

Peer Review File

Article information: <http://dx.doi.org/10.21037/aob-20-57>.

AOB Manuscript revisions:

Note: Since major revisions were made, and much of the text was moved around, the references were re-numbered to flow in order with text. So please use the manuscript version with the revisions as the 'most current' version.

Reviewer 1:

Comment 1: Depending on readership and target audience the section in the Introduction Describing the role of platelet may not be needed.

Reply 1: Agreed. We have adjusted. Please see Page 1 row 35-40.

Changes to the text:

We deleted "Platelets are specialized blood cells that help maintain the integrity of blood vessel walls by providing surfaces on which blood clotting takes place and preventing bleeding by plugging holes in the vessel walls (2)." We also removed this reference from the reference list. A normal platelet count ranges from approximately 150,000 to 400,000 per microliter of blood. If someone has a platelet count lower than 100,000 per microliter of blood with no other reason for low platelets, the diagnosis of ITP is considered (3, 4). There are three phases of the disorder including newly diagnosed (0-3 months); persistent ITP (3-12 months); and chronic ITP (12 months or longer) (3).

Comment 2: The section describing the differences between adult and children could be moved up to follow the statement that "the history of the disorder varies depending on the age at which the ITP is diagnosed".

Reply 2: Good suggestion. We have adjusted in fact we rearranged some of this introduction and then added a background subheading. Please see Page 1 row 35-45, Page 2 row 1-45,

Page 3 row 1-8.

Changes to the text:

Immune thrombocytopenia (ITP) is a rare heterogeneous autoimmune bleeding disorder that causes a lower than normal circulating platelet count from both decreased platelet production and accelerated platelet destruction. This is directly the result of autoantibody and cell-mediated immune responses targeting platelets for destruction (1). Some ITP patients are fortunate to see their disorder resolve permanently with or without the use of medical intervention (2,3). For most patients, living with ITP creates life-long challenges and impacts how they feel and function (3).

PDSA was patient-founded in 1998 empower individuals with immune thrombocytopenia and other platelet disorders through education, advocacy, research, and support. Today, the organization is a powerful force serving and unifying the global ITP community of patients, practitioners, caregivers, advocates and key disease stakeholders.

In this review, we aim to illustrate the patient perspective regarding their perceived unmet needs and the physical and emotional burden of disease in an attempt to highlight areas where healthcare providers treating ITP can enhance their current approach to managing ITP patients. This will be accomplished through a compilation of experiences with ITP collected from work the Platelet Disorder Support Association (PDSA) has done over the years in various capacities, including through the ITP Natural History Study Patient Registry and the externally led Patient-Focused Drug Development (EL-PFDD) meeting (10). Formal results from the ITP Natural History Study Patient Registry and the EL-PFDD meeting have been published previously (8, 10, 30, 32) and will be summarized further here.

In 2017, PDSA with assistance from the National Organization for Rare Disorders (NORD), launched the ITP Natural History Study Patient Registry to better understand ITP patient characteristics, their disease, disease management, and their quality of life to help to establish patient-reported outcomes and leverage ITP patients (and caregivers) as active participants in research. To date, most registry participants are from the USA (85%), female (76%), adult

(between the ages of 18-60 years), who are insured (93%), and have received treatment for their ITP (91%) at some point. Currently, the ITP Natural History Study Patient Registry has 1,110 patients enrolled to date, with 324 adult ITP patients participating in two adult-specific QoL surveys and 44 caregivers participating in one child-specific QoL survey on behalf of their child. The QoL based questions within the registry were created using NIH PROMIS standards (9), and included the following measures in the adult surveys: GRDR:ORDR Model Data, PROMIS SF v1.1 Global Health, PROMIS-57 Profile v2.0 (Investigator version), PROMIS-item bank v2.0 Emotional Support, Short form 8a; and the following for the pediatric survey: the PROMIS Ped-49 Profile v1.1 (Investigator version), and PhenX Toolkit Protocol 220702.

The EL-PFDD meeting, hosted by PDSA on July 26, 2019, integrated patient insights, needs, and priorities into drug development and evaluation and gave the ITP community an opportunity to directly inform the U.S. Food and Drug Administration (FDA) about the realities of living with ITP, the overall QoL of an ITP patient, and what patients need to ultimately achieve the best health outcomes.

