REVIEW ARTICLE

Immune Thrombocytopenic Purpura: Historical Perspective, Current Status, Recent Advances and Future Directions

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Immune thrombocytopenic purpura (ITP) has witnessed many changes and updates over the past decade. The definitions of disease subtypes, course and response to treatment have all been standardized recently. Consequent to the lack of an international consensus management guideline, wide variations exist in treatment practice. This is now being addressed to an extent by the much awaited ITP International Working Group 2010 recommendations. The pathophysiologic mechanisms have been unfolded at cellular, molecular and humoral levels. As a result, many recent advances have taken place in the management of this disorder. This review revisits the history of evolution of ITP, summarizes the current recommendations for management and lists the recent advances and future prospects in this field.

Key words: *Childhood, Immune thrombocytopenic purpura.*

Immune thrombocytopenic purpura (ITP) is variably known as autoimmune thrombocytopenic purpura or immune thrombocytopenia. It is no longer considered 'idiopathic'. Although the recent international consensus meeting suggested the use of the phrase 'immune thrombocytopenia' which includes both primary and secondary subtypes, the familiar terminology of ITP will be adhered to here [1]. ITP has had a long and eventful journey with respect to the understanding of its pathophysiology, diagnostic features and emerging treatment modalities. This review revisits the evolution of this disorder and provides an update on the current definitions, treatment guidelines, recent advances in the field and likely future developments.

Population-based studies have shown that ITP has an incidence of up to 6.4 per 100000 children and 3.3 per 100000 adults per year [2]. The disorder is believed to differ biologically between them, although similarities exist. The diagnosis and management of a typical presentation of childhood ITP is usually not difficult. However, thrombocytopenia secondary to other causes can often confound the picture at presentation. Likewise, children who develop chronic refractory thrombocytopenia can be challenging to treat.

HISTORICAL OVERVIEW

The term purpura originates from the Greek word porphyra, a Mediterranean mollusc which yields a purple dye. The first classical description of ITP was in 1735, by the German poet Paul Werlhof (***Fig.* 1*a***). He referred to a young lady, "without manifest cause, who bled from her nose and mouth and vomited very thick, extremely black blood". He could identify that "about the neck and on the arms, spots partly black, partly violaceous or purple appeared" [3]. As a tribute to this description, ITP is now eponymously known as Werlhof's disease.

The existence of platelets remained elusive until 1874, when the Canadian physician William Osler (***Fig.* 1*b***) drew and described 'pale granular masses' that circulated in the blood [4]. He observed that they agglutinated when removed from circulation, but believed these to be microorganisms. In 1881, the Italian pathologist Giulio Bizzozero (***Fig.* 1*c***) delineated the fundamental role of platelets in hemostasis. In 1889, George Hayem proved the link between purpura and thrombocytopenia by physically performing a platelet count on a patient [5].

The initial popular hypothesis was that ITP resulted from limited production of platelets. This was challenged by a Czechoslovakian medical student Paul Kaznelson (***Fig.* 1*d***), who implicated excessive destruction of platelets by the spleen. In 1916, he persuaded his professor Schloffer to splenectomize a woman with long standing ITP. The preoperative platelet count of 2 rose to 500×10^9/L following splenectomy [5]. The famous Harrington experiment conducted in Missouri in 1951 proved beyond doubt that a humoral factor in the plasma was responsible for platelet destruction. William Harrington, a fellow in hematology at Barnes-Jewish hospital, organized an exchange transfusion of 0.5 L of whole blood between

FIG.1 *Key figures associated with the evolution of ITP: (a) Werlhof, (b) Osler, (c) Bizzozero, (d) Kaznelson. These images are available in the public domain.*

himself and a woman with chronic purpura, whose blood group was the same as his [6]. Prior to the exchange, Harrington and the patient had platelet counts of 250 and 5 × 10^9/L respectively. After exchange, the patient's count remained unaltered at 6 × 10^9/L. Harrington's own count had dropped to 10 × 10^9/L but normalized within a week.

