Pediatric Refractory Immune Thrombocytopenia: a Systematic Review

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Abstract

Pediatric immune thrombocytopenia (ITP) is an acquired disorder associated with autoimmune destruction and impairment of platelet production in children. Some children exhibit poor or transient response to ITP-directed treatments and are referred to as having refractory ITP (rITP). There is currently no consensus on the definition of rITP, nor evidence-based treatment guidelines for patients with rITP. After a survey of pediatric ITP experts demonstrated lack of consensus on pediatric rITP, we pursued a systematic review to examine the reported clinical phenotypes and treatment outcomes in pediatric rITP. The search identified 253 relevant manuscripts; following review, 11 studies proposed a definition for pediatric rITP with no consensus amongst them. Most definitions included sub-optimal response to medical management, while some outlined specific platelet thresholds to define this sub-optimal response. Common attributes identified in this study should be used to propose a comprehensive definition, which will facilitate outcome comparisons of future rITP studies.

Introduction

Pediatric immune thrombocytopenia (ITP) is an acquired autoimmune disorder caused by destruction of platelets and impairment of platelet production which manifests as isolated thrombocytopenia and variable bleeding symptoms in children. ITP can be classified based on disease duration and includes newly diagnosed (0-3 months), persistent (3-12 months), and chronic (>12 months). Evidence-based ITP guidelines and an international consensus report recommend frontline therapy for patients with newly diagnosed ITP to include observation, corticosteroids, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Spontaneous remission has been reported in more than 50% of pediatric patients. Patients with significant bleeding symptoms may undergo additional treatment with either an additional first-line therapy, initiation of thrombopoietin receptor agonists (TPO-RA), rituximab, other immunosuppressant therapy, or splenectomy. The goals of acute treatment are to control active bleeding, improve quality of life, and minimize adverse events, irrespective of platelet count.
Data exist to guide the development of diagnostic and therapeutic approaches for patients with newly diagnosed, persistent, and chronic ITP. Some children will have a poor or transient response to ITP-directed treatments and are referred to as refractory ITP (rITP). An International Working Group defined a group of patients as having rITP if they met two criteria: (1) they failed splenectomy and (2) they either continued to have severe ITP or a risk of bleeding requiring treatment. The 2011 American Society of Hematology (ASH) guidelines also defined rITP as having severe ITP that persisted after splenectomy. However, few pediatric patients undergo splenectomy. As such, the above rITP definition would exclude the majority of challenging pediatric patients. Some children with ITP do not respond or have only a transient response to multiple first and or second-line therapies. These patients are subject to ongoing bleeding risk, and consequently, patients' estimated life expectancy and quality-adjusted life expectancy are severely compromised. In addition to the drawbacks of the current pediatric rITP definitions, there are also no evidence-based guidelines to support treatment approaches in this patient population.

The ITP Consortium of North America (ICON) identified a critical need to examine the current definitions of rITP in children used in the medical literature and in clinical practice. An ICON working group performed a systematic review of the literature to examine current use of the term rITP and surveyed ICON members on clinical use of the term rITP. Based on these findings, the authors propose an updated definition as the first step in developing standardized treatment recommendations for pediatric rITP.

Methods

Study identification

MEDLINE, Embase, and the CENTRAL Trials Registry of the Cochrane Collaboration were searched using the Ovid interface. Searches were limited to English, French, German, Polish, and Spanish languages and to the publication year January 2000 up to July 2021. Searches were designed and conducted by a librarian experienced in systematic reviews, using a method designed to optimize term selection (KoH). Electronic search strategies are presented in Supplemental Appendix A.

Eligibility criteria

Studies where >20% of participants were pediatric (< 18 years of age) and diagnosed with “refractory” or “treatment-resistant” ITP were included in this systematic review. For inclusion, studies needed to report on diagnostic criteria, laboratory work-up, or treatments other than first-line therapy (short course prednisone, IVIG, or anti-D). Commentaries, editorials, narrative reviews, conference abstracts, reviews, case reports or case series with fewer than ten patients were excluded.

