*Open Forum Infectious Diseases*

MAJOR ARTICLE

# Variation in Clinical Practice and Attitudes on Antibacterial Management of Fever and Neutropenia in Patients With Hematologic Malignancy: A Survey of Cancer Centers Across the United States

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***Background.*** Contemporary information regarding fever and neutropenia (FN) management, including approaches to antibacterial prophylaxis, empiric therapy, and de-escalation across US cancer centers, is lacking.

***Methods.*** This was a self-administered, electronic, cross-sectional survey of antimicrobial stewardship physicians and pharmacists at US cancer centers. The survey ascertained institutional practices and individual attitudes on FN management in high-risk cancer patients. A 5-point Likert scale assessed individual attitudes.

***Results.*** Providers from 31 of 86 hospitals (36%) responded, and FN management guidelines existed in most (29/31, 94%) hospitals. Antibacterial prophylaxis was recommended in 27/31 (87%) hospitals, with levofloxacin as the preferred agent (23/27, 85%). Cefepime was the most recommended agent for empiric FN treatment (26/29, 90%). Most institutional guidelines (26/29, 90%) recommended against routine addition of empiric gram-positive agents except for specific scenarios. Eighteen of 29 (62%) hospitals explicitly provided guidance on de-escalation of empiric, systemic antibacterial therapy; however, timing of de-escalation was variable according to clinical scenario. Among 34 individual respondents, a majority agreed with use of antibiotic prophylaxis in high-risk patients (25, 74%). Interestingly, only 10 (29%) respondents indicated agreement with the statement that benefits of antibiotic prophylaxis outweigh potential harms.

***Conclusion.*** Most US cancer centers surveyed had institutional FN management guidelines. Antibiotic de-escalation guidance was lacking in nearly 40% of centers, with heterogeneity in approaches when recommendations existed. Further research is needed to inform FN guidelines on antibacterial prophylaxis and therapy de-escalation.

**Keywords.** bacteria; fever; infection; neutropenia; prophylaxis; stewardship; survey.

Bacterial infections following intensive chemotherapy cause significant morbidity and mortality among patients treated for hematologic malignancy [1, 2]. Risk of infection is directly related to the level of circulating granulocytes, placing patients with prolonged and severe neutropenia at highest risk [3, 4]. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recommend that antimicrobial stewardship programs implement facility-specific guidelines for management of fever and neutropenia (FN), as such approaches optimize antibiotic use and are associated with improved outcomes [5].

National guidelines recommend antibacterial prophylaxis with a fluoroquinolone for patients who are at high risk for FN; however, concerns have emerged regarding this strategy in an era of increasing antibiotic resistance among gram-negative bacteria [6–10]. Additionally, recent studies suggest that earlier de-escalation of empiric antibiotic therapy may be safe and appropriate among patients with FN who have clinically defervesced irrespective of neutrophil count [11–14].

Contemporary information about current and preferred management strategies of FN is lacking. The purpose of this study was to characterize current practices, attitudes, and perceptions on the management of FN among cancer centers in the United States.

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## METHODS

### Patient Consent

This study was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board. It did not include any factors necessitating patient consent.

### Survey Instrument and Sample Population

A 35-question survey (Supplementary Appendix 1) was designed to evaluate and understand institutional guidelines or protocols for the management of FN in high-risk cancer patients, including antibacterial prophylaxis, empiric therapy, and antibiotic de-escalation. The survey also included several questions to characterize use of surveillance testing to identify patients colonized with antibiotic-resistant organisms and surveillance blood cultures. Third, the survey captured attitudes and perceptions about management of FN. Lastly, survey respondents were asked for information regarding their role, years in practice, geographic region, and practice setting.

We identified physicians and pharmacists involved in antimicrobial stewardship at US cancer centers performing >20 adult allogeneic hematopoietic stem cell transplantations (HCTs) annually from the National Marrow Donor Program's "Be the Match" directory [15]. Centers performing <20 HCTs and those devoted solely to pediatric patients were excluded. The survey was distributed via e-mail and was open from November 7, 2019, to December 12, 2019. The potential benefits and risks involved with survey participation were provided in the introductory e-mail that outlined the survey objective, the approach to protecting respondent confidentiality, and the voluntary nature of involvement (Supplementary Appendix 2). Reminder e-mails were sent to nonparticipants every 2 weeks until the survey closed.

