Reducing Repeat Blood Cultures in Febrile Neutropenia: A Single-Center Experience

Evans D. Robinson,1,6 Michael K. Keng,2 Tanya D. Thomas,2 Heather L. Cox,1,3 Stacy C. Park,1 and Amy J. Mathers1,4

1Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia Health, Charlottesville, Virginia, USA; 2Division of Hematology and Oncology, Department of Medicine, University of Virginia Health, Charlottesville, Virginia, USA; 3Department of Pharmacy Services, University of Virginia Health, Charlottesville, Virginia, USA; 4Clinical Microbiology Laboratory, Department of Pathology, University of Virginia Health, Charlottesville, Virginia, USA

Background. Limited data exist to guide blood culture ordering in persistent febrile neutropenia (FN), resulting in substantial variation in practice. Unnecessary repeat blood cultures have been associated with patient harm including increased antimicrobial exposure, hospital length of stay, catheter removal, and overall cost.

Methods. We conducted a single-center study of adult hematology-oncology patients with ≥3 days of FN. The yield of blood cultures was first evaluated in a 2-year historical cohort. Additionally, a pilot pre-/postintervention study was performed in non–stem cell transplant (SCT) patients following a change in our population clinical practice guideline from a recommendation of daily blood cultures to a clinically guided approach. The primary outcome was cultures collected per days of FN after day 3 of persistent FN.

Results. One hundred forty-six episodes of ≥3 days of FN in 108 patients were identified during the historical period. Day 1 blood cultures were positive in 23 of 146 (16%) episodes. Blood cultures were drawn on 374 of 513 (73%) subsequent episodes (day 2–12) and were negative in 366 of 374 (98%). After the intervention, a 53% decrease was observed in the rate of total blood cultures collected (1.4 preintervention vs 0.7 postintervention; P = .03). Blood cultures obtained after 48 hours rarely yielded clinically significant organisms.

Conclusions. Repeat blood cultures are low-yield in persistent FN without new clinical change. A pilot intervention in non-SCT patients successfully reduced the frequency of blood culture collection.

Keywords. blood culture; diagnostic stewardship; febrile neutropenia.

Febrile neutropenia (FN) remains a significant complication of chemotherapy administration [1–3]. As bacteremia complicates upwards of 20% of episodes, blood cultures play a critical role in its prompt evaluation and management [4, 5]. The Infectious Diseases Society of America (IDSA) guidelines recommend obtaining 2 sets of blood cultures on each of the first 3 days of persistent FN [6]. However, there is limited evidence to guide obtainment of blood cultures beyond this point, resulting in institutional practice variation. With no infectious etiology identified in a significant portion of FN episodes [4], unnecessary repeat blood culture collection in nonneutropenic patients has been shown to result in patient harm, including increased antimicrobial exposure, longer length of stay (LOS), unnecessary removal of vascular catheters, and increased healthcare costs [7–11]. The neutropenic population is often lacking in ability to generate new blood cells, and may be particularly impacted by the typical 40 mL of daily blood loss required for 2 sets of blood cultures.

Available studies to date in both adult and pediatric populations have demonstrated a low yield of repeat blood cultures in persistent FN. A retrospective study in pediatric patients [12] found new bacteremia after day 3 of FN without accompanying hemodynamic change in only 1 of 294 (0.3%) episodes with an initial negative blood culture, supporting the IDSA guideline recommendation. Further studies have demonstrated similar low rates of new organism identification after day 1 including 1 of 109 (0.9%) adult and pediatric patients undergoing stem cell transplant (SCT) [13], 3 of 134 (2.2%) episodes of persistent FN in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome [14], and 3 of 242 (1.2%) episodes in a diverse cohort [15].

In our institution, prior institutional practice guidelines recommended daily blood culture collection for adult hematology-oncology patients who experienced persistent fever during neutropenia. In the first part of this study, we sought to characterize the incidence of new pathogen identification during
this historical practice. In August 2021, we implemented a pilot reduction in our non-SCT patients including a change in a population-focused clinical practice guideline with accompanying educational intervention. We additionally provide an analysis of the impact of our practice change on blood culture ordering and clinical outcomes in non-SCT patients.