Study selection and data extraction

Duplicate records were removed, and records retrieved via electronic search were then downloaded and imported into a Reference Manager database and uploaded to InsightScope, a web platform specifically designed to facilitate systematic reviews (KoH). Records were appraised against the inclusion criteria using a three-step method: initial review for inclusion based on defined criteria (MS, KoH), abstract review (LI, SD) with arbitration (ML, RK, JL), and full-text review (LI, SD) with arbitration (ML, RK, JL). All included records subsequently underwent data extraction independently by two reviewers (LI, SD). Variables of interest included country, study design, patient population, refractory ITP definition, treatment regimen, patient outcomes, and laboratory testing.

Provider Refractory ITP survey

A survey was done to gather the opinions of experts in the field. A web-based survey consisting of 19 questions was sent via Survey Monkey, using the Pediatric ITP Consortium of North America Membership listing (1/11/2021), consisting of pediatric hematology/oncology providers with a research or clinical interest in ITP. Reminders were provided during monthly consortium calls, and the survey remained open for 9 months. Providers were asked to complete one survey for each participating institution. Questions were presented as both hypothetical case scenarios as well as simple descriptions (Appendix B). Respondents were
also given an opportunity to provide general comments. The provider survey did not collect information about treatment.

**Results**

**Study characteristics**

In total, 2148 records were identified through the initial database search, resulting in 1470 records for screening. After abstract and full-text screening, a final list of 321 records underwent standardized data extraction. In total, we found 253 records that were relevant to the objective of this study. Eleven out of the 253 records (4.3%) discussed the definition of rITP (Fig. 1). Among the 11 studies that discussed the definition of rITP, seven were retrospective and four were prospective. Seven of the 11 studies specifically included rITP patients. Of the seven studies, three of the studies classified rITP as “chronic ITP,” three of the studies included solely rITP patients, and three of the studies did not differentiate between chronic and rITP.

**Refractory ITP definition**

The variables used when defining rITP included: patient history (7 studies), complete blood count with differential and platelets (3 studies), bleeding risk (3 studies), and splenectomy outcome (1 study) (Table 1). Among the 11 studies, nine defined rITP as being unresponsive to medical treatment options such as splenectomy, corticosteroids, IVIG, cyclosporine, rituximab, and/or mycophenolate mofetil. Six studies further defined rITP as an increased risk of bleeding necessitating treatment, requiring frequent therapeutic intervention or therapy (International Working Group (IWG) definition). Three studies required specific platelet counts for rITP: two studies defined rITP platelet counts as less than 30x10^9/L and one study defined rITP platelet counts as less than 20x10^9/L. One study’s rITP definition included: “unable or disinclined to undergo splenectomy and in whom primary objective is to improve health related quality of life was used”.

**Treatment in Patients with Refractory ITP**

Eight out of 11 studies discussed the treatment for pediatric patients with rITP. Treatment modalities included splenectomy, rituximab, romiplostim, and dapsone (Table 2). The most frequent treatment used in the treatment of rITP was rituximab; the reported efficacy of rituximab in rITP was wide-ranging from 0-72%. For splenectomy, eight out of 13 patients achieved complete remission, 2 partial remission, and 3 had no response. Eight out of 11 studies discussed the treatment for pediatric patients with rITP. Treatment modalities included splenectomy, rituximab, romiplostim, and dapsone (Table 2). The most frequent treatment used in the treatment of rITP was rituximab; the reported efficacy of rituximab in rITP was wide-ranging from 0-72%. For splenectomy, eight out of 13 patients achieved complete remission, 2 partial remission, and 3 had no response.

