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

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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 nontransplant pediatric oncology patients was iteratively created by the Children's Oncology Group (COG) Cancer Control and Supportive Care 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 (88% antibacterial, 100% antifungal) and relapsed acute lymphoblastic leukemia (82% antibacterial, 95% antifungal). Definitions of fever, phagocyte recovery, and antibiotic duration in febrile patients varied. Most institutions administer empiric broad-spectrum antibiotics for nonneutropenic 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 h, 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.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; CBC/d, complete blood count with differential; CCL, COG Cancer Control and Supportive Care; CHG, chlorhexidine gluconate; COG, Children's Oncology Group; CPGs, Clinical practice guidelines; CT, computed tomography; FN, febrile neutropenia; G-CSF, granulocyte colony stimulating factor; IV, intravenous; PJP, *Pneumocystis jirovecii* pneumonia; TTA, time-to-antibiotic; USNWR, US News and World Report.

Leonora R. Slatnick and David Hoogstra contributed equally to this study.

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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.

1 | 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 to antimicrobial prophylaxis, fever management, and other infection-related practices in nontransplant 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.

2 | 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 the Supporting Information). Survey questions excluded stem cell transplant 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, if available, or if not available to the COG site principal investigator at all 227 COG institutions on 29 January, 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 nonresponders for 4 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.

3 | Results

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].

3.1 | 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 h 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-min 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 min, and four institutions (3.1%) report administering intramuscular antibiotics if IV access is not obtained within 60 min. Fourteen institutions (10.9%) do not utilize any particular practice.