Once the etiopathology of ITP was elucidated, various treatment options evolved over time. The British dermatologist Robert Willan had initially 'prescribed' "open fresh air, moderate exercise, a generous diet and the free use of wine" [5]. Following Kaznelson's theory, splenectomy became the definitive treatment and remained so for many decades. Other modalities tried included splenic irradiation, injection of snake venom and irradiation by mercury vapour lamps. The American hematologist Maxwell Wintrobe introduced immunosuppressive therapy with corticosteroids in 1951 [7]. The realization of the role of Fc receptors on splenic macrophages led to the first successful use of intravenous immunoglobulin (IVIG) by Paul Imbach in Switzerland in 1981 [8]. Two years later, James Bussel and his colleagues from New York introduced anti-D therapy [9]. Advances in molecular biology and targeted therapy then paved the way for the use of monoclonal antibodies and thrombopoietin (TPO) agonists, described later [10-12].

DIAGNOSTIC CONSIDERATIONS

ITP is a diagnosis of exclusion. The combination of

TABLE I CAUSES OF THROMBOCYTOPENIA IN CHILDREN

Increased destruction	*Impaired production*
Immune	**Aplasia / dysplasia**
Autoimmune: ITP, SLE, APLS, ES, CVID	Chromosomal abnormalities, Thrombocytopenia absent radius, Congenital amegakaryocytic thrombocytopenia, Fanconi anemia, Dyskeratosis congenita, Myelodysplastic syndrome, Myelofibrosis, Pearson syndrome
Alloimmune: NAIT, PTP	
Drugs: Heparin induced thrombocytopenia	
Non-immune	**Marrow replacement**
Neonatal: TORCH infections, maternal disorders, birth asphyxia, Respiratory distress syndrome, *Necrotizing enterocolitis*	Leukemia, solid tumours, storage disorders, histiocytosis, osteopetrosis
Any age: Infections*, Disseminated intravascular coagulation, Thrombotic thrombocytopenic purpura, Hemolytic uremic syndrome, drugs, Kasabach Merritt syndrome, hypersplenism	
Hereditary	
Bernard Soulier syndrome, Wiskott Aldrich syndrome, May-Hegglin, von Willebrand disease 2b	

*ITP, immune thrombocytopenic purpura; SLE, systemic lupus erythematosus; APLS, anti-phospholipid syndrome; ES, Evans syndrome; CVID, common variable immune deficiency; NAIT, neonatal alloimmune thrombocytopenia; PTP, post-transfusion purpura; * Hepatitis viruses B and C, human immunodeficiency virus and H.pylori have proven associations with thrombocytopenia.*

TABLE II STANDARDIZED TERMINOLOGY RELATED TO ITP (ADAPTED FROM THE RECOMMENDATIONS OF THE VICENZA CONFERENCE, OCTOBER 2007)

Terminology	*Current definition*
Platelet threshold	$<100 \times 10^9$/L (previously defined as $<150 \times 10^9$/L)
Primary ITP	Absence of secondary causes to account for thrombocytopenia (diagnosis of exclusion)
Secondary ITP	Immune thrombocytopenia due to disease or drug exposure
Severe ITP	Bleeding needing treatment regardless of platelet count
Newly diagnosed ITP	From diagnosis to 3 months (previously known as acute ITP until 6 months from diagnosis)
Persistent ITP	3-12 months after diagnosis
Chronic ITP	>12 months after diagnosis (previously defined as >6 months after diagnosis)
Steroid dependent ITP	Need for continuation of steroids for at least 2 months to maintain platelet count $\geq 30 \times 10^9$/L and avoid bleeds
Complete response (CR)	Platelet count $\geq 100 \times 10^9$/L + no bleeding
Response (R)	Platelet count $\geq 30 \times 10^9$/L + at least 2-fold increase from baseline platelet count + no bleeding
No response (NR)	Platelet count $<30 \times 10^9$/L (or) less than 2-fold increase from baseline platelet count (or) bleeding
Refractory ITP	Failure to achieve at least R (or) loss of R after splenectomy + need for treatment to control bleeding