**Survey Results**

There were 25 respondents from the 50 ICON sites (50% response). Questions were posed as 7 case descriptions followed by 5 general questions about types of patients (Supplemental Appendix B). Information about individual providers were not collected. Most respondents completed all questions (20/25). There was little agreement amongst providers for both the case scenarios and patient descriptions as to which patients would be considered refractory. Only one question achieved unanimity amongst respondents: “Is a patient with ongoing symptoms (fatigue) regardless of platelet count responses refractory?” to which respondents universally agreed “no.” Only 55% of respondents felt that patients who fail to respond to initial second line therapy are refractory (Figure 2A). There was a wide variation in the identification of refractory ITP amongst the respondents (Figure 2B). The majority, 96%, of respondents agreed that a patient with chronic ITP and minimal or transient IVIG response and lack of TPO-RA response could be considered refractory. Additionally, 85% said a newly diagnosed patient who failed to respond to IVIG, steroids or TPO-RA and required platelet transfusions for bleeding could be considered refractory (based on case scenarios). Seventy-five percent of respondents agreed that a transient response to IVIG alone was not sufficient to label a patient refractory.

**Discussion**

This systematic review identified 11 studies that reported a definition of pediatric rITP with wide variation...
between studies. After examining the reported definitions, there appears to be general agreement on the following criteria: (1) unresponsive to medical interventions, (2) persistent or recurrent platelet count <20 x10^9/L, and (3) requiring treatment to reduce clinically significant bleeding or risk of bleeding (Table 1). The ICON survey also demonstrates differences in provider definitions of rITP, even among those with expertise in the field (Figure 2A and 2B). A consensus definition would greatly aid researchers in clarifying eligibility and reporting in clinical trials, as well as clinicians in standardizing clinical practice and inter-professional communication.

In addition to the lack of consistency between rITP definitions, there was also no standardized treatment regimen noted. Of the studies that reported on treatment, rituximab was the most commonly prescribed therapy. The American Society of Hematology 2019 guidelines currently recommend rituximab for refractory pediatric ITP following: (1) failure of first line treatment and TPO-RAs in patients with ITP lasting >3 months, (2) patients who suffer from non-life-threatening mucosal bleeding and/or (3) diminished health-related quality of life and do not respond to first line treatments. Overall, response rates to rituximab in pediatric patients range from 23% to 69%. This wide range may be attributed to differences in patient demographics and disease characteristics (ie, prior therapies, duration of disease, severity of disease). Indeed, studies have identified potential predictors for rituximab response, such as gender (female as a positive predictor), patient age (older age as a positive predictor), and treatments prior to rituximab (prior positive response to steroids as a positive predictor). Further, variation in study methodology may also contribute to the wide-ranging response rate of rituximab. Although most patients received the standard dose of rituximab (375 mg/m^2/week of rituximab for 4 weeks), some studies prescribed modified doses and infusion numbers, guided by blood cell count. These treatment schedules were inconsistent as studies failed to provide clear criteria for treatment escalation or tapering, and may likely have confounded the reported results. The comparability and interpretation of results were also complicated by the lack of consistency between studies’ criteria for complete and partial response. Although most studies referenced criterion outlined by the IWG, others constructed their own criteria, ranging from >75x10^9/L to >150x10^9/L. Despite the variation in response, rituximab remains an efficacious monotherapy that warrants further exploration for this challenging patient population.

While most studies involve a single 4-week course of rituximab, one study investigated outcomes following multiple courses of rituximab. In addition, combination therapy involving rituximab, cyclophosphamide, and dexamethasone has been previously used in the treatment of autoimmune cytopenias in adults but it is not clear how well these results will translate to the pediatric setting.

Other treatments that were used in rITP include dapsone, TPO-RAs, and splenectomy. Although it has not been as well-studied in pediatric populations, dapsone has historically been a safe and effective treatment for chronic ITP in adults. The response rate of dapsone ranges from 9-50% while that of splenectomy is 50-70%. Studies involving splenectomy consistently demonstrated partial to complete responses in patients who were refractory to prior treatments. Of note, some studies’ definition of rITP was contingent on patients having undergone splenectomy. Current ASH guidelines list splenectomy as a deferred treatment option after other treatment options have been attempted. Therefore, requiring that the patient failed prior splenectomy is not an appropriate criteria for children with ITP.

Romiplostim appeared in only one study with moderate success, as 5 out of 10 patients showed significant clinical improvement. Currently, TPO-RAs, such as romiplostim, are indicated in pediatric patients who have ITP >3 months and are unresponsive to corticosteroids, immunoglobulins, or splenectomy. Most of the literature pre-dates the approval of TPO-RAs, which may have a role in combination regimens for rITP.

