Clinical Infectious Diseases

MAJOR ARTICLE

Diagnostic Yield of Repeat Blood Cultures and Risk Factors for Bloodstream Infection in Persistent Febrile Neutropenia

Emily A. Rosen,[1,2] Elizabeth M. Krantz,[1] Allison Thibodeau,[3] Keara Kennedy,[1] Leah H. Yoke,[1,2] Frank Tverdek,[4,5] Zahra Kassamali Escobar,[4,5] Jason P. Cooper,[6,7] Masumi Ueda Oshima,[6,7] Paul Hendrie,[6] Marco Mielcarek,[6,7] and Catherine Liu[1,2,7]

[1]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [2]Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, Washington, USA; [3]Clinical Analytics, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [4]Department of Pharmacy, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [5]Department of Pharmacy, University of Washington, Seattle, Washington, USA; [6]Division of Hematology and Oncology, Department of Medicine, University of Washington, Seattle, Washington, USA; and [7]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA

Background. The optimal frequency of repeat blood cultures in persistent febrile neutropenia (FN) remains unknown. This study aimed to identify opportunities for blood culture diagnostic stewardship in persistent FN.

Methods. This was a retrospective cohort study of patients with hematology/oncology diagnoses and an FN episode lasting >3 days. Generalized estimating equation logistic regression models were used to evaluate risk factors for new bloodstream infection (BSI) after FN day 3.

Results. Among 620 patients, the median FN duration was 5 days, with a median of 12 blood culture bottles collected per patient. On FN day 1, 25% of patients had a positive blood culture; on FN days 2–9, <5% of patients per day had a new organism isolated. Among 31 new organisms isolated after FN day 3, 8 (26%) were contaminants. Of 503 patients with ≥1 blood culture collected after FN day 3, 19 (4%) had a new BSI after FN day 3. FN onset in the peri–hematopoietic cell transplant period (from day −7 to day +30) was associated with lower odds of new BSI after FN day 3 (odds ratio, 0.18 [95% confidence interval, .04–.71]; $P = .01$). Thirty-six patients died within 30 days after FN day 3, including 4 with a new BSI after FN day 3; 1 death was attributable to BSI after FN day 3.

Conclusions. Detection of new BSIs after FN day 3 was uncommon, demonstrating the low diagnostic yield of repeat blood cultures after FN day 3. FN episodes in the peri–hematopoietic cell transplant period may be a potential focus for blood culture diagnostic stewardship initiatives.

Keywords. febrile neutropenia; blood cultures; diagnostic stewardship.

Febrile neutropenia (FN) is associated with significant morbidity and mortality among patients with cancer [1, 2]. Bacteremia occurs in 10%–25% of FN episodes [3], but a definitive source of infection is often not identified. Based on expert opinion, national guidelines suggest obtaining 2 sets of blood cultures at the onset of FN and repeating cultures on FN days 2–3; beyond that, repeat cultures are advised only if there is a clinical change [3]. The optimal frequency of repeating blood cultures in FN remains unknown, though several studies in adult and pediatric populations have demonstrated low diagnostic yield for repeat cultures beyond the first few days of FN in clinically stable patients [4–13]].

Excess blood culturing is associated with detection of contaminants, unnecessary antibiotic exposure, misclassification of central line–associated bloodstream infection (BSI), iatrogenic anemia, and longer hospital stays [14–17]. These factors, in combination with recent blood culture bottle shortages, underscore the importance of limiting unnecessary cultures through diagnostic stewardship [18, 19]. Blood culture stewardship is increasingly recognized as a tool to advance antimicrobial stewardship [20] and is of critical importance to mitigate antimicrobial resistance, a growing threat to patients with cancer, who have frequent exposure to antibiotics [21].

To identify opportunities for blood culture stewardship at our cancer center, we conducted a retrospective cohort study to measure incidence of new BSI beyond FN day 3, identify risk factors for BSI after FN day 3, and measure associations between these infections and 30-day mortality.

Received 25 July 2025; accepted 28 October 2025; published online 20 January 2026

Correspondence: E. A. Rosen, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, 1100 Fairview Ave N, Mailstop E4-100, Seattle, WA 98109 (erosen@fredhutch.org).

Clinical Infectious Diseases®

© The Author(s) 2026. Published by Oxford University Press on behalf of Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

https://doi.org/10.1093/cid/ciag014

Downloaded from academic.oup.com/cid/advance-article/doi/10.1093/cid/ciag014/8431375 by guest on 24 August 2026

METHODS

Study Design

This is a single-center retrospective cohort study of adults (aged ≥18 years) with a hematology/oncology diagnosis—including both hematopoietic cell transplant (HCT) and chimeric antigen receptor (CAR) T-cell therapy recipients and non–HCT/CAR T-cell therapy recipients—hospitalized during an FN episode lasting >3 days. The study included FN episodes between 27 March 2021 and 30 June 2024. Only the first qualifying episode per patient was included (Figure 1). The primary outcome was onset of a BSI after FN day 3 due to a new organism not isolated in any earlier blood cultures during the index FN episode. This study was approved by the Fred Hutchinson Cancer Center Institutional Review Board.

