Editorial Commentary

Fever and neutropenia in pediatric oncology and stem cell transplant patients: an editorial commentary on updated international clinical practice guidelines

Alex Hoover[1]^, Beth K. Thielen[2]^, Christen L. Ebens[3]^

[1]Division of Hematology/Oncology, Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA; [2]Division of Infectious Diseases, Department of Pediatrics, Global Pediatrics Program, Minneapolis, MN, USA; [3]Division of Blood and Marrow Transplant & Cellular Therapy, Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

Correspondence to: Christen L. Ebens, MD, MPH. Division of Blood and Marrow Transplant & Cellular Therapy, Department of Pediatrics, University of Minnesota, A528 Mayo Memorial Building, MMC 484, 420 Delaware Street SE, Minneapolis, MN 55455, USA. Email: ebens012@umn.edu.

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One of the most concerning complications of myelosuppressive therapies for pediatric cancer and hematopoietic cell transplant (HCT) patients is fever and neutropenia (FN). Prompt recognition, risk assessment, and appropriate management of FN is crucial to minimize morbidity and mortality. In a recent update of international FN clinical practice guidelines (CPGs), Lehrnbecher *et al.* provide an updated review of evidence in the management of FN in pediatric oncology and HCT patients (1).

The initial edition of these CPGs was published in 2012 and included systematic reviews of the literature focused on key clinical questions in pediatric FN (2). Lehrnbecher and team utilized systematic reviews and meta-analyses of primarily nonrandomized studies, due to the paucity of randomized clinical trials (RCTs) in pediatric FN at the time, to formulate answers to these questions and establish clear practice recommendations. In the subsequent 2017 update of the CPGs, the team added analysis of recent and relevant RCTs to the previously examined observational studies of pediatric FN, increasing the quality of evidence evaluated and presented (3). In the most recent update, review of evidence was limited to only RCTs, further refining the evidence base and clarifying multiple conditional recommendations (1).

The key changes in the 2023 version of the CPGs were the new recommendations to (I) discontinue empiric antibacterial therapy in clinically well and afebrile patients with low-risk FN if blood cultures remain negative at 48 hours despite no evidence of marrow recovery and (II) pre-emptively initiate antifungal therapy for invasive fungal disease in high-risk patients not receiving anti-mold prophylaxis. The first recommendation was made based on two recent RCTs showing that therapy cessation was non-inferior to continuing therapy (4,5). The second new recommendation was based on an RCT showing that pre-emptive therapy reduced the median duration of antifungal therapy in a high-risk FN population (6). The final addition to the 2023 CPG was a good practice statement to initiate empiric antibacterial therapy as soon as possible in clinically unstable FN patients.

Risk stratification

Risk stratification plays a pivotal role in determining the

^ ORCID: Alex Hoover, 0000-0002-2368-296X; Beth K. Thielen, 0000-0001-5922-0241; Christen L. Ebens, 0000-0003-2430-911X.

appropriate management strategies for pediatric oncology and HCT patients with FN. Both the 2012 and 2017 CPGs cite a prior systematic review identifying six unique risk assessment models and scoring systems for identifying low-risk FN patients (key components summarized in *Tab. 3* of Phillips *et al.*, 2012) (7). The authors highlighted these six diverse risk assessments as each had been cross-validated or applied to at least one additional dataset. The diversity of these risk stratification models was quite broad however. For example, one of the six risk stratification models utilized only monocyte count and HCT status to stratify patients, whereas other models used variations of complex scoring systems that included clinical factors such as viral respiratory symptoms and lab values such as C-reactive protein (CRP) or cytopenias. Given the broad scope of the FN CPGs and international target audience, the authors are wary to choose one of the six validated approaches and rather recommend that each individual center adopt one of the risk stratification approaches and incorporate it into routine clinical practice based on ability to implement necessary rules, laboratory turnaround time, etc. (2,3). The hesitation of the CPG authors in selecting a single FN risk assessment strategy is warranted, as each risk assessment underperforms in accuracy when applied to a new dataset. Importantly geographic variations in validity were also highlighted as limiting to broad generalizability (7).

A subsequent assessment of risk stratification approaches across ten centers within a single country, France, underscored the variability in clinical practice starting with inconsistencies in defining a "fever" to the range of criteria considered when defining risk of poor outcomes (8). Without new evidence to support one FN risk stratification strategy over another, high- and low-risk FN in the current CPG update remain undefined (1). While an *ad hoc* risk assessment adoption strategy allows tailoring of risk stratification among pediatric oncology/HCT centers, it somewhat hampers interpretation of many of the key clinical questions given the variability of risk assignment. Based on this variability, we would encourage caution in the application of these CPGs for patients who are stratified as low-risk but may have some high-risk features. For example, some risk stratification approaches fundamentally classify patients with relapsed leukemia as high-risk, while other approaches utilize labs values such as cytopenias and clinical presenting symptoms to stratify, regardless of disease status. Consideration of the context of disease status, recent therapy and other characteristics not mentioned in stratification approaches is crucial.