Conclusion

The systematic literature review and survey presented herein aimed to improve our understanding of pediatric rITP definition and response to treatments. We identified a paucity of studies reporting on rITP definition with no consensus, corroborated by survey results demonstrating an ongoing lack of consensus amongst
experts. Leaders in ITP research must agree on a standardized definition of rITP to ensure reliability and
generalizability of future research. Of note, prior splenectomy should not be included for the pediatric rITP
definition for reasons explored above. Using a standardized definition will then facilitate future research in
the development of evidence-based treatment guidelines for pediatric rITP.

Conflict of Interest Statement/Disclosures:
RK consultancies: Agios Pharmaceuticals, Amgen Inc, Hoffman La Roche, Novo Nordisk, Octapharma AG,
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(Sanofi)
JL consultancies: Agios Pharmaceuticals, Forma Therapeutics, Novartis, Bioproducts, Laboratory
ML consultancies: MPL is an advisory board member for Octapharma, Dova, Principia and Shionogi, a
consultant for Novartis, Shionogi, Dova, Principia, Argenx, Rigel and the DOJ, and has received research
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developing the electronic search strategies.

References


30. Amgen In. NPLATE® (romiplostim) for injection, for subcutaneous use [prescribing information]. Published online 2018.

31. Corporation NP. PROMACTA® (eltrombopag) tablets, for oral use; PROMACTA® (eltrombopag) for oral suspension [prescribing information]. Published online 2018.


Appendix A. Electronic search strategies

Note: Searches were conducted using an Ovid multi-database search and duplicate records were removed online giving preference to MEDLINE, then Embase, with no field preference. Lines 1-18 are optimized for MEDLINE. Lines 19-37 are optimized for Embase and lines 38-56 are optimized for CENTRAL. The next lines isolate the records to the database the search was designed for, combine those sets and then remove duplicate records and final isolate the records from each database again so each can be downloaded and imported into the citation manager using a database-specific import filter.

1. Purpura, Thrombocytopenic, Idiopathic/ or (ITP or Immune thrombocytopen* or autoimmune thrombo-cytopen* or idiopathic thrombocytopen* or werlhof*).ti,ab,kf.

2. (thrombocytopenia and (Evans or immune dysregulation or ALPS or CTLA4 or SLE or CVID)).mp.

3. inherited thrombocytopenia.ti,ab,kf.

4. (thrombocytopenia and inherited marrow failure).ti,ab,kf.

5. 1 or 2 or 3 or 4

6. (refractory or intractable or treatment-resistant or treatment failure* or steroid-dependent or second line or chronic*).ti,ab,kf.

7. (child* or adolesc* or infan* or pediatr* or paediatr*).mp.

8. Terminology as Topic/ or (terminology or nomenclature or definition or criteria or classification).mp.

9. Purpura, Thrombocytopenic, Idiopathic/di or (diagnosis or diagnostic or workup or work-up).ti,ab,kf.

10. Purpura, Thrombocytopenic, Idiopathic/dh, dt, pc, rt, rh, th, cl

11. (therapy or therapeutics or treatment or treatment or management or intervention or Second line or novel or Rituximab or romiplostim or thrombopoietin-receptor agonists or immunosuppress* or glucocorticoid* or prednisone or dexamethasone or eltrombopag or Mycophenolate Mophetil or Mycophenolic acid or Azathioprine or Vin-cristine or vinblastine or Cyclophosphamide or autologous stem cell or dexamethasone or splenectomy*).mp.

