Title: Prevention and Management of Infectious Complications in Pediatric Patients with Cancer: A Survey Assessment of Current Practices Across Children's Oncology Group Institutions

Short Running Title: Infection Management Practices, a COG Survey

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pbc.31532.

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Data availability statement: Data are available on request.

Word count: Abstract:249 words Main text: 3492 words
Number of Tables: 1, Number of Figures 5, Number of Supplemental Figures 3

Key words: febrile neutropenia, pediatric oncology, fungal prophylaxis, infectious complications, supportive care, Children's Oncology Group

Abbreviations Key

CPGs	Clinical practice guidelines
COG	Children's Oncology Group
FN	febrile neutropenia
CCL	COG Cancer Control and Supportive Care
SCT	stem cell transplant
RI	Responsible Investigators
PI	Site Principal Investigator

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AML	acute myeloid leukemia
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
IV	intravenous
TTA	time-to-antibiotic
CBC/d	complete blood count with differential
CT	computed tomography
DNA	deoxyribonucleic acid
CNS	central nervous system
PJP	*Pneumocystis jirovecii*
CHG	Chlorhexidine gluconate
G-CSF	Granulocyte colony stimulating factor
USNWR	US News and World Report

Abstract:

Introduction: While clinical practice guidelines (CPGs) for pediatric oncology infection prophylaxis and management exist, few data describe actual management occurring at pediatric oncology centers.

Methods: An electronic survey querying infection management practices in non-transplant pediatric oncology patients was iteratively created by the Children's Oncology Group (COG) Cancer Control and Supportive Care (CCL) Infectious Diseases Subcommittee and sent to leaders at all COG institutions, limiting each site to one response to represent their institution.

Results: The response rate was 57% (129/227 institutions). Many sites reported utilizing COG-endorsed CPGs for antibacterial (76%) and antifungal prophylaxis (74%), and fever and neutropenia (FN, 64%). Most institutions reported using antimicrobial prophylaxis for patients with acute myeloid leukemia (AML; 88% antibacterial, 100% antifungal) and relapsed acute lymphoblastic leukemia (ALL; 82% antibacterial, 95% antifungal). Definitions of fever, phagocyte recovery, and antibiotic duration in febrile patients varied. Most institutions administer empiric broad-spectrum antibiotics for non-neutropenic fever, although 14% reported withholding antibiotics based on initial clinical status or risk stratification tools. Most respondents reported (70%) admitting FN patients for at least 48

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hours, however 15% have low-risk FN protocols allowing outpatient management. FN patients remain admitted on antibiotics through count recovery in 50% of institutions, whereas the others employed various early discharge/early antibiotic discontinuation strategies

Conclusions: There is often consistency but also substantial variability in reported antimicrobial prophylaxis strategies and management of patients with fever and represents an opportunity for implementation studies to standardize application of CPG recommendations and randomized trials to advance evidence where knowledge gaps exist.

Introduction:

Survival for pediatric patients with cancer has dramatically improved over the past 50 years, partly due to improvements in the management of infectious complications; however, infections are still a major cause of morbidity and mortality. Clinical practice guidelines (CPGs) endorsed by the Children's Oncology Group (COG) have systematically analyzed existing data to provide recommendations for management of febrile neutropenia (FN) and antimicrobial prophylaxis in pediatric patients with cancer[1-4]. Unfortunately, providers routinely encounter clinical decisions related to infectious complications for which CPGs are unavailable or based on limited evidence. In the absence of more rigorous data, clinical management decisions related to infectious complications are often based on retrospective studies, provider experience, or historical practice.

To assess how pediatric oncologists diagnose and prevent infectious complications of cancer therapy at centers across the United States, Canada, Australia, and New Zealand, the Infectious Disease Subcommittee of the COG Cancer Control and Supportive Care (CCL) Committee conducted a survey of current infection management practices at COG institutions. Our primary objective was to describe the current management practices relating

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to antimicrobial prophylaxis, fever management, and other infection-related practices in non-transplant pediatric oncology patients at an institutional level to identify current practices across institutions to identify areas of consistency and variation to guide future efforts for standardizing practices and informing research studies to fill knowledge gaps.

Materials and methods

An initial set of survey questions were developed in Research Electronic Data Capture (REDCap) by A.E, L.R.S., and D.H. and reviewed and edited by B.F. and C.D. The questions were distributed to the COG CCL Infectious Diseases Subcommittee for review and feedback, which was discussed during two separate meetings to finalize the content. (Complete survey in Data Supplement). Survey questions excluded stem cell transplant (SCT) and cell therapy patients. The Vanderbilt Institutional Review Board determined this survey was exempt. The survey was approved by COG leadership for distribution and sent to the COG CCL Responsible Investigators (RIs), if available, or if not available to the COG Site Principal Investigator (PI) at all 227 COG institutions on 1/29/2024. It was stated to forward the survey to someone else at the institution if the respondent was not familiar with their institution's routine practices. Weekly reminders were sent to non-responders for four weeks. Respondent's answers were assumed to represent the common management at their institution. Responses were analyzed using SPSS version 29 statistical software. Institution size was estimated by the number of new oncologic diagnoses per year and number of oncology attendings rotating through the inpatient service. Percentages reported were calculated based on the total number of survey responses unless noted otherwise due to missing responses. Cancers that have a high-risk for infection were defined as acute myeloid leukemia (AML) or relapsed acute lymphoblastic leukemia (ALL) during intensive phases.

Results

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The response rate was 56.8% (129/227 institutions) with one survey filled out per center with no duplicates. There was a relatively even distribution of institution size, estimated by the number of new oncologic diagnoses per year per institution (10-50: 30.2%, n=39; 51-100: 26.4%; n=34; 101-200: 27.1%, n=35; >200: 14.7%, n=19; unknown: 1.6%, n=2); and the number of oncology attendings that rotate through the inpatient oncology service (0-10: 69.0%, n=89; 11-20: 20.9%, n=27; 21-30: 3.1%, n=4; >30: 5.5%, n=7; unknown: 1.6%, n=2). Nearly all institutions (92.2%, n=118/128) reported awareness of established COG-endorsed supportive care CPGs[1-4]. The CPGs most reported to be actively followed by institutions were for antibacterial prophylaxis (76.0%, n=98), antifungal prophylaxis (73.6%, n=95), and fever and neutropenia management (FN; 64.3%, n=83). The *Clostridiodes difficile* CPG was the least frequently utilized (28.8%, n=37), and 18 institutions (14.0%) reported they do not use any of the infection-related COG CPGs[1-4].

Approach to fever

Institutional definitions of fever, severe neutropenia (absolute neutrophil count [ANC] threshold that defines FN), and parameters for bone marrow cell count recovery utilized to discontinue empiric intravenous (IV) antibiotics after FN are outlined in **Figure 1.** Most institutions define fever as a temperature of ≥38.0°C sustained for ≥1 hour or a single temperature of ≥38.3°C (78.3%, n=101) and most institutions (87.6%, n=113) utilize an ANC cutoff of <500 cells/μL for defining severe neutropenia. Definitions of bone marrow count recovery are much more variable (**Figure 1**). For well-appearing patients with FN most institutions reported they use some specific strategies to meet a 60-minute time-to-antibiotic (TTA) metric, including empiric ceftriaxone (47.3%, n=61) or anti-pseudomonal antibiotic administration (61.2%, n=79) prior to knowledge of complete blood count with differential (CBC/d) results. A minority of institutions (7.0%, n=9) give empiric antibiotics prior to blood cultures being obtained if they are not obtained within 60 minutes, and 4 institutions (3.1%)

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report administering intramuscular (IM) antibiotics if IV access is not obtained within 60 minutes. Fourteen institutions (10.9%) do not utilize any particular practice.

Fever and neutropenia (FN) initial testing

Institutional FN management practices vary. There were 46 institutions (35.7%) that reported using a specific FN risk-stratification tool, 8 of which utilize established tools like those highlighted in guidelines by the International Pediatric Fever and Neutropenia Guideline Panel[5]. Initial routine evaluations obtained for well-appearing FN patients without a focal source of infection are shown in **Table 1.** Nearly all institutions reported that they obtain a CBC/d and central line blood cultures, whereas peripheral blood cultures are only obtained routinely at 16 institutions (12.4%). Serum biomarkers such as lactate, procalcitonin, and c-reactive protein are obtained at 14.7%, 20.2%, and 20.9% of centers, respectively.

Antibiotic administration in FN

As shown in **Figure 2**, the most common empiric antibiotic given for routine, well appearing FN patients is cefepime (82.2%, n=106). For FN patients who are critically ill on presentation, cefepime (69.8%, n=90) and vancomycin (89.1%, n=115) are the antibiotic agents most frequently administered. Alternatively, some institutions employ empirical coverage with meropenem (25.6%, n=33), piperacillin-tazobactam (9.3%, n=12), or an adjunctive aminoglycoside such as gentamicin in addition to cefepime (24.0%, n=31) in critically ill patients.

