Immune Thrombocytopenia: American Society of Hematology Guidelines, 2019

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Immune Thrombocytopenia is the commonest cause of thrombocytopenia in young children. A thorough history, examination and peripheral smear evaluation is central to diagnosis. The recent American Society of Hematology guidelines 2019, has shed light on diagnosis and management based on latest available literature. We, herein, delineate the important aspects of these guidelines.

Keywords: *Bleeding, Diagnosis, Intravenous immunoglobulin, Guidelines, Management.*

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by a low platelet count (<100,000/mm^3) due to 'antibody mediated' destruction of platelets and impaired mega-karyopoiesis with peak incidence in 2-5 years old [1]. Despite being the commonest cause of thrombocytopenia in children, there have been more controversies than consensus in its diagnosis and management. The American Society of Hematology first published guidelines on ITP in 1996 with updates published in 2011 and now in December, 2019 to answer the relevant questions in wake of new available evidence. The highlights of the latest update are listed in ***Table* I**. The definitions of 'grades of recommendation' may be referred to in the respective guidelines [1,2]

ITP is termed acute/newly diagnosed, if lasting less than 3 months; persistent, if lasting 3-12 months, and chronic, if persisting beyond 12 months. Majority of children (60-75%) have acute ITP that resolves within 2-3 months of diagnosis, regardless of therapy. ITP may be primary (where no cause is found) or secondary to other conditions like infections (HIV, Hepatitis C, *H. pylori*), autoimmune syndromes (SLE, APLA syndrome), primary immunodeficiency (common variable immune-deficiency i.e. CVID) and drugs (valproate, heparin). As per the latest ASH 2019 guidelines, routine testing for bone marrow aspirate/bone marrow biopsy (Grade 1B), anti-nuclear antibody (grade 2C) and *H. pylori* (grade 2C) is not recommended unless there are clinical pointers. The utility of screening all ITP patients for CVID, hepatitis C, HIV and Hepatitis B is still unclear [1]. Thrombocytopenic syndromes (like Wiskott–Aldrich syndrome) and CVID are important masqueraders of immune thrombocytopenia. While a detailed family history and a meticulous examination may diagnose these mimickers at outset, at times these syndromes are recognized later in cases mislabelled as ITP, who fail to respond to all therapy [3].

Clinically, ITP is characterized by bleeding events that show no linear correlation with the severity of thrombocytopenia [4]. Most of children (62-74%) with ITP spontaneously remit within a year [5]. Therefore, the decision regarding use of platelet enhancing therapy should be based on multiple factors (access to care, patient and provider preferences, risk of bleeding, duration of disease, co-morbidities and age at presentation). In newly diagnosed ITP with no/mild bleeding, the ASH 2019 guidelines recommend observation over treatment irrespective of the platelet count. Moreover, they suggest observation at home is preferable to hospital admission. However, they add that if a decision to observe on outpatient basis is made, it is desirable for the patient to be seen by a pediatrician within 24-72 hours [2]. In those set-ups, where patient follow-up is uncertain due to social/ financial concerns or residence is in remote areas which are far from hospitals, admission to the hospital and treatment is preferable. Similar recommendations have been stated by the Joint working group (JWG) of several European hematology societies (Germany, Austria, and Switzerland) published in 2018, wherein special emphasis has been placed on the patient's choice of therapy [6].

Minimizing the risk of hemorrhage and decreasing the long-term side effects of treatment are the goals of therapy. Treatment is guided by the severity of bleeding rather than on the platelet count. The ASH 2019 guidelines have defined major bleeding as any one of the following (*i*) WHO grade 3 or 4 bleeding, (*ii*) Buchanan severe grade, (*iii*) Bolton-Maggs and Moon major bleeding, (*iv*) IBLS grade 2

or higher, or (*v*) life-threatening bleeding or intracerebral hemorrhage. Minor bleeding is any bleeding not meeting the criteria for major bleeding. Adolescents with ITP are treated as per pediatric guidelines [1].

Acute/newly diagnosed ITP: In a child with newly diagnosed ITP with no/mild bleeding, ASH continues to recommend observation over pharmacotherapy irrespective of the platelet count. However, in a child with moderate to severe bleeding and/or a diminished health related quality of life, a short course of corticosteroids (<7 days) is preferred over intravenous immunoglobulin (IVIG) or anti-D immunoglobulin (anti-D Ig) therapy [2]. A short prednisolone course (2-4 mg/kg/day; maximum 120 mg/day) of 5-7 days is preferable to dexamethasone (0.6 mg/kg/day; maximum 40 mg/day) for 4 days. The European joint working group (JWG) has also endorsed a shorter course of steroids less than 2 weeks, without specifying the preferred type of steroid [6]. ASH 2019 states that as per limited available data IVIG and anti-D Ig have similar benefits, and both are associated with rare but potential black box warnings. Thus, either of them may be used. In practice, the choice between the three available treatments is usually guided by cost, availability and adverse effects [7].

Persistent ITP: If treatment with steroids, IVIG or anti-D Ig has been successful, these options may be used to prevent bleeding as needed, especially in the first 12 months of diagnosis when the possibility of spontaneous remission is high [1].

