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MAJOR ARTICLE

Bloodstream Infections in Hematologic Malignancy Patients With Fever and Neutropenia: Are Empirical Antibiotic Therapies in the United States Still Effective?

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Background. Rising antimicrobial resistance rates may impact the efficacy of empirical antibiotic treatment for febrile neutropenia in high-risk cancer patients. Lacking contemporary data about the epidemiology, antibiotic resistance patterns, and clinical outcomes from bloodstream infections (BSIs) in US cancer patients, it is unclear if current guidelines remain relevant.

Methods. In a cross-sectional study, 14 US cancer centers prospectively identified BSIs in high-risk febrile neutropenic (FN) patients, including those receiving chemotherapy for hematologic malignancies or hematopoietic stem cell transplantation.

Results. Among 389 organisms causing BSI in 343 patients, there was an equal distribution of gram-negative (GN) and gram-positive (GP) bacteria, with variability across centers. Cefepime and piperacillin-tazobactam were the most commonly prescribed empirical antibiotics for FN, at 62% and 23%, respectively; a GP-directed agent was empirically included in nearly half of all FN episodes within the first 24 hours. Susceptibility to fluoroquinolones, cefepime, piperacillin-tazobactam, and carbapenems was 49%, 84%, 88%, and 96%, respectively, among GN isolates. Critical illness (CrI), defined as a new requirement for mechanical ventilation, vasopressor, or death within 30 days, occurred in 15% and did not correlate with fluoroquinolone prophylaxis, organism type, initial antibiotics, or adequacy of coverage. Only severity of illness at presentation, signified by a Pitt bacteremia score $\geq$2, predicted for critical illness within 30 days. Mortality was 4% by day 7 and 10% overall.

Conclusions. In accordance with US guidelines, cefepime or piperacillin-tazobactam remain effective agents or empirical treatment for high-risk cancer patients with FN who are stable at presentation, maintaining high GN pathogen susceptibility and yielding excellent outcomes.

Keywords. bacteremia in cancer patients; bacteremia following chemotherapy; bloodstream infections; empirical antibiotics; febrile neutropenia.

Bacterial bloodstream infections (BSIs) complicate the course of 10%–30% of febrile neutropenic (FN) cancer patients, significantly contributing to morbidity and mortality [1–3]. Prompt administration of empirical antibiotics for FN has been a standard of care for nearly 50 years, generally yielding >90% survival from episodes of FN, compared with significantly worse outcomes in the pre-empirical antibiotic era [4–9]. Monotherapy with mainstay antibiotics including cefepime, piperacillin-tazobactam, or an antipseudomonal carbapenem (imipenem or meropenem) is currently recommended by international guidelines as an initial antibiotic regimen (IAR) for stable patients presenting with FN [1, 10, 11]. However, these antibiotic recommendations are based on epidemiologic data generated nearly 20 years ago, before the emergence of widespread gram-negative antibiotic resistance [12–17]. We continue to rely on FN management guidelines developed in the last century, uncertain if this guidance remains relevant in the absence of contemporaneous BSI data from US cancer patients [1, 11]. Accordingly, we undertook a nationwide survey of BSIs among high-risk cancer patients with fever and neutropenia. The primary objective was to describe the

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current spectrum and susceptibility patterns of bloodstream bacterial isolates derived from a geographically diverse group of US adult high-risk patients with FN. The secondary objectives were to describe initial empirical antibiotic regimens for FN and clinical outcomes within 30 days and to assess whether susceptibility of pathogens to initial empirical antibiotics was related to clinical outcomes.

METHODS

Fourteen high-volume US cancer centers participated in this cross-sectional observational study, each selected for geographic diversity and volume of patients treated for hematologic malignancies and hematopoietic stem cell transplants (HSCTs) (Supplementary Table 1). Centers identified consecutive patients age 19 years and older who received antimicrobial therapy for a BSI associated with a first episode of FN within 14 days after undergoing HSCT or receiving chemotherapy for hematologic malignancy and who were treated at their center at presentation of FN. Clinical information from electronic medical records and microbiologic data from site microbiology laboratories were collected from day 1, the date of the first positive blood culture (index blood culture), to day 30. Approximately 25 bacterial isolates were collected per site beginning in December 2016 through May 2019. Study data were collected and managed using REDCap electronic data capture tools hosted at UNMC [18].

