Peer Review File

Article Information: https://dx.doi.org/10.21037/tp-23-368

Reviewer A

This is a well-written commentary on the recently published updated international clinical practice guidelines for fever and neutropenia in pediatric oncology and stem cell transplant patients. My comments:

1. In the section discussing risk stratification variability and the need for standardization, I suggest specifying some differences between the models or giving concrete examples to demonstrate the issue more clearly.

Reply 1: We agree with this suggestion and have modified this portion of the text to include concrete examples in differences between the risk stratification models.

Changes in the text: Added text in lines 49-53

2. I completely agree with the comments on the lack of standardized guidelines on FN with novel therapies such as CAR-T cells. However, cell-free DNA testing would require more established evidence-based data and availability in order to be relevant for CPG. It is indeed an interesting and promising novel technique worth mentioning and elaborating on in the commentary but I wouldn't be critical of it being unmentioned in the CPG.

Reply 2: We completely agree with the reviewer that cell-free DNA testing remains a novel and unvalidated approach in this patient population. Our intent in mentioning this technology (as well as CAR-T cells) was less of a critique of the CPG and more to highlight areas that may become more relevant in the future and warrant consideration for incorporation.

Changes in the text: Text was modified in lines 120 and 125 to reduce the insinuation of critique and emphasize that further study is needed on this topic

Reviewer B

This is a Commentary regarding the latest version of clinical practice guidelines for children with fever and neutropenia (FN) after myelosuppressive therapies and hematopoietic stem cell transplant (HCT). Overall, this commentary is organized and well-written; however, there are several points which need revisions.

1. I think that the last sentence in the Conclusions is overgeneralized. The authors could rewrite this.

Reply 1: We agree that the final sentence was a broad generalization and have replaced it with a more specific concluding comment regarding the future of FN clinical practice guidelines.

Changes in the text: Text was rewritten as recommended in lines 165-167.

2. p.2, line 23: the team

27 restricted analysis to observational studies and randomized clinical trials (RCTs) of pediatric FN

2017 update said that they focused on pediatric RCTs for therapy-related questions because practice was unlikely to change on the basis of additional observational studies alone.

From my understanding, they left observational studies included in 2012 CPG and added new additional RCTs.

If this is the case, explanation here is not quite accurate. The authors need to elaborate this.

Reply 2: We agree that the phrasing of this text was ambiguous and did not accurately reflect the updated data analysis that was performed in the subsequent CPG's. We have made the suggested changes to the text to clarify that RCT's were added to the previously analyzed studies in the 2017 version.

Changes in the text: Text was modified as recommended in lines 25-29

3. p.3, line 62. In the current CPG update (1), FN risk stratification remains

undefined.

The authors could mention that stratification was unchanged due to lack of new RCTs.

Reply 3: We agree that this statement could use a basis and the text has been modified to convey this point.

Changes in the text: Text modified in lines 65-66

4. line 67. ...are stratified as low risk but may have some high-risk features

The authors could describe examples in order to encourage readers' understanding.

Reply 4: We agree and have added a clinical example of a high-risk feature that could affect risk stratification in one approach, but not necessarily in each approach.

Changes in the text: Text added in lines 71-75

5. line 81. InO and GO are being investigated in upfront therapy trials through the Children's Oncology Group for high risk B-ALL and AML, respectively.

The authors could add NCT numbers.

Reply 5: We agree this helps with clinical relevance and reader access to this information.

Changes in the text: COG trial and NCT numbers added in lines 90-91

6. p.4 line 100. CAR-T therapies are commonly associated with some degree of neutropenia

The authors could elaborate that CAR-T therapies are related to B-cell aplasia and subsequent hypogammagloblinemia and therapy-related grade ≥3 neutropenia (9.3% in ELIANA phase II trial).

Reply 6: Although the focus of the CPG is on fever and neutropenia in particular, B-cell aplasia and hypogammaglobulinemia absolute contribute to infection risk, so we have added the suggested content to the CAR-T section for additional context.

Changes in the text: Text added/modified in lines 107-110

7. p.5 line 128. atypical infections

"Atypical infection" needs definition. Infection due to atypical pathogens, or does it refer to atypical pneumonia?

Reply 7: We agree that this term was too broadly applied and have modified this to reflect our intent to describe detection of invasive fungal or PJP lung infections

Changes in the text: Text modified in line 134