### Data Analysis

Surveys missing a response to >2 questions were excluded from analysis. All included surveys were summarized for questions specific to the individual respondent. If >1 individual from the same institution completed the survey, the first survey that was completed from the institution was selected for institution-level analyses. Responses were summarized using descriptive statistics expressed as frequencies and percentages.

## RESULTS

### Survey Population

Responses were received from 45 (30%) of 148 eligible participants. Of the 45 respondents, 11 (24%) did not answer >2 questions and were excluded from analysis. Among the 34 respondents eligible for analysis, there were 12 (35%) infectious diseases physicians, 17 (50%) infectious diseases or antimicrobial stewardship pharmacists, and 5 (15%) reported as "other"

**Table 1. Summary of Baseline Demographics and Characteristics According to Individual Survey Respondents[a]**

| Characteristic | All Respondents (n = 34) | Infectious Diseases Physicians (n = 12) | Infectious Diseases/Antimicrobial Stewardship Pharmacists (n = 17) | Other[b] (n = 5) |
|---|---|---|---|---|
| Total time in practice, No. (%) | | | | |
| <5 y | 9(31) | 2 (17) | 7 (41) | 0 |
| 5–9 y | 8 (28) | 4 (33) | 4 (24) | 0 |
| 10–14 y | 4 (14) | 3 (25) | 1 (6) | 0 |
| >15 y | 8 (28) | 3 (25) | 5 (29) | 0 |
| Unknown[c] | 5 | 0 | 0 | 5 |
| Total time in practice focused on immunocompromised patients, No. (%) | | | | |
| <5 y | 4 (24) | 2 (17) | 0 | 2 (40) |
| 5–9 y | 5 (29) | 4 (33) | 0 | 1 (20) |
| 10–14 y | 4 (24) | 3 (25) | 0 | 1 (20) |
| >15 y | 3 (18) | 2 (17) | 0 | 1 (20) |
| Not focused on immunocompromised patients | 1 (6) | 1 (8) | 0 | 0 (0) |
| Unknown[d] | 17 | 0 | 17 | 0 |
| Distribution of effort, median (IQR), % | | | | |
| Stewardship | 25 (10–40) | 25 (5–30) | 35 (25–50) | 0 (0–20) |
| Direct patient care | 37.5 (25–60) | 50 (30–72.5) | 25 (20–35) | 50 (45–60) |
| Non–patient care | 15 (10–25) | 15 (10–22.5) | 15 (10–25) | 15 (10–20) |
| Research | 10 (5–20) | 2.5 (0–15) | 10 (10–20) | 20 (10–30) |

Abbreviation: IQR, interquartile range.

[a]Percentages computed among nonmissing data; percentages may not add to 100 due to rounding.

[b]Includes 1 hematology oncology physician, 1 hematology oncology clinical pharmacist, 1 leukemia pharmacist, 1 oncology pharmacist, and 1 immunocompromised infectious diseases specialist.

[c]This question was not asked among respondents with roles other than infectious diseases physician or infectious diseases/antimicrobial stewardship pharmacist.

[d]This question was not asked among infectious diseases/antimicrobial stewardship pharmacists.

**Table 2. Baseline Demographics and Characteristics of Included Institutions**[a]

| Characteristic | Institution-Based Response n = 31 |
|---|---|
| National Cancer Institute–designated center, No. (%) | |
| Yes | 25 (81) |
| No | 6 (19) |
| Practice environment, No. (%) | |
| Academic institution | 27 (87) |
| Other[b] | 4 (13) |
| Work environment region, No. (%) | |
| Northeastern US | 8 (26) |
| Midwestern US | 9 (29) |
| Southern US | 9 (29) |
| Western US | 5 (16) |

[a]Percentages computed among nonmissing data; percentages may not add to 100 due to rounding.

[b]Includes nonacademic, cancer center, and other.

(Table 1), representing 31 (36%) of 86 cancer centers surveyed. Respondents reported dedicating a median of 25% of their time to antimicrobial stewardship–related activities. Among 31 participating cancer centers, the majority (n = 27, 87%) classified the practice environment as an academic hospital, with most (n = 25, 81%) being National Cancer Institute–designated centers; centers were similarly represented across the 4 geographic regions of the United States (Table 2).

