Immune thrombocytopenia (ITP) in children: Initial management

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INTRODUCTION

Immune thrombocytopenia (ITP) of childhood is characterized by isolated thrombocytopenia (platelet count <100,000/microL with normal white blood cell count and hemoglobin). The cause of ITP remains unknown in most cases, although it can be triggered by a viral or environmental trigger or it may be secondary to an underlying immunologic defect [1-3]. ITP was previously known as idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura. The current term **I**mmune **T**hrombocyto**P**enia preserves the widely-recognized acronym "ITP" and acknowledges the immune-mediated mechanism of the disorder, while allowing that patients may have little or no signs of purpura or bleeding [1].

The treatment and prognosis of newly diagnosed and persistent ITP in children will be reviewed here. The management of chronic ITP and the clinical manifestations and diagnosis of ITP are discussed separately. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease" and "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis".)

TERMINOLOGY

The following terms are used in this topic:

- **Primary immune thrombocytopenia (ITP)** – ITP in the absence of other causes or disorders that may be associated with the thrombocytopenia is known as primary ITP and is the main focus of this topic review.

- **Secondary ITP** – Secondary ITP refers to immune-mediated thrombocytopenia with an underlying cause, including drug-induced, or associated with systemic illness (eg, systemic lupus erythematosus, common variable immunodeficiency, human immunodeficiency virus [HIV]). Secondary causes of immune-mediated thrombocytopenia are reviewed separately. (See "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis", section on 'Differential diagnosis' and "Causes of thrombocytopenia in children".)

Primary ITP is categorized into three phases, depending on the duration of the disease course [1]:

- **Newly diagnosed ITP** – ITP within 3 months from diagnosis
- **Persistent ITP** – Ongoing ITP between 3 and 12 months from initial diagnosis
- **Chronic ITP** – ITP lasting more than 12 months

In this terminology schema, there is no "acute" ITP. The clinical features of newly diagnosed, persistent, and chronic ITP are otherwise similar. (See "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis", section on 'Clinical features' and 'Disease course' below.)

Management of newly diagnosed and persistent ITP in children is reviewed here. The management of chronic ITP is discussed separately. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease".)

MANAGEMENT

General measures — We suggest the following measures for pediatric patients with ITP:

- **Activity restriction** – Affected children should be restricted from activities that carry a risk of bleeding from traumatic injury. The emphasis is on prevention of intracranial hemorrhage (ICH). There is no standard approach regarding the specific types of activity to restrict, and there is substantial variation in clinical practice. In general, there is arguably a tendency towards excessive restriction rather than too little. These decisions should be individualized and made in collaboration with the patient and family. In our practice, we suggest that children with platelet count <30,000/microL avoid contact and collision sports (eg, football, boxing, lacrosse, and hockey) and also consider restricting other activities that have substantial risk for traumatic injury (eg, baseball, soccer, skiing, or gymnastics) [3]. For patients who elect to remain active in sports, certain modifications may be warranted (eg, wearing a helmet, avoid "heading" the ball in soccer). Protective helmets reduce but do not eliminate the risk of head injury.

- **Avoidance of antiplatelet and anticoagulant medications** – Antiplatelet medications (eg, aspirin, ibuprofen, other nonsteroidal antiinflammatory drugs [NSAIDs]) and anticoagulants (eg, heparin, enoxaparin, warfarin, direct oral anticoagulants) generally should be avoided if the platelet count is very low (ie, <20,000/microL). In our experience, the risk of clinically significant bleeding with ibuprofen is low. Nevertheless, because of the potential for severe bleeding with its use, we advise avoiding ibuprofen unless it is truly necessary.

  If these medications are necessary, pharmacologic treatment of the ITP may be warranted to increase the platelet count to a safe level (eg, for patients requiring ongoing anticoagulant therapy, the platelet count usually is kept >50,000/microL). (See 'Moderate to high bleeding risk' below.)

  For children with ITP who require antipyretic or analgesic therapy, we suggest starting with acetaminophen. If the child does not have adequate symptom relief with acetaminophen, other agents can be tried such as a cyclooxygenase-2 selective NSAID (eg, celecoxib) since these agents have less antiplatelet activity compared with ibuprofen and aspirin. However, ibuprofen is rarely dangerous if the child does not have active bleeding. Other measures for pain not adequately controlled with acetaminophen include nonpharmacologic measures and/or opioids, if appropriate. These are discussed separately. (See "Pain in children: Approach to pain assessment and overview of management principles", section on 'Nonpharmacologic interventions' and "Pain in children: Approach to pain assessment and overview of management principles", section on 'Opioids'.)

- **Monitoring** – All patients should have ongoing monitoring for development of bleeding symptoms and regular measurements of platelet count, the frequency of which depends on the degree of thrombocytopenia, bleeding symptoms, and other risk factors. (See 'Monitoring' below.)

- **Control of menses** – For postmenarchal female patients, hormonal therapy may be warranted to control or inhibit menses and prevent severe menorrhagia. Antifibrinolytics may also be of use. These therapies are discussed in greater detail separately. (See "Abnormal uterine bleeding in adolescents: Management" and "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Adjunctive therapies'.)

- **Control of epistaxis** – Measures for nose bleeding include keeping the nasal mucosa moist (eg, with a humidifier or saline nose spray), discouraging nose picking, and use of antiallergy remedies (if allergic rhinitis is thought to be contributing). Antifibrinolytics may be needed if bleeding is severe. These therapies are discussed in greater detail

separately. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Adjunctive therapies' and "Management of epistaxis in children".)

- **Education** – Educating the child and caregivers about the risks of ITP is an important aspect of management. In addition to reviewing activity and medication management, as discussed above, the clinician should inform patients and caregivers at the time of diagnosis about symptoms of severe bleeding (eg, severe headache, hematuria, melena, heavy menstrual bleeding) and they should be instructed to consult their clinician if bleeding occurs. Information for patients and families/caregivers is provided below (see 'Information for patients' below). Additional resources include the National Institutes of Health website and the Platelet Disorder Support Association website.

Many of these warnings and precautions generally can be softened and ultimately lifted once ITP is controlled and platelet count is recovering.

Treatment approach

Overview — Management of children with newly diagnosed ITP is based chiefly upon the severity of bleeding symptoms (table 1). The degree of thrombocytopenia, other risk factors, impact of the ITP on quality of life, and values and preferences of the family are also important considerations (algorithm 1).

Most patients with newly diagnosed ITP have mild or no bleeding symptoms. Such patients can generally be managed with "watchful waiting" in the ambulatory setting, provided that the child is discharged to a reliable caregiver and follow-up is ensured. Children with more significant bleeding symptoms may warrant pharmacologic intervention [2,4-6].

The management approach described in the following sections is based upon the available evidence, expert opinion, and usual practice. Many of these considerations are reflected in an international consensus report and guidelines published by the American Society of Hematology [2,6]. (See 'Society guideline links' below.)

Life-threatening bleeding — Fortunately, life-threatening bleeding is rare in childhood ITP; ICH occurs in <1 percent of children with ITP. (See "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis", section on 'Intracranial hemorrhage'.)

If life-threatening hemorrhage occurs (eg, ICH, major trauma, gastrointestinal bleeding with hemodynamic instability, pulmonary hemorrhage with cardiopulmonary compromise), immediate intervention is required. We recommend a combination of **all** of the following therapies [2]:

- Platelet transfusions – Platelet transfusions (as a bolus dose of 10 to 30 mL/kg, generally followed by a continuous infusion). Platelet count should be assessed immediately

following the bolus (ie, 15 minutes after). Frequent testing thereafter is important to ensure that the patient maintains a hemostatic platelet count and to guide additional therapy. Patients with ITP generally require larger-than-normal doses of platelets in transfusion due to rapid destruction. (See "Platelet transfusion: Indications, ordering, and associated risks".)

- Methylprednisolone – Methylprednisolone is given at a dose of 30 mg/kg per day (up to 1 g) intravenously (IV) for three to four days. (See 'Glucocorticoids' below.)