patient history and clinical examination is by far the most important diagnostic tool. At presentation, the clinician should consider the various causes for secondary thrombocytopenia (***Table* I**). Atypical features which should prompt the pediatrician to think away from the diagnosis of ITP include a very young age (relatively rare under 2 years), family history of thrombocytopenia or bleeding, significant lymphadenopathy, hepato-splenomegaly (mild splenomegaly is described in young children with ITP), anemia disproportionate to the degree of bleeding, leukocytosis or leukopenia, deranged clotting screen and a systemically unwell child. Liver and renal function tests, screening for viral infections such as HBV, HCV or HIV and an autoimmune profile may help in selected cases. The vast majority of children who clinically fit with a diagnosis of ITP do not require a bone marrow (BM) examination [13]. Other expensive tests such as immunoglobulin levels, monoclonal antibody-specific immobilization of platelet antigens (MAIPA), platelet survival studies and reticulated platelets are not recommended in typical presentations of ITP. Common variable immune deficiency (CVID) is an important differential diagnosis from an Indian perspective, as children can often present with isolated thrombocytopenia.

Complete blood count and blood film examination by a hematopathologist are usually sufficient to support a clinical suspicion of classical ITP. Morphological features include large platelets on a peripheral blood smear (***Fig.* 2*a*, 2*b***) and an adequate or increased number of megakaryocytes in the BM (***Fig.* 2*c*, 2*d***). In spite of the abundance of megakaryocytes, they produce suboptimal number of platelets [14]. The most important information to be established from blood and marrow examination is the presence of normal erythrocytes, leukocytes and their precursors, thereby excluding other hematological and infiltrative causes (***Table* I**).

In October 2007, the International Working Group on ITP revised the terminologies (***Table* II**) [1]. The previously popular term 'acute ITP' was withdrawn and

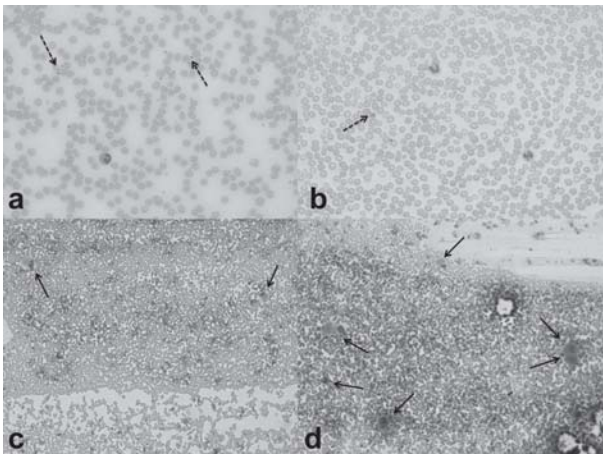

FIG. 2 *Platelets and megakaryocytes. (a) Peripheral smear showing normal platelets (dashed arrows) (b) Peripheral smear showing thrombocytopenia with a large platelet (dashed arrow) in ITP (c) BM with normal number of megakaryocytes (arrows) (d) BM aspirate showing increased megakaryocytes (arrows) in ITP [May-Grunwald-Giemsa stain; a and b, original magnification x 40; c and d, original magnification x 10].*

TABLE III GRADES OF RECOMMENDATIONS FOR THE MANAGEMENT OF ITP

Clinical situation	*Recommendation*	*Grade of evidence*
New presentation of suspected ITP	BM examination is not required if typical features are present	Grade 1B
No bleeding or cutaneous bleeds only	Observation alone	Grade 1B
First line medications	IVIG	Grade 1B
	Corticosteroids	Grade 1B
	Anti-D	Grade 2B
Non-response to first line medications and recurrent mucosal bleeds	Rituximab Splenectomy	Grade 2C Grade 1B
Timing of splenectomy	If severe persistent thrombocytopenia with mucosal bleeds for at least 12 months and failure of 2nd line medications	Grade 2C
Routine immunization	All vaccinations including MMR to be given	Grade 1B

ITP, immune thrombocytopenic purpura; BM, bone marrow; IVIG, intravenous immunoglobulin; MMR, measles mumps rubella.

the cut-off duration for designation as 'chronic ITP' was changed from 6 to 12 months. This was because a considerable proportion of children and adults were noted to achieve remission between the 6-12 month period from diagnosis. 'Newly diagnosed ITP' and 'persistent ITP' are now the recommended terminologies to refer to patients within 3 months and between 3-12 months from diagnosis respectively. Chronic ITP occurs in about 20% of children, with a higher risk if >10 years and/or platelet count $\geq 20 \times 10^9$/L at presentation [15]. About 37-50% of children with chronic ITP achieve remission within 4 years of diagnosis [15,16].