### Institutional Approaches to Antibacterial Prophylaxis, Empiric Therapy, and Antibiotic De-escalation for FN

Twenty-seven of 31 (87%) cancer centers had institutional guidelines that recommend antibacterial prophylaxis for high-risk cancer patients during the period of chemotherapy-induced neutropenia (Table 3). However, the recommendation varied by hematologic diagnosis, with use most frequently for HCT recipients and those with acute leukemia (Figure 1A). The most common, first-line antibacterial prophylaxis agent recommended was levofloxacin, followed by oral cephalosporins when patients were unable to receive the primary agent regardless of disease state (Figure 1B; Supplementary Figure 1).

Twenty-nine (94%) centers had institutional guidelines for treatment of patients with FN. Only 16 of the 29 (55%) provided guidance on therapy according to potential sources or sites of infection. The recommended initial, empiric, broad-spectrum gram-negative antibacterial agent for patients with FN and an indeterminate source included cefepime (n = 26/29, 90%), followed by piperacillin-tazobactam (n = 19/29, 66%) and meropenem (n = 12/29, 41%). Twenty-three (79%) of 29 institutions indicated >1 empiric antibiotic option.

Institution-specific protocols at 2 of 29 (7%) centers recommend the addition of empiric gram-positive therapy for all patients admitted with FN, while 26 (90%) recommend use only

**Table 3. Institutional Approaches to Antibiotic Prophylaxis and Management of FN**

| Survey Item and Potential Response | n = 31, No. (%) |
|---|---|
| Institutional guidelines recommend antibacterial prophylaxis | 27/31 (87) |
| Institutional guidelines/protocols for management of FN are written | 29/31 (94) |
| Institutional guidelines for FN provide guidance on antibacterial agents according to different potential sources/sites of infection | 16/29 (55) |
| Institutional guidelines for FN recommended as initial empiric therapy | |
| Cefepime | 26/29 (90) |
| Piperacillin-tazobactam | 19/29 (66) |
| Meropenem | 12/29 (41) |
| Ceftazidime | 5/29 (17) |
| Institutional guidelines for FN recommend addition of empiric broad-spectrum gram-positive therapy for selected clinical scenarios | 26/29 (90) |
| Hemodynamic instability or other evidence of severe sepsis | 25/26 (96) |
| Radiographic evidence of pneumonia | 18/26 (69) |
| Presence of a central line | 3/26 (12) |
| Presence of a central line with signs/symptoms of infection at entry site | 26/26 (100) |
| Positive blood culture for gram-positive bacteria before final identification/susceptibility testing | 23/26 (88) |
| Skin or soft tissue infection at any site | 22/26 (85) |
| Prior history of methicillin-resistant *Staphylococcus aureus* infection or colonization | 20/26 (77) |
| Prior history of vancomycin-resistant *Enterococcus* infection or colonization | 6/26 (23) |
| Prior history of penicillin-resistant *Streptococcus* infection or colonization | 9/26 (35) |
| Presence of any signs or symptoms of mucositis | 3/26 (12) |
| Severe mucositis if patient is receiving fluoroquinolone prophylaxis and ceftazidime is given as empiric therapy | 12/26 (46) |
| Institutional guidelines for FN include recommendations for de-escalation of empiric broad-spectrum gram-negative therapy | 18/29 (62) |
| Guidance provided on de-escalation among patients with microbiologically documented infections with susceptibility profiles[a] | 13/17 (76) |
| Guidance provided on patients showing recovery from clinically documented infections but without microbiologic confirmation[a] | 9/17 (53) |
| Guidance provided on patients with fever of unknown origin when no pathogen has been identified[a] | 12/17 (71) |
| Time to de-escalation when no source is identified and the patient is afebrile[b] | |
| When afebrile <24 h | 0/12 (0) |
| When afebrile between 24 and 47 h | 1/12 (8) |
| When afebrile between 48 and 72 h | 7/12 (58) |
| When afebrile >72 h | 3/12 (25) |
| Avoid de-escalation and continue empiric broad-spectrum gram-negative therapy until ANC recovery regardless of apyrexia | 1/12 (8) |
| De-escalation strategy when no source identified and patient becomes afebrile | |
| Antibacterial prophylaxis restarted using originally prescribed agent | 15/18 (83) |
| Antibacterial prophylaxis restarted using a different agent than originally prescribed | 2/18 (11) |
| Antibacterial prophylaxis is not restarted | 1/18 (6) |

Abbreviations: ANC, absolute neutrophil count; FN, fever and neutropenia.

