclassifications should not have significantly affected the results of the study. Finally, the study was designed to specifically assess trends within our institution. Given differences in patient characteristics, antimicrobial use patterns, and other patient care and hospital factors (such as the use of CVCs, the frequency of invasive procedures, and the type of surgical procedures), our results may not be generalizable to other institutions.

In summary, our study reports a reemergence of gram-negative organisms as a cause of PHA-BSIs among adults. Although the explanation for this finding remains unclear, it does not seem to be related to changes in specific gram-negative organisms, to antimicrobial resistance, or to the introduction of pathogens coated with silver sulfadiazine–chlorhexidine. This trend has important implications for the management of BSIs. Confirmation of these findings at other institutions would be valuable.

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