TREATMENT CONSIDERATIONS

Following the 2010 international consensus statement, the American Society of Hematology (ASH) updated their ITP management guidelines in 2011, providing evidence-based grades of recommendations (***Table* III**) [17,18].

The majority of children achieve spontaneous remission and do not suffer major bleeding complications despite a platelet count $<10 \times 10^9$/L. The expectant 'watch and wait' policy of management is recommended for such patients. In the absence of 'wet bleeding', the child does not require hospitalization. The frequency of follow up blood counts should be limited to every 1-2 weeks initially and lesser thereafter, in order to avoid unnecessary hospital visits and anxiety. The incidence of intracranial hemorrhage (ICH) in children with ITP is 0.1-0.5% and cannot be predicted precisely with confidence [19]. Parents should be educated about the natural history of ITP and must be warned against the use of non-steroidal anti-inflammatory drugs, intramuscular injections and contact sports. Routine activities, schooling and vaccinations using the subcutaneous route should be encouraged. In children with platelet count $\geq 30 \times 10^9$/L, intramuscular vaccination followed by firm pressure for 5 minutes is generally considered safe.

The decision to treat should not be based solely on the platelet count and must take into account the severity of bleeding and associated risk factors. The available therapeutic options and response rates are summarized in ***Table* IV** [15,17,20-24]. The recent ASH guideline regards IVIG, steroids and anti-D for children with RhD positive blood groups as first line treatment options [18]. Immunomodulatory drugs for refractory cases include azathioprine, cyclosporin A (CSA), mycophenolate mofetil (MMF), dapsone, danazol and cytotoxic agents [20-24]. Four doses of rituximab at weekly intervals is now emerging as an effective latter line of therapy in non-responders.

Splenectomy remains the definitive treatment for ITP refractory to medical measures. Overwhelming post-splenectomy infection (OPSI) is a significant complication, with maximal risk in children <5 years and especially <2 years of age [16]. Splenectomy should hence be delayed beyond 6 years of age, preferably with severe thrombocytopenia $<10 \times 10^9$/L and recurrent mucosal bleeds persistent for at least 12 months and failure of second line medications [15,17,18,25]. Splenectomy has an excellent and durable complete response (CR) rate of 75% [25,26]. Children should be vaccinated against pneumococcus, meningococcus and *H.influenzae* at least 2 weeks beforehand. The current recommendations for penicillin prophylaxis is for until at least 5 years of age and for a minimum of 1 year after the

TABLE IV THERAPEUTIC OPTIONS FOR IMMUNE THROMBOCYTOPENIC PURPURA

Treatment and schedule	*Time to response*	*Duration of response*	*Response rate*	*Comments*
Watch and wait	2 wk - 6 mo	Long term	2/3 rd of children	Recommended if no 'wet bleeds'
IVIG 1 g/kg IV single dose	48 h	2-3 wk	>80%	1/3 rd of children relapse after 6 wk
Prednisolone 1 mg/kg PO × 7 d; taper over 3 wk (or) 4 mg/kg PO for 4 d	2-7 d	Variable	>75%	Consider BM to exclude other causes
Anti-D 50-75 ug/kg IV single dose	24 h	2-3 wk	50-75%	Similar to IVIG but repeated doses may elicit longer responses
Methyl prednisolone 30 mg/kg IV × 3 d then 20 mg/kg IV × 4 d	48 h	Short	60-100%	Consider BM to exclude other causes
Dexamethasone 28-40 mg/m^2/day PO in pulses	72 h	Short	>80%	Not recommended due to unacceptable side effects
Azathioprine 1-2 mg/kg/d PO	2-3 mo	Long term in 25% responders	40%	Adjust dose to prevent neutropenia
Rituximab 375 mg/ m^2/wk IV × 4 wk	2-3 wk	Long term	Up to 80%	Anti-CD20; helps to delay splenectomy; cost constraints
Splenectomy	24 h	Long term	75%	Failures reported if accessory spleen
Dapsone 1-2 mg/kg/d PO (max 100 mg)	3 wk	Sustained response 2/3 rd of patients off therapy	50-60%	Caution in in G6PD deficiency
CSA 5 mg/kg/d PO in 2 divided doses	3 wk	Long term if maintained on 2 mg/kg/d	40-55%	Requires monitoring of drug levels unless using low dose maintenance
MMF 10 mg/kg PO BD	4-6 wk	Short term after stopping	60%	Headache is a dose limiting side effect
Danazol 5-10 mg/kg/d PO	3-6 mo	Short term after stopping	50%	Limited pediatric data
Vincristine (max 2 mg/dose) 1.5 mg/m^2/wk IV × 6 wk	4-6 wk	Long term	Insufficient data in children	Cytotoxic agent
Vinblastine (max 10 mg/dose) 0.1 mg/kg/wk IV × 6 wk	4-6 wk	Long term	Insufficient data in children	Cytotoxic agent
Cyclophosphamide 500-1000 mg/m^2 IV every 4 wk	2-3 mo	Long term	20-40%	Cytotoxic agent

