Immune Thrombocytopenia (ITP) in Children - Pediatric - Inpatient/Ambulatory/Emergency Department
External Clinical Practice Guideline Endorsement

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Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder in which a low platelet count (<100 x 10^9/L) results from destruction of existing platelets and impaired production of new platelets. ITP is the most common cause of thrombocytopenia in children, with an estimated incidence of ~2-10 cases per 100,000 children annually (peak incidence between ages 2-5 years)[1-5]. A typical presentation involves an otherwise healthy child with petechiae, bruising, and/or mild mucosal bleeding. In most pediatric cases, ITP is mild and resolution often occurs without intervention; when treatment is required, approximately three-quarters will respond to 1st line therapies. However, severe bleeding does occur rarely (≤1%) and is the primary concern given the risk of severe morbidity and mortality[1-5].

ITP can be primary or secondary in nature; primary ITP is when there are no other apparent causes of thrombocytopenia and secondary ITP is when there is an identifiable associated condition[1,6,7]. Primary ITP makes up the majority (~80%) of cases[1,6,7] and is the focus of this guideline. ITP is also categorized based on the duration of thrombocytopenia as follows[1]:

- Newly diagnosed ITP (<3 months duration)
- Persistent ITP (3-12 months duration)
- Chronic ITP (>12 months duration)

In 2019, the American Society of Hematology (ASH) published an update to their 2011 clinical practice guideline[8] for the management of ITP in adults and children. This update[1] addressed 21 questions based on a review and appraisal of the primary literature through 2017; recommendations 10-21 and 2 good practice statements are specific to the management of children with newly diagnosed ITP. These guidelines are intended to address the management of patients with non-life-threatening bleeding and are noted to exclude emergency management and pregnancy. In this endorsement guideline, we outline recommendations for the management of children with ITP who do not have severe bleeding requiring emergency care.

Scope

Intended User(s): Physicians, Advanced Practice Providers, Nurses, Pharmacists

Objective(s): To provide standardized, evidence-based guidelines for the assessment and management of primary ITP in children

Target Population: Children (age 1-17 yrs) with suspected primary ITP

Clinical Questions Considered:

- When should children with ITP be admitted to the hospital for treatment?
- What treatments are recommended for children with newly diagnosed ITP?
- What treatments are recommended for children with ITP who do not respond to first-line therapies?

Definitions[1]

Thrombocytopenia: Platelet count <100 x 10^9/L
Newly diagnosed ITP: <3 months duration
Persistent ITP: 3-12 months duration
Chronic ITP: >12 months duration
Minor bleeding: bleeding that involves only cutaneous manifestations (i.e. bruising, petechiae)

Non-life-threatening mucosal bleeding: Bleeding that involves only mucosal surfaces and does not require emergent transfusion or intervention (i.e. epistaxis, gum bleeding, menorrhagia)
Remission: Platelet count >100 x 10^9/L at 12 months

Recommendations

Diagnosis

As there is no single test that identifies ITP, a diagnosis of primary ITP is established on a clinical basis through a patient history, physical examination, complete blood count and peripheral smear[1,3-6,8]. A diagnosis of ITP is made when these examinations yield:

- isolated thrombocytopenia (<100 x 10^9/L) on the CBC
- no abnormal findings on peripheral smear
- an absence of findings that would raise concern for other causes of thrombocytopenia

When patients meet the typical criteria outlined above, there is no need to investigate further for potential underlying autoimmune or bone marrow conditions. Therefore, additional tests such as a bone marrow biopsy, antinuclear antibody testing, or immunoglobulin testing are not routinely recommended to establish the diagnosis[1,3-6,8] (*see Table below for ASH recommendations against such testing in specific scenarios*). If atypical features are present or there is concern for other conditions associated with thrombocytopenia (i.e. systemic illness, infection, malignancy, autoimmune illness, medications), consider hematology consultation and additional referrals to help guide further work-up (*UW Health Best Practice Statement*).