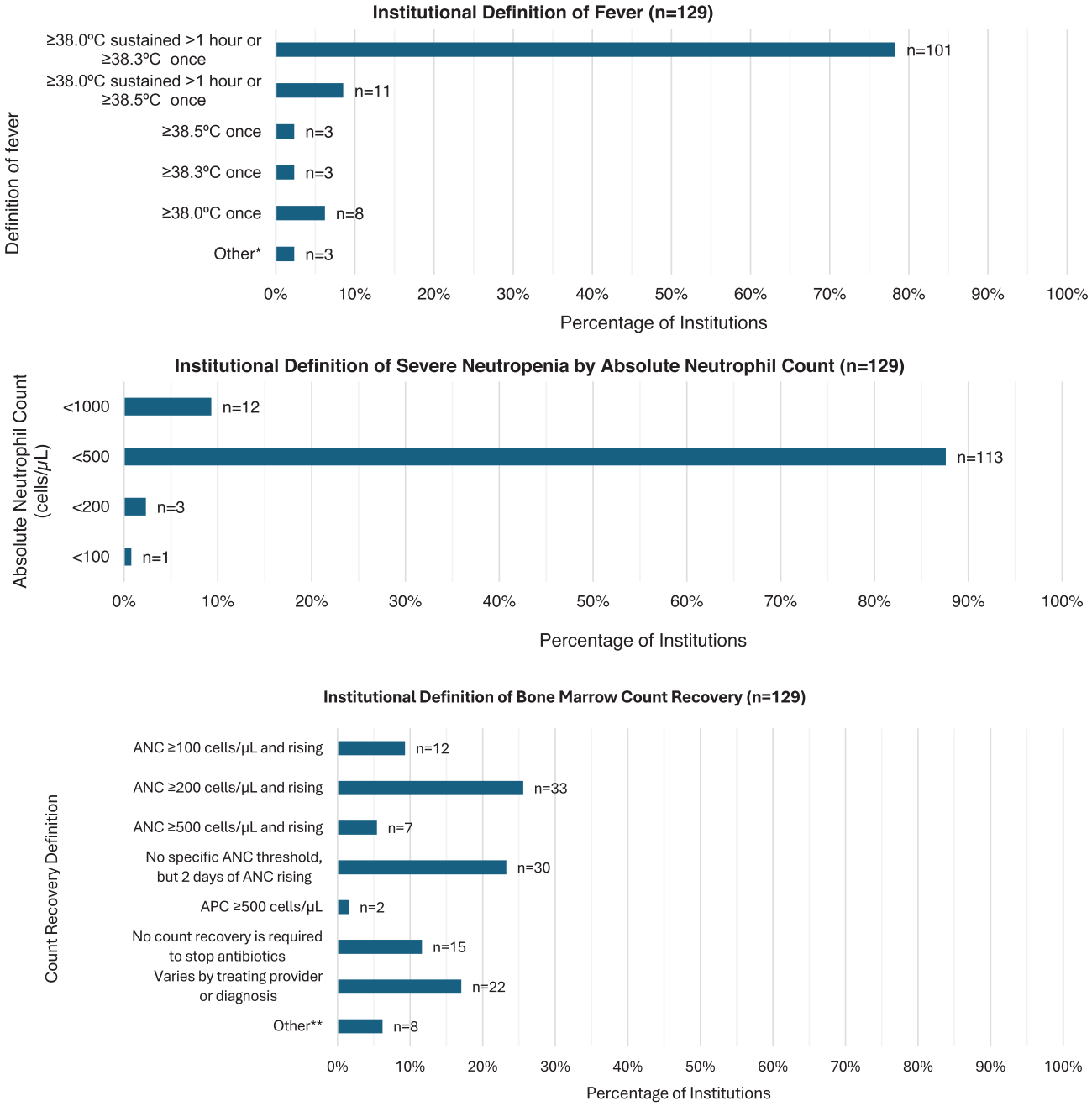


FIGURE 1 | Institutional definitions of fever, severe neutropenia, and bone marrow count recovery. ANC = absolute neutrophil count; APC = absolute phagocyte count in cells/μL = [total white blood cell count (10^3 cells/μL × % neutrophils + % bands + % monocytes)]; AMC = absolute monocyte count. *Other definitions of fever: varies based on outpatient (≥38.3°C) or inpatient (≥38.3°C sustained or ≥38.5°C once) setting ($n = 1$); ≥37.5°C or ≥37.8°C if axillary sustained or ≥38.3°C once. **Other count recovery definitions: varying combinations of ANC, APC, and/or AMC ($n = 7$); ANC ≥ 250 and rising ($n = 1$).

3.2 | FN Initial Testing

Institutional FN management practices vary. There were 46 institutions (35.7%) that reported using a specific FN risk-stratification tool, eight 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.

3.3 | 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

TABLE 1 | Studies performed for initial evaluation of routine FN and prolonged FN > 96 h without a source of infection.