Patient Consent

Institutional review boards (IRBs) at University of Nebraska Medical Center (UNMC), the coordinating site, and at all participating sites approved the protocol and waived consent for enrollment.

Definitions and Inclusion Criteria

Fever and neutropenia were defined as a temperature >38.0° C and an absolute neutrophil count (ANC) of <500 cells/μL (or expected to fall below that level within 48 hours). Afebrile neutropenic patients were included if the treating physician judged that the patient had signs and/or symptoms consistent with bacteremia. Index blood cultures were drawn soon after the onset of FN (day 1) per standard of care and institutional protocols; empirical antibiotics were started within 12 hours thereafter, recognizing that ideally antibiotics should be started within 1 hour of presentation of FN. Receipt of prophylactic antibiotics before FN was acceptable, but patients receiving systemic antibiotics for other reasons within 3 days before day 1 were excluded. Patients whose index blood cultures became positive for pathogenic bacteria were enrolled in the study. Those with 1 of 2 blood culture sets positive for possible skin contaminants including coagulase negative staphylococci (CoNS), *Cutibacterium* and *Bacillus* species, diphtheroids, or micrococci were excluded. Polymicrobial and anaerobic BSIs were included for epidemiologic purposes, but outcome analyses were limited to aerobic single-organism bacteremias.

The initial antibiotic regimen was defined as the antibiotic regimen administered immediately after index blood cultures were drawn (day 1). Modified IAR refers to the antibiotic regimen at 24 hours after presentation including all changes to the IAR (additions, switches, or discontinuations). The modified IAR definition was used to assess whether antibiotic changes in the first 24 hours would better approximate "early" coverage compared with IAR immediately prescribed after index blood cultures. Adequacy of antibiotic coverage was based on a "match" or "mismatch" between site laboratory susceptibility reports available to treating physicians and initial IAR or modified IAR at 24 hours. If susceptibility testing was unavailable for a specific antibiotic agent used, 2 investigators (A.Z. and A.F.) independently reviewed the reported susceptibility panels and interpreted whether the isolate was susceptible or nonsusceptible to the IAR based on a predetermined set of rules predicting probable antibiotic coverage of various pathogens (Supplementary Table 2). For example, cefepime susceptibility was inferred from susceptibility to first-, second-, and third-generation cephalosporins. If susceptibility data could not be interpreted for initial regimens, the isolate was excluded from matching analysis.

The primary clinical outcome measure was the development of a "critical illness" (CrI), defined as any 1 of 3 complications: a new requirement for ventilatory or vasopressor support or death from any cause occurring after day 1 and until day 30. Factors potentially influencing the composite CrI end point were analyzed, including organism type, IAR antibiotics, adequacy of antibiotic coverage, fluoroquinolone prophylaxis use, and Pitt bacteremia score at presentation.

Statistics

Patient characteristics and clinical measurements were summarized using counts and percentages for categorical data and median and range for continuous data. Characteristics of patients who did and did not develop CrI were compared using the chi-square test for categorical variables and the *t* test (or Wilcoxon rank-sum test) for continuous variables. CrI-free survival was defined as the time from day 1 to the first occurrence of any 1 of the 3 adverse events that occurred before day 30 and was calculated using the Kaplan-Meier method; patients who experienced no critical event in that timeframe were censored at day 30. Cox regression, using similar definitions of CrI survival, was performed to assess the effect of clinical characteristics on CrI-free survival in univariate and multivariable analysis, and results were presented as hazard ratios. All analyses were done using SAS, version 9.4, and *P* values <.05 were considered statistically significant.