Respondents were asked to identify clinical scenarios that would prompt broadening of antibiotic coverage in FN patients at their institution (**Figure 3)**. The most common reason for the addition of vancomycin is for severe ill appearance. Sites reported adding empiric coverage for anaerobic organisms in the setting of significant abdominal pain or concern for neutropenic enterocolitis (93%, n=120), peri-rectal pain (74.4%, n=96), cellulitis (14.7%, n=19), and patient severe ill-appearance (50.4%, n=65).

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FN length of stay management

The majority of institutions admit all patients with FN for at least 48 hours (69.0%, n=89), and 21 centers (14.1%) initially admit patients with FN and send some low-risk patients home prior to 48 hours. A subset of institutions (14.8%, n=19) reported having a protocol in place for managing low-risk FN on an outpatient basis and discharge on either IV (n=6) or oral (n=13) antibiotics. As outlined in the flowchart in **Figure 4A**, in patients without high-risk diagnoses for infection initially admitted with FN who are afebrile >24 hours with negative blood cultures >48 hours, 49.6% (n=64) of institutions will continue empiric IV antibiotics until count recovery. Among the 45.7% (n=59) of institutions that will discontinue empiric IV antibiotics after 48 hours of negative blood cultures, 40.7% (n=24) will keep patients admitted for observation for varying durations and 59.3% (n=35) will discharge patients home, frequently on oral antibiotics (74.3%, n=26/35).

As outlined in **Figure 4B**, in patients *with* high-risk diagnoses who have fever during induction therapy who are afebrile >24 hours and have negative blood cultures >48 hours, 26.4% (n=34) of institutions discontinue empiric IV antibiotics before phagocyte recovery, 21.7% (n=28) discontinue IV antibiotics after they've been administered for at least 7 days, and 42.6% (n=55) continue empiric IV antibiotics until count recovery. Other institutions (9.3%, n=12) report provider variability, discontinuing IV antibiotics after they've been administered for a set duration other than 7 days, and/or discontinuing empiric IV antibiotics depending on the timing of fever in relation to cancer diagnosis and onset of chemotherapy. If empiric IV antibiotics are discontinued prior to count recovery in this group, it is more common to de-escalate to antibacterial prophylaxis (32.6%, n=42), rather than observe off antibiotics (11.6%, n=15). Inpatient observation versus discharge practices for these patients vary (**Figure 4B**).

Persistent FN ≥96 hours without a source of infection

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Routine testing performed for persistent FN ≥96 hours without a source of infection is shown in **Table 1.** Radiographic imaging to evaluate for occult infection is common. Computed tomography (CT) chest (93.0%, n=120), abdominal CT (72.1%, n=93), and abdominal ultrasound (20.9%, n=27) are the most common imaging studies obtained. CT sinuses are performed in over half of institutions (57.4%). Laboratory evaluations including serum galactomannan (65.1%, n=84) and β-D-glucan (49.6%, n=64) are commonly obtained, and newer techniques such as plasma cell-free microbial DNA testing are routinely performed at only 16.3% (n=21) of institutions. At 69.5% of institutions (n=89/128), diagnostic testing for invasive fungal disease is performed in any oncology patient with FN ≥96 hours without a source of infection, whereas 30.5% (n=39/128) centers only perform these evaluations in patients meeting specified criteria to be high-risk for invasive fungal disease. Most institutions (82.0%, n=105/128) utilize an empiric approach to antifungal agent initiation in that they perform fungal diagnostic testing and start empiric antifungal therapy regardless of results. Fewer centers (14.8%, n=19/128) utilize a preemptive approach, only initiating antifungal therapy if the diagnostic evaluation is suggestive of an invasive fungal disease.

Non-neutropenic fever

In well-appearing patients with non-neutropenic fever (ANC ≥500 cells/μL), most institutions routinely give empiric IV antibiotics (85.3%, n=110), but a subset of institutions withhold empiric IV antibiotics based on a risk stratification tool (7.0%, n=9) or clinical appearance (7.0%, n=9) with one non-responder. If empiric antibiotics are given in this group, the most common agent is ceftriaxone (86.8%, n=112), although broader agents such as cefepime (7.0%, n=9) or piperacillin-tazobactam (3.1%, n=4) are given at some institutions, and there were 2 (1.6%) unknown responses.

Antibacterial prophylaxis and observation through count recovery:

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As shown in Supplemental **Figure 1**, antibacterial prophylaxis during neutropenia without fever is common in patients with diagnoses that are high-risk for infection including AML (87.6% of institutions, n=113), relapsed ALL (82.2%, n=106), leukemia patients with trisomy 21 (74.4%, n=96), and infant ALL (68.2%, n=88), and some institutions (range 3-17 depending on diagnosis) report that the decision to give antibacterial prophylaxis is provider dependent. There is a split between institutions that do (37.2%, n=48) and do not (38.0%, n=49) administer antibacterial prophylaxis in high-risk ALL during induction, and 11 sites (8.5%) report that the decision is provider dependent. Fluoroquinolones are the most common agents utilized for antibacterial prophylaxis, but a small subset use cefepime.

Patients deemed high-risk for infection, including AML in induction I (94.6%, n=122), AML during other phases (83.7%, 108), infant ALL (86.8%, n=108), leukemia patients with trisomy 21 (79.8%, n=103), and relapsed ALL during intensive phases (70.5%, n=91) are commonly kept inpatient through count recovery. However, some sites (n=4-25, depending on diagnosis) will discharge these patients on prophylactic antibiotics prior to count recovery. Practices vary for infants with central nervous system (CNS) tumors, with 52 centers (40.3%) keeping patients admitted through count recovery, and 55 (42.6%) discharging with (n=15) or without (n=40) prophylactic antibiotics. Detailed results regarding observation through cell count recovery are outlined in **Supplemental Figure 2.**

Antifungal prophylaxis

Antifungal prophylaxis agents utilized for patients with newly diagnosed and relapsed AML and high-risk ALL are outlined in **Figure 5**. Echinocandins are the most frequently utilized in these populations followed by azole agents. Voriconazole was reported as the most common azole agent except in newly diagnosed high-risk ALL, where fluconazole was more common. Among patients with ALL, the most common phase of therapy to include antifungal prophylaxis is induction. If azole prophylaxis is used, 83 institutions (64.3%) reported that

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they hold azole prophylaxis around vincristine administration, 14.7% (n=19) do not hold azoles, and 3.1% (n=4) report other practices such as dose reduction of vincristine or holding the azole only in the setting of neuropathy, and there were 4 unknown responses.

Pneumocystis jirovecii pneumonia (PJP) prophylaxis

Oral sulfamethoxazole-trimethoprim is standard first-line therapy for PJP prophylaxis, however in the event of adverse effects such as delayed phagocyte recovery, a second-line alternative may be given. If oral sulfamethoxazole-trimethoprim is withheld for non-allergy related reasons, IV pentamidine is the most utilized second-line therapy (48.1%, n=62) followed by inhaled pentamidine (31.0%, n=40), and rechallenging with sulfamethoxazole-trimethoprim (22.5%, n=29). Dapsone and atovaquone are rarely used as alternative agents (n=3 institutions each); **Supplemental Figure 3**. Responses varied regarding when providers typically discontinue PJP prophylaxis. Institutions reported that they discontinue PJP prophylaxis 3 months (42.6%, n=55) or 6 months (40.3%, n=52) after completion of chemotherapy, 15 centers (11.6%) reported that this is provider dependent, 6 institutions (4.7%) discontinue prophylaxis based on absolute lymphocyte count, and there was 1 unknown response (<1.0%).

Chlorhexidine gluconate (CHG)

Most institutions reported using topical CHG either in all oncology patients (65.9%, n=85) or a subset of patients (5.6%, n=7), whereas 23 institutions (17.8%) do not use CHG wipes, and 14 respondents (10.9%) were unknown/unsure of CHG bathing practices at their institution. Among the 23 centers that do not use CHG, some (56.5%, n=13) reported that CHG was never utilized at their institution, 6 (26.1%) reported that CHG was used previously, then stopped, and 4 (17.4%) were unsure.

Granulocyte colony stimulating factor (G-CSF) use in hematologic malignancy

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When asked about G-CSF use in patients with hematologic malignancies with persistent FN, many institutions (72.9%, n=94) endorsed occasional G-CSF use in critically ill patients with infection, and less commonly in higher risk patients (e.g. relapsed ALL) with prolonged FN (10.1%, n=13). A few institutions reported that G-CSF is commonly used to expedite count recovery (3.9%, n=5), whereas others reported that they do not use G-CSF in patients with hematologic malignancies (14.0%, n=18), or that there is variability based on provider/clinical scenario (4.7%, n=6), and there was 1 unknown response.

