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Central Line–Associated Bloodstream Infections in Adult Hematology Patients with Febrile Neutropenia: An Evaluation of Surveillance Definitions Using Differential Time to Blood Culture Positivity

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Abstract

We used differential time to positivity between central and peripheral blood cultures to evaluate the positive predictive value (PPV) of the National Healthcare Safety Network central line–associated bloodstream infection (CLABSI) surveillance definition among hematology patients with febrile neutropenia. The PPV was 27.7%, which suggests that, when the definition is applied to this population, CLABSI rates will be substantially overestimated.

Accurate surveillance definitions are necessary to evaluate the impact of interventions to prevent central line–associated bloodstream infections (CLABSI). The National Healthcare Safety Network (NHSN) definition for CLABSI has been applied extensively in intensive care unit (ICU) settings, but few studies have examined its performance among patients with febrile neutropenia.^{1–3} In contrast to the NHSN, the Australian Council of Healthcare Standards (ACHS) describes a second surveillance category designated as “neutropenia related.”⁴ The ACHS state that primary bacteremia among neutropenic patients should be considered to be neutropenia related unless there is strong evidence for central line–associated infection, such as heavy growth of an identical organism from a central line tip.⁴

Differential time to positivity (DTP) is a technique used to diagnose central line infections without line removal in patients with febrile neutropenia.^{5–7} According to this technique, central line infection is likely if blood collected via a central line registers growth with an incubation time more than 2 hours less than that of an equal volume collected at the same time from a peripheral vein.^{7–9} We used DTP as a gold standard to evaluate the performance

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of the NHSN and ACHS CLABSI surveillance definitions among adult hematology patients with febrile neutropenia at our hospital.

Methods

Setting and participants

Auckland City Hospital (ACH) is a tertiary referral hospital in New Zealand with a general hematology and bone marrow transplant unit. All episodes of primary bacteremia among adult hematology patients at ACH are prospectively categorized as either CLABSI or neutropenia related using ACHS surveillance definitions (without consideration of DTP). We used the resulting records to identify all episodes of primary bacteremia among adult hematology patients between January 1, 2008, and December 31, 2010. Episodes were excluded if (1) paired central and peripheral blood cultures were not collected, (2) the same organism was not recovered from central and peripheral blood cultures or times to positivity were not available, (3) the patient did not have febrile neutropenia, or (4) the patient did not have a central line for 48 hours or more before blood culture collection.

Definitions

Primary bacteremia was defined as a positive blood culture result without a clear clinical focus of infection other than the central line. Febrile neutropenia was defined as a temperature of 38°C or higher and a neutrophil count of less than 1.0×10^9 neutrophils/L on the day of blood culture sample collection. An episode was defined as 1 or more positive blood culture sets within a 14-day period. Species were broadly predefined as skin organisms (including *Staphylococcus aureus*) or gastrointestinal organisms (Table 1). Catheter-related bloodstream infection (CRBSI) refers to categorizations determined by DTP, whereas CLABSI refers to categorizations based on surveillance definitions.

Data collection and determination of differential time to positivity

All blood cultures were incubated using the BACTEC 9240 platform, which records the time of incubation in the instrument before registering positive for growth (defined as time to positivity). Copies of these records in our laboratory are routinely retained and were consulted retrospectively to determine the DTP for each episode. When cultures of blood specimens from more than 1 lumen and/or more than 1 bottle were positive, the DTP was calculated by combining the shortest time to positivity for bottles drawn from the central line with the longest time to positivity for bottles collected from the peripheral vein to avoid under-classification of CRBSI. Paired cultures used to calculate the DTP had to be collected within a 2-hour period. When DTP was applied as a gold standard, episodes with a DTP of less than 2 hours were recategorized as neutropenia related, and those with a DTP of 2 hours or more were recategorized as CRBSI. Clinical records were used to record a variety of putative risk factors for CRBSI (Table 1).

Results

During the 3-year study period, 188 adult hematology patients had a total of 295 episodes of primary bacteremia. Of these, 126 (42.7%) of 295 episodes had paired central and peripheral cultures that grew identical bacterial species. Thirteen episodes were excluded from additional analysis because of incomplete documentation of DTP. Of the remaining 113 episodes, 90 occurred in 73 patients with febrile neutropenia. Applying DTP as a gold standard to each episode, we determined that 25 (27.7%) of 90 episodes were CRBSI and that the remaining 65 (72.2%) of 90 episodes were neutropenia related.

Although the NHSN definition classified all episodes of primary bacteremia as CLABSI, the ACHS definition categorized 28 (31.1%) of 90 as CLABSI and 62 (68.9%) of 90 as neutropenia related. Nonetheless, applying the ACHS definition without considering DTP resulted in frequent misclassification of individual episodes and gave positive predictive values (PPV) and negative predictive values (NPV) of 28.6% and 72.6%, respectively. The NHSN definition does not permit non-CLABSI episodes of primary bacteremia and thus, by definition, had no calculable NPV and a PPV of 27.7%. The distribution of DTP values obtained is shown in Figure 1. Episodes of CRBSI were less likely to occur in patients with a diagnosis of acute myeloid leukemia (AML; $P = .016$) and were more likely to be caused by skin organisms ($P = .028$). Conversely, neutropenia-related episodes were more likely to be caused by gastrointestinal organisms ($P = .0003$).