RESULTS

Patient Characteristics

Between December 2016 and May 2019, 14 US cancer centers identified 343 consecutive patients with an initial episode of FN associated with bacterial bloodstream infection, including 389 separate isolates (Table 1). Most patients (68%) underwent nontransplant chemotherapy regimens, primarily for acute myeloid leukemia (AML), and 32% received an allogeneic or autologous HSCT (Table 1). Fluoroquinolone prophylaxis was utilized in 57% before FN, while 5% received other agents. Thirty-six patients (10%) had a maximum temperature of ≤38.0°C on the day of presentation. Likewise, on day 1 these high-risk FN patients had a median Pitt score (range) of 1 (0–13), indicating general clinical stability; however, 10% required vasopressors, and 3% needed ventilatory support. In an effort to identify a sensitive discriminatory value to predict for CrI, the Pitt bacteremia score was retrospectively dichotomized into a high- and low-risk (≥2, <2) categorical variable [19, 20].

Initial Antibiotic Regimen and Modifications

Cefepime was the mainstay IAR agent utilized in two-thirds of patients with FN, while 23% received piperacillin-tazobactam and 8% received meropenem (Supplementary Table 3). Additional empirical antibiotics against potential resistant gram-positive organisms were simultaneously given in almost half of episodes, including vancomycin (41%), linezolid (6%), and daptomycin (1%). Aminoglycosides were initially added to a mainstay IAR agent in 6% of episodes. Modifications to initial empirical antibiotics were made after the IAR and within the first 24 hours in 114 of 343 episodes (33%) (Supplementary Table 4). Addition of vancomycin was most common, accounting for 48% of modifications. Switching to another beta-lactam agent represented 39% of modifications. Aminoglycosides were added in 8%, and cessation of vancomycin or aminoglycosides occurred in 11% and 7%, respectively.

Bloodstream Isolates

There were 389 bacterial isolates causing BSI among 343 patients enrolled (Table 2). The majority of BSIs were caused by a single aerobic bacterial isolate (n = 290) with similar distribution among gram-negative (GN) and gram-positive (GP) isolates. Strict anaerobes accounted for only 4% of single-organism bacteremias. Polymicrobial infections represented 12% of episodes. *E. coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa* were the predominant GNs identified, representing 22%, 9%, and 7%, respectively, of all isolates. Viridans group streptococci (VGS) represented 24%, *Staphylococcus aureus* 8%, and enterococci 4% of all BSIs. The distribution of organisms varied significantly according to the individual centers (Supplementary Figure 1).

Table 1. Baseline Characteristics at Day 1 (n = 343 Patient Episodes)

Characteristics	No. (%)
Age, median (range), y	57 (20–89)
Female	145 (42)
Primary diagnosis	
AML	171 (50)
Lymphoma	54 (16)
MM	47 (14)
ALL	38 (11)
MDS	9 (3)
Other	24 (7)
Therapy causing neutropenia	
Allogeneic HSCT	46 (13)
Autologous HSCT	65 (19)
Chemotherapy without HSCT	232 (68)
Fluoroquinolone prophylaxis	194 (57)
Absolute neutrophil count, median (range), neutrophils/μL	0 (0–500)
MASCC score, median (range)	19 (5–26)
Pitt bacteremia score	
<2	293 (85)
≥2	50 (15)
Vasopressor support	33 (9.6)
Mechanical ventilation	10 (3.0)
CVC or PICC	314 (92)

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CVC, central venous catheter; HSCT, hematopoietic stem cell transplant; MASCC, Multinational Association Supportive Care of Cancer risk index; MDS, myelodysplastic syndrome; MM, multiple myeloma; PICC, peripherally inserted central catheter.