Discussion:

We identified some infection supportive care practices that are similar across 129 COG institutions but also found notable practice variability. Although >90% of responding COG institutions are aware of established COG-endorsed evidence-based CPGs[6] for infection management and report implementing these, practice is often not consistent.

Reported FN management was somewhat variable. Most institutions use the Infectious Diseases Society of America definition of fever and a similar threshold for severe neutropenia[7]. Although approximately 70% of centers admit all FN patients for ≥48 hours, some institutions reported the CPG supported practice of moving toward shorter admissions for low-risk patients or even incorporating low-risk FN protocols that allow for purely outpatient management[3, 8, 9]. Demonstrating the safety and feasibility of these practices is important to allow for other institutions to potentially adopt management styles that allow for better quality of life, are more cost-effective, and result in less hospital time for low-risk patients[10, 11]. Similarly, nearly half of institutions will discontinue empiric IV antibiotics in FN patients who are afebrile >24 hours with negative blood cultures >48 hours and either observe off antibiotics until count recovery or discharge home on oral antibiotics, suggesting antibiotics may not always needed through count recovery[12-16].

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In concordance with CPG guidelines, nearly all centers obtain central line blood cultures in febrile patients[3] however, routine collection of peripheral blood cultures is rare, likely in efforts to minimize needle sticks and patient discomfort. In addition to CBCs, some centers obtain inflammatory markers in routine FN evaluation. Although there are some data regarding use of these in the pediatric oncology population[17-23], additional studies are needed to understand the utility of these lab results. Most institutions utilize a CPG-recommended broad-spectrum empiric antibiotic in FN patients. The COG-endorsed FN CPG strongly recommends against broadening empiric antibiotic coverage based solely on persistent fever, however, 36% of respondents reported adding vancomycin in this clinical situation.

In patients with prolonged FN>96 hours, most centers utilize an empiric approach to antifungal initiation rather than a pre-emptive antifungal approach in high-risk patients and consider withholding empiric antifungal therapy in low-risk patients[3]. In this scenario, most centers obtain lung (strong recommendation) and abdominal imaging (conditional recommendation)[3]. However, guideline inconsistent care was seen in those with persistent neutropenic fever >96 hours as CT sinuses are obtained in >50% of centers despite a conditional recommendation to reserve this for patients with localizing symptoms, and evaluations including serum galactomannan and β-D-glucan are routinely obtained at many institutions despite a conditional recommendation (galactomannan) and strong recommendation (β-D-glucan) against routinely performing these assays for prolonged FN[3, 24].

Antibacterial prophylaxis, usually with a quinolone, is used at most centers in patients with AML and relapsed ALL during intensive phases. This is concordant with a weak CPG recommendation to use prophylaxis in this group driven by results of a COG study demonstrating a reduction in bacterial infections in this population receiving levofloxacin prophylaxis[1, 25-27]. Despite a weak recommendation to not give antibacterial prophylaxis to

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368 those in ALL induction, nearly half the sites report doing this. Although there are published
369 observational data supporting safety and effectiveness of fluoroquinolone prophylaxis for
370 ALL induction[28, 29], further studies are needed to confirm benefit in ALL as fluroquinolone
371 prophylaxis may increase the risk of fluoroquinolone-resistant infections[30 31].
372 In concordance with the COG-endorsed CPG, most centers utilize antifungal prophylaxis for
373 patients at the highest risk for infection, including AML. Echinocandins are the most utilized
374 agents in AML in concordance with published results of the COG ACCL0933 study[2, 32]. Most
375 sites use antifungal prophylaxis in relapsed ALL, which is consistent with the weak
376 recommendation in the COG-endorsed CPG, but 69% give antifungal prophylaxis for newly
377 diagnosed high-risk ALL patients despite a lack of recommendation for antifungal
378 prophylaxis in this population in the CPG [2]. Further studies are needed to determine the
379 optimal strategy for fungal prophylaxis in non-AML leukemia patients[33].
380 Evidence-based practice changes may be difficult to implement when non-evidenced based
381 practices are perceived to be efficacious and assumed to have limited downside, especially
382 when proposed changes involve de-escalation of care that may appear to increase the risk of
383 infectious complications. While this change inertia is understandable there is increasingly
384 robust medical literature to support the safety of many such de-escalations of care[34]. Three
385 specific examples of reported current practices that remain prevalent despite published data
386 supporting a “less is more” approach include ongoing use of CHG wipes, implementing
387 practice measures to meet a time-to-antibiotic metric in well-appearing patients with FN, and
388 utilization of empiric broad-spectrum antibiotics in non-neutropenic fever. Our survey found
389 that >65% of institutions currently use CHG wipes for all oncology patients despite the only
390 randomized placebo-controlled study on the topic demonstrating that routine CHG wipe
391 usage did not decrease bacterial infections in this population[35]. Similarly, the 60-minute
392 (TTA) metric for FN patients that was previously incorporated as a US News and World

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Report (USNWR) quality metric was extrapolated from adult patients with septic shock. Since then, recent retrospective studies have found that a longer TTA is not associated with inferior clinical outcomes in non-ill-appearing pediatric patients with FN and this metric was removed from the USNWR scoring [36, 37]. According to these survey results, these emerging data have not had impact on current practices, as most institutions report still employing at least one measure to try and "beat" the prior 60-minute metric. Lastly, 84% of respondents reported administering empiric antibiotics in non-neutropenic febrile patients despite multiple published reports highlighting the safety of a risk-stratified approach to observation without antibiotics in these patients[38, 39]. These examples in addition to established literature demonstrating a theme of variability in guideline-consistent care[40-43] highlight that real-life practice change lags behind the publication of practice-changing data, thus there is a need for innovative approaches to disseminate and implement evidence based management strategies.

This study has limitations. These results are subject to response bias as only 57% of COG institutions were represented and the responses describe "reported management" which could differ from "actual management" if clinical charts were audited. We attempted to minimize this by designing objective rather than opinion-based questions. Although we tasked the provider with the most knowledge of infectious supportive care practices at each institution with filling out the survey, there may be variability among providers, especially at larger institutions that have several different clinical services. Another limitation, the survey questions did not specifically account for the potential impact of institutional infrastructure and logistical barriers which may preclude the implementation of some management practices. For example, some institutions may not have the infrastructure for the observation and follow-up that are necessary to allow for an outpatient FN protocol or early discharge practices for febrile patients. Lastly, this study only surveyed COG institutions which limits

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the generalizability of results and implications, especially when considering centers in lower and middle income countries.

Conclusions

This survey highlighted practice-variability in many clinical scenarios relating to infectious complications of cancer therapy that pediatric oncologists routinely encounter. While there are areas for improvement, including care that is clearly discordant with established guidelines and opportunities to standardize areas of practice variability and improve implementation strategies[44], there are also exciting emerging practices that may gain momentum and lead to further research and improvements in supportive care practices in the future.

Conflict of Interest statement: DH, CNN, PP, TP, JW (Wilkes), LD, EG, KJ, DW, CE, CA, JT, SA, MB, JB, JH, ZP, TG, JR, JD, AW, RR, DC, CC, AE have no conflicts of interest to report. EO (consulting services: Jazz Pharmaceuticals). LRS (consulting services: Y-mAbs Therapeutics). BTF (research support from Merck and Pfizer; data safety monitoring board for Astellas). JW [Wolf] (Karius Inc [In kind support for investigator-initiated research]; Scynexis Inc [In kind support for investigator-initiated research]; Pfizer inc [support for investigator-initiated research]; Merck inc [Participation in industry-initiated research].