Definitions

A day of FN was defined as any day with a measured temperature ≥38°C and an absolute neutrophil count (ANC) ≤500

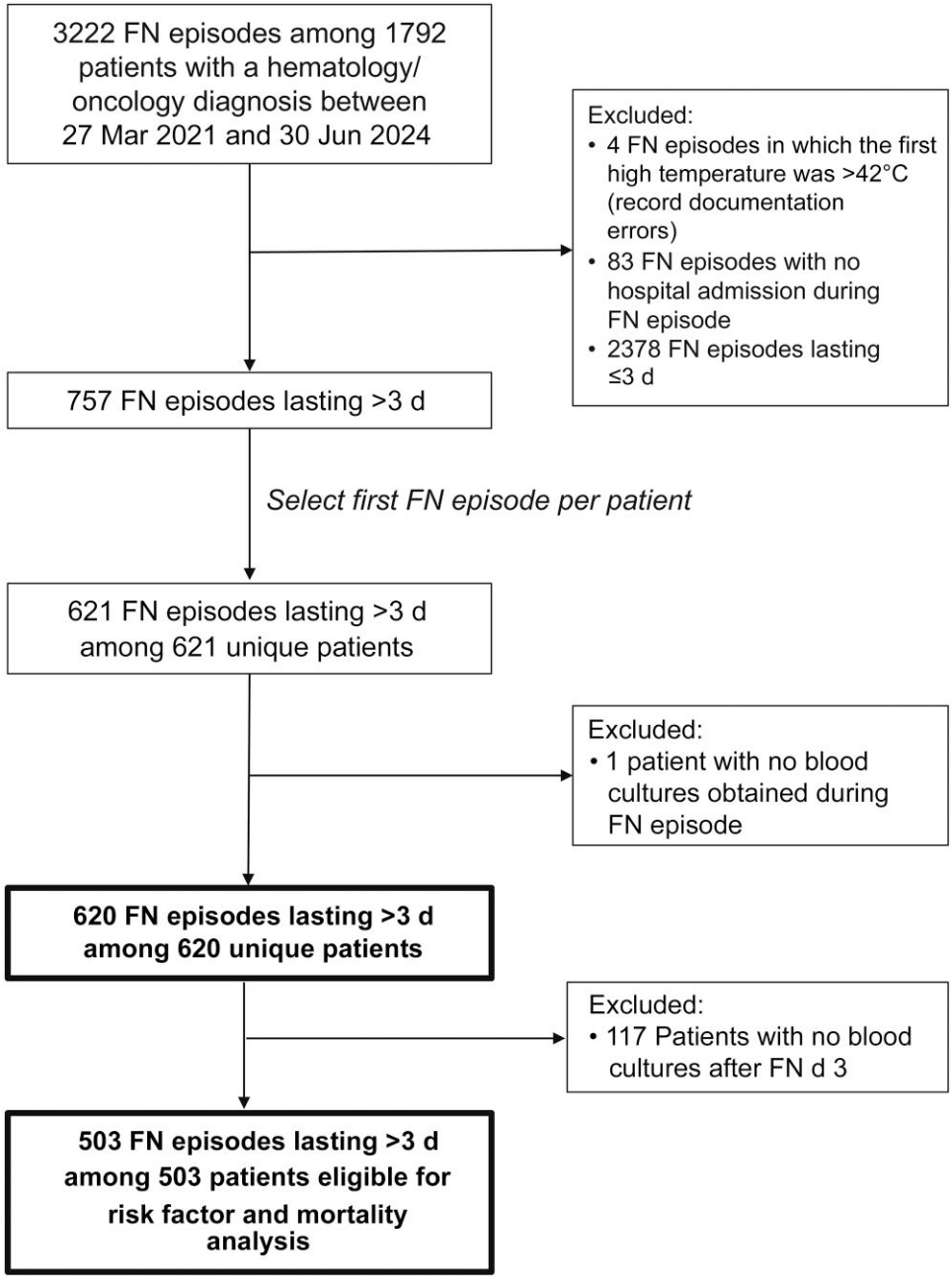

Figure 1. Flow chart illustrating study inclusion and exclusion criteria. A total of 620 patients were included in the descriptive analysis summarizing the timing of positive blood cultures during episodes of persistent febrile neutropenia (FN); 503 patients who had ≥1 blood culture collected after FN day 3 were eligible for the risk factor and 30-day mortality analyses.

Downloaded from academic.oup.com/cid/advance-article/doi/10.1093/cid/ciag014/8431375 by guest on 24 August 2026

cells/μL measured within 24 hours before or after the qualifying temperature. The start of an FN episode was the first day FN criteria were met. The end of an FN episode was the last day of FN that was followed by ≥2 consecutive days on which criteria for a day of FN were no longer met. An FN skip day was any non-FN day within an FN episode that was immediately preceded and followed by an FN day.

A blood culture set was defined as 2 bottles; if bottle-level data were missing, we assumed that 2 bottles were collected per set, according to institutional standard practice. A positive culture was any blood culture growing ≥1 organism. A positive blood culture after FN day 3 was considered a new BSI if the following criteria were met: (1) ≥1 organism in the blood culture was a new organism, not isolated in any previous blood cultures from the same FN episode; and (2) ≥1 new organism was not a contaminant. If ≥1 organism meeting criteria for BSI was isolated on the same FN day, this was considered a single, polymicrobial BSI. If a patient had onset of BSIs due to new organisms on different FN days, these were considered separate BSIs.

Data Collection

FN episode dates, patient demographics, admission dates, hematology/oncology diagnoses, HCT/CAR T-cell treatment dates (if applicable), and mortality data were extracted from the medical record, in addition to all blood cultures and temperatures measured during FN episodes. To determine whether positive blood cultures after FN day 3 represented a true BSI or contaminant, records were reviewed by 2 infectious diseases clinicians. A positive culture was deemed a contaminant if agreed upon by both reviewers; in cases of disagreement, the positive culture was designated as a BSI. Contaminant determination criteria are described in the Supplementary materials.

To assess clinical stability at the time of each new BSI after FN day 3, records were reviewed to capture clinical parameters used for sepsis identification [22]. At the conclusion of each review, investigators recorded their overall assessment of patient clinical stability at the time of each BSI diagnosis. Record review was performed by 2 investigators; discrepancies were adjudicated by a third investigator unless noted. The BSI-attributable mortality rate was assessed using a similar process, described in the Supplementary materials.