12. 5 and 6 and 7 and (9 or 10 or 11)

13. 5 and 7 and 8
14. 12 or 13
15. limit 14 to yr="2000 - 2021"
16. limit 15 to (english or french or german or polish or spanish)
17. limit 16 to (comment or editorial or letter)
18. 16 not 17
19. Idiopathic Thrombocytopenic Purpura/ or (ITP or Immune thrombocytopen* or autoimmune thrombocytopen* or idiopathic thrombocytopen* or werlhof*).ti,ab,kw.
20. (thrombocytopenia and (Evans or immune dysregulation or ALPS or CTLA4 or SLE or CVID)).mp.
21. inherited thrombocytopenia.ti,ab,kw.
22. (thrombocytopenia and inherited marrow failure).ti,ab,kw.
23. or/19-22
24. (refractory or intractable or treatment-resistant or treatment failure* or steroid-dependent or second line or chronic).ti,ab,kw.
25. (baby* or babies* or newborn* or infant* or neonat* or preschool* or pre-school* or child* or pediatric* or paediatric* or teen* or adolescents* or paediatric* or paediatric*).mp.
26. Nomenclature/ or (terminology or nomenclature or definition or criteria or classification).mp.
27. Idiopathic Thrombocytopenic Purpura/di or (diagnosis or diagnostic or workup or work-up).ti,ab,kw.
28. Idiopathic Thrombocytopenic Purpura/dt, pc, rt, rh, th, cl
29. (therapy or therapeutics or treatment or management or intervention or Second line or novel or Rituximab or romiplostim or thrombopoietin-receptor agonists or immunosuppress* or glucocorticoid* or prednisone or dexamethasone or eltrombopag or Mycophenolate Mofetil or Mycophenolic acid or Azathioprine or Vin-cristine or vinblastine or Cyclophosphamide or autologous stem cell or dexamethasone or splenectomy*).mp.
30. 23 and 24 and 25 and (27 or 28 or 29)
31. 23 and 25 and 26
32. 30 or 31
33. limit 32 to yr="2000 - 2021"
34. limit 33 to (english or french or german or polish or spanish)
35. limit 34 to embase
36. limit 35 to (editorial or letter or "review")
37. 35 not 36
38. (ITP or Immune thrombocytopen* or autoimmune thrombocytopen* or idiopathic thrombocytopen* or werlhof*).ti,ab,kw.
39. (thrombocytopenia and (Evans or immune dysregulation or ALPS or CTLA4 or SLE or CVID)).mp.
40. (thrombocytopenia and inherited marrow failure).ti,ab,kw.
41. inherited thrombocytopenia.ti,ab,kw.
42. or/38-41
43. (refractory or intractable or treatment-resistant or treatment failure* or steroid-dependent or second line or chronic).ti,ab,kw.
44. (baby* or babies* or newborn* or infant* or neonat* or preschool* or pre-school* or child* or pediatric* or paediatric* or teen* or adolescent* or pediatric* or paediatric*).mp.
45. (terminology or nomenclature or definition or criteria or classification).mp.
46. (diagnosis or diagnosis or workup or work-up).ti,ab,kw.
47. (therapy or therapeutics or management or intervention or Second line or novel or Rituximab or romiplostim or thrombopoietin-receptor agonists or immunosuppress* or glucocorticoid* or prednisone or dexamethasone or eltrombopag or Mycophenolate Mofetil or Mycophenolic acid or Azathioprine or Vin-cristine or vinblastine or Cyclophosphamide or autologous stem cell or dexamethasone or splenectomy*).mp.
48. 42 and 43 and 44 and (46 or 47)
49. 42 and 44 and 45
50. 48 or 49
51. limit 50 to yr=’2000 - 2021’
52. 18 use medall
53. 37 use emczd
54. 51 use cctr
55. or/52-54
56. remove duplicates from 55
57. 56 use medall
58. 56 use emczd
59. 56 use cctr

Appendix B. Provider rITP survey

REFRACTORY ITP SURVEY:

1. Case Vignettes:
2. A 3 year-old previously healthy F presents with diffuse bruising, petechiae, and a few wet purpura over the oral mucosa. She is found to have isolated thrombocytopenia (4k), with platelet size variance on smear review (including large and giant platelets), and some reactive-appearing lymphocytes, but no blasts or other morphological abnormalities consistent with a diagnosis of Acute ITP. Parents are extremely anxious about ongoing injuries for this active toddler, and also live ~3 hours from the nearest major medical center. Therefore, the decision is made to proceed with frontline platelet-directed therapy. She receives IVIG 1 g/kg, and although cutaneous symptoms are slightly improved ~5 days later, platelet count remains <10k. She is started on oral prednisone 4 mg/kg/day divided BID at this point; and CBC one week later reveals platelet count remaining fairly unchanged, at 12k. She has had no major bleeding events, but continues to have some mild intermittent wet purpura, and diffuse cutaneous symptoms; with significant anxiety from parents. Blood type is A-; so the decision is made to proceed with a second dose of IVIG 1 g/kg following which, symptoms briefly improve, but return to baseline within 1 week, at the time CBC reveals platelet count remaining at 10k.