**METHODS**

**Study Design**

We conducted a retrospective cohort study of adult inpatients with FN at a 671-bed tertiary care hospital (University of Virginia Medical Center, Charlottesville). Patients ≥18 years of age who were admitted to the hematology-oncology service were evaluated for study inclusion by querying the institution’s database between 1 August 2019 and 31 January 2022. Patients who had at least 1 blood culture drawn and 3 or more consecutive calendar days of FN were included. A cohort of all patients/episodes (including SCT) during a 2-year period prior to the intervention (1 August 2019 to 31 July 2021) comprised the historical analysis. For the purposes of the historical cohort, episodes with >48 hours of defervescence prior to recurrence were included as a new episode.

For the comparative pre-/postintervention analysis, only the first episode for each patient during the entire study period was included. Patients with a history of SCT were excluded. Patients were divided into a 2-year preintervention (1 August 2019 to 31 July 2021) and 6-month postintervention (1 August 2021 to 31 January 2022) cohort. The primary outcome was cultures collected per days of FN after day 3 of FN. Secondary outcomes assessed included new-onset bacteremia/fungemia, intensive care unit (ICU) transfer, LOS, in-hospital mortality, and 30-day mortality.

**Data Collection and Definitions**

Baseline and outcomes data were collected retrospectively from the institution’s central data warehouse and verified upon review of the electronic health record. Fever was defined as a single temperature ≥38.0°C (≥100.4°F). Severe neutropenia was defined as an absolute neutrophil count (ANC) <500 cells/µL. Each patient-day where a temperature ≥38°C and ANC <500 cells/µL were recorded was registered as a day of FN. Persistent FN was defined as 3 or more consecutive calendar days of FN. If no blood cultures were collected on day 1 of FN until after the subsequent midnight, the subsequent day was considered day 1 of FN. Additional exceptions are detailed in the Supplementary Methods. Bloodstream infection sources were defined according to the Centers for Disease Control and Prevention criteria [16, 17]. Blood culture results were assessed as a true pathogen versus a likely contaminant using National Health Safety Network (NHSN) criteria for commensal organisms [17] as well as the care team’s decision to treat as a pathogen.

**Standard Practice and Intervention**

The adult hematology-oncology services are staffed by rotating internal medicine residents, hospitalists, and advanced practice providers. During the entire study period, blood cultures were collected at the treating team’s discretion. Microbiologic processing is detailed in the Supplementary Methods. Antimicrobial management was per local guidelines with

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**Figure 1.** Included study participants. Abbreviation: FN, febrile neutropenia.

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Table 1. Baseline Patient/Episode Characteristics During Historical Period

| Characteristic                                      | Episodes (N = 146)* |
|-----------------------------------------------------|---------------------|
| Age, y, median (IQR)                                | 56 (43–65)          |
| Female sex                                          | 61 (42)             |
| Malignancy                                                                 |
| AML                                                  | 109 (75)            |
| Lymphoma                                            | 10 (6.8)            |
| MDS                                                 | 10 (6.8)            |
| ALL                                                 | 9 (6.2)             |
| Other hematological malignancy                      | 5 (3.4)             |
| Multiple myeloma                                    | 2 (1.4)             |
| Solid tumor                                         | 1 (0.7)             |
| Stem cell transplant, type                          |                     |
| Allogeneic                                          | 30 (21)             |
| Autologous                                          | 3 (2.1)             |
| Prior bacteremia/fungemia (same admission)          | 14 (9.6)            |
| At FN onset                                                                 |
| FN present at admission                             | 41 (28)             |
| CVC present                                         | 113 (77)            |
| Antibacterial prophylaxis                            | 42 (29)             |
| Antifungal prophylaxis                               | 98 (67)             |
| Therapeutic antimicrobials                           | 54 (37)             |
| Episode characteristics                              |                     |
| Duration of FN, median (IQR)                        | 4 (3–5)             |
| Index organism (bacteremia/fungemia)                |                     |
| Streptococcus spp                                   | 8 (5.5)             |
| Anaerobe                                            | 6 (4.1)             |
| Enterobacterales spp                                | 5 (3.4)             |
| Staphylococcus aureus                               | 3 (2.1)             |
| Coagulase-negative Staphylococcus                    | 2 (1.4)             |
| Candida spp                                         | 1 (0.7)             |
| Polymicrobial                                       | 3 (2.1)             |
| Index source                                        |                     |
| Gastrointestinal                                    | 13 (54)             |
| Catheter-related                                    | 5 (21)              |
| SSTI                                                | 4 (17)              |
| Respiratory                                         | 1 (4.2)             |
| Urine                                               | 1 (4.2)             |
| Infectious diseases consulted                       | 96 (67)             |

Data are presented as No. (%) unless otherwise indicated.
Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CVC, central venous catheter; FN, febrile neutropenia; IQR, interquartile range; MDS, myelodysplastic syndrome; SSTI, skin and soft tissue infection.