Standard Blood Culturing Practices

Internal guidelines recommend 2 sets of blood cultures at FN onset before antibiotic initiation. For HCT/CAR T-cell therapy recipients with FN, guidelines recommend repeating 2 sets of blood cultures every 24 hours. For non–HCT/CAR T-cell therapy recipients with FN, cultures may be obtained every 24 hours, or less frequently if the patient's clinical status is not worsening. Our center experienced a blood culture bottle shortage between 13 August 2021 and 6 March 2022. During this time, standard practices were temporarily revised to recommend cultures every 48 hours for continuously febrile but hemodynamically stable patients. Standard treatment for FN and antimicrobial prophylaxis protocols are described in the Supplementary materials.

Statistical Analysis

The primary outcome was new BSI after FN day 3, defined as a binary variable for presence or absence of BSI onset for each day with blood cultures collected after FN day 3; >1 new BSI after FN day 3 per patient could be included. Patients without any blood cultures collected after FN day 3 were excluded from analyses of the frequency of and risk factors for new BSIs after FN day 3. Prespecified candidate risk factors were limited due to few BSI events after FN day 3 but included (1) hospital-onset FN (FN onset >2 days after admission), a previously reported risk factor for BSI in FN [23]; (2) FN onset in the peri-HCT period (from day −7 to day +30; corresponding to conditioning through pre-/early engraftment); and (3) presence of a mucosal barrier injury (MBI)–associated organism in a blood culture from FN days 1–3, chosen as a possible marker of mucositis. MBI-associated organisms were defined per the National Healthcare Safety Network (NHSN) 2019 organisms list [24].

To estimate associations between candidate risk factors and new BSI after FN day 3, we used logistic regression with generalized estimating equations (GEEs) to account for correlation among multiple blood culture days on which new BSI after FN day 3 was measured within the same patient. These models used an independence working correlation and weighting to accommodate informative cluster size; additional details, including multivariable model selection, are described in the Supplementary materials.

To assess outcomes associated with new BSIs after FN day 3, we computed the 30-day mortality rate using FN day 4 as time zero, with survival time defined as the number of days from FN day 4 to either death or censoring 30 days after FN day 4, whichever came first. We constructed Kaplan-Meier curves to illustrate timing of deaths within this period. To estimate associations between new BSIs after FN day 3 and the mortality rate, we used Cox proportional hazards models with a time-dependent covariate for new BSI after FN day 3 and adjustment variables for age, acute myeloid leukemia versus other diagnoses, and duration of FN (time dependent). Additional model details are described in the Supplementary materials. Analyses were performed using STATA SE software, version 18.0.

RESULTS

Patient and FN Episode Characteristics

Among 1792 patients with 3222 FN episodes during the study period, 620 patients with 620 FN episodes were included (Figure 1). The median age was 57 years, and 382 patients

Downloaded from academic.oup.com/cid/advance-article/doi/10.1093/cid/ciag014/8431375 by guest on 24 August 2026

Table 1. Baseline Patient Characteristics

Patient Characteristic	Patients, No. (%)[a]		
	No Blood Cultures After FN d 3 (n = 117)	≥1 Blood Culture After FN d 3 (n = 503)	Total Cohort (N = 620)
Age at start of FN episode, median (IQR), y	58 (45–67)	57 (40–65)	57 (40–65)
Sex			
Male	72 (61.5)	310 (61.6)	382 (61.6)
Female	45 (38.5)	193 (38.4)	238 (38.4)
Race			
White	90 (76.9)	380 (75.5)	470 (75.8)
Asian	15 (12.8)	59 (11.7)	74 (11.9)
Black or African-American	5 (4.3)	19 (3.8)	24 (3.9)
American Indian or Native Alaskan	3 (2.6)	8 (1.6)	11 (1.8)
Native Hawaiian or Pacific Islander	1 (0.9)	8 (1.6)	9 (1.5)
Other	0 (0.0)	7 (1.4)	7 (1.1)
Multiple races	3 (2.6)	11 (2.2)	14 (2.3)
Declined to answer	0 (0.0)	11 (2.2)	11 (1.8)
Ethnicity			
Hispanic or Latino/a or Latinx	9 (7.7)	50 (9.9)	59 (9.5)
Not Hispanic or Latino/a or Latinx	107 (91.5)	448 (89.1)	555 (89.5)
Declined to answer or unable to collect	1 (0.9)	5 (1.0)	6 (1.0)
Diagnosis at FN start			
Leukemia	55 (47.0)	254 (50.5)	309 (49.8)[b]
MDS/MPN	23 (19.7)	41 (8.2)	64 (10.3)[c]
Lymphoma	18 (15.4)	114 (22.7)	132 (21.3)
MM/other plasma cell disorder	13 (11.1)	53 (10.5)	66 (10.6)
Other hematology diagnoses[d]	1 (0.9)	5 (1.0)	6 (1.0)
Solid tumor	7 (6.0)	36 (7.2)	43 (6.9)
HCT/CAR T-cell therapy status at FN start[e]			
No HCT/no CAR T-cell therapy	59 (50.4)	255 (50.7)	314 (50.6)
≥1 HCT/no CAR T-cell therapy	48 (41.0)	199 (39.6)	247 (39.8)
No HCT/≥1 CAR T-cell therapy	8 (6.8)	35 (7.0)	43 (6.9)
≥1 HCT/≥1 CAR T-cell therapy	2 (1.7)	14 (2.8)	16 (2.6)
Timing of FN start			
FN start before admission	6 (5.1)	42 (8.3)	48 (7.7)
FN start same day as admission	37 (31.6)	148 (29.4)	185 (29.8)
FN start after admission	74 (63.2)	313 (62.2)	387 (62.4)
Time from FN start to admission date, among patients admitted after FN start, median (IQR), d	1 (1–1)	1 (1–1)	1 (1–1)
Time from admission date to FN start, among patients admitted before FN start, median (IQR), d	8 (3–14)	9 (4–12)	9 (4–12)
FN duration, median (IQR; range), d	4 (4–4; 4–7)	6 (4–7; 4–43)	5 (4–7; 4–43)
No. of blood culture bottles collected during FN, median (IQR; range)	8 (6–10; 2–18)	16 (10–20; 2–80)	12 (8–18; 2–80)
Candidate risk factors for new BSI after FN d 3			
Hospital-onset FN (FN start >2 d after hospital admission)			
No	57 (48.7)	243 (48.3)	300 (48.4)
Yes	60 (51.3)	260 (51.7)	320 (51.6)
FN episode started during peri-HCT period (d −7 to d +30)			
No	76 (65.0)	327 (65.0)	403 (65.0)
Yes	41 (35.0)	176 (35.0)	217 (35.0)