Acknowledgements/Funding Information: National Institute of Health, Grant Numbers: U10CA098543, U10CA180886, The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export

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procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

References:

1. Lehrnbecher T, Fisher BT, Phillips B, et al. Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation. *Clin Infect Dis*. Jun 24 2020;71(1):226-236. doi:10.1093/cid/ciz1082
2. Lehrnbecher T, Fisher BT, Phillips B, et al. Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients. *J Clin Oncol*. Sep 20 2020;38(27):3205-3216. doi:10.1200/JCO.20.00158
3. Lehrnbecher T, Robinson PD, Ammann RA, et al. Guideline for the Management of Fever and Neutropenia in Pediatric Patients With Cancer and Hematopoietic Cell Transplantation Recipients: 2023 Update. *J Clin Oncol*. Mar 20 2023;41(9):1774-1785. doi:10.1200/JCO.22.02224
4. Patel P, Robinson PD, Fisher BT, et al. Guideline for the management of Clostridioides difficile infection in pediatric patients with cancer and hematopoietic cell transplantation recipients: 2024 update. *EClinicalMedicine*. Jun 2024;72:102604. doi:10.1016/j.eclinm.2024.102604
5. Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation

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Recipients: 2017 Update. *J Clin Oncol*. Jun 20 2017;35(18):2082-2094. doi:10.1200/JCO.2016.71.7017

6. Marchak JG, Beauchemin MP, Broglie L, et al. Impact of the Children's Oncology Group's supportive care clinical practice guideline endorsement program: An institutional survey. *Pediatr Blood Cancer*. Oct 2024;71(10):e31178. doi:10.1002/pbc.31178

7. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis*. Mar 15 2002;34(6):730-51. doi:10.1086/339215

8. Bourgeois W, Paolino J, Garland R, et al. Outpatient Management of Fever and Neutropenia in Low-risk Children with Solid Tumors: A Quality Improvement Initiative. *Pediatr Qual Saf*. Sep-Oct 2024;9(5):e771. doi:10.1097/pq9.0000000000000771

9. Jackson TJ, Napper R, Haeusler GM, et al. Can I go home now? The safety and efficacy of a new UK paediatric febrile neutropenia protocol for risk-stratified early discharge on oral antibiotics. *Arch Dis Child*. Mar 2023;108(3):192-197. doi:10.1136/archdischild-2021-323254

10. Morgan JE, Phillips B, Stewart LA, Atkin K. Quest for certainty regarding early discharge in paediatric low-risk febrile neutropenia: a multicentre qualitative focus group discussion study involving patients, parents and healthcare professionals in the UK. *BMJ Open*. May 14 2018;8(5):e020324. doi:10.1136/bmjopen-2017-020324

11. Tew M, De Abreu Lourenco R, Gordon JR, et al. Cost-effectiveness of home-based care of febrile neutropenia in children with cancer. *Pediatr Blood Cancer*. Jul 2022;69(7):e29469. doi:10.1002/pbc.29469

12. Lehrnbecher T, Stanescu A, Kuhl J. Short courses of intravenous empirical antibiotic treatment in selected febrile neutropenic children with cancer. *Infection*. Jan 2002;30(1):17-21. doi:10.1007/s15010-002-2094-1

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Author Manuscript

13. Seneviratne N, Yeomanson D, Phillips R. Short-course antibiotics for chemotherapy-induced febrile neutropaenia: retrospective cohort study. *Arch Dis Child*. Sep 2020;105(9):881-885. doi:10.1136/archdischild-2019-317908

14. Butters C, Thursky K, Hanna DT, et al. Adverse effects of antibiotics in children with cancer: are short-course antibiotics for febrile neutropenia part of the solution? *Expert Rev Anti Infect Ther*. Mar 2023;21(3):267-279. doi:10.1080/14787210.2023.2171987

15. Manji A, Beyene J, Dupuis LL, Phillips R, Lehrnbecher T, Sung L. Outpatient and oral antibiotic management of low-risk febrile neutropenia are effective in children--a systematic review of prospective trials. *Support Care Cancer*. Jun 2012;20(6):1135-45. doi:10.1007/s00520-012-1425-8

16. Peters S, Adler M, Rossoff J. Outcomes of Children Discharged Prior to Absolute Neutrophil Count Recovery After Admission for Febrile Neutropenia. *J Pediatr Hematol Oncol*. Nov 1 2023;45(8):e948-e952. doi:10.1097/MPH.0000000000002757

17. Slatnick LR, Miller K, Scott HF, et al. Serum lactate is associated with increased illness severity in immunocompromised pediatric hematology oncology patients presenting to the emergency department with fever. *Front Oncol*. 2022;12:990279. doi:10.3389/fonc.2022.990279

18. Miedema KG, de Bont ES, Elferink RF, et al. The diagnostic value of CRP, IL-8, PCT, and sTREM-1 in the detection of bacterial infections in pediatric oncology patients with febrile neutropenia. *Support Care Cancer*. Oct 2011;19(10):1593-600. doi:10.1007/s00520-010-0987-6

19. Santolaya ME, Alvarez AM, Becker A, et al. Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia, and fever. *J Clin Oncol*. Jul 15 2001;19(14):3415-21. doi:10.1200/JCO.2001.19.14.3415

Author Manuscript

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20. Santolaya ME, Cofre J, Beresi V. C-reactive protein: a valuable aid for the management of febrile children with cancer and neutropenia. *Clin Infect Dis*. Apr 1994;18(4):589-95. doi:10.1093/clinids/18.4.589

21. Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K. The role of procalcitonin in febrile neutropenic patients: review of the literature. *Infection*. Oct 2008;36(5):396-407. doi:10.1007/s15010-008-7374-y

22. Phillips RS, Wade R, Lehrnbecher T, Stewart LA, Sutton AJ. Systematic review and meta-analysis of the value of initial biomarkers in predicting adverse outcome in febrile neutropenic episodes in children and young people with cancer. *BMC Med*. Jan 18 2012;10:6. doi:10.1186/1741-7015-10-6

23. Doerflinger M, Haeusler GM, Li-Wai-Suen CSN, et al. Procalcitonin and Interleukin-10 May Assist in Early Prediction of Bacteraemia in Children With Cancer and Febrile Neutropenia. *Front Immunol*. 2021;12:641879. doi:10.3389/fimmu.2021.641879

24. Whitehurst DA, Friedman DL, Zhao Z, et al. A comprehensive assessment of the prolonged febrile neutropenia evaluation in pediatric oncology patients. *Pediatr Blood Cancer*. Mar 2024;71(3):e30818. doi:10.1002/pbc.30818

25. Alexander S, Fisher BT, Gaur AH, et al. Effect of Levofloxacin Prophylaxis on Bacteremia in Children With Acute Leukemia or Undergoing Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial. *JAMA*. Sep 11 2018;320(10):995-1004. doi:10.1001/jama.2018.12512

26. Dufrayer MC, Rechenmacher C, Meneses CF, et al. Safety of levofloxacin as an antibiotic prophylaxis in the induction phase of children newly diagnosed with acute lymphoblastic leukemia: an interim analysis of a randomized, open-label trial in Brazil. *Braz J Infect Dis*. Mar-Apr 2023;27(2):102745. doi:10.1016/j.bjid.2023.102745

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Author Manuscript

27. Van Weelderen RE, Klein K, Goemans BF, Tissing WJE, Wolfs TFW, Kaspers GJL. Effect of Antibacterial Prophylaxis on Febrile Neutropenic Episodes and Bacterial Bloodstream Infections in Dutch Pediatric Patients with Acute Myeloid Leukemia: A Two-Center Retrospective Study. *Cancers (Basel)*. Jun 28 2022;14(13)doi:10.3390/cancers14133172

28. Wolf J, Tang L, Flynn PM, et al. Levofloxacin Prophylaxis During Induction Therapy for Pediatric Acute Lymphoblastic Leukemia. *Clin Infect Dis*. Nov 13 2017;65(11):1790-1798. doi:10.1093/cid/cix644

29. Yang M, Lu X, Xin L, et al. Comparative effectiveness and safety of antibiotic prophylaxis during induction chemotherapy in children with acute leukaemia: a systematic review and meta-analysis. *J Hosp Infect*. Jun 2023;136:20-29. doi:10.1016/j.jhin.2023.03.003

30. Koo J, Hord J, Gilliam C, et al. Levofloxacin prophylaxis in pediatric oncology and hematopoietic stem cell transplantation: a literature review. *Pediatr Hematol Oncol*. Sep 2024;41(6):432-448. doi:10.1080/08880018.2024.2353888

31. Margolis EB, Hakim H, Dallas RH, et al. Antibiotic prophylaxis and the gastrointestinal resistome in paediatric patients with acute lymphoblastic leukaemia: a cohort study with metagenomic sequencing analysis. *Lancet Microbe*. Apr 2021;2(4):e159-e167. doi:10.1016/s2666-5247(20)30202-0

32. Fisher BT, Zaoutis T, Dvorak CC, et al. Effect of Caspofungin vs Fluconazole Prophylaxis on Invasive Fungal Disease Among Children and Young Adults With Acute Myeloid Leukemia: A Randomized Clinical Trial. *JAMA*. Nov 5 2019;322(17):1673-1681. doi:10.1001/jama.2019.15702

33. Yeoh DK, Haeusler GM, McMullan BJ, et al. Antifungal use in children with acute leukaemia: state of current evidence and directions for future research. *J Antimicrob Chemother*. May 29 2022;77(6):1508-1524. doi:10.1093/jac/dkac060

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Author Manuscript

34. Wattier RL, Esbenshade AJ. From "More is Better" to "Less is More": A Commentary on Antimicrobial Use in Pediatric Oncology. *J Pediatric Infect Dis Soc*. May 30 2022;11(5):229-238. doi:10.1093/jpids/piab111