Table 2. Bacterial Isolates Causing Bacteremia

Bacteria Genus/Species	No. of Isolates (%)
Total (n = 389)	
Gram-negative organisms	183 (47)
E. coli	86 (22)
Klebsiella sp.	34 (9)
Pseudomonas aeruginosa	28 (7)
Enterobacter cloacae	20 (5)
Stenotrophomonas	3 (1)
Other Enterobacterales[a]	5 (1)
Other gram-negative[b]	7 (2)
Gram-positive organisms	189 (49)
Viridans group streptococci	92 (24)
Staphylococcus aureus	33 (8)
Oxacillin-resistant	18 (5)
Oxacillin-susceptible	15 (4)
Coagulase-negative staphylococci	27 (7)
Enterococcus sp.	18 (4)
Vancomycin-resistant	10 (3)
Vancomycin-susceptible	8 (2)
Rothia sp.	9 (2)
Streptococcus pneumoniae	3 (0.5)
Other gram-positive	8 (2)
Anaerobes	17 (4)

[a]Two *Citrobacter freundii*, 2 *Serratia marcescens*, 1 *Pantoea agglomerans*.

[b]Three *Achromobacter* sp., 1 *Acetobacter*, 1 *Capnocytophaga*, 1 *Moraxella catarrhalis*, 1 *Burkholderia cepacia*.

Antibiotic Susceptibilities

Rates of isolate susceptibility to mainstay antibiotics (cefepime, piperacillin-tazobactam, and antipseudomonal carbapenems) ranged from 84% to 96%, based on site lab data and, for some isolates, by investigator interpretation according to predetermined rules (Supplementary Table 2). Cefepime had activity against 84% of GNs, including 85% of Enterobacterales and 93% of *Pseudomonas aeruginosa* (Table 3). Piperacillin-tazobactam was active against 88% of GNs, including 87% of Enterobacterales and 92% of *Pseudomonas aeruginosa*. Data for carbapenems were reported in only 96/183 (52%) GN isolates, with 96% GNs susceptible, including 98% (96/98) of Enterobacterales and 86% (19/22) of *Pseudomonas aeruginosa*. Fluoroquinolones had activity against only 49% of GNs, including 47% of Enterobacterales and 70% of *Pseudomonas aeruginosa*.

Among VGS isolates tested by site labs, 30/82 (37%) were resistant to penicillin, 3/74 (4%) were resistant to ceftriaxone, and levofloxacin resistance was demonstrated in 31/43 (72%). We interpreted ceftriaxone susceptibility to be a proxy for cefepime susceptibility as both have susceptible breakpoints of $\leq$1 μg/mL [21]. More than half of all *Staphylococcus aureus* isolates were resistant to oxacillin (ie, MRSA), and more than half of *Enterocccus* species were resistant to vancomycin (ie, VRE) (Table 2).

Match and Mismatch

A total of 94% GN (137/146) and 89% GP (128/144) aerobic isolate susceptibilities were evaluated for match or mismatch with IAR antibiotics based on availability of site data. Adequacy of coverage was 86% for IAR and 93% for modified IAR by 24 hours among single-organism aerobic GN BSIs (Table 4). Among aerobic single-organism GP BSIs, 80% were adequately covered by IAR, and 86% with modifications by 24 hours. Polymicrobial bacteremias were not evaluated.

Outcomes

By day 30, neutropenia resolved in 78% of patients, with a median neutropenia duration (range) of 10 (1–30) days) (Supplementary Table 5). A recurrent BSI caused by a new organism occurred in 10% of patients (n = 36) by day 30, including 15 GN, 21 GP, and 3 *Candida* spp. (Supplementary Table 6). Overall, $\geq$1 CrI event occurred in 50 patients (14.6%) by day 30 (composite end point), including a new need for mechanical ventilation (4.4%) or for vasopressor support (4.7%). Of the 290 patients with a single aerobic BSI, 41 patients met the composite end point. Mortality by 7 days after FN presentation was 3.6% (11/302) among single-organism bacteremias and 9.3% (28/302) by day 30. Among all 343 patients (including polymicrobial BSIs), 30-day mortality was 9.6% (33/343).