3. Would you consider this refractory ITP? Yes/No
4. Would you work this patient up for alternate etiologies of thrombocytopenia at this time (vs. continued observation, or second-line management)? Yes/No
5. If so, what additional work-up would you obtain? (check all that apply)
6. HIV
7. Hepatitis
8. H. Pylori
9. CMV and/or EBV
10. ANA Profile
11. Immunoglobulins
12. Lymphocyte subsets
13. Complement levels
14. ALPS work-up

This patient continues to have cutaneous symptoms and platelet count fluctuating between 10k and 30k over the next several months, but no major bleeding events. After ~1 year, parents feel that patient’s quality of life is suffering significantly (due to activity and environment restrictions), and they would like to be able to send her to pre-K safely, without major restrictions. Therefore, the decision is made to initiate second-line therapy, and parents choose TPO-RA therapy. After several weeks of therapy, patient shows minimal platelet response with romiplostim; and is transitioned to eltrombopag therapy. Again, cutaneous symptoms are improved, but platelet count remains fairly unchanged (<50k).

Would you consider this refractory ITP? Yes/No
Would you work this patient up for alternate etiologies of thrombocytopenia at this time (vs. continued observation, or second-line management)? Yes/No
If so, what additional work-up would you obtain? (check all that apply)
1. HIV
2. Hepatitis
3. H. Pylori
4. CMV and/or EBV
5. ANA Profile
6. Immunoglobulins
7. Lymphocyte subsets
8. Complement levels
9. ALPS work-up

Given continued concern from parents, lifestyle restrictions, and intermittent minor bleeding events, the decision is made to continue pursuing other potential second-line therapies. She is treated with rituximab (375 mg/m²/week x4), and shows an excellent clinical and platelet response (100k – 200k range).

Would you consider this refractory ITP? Yes/No
Would you work this patient up for alternate etiologies of thrombocytopenia at this time (vs. continued observation, or second-line management)? Yes/No
If so, what additional work-up would you obtain? (check all that apply)
1. HIV
2. Hepatitis
3. H. Pylori
4. CMV and/or EBV
5. ANA Profile
6. Immunoglobulins
7. Lymphocyte subsets
8. Complement levels
9. ALPS work-up
After ~9 months, patient’s platelet counts again begin trending downward, eventually to her former baseline ~10k – 30k; and similar clinical symptoms return. The decision is made to proceed with splenectomy at this point, and patient responds very well with post-surgical platelet count to a peak of ~500k.

Would you consider this refractory ITP? Yes/No

Would you work this patient up for alternate etiologies of thrombocytopenia at this time (vs. continued observation, or second-line management)? Yes/No

If so, what additional work-up would you obtain? (check all that apply)