35. Zerr DM, Milstone AM, Dvorak CC, et al. Chlorhexidine gluconate bathing in children with cancer or those undergoing hematopoietic stem cell transplantation: A double-blinded randomized controlled trial from the Children's Oncology Group. *Cancer*. Jan 1 2021;127(1):56-66. doi:10.1002/cncr.33271

36. Koenig C, Kuehni CE, Bodmer N, et al. Time to antibiotics is unrelated to outcome in pediatric patients with fever in neutropenia presenting without severe disease during chemotherapy for cancer. *Sci Rep*. Aug 18 2022;12(1):14028. doi:10.1038/s41598-022-18168-x

37. De Castro GC, Slatnick LR, Shannon M, et al. Impact of Time-to-Antibiotic Delivery in Pediatric Patients With Cancer Presenting With Febrile Neutropenia. *JCO Oncol Pract*. Feb 2024;20(2):228-238. doi:10.1200/OP.23.00583

38. Esbenshade AJ, Zhao Z, Baird A, et al. Prospective Implementation of a Risk Prediction Model for Bloodstream Infection Safely Reduces Antibiotic Usage in Febrile Pediatric Cancer Patients Without Severe Neutropenia. *J Clin Oncol*. Sep 20 2020;38(27):3150-3160. doi:10.1200/JCO.20.00591

39. Zhao Z, Patel PA, Slatnick L, et al. Prospective External Validation of the Esbenshade Vanderbilt Models Accurately Predicts Bloodstream Infection Risk in Febrile Non-Neutropenic Children With Cancer. *J Clin Oncol*. Mar 1 2024;42(7):832-841. doi:10.1200/JCO.23.01814

40. Dupuis LL, Fisher BT, Sugalski AJ, et al. Clinical practice guideline-inconsistent management of fever and neutropenia in pediatric oncology: A Children's Oncology Group study. *Pediatr Blood Cancer*. Apr 2024;71(4):e30880. doi:10.1002/pbc.30880

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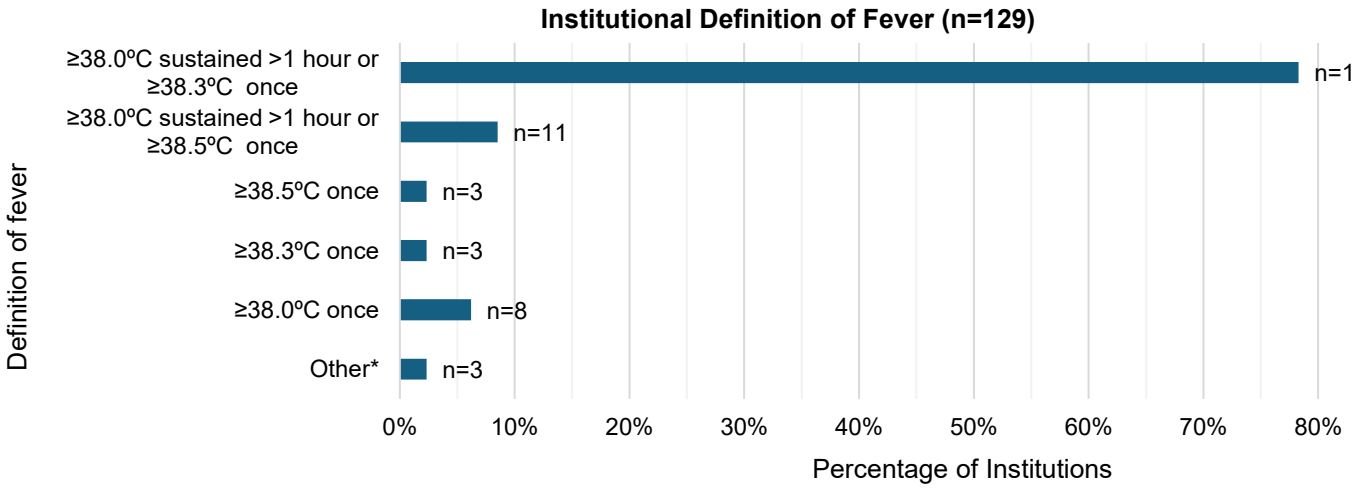
41. Haeusler GM, Slavin MA, Bryant PA, Babl FE, Mechinaud F, Thursky KA. Management of fever and neutropenia in children with cancer: A survey of Australian and New Zealand practice. *J Paediatr Child Health*. Jul 2018;54(7):761-769. doi:10.1111/jpc.13899

42. Wright JD, Neugut AI, Ananth CV, et al. Deviations from guideline-based therapy for febrile neutropenia in cancer patients and their effect on outcomes. *JAMA Intern Med*. Apr 08 2013;173(7):559-68. doi:10.1001/jamainternmed.2013.2921

43. Papan C, Reifenrath K, Last K, et al. Antimicrobial use in pediatric oncology and hematology in Germany and Austria, 2020/2021: a cross-sectional, multi-center point-prevalence study with a multi-step qualitative adjudication process. *Lancet Reg Health Eur*. May 2023;28:100599. doi:10.1016/j.lanepe.2023.100599

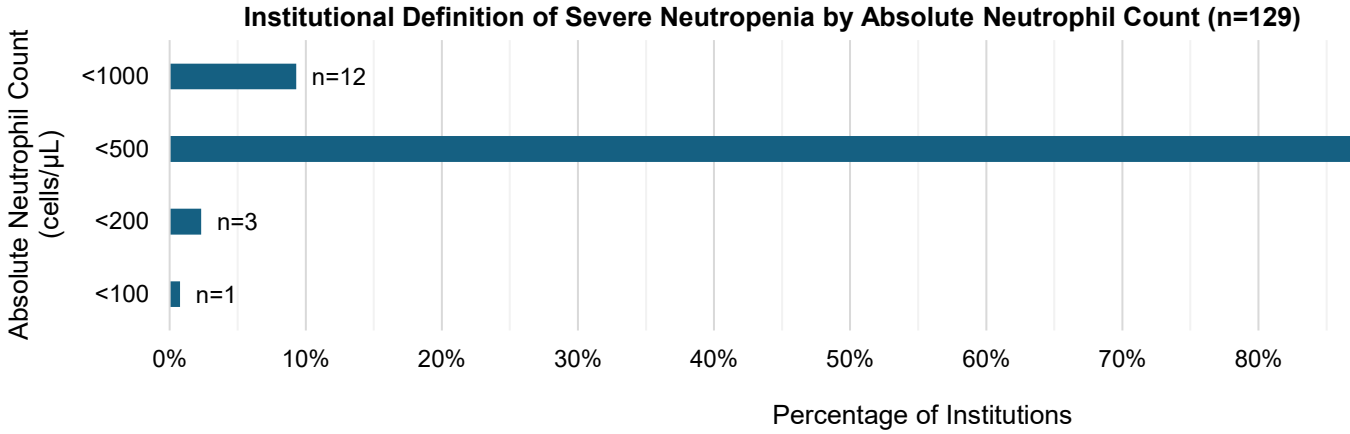
44. Nathan N, Powell BJ, Shelton RC, et al. Do the Expert Recommendations for Implementing Change (ERIC) strategies adequately address sustainment? *Front Health Serv*. 2022;2:905909. doi:10.3389/frhs.2022.905909

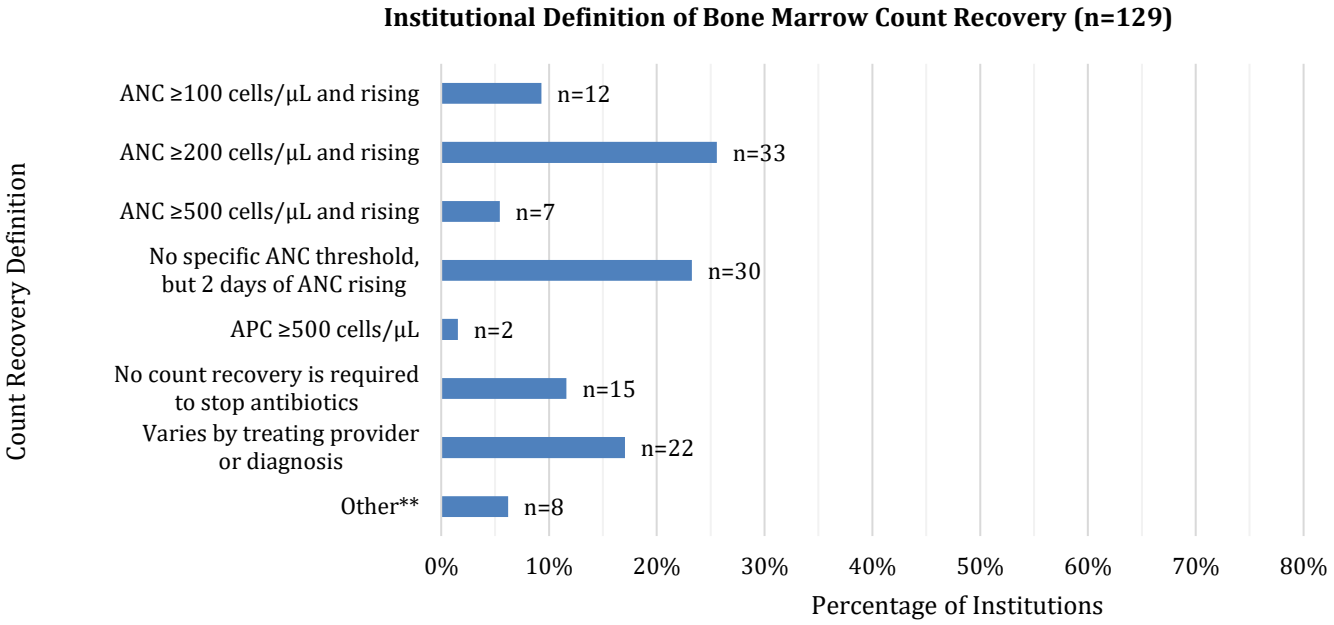
Figure 1: Institutional Definitions of Fever, Severe Neutropenia, and Bone Marrow Count Recovery