Background

While all age groups are susceptible to the development of ITP (2, 10), the expected natural history of the disorder varies depending on the age at which the ITP diagnosis is made. Most adults (80%) who are diagnosed with ITP will develop the chronic form of ITP, whereas the majority (80%) of children with ITP will see their ITP resolve within the first year. As a result, adult and pediatric cases of ITP are often managed differently (5). Regardless of age or disease phase, the majority of ITP patients do not experience significant bleeding events (4). Patients with ITP may exhibit symptoms of petechiae, purpura, and gastrointestinal and/or urinary mucosal tract bleeding (1). The greatest concern with ITP is the risk of significant internal bleeding, such as an intracranial hemorrhage. Other clinically significant concerns include complications from internal bleeding and an elevated risk of thrombosis and thromboembolism (12). Management depends on severity of symptoms, platelet count, age, lifestyle, response to therapy and its side effects, the presence of other concomitant medical

issues that affect the risk of bleeding, quality of life, financial barriers, and personal preferences of both the patient and the doctor.

Patients with ITP face many challenges. Actual disease burdens and perceived disease risks both influence the physical, emotional, and social health of patients and families living with ITP impacting negatively on their overall health-related quality of life (HRQoL) (13-22). ITP is associated with considerable morbidity and mortality affecting all facets of life. Due to the heterogeneity of ITP's pathophysiology and disease course, living with ITP can be difficult and unpredictable despite several available therapies with different mechanisms of action. ITP patients experience a range of physical and emotional consequences as they monitor their platelet count, balance treatment side effects, and manage the fear of bleeding and frequent reality of relapse (23).

Comment 3: I would caution stating that patients are in remission if they have a platelet count of 50k without treatment. This should instead be considered a treatment free response. Also for this statement the authors should be clear that is not all patients but those who received treatment with romiplostim.

Reply 3: Good points. We have adjusted. Please see Page 1 row 38-39.

Changes to the text:

We removed the following text "having platelet counts greater than 50,000 per microliter of blood". We also enhanced the text to support recommendation and it now reads: "Some patients are fortunate they see their ITP resolve permanently with our without the use of medical intervention (2,3).

Comment 4: When the authors introduce the ITP registry and the Patient focused drug Development they could perhaps mention that formal results from these were published previously and will be summarized again here and include reference.

Reply 4: We can incorporate this. Please see Page 2 row 7-9.

Changes to the text:

Added: Formal results from the ITP Natural History Study Patient Registry and the EL-PFDD meeting have been published previously (8, 10, 30, 32) and will be summarized further here.

Comment 5: I would state specifics or provide a reference for the two-adult specific QoL and one Child QoL measures that were used

Reply 5: Ok. We've incorporated both. Please see Page 2 row 20-24.

Changes to the text:

The QoL based questions within the registry were created using NIH PROMIS standards (9) and included the following measures in the adult surveys: GRDR:ORDR Model Data, PROMIS SF v1.1 Global Health, PROMIS-57 Profile v2.0 (Investigator version), PROMIS-item bank v2.0 Emotional Support, Short form 8a; and the following for the pediatric survey: the PROMIS Ped-49 Profile v1.1 (Investigator version), and PhenX Toolkit Protocol 220702.

Added reference 56.

Comment 6: I would be specific for sources of some statements. For example “In ITP patients believe increasing energy level is one of the top treatment goals...” should perhaps include “respondents to the ITP world impact survey stated that...”

Reply 6: Sounds good. We will adjust. Please see Page 3 row 3-7.

Changes to the text:

Now reads: “In fact, respondents to the ITP World Impact Survey (I-WISh) stated that increasing energy levels is one of the top treatment goals (24), alongside finding a medication that reduces fatigue, anxiety around platelet count, and bruising (16, 20, 22).

Comment 7: Reference 40 does not seem to be the right reference for the statement of what patients with ITP want as it is a review regarding guidelines and gaps in guidelines

Reply 7: Apologies. I believe I may have taken this out of context. I will quote the source it

came from “Beyond the Platelet Count” a PDSA resource. Please see Page 3 row 16-17.

Changes to the text:

Patients with ITP want treatments they can afford, that last, and don’t cause additional health concerns as a side-effect or compromise their emotional well-being (26, 27, 43).” Added references and the Beyond the Platelet Count is ref 43.

Comment 8: Please provide a percentage and reference for the statement “ The high percentage of individuals who struggle to complete daily tasks...”