Downloaded from academic.oup.com/cid/advance-article/doi/10.1093/cid/ciag014/8431375 by guest on 24 August 2026

Table 1. Continued

Patient Characteristic	Patients, No. (%)[a]		
	No Blood Cultures After FN d 3 (n = 117)	≥1 Blood Culture After FN d 3 (n = 503)	Total Cohort (N = 620)
MBI-associated organism in a blood culture on FN d 1–3			
No	107 (91.5)	420 (83.5)	527 (85.0)
Yes	10 (8.5)	83 (16.5)	93 (15.0)

.Abbreviations: BSI, bloodstream infection; CAR, chimeric antigen receptor; FN, febrile neutropenia; HCT, hematopoietic cell transplant; IQR, interquartile range; MBI, mucosal barrier injury; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasm.

[a]Data represent no. (%) of patients unless otherwise noted.

[b]Among these 309 patients, 214 had acute myeloid leukemia, and 54 had acute lymphoid leukemia. The remaining 41 patients had chronic lymphoid leukemia, chronic myeloid leukemia, or other acute leukemia.

[c]Forty-nine patients had MDS, and 15 had MPN.

[d]Including aplastic anemia, hemophagocytic lymphohistiocytosis, sickle cell disease, and amyloidosis.

[e]Patients were considered HCT and/or CAR T-cell therapy recipients at the time of FN start if the FN start date was on or after day 0 of HCT and/or CAR T-cell therapy.