1. HIV
2. Hepatitis
3. H. Pylori
4. CMV and/or EBV
5. ANA Profile
6. Immunoglobulins
7. Lymphocyte subsets
8. Complement levels
9. ALPS work-up
10. A 4 year-old previously healthy M presents with diffuse bruising and petechiae, along with recent epistaxis episodes, all resolving in <5 minutes. He is found to have isolated thrombocytopenia (6k), with platelet size variance on smear review (including large and giant platelets), and some reactive-appearing lymphocytes, but no blasts or other morphological abnormalities consistent with a diagnosis of Acute ITP. Given his lack of significant bleeding symptomatology, and parental comfort level, the decision is made to proceed with thorough education, return precautions, and observational management. Patient returns in ~2-3 weeks, with no major bleeding events or concerns, and platelet count remaining <10k. Observation is continued. However, ~2 weeks later, patient presents with hematuria, and is admitted for platelet-directed therapy. IVIG 1 g/kg is administered, but platelet count remains ~unchanged over the subsequent 48 hours, and patient’s hematuria persists, with Hgb dropping from 11.8 to 9 g/dL. IV methylprednisolone is initiated, at 30 mg/kg (max 1 g) IV daily doses; but the following day, patient’s hematuria has not improved, and Hgb is now 8 g/dL. Patient is DAT negative, blood type O+, and has no evidence of renal dysfunction. Therefore, anti-D immune globulin 75 mcg/kg is administered; but again, patient’s platelet count remains <10k over the next ~36 hours (on continued methylprednisolone as well), with Hgb trending down to ~7 g/dL. Romiplostim 10 mcg/kg is administered x1, and patient is planned for slow platelet drip/transfusion.

11. Would you consider this refractory ITP? Yes/No
12. Would you work this patient up for alternate etiologies of thrombocytopenia at this time (+/- continued emergent/second-line ITP management)? Yes/No

If so, what additional work-up would you obtain? (check all that apply)

1. HIV
2. Hepatitis
3. H. Pylori
4. CMV and/or EBV
5. ANA Profile
6. Immunoglobulins
7. Lymphocyte subsets
8. Complement levels
9. ALPS work-up
10. An 8 year-old M presents with increased bruising and episodes of epistaxis over the past ~month, and is found to have isolated thrombocytopenia (to 18k), with elevated immature platelet fraction (13%), and smear review showing platelet size variance (including large and giant platelets), and no other
morphological abnormalities (including of RBC’s or WBC’s). Thyroid function, renal function, liver function, and nutritional evaluation is all within normal limits; and he is diagnosed with Acute ITP. Given lack of significant bleeding symptomatology or risk, observational management is recommended. Throughout ~3-4 months of follow-up, symptoms are unchanged, and platelet count remains between 10k - 20k. However, he subsequently presents with worsening epistaxis, now lasting up to 15-20 minutes before resolving, occurring more frequently, and resulting in a mild anemia (Hgb ~10 g/dL). The decision is made to proceed with platelet-directed therapy, and he is given IVIG 1 g/kg, with excellent clinical response. Additionally, platelet count 3 days later has increased to 170k; and remains >100k for ~4 weeks. About 2 months after IVIG therapy, however, patient again develops worsening epistaxis/bleeding, and is found to have platelet count 15k. He is ~6 months from initial diagnosis, with persistent ITP; and declines any “long-term” treatment options. However, as symptoms persist/worsen, he requests to proceed with another dose of IVIG. He is given another 1 g/kg; but this time with peak platelet count to 80k, and returning to baseline (between 10k-20k) within ~2 weeks. Subsequently, he wishes to proceed with a trial of short-term prednisone, and receives 2 mg/kg/day divided BID for 2 weeks with excellent response (platelet count to 120k near the end of 2 weeks’ prednisone therapy). However, platelet count returns to baseline within ~2 weeks. He continues observation for another ~month; but again requests short-term prednisone therapy when epistaxis worsens. Peak platelet count is ~70k, and returns to baseline within ~1 week of therapy. Discussions are re-initiated regarding second-line treatment options, given patient’s lack of sustained response to front-line/rescue treatment options, and the persistent need for ITP therapy, in light of his persistent bleeding symptoms.

11. Would you consider this refractory ITP? Yes/No
12. Would you work this patient up for alternate etiologies of thrombocytopenia (vs. proceeding with second-line ITP management)? Yes/No

If so, what additional work-up would you obtain? (check all that apply)