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Abbreviations: ANC=Absolute neutrophil count; APC=Absolute phagocyte count in cells/μL=[total white blood cell count (10^3 cells/μL bands + % monocytes]; AMC = Absolute monocyte count

*Other definitions of fever: Varies based on outpatient (≥38.3ºC) or inpatient (≥38.3ºC sustained or ≥38.5ºC once) setting (n=1); ≥37.5 axillary sustained or ≥38.3ºC once)

**Other count recovery definitions: Varying combinations of ANC, APC,and/or AMC (n=7); ANC≥250 and rising (n=1)

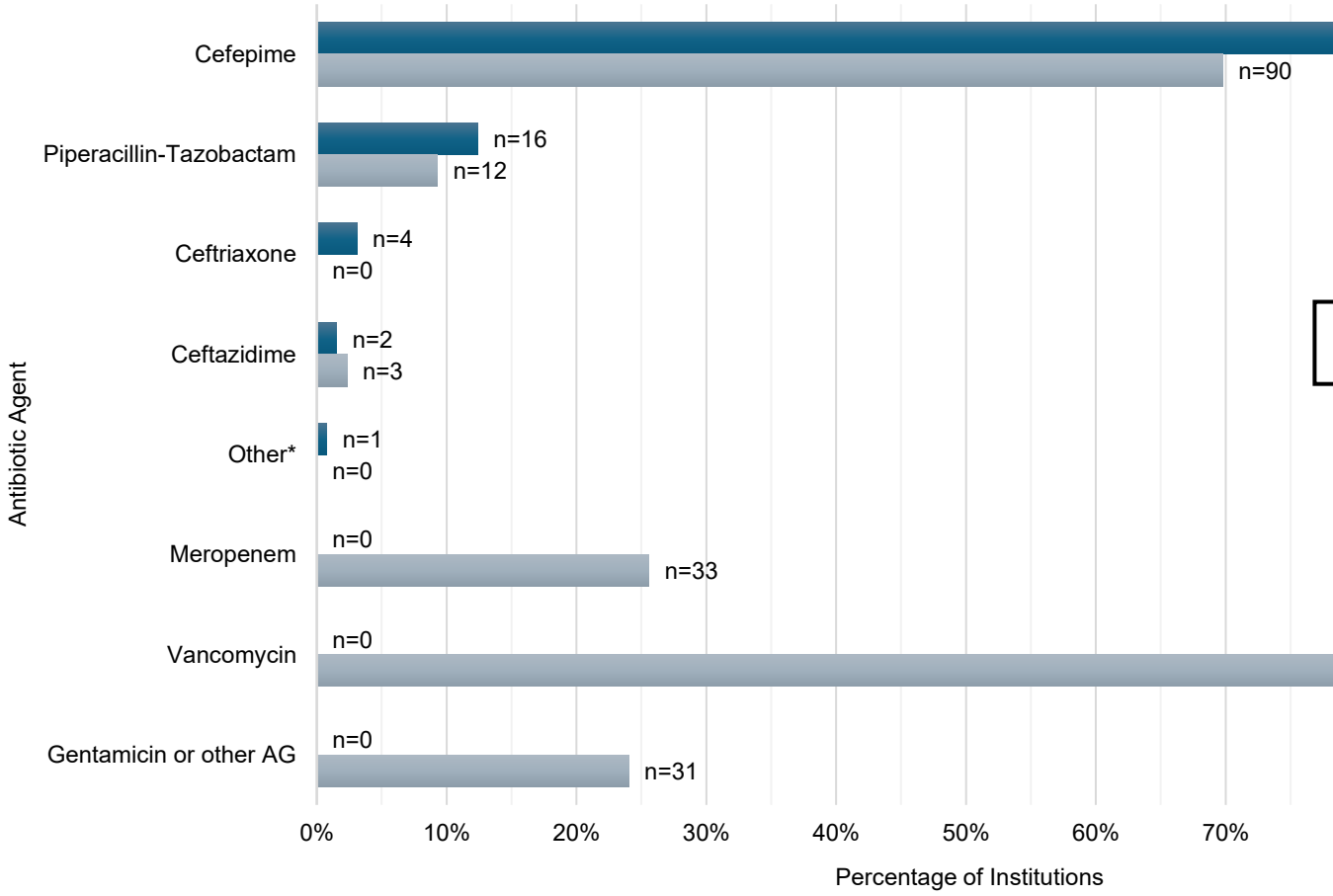
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Figure 2: Empiric Antibiotic Choices for Routine FN Patients and Critically Ill-Appearing FN Pat