[a]One institution with guidelines for de-escalation of empiric broad-spectrum gram-negative therapy did not respond to questions about clinical scenarios for de-escalation.

[b]Among institutions that have de-escalation strategies for patients with fever of unknown origin when no pathogen has been identified.

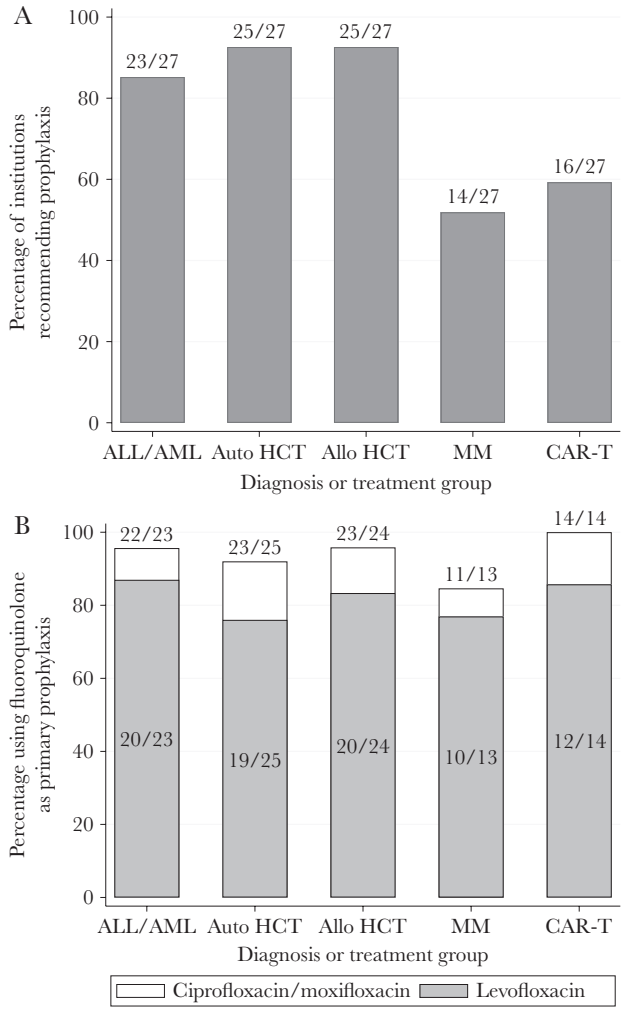


**Figure 1.** Frequency and type of recommended antibacterial prophylaxis according to high-risk hematologic diagnosis or treatment group at surveyed institutions. A, Percentage of institutions with guidelines recommending antibacterial prophylaxis for specific diagnosis or treatment groups among 27 institutions that reported having written guidelines that recommend antibacterial prophylaxis for high-risk cancer patients during chemotherapy-induced neutropenia. Numbers on top of the bars show the numerators and denominators. B, Percentage of institutions recommending fluoroquinolones as the primary agent for antibacterial prophylaxis for specific diagnosis or treatment groups among institutions who reported having guidelines for prophylaxis for the specific group and who responded to the question regarding primary agent. Numbers on top of the bars show the numerators and denominators for fluoroquinolone use. Shaded portions of the bars represent levofloxacin (with numerators and denominators shown within the shaded portion), and unshaded portions represent ciprofloxacin or moxifloxacin. "Other" agents were selected for primary antibacterial prophylaxis without agent identification in ALL/AML (n = 1), auto HCT (n = 2), allo HCT (n = 1), MM (n = 2), and CAR-T (n = 0). Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T-cell therapy; HCT, hematopoietic stem cell transplantation; MM, multiple myeloma.

for specific clinical scenarios; 1 (3%) center did not recommend addition of empiric gram-positive therapy. Among the 26 centers that recommended empiric gram-positive therapy for specific clinical scenarios, the most common indications for use were presence of a central venous catheter in combination with signs and symptoms of infection (n = 26, 100%), sepsis syndrome with hemodynamic instability (n = 25, 96%), positive blood culture for gram-positive bacteria before final identification is available (n = 23, 88%), skin and soft tissue infection (n = 22, 85%), a prior history of infection caused by methicillin-resistant *Staphylococcus aureus* (n = 20, 77%), or radiographically documented pneumonia (n = 18, 69%). Among the 28 centers with protocols that recommend the addition of gram-positive therapy for patients admitted with FN, vancomycin was the most frequently recommended agent (n = 26, 93%).