Risk Factors for Critical Illness

On univariate Cox regression analysis, the use of meropenem as IAR and a Pitt bacteremia score $\geq$2 were associated with higher rates of CrI by day 30 in single–aerobic organism BSI (Table 5). Only Pitt score $\geq$2 retained statistical significance on multivariate analysis (hazard ratio [HR], 2.82; $P = 0.003$). Antibiotic prophylaxis was not protective against development of CrI compared with no prophylaxis (HR, 1.68; $P = 0.1$). GN bacteremia trended toward significance on univariate analysis ($P = 0.06$) but was not associated with CrI on multivariate analysis. Mismatch of bloodstream isolate to IAR or modified IAR was not associated with increased CrI risk by day 30. Furthermore, no deaths occurred by day 7 in those with inadequate IAR (ie, mismatch).

DISCUSSION

The BISHOP study represents the first detailed overview of the bloodstream infection epidemiology among febrile neutropenic patients undergoing treatment for hematologic malignancies or stem cell transplantation at cancer centers across the United States, thus providing essential contemporary data to inform management for this vulnerable population. It updates and extends a prior national study published in 2003 that examined a mixed population of low- and high-risk cancer patients, including some non-neutropenic individuals, with bloodstream infections [13]. Enrolling only hematologic malignancy patients whose FN followed intensive chemotherapy or HSCT focused attention on those at greatest risk for morbidity and mortality associated with BSIs. Importantly, the BISHOP data demonstrated an equal distribution of GN and GP BSIs in neutropenic patients, representing an epidemiologic shift from a predominance of GP organisms noted by studies earlier this century [6,13]. Similar trends have been reported by European and Australian centers since the early 2000s [9, 17, 22, 23]. However, intercenter variability in both isolate distribution and resistance patterns of bacterial isolates across the United States was striking, underscoring the crucial importance of local epidemiology in managing FN patients.

Cefepime was the mainstay antibiotic employed in a two-thirds majority of FN episodes. Despite concerns that widespread extended-spectrum beta-lactamases (ESBLs) among GN organisms may be eroding cephalosporin efficacy internationally, the current finding that cefepime remains broadly employed suggests that it remains a reliable tool in FN management in the United States [23]. This practice contrasts with a recent survey of European and Asian transplant centers finding cefepime IAR use in only 14.3%, with piperacillin-tazobactam monotherapy preferred in two-thirds of centers [22]. Several meta-analyses have linked cefepime to increased mortality outcomes, although others have strongly refuted that finding [24–26]. Cefepime was not associated with

Table 3. Gram-Negative Isolates Susceptibilities

Organism Susceptible/Tested, No. (%)	Cefepime	Piperacillin-Tazobactam	Carbapenem	Fluoroquinolone	Aminoglycoside
All gram-negatives[a]	150/178 (84)	145/164 (88)	119/124 (96)	85/173 (49)	147/175 (84)
Enterobacterales	123/145 (85)	118/135 (87)	96/98 (98)	65/139 (47)	120/143 (84)
Pseudomonas aeruginosa	26/28 (93)	23/25 (92)	19/22 (86)	19/27 (70)	27/28 (96)

Abbreviation: GNR, Gram-negative rods.

[a]One hundred eighty-three GNR, including 145 Enterobacterales and 28 *Pseudomonas aeruginosa*.

increased CrI in the BISHOP survey, but the study was underpowered to detect a small mortality increment.

US clinicians employed vancomycin or another GP-directed agent in over half of all FN episodes as an adjunct to mainstay antibiotics, suggesting a reluctance to rely solely on beta-lactam coverage. Site laboratory susceptibility data indicated that GP isolates, including most VGS (96%) and nearly half of *Staphylococcus aureus* isolates, would have been adequately covered by cefepime, calling into question the need for additional GP coverage rather than cefepime monotherapy. Furthermore, resistant GP infections were rare, with only 5% MRSA, 4% enterococci, and 7% CoNS demonstrated among overall isolates. VGS remains a concern at some centers, however, as penicillin resistance is high at 37% overall. It remains unclear whether piperacillin-tazobactam or carbapenems will cover those organisms; we are pursuing this question in our laboratory.