Reply 8: We modified the statement above for further accuracy focusing more of fatigue as the debilitating factor. Please see Page 3 row 32-35 and page 4 row 1-4.

Changes to the text:

A number of individuals struggle to complete daily tasks and activities due to fatigue associated with their ITP. For instance, work attendance, work productivity, and chores have been reported to be impacted by just over half of all ITP patients (20, 31). Respondents to the ITP world impact survey stated that overall, 84% experienced reduced energy levels and 77% stated ITP reduced their capacity to exercise, 75% of ITP patients reported they were unable to perform daily tasks, and 70% reported their social life was impaired due to their ITP (15). This reveals just how debilitating the disease is, and how no aspect of life is free from its reach.

Comment 9: It might be nice to have a bit of background on the PDSA to have context of who might be represented in the survey results

Reply 9: Agreed this is needed so we incorporated this. Please see Page 2 row 11-24.

Changes to the text:

We moved the following paragraphs up to the beginning and included more information so it now reads: In 2017, PDSA with assistance from the National Organization for Rare Disorders (NORD), launched the ITP Natural History Study Patient Registry to better understand ITP patient characteristics, their disease, disease management, and their quality of life to help to

establish patient-reported outcomes and leverage ITP patients (and caregivers) as active participants in research. To date, most registry participants are from the USA (85%), female (76%), adult (between the ages of 18-60 years), who are insured (93%), and have received treatment for their ITP (91%) at some point. Currently, the ITP Natural History Study Patient Registry has 1,110 patients enrolled to date, with 324 adult ITP patients participating in two adult-specific QoL surveys and 44 caregivers participating in one child-specific QoL survey on behalf of their child. The questions within the registry were created using NIH PROMIS standards in partnership with (NORD).

Comment 10: When discussing depression the authors could highlight the relationship between corticosteroids and depression as well as possible depression from living with the disease itself. There is a nice study by Jim George's group highlighting that patients were more bothered by steroid side effects than what their physicians asked about or appreciated.

Reply 10: Agreed. We added that key paper it is now included in references. Please see Page 8 row 7-11.

Changes to the text:

Added: "It is not clear whether depression seen in associated with ITP is a result of living with a chronic disease, or whether it is due to the disease itself, or whether it's a side-effect of treatment, such as with corticosteroids, a common ITP therapy. The effects on mental health from corticosteroids among patients with ITP has been documented, including how such effects are often under-appreciated by health care providers (39)."

Comment 11: I think that in reference to patients wanting better prediction of bleeding risk the real unmet need is that we currently don't actually have a way of doing this. There are a few studies that show some link but overall, we are very poor at identifying the patients that will go on the bleed if they have little or no bleeding at diagnosis or how to adjust determine risk of future bleeding following a first bleed.

Reply 11: There isn't a strong way to predict who will bleed critically if at presentation there

are no bleeding symptoms present (apart from severely low platelet counts) however, there are enough publications already out there that characterize warnings signs for increased serious bleeding. The goals of therapy are to treat a bleed, and to prevent a bleed. Due to the rarity and heterogeneity of immune thrombocytopenia, this is going to continue to be the case and a more active approach is needed for some ITP patients. Many patients are up to date on the latest ITP literature and become 'experts' caring for their child literally consumed by ITP on a daily basis. They expect their providers to have that same level of expertise so be able to work together to keep their child safe. Please see Page 10 row 10-16.

Changes to the text:

To date, there isn't a standard way to predict who will develop a critical life-threatening bleed. However, there is substantial guidance published to delineate which ITP patients deserve the opportunity for treatment not only to stop an active bleed, but to prevent a critical/major bleed which is an established therapeutic goal (46, 47). Critical bleeds tend to occur more in patients with critically low platelet counts who also have bleeding such as 'wet' oral bleeds, recurrent gingival bleeding, gastrointestinal bleeding, hematuria, and often have a poor or lack of response to steroids (48-54). References 48-54 added to the reference list.

Comment 12: Perhaps the first section under unmet needs could be split into further categories or moved to other sections. Some relates to communication but other information relates to risk of bleeding and watchful waiting" knowledge about the disease etc.

Reply 12: We can split into further categories and move a few things around – good suggestion. Please see Page 8 row 17-45, Page 9 row 1-46, Page 10 row 1-46, Page 11 row 1-43, Page 12 row 1-32, Page 13 row 1-33.