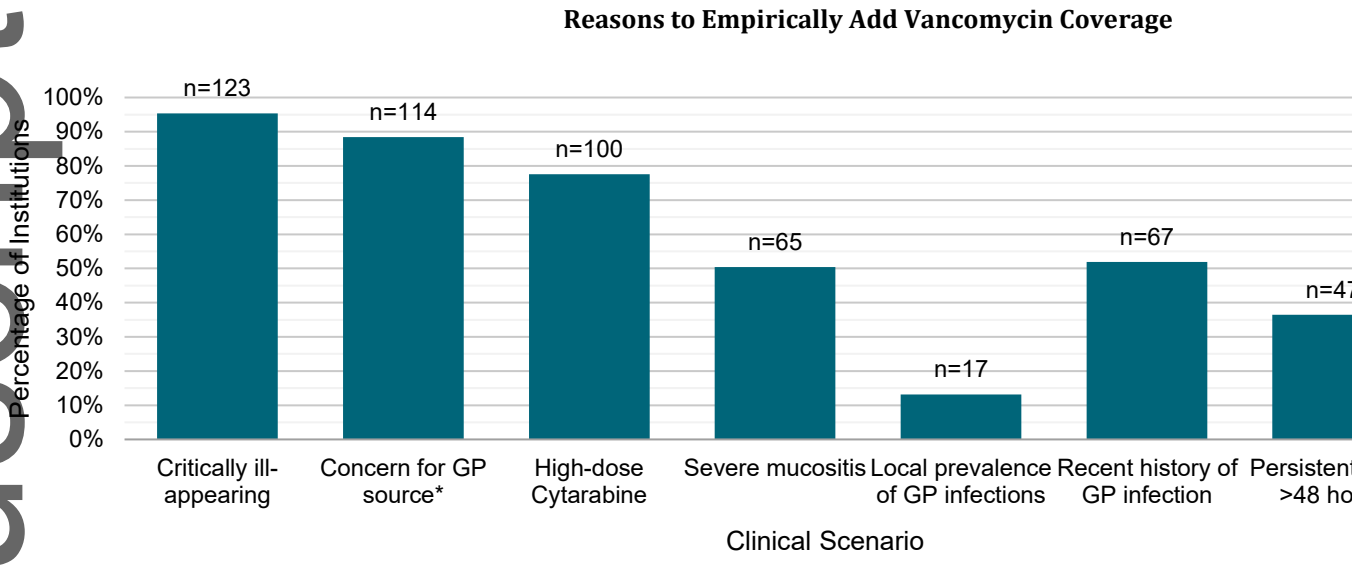


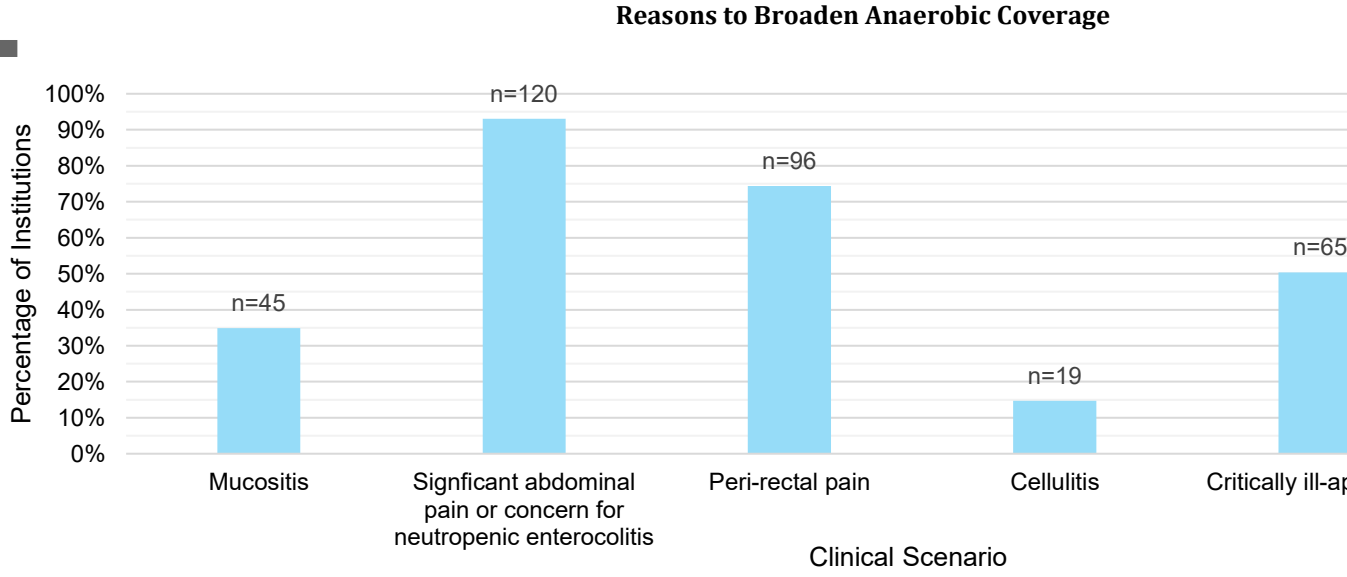
Abbreviations: FN=Fever and neutropenia; AG=Aminoglycoside antibiotic
*Other: Provider/situation dependent (n=1)

Figure 3: Reasons to Expand Antibiotic Coverage in FN Patients (n=129)

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Abbreviations: FN=Fever and neutropenia; GP=Gram positive

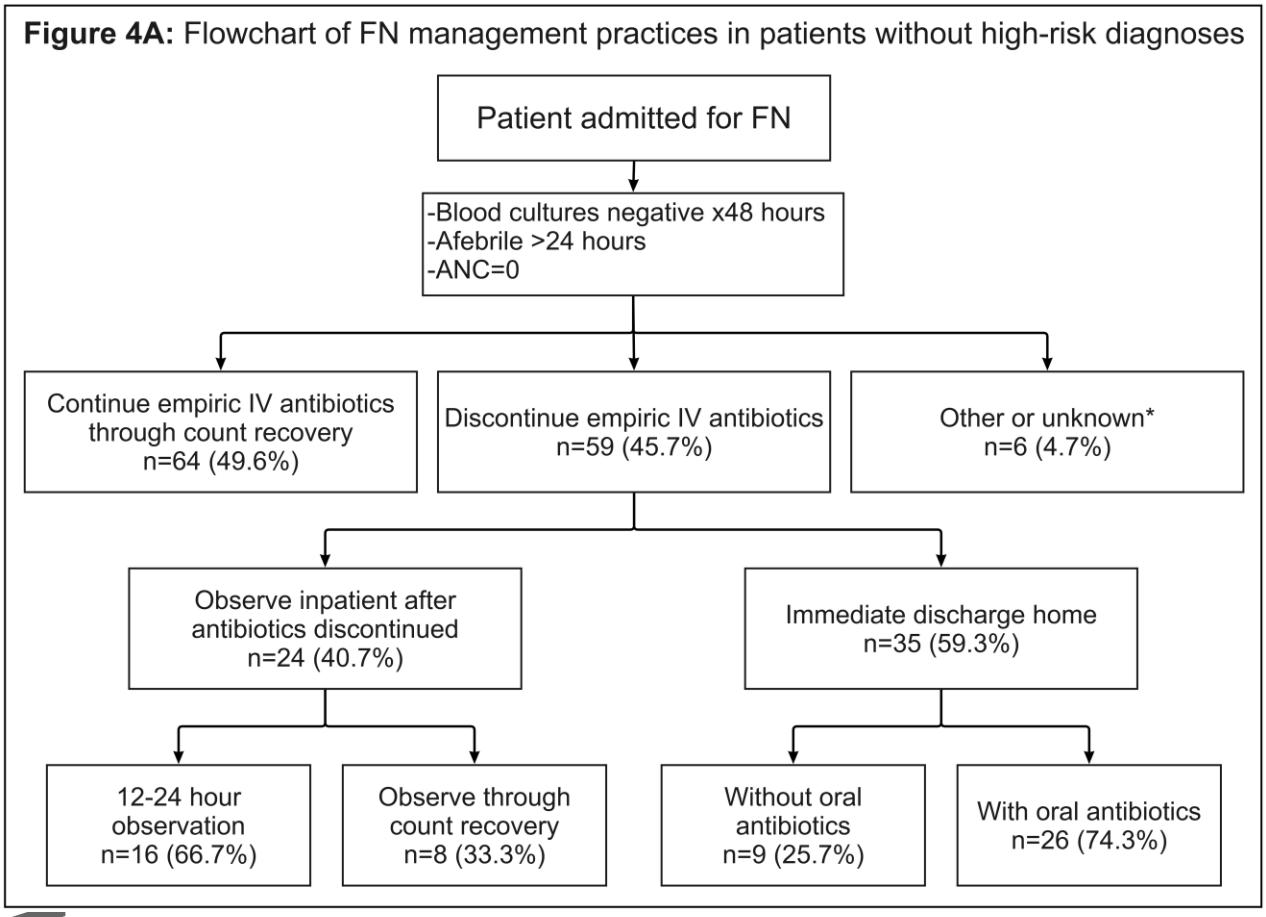
*Other reasons to add vancomycin: Concern for central nervous system infection, indwelling device such as ventriculoperitoneal shunt, MRSA colonization, AML diagnosis, added for all high-risk patients

Figure 4: Flowchart of FN Management Practices in Patients without Diagnoses that are High-Risk for Infection (4A) and Patients with Diagnoses that are High-Risk for Infection with Fever during Induction

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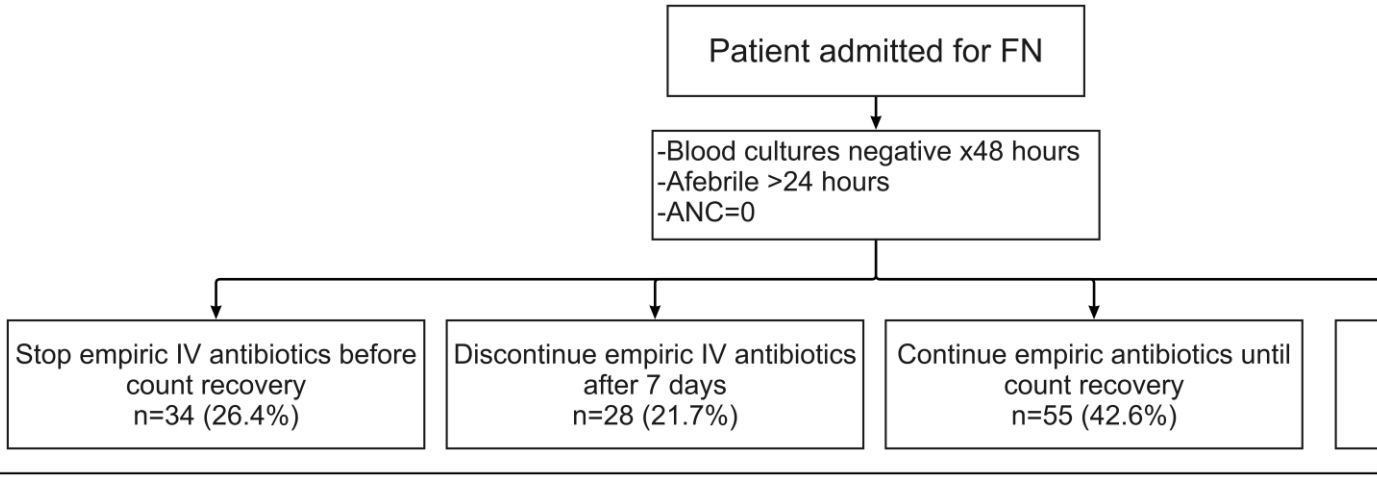
Figure 4A: Flowchart of FN management practices in patients without high-risk diagnoses



Abbreviations: FN=Fever and neutropenia; ANC=Absolute neutrophil count; IV=Intravenous