Among the 29 centers with institutional guidelines for management of FN, 18 (62%) provided some recommendations for de-escalation of broad-spectrum, gram-negative antibacterial therapy (Table 3). Upon de-escalation, 15/18 (83%) centers indicated that their guidelines recommended restarting antibacterial prophylaxis using the originally prescribed prophylactic agent. Of the possible scenarios, the most common clinical scenario for de-escalation was for patients with microbiologically documented infections who had available sensitivities (n = 13/17, 76%). Nine centers (53%) also provided guidance for de-escalation among FN patients showing recovery from clinically documented infections but without any microbiologic findings. Lastly, 12 (71%) centers provided guidance regarding management of clinically stable patients with ongoing neutropenia but without a source of infection. In this scenario, de-escalation was recommended if the patient was afebrile for 24–47 hours by 1 (8%) center, 48–72 hours by 7 (58%) centers, and >72 hours by 3 (25%) centers. One (8%) institutional guideline recommended continuing empiric broad-spectrum gram-negative therapy until neutrophil recovery regardless of apyrexia in patients admitted for FN when an infectious source could not be identified.

#### Institutional Protocols on Surveillance Cultures in Cancer Patients

Fourteen (45%) of 31 centers reported performing surveillance testing to identify patients colonized with multidrug-resistant organisms (MDROs). All 14 centers reported surveillance cultures for MDROs among autologous and allogeneic HCT recipients, 13 (93%) conducted MDRO surveillance for acute leukemia patients, while a smaller proportion reported doing this in multiple myeloma (n = 9, 64%) and CAR T-cell therapy patients (n = 10, 71%). Screening included methicillin-resistant *Staphylococcus aureus* (9/14, 64%), vancomycin-resistant *Enterococcus* (VRE; 12/14, 85%), extended-spectrum beta-lactamase or carbapenemase-producing gram-negative organisms (6/14, 43%), and *Clostridioides difficile* (2/14, 14%). Four of 29 (14%) responding institutions reported having guidelines that recommended routine blood culture surveillance in HCT recipients receiving steroids for graft-vs-host disease.

### Individual Attitudes About Antibacterial Prophylaxis and Management of Neutropenic Fever

Figure 2 displays the level of agreement with individual attitudes and perceptions about management of patients with FN among the 34 respondents. The majority (25/34, 74%) believed that existing published data supported antibacterial prophylaxis for cancer patients at high risk of developing prolonged and severe neutropenia from cytotoxic chemotherapy. Additionally, 25 (74%) respondents reported that they would use antibacterial prophylaxis in this setting. Conversely, only a minority (10/34, 29%) of individuals indicated that the benefits of preventing infections outweighed current risks of drug resistance associated with antibacterial prophylaxis, and 18 (53%) reported that they feel infections are going to occur regardless of antibacterial prophylaxis during the period of neutropenia. Physicians and pharmacists differed in terms of perceptions regarding risks and benefits of antibacterial prophylaxis, with 11/14 (79%) physicians indicating that infections occurred regardless of prophylaxis compared with 7/20 (35%) pharmacists. Additionally, 6/14 (43%) physicians disagreed with the statement that preventing infection outweighs risk of resistance compared with 4/20 (20%) pharmacists (Supplementary Figures 2 and 3).

The majority (26/34, 76%) believed that rapid diagnostics assist with earlier time to antibacterial de-escalation, while 29 (85%) felt that the current evidence supports shorter courses of