1. HIV
2. Hepatitis
3. H. Pylori
4. CMV and/or EBV
5. ANA Profile
6. Immunoglobulins
7. Lymphocyte subsets
8. Complement levels
9. ALPS work-up
10. A 13 year-old F presents with increased bruising and mild menorrhagia over the past 1-2 months, and is found to have isolated thrombocytopenia (to 13k), with elevated immature platelet fraction (12%), and smear review showing platelet size variance (including large and giant platelets), and no other morphological abnormalities (including of RBC’s or WBC’s). Thyroid function, renal function, liver function, and nutritional evaluation is all within normal limits; and she is diagnosed with Acute ITP. Given lack of significant bleeding symptomatology or risk, observational management is recommended. Throughout ~3-4 months of follow-up, however, she reports extreme fatigue, preventing her from participating in prior extracurricular activities or completing school work as before. She is treated for iron deficiency (with improvement in iron stores); and initiated on hormonal control for menorrhagia (with regulation of cycles and flow per report); although remaining non-anemic throughout this period of follow-up. No platelet-directed therapy is initiated throughout these first 3-4 months, and platelet count remains unchanged, between 10k - 20k. She begins to report falling grades in school; and parents are very concerned with her level of fatigue, and inability to participate in routine activities. Therefore, patient is treated with a one-time course of prednisone (2 mg/kg/day), with excellent platelet response, to a peak of 160k, and some improvement in fatigue throughout this course of short-term prednisone therapy. At ~6 months from time of diagnosis, discussion regarding potential second-line therapies are initiated, and she chooses a trial of eltrombopag therapy. Again, platelet response is achieved (to
~100k, stably); with no notable side effects; but she reports only slight improvement in fatigue after ~2-3 months of TPO-RA therapy.

11. Would you consider this refractory ITP? Yes/No
12. Would you work this patient up for alternate etiologies of thrombocytopenia (vs. continuing with second-line ITP-directed management and/or evaluating for secondary ITP)? Yes/No

If so, what additional work-up would you obtain? (check all that apply)

1. HIV
2. Hepatitis
3. H. Pylori
4. CMV and/or EBV
5. ANA Profile
6. Immunoglobulins
7. Lymphocyte subsets
8. Complement levels
9. ALPS work-up

Categorical Questions:

1. Is a patient who does not respond at all to first line therapies refractory? Y/N
2. Is a patient who has a transient response to first line treatments but quickly loses that response refractory? Y/N
3. Is a patient who requires ongoing treatment to maintain a response refractory? Y/N
4. Is a patient who fails to respond to one or more second line treatments (regardless of first line therapy responses) refractory?
5. Is a patient with ongoing symptoms (fatigue) regardless of platelet count responses refractory? Y/N

FIGURE 2 A) Respondents answers to determine rITP status to given scenarios, highlighting frequency of yes/no responses. B) Itemized responses by each participant to whether given scenarios are classified as rITP, indicating lack of consistency across providers and questions.

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Table 1.docx available at https://authorea.com/users/508715/articles/586386-pediatric-
refractory-immune-thrombocytopenia-a-systematic-review

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Table 2.docx available at https://authorea.com/users/508715/articles/586386-pediatric-refractory-immune-thrombocytopenia-a-systematic-review
Identification of studies via databases and registers

**Identification**
- Records identified from:
  - Databases (n = 2148)
  - Registers (n = 0)

**Records removed before screening:**
- Duplicate records removed (n = 678)
- Records marked as ineligible by automation tools (n = 0)
- Records removed for other reasons (n = 0)

**Records screened (n = 1470)**

**Records excluded (n = 1135)**

**Reports sought for retrieval (n = 335)**

**Reports not retrieved (n = 14)**

**Reports assessed for eligibility (n = 321)**

**Reports excluded:**
- Did not define refractory ITP (n = 242)
- Ineligible population (adults only) (n = 39)
- Ineligible population (newly-diagnosed, non-refractory ITP) (n = 3)
- Ineligible population (does not describe population with refractory ITP) (n = 2)
- Ineligible study design (n = 16)
- Incorrect Language (n = 7)
- No mention of outcome of interest (n = 1)

**Studies included in review (n = 11)**
- Reports of included studies (n = 11)
**FIGURE 1** PRISMA flow chart for study selection. The figure shows the flow of records for the systematic review. Although 242 out of 321 studies met the inclusion criteria for the systematic review, those studies did not define rITP and were ultimately excluded from the systematic review, leaving 11 studies that met the initial inclusion criteria and defined rITP.