- Intravenous immune globulin (IVIG) – IVIG is given at a dose of 1 g/kg per day for one to three days (see 'Intravenous immune globulin' below).

  Anti-D immune globulin (anti-D) can be added to the regimen in Rh-positive, direct antiglobulin test (DAT)-negative patients; however, the additional benefit of this agent in this setting is uncertain. IV anti-D is administered at a dose of 75 micrograms/kg as a single dose. IV anti-D can be a useful part of combination therapy, even in splenectomized patients despite its relative lack of efficacy when used as the sole agent in these patients [7]. Anti-D should not be given if the patient's DAT status is unknown, which is often the case in emergency situations. However, DAT testing is usually resulted quickly, so once the DAT status is confirmed to be negative and the blood type Rh+, IV anti-D can be given at the end of the IVIG infusion. (See 'Anti-D immune globulin' below.)

In addition, we often administer a high dose of a thrombopoietin receptor agonist (TPO-RA). We usually use subcutaneous romiplostim in this setting since the acutely ill patient may not tolerate oral medications. The appropriate dose of romiplostim in this setting is undefined; we typically use the highest dose (ie, 10 mcg/kg). The TPO-RA agent has little impact on the acute bleeding event (there typically is a five- to seven-day delay before a response is seen); however, it may boost and prolong the platelet response in the days following the bleeding event, which may reduce the risk of rebleeding. This practice is not standardized, and other experts may chose not to use romiplostim in this setting. Additional details about TPO-RAs are provided separately. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Thrombopoietin receptor agonists'.)

Combination treatment is more effective in immediately raising the platelet count than single-agent therapy [7]. A more limited version of these four treatments may be used if there is a risk of such an event (eg, head trauma without evidence of ICH; unexplained headache; or gastrointestinal, genitourinary, or gynecologic bleeding that is heavy) but not such as to create a risk of immediate loss of life. (See 'Severe, non-life-threatening bleeding' below.)

Additional interventions that have been used in patients with life-threatening bleeding but for which supporting evidence is limited include the following:

- Recombinant human factor VIIa. (See "Recombinant factor VIIa: Administration and adverse effects", section on 'Pediatric considerations'.)

- Vincristine [8]. (See "Initial treatment of immune thrombocytopenia (ITP) in adults", section on 'Other therapies and multiagent combinations'.)

- Antifibrinolytic agents (eg, epsilon aminocaproic acid, tranexamic acid) [9,10]. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Adjunctive therapies'.)

- Splenectomy – Emergency splenectomy may be lifesaving for patients with catastrophic bleeding that is refractory to medical management but should be considered as a last resort. Splenectomy may be challenging to perform in patients with active hemorrhage, who are inherently unstable, and should be performed by an experienced surgeon. The time required to arrange splenectomy may reduce the desired (urgent) effect. In one series describing 40 children with ITP who suffered an ICH, splenectomized patients had worse outcomes, but this was likely due to selection bias [11]. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Splenectomy'.)

- Interventions to reduce intracranial pressure (eg, mannitol, hypertonic saline, craniectomy) for some patients with severe ICH. (See "Elevated intracranial pressure (ICP) in children: Management" and "Management of acute moderate and severe traumatic brain injury", section on 'Surgical treatment'.)

Severe, non-life-threatening bleeding — For severe mucosal bleeding or suspected internal hemorrhage that requires immediate medical attention but that is not life-threatening (eg, gastrointestinal bleeding without hemodynamic instability, pulmonary hemorrhage without cardiopulmonary compromise, severe prolonged epistaxis, muscle or joint hemorrhage), therapy is similar to that described above for life-threatening bleeding, with the following modifications:

- Platelet transfusions may not be needed – Platelet transfusions are generally reserved for patients with active life-threatening hemorrhage. However, platelet transfusions may be necessary for patients with non-life-threatening bleeding who do not achieve an adequate response with other treatments (eg, if the response is too slow or if the platelet count does not increase to an acceptable level) and those who require surgery. If platelet transfusions are used for any surgery other than splenectomy for ITP, one or more other therapies of ITP as described below should be instituted to further support the patient's postoperative platelet count since the transfused platelets would likely have a short half-life.

- Combination therapy – Rather than giving all three agents (methylprednisolone, IVIG, and IV anti-D) for up to four days, a measured approach using one or two of these agents for fewer days may be sufficient. The choice of agents can be guided by the patient's previous treatment response, if such experience exists. The choice and duration of therapy can be modified depending upon the response to treatment (ie, amelioration of bleeding and rise in platelet count).

As with life-threatening bleeding, we often administer a dose of a TPO-RA (eg, romiplostim [given subcutaneously] or eltrombopag [given orally]) to increase the likelihood of a higher platelet response. This practice is based on clinical experience and indirect evidence from other settings (eg, chronic ITP). These agents are discussed in greater detail separately. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Thrombopoietin receptor agonists'.)

Adjunctive antifibrinolytic agents (eg, epsilon aminocaproic acid or tranexamic acid) may be helpful in patients with severe bleeding, although data are limited and increased risk of thrombosis has been reported [9,10,12]. In addition, for patients with menorrhagia, hormonal therapy may be warranted. These interventions are discussed in greater detail separately. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Adjunctive therapies' and "Abnormal uterine bleeding in adolescents: Management", section on 'Acute management of severe anovulatory uterine bleeding'.)

Moderate to high bleeding risk — For patients who currently lack evidence of severe bleeding, but who are deemed to be at moderate to high risk for bleeding complications, we suggest pharmacologic treatment.

- **Definition of "moderate to high bleeding risk"** – The risk of developing serious bleeding complications depends on the degree of thrombocytopenia, severity of bleeding symptoms (table 1), and additional risk factors. Though consensus is lacking and treatment is individualized, we generally define moderate to high bleeding risk as **any** of the following:

  - Grade 3 bleeding symptoms (mucosal bleeding) (table 1)

  - Planned surgery or invasive procedure that is likely to induce blood loss (see 'Surgery/invasive procedures' below)

  - Platelet count <30,000/microL, **plus** one or more of the following risk factors:

    - Use of antiplatelet or anticoagulant medications (eg, NSAIDs, heparin)
    - Concomitant bleeding disorder (eg, von Willebrand disease)
    - Very active lifestyle subjecting the patient to frequent trauma (that cannot be controlled with activity restriction)

- Close follow-up and/or other required parental supervision cannot be assured or access to medical care is limited

- **Choice of initial therapy** – The choice of initial first-line ITP treatment (eg, glucocorticoid, IVIG, and/or anti-D) depends in part on how rapid an increase in platelet count is desired:

  - **Rapid rise in platelet count is desired** – When a rapid rise in platelet count is desired, we suggest treatment with IVIG or anti-D (the latter is used only in Rh-positive, DAT-negative, non-splenectomized patients without evidence of hemolysis).

    Examples of circumstances wherein a rapid rise in platelet count may be desired include:

    - Planned surgery or procedure that is likely to induce blood loss – Management of ITP in the setting of surgery and invasive procedures is discussed in greater detail below. (See 'Surgery/invasive procedures' below.)

    - A child presenting after sustaining head trauma without evidence of ICH (however, if there is clinical concern for ICH following head trauma, more intensive therapy is warranted, as discussed above). (See 'Severe, non-life-threatening bleeding' above.)

    - A child presenting with severe unexplained headache.

    IVIG is given as a single dose of 1 g/kg; IV anti-D is given as a single dose of 75 micrograms/kg. In our practice, we also treat these patients with a single dose of IV methylprednisolone (30 mg/kg [up to 1 g]) to augment the platelet response and ameliorate the side effects of IVIG or IV anti-D [13]. Others do not treat with concomitant methylprednisolone.

    IVIG and anti-D are the preferred first-line therapies in these settings because they increase the platelet count more rapidly than glucocorticoids alone [14]. An increase in the platelet count is usually observed within 24 hours of administration of either agent. (See 'Intravenous immune globulin' below and 'Anti-D immune globulin' below.)