Treatment

UW Health endorses the recommendations pertaining to children (#10-21) within the American Society of Hematology (ASH) 2019 guidelines[1] for immune thrombocytopenia and also the carried over recommendations from 2011 ASH guideline[8] that were not changed/updated in 2019. The endorsed ASH Guideline recommendations for the management of children with ITP are summarized in Table 1.

Appendix A includes an algorithm that is based on these recommendations, outlining our internal guidance for the management of pediatric ITP. Finally, Table 2 provides a summary of key details for each of the first- and second-line medical therapies for ITP.

The decision on whether to treat is not based on platelet count alone but instead takes into consideration the bleeding risk and health-related quality of life (HRQoL) of the patient[1,3-6,9]. HRQoL is not explicitly defined in the ASH Guideline, but considerations include not only physical health but also mental and social domains; examples from these latter domains may include restrictions on activities, anxiety due to the risk of bleeding, depression, fatigue, and the burden of treatment and monitoring. The overall treatment goals are to keep children safe, resolve bleeding and any symptoms, and minimize lab draws. The frequency of laboratory monitoring will vary according to patient specific considerations including clinical stability, the presence or absence of symptoms (bleeding, fatigue, diminished QOL), platelet count value and trend, and any treatment being used[10]. Until remission is achieved, labs (i.e. CBC) should generally be considered every 1-4 weeks; more frequent monitoring (i.e. weekly) should be considered when there are symptoms requiring treatment and/or more severe thrombocytopenia, whereas less frequent monitoring (i.e. monthly) is appropriate if the child is asymptomatic and has only moderate thrombocytopenia.

Platelet transfusions are indicated only in the presence of severe bleeding and life-threatening situations, and are not used to attempt to reach an arbitrary platelet count value[3,4,11]. While platelets are < 50 x 10^9/L, children should be on activity restrictions (when feasible) to avoid injury and medications that might adversely affect platelet function and increase bleeding risk (i.e. NSAIDs, aspirin) should be avoided[4,10].

Table 1. Summary of ASH Guideline Recommendations for the Management of ITP[1,8]

Topic	Recommendations	Level
Diagnostic (Carried forward from 2011 ASH Guideline)		
Diagnosis of ITP	We recommend: • Bone marrow examination is unnecessary in children and adolescents with the typical features of ITP • Bone marrow examination is not necessary in children who fail IVIG therapy	Grade 1B
	We suggest: • Bone marrow examination is also not necessary in similar patients prior to initiation of treatment with corticosteroids or before splenectomy • Testing for antinuclear antibodies is not necessary in the evaluation of children and adolescents with suspected ITP	Grade 2C
Testing in treatment nonresponders	We recommend against routine testing for *H. pylori* in children with chronic ITP	Grade 1B
Management of MMR-associated ITP (Carried forward from 2011 ASH Guideline)		
MMR vaccine - associated ITP considerations	Children with a history of ITP who are unimmunized receive their scheduled first MMR vaccine	Grade 1B
	In children with either nonvaccine or vaccine-related ITP who have already received their first dose of MMR vaccine, vaccine titers can be checked; if the child displays full immunity (90% to 95% of children), then no further MMR vaccine should be given; if the child does not have adequate immunity, then the child should be reimmunized with MMR vaccine at the recommended age.	Grade 1B
Treatment Setting (From ASH 2019 Guideline)		
Outpatient vs. Inpatient Management	In children with newly diagnosed ITP and a platelet count of <20 x 10^9/L who have no or mild bleeding (skin manifestations) only, the ASH guideline panel suggests against admission to the hospital rather than outpatient treatment	Conditional, Very low certainty of evidence
	In children with newly diagnosed ITP and a platelet count of ≥20 x 10^9/L who have no or mild bleeding (skin manifestations) only, the ASH guideline panel suggests against admission to the hospital rather than outpatient treatment	Conditional, Very low certainty of evidence
	The referring physician should ensure that the patient has follow-up with a hematologist within 24 to 72 hours of diagnosis.	Good practice statement
Medical Management (From ASH 2019 Guideline)		
Treatment vs. Observation	In children with newly diagnosed ITP who have no or minor bleeding, the ASH guideline panel suggests observation rather than corticosteroids	Conditional, Very low certainty of evidence