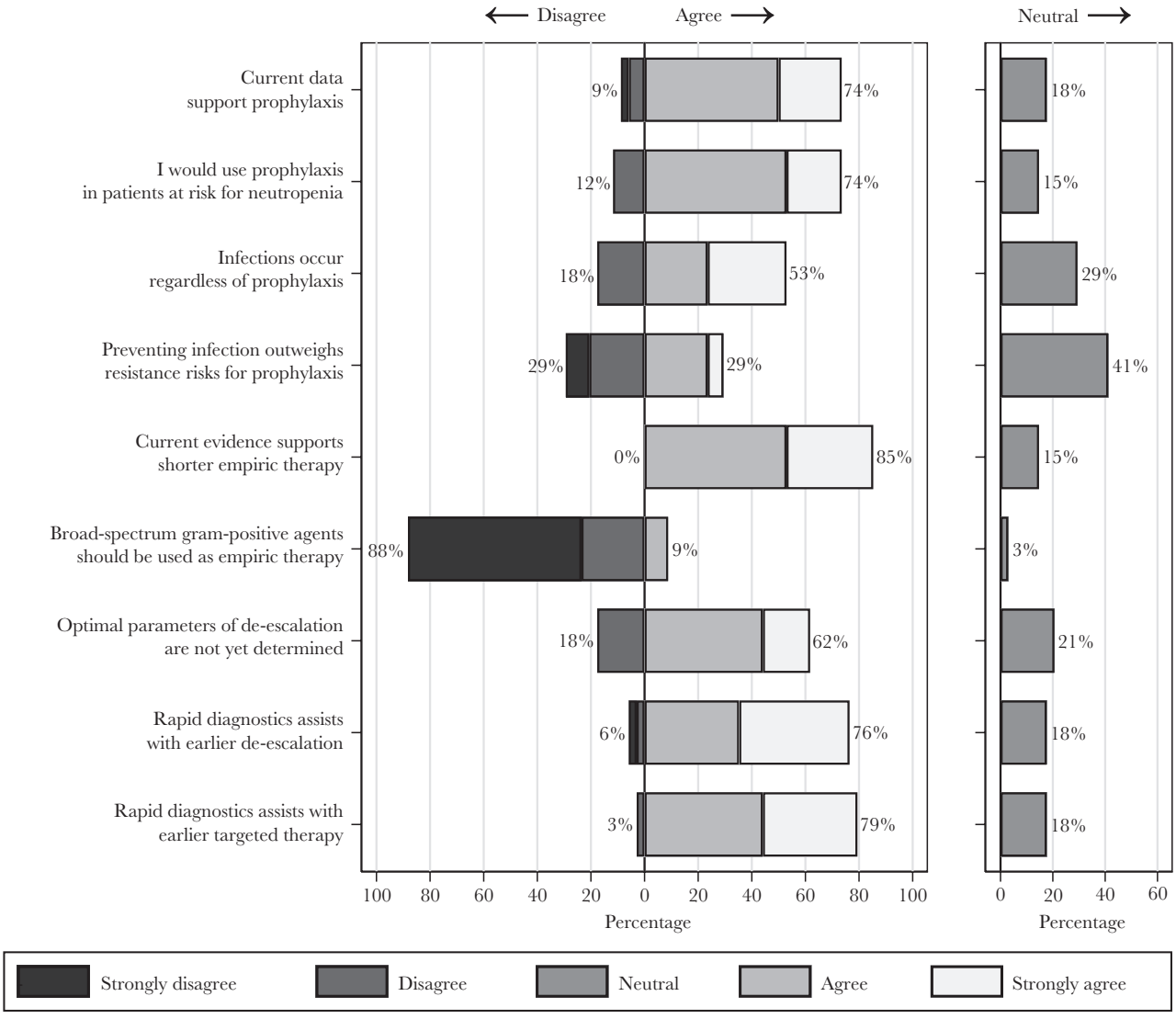


**Figure 2.** Level of agreement with attitudes about supportive literature, practice, and available agents for the management of high-risk cancer patients receiving chemotherapy. Bars shown represent the percentage of 34 respondents who strongly disagreed, disagreed, neither disagreed nor agreed, agreed, or strongly agreed with each statement shown along the y-axis. The percentages shown to the left of the bars in the main plot are the combined percentage of respondents who either disagreed or strongly disagreed, the percentages shown to the right of the bars in the main plots are the combined percentage of respondents who either agreed or strongly agreed, and the percentages shown to the right of the neutral bars are the percentages of respondents who neither agreed nor disagreed.

empiric antibacterial therapy for uncomplicated FN. However, 21 (62%) of 34 respondents believed that the optimal parameters for antibiotic de-escalation have yet to be determined.