Mainstay antibiotics adequately covered GN monomicrobial bacteremias at high rates, 86% initially and with improvement to 93% at 24 hours with modifications, likely contributing to the excellent day 7 survival (96.8%) among these patients. Multiple reports have linked initial inadequate antibiotic therapy, unmatched to pathogen susceptibility, with increased mortality in a variety of bacteremic populations [9, 14, 15, 23, 27]. No such association was noted herein between inadequate IAR coverage and CrI by 30 days, but the low incidence rates of CrI and mismatching preclude strong conclusions. Notably, CrI events were also unrelated to organism type or fluoroquinolone prophylaxis. A Pitt score ≥2 at presentation was the only predictive factor for subsequent CrI on multivariate analysis, indicating that even mild clinical instability at presentation may indicate an unfavorable outcome.

The limitations of this study included the site laboratory variability in antibiotic chosen for susceptibility testing and in minimal inhibitory concentration (MIC) reporting for isolates. Additionally, absent a control group of nonbacteremic patients, BSI incidence and comparative outcomes were not assessed. Finally, as participation was limited to high-volume cancer centers, the applicability of results to smaller centers and individual practices is uncertain.

In summary, the BISHOP survey provides a snapshot of current bloodstream pathogens, their antimicrobial susceptibilities, and empirical antimicrobial therapies in high-risk patients with FN in the United States, with the significant finding that standard antibiotic regimens are generally adequate and yield good outcomes. However, there is tremendous

Table 4. Adequacy of IAR and Modifications by Day 1 Among Single Bacteremia Patients

Bacteremia Type	Single Gram-Negative, No. (%) (n = 146; 137 evaluable)	Single Gram-Positive, No. (%) (n = 144; 128 evaluable)
Initial regimen match	118 (86)	102 (80)
Initial regimen mismatch	19 (13)	26 (18)
No data available	9 (6)	16 (11)
Modified[a] by 24 h IAR match	129 (93)	117 (87)
Modified[a] by 24 h IAR mismatch	10 (7)	15 (11)
No data available	7 (5)	12 (8)

Percentages of match and mismatch reflect bloodstream infections for which susceptibility data were available and evaluable; thus the denominator shown is less than the total number of isolates, as some data were missing. Evaluation methods are outlined in the Methods and in the Supplementary Data.

Abbreviations: FN, febrile neutropenic; IAR, initial antibiotic regimen.

[a]Modified IAR reflects coverage at 24 hours after presentation with FN.

Table 5. Cox Regression Results for Critical Illness

Clinical Presentation	No.	Univariate HR (95% CI)	Univariate *P* Value	Multivariate HR (95% CI)	Multivariate *P* Value
Match					
Yes	245	Ref	.49	Ref	.20
No	45	1.32 (0.35–1.65)		1.69 (0.27–1.32)	
Pitt group			.0001		.003
Pitt <2	246	Ref		Ref	
Pitt ≥2	44	3.49 (1.84–6.65)		2.82 (1.42–5.60)	
Isolate type[a]					
Gram-positive	144	Ref	.06	Ref	.16
Gram-negative	146	1.83 (0.97–3.45)		1.60 (0.83–3.11)	
Meropenem IAR			.02		.13
No	263	Ref		Ref	
Yes	27	2.59 (1.20–5.61)		1.92 (0.82–4.50)	
Prophylactic antibiotic			.10		.20
Yes	182	Ref		Ref	
No	108	1.68 (0.91–3.10)		1.51 (0.81–2.83)	

Abbreviations: BSI, bloodstream infection; HR, hazard ratio; IAR, initial antibiotic regimen.

[a]Anaerobic and polymicrobial BSIs were excluded. Two hundred ninety patients had single-isolate aerobic BSI, with 41 patients developing critical illness.

variability in types of bloodstream isolates and in susceptibilities among institutions. National guidelines should be regarded as roadmaps that provide general directions, but local resistance patterns must serve as the primary evidence for selection of empirical antibiotic regimens for a particular center, in the context of individual patients' risk factors and clinical presentations.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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