	In children with newly diagnosed ITP who have no or minor bleeding, the ASH guideline panel recommends observation rather than IVIG	Strong, Moderate certainty of evidence
	In children with newly diagnosed ITP who have no or minor bleeding, the ASH guideline panel recommends observation rather than anti-D immunoglobulin	Strong, Moderate certainty of evidence
Treatment of children with non–life-threatening mucosal bleeding and/or diminished HRQoL	In children with newly diagnosed ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL, the ASH guideline panel suggests corticosteroids rather than anti-D immunoglobulin	Conditional, Low certainty of evidence
	In children with newly diagnosed ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL, the ASH guideline panel suggests corticosteroids rather than IVIG	Conditional, Low certainty of evidence
	In children with newly diagnosed ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL [*and* whom cannot tolerate/receive corticosteroids OR previously failed corticosteroids], the ASH guideline panel suggests either anti-D immunoglobulin or IVIG	Conditional, Low certainty of evidence
Corticosteroid duration and type	In children with newly diagnosed ITP who have non–life-threatening bleeding and/or diminished HRQoL, the ASH guideline panel recommends against courses of corticosteroids longer than 7 days rather than courses 7 days or shorter	Strong, Very low certainty of evidence
	In children with newly diagnosed ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL, the ASH guideline panel suggests prednisone (2-4 mg/kg per day; maximum, 120 mg daily, for 5-7 days) rather than dexamethasone (0.6 mg/kg per day; maximum, 40 mg per day for 4 days)	Conditional, Very low certainty of evidence
Management of children with ITP who do not have a response to 1st line treatment	In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests the use of TPO-RAs rather than rituximab	Conditional, Very low certainty of evidence
	In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests TPO-RAs rather than splenectomy	Conditional, Very low certainty of evidence
	In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests rituximab rather than splenectomy	Conditional, Very low certainty of evidence
	The treating physician should ensure that the patient has appropriate immunizations prior to splenectomy and that they receive counseling regarding antibiotic prophylaxis following splenectomy. The treating physician should educate the patient on prompt recognition and management of fever and refer to current recommendations on pre- and post-splenectomy care.	Good practice statement

Table 2. Summary of Key Points for 1st and 2nd Line Medications for ITP in Children