*Other practices include use of a risk stratification tool (n=1), continuing empiric IV antibiotics for 7 days or until ANC recovery (n=1), and provider dependent management (n=2), unknown (n=2)

Figure 4B: Flowchart of FN management practices in patients with high-risk diagnoses



Abbreviations: FN=Fever and neutropenia, ANC=Absolute neutrophil count; IV=Intravenous

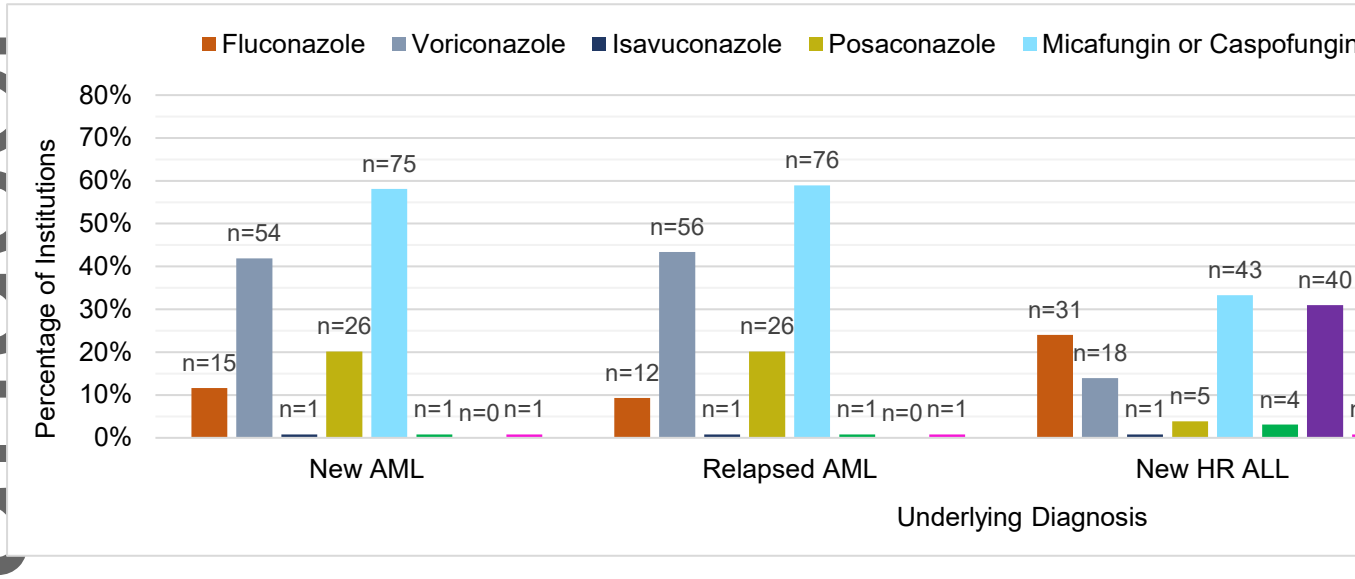
*Other responses: Provider dependent management (n=5), Discontinue empiric antibiotics after a specific timeframe other than 7 days, Depends on timing of fever and/or chemotherapy initiation (n=4)

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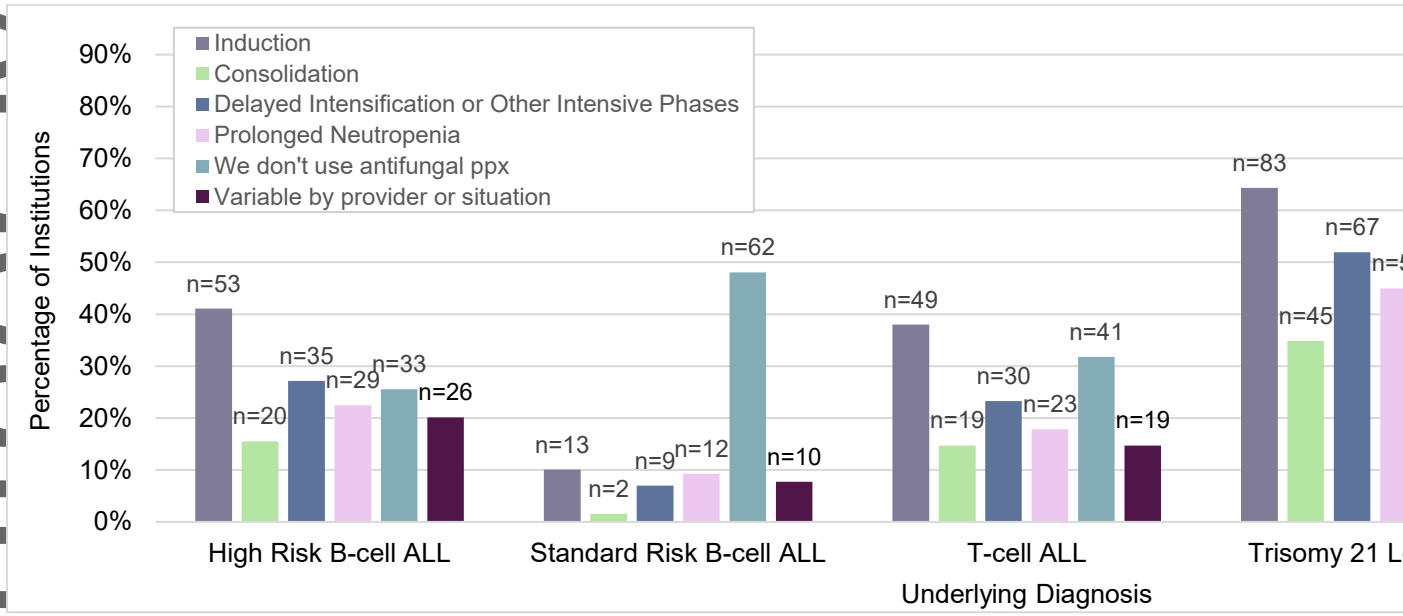
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Figure 5: Antifungal Prophylaxis Utilization in Leukemia Patients Among Responding Institutions (N=129)

A) Antifungal Prophylaxis Agent Grouped by Patient Diagnosis



B) Utilization of fungal prophylaxis based on type of leukemia and phase of therapy



Abbreviations: AML=Acute myeloid leukemia, ALL=Acute lymphoblastic leukemia

*Other antifungal agents: Anidulafungan (n=1 for each diagnosis category)

Table 1: Studies Performed for Initial Evaluation of Routine FN and Prolonged FN>96 Hours Without a Source of I		
Initial Evaluation of Routine FN		
Laboratory Study	**# of YES Responses**	**% YES of Total Respon**

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Complete blood count with differential	127	98.4%
Central line blood culture	127	98.4%
Electrolyte panel (BMP)	87	67.4%
Liver enzymes (AST/ALT)	74	57.4%
C-reactive protein	27	20.9%
Procalcitonin	26	20.2%
Serum lactate	19	14.7%
Peripheral blood culture	16	12.4%
Infectious Testing		
Respiratory viral panel (symptomatic)	108	83.7%
Respiratory viral panel (even if asymptomatic)	12	9.3%
Chest X-ray (symptomatic)	90	69.8%
Chest X-ray (even if asymptomatic)	1	0.8%
Urine culture (symptomatic)	83	64.3%
Urine culture (even if asymptomatic)	18	14.0%
SARS-COV-2 test (symptomatic)	84	65.1%
SARS-COV-2 test (even if symptomatic)	24	18.6%
Flu test in season (symptomatic)	91	70.5%
Flu test in season (even if asymptomatic)	17	13.2%
Evaluation of Prolonged FN>96 Hours		
Laboratory or Other Study		
Galactomannan (Serum)	84	65.1%
β-D-glucan (Serum)	64	49.6%
Respiratory viral PCR panel	57	44.2%
Blood/plasma viral PCR (e.g. adenovirus, CMV, etc)	44	34.1%
Blood cell-free microbial DNA testing	21	16.3%
Bedside nasal scope by otolaryngology	8	6.2%
Other*	6	4.9%
Ophthalmology exam	3	2.3%
Imaging		
Chest	?122	?94.6%
CT	120	93.0%
Chest X-ray	2	1.6%
Abdomen/pelvis	121	93.8%
CT	93	72.1%
Ultrasound	27	20.9%
MRI	1	0.8%
CT sinuses	74	57.4%

Abbreviations: FN=Fever and Neutropenia; AST=Aspartate transaminase; ALT=Alanine aminotransferase; BMP=Basic metabolic panel; PCR=Polymerase chain reaction; CMV=Cytomegalovirus; CT=Computed tomography; MRI=Magnetic Resonance Imaging

*Other studies for prolonged FN: CT Sinuses based on age and symptoms (n=3); Variable by provider and/or clinical scenario (n=3)

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