Discussion

Our data suggest that a large proportion of primary bacteremia episodes among hematology patients with febrile neutropenia are unlikely to be due to central line infection. This conclusion is supported by the findings of Seifert et al,¹⁰ who used DTP and paired quantitative cultures to determine that, among a similar cohort of febrile neutropenic patients, only 37% of bacteremia episodes were attributable to the central line. Moreover, the frequency distribution of DTP values that we observed (Figure 1) is consistent with the notion that the episodes that were not related to a central line had a roughly symmetrical distribution of DTP values around 0 hours and that true central line infections skewed the distribution to the right. The source of neutropenia-related episodes is unknown, although possibilities include exit site line infections and gastrointestinal translocation. The possibility that gastrointestinal translocation is an important contributor is supported by our observation of an association between neutropenia-related episodes and gastrointestinal organisms. Notably, neutropenia-related episodes were also more common among patients with AML, possibly because of high rates of mucositis in this patient group. Although infections confined to the outer surface of the line cannot be definitively excluded, it is unlikely that such infections were common, because only 1 (1.5%) of 65 episodes had clinical evidence of exit site infection (data not shown).

When the ACHS definition was applied, the percentage of CLABSI episodes was similar, irrespective of whether DTP was taken into account. Nonetheless, the PPV of the ACHS definition was poor (28.6%), which indicated that, when DTP was not considered, individual episodes were frequently misclassified.

Our study has limitations. First, we were unable to ensure that equal volumes were inoculated into peripheral and central blood culture bottles (which is a variable that could affect DTP). Second, paired blood samples were not always incubated simultaneously. Finally, paired blood samples were not always collected. It is therefore possible that the 90 episodes of febrile neutropenia that we analyzed were not a representative sample.

Nonetheless, our data are remarkably consistent with earlier findings¹⁰ and suggest that the current NHSN surveillance definition has poor PPV when applied to patients with febrile neutropenia. Introducing a surveillance subcategory of “neutropenia related” and using DTP to distinguish such episodes from CLABSI whenever possible seems a reasonable and feasible strategy to improve the current surveillance definition in this patient group.

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Figure 1.

Distribution of differential time to positivity (DTP) values for the 90 episodes of primary bacteremia in adult hematology patients with febrile neutropenia. Hatched bars represent episodes classified as central line-associated bloodstream infection (CLABSI) using the conventional 2-hour DTP threshold, and solid bars represent episodes classified as neutropenia related.

Table 1

Comparison of Characteristics between Patients Classified as Having Catheter-Related Bloodstream Infection (CRBSI) and Patients Classified as Having Febrile Neutropenia-Related Bacteremia Using Differential Time to Positivity

Characteristic	CRBSI	Neutropenia-related bacteremia	P ^a
Mean age, years	49.1	48.0	.49
Female sex	11/25 (44)	27/65 (41.5)	>.99
Tunneled line	23/25 (92)	52/65 (80)	.22
Peripherally inserted central cannula	2/25 (8)	12/65 (18.5)	.33
Acute myeloid leukemia	9/25 (36)	43/65 (66.2)	.016
Acute lymphocytic leukemia	3/25 (12)	8/65 (12.3)	>.99
Receipt of transplant	12/25 (48)	17/65 (26.2)	.076
Mean catheter-days before bacteremia	44.7	36.5	.37
Skin organism ^b	10/25 (40)	11/65 (16.9)	.028
Gastrointestinal organism ^c	7/25 (28)	46/65 (70.8)	.0003
Mixed skin and gastrointestinal organisms ^d	8/25 (32)	4/65 (6.2)	.003
Mean duration of neutropenia before bacteremia, days	10.41	10.33	.98

NOTE. Data are proportion (%) of patients, unless otherwise indicated.

^a χ^2 or Fisher's exact test were used to compare categorical variables, and Student *t* test was used for continuous variables.

^b Skin organisms included coagulase-negative staphylococci (13/21; 61.9%), *Corynebacterium* species (1/21; 4.8%), *Staphylococcus aureus* (5/21; 23.8%), *Acinetobacter* species and *S. aureus* (1/21; 4.8%), and *S. aureus* and coagulase-negative staphylococci (1/21; 4.8%).

^c Gastrointestinal organisms included Enterobacteriaceae (37/53; 69.8%), *Viridans streptococci* (10/53; 18.9%), *Streptococcus agalactiae* (1/53; 1.9%), mixed Enterobacteriaceae (1/53; 1.9%), Enterobacteriaceae and *Pseudomonas aeruginosa* (1/53; 1.9%), *Enterococcus* species (1/53; 1.9%), Enterobacteriaceae and *Viridans streptococci* (1/53; 1.9%), and *P. aeruginosa* (1/53; 1.9%).

^d Mixed skin and gastrointestinal organisms included Enterobacteriaceae and coagulase-negative staphylococci (5/12; 41.7%); *S. aureus* and Enterobacteriaceae (2/12; 16.7%); *S. aureus*, *Streptococcus pneumoniae*, and group C *Streptococcus* (1/12; 8.3%); coagulase-negative staphylococci and enterococci (1/12; 8.3%); nonfermenting gram-negative bacilli and coagulase-negative staphylococci (1/12; 8.3%); *Corynebacterium* species, coagulase-negative staphylococci, and *Pseudomonas stutzeri* (1/12; 8.3%); and *Acinetobacter* species and Enterobacteriaceae (1/12; 8.3%).