Peer Review File

Article information: http://dx.doi.org/10.21037/aob-20-96

Review Comments

Subject: Major Revision

Reviewer 1:

Decision: Major Revision

Comments:

Pediatric immune thrombocytopenia (ITP) is a heterogeneous autoimmune condition with variability in etiology, bleeding, need for treatment and response to therapy, as well as duration of disease. In the manuscript "Pediatric Immune Thrombocytopenia (ITP) Treatment", authors focused the initial management of pediatric ITP patients including early laboratory assessments and front-line therapies.

Couple questions are required to be answered:

(1)For most children, initial management involves attention to screening for underlying secondary causes of ITP. What are the secondary causes of ITP?

Reply: Thank you for highlight this crucial point. Secondary causes of ITP and relevant workup are described in the text, but language has been updated to more explicitly identify where secondary causes of ITP are being discussed.

Changes in text: Text has been modified on page 3, line 93, "Causes of secondary ITP are discussed further under second line workup below"; page 6, line 210-211 "**Secondary ITP Diagnostic Workup** Children with chronic ITP warrant further evaluation for secondary ITP, or"; page 6. Line 218, "Conditions associated with secondary ITP"; page 6, line 230-231, "Minimum screening for disorders frequently implicated as causing secondary ITP or those for which diagnosis".

(2)What are the diagnostic criteria for ITP? And in initial laboratory tests, which was the most important, or should be paid more attention?

Reply: The International Workup Group definition of ITP, which defines ITP as a diagnosis of exclusion characterized by isolated thrombocytopenia with platelets less than $100x10^9$/L was included under the header "Importance of Defining ITP". Under the header "Initial Workup", lab tests are now defined as obligatory, (CBC, reticulocyte and peripheral smear) or recommended (DAT and quantitative immunoglobulins). The relevance of a DAT and immunoglobulins are highlighting as guiding therapy or uncovering suggestion of secondary causes of ITP.

Changes to Text: For clarity, the definition of ITP was moved to the start of the section "Importance of Defining ITP" on page 3, lines 86-88. Rewording to stratify importance of lab testing is on page 2, lines 64-68.

(3) Based on what to select the initial therapy plan (Corticosteroids or Intravenous immune globulin)?

Reply: Thank for pointing out this deficiency. Prior to describing each first line therapy in detail, a paragraph was expanded to delineate why corticosteroids are suggested as first line therapy over IVIG or anti-D immune globulin. This paragraph draws from the 2019 ASH ITP Guidelines and

highlights ease of administration, cost and side effect profile. It is emphasized here that for more severe bleeding or emergent cases IV regimens are preferred for faster onset. In depth discussion of IVIG is avoided however at the behest of the editors who have allocated a separate full manuscript to IVIG therapy in children.
Changes to Text: Aforementioned paragraph is located on page 4, lines 129-140.

(4) Among these adverse events occurred in first line therapy for ITP, which one is the worse? How to handle with it?
Reply: The most important side of effect of anti-D immune globulin is intravascular hemolysis which could lead to multi-organ failure and death. Text has been modified to reflect that severe intravascular hemolysis as the most feared side effect. The recommended monitoring for hemolysis is already included in the text, however management of hemolysis is now further described as supportive care. Because IVIG is focused on in another manuscript in this edition, the description of black box warnings for thrombosis and renal failure related to IVIG is only briefly described in the paragraph describing selection of first line agents.
Changes to Text: Paragraph stratifying first line agents, page 4, lines 129-140. Text further modified regarding the severity of anti-D immune globulin side effects on page 5, lines 177-179 and 181-183.

(5) TPO-RAs were the first line treatment drugs or second line treatment drugs for ITP?
Reply: TPO-RAs are already described as the initial second line treatment for ITP after failure to respond to upfront therapy. TPOs are introduced under the header "Second Line Therapy Options".
Changes to Text: Page 7, lines 245-6, first line agents are now listed in parenthesis to highlight the distinction of TPO-RAs as second line agents.

(6)How about the FcRn antagonists as the second line treatment options for ITP?
Reply: Thank for you pointing out that description of this novel class of therapeutics was lacking. While mentioned briefly, the text has been expanded to provide some details on the status of trials for efgardigomod and rozanolixizumab, though neither are being trialed in pediatrics yet.
Changes to Text: Paragraphs added to page 10, lines 403-410.

(7) A patient with ITP was diagnosed as chronic infections (e.g. HIV, hepatitis, cytomegalovirus, H.Pylori) in second line diagnostic workup. What is the treatment option in second line treatment?
Reply: Thank you for this comment. The text has been updated to comment briefly on management of chronic infections. Text now emphasizes treating the underlying condition and using supportive therapy for thrombocytopenia if needed with standard first line agents for ITP treatment.
Changes to Text: Examples of management of ITP secondary to chronic infections is added to page 6, lines 223-228.

(8) Whether or not the therapeutic schedule of ITP is the same for child and adult?
Reply: Comments have been added to highlight differences in ITP management in pediatrics and

adults. The primary difference in adult versus pediatric management is how patients are managed at the time of diagnosis, with asymptomatic or mildly affected children being observed regardless of their platelet count. The emphasis on avoiding splenectomy in children who have a high likelihood of spontaneous resolution is also added.

Changes to Text: The recommendation to treat asymptomatic or minimally affected adults based on platelet count versus the standard of cautious observation in children regardless of platelet count is noted on page 3, lines 109-111. Discussion of how, unlike adults, splenectomy is strongly avoided in children if possible on page 6, lines 238-240.

Reviewer 2:

Decision: Minor Revision

The authors have written a concise but thorough primer on the approach to management of pediatric ITP, highlighting mechanisms of action as well as expected outcomes and potential adverse effects of various pharmacologic treatments.

A few suggestions for revision:

(1) Initial Workup: Quantitative immunoglobulins "may be considered" at initial diagnosis per listed reference (Provan). Describing it as "crucial" prior to treatment overstates the current consensus recommendations.

Reply: We agree that the importance of testing baseline qualitative immunoglobulin is overstated in the context of current consensus guidelines. This sentence has been modified to state it is "valuable" to test immunoglobulin prior to IVIG dosing.

Changes to Text: Page 3, line 81.

(2) No image is included for Figure 2

Reply: Thank for you identifying this omission. Figure 2 was attached in the original submission, but erroneously was not pasted into the full text file. Image has been added to the full text file

Changes to Text: Figure 2 added into main text file, page 20.

(3) Minor editing is required with attention to punctuation and wording. For instance:

·Missing word "on" in 1st sentence of 2nd paragraph of introduction.

·Lack of Oxford comma in 3rd sentence of 2nd paragraph of intro makes it clunky.

·Unnecessary comma after DAT in 3rd sentence of initial workup.

·"See figure 2" needs to be in parentheses or somehow set aside from sentence.

·"circulating" instead of "circulate" Page 5, line 178

·"is inherent" instead of "in inherent"

·"Ruxolitinib" instead of "ruxolitib"

Reply: We appreciate the editor's careful review of the text. The errors noted above have been corrected and the manuscript reviewed again for punctuation and spelling.

Changes to text: Page 2, line 57-58; page 1, line 69; page 4, line 124; page 5, line 170; page 5, line 184; page 10, line 395.