procedure [16,27]. Many clinicians however, prefer to be more conservative in this regard and recommend antibiotic prophylaxis lifelong. Prior response to IVIG is associated with a higher success rate after splenectomy, whereas non-response is not a predictor of failure.

Platelet transfusions have no role, other than in life threatening situations. For emergency treatment, a combination of intravenous methyl prednisolone and IVIG/anti-D along with transfusion of a supra-normal dose of platelets (up to 30 ml/kg) is recommended [17]. Antifibrinolytics such as tranexamic acid 10-15 mg/kg intravenously 6-hourly are useful to control bleeding. For elective surgery, the desirable platelet count cut-off is dependent on the bleeding risk. Thresholds of ≥30, ≥50 and ≥100 × 10^9/L are suggested for low risk, high risk and neurosurgery, respectively [19].

RECENT ADVANCES

Sophisticated immunological and molecular techniques have facilitated a better understanding of the pathophysiology at cellular and humoral levels. MAIPA has helped to demonstrate autoantibodies against GpIIb/IIIa receptor on the platelet surface as the basis for ITP [28,29]. Although not required for the clinical work-up of

suspected ITP, it is infrequently used for diagnosis in patients with atypical presentation. Electron microscopic studies have illustrated megakaryocyte changes including non-classic apoptosis, cytoplasmic vacuolation, swelling of mitochondria and condensation of nuclear chromatin [30]. Pathogenic roles of cytotoxic and regulatory T-lymphocytes (Tregs) have also recently been recognized [31,32]. Reduced levels of TPO, the primary stimulator of platelet synthesis, is now known to occur in patients with ITP [35]. TPO acts through its receptor c-mpl to promote proliferation, differentiation and maturation of megakaryocytes.

Therapeutic advances have paralleled the above immunobiological breakthroughs, capitalizing on the unfolding of causative mechanisms. The anti-CD20 monoclonal antibody rituximab is emerging as the standard of care in children and adults with chronic refractory ITP [10,17]. The initial excitement around others such as anti-CD52 (alemtuzumab or campath-1H) and anti-CD40 ligand have not translated into long term clinical remissions [11,34]. The TPO agonists romiplostim and eltrombopag have recently successfully been through safety and efficacy trials [12,35-37]. In an age-stratified, randomized, placebo controlled study on 22 children with chronic ITP, Bussel, *et al.* demonstrated that 88% achieved platelet count $\geq 50 \times 10^9$/L after weekly subcutaneous injections of romiplostim at a median dose of 5 μg/kg [35]. The phase III randomized multicenter placebo controlled trial by Bussel, *et al.* [36] on 114 adults with chronic ITP has reported a rise in platelet count $\geq 50 \times 10^9$/L within 2 weeks in over half the patients who received oral eltrombopag 50 mg daily. Despite these data, it should be noted that TPO agonists are not yet approved for use in children and hence are not currently recommended. Recombinant factor VIIa has now been successfully used for hemostasis in patients with ITP following life threatening bleeds [38].