## DISCUSSION

This study evaluated contemporary practices and perceptions in FN management among 31 cancer centers across geographically diverse regions in the United States. The majority of centers have institutional guidelines that outline the use of antibacterial prophylaxis in high-risk patients during the period of chemotherapy-induced neutropenia and management of FN. However, nearly 40% of centers lacked guidance on antibiotic de-escalation. Among those centers providing de-escalation guidance, we noted heterogeneity in de-escalation approaches, particularly for patients who defervesce without an identifiable source. Interestingly, although most respondents supported use of antibacterial prophylaxis, a minority indicated that the benefit of preventing infections associated with antibacterial prophylaxis was outweighed by the current risks of drug resistance and that infections during the period of chemotherapy-induced neutropenia would occur regardless of whether antibacterial prophylaxis was prescribed.

Institutional guidelines for FN have been reported to be largely in accordance with guidelines published by the IDSA and the National Comprehensive Cancer Network (NCCN) [7, 16, 17]. A recently published survey of blood and marrow transplantation centers across Europe and Asia also found that 94% of centers had written local guidelines on the management of FN [18]. While we did not request information on guideline adherence, institutions should periodically assess prescriber patterns to ensure appropriate and judicious antimicrobial selection and administration to identify improvement opportunities [19, 20].

Most institutional guidelines recommended antibacterial prophylaxis for patients at high risk of prolonged and severe neutropenia, with levofloxacin being the most commonly recommended agent in accordance with published national and international guidelines [16, 21, 22]. Differences in surveys preclude direct comparison; however, use of antibacterial prophylaxis appears to be higher in the United States than elsewhere, reflecting different approaches in other countries [18]. The European Society of Medical Oncology (ESMO) and Australian guidelines discourage use of fluoroquinolones for prophylaxis due to lack of evidence of mortality benefit and concern regarding antimicrobial resistance [23, 24]. Although 2 prior meta-analyses including studies from 1973 to 2010 found that antibacterial prophylaxis significantly reduced the risk of all-cause mortality, a meta-analysis including studies from 2006 to 2014 did not find any effect of fluoroquinolone prophylaxis on mortality [25–27]. The controversial role of fluoroquinolone prophylaxis has been previously described and is illustrated by the seeming discordance by individual respondents, who generally appeared to support use of prophylaxis but seemed less certain about whether the benefits outweigh risks [28, 29]. A recent study in HCT recipients found that nearly one-third of those colonized with fluoroquinolone-resistant Enterobacterales (FQRE) developed a gram-negative bloodstream infection compared with 1% of those not colonized with FQRE, suggesting that institutions take into consideration the resistance profile of colonizing enteric bacteria [30]. Centers that prescribe antibacterial prophylaxis should conduct regular surveillance for occurrence of breakthrough infections, particularly from multidrug-resistant gram-negative organisms [9, 31]. Increased rates of multidrug-resistant pathogens, in particular *Escherichia coli* and *Pseudomonas aeruginosa,* have been shown to increase hospital length of stay and infection-related mortality in patients with leukemia [31, 32]. Stewardship programs at cancer centers should routinely monitor trends in fluoroquinolone resistance through their annual antibiogram [29, 33].

In accordance with published guidelines, empiric monotherapy for FN with a broad-spectrum antipseudomonal agent was the most common approach. While many centers utilized cefepime as the first-line agent, several institutions reported use of meropenem in selected scenarios. Institutional antibiograms or stratified antibiograms for an oncology ward or cancer patients, if available, should be used when developing local guidelines for empiric antibiotic therapy selection; additionally, history of, or colonization with, multidrug-resistant gram-negatives may also aid decisions about individualized empiric therapy. This could preserve the broadest-spectrum agents such as carbapenems for complex patients.

All but 2 institutions recommended against the routine addition of an empiric gram-positive agent for all patients admitted with FN and favored use in specific scenarios. This is consistent with national guidelines and existing literature, which do not support the routine addition of empiric gram-positive therapy among patients with FN [8, 16, 21]. A Cochrane review found no difference in mortality or treatment failure among those who received empiric gram-positive therapy and a higher rate of adverse events, including rash [34]. Studies also demonstrate no benefit of empiric coverage for VRE among colonized patients [35, 36]. We did not, however, assess whether centers evaluated adherence to guideline recommendations regarding use of empiric gram-positive therapy. This may represent an opportunity for antimicrobial stewardship programs. In a retrospective study of 128 adult cancer patients at a large community teaching hospital, 62% had an inappropriate indication for vancomycin use [37]. Another study of adult patients with FN observed inappropriate empirical vancomycin use in 31% of patients; conversely, vancomycin was not prescribed to 32% of patients with appropriate indications for use [6]. A targeted approach toward vancomycin prescribing in patients for whom there are clear indications for use may minimize toxicity while ensuring treatment among those most likely to benefit.