Initial evaluation of routine FN		
Laboratory study	**No. of yes responses**	**Percentage of yes of total responses ($n = 129$)**
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 h		
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 and CMV)	44	34.1
Blood cell-free microbial DNA testing	21	16.3
Bedside nasal scope by otolaryngology	8	6.2
Other[a]	6	4.9
Ophthalmology examination	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: ALT = alanine aminotransferase; AST = aspartate transaminase; BMP = basic metabolic panel; CMV = cytomegalovirus; CT = computed tomography; FN = fever and neutropenia; MRI = magnetic resonance imaging.; PCR = polymerase chain reaction.

[a]Other studies for prolonged FN: CT sinuses based on age and symptoms ($n = 3$); variable by provider and/or clinical scenario ($n = 3$).

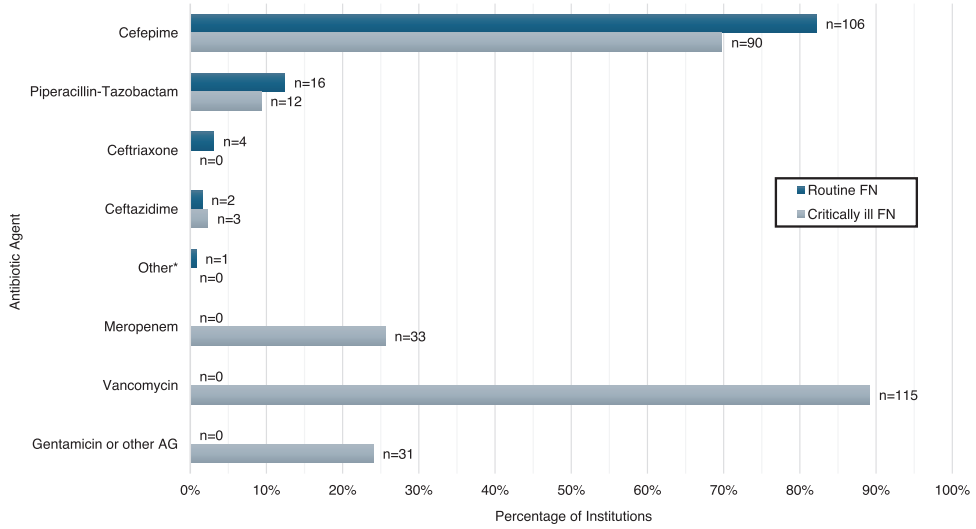


FIGURE 2 | Empiric antibiotic choices for routine FN patients and critically ill-appearing FN patients ($n = 129$). FN = fever and neutropenia; AG = aminoglycoside antibiotic. *Other: Provider/situation dependent ($n = 1$).