Changes to the text:

Unmet patient needs Communication

- Open and timely communication with ITP providers

ITP can be overwhelming for patients and their families and often can lead to isolation. Patients and their families want robust up-to-date information about ITP at the time of their

diagnosis and throughout their care.

Families want detailed protocols to provide to workplaces and schools with knowledge on what to do regarding limitations and when bleeding happens. A plan that is frequently updated as symptoms change. This need has previously been documented among parents of children with complex often rare disorders (40).

Connection

- Patients and caregivers want to be able to reach their specialist when questions come up or new symptoms appear for reassurance and guidance.

Patients want to be involved in their own management plan and they want to have more of a 'partnership' with their ITP providers. Patients want to be included in treatment decisions and they want to be educated on all available treatment options, included those not covered through their own public or private health insurance.

ITP patients often wish for the ability to connect with other families/patients with ITP who understand what it is like to live with their disorder.

Education and Patient Perceived Knowledge Deficits:

- Patients and caregivers want providers to have current knowledge about ITP and be aware of updated guidelines (10, 41, 42, 46), clinical trials and research, and all available second-line therapies.

Often, the discovery of a low platelet count is made by an emergency physician or a family doctor when a patient shows up with unexplained bruising or petechiae (42). Patients want ITP specialists to educate their colleagues to provide correct information and management recommendations while they wait for a hematologist to become involved.

ITP patients want to be informed of the risks and benefits so they can make an informed choice aligned with their treatment goals. Patients also want to be made aware of resources about their disease and how to connect with others living with their same rare disease (43). This need has also previously been documented among parents of children with complex and often rare disorders (44).

Some patients express their provider is unaware of what treatments are available to ITP patients and when it's appropriate to suggest their use. This includes not being sure when to consider splenectomy in both adult and pediatric ITP, and the overuse of corticosteroids and other deviations from recommended guidelines (42). While there are newer therapies available for ITP, still many ITP patients report they are receiving corticosteroids for longer durations than necessary (10, 45). In our registry more ITP patients (88%) have tried steroids by far more than any other available treatment regime (30). Table 1. Considered first-line therapy, steroids are less expensive than most other ITP medications, they are readily available and often increase a patients' platelet count, however this approach does not recognize the long-term burden steroids cause and the impact of daily living. Newer ITP therapies such as

thrombopoietin receptor agonists (TPO-RAs) have been shown to be effective with fewer side effects, and current guidelines suggest that if used earlier in the course of the disease, there may be better clinical outcomes for patients (42, 46). The stories patients share with PDSA of their healthcare providers who over-treat or incorrectly treat ITP patients due to their minimal or outdated knowledge about this rare disease are too common.

Enhanced understanding of bleeding risks

- Enhanced understanding is needed on when to modify individual management plans (when to treat and why) and a proper understanding of the 'watchful waiting' approach (what is it, and what it isn't) (41), and what to do when bleeding patterns change (Figure 3).

To date, there isn't a standard way to predict who will develop a critical life-threatening bleed. However, there is substantial guidance published to delineate which ITP patients deserve the opportunity for treatment not only to stop an active bleed, but to prevent a critical/major bleed which is an established therapeutic goal (46, 47). Critical bleeds tend to occur more in patients with critically low platelet counts who also have bleeding such as 'wet' oral bleeds, recurrent gingival bleeding, gastrointestinal bleeding, hematuria, and often have a poor or lack of response to steroids (48-54).

Many hematologist-oncologists who take care of patients with ITP may dedicate more time to other diseases perceived as more serious, for example, blood cancers. Therefore, they may not keep up-to-date on how to best manage patients with ITP. This results in limited availability to patients of up-to-date treatments, misuse of certain treatments or persisting with ineffective treatments, or the patient being told that they cannot be successfully treated and left with a very low platelet count, bleeding, and the aforementioned mental and physical symptoms. Similar information from a study in Italy focused on children with ITP found that caregivers wanted more empathy, humanity, and professionalism from ITP providers treating their children (19). While ITP may be 'benign' it certainly wreaks havoc to those who live with it, and those who have lost a family member from having ITP.