*Statistical tests performed: Wilcoxon rank-sum test, Pearson χ² test, and Fisher exact test.

ultimate prescribing decisions determined by the treating team. Cefepime was the preferred empiric antimicrobial of choice with vancomycin added per IDSA guidelines [6]. Empiric micafungin was typically added after day 4 of persistent fever. Institutional guidelines recommended ciprofloxacin as first-line antibacterial prophylaxis agent post-SCT until count recovery. Posaconazole was the recommended antifungal prophylaxis during induction chemotherapy for AML and post-autologeneic SCT (fluconazole recommended post–autologous SCT). Central venous catheter (CVC) removal and additional source control measures were determined by the treating team.

Prior to August 2021, our patient population focused clinical practice guideline for FN recommended a set of blood cultures from each CVC lumen of each central venous access device and 2 sets of percutaneous cultures at onset of FN, with 1 set of cultures from the central venous access device and 1 set of percutaneous cultures for each subsequent day indefinitely. Following August 2021, the local guideline was updated to recommend against further blood culture collection after day 3 of persistent FN, except in the setting of new hemodynamic instability, prior positive cultures, or as recommended by the infectious diseases consult service. A flow diagram detailing the updated clinical practice guideline is included in the Supplementary Methods. Rotating housestaff were provided education on the updated practice change at service orientation, and unit nursing staff received education in unit huddles and completed a Qualtrics module outlining the updated changes to the FN clinical practice guideline.

Statistical Analysis
Analyses were performed using statistical software R, version 4.1.2 (R Core Team, Vienna, Austria) [18]. For categorical data, Pearson χ² and Fisher exact test were used as appropriate. For continuous data, the Wilcoxon rank-sum test was used. Incidence rates and incidence rate ratios (IRRs) were calculated with the fmsb R package, version 0.7.3 [19]. P values <.05 were considered statistically significant.

RESULTS
Historical Analysis
A total of 740 FN episodes in 316 patients were identified with a total of 146 FN episodes in 108 patients meeting the inclusion criteria of ≥3 days of persistent FN with at least 48 hours of defervescence between episodes (Figure 1). Baseline characteristics during this period are detailed in Table 1: Only 1 of 146 (0.7%) episodes occurred in a patient with a nonhematological malignancy and 33 of 146 (23%) episodes occurred in SCT patients. The remainder of episodes were in patients with hematological malignancy (112/146 [76%]), which was primarily AML (109/146 [75%]). The majority of FN episodes (105/146 [72%]) occurred after admission, with a median duration of 4 days (interquartile range, 3–5 days). Thirteen episodes (9%) occurred at least 48 hours after a prior episode of persistent FN. The number of episodes reaching each consecutive day, proportion of episodes each day with at least 1 blood culture drawn, and culture yield are detailed in Figure 2. On day 1 of FN, 23 of 146 (16%) episodes had index bacteremia/fungemia. Blood cultures were drawn on 374 of 513 (73%) subsequent episode-days (day 2–12) and were negative in 366 of 374 (98%). New organisms were identified after day 3 of FN (days 4 and 5) in 2 episodes, including 1 commensal organism that the treating team considered a pathogen.
Staphylococcus epidermidis) and 1 pathogen (Escherichia coli) that occurred in the setting of new clinical instability; details of all new organisms isolated after day 1 of FN are included in Supplementary Table 1.

Comparative Analysis
Inclusion of only the first episode of persistent FN per patient during the entire time period and exclusion of SCT patients resulted in 83 patients/episodes in the preintervention cohort and 14 patients/episodes in the postintervention cohort (Figure 1) for the comparative analysis. Patient demographics, underlying malignancy, receipt of antecedent prophylactic/therapeutic antimicrobials, and infectious diseases consultation were similar between groups (Table 2). AML was the underlying malignancy in the majority of cases in both groups. Proportion of episode-days with at least 1 blood culture collected and culture yield for both cohorts are detailed in Figure 3 and Supplementary Table 2. Positive day 1 cultures were observed in 15 of 83 (18%) preintervention episodes and 4 of 14 (29%) postintervention episodes ($P = .58$). Regarding the primary outcome (Table 2), in the postintervention period a significant decrease was observed in the incidence rate of total cultures collected after day 3 (1.4 preintervention vs 0.7 postintervention; IRR, 0.47; $P = .03$). There was also an absolute decrease in the number of days after day 3 with at least 1 blood culture collected and total blood cultures collected per admission postintervention, though these did not reach statistical significance. No new pathogens were observed in the postintervention cohort after day 1 of persistent FN. No significant difference in new-onset bacteremia/fungemia, ICU transfer, LOS, or mortality was observed.