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%, $n = 65$).

3.4 | FN Length of Stay Management

The majority of institutions admit all patients with FN for at least 48 h (69.0%, $n = 89$), and 21 centers (14.1%) initially admit patients with FN and send some low-risk patients home prior to 48 h. 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 h with negative blood cultures >48 h, 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 h 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 h and have negative blood cultures >48 h, 26.4% ($n = 34$) of institutions discontinue empiric IV antibiotics before phagocyte recovery, 21.7% ($n = 28$) discontinue IV antibiotics after they have 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 have 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).

3.5 | Persistent FN ≥96 h Without a Source of Infection

Routine testing performed for persistent FN ≥96 h 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 h 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

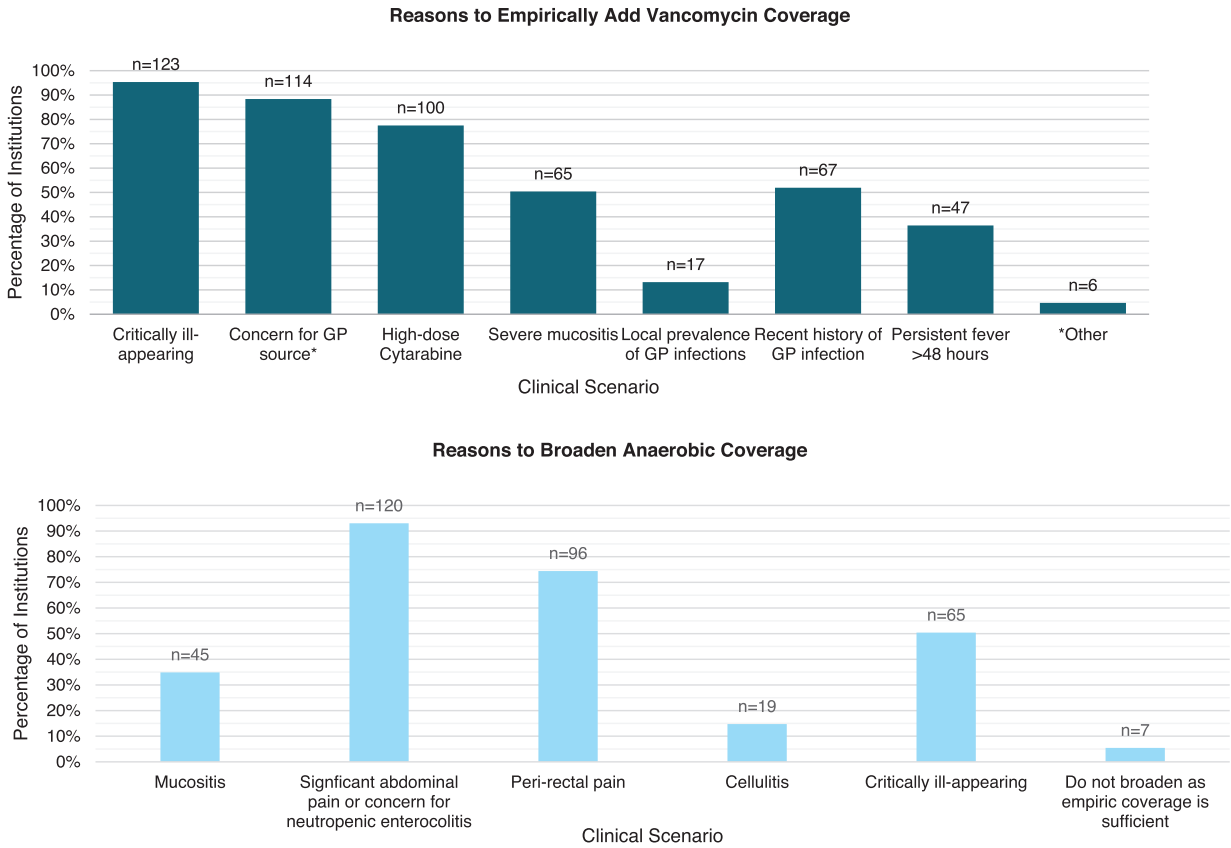


FIGURE 3 | Reasons to expand antibiotic coverage in FN patients ($n = 129$). Reasons to empirically add vancomycin coverage. Reasons to broaden anaerobic coverage. FN = fever and neutropenia; GP = gram positive. *Other reasons to add vancomycin: Concern for central nervous system infection, indwelling device such as ventriculoperitoneal shunt, MRSA colonization, AML diagnosis, added for all high-risk patients.

therapy if the diagnostic evaluation is suggestive of an invasive fungal disease.

3.6 | Nonneutropenic Fever

In well-appearing patients with nonneutropenic fever (ANC $\geq$ 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 nonresponder. 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 two (1.6%) unknown responses.

3.7 | Antibacterial Prophylaxis and Observation Through Count Recovery

As shown in Figure S1, 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 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 Figure S2.