Patients want their health care providers to know that platelet counts matter, but it should not be the sole driver behind management decisions. Rather, therapy should be based on mitigating bleeding symptoms and improving HRQoL (10, 46). Patients and caregivers want providers to personalize risks for serious bleeding based on their personal (or their child's own) clinical history. This would include risk stratification when discussing the probability of an ICH so that ITP patients who experience serious bleeding events are not provided with the same exact ICH risk as ITP patients whose have minimal bleeding such as mild petechia and bruising. Family members who lost a relative to ITP from an intracranial hemorrhage (ICH) want providers to be vigilant about monitoring their ITP patients for an ICH and other severe

bleeding events even though they are a rare complication. This includes being knowledgeable about published increased risks and the various ways symptoms of an ICH may present. One of the EL-PFDD panel members and video contributors spoke about their child who died suddenly and unexpectedly from an ICH secondary to ITP said “we [he and his wife] want to create this environment and perhaps change protocol, guidelines, so hopefully another family doesn’t have to go through this event” (Figure 3).

Diagnostic improvements:

- Patients want to understand if their ITP is primary or secondary, and they wish to receive their diagnosis in a timely manner.

Since ITP is a diagnosis of exclusion (44) it can be challenging to confirm whether ITP is primary or due to an underlying secondary cause. Most patients want to understand if their thrombocytopenia is genetic and if there are risks to other family members. Genetic testing for thrombocytopenia is available, and patients are

interested in learning more about when such testing would be appropriate for them. Patients also want their diagnosis in a timely manner. Using data from our registry, 32% had to wait for over a year after the onset of symptoms to be officially diagnosed with ITP (8).

Treatments:

- There is an urgent unmet need for new and efficient therapies, especially those that target unexplored disease mechanisms, to easily and safely treat and manage ITP and improve the quality of life for ITP patients (43, 55).

One of the greatest frustrations expressed from patients regarding managing their ITP is the high likelihood of relapse following standard first-line therapies (steroids and IVIG) that will lose their clinical effectiveness often long before their side-effects resolve. Often, the

side-effects associated with treating ITP outweigh the decision to treat a low platelet count, leaving some patients at risk for bleeding. A panellist at the EL-PFDD meeting who had spent eight years training for wrestling on a varsity team and a career in the military stated: “I was crushed ... I gained 18 pounds from prednisone in one month. I started getting bullied by the people I had wrestled with all those years. I was devastated” (Figure 1). Another panellist stated: “So many of us hang our hopes on the next treatment” (Figure 2). ITP patients and their physicians currently cycle through a series of treatment options, each with limitations and challenges (10). In the end, patients are looking for a treatment that lasts and does not negatively impact their QoL (55). Ideally, therapies should have fewer side effects and patients should not feel forced into splenectomy or continued steroid use or run out of treatment choices.

(Table 1).

Access issues:

- Patients want their health care providers to advocate to change existing policies and enable ITP patients to access the most appropriate treatments when needed.

Access to newer ITP therapies can be a challenge depending on insurance coverage and country of origin. Sometimes, the ‘most appropriate’ treatment to improve disease symptoms and HRQoL cannot be accessed until the ITP patient has demonstrated previous failure to a less effective therapy, or there is a need to select from treatment lines in a step-like fashion which does not meet current standard guidelines for ITP management. Public drug funding programs are limited and often do not cover off-label use. Patients often need private insurance or have to pay out-of-pocket costs. For minors, drug coverage may end the moment they finish school or turn 21-25 years of age if they are currently using a parents’ private insurance plan. PDSA patient members (Figure 1 and 2) outline the importance of obtaining the ‘most appropriate’ therapy.

Patients are motivated to participate in anything that could help control their platelet count and ITP symptoms and believe that limited/no access to clinical trials or newer treatments is a gap in care due to previously established clinical end-points. Currently, within our patient registry, 93% of participants have indicated they would be willing to be part of a clinical trial for ITP. On-going research, clinical studies, and therapeutic development are vital to improving the treatment landscape, giving patients more choices with which to live their lives fully, with few side-effects and long-term control of their ITP (8). Participation in research also allows for priorities of rare-disease patients to be recognized. Often access to clinical trials and research opportunities depends on geography and whether their health care provider is aware of them. Patients want studies to address the burden of their disease beyond the platelet count. Patients want increased awareness in public and professional health communities and comprehensive treatment centers to improve care and outcomes. Raising awareness for ITP in the clinical sphere is crucial in better informing medical professionals, and raising public awareness for ITP is vital in empowering patients to take control of their disease. Collaboration with ITP experts and establishing centers of excellence worldwide for ITP and other platelet disorders could mitigate the risk posed by non-specialists treating thrombocytopenia patients, thus improving treatment options, therapeutic experience, and quality of life.