DISCUSSION
In this study, we found a very low yield of repeat daily blood cultures after day 1 of persistent FN. Our institution’s historical practice of daily blood cultures with persistent FN allowed us to assess the incidence of new pathogens after the initial day of FN. While day 1 blood cultures were high-yield in both groups during the comparative analysis with a positivity rate of 20% (19/97), after day 1, only 3 new organisms were identified during 339 days when cultures were collected (0.9%) and only 2 new organisms during 145 days of cultures collected after day 3 (1.4%). One of these episodes (E coli) occurred in the setting of hemodynamic change prompting ICU transfer, wherein repeat blood cultures would still be recommended by our updated guideline. The other episode met NHSN criteria for a commensal organism, although the treating team decided to treat as a pathogen resulting in vancomycin administration (coagulase-negative Staphylococcus). Our findings were similar to prior studies in that we observed a very low yield of repeat cultures identifying new bacteremia (12–15). Based on these findings, we would favor a clinically informed approach to
To our knowledge, this is the first study to additionally evaluate an intervention designed to reduce utilization of repeat blood cultures in adult patients with persistent FN. Following

### Table 2. Baseline Patient/Episode Characteristics and Outcomes Pre- and Postintervention

| Characteristic                                              | Preintervention (n = 83 Episodes) | Postintervention (n = 14 Episodes) | P Value* |
|-------------------------------------------------------------|-----------------------------------|-----------------------------------|----------|
| **Age, y, median (IQR)**                                    | 56 (42–66)                        | 51 (44–65)                        | .72      |
| **Female sex**                                              | 35 (42)                           | 8 (57)                            | .30      |
| **Malignancy**                                              |                                   |                                   | .11      |
| AML                                                         | 65 (78)                           | 9 (64)                            |          |
| ALL                                                         | 5 (6)                             | 1 (7)                             |          |
| Lymphoma                                                    | 5 (6)                             | 1 (7)                             |          |
| MDS                                                        | 5 (6)                             | 0 (0)                             |          |
| Other hematological malignancy                              | 2 (2)                             | 1 (7)                             |          |
| Solid tumor                                                 | 1 (1)                             | 2 (14)                            |          |
| Prior bacteremia/fungemia (same admission)                  | 11 (13)                           | 2 (14)                            | >.99     |
| **At FN onset**                                             |                                   |                                   |          |
| FN present at admission                                     | 27 (33)                           | 5 (36)                            | >.99     |
| CVC present                                                 | 66 (80)                           | 10 (71)                           | .49      |
| Antibacterial prophylaxis                                   | 16 (19)                           | 2 (14)                            | >.99     |
| Antifungal prophylaxis                                      | 53 (64)                           | 6 (43)                            | .14      |
| Therapeutic antimicrobials                                  | 31 (37)                           | 3 (21)                            | .37      |
| **Episode characteristics**                                 |                                   |                                   |          |
| Duration of FN, median (IQR)                                | 4 (3–5)                           | 3 (3–4)                           | .25      |
| Index organism (bacteremia/fungemia)                        |                                   |                                   |          |
| Streptococcus spp                                           | 4 (5)                             | 1 (7)                             | .55      |
| Enterobacterales spp                                        | 4 (5)                             | 1 (7)                             | .55      |
| Anaerobe                                                    | 3 (4)                             | 0 (0)                             | >.99     |
| Staphylococcus aureus                                       | 2 (2)                             | 0 (0)                             | >.99     |
| Candida spp                                                 | 1 (1)                             | 1 (7)                             | .27      |
| Coagulase-negative Staphylococcus                           | 0 (0)                             | 1 (7)                             | .14      |
| Polymicrobial                                               | 1 (1)                             | 0 (0)                             | >.99     |
| **Index source**                                            |                                   |                                   | .58      |
| Gastrointestinal                                            | 9 (60)                            | 1 (33)                            |          |
| Catheter-related                                            | 3 (20)                            | 2 (67)                            |          |
| SSTI                                                       | 2 (13)                            | 0 (0)                             |          |
| Urine                                                      | 1 (7)                             | 0 (0)                             |          |
| Infectious diseases consulted                               | 58 (70)                           | 9 (64)                            | .76      |
| **Blood culture collection**                                |                                   |                                   |          |
| Total culture sets collected/days of FN (post–day 3; IR)   | 207/146 (1.4)                     | 8/12 (0.7)                        | .03      |
| Days with cultures collected/days of FN (post–day 3)       | 104/146 (71%)                     | 4/12 (33%)                       | .13      |
| Days with cultures collected/days of FN (all)              | 306/395 (77%)                     | 36/54 (67%)                       | .39      |
| Total culture sets collected/days of FN (all; IR)          | 673/4395 (1.5)                    | 86/54 (1.6)                       | .55      |
| Total culture sets (during admission), median (IQR)        | 13 (8–18)                         | 10 (6–12)                         | .06      |
| **Clinical outcomes**                                       |                                   |                                   |          |
| New-onset bacteremia/fungemia                               | 4 (5)                             | 0 (0)                             | >.99     |
| ICU transfer                                                | 10 (12)                           | 1 (7)                             | >.99     |
| LOS (from start of FN episode), d, median (IQR)            | 16 (11–24)                        | 14 (9–18)                         | .39      |
| In-hospital mortality                                       | 1 (1)                             | 0 (0)                             | >.99     |
| 30-d mortality                                              | 3 (4)                             | 0 (0)                             | >.99     |