3.8 | 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

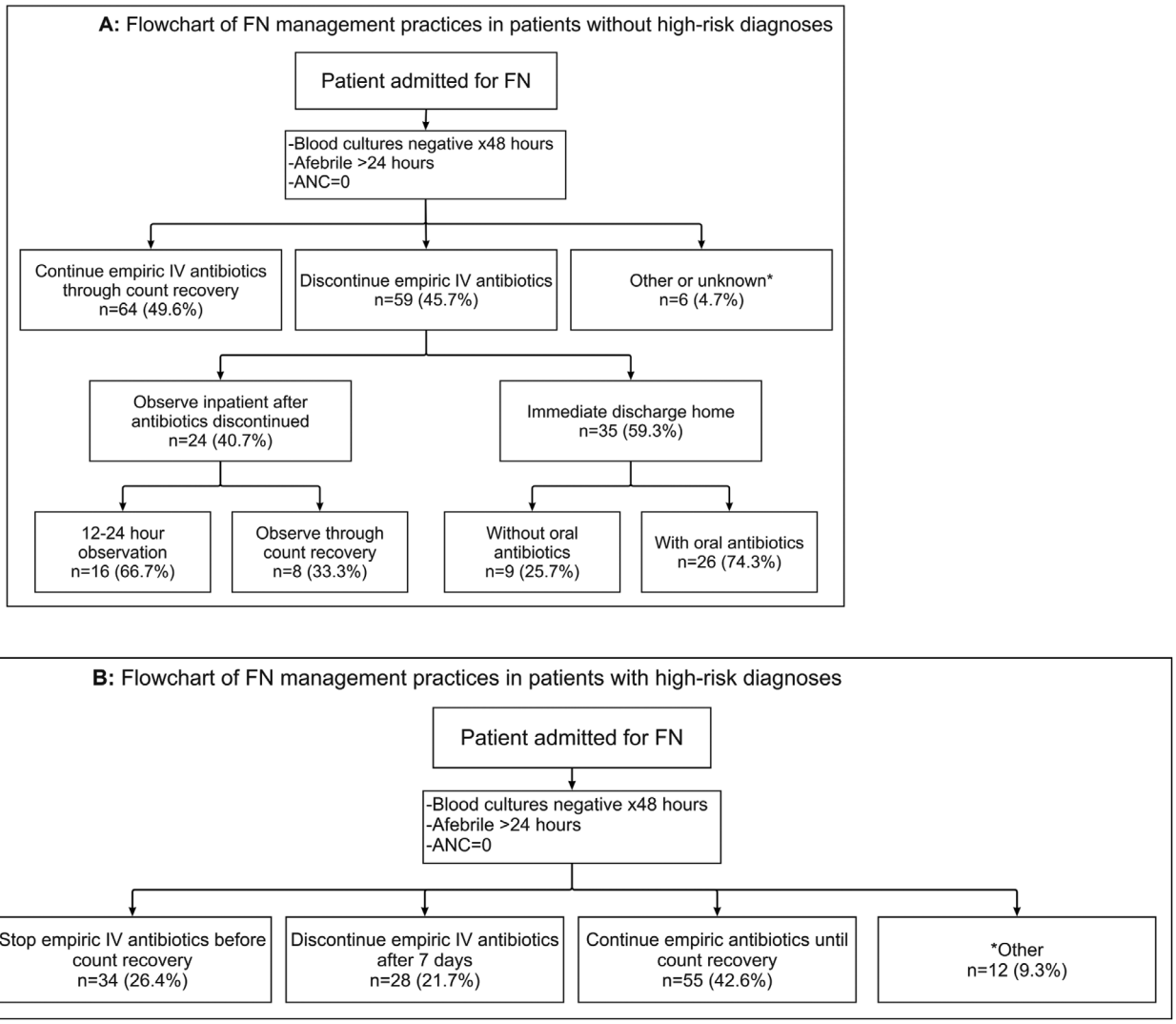


FIGURE 4 | Flowchart of FN management practices in patients without diagnoses that are high-risk for infection (A) and patients with diagnoses that are high risk for infection with fever during induction (B). FN = fever and neutropenia; ANC = absolute neutrophil count; IV = intravenous. *Other practices 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 ($n = 2$). 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 ($n = 4$).

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 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 four unknown responses.

3.9 | *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 nonallergy-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; Figure S3). 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, six institutions (4.7%) discontinue prophylaxis based on absolute lymphocyte count, and there was one unknown response (<1.0%).