Drug	Dosing Information (Assumes normal organ function)	Contraindications, Warnings / Precautions, Drug Interactions	Adverse Effects (Select common and significant toxicities reported here; refer to Lexi-comp® for complete list)	Clinical Pearls (Pearls are based on expert opinions from internal subject matter experts regarding drug selection, patient monitoring)
First-line Acute Therapies				
Prednisone	2-4 mg/kg/day orally (max 120 mg daily) in 3-4 divided doses, for 5-7 days	Review in Lexi-comp®	Gastritis Insomnia Mood/behavior changes Increased appetite, weight gain Hypertension Hyperglycemia	Time to response: 2-7 days Prolonged durations are not recommended and tapers are not needed with short durations. Prednisone is preferred over dexamethasone.
IVIG	0.8–1 g/kg IV for 1-2 days[3,4,6,11] Alternative Dosing: 400 mg/kg IV for 5 days See UW Health IVIG Guideline for further details regarding pre-medication, infusion rates, monitoring.	Review in Lexi-comp®	Headache Fever, chills Nausea, vomiting Infusion reactions Hypersensitivity reaction Rare (<1%) possibilities include: Thrombosis, renal failure, hemolytic anemia, and aseptic meningitis	Time to response: 1-2 days (usually within 24 hrs) May be preferred when a rapid rise in platelet count is needed and can be used in combination with corticosteroids for more severe cases
Anti-D Ig	50–75 mcg/kg over slow IV push (3-5 min)	Review in Lexi-comp®	Fever, chills Headache Infusion reactions Severe intravascular hemolysis is a rare possibility –monitor for 8h post-infusion	Time to response: 1-2 days May be considered as an alternative to IVIG in select patients; Patient must be Rh-positive, DAT-negative, and not splenectomized
Second-line Therapies				
Eltrombopag (TPO receptor agonist)	1–6 y: 25 mg/day orally >6-yrs: 50 mg/day orally (Reduce initial dose to 25 mg once daily if East/Southeast Asian ancestry (e.g., Chinese, Japanese, Korean, Taiwanese) Max dose 75 mg/day Take without a meal or with a meal low in calcium (=50 mg) and ≥ 2 hrs before and 4 hrs after Ca-containing foods or medications/supplements containing Ca, Fe, Al, Mg, Se, or Zn.	Review in Lexi-comp®	Abdominal pain Diarrhea Headache Arthralgia, myalgia Abnormal hepatic function tests	Re-evaluate platelet count in 2 weeks after initiation and use lowest dose that achieves platelet count goal (i.e. >50k) to reduce bleeding. • Eltrombopag: If below goal, increase in 12.5mg-25mg increments bi-weekly to max dose • Romiplostim: If below goal, increase by 1 mcg/kg weekly to max dose Discontinue if platelet count does not respond to a level that avoids clinically important bleeding after 4 weeks at the max daily dose. Thrombocytopenia is likely to recur following treatment cessation, but some (10-30%) may experience sustained response after taper and discontinuation
Romiplostim (TPO receptor agonist)	Initial 1 mcg/kg subcutaneously once weekly (Dosing range 1-10 mcg/kg weekly)	Review in Lexi-comp®	Rash Abdominal pain Diarrhea Headache Arthralgia, myalgia	
Rituximab	375 mg/m^2 IV infusion weekly × 4 doses[4,12]	Review in Lexi-comp®	Headache Fever, Chills Urticaria Serum sickness Progressive multifocal leukoencephalopathy (Rare)	Time to response: 3 weeks

* Medication information obtained from Lexi-comp® drug monographs except where cited otherwise. Clinical Pearls are based on expert opinions from UW Health subject matter experts.

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Conflicts of Interest

All guideline workgroup members are expected to follow institutional policies and procedures around conflicts of interest. Actions in which a guideline member discloses a conflict of interest relevant to the guideline topic may include, but is not limited to, abstaining from voting, dismissal during comment and voting period, or recusal from requesting and/or participation in the decision-making process.

Methodology

Development Process

Each guideline is reviewed and updated approximately every 3-5 years, but will vary in consideration of the primary literature and relevant practice changes. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Formulate the Recommendations:

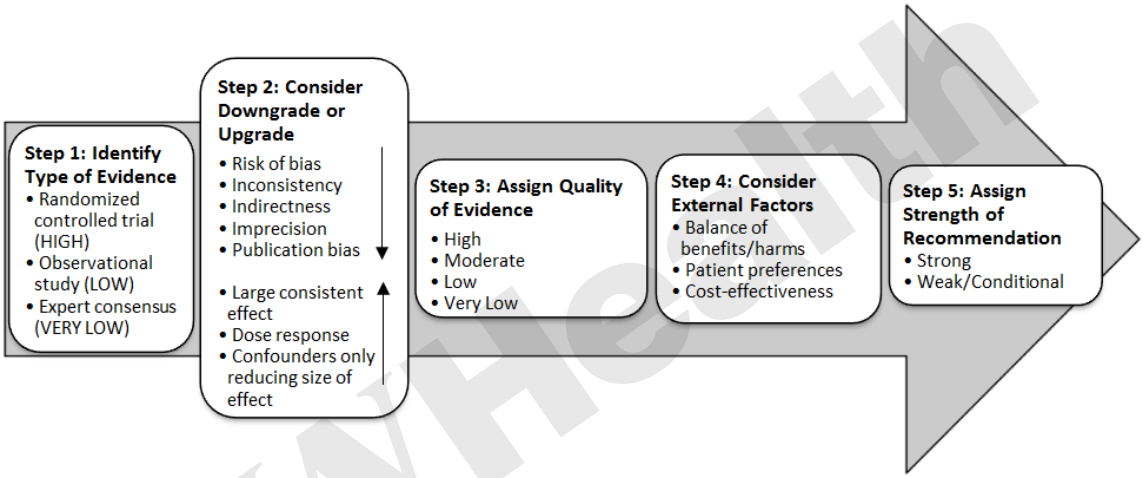
Following a review and discussion of the literature, including the available national guidelines, the workgroup members agreed to adopt recommendations pertaining to children developed by American Society of Hematology (ASH)[1,8]. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate). As the ASH ITP Guideline[1,8] is considered to represent the gold standard for guideline-directed therapy for pediatric ITP by UW Health internal experts, a formal AGREE II guideline appraisal was not completed.

Methodology of the ASH 2019 Guideline[1] for Immune Thrombocytopenia included an update to their systematic review and appraisal of the evidence (up to May, 2017). The guideline panel (8 adult experts, 5 pediatric experts, 2 methodologists with expertise in ITP, and 2 patient representatives) utilized the GRADE approach to conducting the evidence review and developing recommendations. Following the GRADE approach, the ASH guidelines provide evidence ratings for each of their recommendations in 4 potential categories: High, Moderate, Low, and Very low certainty of evidence. Recommendations are categorized as either "Strong" or "Conditional"[1]. UW Health-developed guidelines also employ the GRADE approach, and our current corresponding definitions for these categories are outlined below. Table 4 of the ASH 2019 guideline provides the intended interpretations of their recommendation labels for the different intended audiences including patients, clinicians, policy-makers, and researchers.

The ASH 2011 Guideline for Immune Thrombocytopenia utilized the following definitions for assigning a strength of recommendation and evidence rating:

Strength of Recommendation	
1	Indicates a high degree of confidence that the desirable outcomes of an intervention exceed the undesirable effects (or vice versa) in most patient populations.
2	Indicates a lower degree of confidence that the desirable outcomes outweigh undesirable outcomes (or vice versa).
Quality of Evidence Ratings	
A	The recommendation is supported by consistent evidence from randomized controlled trials (RCTs) or exceptionally strong observational studies
B	The recommendation is supported by RCTs with important limitations or strong evidence from observational studies
C	The recommendation is derived from RCTs with serious flaws, weaker observational studies, or indirect evidence

GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.
Very Low - Internal Expert Opinion	The true effect is likely to be substantially different from the estimated effect. This category of recommendation for or against a specific intervention is derived strictly from the expert opinions of UW Health healthcare professionals with experience in the relevant specialty(ies). This is used in the absence of published evidence or external opinion addressing the specific intervention.

GRADE Ratings for Recommendations For or Against Practice

Strong (S)	Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)
Conditional (C)	May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)
Good Practice Statement	Generally, should be performed (i.e., the expected benefit of the treatment is substantial, expected costs or risk are minimal, and patient values and circumstances are unlikely to affect the decision.) This classification is used for recommendations that guideline members feel are important and for which there is uniform support, but for which evidence directly assessing the specific intervention (or practice) is not available and is highly unlikely to ever be studied (because it may not be warranted or feasible). Such recommendations may have strong indirect evidence of support