FUTURE DIRECTIONS

Research so far has identified that ITP results from both accelerated platelet destruction and defective production of platelets by megakaryocytes. We also now know that both B and T lymphocytes contribute to its pathogenesis, ie., autoimmunity of ITP has both a humoral and a cellular basis. Dysregulation of the B-cell survival pathway comprising of B-cell activating factor (BAFF), A Proliferation Inducing Ligand (APRIL), B-cell maturation antigen (BCMA) and their receptors has been proposed as an important component of autoimmunity in ITP [39]. Therapeutic blockade of this pathway is a promising treatment option for the future. Similar targeted interventions against Tregs could also potentially reverse the autoimmunity [31,32].

Newer monoclonal antibodies under investigation currently include anti-Fc receptor (MDX-33), anti-FcγRI and anti-FcγRIII (GMA-161) [40]. Experimentation with rozrolimupab, a symphobody against the RhD antigen, is underway [41]. Another avenue being explored is using an inhibitor of spleenz tyrosine kinase (Syk) [42]. It is also hoped that romisplostim and eltrombopag, both now approved by FDA (USA) and NICE (UK) for use in adults with refractory thrombocytopenia, will accumulate more convincing safety data in children over the next decade.

Controversial Aspects in Diagnosis and Treatment

Age at presentation: Many pediatricians are reluctant to diagnose ITP in young infants. Rarely, this disorder can present in babies <6 months of age. Over a 2-year period at Great Ormond Street Hospital (GOSH), we have followed up four babies aged under 6 months, in whom ITP was established as a diagnosis of thorough exclusion of leukemia, bone marrow failure and immunodeficiency states. Maternal platelet counts were normal in all cases; bone marrow showed increased megakaryocytes and counts recovered either spontaneously or with IVIG/ prednisolone. Sandoval, *et al.* [43] reported ITP in 11 babies under 6 months of age in their 15-year retrospective analysis. All patients responded favourably to treatment, with a high rate of spontaneous remissions and a low incidence of chronic ITP.

Need for marrow evaluation: There are reports of missed leukemia and hemophagocytic lymphohistiocytosis (HLH) following steroid therapy in patients wrongly diagnosed with ITP. Presence of atypical features should make the clinician strongly consider a bone marrow evaluation [13]. In resource-poor countries like India, it has been argued that the accuracy of automated cell counters is not uniformly reliable and hence a low threshold is required for assessing the marrow [44].

Safe platelet count: There are wide discrepancies in treatment practice across the world [45]. For years, the ASH had recommended first line treatment with IVIG to achieve a 'safe' platelet count $\geq 20 \times 10^9$/L [26,45]. In contrast, the British Society for Haematology (BSH) favors the watch and wait policy of management [45,46]. At GOSH, standard practice is not to treat howsoever low the platelet count is, unless there are additional risk factors or wet bleeds. It must be noted that in their most recent 2011 updated guideline, ASH has also moved towards the watch and wait policy [18].

Emerging role of rituximab: There is a general consensus that splenectomy should be avoided as far as possible in children. Rituximab now has good efficacy data with up

to 80% response rate in previously refractory patients. Currently the cost of this drug precludes its use in many situations. With a potential reduction in cost in future, rituximab may become the standard of care, thus obviating the need for splenectomy in a significant proportion of children [25].

Safety concerns of TPO agonists: Despite the efficacy of TPO agonists in refractory patients, concerns have been raised on their long term safety [12]. Romiplostim has been associated with venous and arterial thromboembolic events in adult patients. Eltrombopag has caused hepatobiliary impairment in 10% of adults. Both drugs have also been linked with bone marrow fibrosis.

CONCLUSIONS

There is now a reasonably clear understanding of the pathophysiology of ITP. As a result, the repertoire of therapeutic options has expanded. Clinicians should be aware of the strength of evidence base for each modality of treatment. However, the most important aspect in the management is to give adequate consideration to alternate diagnoses at presentation. Atypical features are not uncommon and should encourage the clinician to actively rule out secondary thrombocytopenia. The management of refractory ITP patients with recurrent bleeds, albeit rare, is quite challenging. Available second or subsequent lines of therapy are to be used wisely in such situations, weighing the benefits versus risks in each individual child. Referral to a pediatric hematologist is recommended for children with unusual presentations and resistant thrombocytopenia.

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