Data are presented as No. (%) unless otherwise indicated. Bold data indicate statistical significance (P ≤ .05).

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CVC, central venous catheter; FN, febrile neutropenia; ICU, intensive care unit; IQR, interquartile range; IR, incidence rate; LOS, length of stay; MDS, myelodysplastic syndrome; SSTI, skin and soft tissue infection.

*a*Statistical tests performed: Wilcoxon rank-sum test, Pearson $\chi^2$ test, Fisher exact test.

*b*Incidence rate ratio (IRR), 0.47 (95% confidence interval [CI], .23–.95).

*c*IRR, 0.46 (95% CI, 1.7–1.27).

*d*IRR, 0.86 (95% CI, 61–2.21).

*e*IRR, 0.93 (95% CI, 74–1.17).

repeat blood cultures for ongoing FN after day 3 (eg, new hemodynamic instability, end-organ dysfunction, ICU transfer, or mental status change).
a local practice guideline change recommending against repeat blood cultures in clinically stable patients after day 3 of persistent FN, we observed a 53% decrease in cultures collected. Though blood cultures were still obtained after 3 days at the treating team’s discretion, the significant change we observed following this initial intervention suggests that ordering providers were comfortable in adapting their clinical practice.

While we did not observe any associated increase in adverse outcomes after the intervention, a major limitation of this study was the short intervention period with a small number of cases, which limited our ability to detect these outcomes as well as assess the maintenance of the target effect. SCT patients were excluded from the comparative analysis to allow a pilot evaluation of the efficacy and safety of this quality intervention prior to expansion to our SCT population, which has now occurred. We observed a significant decrease in blood culture ordering post–day 3, however, the observed decrease in overall blood culturing did not reach statistical significance. We suspect that future study of this intervention including SCT patients at risk for prolonged neutropenia will further demonstrate

Figure 3. Comparison of pre- and postintervention blood culture collection rates and positivity for new pathogens. Total episodes with persistence of febrile neutropenia are listed for each consecutive day.
this impact. Additional limitations of our study include its retrospective and single-center design. Assessment of additional negative consequences of unnecessary blood culture utilization, both established and theoretical, were not within the scope of this study. While we did not assess overall antimicrobial exposures, unnecessary repeat blood cultures may lead to inappropriate antibiotic use targeting organisms that are likely contaminants. Additionally for this population, the potential for iatrogenic anemia with need for increased blood transfusion would be particularly important to understand. In our cohort, only 8 sets of blood cultures were collected in the postintervention group after day 3 of FN, compared to a projected 17 sets based on the preintervention rate of 1.4 blood cultures collected per day of FN after day 3. Assuming a standard 40 mL of blood per blood culture set would suggest that 360 mL of blood was preserved across these 14 episodes.

In summary, we provide further evidence to support the IDSA guideline recommendation to limit repeat blood culture collection for hematologic-oncology patients with persistent FN without new clinical change. Though these patients remain at higher risk for bacteremia, a thorough initial investigation identifies the vast majority of episodes with positive cultures. If blood cultures are negative on day 1, repeat blood cultures should be guided by careful assessment of new clinical signs.

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 copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Patient consent. This study was initially undertaken as a quality improvement intervention and determined to be exempt by the Institutional Review Board (IRB) for Health Sciences Research at the University of Virginia (IRB 23762).

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