  - **Rapid or urgent increase is not necessary** – For patients at moderate risk for bleeding complications in whom a rapid rise in platelet count is not necessary, we suggest initial treatment with oral glucocorticoids. Acceptable regimens include prednisone 2 to 4 mg/kg per day (maximum 120 mg per day) orally for five to seven days or dexamethasone 0.6 mg/kg per day (maximum 40 mg per day) orally for four days [6].

The preference for oral glucocorticoids in this setting is largely based on cost considerations and ease of administration. The choice of agent is also influenced by patient values and preferences, as well as the provider's experience with the agent. IV steroids, IVIG, and anti-D are reasonable alternatives. A TPO-RA agent may be reasonable in a select subset of newly diagnosed patients (ie, those who are likely to need prolonged support of the platelet count and who have recently used or are currently taking glucocorticoids [eg, for management of an underlying autoimmune disorder such as systemic lupus erythematosus or autoimmune lymphoproliferative syndrome]). TPO-RAs are discussed separately. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Thrombopoietin receptor agonists'.)

Patients with grade 3 bleeding symptoms at presentation are at increased risk of experiencing subsequent severe bleeding episodes [15,16]. This was demonstrated in a clinical trial involving 200 children with newly diagnosed ITP who were randomly assigned to early treatment with a single dose of IVIG or careful observation with treatment only in the case of severe bleeding [16]. For children with grade 3 bleeding symptoms at presentation (n = 80), the rate of severe bleeding episodes during the first month was higher in the observation group compared with the IVIG group (17 versus 0 percent, respectively). For children with grade 1 or 2 bleeding symptoms at presentation, the rate of severe bleeding episodes during the first month was very low in both groups (2 and 0 percent).

Some patients with these risk factors may not respond to standard treatment and may require more aggressive either combination treatment or early use of a second-line agent, as described below [7,11,14]. (See 'Response to treatment' below.)

Patients without any of these risk factors generally do not require pharmacologic intervention and can be managed with "watchful waiting." (See 'Low bleeding risk' below.)

Low bleeding risk — Children with no bleeding or mild bleeding (ie, grade 0 to 2 cutaneous bleeding only, such as bruising and petechiae) (table 1) without any of the risk factors or circumstances described above generally do not require pharmacologic intervention and can be managed with "watchful waiting."

Arguments in favor of "watchful waiting" without early pharmacologic intervention are based upon the following observations:

- The available therapies (IVIG, IV anti-D, and steroids) do not appear to have curative effects. Approximately 50 to 70 percent of children recover from ITP within three to six months of presentation, with or without treatment [16-18]. Younger children and those with abrupt onset of bleeding symptoms have the greatest likelihood of recovering spontaneously [19,20]. (See 'Disease course' below.)

- Serious bleeding is uncommon in children who initially present with no or mild (ie, grade 0 to 2) bleeding symptoms. (See "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis", section on 'Serious hemorrhage'.)

- Pharmacologic interventions for ITP all have potential for adverse effects.

Though we suggest an approach of "watchful waiting" for most children with low bleeding risk, the decision should be made in collaboration with the family. Some providers may offer treatment to children with low bleeding risk if there is a high degree of fear or anxiety in the patient or caregivers or if the family will not accept watchful waiting. This is particularly relevant for patients with very low platelet counts (ie, <10,000). For children with substantially impaired quality of life due to symptoms (especially fatigue), anxiety about bleeding risks, or for whom restriction of activity would be especially burdensome, pharmacologic therapy may be a reasonable option (after discussing with the patient and/or caregivers and carefully weighing the potential risks and benefits). Potential but unproven benefits of this approach include relaxing restrictions on activity, improving quality of life, and preventing sequelae from bleeding; however, these must be weighed against the risks of side effects from ITP medications. Treatment may reduce the psychological burden for the parents of children with ITP, as shown in a pilot study of children treated with a TPO-RA [21].

Surgery/invasive procedures — Platelet count thresholds for surgery or invasive procedures are higher than thresholds to prevent spontaneous bleeding. Typical thresholds for different types of invasive procedures are presented separately. (See "Platelet transfusion: Indications, ordering, and associated risks", section on 'Preparation for an invasive procedure'.)

Any first-line ITP therapy (eg, glucocorticoids, IVIG, anti-D) may be used in this setting. Considerations include the timing of surgery, desired platelet count, and patient's prior treatment response (if such experience exists). For urgent or emergency procedures, we suggest IVIG plus IV methylprednisolone. Ideally, treatment is initiated two to three days prior to surgery to optimize the hemostatic effect. For emergency procedures, platelet transfusions are often required in addition to pharmacologic therapy. Depending upon the patient's past history of treatment, a TPO-RA may be a useful adjuvant in this setting if it is important to maintain a higher platelet count for a period of time postoperatively. These agents may require a longer "run in" to find the optimal dose for the patient without overshooting. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Thrombopoietin receptor agonists'.)

For elective procedures, in most cases, properly timed glucocorticoids and/or IVIG can be used to raise the platelet count to the desired target. We generally use the agent that has been effective for the patient previously. Many experts prefer IVIG or TPO-RA agents over

steroids in this setting due to theoretical concerns about infection or impaired wound healing with steroids.

Platelet transfusions are only transiently effective in patients with ITP. Thus, if possible, the preferred approach is to provide pharmacologic treatment preoperatively to increase the patient's own platelet count. This generally achieves a higher platelet count and lasts longer. If platelet transfusion is necessary, a continuous infusion may be required to achieve a durable response. Depending upon the procedure, ITP therapies may be supplemented by another approach (ie, simultaneous use of antifibrinolytics).

Target platelet count — For patients who are managed with pharmacotherapy, treatment is aimed at increasing the platelet count above a threshold that stops bleeding or reduces the risk of serious bleeding. We generally use a target of ≥20,000 to 30,000/microL in most cases (except in the case of life-threatening bleeding or surgery, for which higher platelet counts may be necessary). (See 'Life-threatening bleeding' above and 'Surgery/invasive procedures' above.)

ITP therapies are temporizing interventions intended for short-term use to expeditiously reduce risk of hemorrhage. The goal of these treatments is **not** to achieve a normal platelet count. In particular, long-term steroid use is virtually never indicated in children and other options should be pursued in patients requiring treatment longer than one to two months.

As previously discussed, target platelet counts for surgeries and invasive procedures are higher than thresholds to prevent spontaneous bleeding and depend on the nature of the procedure. Appropriate platelet count levels for different invasive procedures are presented separately. It is important to recognize that these thresholds are approximations and have not been substantiated in prospective studies. (See "Platelet transfusion: Indications, ordering, and associated risks", section on 'Preparation for an invasive procedure'.)

Monitoring — Monitoring of patients with ITP, regardless of whether managed with pharmacologic therapy or "watchful waiting," should include regular clinical assessments and measurement of the platelet count. The frequency of monitoring depends on disease severity and treatment as well as parental and patient reliability.

In our practice, for patients managed in the outpatient setting, we typically monitor platelet counts once weekly initially. Hospitalized patients typically require more frequent monitoring (daily initially). The interval between testing can be gradually increased as the clinical picture stabilizes and the patient/family become more comfortable with the diagnosis. When recovery of platelet counts is detected, the interval between visits may be further lengthened, but monitoring should continue until the platelet count has returned to normal (>150,000/microL) and is stable without treatment. This recovery occurs within one to three

months after presentation in one-half of children with ITP and by six months in approximately 60 to 75 percent of children [17,18]. (See 'Disease course' below.)

In our practice, we stop monitoring after the platelet count has returned to normal and has remained stable for two to six months. After this type of stable remission, recurrence of ITP is rare, occurring in <5 percent of cases [22]. A few patients have well-compensated or recurrent chronic ITP, with platelet counts that are usually normal but intermittently punctuated by relapses triggered by infection.