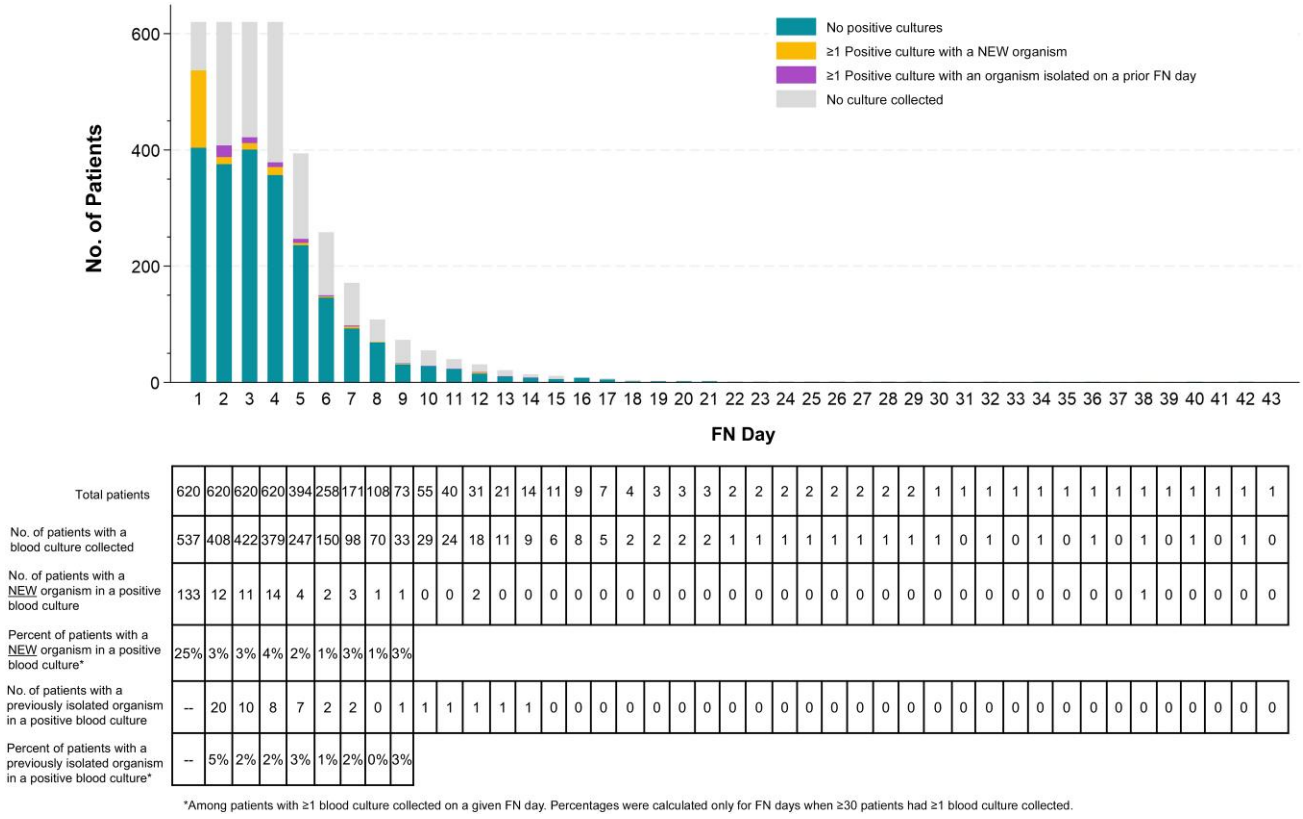

Figure 2. Bar chart summarizing blood culture results among the total cohort of 620 patients by day of febrile neutropenia (FN). The table summarizes the total number of patients with FN per day (FN episode duration, 4–43 days), the number of patients with ≥1 blood culture collected on each FN day, the number and percentage of patients per FN day with a new organism growing in blood culture (defined as an organism not isolated in any blood cultures from an earlier day within the same FN episode), and the number and percentage of patients per FN day with an organism growing in blood culture that was isolated on a previous day of the same FN episode. The percentage of patients with a new or previously isolated organism per FN day was calculated only for FN days on which ≥30 patients had ≥1 blood culture collected.

(62%) were male. The most common underlying diagnosis was leukemia (309 patients [50%]), followed by lymphoma (132 patients [21%]). At FN onset, 306 patients (49%) had received an HCT and/or CAR T-cell therapy (Table 1).

Among the 620 FN episodes, the median duration was 5 days (interquartile range, 4–7 days) and the median number of blood culture bottles collected per episode was 12 (8–18). Among 537 patients with ≥1 blood culture collected on FN day 1, 133 (25%) had ≥1 positive blood culture on that day (Figure 2), and 25 of 133 (19%) had a follow-up blood culture on a later FN day in which an organism grew that had been previously isolated on FN day 1. On FN days 2–9, when ≥30

Downloaded from academic.oup.com/cid/advance-article/doi/10.1093/cid/ciag014/8431375 by guest on 24 August 2026

patients had a blood culture collected, the proportion of patients per FN day with ≥1 new organism detected was 1%–4% and the proportion with a previously isolated organism was 0%–5% (Figure 2).

New Organisms in Blood Cultures After FN Day 3

Thirty-one new organisms were identified in positive blood cultures after FN day 3 among 25 patients. Of these new organisms, 19 (61%) were gram positive, 9 (29%) were gram negative, and 3 (10%) were yeast. Overall, 8 of 31 new organisms (26%; 7 coagulase-negative *Staphylococci* and 1 *Bacillus* species) were determined to be contaminants; 5 of 8 patients received treatment with vancomycin that they may not have otherwise received. The remaining 23 new organisms were predominantly gastrointestinal commensals (Supplementary Table 1).

New BSI After FN Day 3

Overall, 503 patients who had a total of 1110 blood culture collection days after FN day 3 were eligible for assessment of new BSIs after FN day 3 (Figure 1 and Table 1). The median number of days with blood cultures collected after FN day 3 per patient was 1 (range, 1–20 days). Of the 503 patients, 34 (7%) had ≥1 positive blood culture after FN day 3, and 25 (5%) had ≥1 new organism isolated. After exclusion of contaminants, 19 of 503 patients (4%) had a new BSI after FN day 3, including 1 patient with 2 separate BSIs with onset after FN day 3. Onset of BSI occurred on 20 of 1110 culture collection days (2%) after FN day 3.

Tachycardia and/or tachypnea preceded most of the 20 new BSIs after FN day 3, whereas hypotension preceded only 1 (Table 2). While patients were assessed as unstable or possibly unstable by ≥1 reviewer in 12 of 20 BSIs (60%), there was heterogeneity in reviewer assessments, with agreement of overt clinical instability by both reviewers in 3 of 20 BSIs (15%) diagnosed after FN day 3 (Supplementary Table 2). Two of 20 BSIs diagnosed after FN day 3 were detected immediately after an FN skip day (Supplementary Figure 1). Gastrointestinal tract translocation and/or central venous catheters were the most common suspected sources of infection (Supplementary Table 3).

New BSI after FN day 3 was less common among patients with FN onset in the peri-HCT period compared with other patients (0.9% vs 2.2% of culture days; Table 3). In a multivariable GEE logistic regression model, patients with FN onset in the peri-HCT period had significantly lower odds of new BSI after FN day 3 than patients whose FN episode did not start in this time window (odds ratio, 0.18 [95% confidence interval (CI), .04–.71]; $P = .01$).

Table 2. Clinical Parameters Observed With New Bloodstream Infections After Febrile Neutropenia Day 3

Parameter	BSIs, No. (%) (n = 20)
SBP ≤90 mm Hg within 8 h before BSI	
No	19 (95.0)
Yes	1 (5.0)
Pulse rate ≥100/min within 8 h before BSI	
No	6 (30.0)
Yes	14 (70.0)
Respirations ≥22/min within 8 h before BSI	
No	8 (40.0)
Yes	12 (60.0)
Lactate elevated within 8 h before BSI	
No (or lactate value not available)	19 (95.0)
Yes	1 (5.0)
Patient already admitted to ICU at BSI onset	
No	17 (85.0)
Yes	3 (15.0)
Patient transferred to ICU within 24 h before or after BSI onset	
No	18 (90.0)
Yes	2 (10.0)
Change in mental status within 8 h before BSI[a]	
No	17 (85.0)
Yes	3 (15.0)

Abbreviations: BSI, bloodstream infection; ICU, intensive care unit; SBP, systolic blood pressure.

[a]Although the overall percentage of BSIs with or without change in mental status was identical between the 2 reviewers, there was not 100% agreement between the 2 reviewers at the individual BSI-patient level. Adjudication by a third reviewer was not performed in this case, given the difficulty of assessing for an acute change in mental status by retrospective record review.