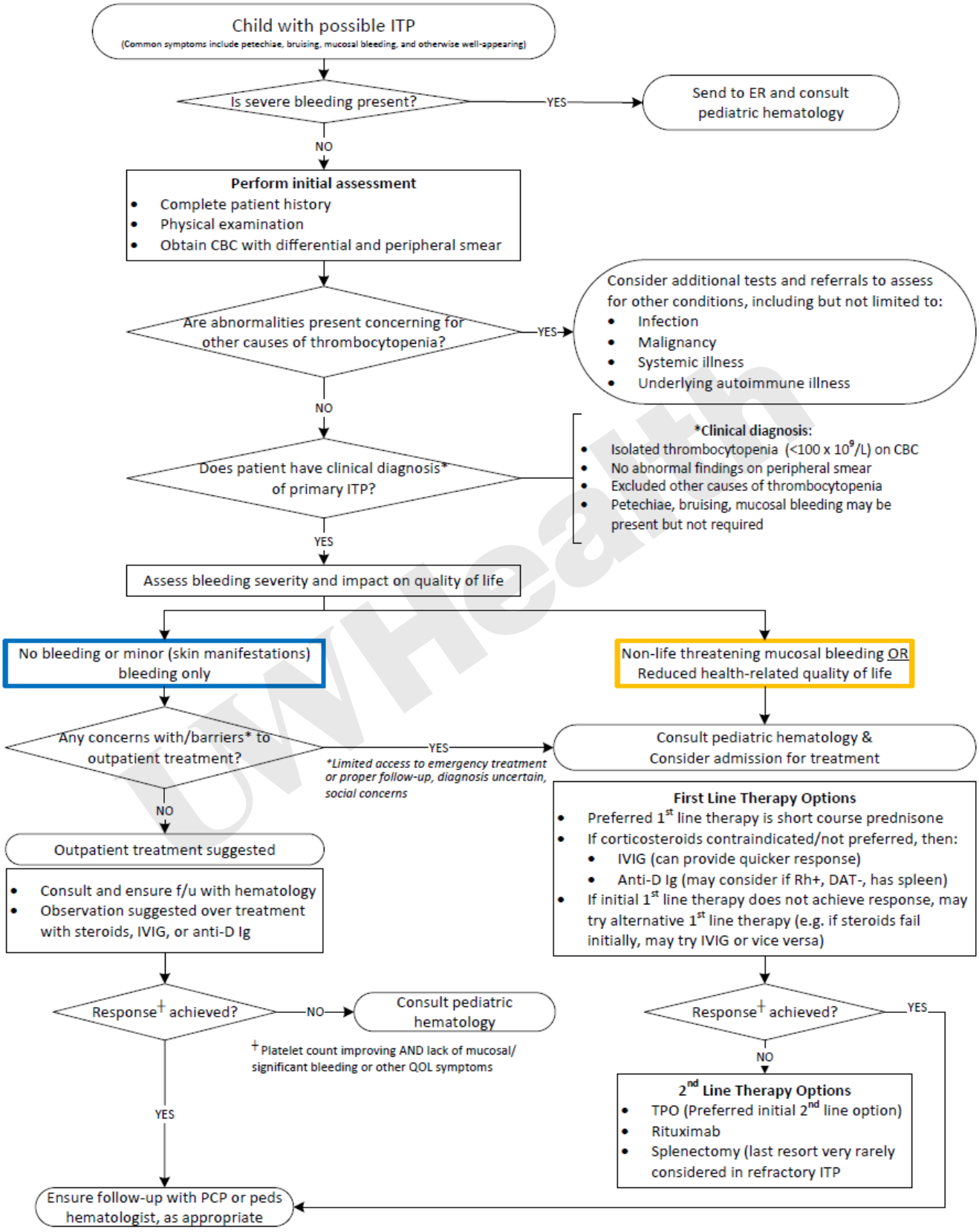
Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics
% of ITP patients without bleeding or minor bleeding only undergoing period of observation vs. treatment
% of children with ITP treated in ambulatory setting
% of children with ITP receiving preferred 1st-line therapies

Patient Resources
Immune Thrombocytopenic Purpura (IRP) [HF 4787]

Appendix A. Management of Immune Thrombocytopenia in Children



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