Response to treatment

Expected response — Approximately 75 to 90 percent of patients respond to initial treatment with first-line therapies. The timing of the response is variable and depends on which agent is used (1 to 4 days for IVIG and IV anti-D, 3 to 14 days for oral glucocorticoids) (table 2) [2,23].

Genetic variations in the immunoglobulin G (IgG) Fc receptor IIb (FCGR2B) appear to influence the response to IVIG and the likelihood of achieving early complete remission [16,24]. Patients expressing the FCGR2B-2321 allele have a high likelihood of compete response, whereas patients who express homozygous FCGR2B-232T are less likely to respond. However, this finding has not been confirmed in other studies and this testing is rarely performed in routine clinical practice. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Genetic factors'.)

Poor response to initial therapy — For patients who do not have an adequate response to the initial treatment (ie, ongoing moderate or severe bleeding symptoms in the setting of persistent platelet count <20,000/microL), management includes:

- **Changing to or adding another first-line agent** – We generally change to another first-line therapy or use a combination of therapies. For example, for a patient who did not initially respond well to oral glucocorticoids, we might add IVIG with or without IV methylprednisolone. (See 'First-line therapies' below.)

- **Assessment for other causes of thrombocytopenia** – A poor response to therapy should also prompt reassessment of the patient's clinical picture to identify any new findings that may suggest another cause of thrombocytopenia, such as malignancy or bone marrow failure. If atypical features are noted (eg, lymph node enlargement; organomegaly; bone or joint pain; fevers; new laboratory findings of neutropenia, leukocytosis, or anemia not explained by bleeding; or abnormal peripheral blood smear), further evaluation, including bone marrow examination, is warranted [25]. This is discussed separately. (See "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis", section on 'Further evaluation'.)

We also generally evaluate for cytomegalovirus infection in refractory cases because, if cytomegalovirus is present, antiviral treatment may restore responsiveness to immunoglobulin therapy, while glucocorticoid and other immunosuppressive treatment may worsen the ITP [26]. (See "Overview of cytomegalovirus infections in children", section on 'Laboratory diagnosis'.)

Relapses — Approximately one-third to one-half of patients who initially respond to treatment with first-line therapies experience recurrent severe thrombocytopenia after the therapeutic effects of these medications wane [2]. There are no specific standards to guide decisions about retreatment of such patients. In our practice, we treat recurrences according to the same indications used for initial treatment. (See 'Treatment approach' above.)

If the patient initially had a robust response and subsequently requires re-treatment, we generally use the same agent (table 2). We do not switch to a different treatment merely because the patient relapsed, because other treatments are unlikely to have a more durable response (with the possible exception of rituximab). (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Rituximab'.)

It is reasonable to change agents in the following circumstances:

- Adverse reactions to treatment – We change agents in this setting only if there were problematic reactions to the treatment that cannot be easily ameliorated with enhanced premedication, slower infusion time, or changing the brand (as is sometimes helpful with IVIG). Infusions of anti-D should be spaced sufficiently far apart so that any anemia and reticulocytosis related to the previous anti-D treatment have resolved (typically a minimum of two to three weeks between treatments).

- Prolonged use of glucocorticoids – Long-term glucocorticoid use (ie, more than a few weeks) should be **avoided** [6]. Other options should be pursued in patients requiring prolonged or frequent courses of glucocorticoids.

After retreatment, the frequency of laboratory monitoring is individualized, depending on the patient's individual risk factors for bleeding and whether the patient tends to have physical findings or symptoms (eg, fatigue) that serve to identify a relapse.

Some patients require multiple courses of treatment before recovering. Others receive multiple courses of treatment with transient responses each time but do not achieve remission (ie, they develop persistent or chronic ITP). The treatment of chronic ITP is discussed in a separate topic review. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease".)

FIRST-LINE THERAPIES

Overview — When it is decided to use pharmacologic therapy to acutely increase the platelet count, first-line treatment options include glucocorticoids, intravenous immune globulin (IVIG), and intravenous (IV) anti-D immune globulin (anti-D) (table 2) [2,27]. The duration of acute symptomatic thrombocytopenia is shortened and signs of bleeding reduced by any of these three modalities compared with no treatment [28-39].

There is substantial practice variation regarding selection and dosing of these different therapies. Selection among the agents is driven by considerations of the patient's condition (as detailed above), cost, availability, and ease of administration [6,40]. Glucocorticoids are less costly, though the cost differential depends upon whether hospitalization is part of the management plan. In addition, some providers routinely perform a bone marrow examination before treating with glucocorticoids (though it is not our practice to do so in children with typical features of ITP), which further increases the burdens and costs of that treatment pathway. (See "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis", section on 'Indications for bone marrow examination'.)

The following sections review the dosing and efficacy of different ITP treatments. The approach to selecting among these is described above. (See 'Treatment approach' above.)

Glucocorticoids — For pediatric patients requiring treatment for ITP, glucocorticoids are effective in increasing the platelet count and are appropriate first-line agents as monotherapy (particularly if the bleeding risks are not severe) or in combination with other agents [6].

A variety of dose regimens have been used, and there is insufficient evidence to determine if any approach is superior to the others [6]. Our practice is to administer glucocorticoids as a short course at a relatively high dose to try to minimize toxicity associated with long-term use and because of a potentially more rapid onset of action. The following steroid regimens are commonly used [6,28,38]:

- Dexamethasone 0.6 mg/kg per day (maximum 40 mg per day) for four days orally or IV (no taper needed for this short course)
- Prednisone 2 to 4 mg/kg per day (maximum 120 mg per day) orally for five to seven days (with or without a taper)
- Methylprednisolone 30 mg/kg (maximum 1000 mg per day) as a single daily IV dose for three to four days (no taper needed for this short course)

The efficacy of glucocorticoids for treating pediatric ITP is supported by randomized trials demonstrating that they increase platelet counts more rapidly compared with placebo [6,28,32]. Although most patients respond to glucocorticoids, a drop in platelet count after the steroids are discontinued is common, unless spontaneous remission has occurred in the

interim. Repeated courses of treatment may be necessary if significant bleeding symptoms persist or recur, but ongoing or intermittent use for >1 to 2 months is discouraged. (See 'Expected response' above.)

Side effects of glucocorticoids include behavioral change, sleep disturbance, hypertension, increased appetite, gastritis, and weight gain. Avoidance of chronic treatment with these agents is preferable because of these side effects, as well as the long-term consequence of poor growth, osteoporosis, immune suppression, and, less frequently, other issues (including pancreatitis). Alternative therapies such as IVIG, IV anti-D, or second-line agents (eg, rituximab, thrombopoietin receptor agonists [TPO-RAs]) should be considered for children who require prolonged or repeated therapy. (See "Major side effects of systemic glucocorticoids".)

Glucocorticoids are presumed to have both rapid effects (reducing reticuloendothelial system phagocytosis of antibody-coated platelets [41,42] and improving vascular integrity [43]) and delayed effects (reducing production of anti-platelet antibodies).

Intravenous immune globulin — If pharmacologic therapy is used, we suggest IVIG as a first-line choice, particularly when a rapid rise in platelet count is desired. IVIG is typically administered as a single dose of 0.8 to 1 g/kg. A single-dose regimen of IVIG appears to be preferable to regimens that divide the IVIG into several smaller doses [6,23,38]. An increase in the platelet count is usually observed within 24 hours of administration.

IVIG therapy is superior to glucocorticoids or no treatment when early recovery of platelet numbers is desired [23,38,39,44-46]. This was best illustrated in a meta-analysis that demonstrated that children treated with IVIG were more likely to achieve a platelet count >20,000/microL at 24 hours after initiation of therapy as compared with those receiving glucocorticoids [23]. Similar advantages of IVIG were noted at 48 and 72 hours.

Early treatment with IVIG does not appear to reduce the likelihood of developing chronic ITP, although remission may be achieved sooner [16]. (See 'Disease course' below.)