30-Day All-Cause Mortality Rate

Thirty-six of 503 patients died within 30 days after FN day 3 (7.2% [95% CI, 5.2%–9.8%]; Supplementary Figure 2); 4 of 36 deaths were among patients with a new BSI after FN day 3. One death was attributable to sepsis from the new BSI after FN day 3; the other 3 deaths were not directly related to new BSI after FN day 3. With adjustment for age, acute myeloid leukemia diagnosis, and FN duration, a Cox proportional hazards model estimated new BSI after FN day 3 was associated with a significantly increased 30-day mortality rate (hazard ratio, 3.22 [95% CI, 1.12–9.25]; $P = .03$) (Table 4).

DISCUSSION

In a cohort of >500 patients with persistent FN, new BSIs after FN day 3 were identified in 4% of patients and on 2% of days with cultures collected. FN onset in the peri-HCT period (day −7 to day +30) was associated with 80% lower odds of a new BSI after FN day 3. Among new organisms in blood cultures after FN day 3, 26% were contaminants, with more than half leading to excess vancomycin use, highlighting the importance of diagnostic stewardship in this population. While new BSIs after FN day 3 were rare, they were associated with an increased 30-day all-cause mortality rate. Most deaths were not directly attributable to the index BSI, suggesting that these

Downloaded from academic.oup.com/cid/advance-article/doi/10.1093/cid/ciag014/8431375 by guest on 24 August 2026

Table 3. Generalized Estimating Equation Logistic Regression Model Estimates for Associations With New Bloodstream Infection After Febrile Neutropenia Day 3

Candidate Risk Factor	New BSIs After FN d 3/Total Blood Culture Days (%)	Univariable Models		Multivariable Model	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Hospital-onset FN (FN start >2 d after hospital admission)					
No	8/576 (1.4)	1.00 (Ref)	…	1.00 (Ref)	…
Yes	12/534 (2.3)	1.72 (.52–5.72)	.38	2.79 (.80–9.70)	.11
FN start during peri-HCT period (d −7 to d +30)					
No	17/785 (2.2)	1.00 (Ref)	…	1.00 (Ref)	…
Yes	3/325 (0.9)	.26 (.07–1.00)	.05	.18 (.04–.71)	.01
MBI-associated organism in blood culture on FN d 1–3					
No	15/865 (1.7)	1.00 (Ref)	…	…	…
Yes	5/245 (2.0)	0.70 (.23–2.07)	.52	…	…

Abbreviations: BSI, bloodstream infection; CI, confidence interval; FN, febrile neutropenia; HCT, hematopoietic cell transplant; MBI, mucosal barrier injury; OR odds ratio; Ref, reference.

Table 4. Cox Model Estimates for Associations Between Clinical Parameters and 30-Day Mortality Rate

Covariate	Multivariable Model	
	Adjusted HR[a] (95% CI)	*P* value
Age at FN onset		
≤65 y	1.00 (Ref)	…
>65 y	2.36 (1.20–4.65)	.01
Diagnosis		
Other than AML	1.00 (Ref)	…
AML	1.00 (.51–1.99)	.99
New BSI After FN d 3[b]		
No	1.00 (Ref)	…
Yes	3.22 (1.12–9.25)	.03
Duration of FN episode (for each 1-d increase)[b]	1.14 (1.04–1.25)	.006

Abbreviations: AML, acute myeloid leukemia; BSI, bloodstream infection; CI, confidence interval; FN, febrile neutropenia; HR, hazard ratio; Ref, reference.

[a]Model is adjusted for all variables shown in the table.

[b]Modeled as a time-dependent covariate.

late infections may be a marker for a worse short-term prognosis.

To our knowledge, this is the largest cohort study examining diagnostic utility of repeat blood cultures in persistent FN, and it corroborates existing literature demonstrating <5% yield of repeat blood cultures for detecting new pathogens [4–13]. However, assessment of risk factors for positive repeat blood cultures in FN has been limited by small sample sizes in several previous studies [4, 6, 8–12].

We observed a reduced risk of new BSIs after FN day 3 among patients with FN onset in the peri-HCT period, compared with patients with FN onset outside the peri-HCT period and non-HCT recipients. This finding could be explained by differences in standard blood culturing practices at our center, as HCT/CAR T-cell therapy recipients typically have repeat cultures daily, whereas culture frequency is per clinician discretion for non–HCT/CAR T-cell therapy recipients with FN. We also speculate that patients with persistent FN outside the peri-HCT period may be more likely to have a higher burden of active cancer (eg, due to newly diagnosed or relapsed disease) or other comorbid conditions associated with delayed neutrophil engraftment, which may modulate BSI risk.

New BSIs after FN day 3 were also associated with an increased 30-day all-cause mortality rate. However, a causal relationship is not clear, as only 1 death was directly attributable to new BSI after FN day 3, and our model could be affected by confounding, given the limited number of covariates we were able to include. We hypothesize that these BSI events may primarily be an indicator of patients with poor prognosis, and this association alone should not justify more frequent culturing in these patients. Additional studies are needed to further characterize the BSI-related mortality rate in FN.

We observed a slightly greater frequency of new BSI after FN day 3 for patients with hospital-onset FN, but this difference was not statistically significant. Rosenblum et al [23] found hospital-onset FN was a risk factor for a positive repeat blood culture in pediatric patients with FN.

We hypothesized that severe mucositis may increase the risk of new BSIs after FN day 3 due to translocation of gut microbes into the bloodstream [25]. Although we postulated that bacteremia from an MBI-associated organism during FN days 1–3 may be a surrogate marker for mucositis, this was not a significant risk factor in our model. While some studies found that recent BSI was a risk factor for a positive repeat culture in FN [10, 23], another study including HCT recipients with BSI within 24 hours of FN onset demonstrated a low yield of follow-up blood cultures [12]. Further studies are needed to understand whether prior BSI affects the risk of subsequent BSI during FN.