More treatment options for children with ITP:

- While treatment options are expanding for children with ITP many of the newer innovative therapies are approved for use only in adults, but not for children.

Young ITP patients share the financial challenges involved in accessing new treatments, and how long it took to obtain effective treatment (Figure 1). Since there are less children with ITP requiring treatment compared to adults, the fear is that effective therapies will continue to be out of reach for many. Access to additional therapeutic options could reduce the emotional toll the disease has on children, who often suffer the most from restricted activities (18).

Acknowledgement of their ITP experience:

- Patients want their providers to have a better understanding of their disease experience.

Everyone's journey with ITP is unique. For many adults and children with ITP, the impact on their significant levels of fatigue, anxiety, and depression deserve a greater appreciation because it affects all aspects of their HRQoL. Patients are the experts on what it's like to live with ITP and can best identify and articulate the impact ITP has on their everyday life. They want their providers to listen to their symptoms and challenges without judgement or correction. Many patients report their fatigue is not recognized as part of their ITP or that the emotional toll ITP has on their life is not recognized or valued (15, 16, 20, 22). This is a tragedy considering these are the effects of living with ITP that matter most to patients.

Reviewer 2:

Comment 13: Expressions such as labyrinth of challenges " showcase the patient Perspectives "robbed of the ability to" "gaps in care" should be avoided in a medical journal manuscript.

Reply 13: Thank you. We have removed such expressions and replaced with the

following changes detailed below. Please see Page 3 row 1, Page 2 row 1, Page 3 row 30-32, Page 8 row 14 (Abstract page 1 row 21-23 and 24-28), Page 9 row 17.

Changes to the text: Removed the word "labyrinth" and replaced with "many". Removed the word "showcase" and replaced with "illustrate." Removed the word "robbed" and replaced with: Many patients and caregivers expressed that they or their loved ones have had opportunities taken from them to participate in activities they love or pursue things they are passionate about (Figures 1-3)." Removed the term 'gaps in care' in four places and replaced with:

- The following are patient perceived deficiencies in care identified by individuals with ITPs

who are PDSA members for the purpose of striving for change and enhanced management.

- Communication, Education and Patient Perceived Knowledge
- Here, we review the patients' perspective on unmet needs, and the physical and emotional burden of disease in an attempt to highlight areas where healthcare providers treating ITP can enhance their current approach to managing a patient with this rare disease.
- Unmet needs identified include knowledge and communication deficiencies, the need for diagnostic improvements, access issues to the most appropriate treatments, and awareness of the extent to which ITP impacts HRQoL both on a physical and mental health level.
- Education and Patient Perceived Knowledge Deficits

Comment 14: ...critical comparisons between the presented cohorts" who like to talk about their disease issues and those of control groups as well as subgroups of disease with different severities.

Reply 14: This current study is intended to share the patient perspective through a non-profit support group dedicated to enhancing patient care and representing the patient voice. It is a compilation of our projects sharing the patient voice. In order to add in some type of a 'control' cohort we incorporated national mental health data from the general population. For greater comparison, we also included information on QoL findings identified among others with autoimmune disease. Please see Page 4 row 10-14, Page 6 line 11-12.

Changes to the text:

Under fatigue section – Fatigue is the most common symptom reported by patients with ITP regardless of age (29, 32, 33). In many cases, it is the most severely debilitating symptom reported by patients living with ITP (21, 23). This is also supported by research from within the autoimmune disease community, where fatigue rates are high, revealing 98% of patients with an autoimmune disease suffer from fatigue, and almost 60% reporting their fatigue levels are the most debilitating symptoms of their disorder (56). Unfortunately, many providers still undervalue the impact fatigue has on patients living with ITP (15, 16, 20, 25).

Added reference 56 to references.

Under pain section – Pain is not typically reported in the literature as a symptom of ITP. Approximately 15% children are reported to experience pain in the general population, as reported by their parents or caregiver (34). Within our pediatric ITP population, 42% reported they felt pain as part of their ITP. For some ITP patients (9%) this interfered with their ability to finish their schoolwork (32). Sleep was also impacted by pain; in fact, 36% reported difficulties falling asleep in the last seven days (32) (Figure 6). It is unclear the exact nature or etiology of their pain, if it is treatment related or part of the disease. Future directions should look to see if pain and pain-induced sleep disturbances are also present among adults represented in our database. Added reference 34 to the reference list.