Adverse reactions to IVIG are common. The risk of adverse reactions generally correlates with the dose of IVIG and the rate of infusion. Adverse effects may be lessened by administering IVIG in smaller doses over several days (eg, daily infusions for three to five days rather than one or two days). However, this likely results in a slower platelet rise, and it is more burdensome on the patient and the medical system. Most reactions are mild to moderate, transient, reversible events such as headache, chills, or flushing. Potentially serious reactions (which may include anaphylaxis, transfusion reactions, aseptic meningitis, thromboembolic events, renal impairment, or severe hemolysis) occur in 2 to 6 percent of patients [47]. Headache is the most common side effect (30 to 70 percent, depending on a number of factors including brand) and is often delayed. Other common side effects include fatigue,

abdominal pain, and myalgia. In some cases, very severe headaches may occur as a result of aseptic meningitis. Severe headaches and aseptic meningitis appear to be more common in patients with a history of migraine headaches. Additional hydration may help to reduce headaches. Transient neutropenia (absolute neutrophil count <1500/microL) develops in up to 30 percent of patients [48], but this effect is very short-lived and clinically unimportant. Adverse effects may be more pronounced in older patients. Adverse effects of IVIG are discussed in greater detail separately. (See "Intravenous immune globulin: Adverse effects".)

Acetaminophen and/or diphenhydramine may be administered as premedication to minimize side effects. In addition, in our practice, we routinely co-administer IV methylprednisolone (30 mg/kg, up to 1 g) with IVIG for the purpose of minimizing side effects, particularly headache. Other experts do not advocate treating with concomitant methylprednisolone. A meta-analysis of observational studies raised concerns that co-administration of methylprednisolone and IVIG is associated with increased risk of developing chronic ITP, but this finding was likely confounded by other factors [49]. (See "Overview of intravenous immune globulin (IVIG) therapy", section on 'Premedications'.)

The exact mechanism of action of IVIG is incompletely understood and is likely multifactorial. There are many lines of evidence suggesting that the rapid increase in platelet count results from slowing of platelet destruction by inhibition of phagocytosis. Exactly how this occurs is still unknown. One hypothesis is that IVIG inhibits phagocytosis by upregulating the inhibitory IgG Fc receptor IIB (FCGR2B). Studies in ITP in adults with inhibitors of FcRn suggest that this contributes to the IVIG effect by reducing the level of antiplatelet antibodies. (See "Overview of intravenous immune globulin (IVIG) therapy", section on 'Mechanisms of action'.)

Anti-D immune globulin — Anti-D (also known as Rho[D] immune globulin) is a reasonable alternative to IVIG for appropriately selected children with ITP. Anti-D is ineffective when used in patients with Rh-negative blood type or those who have had splenectomy [50]. Anti-D also should not be used in patients with clinically significant anemia, marked reticulocytosis, or positive direct antiglobulin test (DAT; also known as Coombs test), unless this result is attributable to recent administration of anti-D [6]. Anti-D should also be avoided in patients with underlying comorbidities such as renal abnormalities, cirrhosis, or acute febrile illness. (See "Anti-D immune globulin (Rho[D] immune globulin): Pediatric drug information".)

When treatment with anti-D is selected, we administer approximately 75 micrograms/kg (375 international units/kg) IV as a single dose. At this dose, anti-D appears to have comparable efficacy as IVIG [14,38,45].

We also co-administer a single dose of methylprednisolone (30 mg/kg, up to 1 g maximum) as a premedication to increase efficacy and minimize side effects. Others do not routinely treat with concomitant methylprednisolone.

Pretreatment laboratory testing should include baseline measures of a complete blood count, DAT, blood urea nitrogen, creatinine, and urine analysis to assess for evidence of hemolysis, renal dysfunction, or hematuria [6,51]. Blood group typing and DAT should be performed, even if already known, because only Rh-positive patients are eligible for anti-D treatment. Patients should be monitored for eight hours after the infusion [52]. During treatment, patients should be monitored for hemoglobinuria (by urinalysis or dipstick) every few hours and, if any reaction occurs, a follow-up complete blood count should be performed.

Anti-D has several advantages compared with IVIG:

- Somewhat lower risk of infusion-related side effects such as headache and flu-like symptoms [38].
- Reduced donor exposure.
- Anti-D can be infused rapidly (in minutes), as compared with the slower infusion time required for IVIG (hours). However, anti-D requires pretreatment laboratory testing (described below) and a period of eight hours of observation and monitoring after infusion.
- In the United States, it is often difficult to obtain same-day approval for outpatient IVIG and approval for anti-D may be easier.

Anti-D has the disadvantage of rare but serious adverse effects that occur primarily in patients with underlying comorbidities, consisting of severe intravascular hemolysis (occurring in approximately 1:1115 treatments), with the possibility of concomitant renal failure, disseminated intravascular coagulation, and even death [51].

The efficacy of IV anti-D was shown in a randomized controlled trial in which 105 children were assigned to receive a single dose of either anti-D or IVIG [14]. At 24 hours, the response to therapy (defined as a platelet count >20,000/microL) was similar in both groups (72 and 77 percent, respectively). At seven days, the mean platelet count was higher in the anti-D group compared with IVIG (312 versus 195/microL).

IV anti-D acts by coating red cells with antibodies so that they bind the Fc gamma receptors in the reticuloendothelial system, interfering with removal of antibody-coated platelets. Consistent with this mechanism, anti-D is only effective in patients with Rh-positive blood types because only their red cells can be coated with anti-D. (See "Initial treatment of immune thrombocytopenia (ITP) in adults", section on 'IVIG dosing and administration'.)

SECOND-LINE THERAPIES

Second-line agents include:

- Rituximab (see "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Rituximab')
- Thrombopoietin receptor agonists (TPO-RAs; eg, eltrombopag, romiplostim) (see "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Thrombopoietin receptor agonists')
- Alternative immunosuppressive agents (eg, azathioprine, 6-mercaptopurine, mycophenolate mofetil, sirolimus, cyclosporine) (see "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Other agents')

These agents traditionally have been reserved for patients with ITP lasting ≥3 to 6 months whose symptoms and risks are not adequately controlled using standard therapies. However, second-line therapies are increasingly used earlier in the treatment course, particularly in children who have persisting thrombocytopenia and those who remain dependent on glucocorticoid therapy to control symptoms. Second-line therapies are described in greater detail separately. (See "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Ongoing management (second-line therapies)'.)

OUTCOME

Disease course — The majority of affected children recover from ITP within three to six months of presentation, with or without treatment [17,18].

Approximately 10 to 20 percent of affected children go on to have chronic ITP, which is defined as thrombocytopenia for more than 12 months since presentation [1,16,17,53,54]. (See 'Terminology' above.)

- **Risk factors for chronic ITP** – Factors that appear to be associated with increased risk of developing chronic ITP include [17-20,24,49,55-57]:
  - Older age
  - Less severe thrombocytopenia at the initial diagnosis
  - Insidious onset of symptoms
  - Lack of preceding infection or vaccination prior to development of ITP
  - Lack of mucosal bleeding at diagnosis

  However, these findings do not reliably predict whether chronic ITP will develop in a specific patient.

- **Impact of pharmacologic therapy** – Early pharmacologic intervention has not been shown to reduce the likelihood of developing chronic ITP. This was demonstrated in a clinical trial in which 200 children with newly diagnosed ITP were randomly assigned to

early treatment with a single dose of intravenous immune globulin (IVIG) or careful observation with treatment only in the case of severe bleeding [16]. Upfront treatment with IVIG led to faster recovery of platelet counts and fewer severe bleeding events (1 versus 9 percent); however, the rate of progression to chronic ITP was similar in both groups (10 and 12 percent). Of note, most patients who experienced severe bleeding events in this trial had grade 3 bleeding symptoms at presentation and thus would have received treatment according to our approach outlined above. (See 'Moderate to high bleeding risk' above.)