FN with novel therapies

One key facet of pediatric oncology that is not addressed in the updated CPG's or the risk stratification systems is the particular infection risk for patients receiving novel therapies such as targeted drugs, biotherapies and cellular therapies which have been increasing in use in pediatric oncology over the last decade (9). A recent position paper from the European Conference on Infections in Leukemia (ECIL) provides updates on current knowledge of infections associated with targeted and biotherapies and provides recommendations for a rational clinical management of prevention and treatment of infections in leukemia patients (10). Although this review targets patients with leukemia and includes both adults and pediatric patients, it provides updated recommendations on both antibody-based therapies such as inotuzumab ozogamicin (InO) and gemtuzumab ozogamicin (GO), targeted small molecules like FLT3 and IDH inhibitors and the increasingly utilized BCL-2 inhibitor, venetoclax. Currently, InO and GO are being investigated in upfront therapy trials through the Children's Oncology Group for high-risk pre-B acute lymphoblastic leukemia (B-ALL) and acute myeloid leukemia (AML), respectively [InO AALL1732 (NCT03959085), GO AAML1831 (NCT04293562), GO previously assessed upfront in AAML0531 (NCT00372593)]. As these therapies are incorporated into standard of care regimens for pediatric oncology patients, improved knowledge surrounding the risk of infections and guidelines for appropriate empiric antimicrobial agents will be essential. Another recent review focused particularly on pediatric leukemia and lymphoma patients describes the risks of both acute infectious complications such as FN and longer-term effects of these therapies and their effects such as B-cell aplasia and hypogammaglobulinemia (11). Specific novel therapies such as pembrolizumab and blinatumomab have been associated with quite low rates of FN and severe infection, while therapies such as GO and chimeric antigen receptor T-cell (CAR-T) therapies have higher risks of grade 3 infections and FN. Inclusion of these therapies into risk-stratification systems and FN clinical guidelines will be crucial as these drugs move forward into upfront oncologic regimens.

CAR-T therapies, in particular, exist in a crossover between traditional chemotherapy-based oncology and myeloablative or reduced intensity stem cell transplantation and therefore confer a unique and understudied infectious risk. Administered with lymphodepleting chemotherapy

and with myelosuppressive cytokine-mediated activity itself, CAR-T therapies are commonly associated with some degree of neutropenia, as well as other immunosuppressive effects related to B-cell targeting including hypogammaglobulinemia. The ELIANA trial that led to the U.S. Food and Drug Administration (FDA) approval of tisagenlecleucel in pediatric patients reported a 35% occurrence rate of Grade III–IV febrile neutropenia and 43% rate of any grade infection among 75 patients treated (12). A subsequent investigation at St. Jude Children's Research Hospital particularly highlighted the characteristics of post-CAR-T infections, including type of infection and risk factors for infections (13). Investigators found that in 38 patients evaluated, bacterial bloodstream infections were the most common infectious complication post-CAR-T while viral infections, including reactivations, occurred infrequently and fungal infections were quite rare. Larger, more robust studies of CAR-T related infectious complications in pediatric patients will be needed to establish antimicrobial CPGs and empiric anti-infective strategies more formally.

Novel diagnostic strategies

One novel infection investigative technique that is not mentioned in Lehrnbecher and team's updated CPGs is the use and timing of cell-free DNA infectious testing. Metagenomic next-generation sequencing (Karius® testing) of plasma cell-free DNA has emerged as an attractive diagnostic modality allowing broad-range pathogen detection, noninvasive sampling, and earlier diagnosis (14). Although the comprehensive clinical impact of this testing technique continues to be studied and further validation of the platform is needed, multiple investigations have shown its ability to identify otherwise unculturable or undetectable infections, particularly in severely immunocompromised leukemia and HCT patients (14-16). Specifically in the FN setting, this testing platform has shown high rates of positive agreement with culture results and reduced overall calculated time to diagnosis (TTD) compared to standard microbiological testing (17). One of the pitfalls of this technique remains the difficulty of obtaining real-time results, however as the platform improves and TTD shortens, the testing could have a significant impact on antibiotic stewardship and the minimization of unnecessary antimicrobial exposure in FN patients (17). High sensitivity techniques such as this to detect commonly cryptogenic and highly morbid infections like invasive fungal infections or *Pneumocystis jirovecii* pneumonia earlier may impact the testing recommendations and ability to modify antimicrobial coverage earlier in high-risk FN patients (18).

International impact and application

As we consider the impact of the evolving landscape of pediatric oncology and HCT therapies and infection detection strategies, we must also consider how to apply these recommendations to resource-constrained global settings. Such attention is critical as over 80% of global pediatric cancers occur among children living in low- and middle-income countries (LMICs) (19). Moreover, despite significant gaps in data on the incidence of and mortality from childhood cancers in many LMICs, the existing data demonstrates nearly four-fold higher mortality rates from childhood cancers between regions of Africa and Asia as compared to North America (19). In high-income countries (HICs), infections are a major contributor to treatment-related mortality (20) but comparable data are lacking from most LMICs, highlighting an important need for future research. In other aspects of oncological care, adaptations have been published to address contextual differences between HICs and LMICs (21). Similar adaptations will likely be needed in the management of FN due to these contextual differences. For example, access to investigations such as blood cultures and imaging are lacking in many resource-constrained settings and may be cost prohibitive if available, limiting the diagnostic data upon which to make evidence-based management decisions (22,23). Furthermore, reported rates of drug resistance are also higher (24), suggesting the need to adapt recommendations for first-line empiric therapies based on local epidemiology.

Conclusions

Lehrnbecher *et al.* provide an updated and distinctively comprehensive critical review of the literature for pediatric FN in oncology and HCT, establishing well-defined CPGs for providers across many healthcare settings who care for these patients (1). As oncology and stem cell transplantation shift to incorporate more precision medicine with targeted therapies, lower toxicities and myelosuppression, and improved detection of infectious sources, these CPGs will need to be continuously evaluated. As highlighted by the difficulty defining a generalizable risk stratification approach for FN in pediatric oncology and HCT, adaptations will also be needed for this CPG to be practical for implementation

in resource-constrained settings. As oncologic care continues to evolve, separation of FN CPGs by patient population and characteristics may become necessary as the growth in treatment options adds complexity.

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