Whereas several prior studies concluded that clinical instability predicts BSI in FN [4, 5, 8], we observed that new BSI after FN day 3 was often not preceded by overt clinical instability. Two

Downloaded from academic.oup.com/cid/advance-article/doi/10.1093/cid/ciag014/8431375 by guest on 24 August 2026

investigators reviewed records and found that hypotension, elevated lactate levels, and ICU transfer were uncommon, leading up to the detection of new BSI after FN day 3, with heterogeneity in overall assessments of clinical instability. These findings suggest that traditional markers of sepsis and provider assessment may not reliably identify patients with new BSI in persistent FN, though conclusions are limited by the lack of a comparator group. The presence of chills has been associated with BSI in FN [6], but we were unable to assess this retrospectively.

Based on these findings, our center is revising standard blood culturing practices to reduce frequency of routine cultures in clinically stable patients beyond FN day 3, emphasizing instead that the collection of repeat cultures should be guided by changes in patient clinical status, even if these signs may be subtle. Development of machine learning prediction tools for BSI in patients who are immunocompromised [26] and novel diagnostics—such as metagenomic next-generation sequencing and host-response profiling to distinguish between infectious and noninfectious causes of fever [27, 28]—are important areas for future study and may further inform blood culture stewardship and empiric antimicrobial therapy.

This study had several limitations. First, the retrospective design is inherently subject to confounding and is limited by a fixed sample size. In addition, we may have underestimated the frequency of new BSIs after FN day 3, as cultures were not collected on all FN days and we excluded patients with moderate neutropenia (ANC, 501–1000 cells/μL). Although FN definitions vary, our ANC threshold of ≤500 cells/μL is used in published guidelines [3], and allowing isolated skip days within FN episodes likely increased our ability to detect clinically significant BSIs. The relative rarity of the primary outcome limited the number of covariates that could be included in the multivariable GEE model and thus limited our assessment of other potential risk factors for BSI after FN day 3. Our model also assumed that any FN days without cultures collected occurred at random, but this is likely not true in practice, due to differences in culturing guidelines for HCT/CAR T-cell therapy recipients versus non–HCT/CAR T-cell therapy recipients at our center, temporary modifications to guidelines during the blood culture bottle shortage during the study period, and lower likelihood that cultures were ordered on FN skip days than on other FN days. Finally, this was a single-center study, which may limit its generalizability to other centers, where antibacterial prophylaxis and empiric antibiotics for FN as well as local microbiology and resistance patterns may differ [29].

In conclusion, we observed a limited yield of repeat blood cultures in persistent FN with a low rate of new organisms isolated from cultures after FN day 3. A quarter of these new organisms represented contaminants and often resulted in excess antibiotic exposure. Opportunities exist to improve blood culture stewardship in FN, particularly among patients with FN in the peri-HCT period, who had significantly lower odds of new BSI after FN day 3. Although rare, new BSI after FN day 3 was associated with an increased 30-day mortality rate. Further studies are needed to determine the optimal frequency of repeat blood cultures in FN, in addition to the impact on antibiotic utilization and the role of novel prediction and diagnostic tools in the management of these patients.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

Author contributions. Study conceptualization and design, data interpretation, manuscript preparation, and critical review: E. A. R., E. M. K., and C. L. Data collection: E. A. R., A. T., K. K., L. H. Y, and C. L. Data analysis: E. A. R. and E. M. K. All other authors critically reviewed the manuscript and provided relevant clinical expertise.

Acknowledgments. REDCap, used for data collection for this project, is supported by the Institute of Translational Health Sciences (ITHS). National Institutes of Health awards to ITHS did not provide direct funding for this project.

Disclaimer. The content of this article is the authors' responsibility and does not necessarily represent the views of the National Institutes of Health.

Financial support. This work was supported by the National Institutes of Health (grants T32AI118690 supporting E. A. R and P30CA015704 to the Fred Hutchinson Cancer Center).

Potential conflicts of interest. E. A. R. reports a travel award from the Infectious Diseases Society of America for attendance at IDWeek 2024. L. H. Y. reports payment/honoraria for presentations from ThriveAP, the American Academy of Physician Associates, Johns Hopkins University, and the Association of PAs in Oncology; support for conference attendance from the Infectious Diseases Society of America and the International Immunocompromised Host Society; and a leadership role in the University of Washington Physicians Board of Regents and the Washington Academy of Physician Associates Board. Z. K. E. reports support from SIDP Breakpoints for a podcast lecture and support from conference organizers for attendance at IDWeek 2024 and MAD-ID 2025. P. H. reports a leadership role in the Erdheim-Chester Disease Global Alliance. C. L. reports research support from SNIPR Biome and travel support from the Society for Healthcare Epidemiology of America (SHEA) for an invited lecture at the SHEA Spring 2025 conference. All other authors report no potential conflicts.