Chronic ITP: In children with "newly diagnosed" ITP or persistent ITP with non-response to first line pharmacotherapy or those with chronic ITP, second line pharmacotherapy is suggested wherein thrombopoietin receptor agonists (TPO-RAs) (romiplostim, eltrombopag *etc*.) are preferred over rituximab. This is premised on acceptable response to TPO-RA with low side effects and avoidance of immunosuppression. Similar views were given by the European JWG [6]. Other treatment options include high dose dexamethasone (0.6 mg/kg/d for 4 days every 4 weeks for 6 cycles) [1]. Use of alternate immunosuppressive agents (dapsone, azathioprine, danazol, mycophenolate mofetil, cyclosporine, cyclophosphamide, anti-CD52 monoclonal antibody, vinca alkaloids) and combination of different agents has been tried but data are sparse and hence ASH 2019 categorically mentions that recommendations were not feasible. Splenectomy should be deferred, if possible, to

Table I Highlights of Updates From the Previous ASH, 2011 and Current ASH, 2019 ITP Guidelines

	ASH, 2011guidelines	*ASH, 2019 guidelines*
Outpatient *vs* Inpatient management	No recommendation	A child with newly diagnosed ITP with no/mild bleeding may be managed at home irrespective of the platelet count.*
		However, if the diagnosis is uncertain or follow up is difficult, admission is preferable.
Treatment *vs* observation	A child with newly diagnosed ITP with no/mild bleeding may be managed with observation alone, irrespective of platelet count	In a child with newly diagnosed ITP with no/mild bleeding, observation is preferable to pharmacotherapy (steroids,* IVIG,# anti-D Ig#) irrespective of platelet count
First line pharmacotherapy	Single dose IVIG (0.8-1g/kg) or a short course of corticosteroids can be used. IVIG can be used if a more rapid rise in platelets is required.	Short course of steroids (<7 d) is preferred over IVIG or anti D therapy*
Steroid type and duration as first line pharmacotherapy	No steroid type or dose is preferred over the other	A short prednisolone course (2-4 mg/kg/d; max. 120 mg/d) of 5-7 d is preferable to dexamethasone (0.6 mg/kg/d; max. 40 mg/d) for 4 d*
IVIG *vs* anti D as first line pharmacotherapy	Grade of recommendation for use of IVIG as first line (grade 1B) is stronger than Anti-D Ig (grade 2C)	Either IVIG or anti-D Ig may be used*
Newly diagnosed ITP who are treatment non-responders (*i.e.* non responsive to first line therapy)/Persistent ITP/ Chronic ITP	Rituximab or high dose dexamethasone may be used for treatment both of which are preferred over splenectomy.	In children with non-response to first line therapy, TPO receptor agonists are preferred over rituximab which is preferred over splenectomy.

*ITP: Immune thrombocytopenic purpura; *Conditional recommendation based on low certainty of the evidence of effects; #strong recommendation based on moderate certainty in the evidence of effects.*

Table II Treatment of Immune Thrombocytopenic Purpura

Category	*Symptoms/treatment options*	
Newly diagnosed ITP or Persistent ITP*	No/mild bleeding: Close observation (grade 1B) Moderate bleeding: Short course steroids/IVIG/anti-D Ig* Severe bleeding: Short course Steroids/IVIG/anti-D Ig (along with platelet transfusion in life threatening bleeds)	
Chronic ITP	No/mild bleeding	Observation
	Moderate to severe bleeding	Available therapies include: • TPO receptor agonists (Romiplostim, Eltrompobag)# • High dose dexamethasone$ • Rituximab^ • Other immunosuppressive agents • Splenectomy (along with platelet transfusion in life threatening bleeds)

**The doses of drugs used are as follows: Prednisolone 2-4 g/kg/d for 5-7 d; Dexamethasone 0.6 mg/kg/d for 4 d; IVIG 1 g/kg/d for 1-2 d; Anti-D Ig 50-75 mg/kg; #Romiplostim 1-10 µg/kg SC wkly; Eltrombopag>6-y-old 50 mg/d oral, 1-6 y: 25 mg/d oral; $High dose dexamethasone: 0.6 mg/kg/d for 4 d every 4 wks for 6 cycles;^Rituximab (anti CD20 monoclonal antibody) is given at dose of 375 mg/m^2/wk for 4 doses.*

beyond 12 months from disease onset. It may be the last resort in situations where ITP is unresponsive to all other therapy, the child shows intolerance to other drugs and quality of life is impaired. These recommendations are in concurrence with those of the European JWG [6].

In the Indian scenario, the cost and availability of TPO-RAs is prohibitive which makes them unsuitable as a frontline therapy [7]. Rituximab is promising with a median response duration of 12.8 months, relative ease of availability and tolerable side effects [8]. In cases where there is non-response to rituximab or availability is an issue, high dose dexamethasone and dapsone have been used as alternatives. Although high dose steroids have a good efficacy, their long-term use is associated with significant adverse effects. Dapsone is an easily available low-cost drug with response rates of around 50%; hemolysis and methemoglobinemia being important side effects and to be avoided in G6PD deficient individuals [9].

Secondary ITP: Treatment is directed towards the underlying cause [1]. Withdrawal of the causative drug results in remission of drug-induced ITP. ASH 2019 reiterates that children with ITP should receive first MMR vaccine per routine schedule (grade1B). Those who have already received MMR previously can get a vaccine titre done to assess need for booster dose [1]. A summary of available treatment options is given in ***Table* II**.

Assessment of response to treatment: The International working group provides specific recommendations for assessing the response to ITP treatments [10]. Although not based on evidence, these thresholds provide a useful standardization that will allow better comparison of responses between studies and the ASH 2019 endorses the same.

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