3.10 | 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

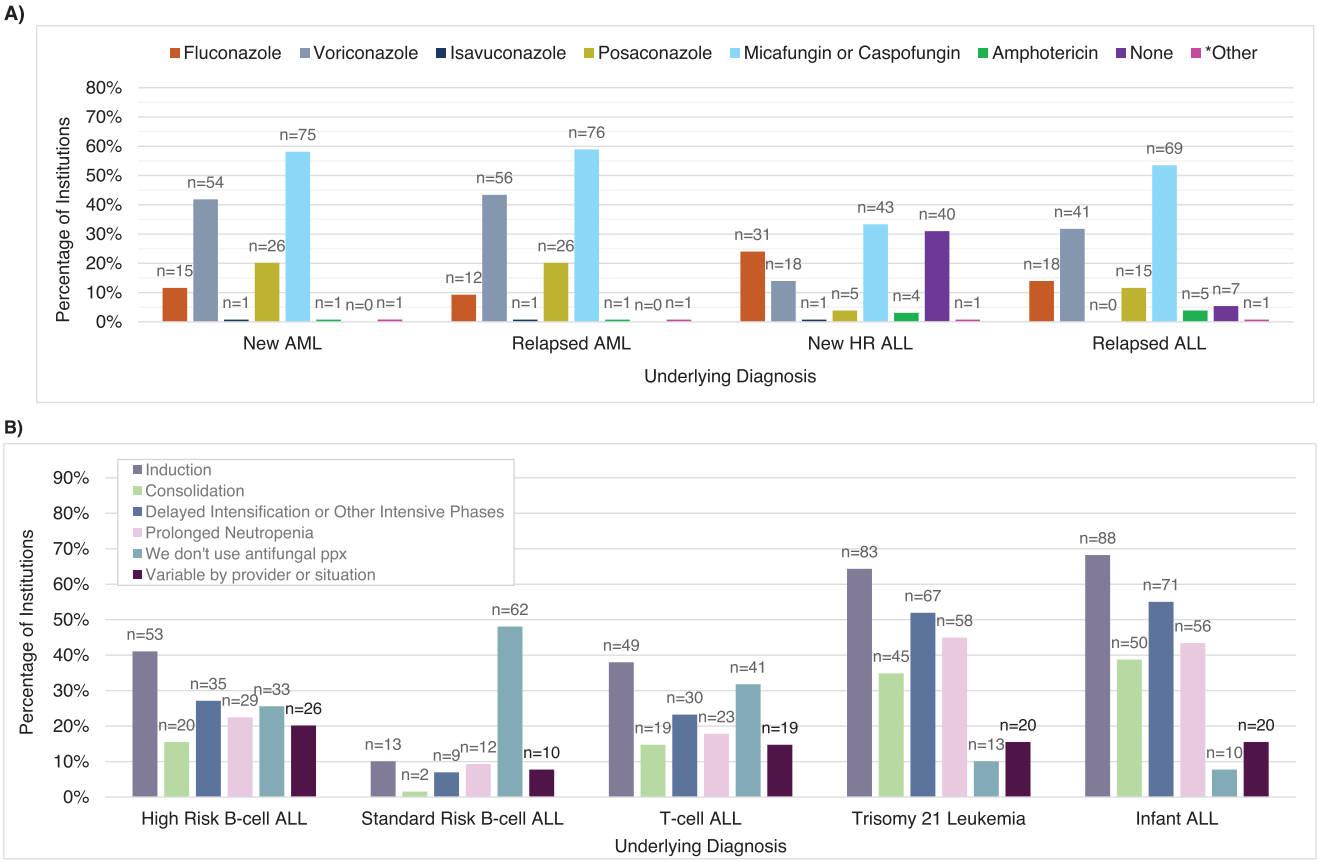


FIGURE 5 | Antifungal prophylaxis utilization in leukemia patients among responding institutions ($N = 129$). (A) Antifungal prophylaxis agent grouped by patient diagnosis. (B) Utilization of fungal prophylaxis based on type of leukemia and phase of therapy. Abbreviations: AML = acute myeloid leukemia, ALL = acute lymphoblastic leukemia. *Other antifungal agents: Anidulafungan ($n = 1$ for each diagnosis category).

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, six (26.1%) reported that CHG was used previously, then stopped, and four (17.4%) were unsure.

3.11 | Granulocyte Colony Stimulating Factor (G-CSF) Use in Hematologic Malignancy

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 one unknown response.

4 | 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 h, 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 h with negative blood cultures >48 h 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].

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 h, 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 h 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 those in ALL induction, nearly half the sites report doing this. Although there are published observational data supporting safety and effectiveness of fluoroquinolone prophylaxis for ALL induction [28, 29], further studies are needed to confirm benefit in ALL as fluroquinolone prophylaxis may increase the risk of fluoroquinolone-resistant infections [30, 31].

In concordance with the COG-endorsed CPG, most centers utilize antifungal prophylaxis for patients at the highest risk for infection, including AML. Echinocandins are the most utilized agents in AML in concordance with published results of the COG ACCL0933 study [2, 32]. Most sites use antifungal prophylaxis in relapsed ALL, which is consistent with the weak recommendation in the COG-endorsed CPG, but 69% give antifungal prophylaxis for newly diagnosed high-risk ALL patients despite a lack of recommendation for antifungal prophylaxis in this population in the CPG [2]. Further studies are needed to determine the optimal strategy for fungal prophylaxis in non-AML leukemia patients [33].

Evidence-based practice changes may be difficult to implement when nonevidence-based practices are perceived to be efficacious and assumed to have limited downside, especially when proposed changes involve de-escalation of care that may appear to increase the risk of infectious complications. While this change inertia is understandable there is increasingly robust medical literature to support the safety of many such de-escalations of care [34]. Three specific examples of reported current practices that remain prevalent despite published data supporting a "less is more" approach include ongoing use of CHG wipes, implementing practice measures to meet a time-to-antibiotic metric in well-appearing patients with FN, and utilization of empiric broad-spectrum antibiotics in nonneutropenic fever. Our survey found that >65% of institutions currently use CHG wipes for all oncology patients despite the only randomized placebo-controlled study on the topic demonstrating that routine CHG wipe usage did not decrease bacterial infections in this population [35]. Similarly, the 60-min (TTA) metric for FN patients that was previously incorporated as a US News and World 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-min metric. Lastly, 84% of respondents reported administering empiric antibiotics in nonneutropenic 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 is that 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 that limits the generalizability of results and implications, especially when considering centers in lower income and middle-income countries.

5 | 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.

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Conflicts of Interest

Etan Orgel provided consulting services to Jazz Pharmaceuticals. Leonora R. Slatnick provided consulting services to Y-mAbs Therapeutics. Brian T. Fisher received research support from Merck and Pfizer, and also worked for data safety monitoring board for Astellas. Joshua Wolf acknowledges Karius Inc., Scynexis Inc., and Pfizer Inc. for in kind support for investigator-initiated research, and Merck Inc. for participation in industry-initiated research. The remaining authors declare no conflicts of interest.

Data Availability Statement

Data are available on request.

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Supporting Information

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