Under anxiety and depression section - In the general population, anxiety disorders affect over 18% annually (35, 36). Over 7% of the general population experience clinical depression each year (36).

Comment 15: Additions of possible solutions of the described problems would enhance the attractiveness of the manuscript not only the wish to participate in trials of new drugs” but also participation in scientific “ socio-psychological ” behavioral studies. Such studies may influence caregivers “general practitioners and experts in the field.

Reply 15: Agree. We will add in something to that effect. Please see Page 8 row 28-36, Page 9 row 4-9, 43-46 Page 10 row 1-2, 45-46, Page 11 row 17-20, Page 12 row 2-5, and Page 13 row 30-33.

Changes to the text:

Unmet patient needs Communication section - Possible solution: Health care providers treating ITP patients should have standard protocols to provide to workplaces, schools, and ITP families regarding when to seek medical attention, what symptoms to report, and possible restrictions if they apply. Health care providers could consider connecting with the PDSA for patient resources to give to newly diagnosed adults and children with ITP. If ITP management is provided through a specialist within a hospital setting, health care providers

could also consider ensuring all providers among the hematology/oncology team manage ITP patients similarly guided by professional practice guidelines to ensure that patient care does not change depending on the provider seen within that same institute, for optimal patient care.

Connection section - Possible solution: ITP patients (or their parent/caregiver) should be provided with a number to call after-hours and during the day if they have any questions or concerns. These calls should be included in the patient's medical record. Health care providers could also consider referring their ITP patients/families to the PDSA to connect with other individuals and families with ITP, and gain access to support groups and discussion groups often with an ITP specialist.

Education and Patient Perceived Knowledge Deficits section - Possible solution: Health care providers treating ITP patients should stay onto of current disease

information, included updated protocols and best practices. Since ITP is heterogenous and a rare disease, it is essential that health care providers consider using guidelines

written by ITP experts when making clinical judgements. They could also consider when new guidelines are developed to hold rounds or present to their colleagues such as pediatricians, family doctors, emergency staff, and inpatient providers.

Enhanced understanding of bleeding risks section - Possible solution: Since knowledge in medicine expands rapidly, professional organizations for hematologists could consider implementing updated educational initiatives based on evidence based best practices that are mandatory for all hematologists. Consider also ensuring all front-line health care providers are trained to deal with atypical ITP, such as chronic severe thrombocytopenia in association with moderate-severe bleeding.

Diagnostic improvements section - Possible solution: Consider genetic testing for chronic

ITP patients, particularly children who are unresponsive to steroids. To provide optimal knowledge of the risks and benefits of genetic testing, providers could consider referring their patients to a genetic counsellor to discuss if testing is relevant for them.

Treatments section in addition to access issue section and more treatment options for children with ITP section - Possible solution: Health care providers treating ITP patients could consider taking any opportunity they are presented with to advocate for their patients for innovative ways to treat ITP. This possible solution applies when talking about access issues and better treatments for pediatric ITP patients.

Acknowledgement of their ITP experience section - Possible solution: Consider asking ITP patients at each visit how they have been doing mental health wise, and physically, in addition to asking about sports and bleeding events. When patient's report fatigue, consider refraining from saying fatigue isn't part of ITP even though its pathophysiology is not well understood.

Reviewer 3:

Comment 16: Conflicts of Interest Statement: We found that the COI part of the manuscript is not consistent with the COI forms. Please click the "Generate Disclosure Statement" bottom in the forms and add each section 6 of the form of every author to COI part of the article, which is behind "All authors have completed the ICMJE uniform disclosure form."

Reply 16: Thank you – please let us know if you need more information. We've corrected our statement since I had submitted late one COI. Please see Page 14 row 33-38.

Changes to the text:

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://www.icmje.org/conflicts-of-interest/>). The authors have no financial conflicts of interest to declare, however it has been declared that one of the authors had a child who passed away from immune thrombocytopenia. Reporting grants and other from

Amgen, grants from Argenx, grants and other from Pfizer, grants from Principia, grants from Rigel, grants and other from UCB, grants and other from Novartis, grants from CSL Behring, outside the submitted work.