Downloaded from academic.oup.com/cid/advance-article/doi/10.1093/cid/ciag014/8431375 by guest on 24 August 2026

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Boccia R, Glaspy J, Crawford J, Aapro M. Chemotherapy-induced neutropenia and febrile neutropenia in the US: a beast of burden that needs to be tamed? Oncologist **2022**; 27:625–36.
2. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer **2006**; 106:2258–66.
3. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis **2011**; 52:e56–93.
4. Robinson ED, Keng MK, Thomas TD, Cox HL, Park SC, Mathers AJ. Reducing repeat blood cultures in febrile neutropenia: a single-center experience. Open Forum Infect Dis **2022**; 9:ofac521.
5. Haeusler GM, De Abreu Lourenco R, Clark H, et al. Diagnostic yield of initial and consecutive blood cultures in children with cancer and febrile neutropenia. J Pediatric Infect Dis Soc **2021**; 10:125–30.
6. Kimura SI, Gomyo A, Hayakawa J, et al. Clinical significance of repeat blood cultures during febrile neutropenia in adult acute myeloid leukaemia patients undergoing intensive chemotherapy. Infect Dis (Lond) **2017**; 49:748–57.
7. Heriot GS, Tam C, Waters MJ. Factors predicting the identification of new organisms in follow-up blood cultures drawn during episodes of neutropenic sepsis. Br J Haematol **2017**; 182:451–3.
8. Petty LA, Sokol EA, Bartlett AH, McNeer JL, Alexander KA, Pisano J. Repeated blood cultures in pediatric febrile neutropenia: would following the guidelines alter the outcome? Pediatr Blood Cancer **2016**; 63:1244–9.
9. Neemann K, Yonts AB, Qiu F, Simonsen K, Lowas S, Freifeld A. Blood cultures for persistent fever in neutropenic pediatric patients are of low diagnostic yield. J Pediatric Infect Dis Soc **2016**; 5:218–21.
10. Wattier RL, Dvorak CC, Auerbach AD, Weintrub PS. Repeat blood cultures in children with persistent fever and neutropenia: diagnostic and clinical implications. Pediatr Blood Cancer **2015**; 62:1421–6.
11. Serody JS, Berrey MM, Albritton K, et al. Utility of obtaining blood cultures in febrile neutropenic patients undergoing bone marrow transplantation. Bone Marrow Transplant **2000**; 26:533–8.
12. Sheu M, Molina Garcia S, Shrivastava G, et al. Yield of repeat blood cultures in acute myeloid leukemia patients with febrile neutropenia and bacteremia following allogeneic hematopoietic stem cell transplant. Transpl Infect Dis **2024**; 26: e14345.
13. Jafri F, Knoll BM. Low diagnostic yield of repeat blood cultures in adult haematologic malignancy patients with persistent neutropenic fever. J Intern Med **2021**; 289:584–7.
14. Fabre V, Carroll KC, Cosgrove SE. Blood culture utilization in the hospital setting: a call for diagnostic stewardship. J Clin Microbiol **2022**; 60:e0100521.
15. Coffey KC, Morgan DJ, Claeys KC. Diagnostic stewardship: what impacts antibiotics use? Curr Opin Infect Dis **2023**; 36:270–5.
16. Singh HK, Claeys KC, Advani SD, et al. Diagnostic stewardship to improve patient outcomes and healthcare-associated infection (HAI) metrics. Infect Control Hosp Epidemiol **2024**; 45:405–11.
17. Stohs E, Chow VA, Liu C, et al. Limited utility of outpatient surveillance blood cultures in hematopoietic cell transplant recipients on high-dose steroids for treatment of acute graft-versus-host-disease. Biol Blood Marrow Transplant **2019**; 25:1247–52.
18. Ryder JH, Van Schooneveld TC, Diekema DJ, Fabre V. Every crisis is an opportunity: advancing blood culture stewardship during a blood culture bottle shortage. Open Forum Infect Dis **2024**; 11:ofae479.
19. Shelly MJ, Kunz A, Mittal J, Corwin DS, Chapman C, Ender PT. Efficacy of a multicenter hospital network's approach to enacting blood culture stewardship during a global shortage. Open Forum Infect Dis **2025**; 12:ofaf294.
20. Ku TSN, Mohajer A, Newton M, et al. Improving antimicrobial use through better diagnosis: the relationship between diagnostic stewardship and antimicrobial stewardship. Infect Control Hosp Epidemiol **2023**; 44:1901–8.
21. Gottesdiener LS, Satlin MJ. Global impact of antibacterial resistance in patients with hematologic malignancies and hematopoietic cell transplant recipients. Transpl Infect Dis **2023**; 25:e14169.
22. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med **2021**; 49:e1063–143.
23. Rosenblum J, Lin J, Kim M, Levy AS. Repeating blood cultures in neutropenic children with persistent fevers when the initial blood culture is negative. Pediatr Blood Cancer **2013**; 60:923–7.
24. Centers for Disease Control and Prevention. NHSN organisms list. Available at: https://www.cdc.gov/nhsn/pdfs/validation/2019/2019-NHSN-Organisms-List-Validation.xlsx. Accessed 31 May 2025.
25. Satheeshkumar PS, Blijlevens N, Sonis ST. Application of big data analyses to compare the impact of oral and gastrointestinal mucositis on risks and outcomes of febrile neutropenia and septicemia among patients hospitalized for the treatment of leukemia or multiple myeloma. Support Care Cancer **2023**; 31:199.
26. Lind ML, Mooney SJ, Carone M, et al. Development and validation of a machine learning model to estimate bacterial sepsis among immunocompromised recipients of stem cell transplant. JAMA Netw Open **2021**; 4:e214514.
27. Langelier C, Kalantar KL, Moazed F, et al. Integrating host response and unbiased microbe detection for lower respiratory tract infection diagnosis in critically ill adults. Proc Natl Acad Sci U S A **2018**; 115:E12353–E62.
28. Kalantar KL, Neyton L, Abdelghany M, et al. Integrated host-microbe plasma metagenomics for sepsis diagnosis in a prospective cohort of critically ill adults. Nat Microbiol **2022**; 7:1805–16.
29. Zimmer AJ, Stohs E, Meza J, et al. Bloodstream infections in hematologic malignancy patients with fever and neutropenia: are empirical antibiotic therapies in the United States still effective? Open Forum Infect Dis **2022**; 9:ofac240.

Downloaded from academic.oup.com/cid/advance-article/doi/10.1093/cid/ciag014/8431375 by guest on 24 August 2026