Earlier observational studies reported conflicting results with some showing an association between early treatment with IVIG and lower rates of chronic ITP [57,58], while others did not find any association between early treatment and subsequent development of chronic ITP [59].

Limited evidence suggests that treatment with IVIG compared with other therapies may be associated with a slightly lower likelihood of developing chronic ITP. In a meta-analysis of nine randomized trials, chronic ITP was less likely among patients treated with IVIG compared with steroids (18 versus 25 percent, respectively; relative risk 0.71, 95% CI 0.52-0.99) [23]. Similarly, in a meta-analysis of 54 observational studies, treatment with IVIG alone (but not in combination with methylprednisolone) was associated with a lower likelihood of developing chronic ITP (odds ratio 0.71, 95% CI 0.52-0.97) [49].

Based on the available evidence, treatment should be directed at control of symptoms (ie, stopping severe hemorrhage, minimizing the risk of bleeding, and improving quality of life) rather than preventing development of chronic ITP. (See 'Treatment approach' above.)

Bleeding complications — The risk of serious bleeding in children with newly diagnosed ITP is approximately 3 percent, and the risk of intracranial hemorrhage (ICH) is approximately 0.5 percent [15,60,61]. Whether pharmacologic therapy reduces the risk of ICH and other life-threatening complications of ITP remains unproven. Large prospective trials would be necessary to answer this question, but this is not feasible, given the rarity of severe bleeding events. Indirect evidence that treatment may impact bleeding complications comes from the observation that bleeding risk appears to be related to the degree and persistence of thrombocytopenia and that the majority of patients who are treated respond with an increase in their platelet counts [7,18,27]. (See "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis", section on 'Serious hemorrhage'.)

In a registry study of 501 patients from the five Nordic countries, approximately 85 percent of the patients were deemed to be "at risk" for serious bleeding (defined as platelet count <20,000/microL) at the time of presentation [18]. Approximately 60 percent of patients

received pharmacologic treatment (most commonly IVIG) within two weeks of diagnosis. The "at-risk" period lasted <1 month in 75 percent of patients and persisted for >6 months in 10 percent. There were 33 episodes of mucosal bleeding (epistaxis, oral bleeding, menorrhagia, or rectal bleeding), which were more common among patients with severe thrombocytopenia, and no episodes of life-threatening bleeding or ICH. Fifteen of the bleeding episodes required blood transfusion.

Mortality — Mortality is very rare in children with ITP. Mortality in newly diagnosed patients is almost entirely due to catastrophic bleeding complications, particularly ICH, whereas mortality and morbidity in patients with chronic ITP may be due to infections as a complication of long-term immunosuppressive treatment.

In one study, children with ICH had a 25 percent mortality rate and 33 percent of the survivors had neurologic complications at median follow-up of 11 months [11]. Outcomes were somewhat better for patients whose ICH was precipitated by head trauma or who presented with ICH, compared with those who developed ICH after diagnosis of ITP.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Immune thrombocytopenia (ITP) and other platelet disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Immune thrombocytopenia (ITP) (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Treatment approach** – Initial management of children with newly diagnosed ITP may be either "watchful waiting" or pharmacologic intervention. First-line treatment options include glucocorticoids, intravenous immune globulin (IVIG), and intravenous (IV) anti-D immune globulin (anti-D) (table 2). The choice of therapy is based upon the severity of bleeding symptoms (table 1), degree of thrombocytopenia, and additional patient-specific risk factors (algorithm 1) (see 'Treatment approach' above and 'First-line therapies' above):

  - **Life-threatening bleeding** – For children with ITP who have life-threatening bleeding (eg, intracranial hemorrhage [ICH], gastrointestinal bleeding with hemodynamic instability, pulmonary hemorrhage with cardiopulmonary compromise), we recommend platelet transfusion and combination pharmacotherapy (**Grade 1B**). For most patients, we suggest combined therapy with high-dose IV methylprednisolone **plus** IVIG, rather than either agent alone (**Grade 2C**). Anti-D can be added to the regimen in Rh-positive, direct antiglobulin test [DAT]-negative patients; however, the additional benefit of anti-D in this setting is uncertain and practice varies. In addition, we suggest a high dose of a thrombopoietin receptor agonist (TPO-RA; eg, romiplostim) (**Grade 2C**). Though this agent has little impact on the acute bleeding event, it may boost and prolong the platelet response in the days following the bleeding event. (See 'Life-threatening bleeding' above and "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Thrombopoietin receptor agonists'.)

  - **Severe bleeding** – For children with severe mucosal bleeding or suspected internal hemorrhage that requires immediate medical attention but that is not life-threatening (eg, gastrointestinal bleeding without hemodynamic instability, pulmonary hemorrhage without cardiopulmonary compromise, severe prolonged epistaxis, muscle or joint hemorrhage), treatment is similar to that described above for life-threatening bleeding. However, rather than giving all three agents (methylprednisolone, IVIG, and anti-D) for up to four days, a measured approach using only one or two of these agents for fewer days may be sufficient. Platelet transfusion is usually not necessary if bleeding is not life-threatening but may be warranted in patients requiring surgery and those with ongoing hemorrhage. As with life-threatening bleeding, a single dose of a TPO-RA may increase the likelihood of a higher platelet response. (See 'Severe, non-life-threatening bleeding' above.)

  - **Moderate to high risk for bleeding** – For patients who currently lack severe bleeding symptoms but are deemed to be at moderate to high risk for bleeding complications (based on bleeding symptoms, platelet count, and other risk factors,

as outlined in the algorithm and described above (algorithm 1)), we suggest pharmacologic therapy rather than watchful waiting (**Grade 2B**). The choice of initial treatment depends on how rapid a response is desired (algorithm 1):

- When a rapid rise in platelet count is desired, we suggest IVIG or anti-D (the latter is used only in Rh-positive, DAT-negative, non-splenectomized patients without evidence of hemolysis) (**Grade 2B**). IVIG is given as a single dose of 1 g/kg; IV anti-D is given as a single dose of 75 micrograms/kg. In our practice, we also administer a single dose of IV methylprednisolone (30 mg/kg [up to 1 g]) to augment the platelet response and ameliorate the side effects of IVIG or IV anti-D. Others do not treat with concomitant methylprednisolone.

- For patients in whom a rapid rise in platelet count is not necessary, we suggest initial treatment with oral glucocorticoids (**Grade 2C**). Acceptable regimens include prednisone 2 to 4 mg/kg per day (maximum 120 mg per day) orally for five to seven days or dexamethasone 0.6 mg/kg per day (maximum 40 mg per day) orally for four days. The preference for these agents in this setting is largely based on cost considerations and ease of administration. IV steroids, IVIG, and anti-D are reasonable alternatives.

- **Low bleeding risk** – For children with no bleeding or mild bleeding symptoms (ie, cutaneous bleeding only, such as bruising and petechiae) without additional risk factors, we suggest "watchful waiting" rather than pharmacologic intervention (**Grade 2C**). This option, in particular, requires extensive discussion with patients and their caregivers. (See 'Low bleeding risk' above.)

- **General measures** – Management of pediatric patients with ITP includes activity restriction, avoidance of antiplatelet and anticoagulant medications, regular monitoring of platelet count, and monitoring for clinical bleeding. (See 'General measures' above and 'Monitoring' above.)

- **Management of refractory ITP and relapses** – For patients who do not have an adequate response to initial treatment (ie, ongoing moderate or severe bleeding symptoms in the setting of persistent thrombocytopenia), we generally change to another first-line therapy or use a combination of therapies. (See 'Poor response to initial therapy' above.)

  Second-line agents (eg, rituximab and TPO-RAs [eltrombopag, romiplostim]) have traditionally been reserved for patients with ITP lasting ≥3 to 6 months whose symptoms and risks are not adequately controlled using first-line therapies. However, second-line therapies are increasingly used earlier in the treatment course, particularly in children who have persistent thrombocytopenia and those who remain dependent on

glucocorticoid therapy to control symptoms. (See 'Second-line therapies' above and "Immune thrombocytopenia (ITP) in children: Management of chronic disease", section on 'Ongoing management (second-line therapies)'.)