While all institutional guidelines provided recommendations on the use of empiric antibiotics, an opportunity identified was the development of pathways to assist in antibiotic de-escalation, which was lacking in about 40% of those surveyed. There was heterogeneity in the approach among centers with established de-escalation protocols, including the time window following resolution of fever in which de-escalation occurred and whether neutrophil recovery should be considered. These differences may reflect the variation among national and international guidelines regarding the duration of empiric antibiotic therapy in FN. Clinical practice guidelines by the IDSA recommend empiric broad-spectrum antibiotic therapy until absolute neutrophil count (ANC) recovery (ANC ≥500 cells/ μL) as the preferred approach; however, for patients with resolution of signs and symptoms of infection and in whom an appropriate treatment course has been completed, the guidelines offer an alternative approach with consideration of oral fluoroquinolone prophylaxis until ANC recovery [16]. It should be noted that these guidelines were published before contemporary studies examining the impact of early de-escalation [11, 12, 38]. The European Conference in Leukemia guidelines takes an earlier approach to antibiotic de-escalation by recommending discontinuation of empiric antibiotics after ≥72 hours of intravenous antibiotics in patients who are hemodynamically stable and afebrile for ≥48 hours, regardless of ANC or expected duration of neutropenia [17]. Notably, the 2020 NCCN update offers 3 different options for de-escalation of neutropenic patients with resolution of fever of unknown source: (1) discontinuation of therapy, (2) de-escalation to prophylaxis, or (3) continuation of empiric therapy until ANC recovery [21]. A randomized clinical trial of high-risk patients with hematologic malignancies and FN found that discontinuation of empiric antibiotic therapy after 72 hours of apyrexia and clinical recovery was safe and resulted in less antibiotic exposure compared with an ANC recovery-directed approach [11]. Observational studies have also suggested that earlier discontinuation or de-escalation of antibiotic therapy is safe and reduces broad-spectrum antibiotic exposure [38–40]. However, most were small retrospective studies that differed in methodology, and approaches to de-escalation may not have been powered to detect differences in clinical outcomes. Results from our survey reflect uncertainty in the available evidence, with >60% of individual participants indicating that they feel the optimal parameters for antibiotic de-escalation have yet to be determined. Additional prospective studies are needed to determine the optimal timing and approach to antibiotic de-escalation including use of rapid diagnostics in specific, high-risk cancer patient populations.

Our study had several limitations. The survey population consisted of physicians and pharmacists overseeing adult antimicrobial stewardship at US cancer centers and may not reflect practices for pediatric patients with cancer or centers outside of the United States. Additionally, the response rate was low, and respondents were primarily based at academic medical centers, so our results may not be generalizable to all cancer centers such as those with community-based practices. Further, the registry provided limited hospital characteristics beyond number of transplants performed annually; therefore, it is unknown if there are any differences between programs where our survey was completed and where it was not. However, the practices in smaller centers should be similar as we received responses from centers from geographically diverse regions. Third, the small sample size, although diverse in geography, precluded testing for associations between responses and any respondent characteristics. Furthermore, a limited number of survey questions precluded elaboration on nuances of treatment practices or provider perceptions about FN management. Follow-up surveys are needed to gain further understanding of additional knowledge gaps. Lastly, the survey relied on individual recall of institutional protocols. However, by targeting the survey to those individuals involved in stewardship programs, we included those most likely to be involved with development of FN management pathways, where recall and awareness would be highest.

## CONCLUSIONS

Most US cancer centers surveyed had institutional FN management guidelines in place. Most centers recommend use of antibacterial prophylaxis among high-risk patients during neutropenia and empiric broad-spectrum antibiotic treatment concordant with national guideline recommendations. Opportunities exist at several centers to provide guidance on the approach to antibiotic de-escalation. Future research to inform FN management is needed on infection diagnostics, therapy de-escalation, and to re-evaluate the risk/benefit balance of antibacterial prophylaxis in an era of growing antimicrobial resistance.

### 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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