Many patients experience recurrent severe thrombocytopenia after the therapeutic effects of these medications wane. In our practice, we treat recurrences according to the same indications used for initial treatment. If the patient initially had a robust response and subsequently requires retreatment, we generally use the same agent. However, long-term glucocorticoid use (ie, >1 to 2 months) should be avoided and other options should be pursued in patients requiring prolonged or frequent courses of glucocorticoids. (See 'Response to treatment' above and 'Relapses' above.)

- **Disease course** – Most children with ITP recover within three to six months of presentation, with or without treatment. Approximately 10 to 20 percent of affected children go on to have chronic ITP, which is defined as thrombocytopenia for >12 months since presentation. Risk factors for developing chronic ITP include older age, less severe thrombocytopenia at the initial diagnosis, insidious onset of symptoms, and lack of preceding infection or vaccination prior to development of ITP. Early pharmacologic intervention does not appear to reduce the likelihood of developing chronic ITP. (See 'Disease course' above.)

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Topic 5917 Version 39.0

GRAPHICS

Modified Buchanan and Adix bleeding score for pediatric immune thrombocytopenia (ITP)

Grade	Severity	Description
0	None	No bleeding of any kind
1	Minor	Few petechiae (≤100 total) and/or ≤5 small bruises (≤3 cm diameter) No mucosal bleeding
2	Mild	Many petechiae (>100 total) and/or >5 large bruises (>3 cm diameter)
3	Moderate – Low risk	Blood crusting in nares, painless oral purpura, oral/palatal petechiae, buccal purpura along molars only, mild epistaxis ≤5 minutes
	Moderate – High risk	Epistaxis >5 minutes, hematuria, hematochezia, painful oral purpura, significant menorrhagia
4	Severe	Mucosal bleeding or suspected internal hemorrhage (lung, muscle, joint, etc) that requires immediate medical attention or intervention
5	Life-threatening/fatal	Documented intracranial hemorrhage or life-threatening or fatal hemorrhage at any site

ITP: immune thrombocytopenia.

Graphic 89047 Version 6.0

Our approach to the initial treatment of pediatric patients with newly diagnc (ITP) based on severity of bleeding symptoms and other risk factors

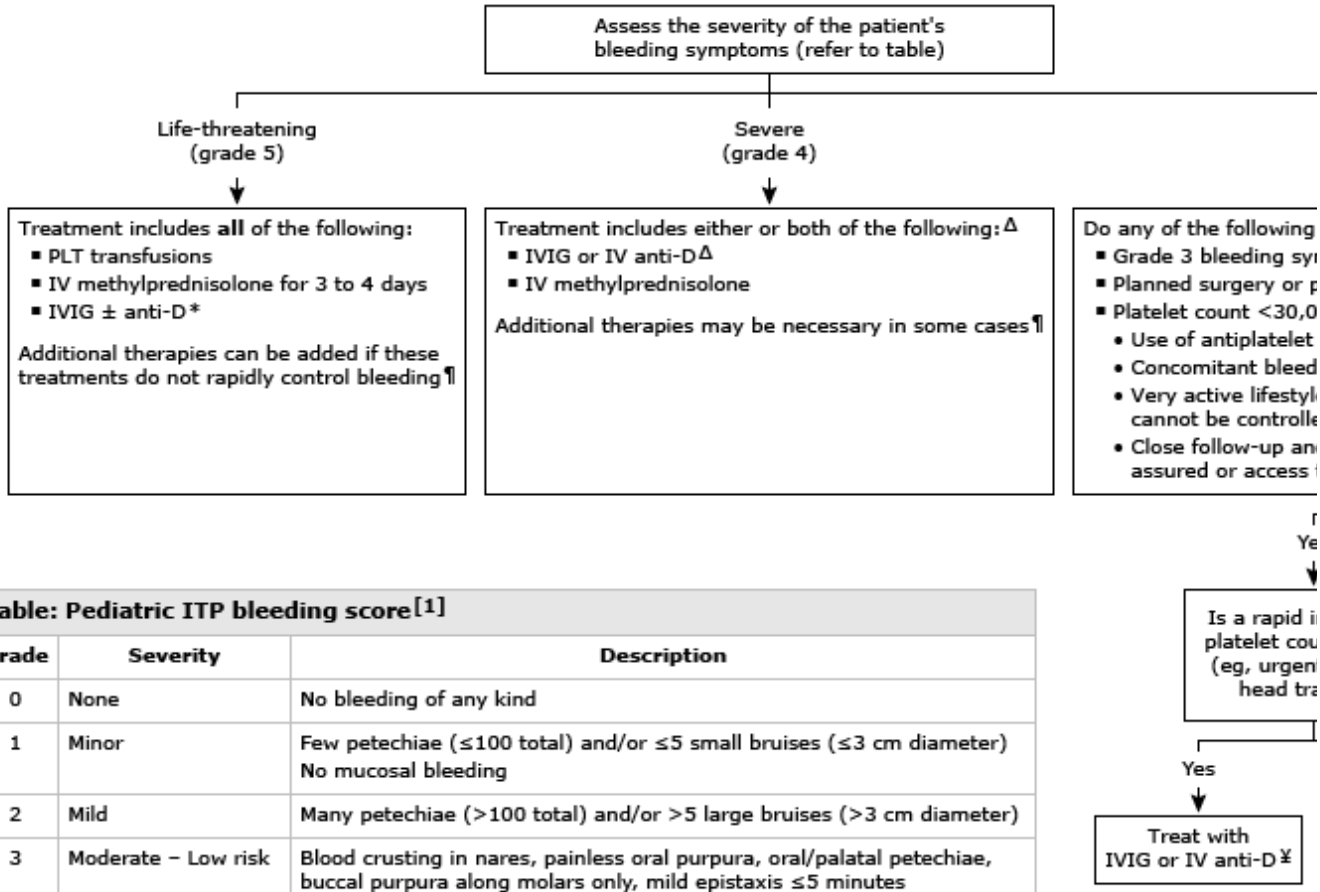

Table: Pediatric ITP bleeding score[1]

Grade	Severity	Description
0	None	No bleeding of any kind
1	Minor	Few petechiae (≤100 total) and/or ≤5 small bruises (≤3 cm diameter) No mucosal bleeding
2	Mild	Many petechiae (>100 total) and/or >5 large bruises (>3 cm diameter)
3	Moderate – Low risk	Blood crusting in nares, painless oral purpura, oral/palatal petechiae, buccal purpura along molars only, mild epistaxis ≤5 minutes
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4	Severe	Mucosal bleeding or suspected internal hemorrhage (lung, muscle, joint, etc) that requires immediate medical attention or intervention
5	Life-threatening/fatal	Documented intracranial hemorrhage or life-threatening or fatal hemorrhage at any site

This algorithm summarizes our suggested approach to treating pediatric patients with newly diagnosed I diagnosis). Management is not standardized, and practice may vary from center to center. Our suggested severity of bleeding symptoms. Other important considerations include degree of thrombocytopenia, oth antiplatelet or anticoagulant medications), quality of life, and values and preferences of the patient/careg use in conjunction with additional UpToDate content on ITP in children. Refer to UpToDate topics on the r additional details of our approach, including the evidence supporting the efficacy of these treatments. Fo persistent ITP (ongoing ITP between 3 and 12 months from the initial diagnosis) and chronic ITP (ie, ITP la UpToDate content on these issues.

ITP: immune thrombocytopenia; PLT: platelet; IV: intravenous; IVIG: intravenous immune globulin; anti-D as anti-Rho immune globulin); NSAID: nonsteroidal antiinflammatory drug; DAT: direct antiglobulin test.

* Anti-D may be used instead of or in addition to IVIG in Rh-positive, DAT-negative, non-splenectomized p the patient's DAT status is unknown, which is often the case in emergency situations. If DAT is negative ar include anti-D as part of combination therapy in patients with life-threatening bleeding. IV anti-D can be a splenectomized patients despite its relative lack of efficacy when used as the sole agent in these patients this setting. In non-emergency situations, anti-D is generally used as an alternative to IVIG rather than ar

¶ Additional interventions that have been used patients with severe or life-threatening bleeding based up human factor VIIa, vincristine, adjunctive antifibrinolytic agents (eg, epsilon aminocaproic acid or tranexa splenectomy. For patients with severe menorrhagia, hormonal therapy may be warranted. In addition, we thrombopoietin receptor agonist (eg, romiplostim) in patients with severe bleeding. This practice is not st generally reserved for patients with active, life-threatening bleeding. However, PLT transfusions may be r threatening bleeding who require surgery and for those who do not achieve an adequate response with c too slow or if the PLT count does not increase to an acceptable level). Refer to separate UpToDate conten these therapies.

Δ For severe bleeding that is not life-threatening (gastrointestinal bleeding without hemodynamic instabi cardiopulmonary compromise, severe prolonged epistaxis, muscle or joint hemorrhage), the components for life-threatening bleeding; however, rather than giving all 3 agents (IVIG, IV anti-D, and methylpredniso approach using only 1 or 2 of these agents for fewer days may be sufficient. The choice of agents can be treatment response if such experience exists. The choice and duration of therapy also depends upon the

◇ Target platelet counts for patients undergoing surgery or invasive procedures are higher than thresho and depend on the nature of the procedure. Refer to UpToDate topics on ITP and platelet transfusion the

§ For children with substantially impaired quality of life due to symptoms (especially fatigue) or anxiety ab therapy may be a reasonable option (after discussing with the patient and/or caregivers and carefully we

¥ IVIG and anti-D are our preferred agents for most patients deemed to be at moderate to high risk of ble count is desired. In addition, in our practice, we typically treat these patients concomitantly with a single to augment the platelet response and ameliorate the side effects of IVIG and anti-D. This practice is not s routinely treat with methylprednisolone. Glucocorticoids alone are a reasonable alternative in this setting have more delayed onset compared with IVIG. Refer to UpToDate content on management of ITP in child

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Source:

1. *Table reproduced from: Schoettler ML, Graham D, Tao W, et al. Increasing observation rates in low-risk pediatric immune th assessment and management plan (SCAMP®). Pediatr Blood Cancer 2017; 64:10.1002/pbc.26303. https://onlinelibrary.wile* *2017 John Wiley & Sons Ltd. Reproduced with permission of John Wiley & Sons Inc. This image has been provided by or is ov before it can be downloaded to PowerPoint, printed, shared or emailed. Please contact Wiley's permissions department eith RightsLink service by clicking on the 'Request Permission' link accompanying this article on Wiley Online Library (https://onl*

Graphic 115184 Version 2.0

First- and second-line treatment options for children with immune thrombocytopenia (ITP)

Treatment	Initial response* (days)[1]	Peak response¶ (days)[1]	Initial response rate	Toxicities/risks	Su re
First-line options for newly diagnosed or persistent ITP					
Watchful waiting	A few days to 3 to 6 months		Spontaneous complete remission occurs in 50% within one month of presentation and 75% by six months	Risk of preventable hemorrhage (low risk); need for activity restriction; familial anxiety.	Rel aft spo rer unl
IVIG[Δ] Life-threatening bleeding: 1 gram/kg per day IV for one to three days Non-life-threatening bleeding: 0.8 to 1 gram/kg IV, as a single dose	1 to 3	2 to 7	Initially effective in >80% of patients	Side effects include headache (can be severe [eg, aseptic meningitis]), nausea, vomiting, fever, chills, body aches. These can be minimized with premedication and prolonging infusion time.[Δ] Transient neutropenia also may occur.	On pat bel acc pla thr aft we
Anti-D[Δ ◇] 75 micrograms/kg IV, as a single dose	1 to 3	3 to 7	Initially effective in 70 to 80%	Headache (less common than with IVIG), fever, chills, nausea, and vomiting. Side effects may be reduced with premedication.[Δ] Mild hemolysis is common (eg, fall in hemoglobin by 1 to 2 g/dL). DIC and severe hemolysis or renal failure may rarely occur. Anti-D is contraindicated in	Sim IVI alt lon res hav des wit dos

				patients who are Rh-negative or DAT-positive, or have had splenectomy.	
Methylprednisolone 30 mg/kg as a single daily dose IV for 3 to 4 days (maximum 1000 mg per day)	2 to 14	7 to 28	Initially effective in 75 to 80%	Behavioral change, sleep disturbance, hypertension, impaired glucose tolerance.	In qu on pat pla cou bel acc thr aft we
Prednisone 4 mg/kg per day orally for 7 days, followed by rapid tapering[§] (maximum 240 mg/day)	4 to 14	7 to 28	Initially effective in up to 75%	Same as for methylprednisolone above. Prolonged usage may cause weight gain, osteopenia, cataracts, and growth failure.	In pat pla cou bel acc pla thr aft tap unl cou pre is pro
Dexamethasone 24 mg/m^2 for 4 days orally or IV[§] (maximum 40 mg/day)	2 to 14	4 to 28	Initially effective in up to 75%	Same as for methylprednisolone above.	In of pla cou bel acc thr aft we
Second-line options for chronic ITP					
Rituximab[3] 375 mg/m^2 weekly for four weeks	7 to 56	14 to 180	Initial response in 40 to 50%	Urticarial rash, headache, fever, and chills (mild and transient). Serum sickness in up to 10% of children.	25 ter res or yea tre

Thrombopoietin receptor agonists (eg, eltrombopag[4], romiplostim[5])¥	5 to 7	Not established	Approximately 80% of patients achieve a response	Transaminitis, mild respiratory illness, headache, epistaxis, cataract (rare).	The res las lon dru cor the do typ ind rer
Splenectomy	1 to 56	7 to 56	60 to 70% long-term response	Complications include sepsis and portal vein thrombosis.	70 res ma pla res ove

Refer to UpToDate topic on the treatment of ITP in children for details of our approach to the initial and subsequent treatment of ITP and the overall efficacy of these treatments.

IVIG: intravenous immune globulin; IV: intravenously; Anti-D: anti-Rho (D) immunoglobulin; DIC: disseminated intravascular coagulation; DAT: direct antiglobulin test (also known as direct Coombs test).

* Initial response is the first time that a response could be reasonably expected.

¶ Peak response is the time after which a response becomes less likely at typically used doses. These data do not address the quality of the response (ie, absolute platelet count reached or percent increase from baseline) or the likelihood of a response for any given treatment.

Δ When treating with either IVIG or anti-D, acetaminophen and/or diphenhydramine may be administered as premedication to minimize side effects. In our practice, we also coadminister a single dose of methylprednisolone 30 mg/kg (up to 1 gram maximum) to increase efficacy and to minimize side effects (especially headache).

◇ Anti-D should **not** be used in in patients who are Rh-negative or those with a positive DAT, unless this result is attributable to recent administration of anti-D. Anti-D should generally not be used in splenectomized patients because it is not effective in this group. However, in patients with severe bleeding, anti-D may be a useful part of combination therapy, even in splenectomized patients, despite its relative lack of efficacy when used as the sole agent in these patients. Anti-D should be used with care in patients with substantial comorbidities or who have evidence of anemia or hemolysis.

§ For treatment with glucocorticoids, a variety of regimens have been used effectively. In our practice, we generally administer glucocorticoids as a short course at a very high dose to minimize toxicity associated with long-term use and because of a potentially more rapid onset of action. Refer to UpToDate topics on management of ITP in children for additional details.

¥ Thrombopoietin receptor agonists are not established treatments for children with ITP. Pediatric dosing has not been established. Refer to UpToDate topics on treatment of ITP in children for additional details.

Additional data from:

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Graphic 89045 Version 10.0

Contributor Disclosures

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