Current Practice

Management of immune thrombocytopenia in children

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Introduction
Immune thrombocytopenia is characterised by immune-mediated destruction of platelets, leading to isolated thrombocytopenia[1]. It was previously referred to as Idiopathic Thrombocytopenic Purpura and Immune Thrombocytopenic Purpura. The current terminology of Immune thrombocytopenia (ITP) acknowledges the immune-mediated mechanism of thrombocytopenia; however, it removes the prominence of 'purpura', which is not essential for diagnosis. Still, the acronym ITP is widely used[2].

Epidemiology
ITP is more common in children than adults, with the highest prevalence in the 2 to 5-year-old age group. The annual incidence of ITP is between 1 to 6 cases per 100,000 children. Childhood ITP is more common in boys than girls. However, in adolescents, girls are more commonly affected than boys[3].

Pathophysiology
The pathophysiology of ITP is characterised by immune-mediated destruction of platelets. The platelet destruction is predominantly mediated by autoantibodies formed against the platelet membrane antigen glycoprotein IIb/IIIa complex. The antibody-coated platelets are destroyed by tissue macrophages, mainly in the spleen. In addition to antibody-mediated destruction, a T-cell-mediated mechanism may also play a role in destroying megakaryocytes in the bone marrow, at least in a subset of patients[4].

The onset of ITP is usually triggered by a viral infection, immunisation, or environmental factors. ITP is reported to occur 1-4 weeks after infections by Epstein-Barr, influenza, and varicella zoster viruses and COVID-19. Vaccination with Mumps-measles-rubella (MMR), Hepatitis B, Varicella-zoster, and COVID-19 vaccines are reported to trigger ITP.

Classification
ITP is classified based on the duration of thrombocytopenia into newly diagnosed ITP (<3 months), persistent ITP (3-12 months) and chronic ITP (>12 months). Newly diagnosed and persistent ITP categories were previously referred to as 'Acute ITP' (Table 1)[2].

Table 1: ***Classification of immune thrombocytopenia (ITP)***

Classification	Definition
Newly diagnosed ITP	Thrombocytopenia for less than 3 months
Persistent ITP	Thrombocytopenia lasting 3-12 months
Chronic ITP	Thrombocytopenia for more than 12 months

Aetiology
ITP is idiopathic in a majority of children and hence, routine evaluation of a secondary cause is not indicated in a child with newly diagnosed ITP. When ITP is not associated with other causes or disorders, it is termed 'Primary ITP'. The probability of a secondary cause increases with the age of the child and in chronic ITP. When ITP is associated with an underlying cause, it is termed 'Secondary ITP' (Table 2)[5].

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Table 2: ***Causes of secondary immune thrombocytopenia***

Category of disease	Causes/diseases
Autoimmune diseases	Systemic lupus erythematosus (SLE) Autoimmune lymphoproliferative syndrome
Immunodeficiency disorders	Common variable immunodeficiency (CVID) Selective IgA deficiency
Infections	Human immunodeficiency virus (HIV) Hepatitis C *Helicobacter pylori* infection

Clinical features

ITP can be asymptomatic and incidentally detected following a full blood count done for other indications. The most common clinical feature (86%) is cutaneous bleeding manifesting as petechiae, purpura and ecchymoses. Petechiae are pinpoint non-blanching cutaneous haemorrhages less than 5mm, and purpura are skin bleeds between 5mm and 1cm. Ecchymoses are purplish, non-blanching patches larger than 1cm[6].

The other common type of bleeding in ITP is mucosal bleeding, which includes epistaxis (20%), oral mucosal bleeding (19%), haematemesis, melaena, haematuria and menorrhagia. Conjunctival and retinal haemorrhages are infrequent. Deep bleeds such as haemarthrosis and muscle haematoma are very rare in ITP. Intracranial bleeding is the most severe life-threatening form of bleeding in children with ITP. Fortunately, the incidence of intracranial haemorrhage is exceedingly rare (0.1%-0.8%). Other life-threatening bleeds include massive gastrointestinal haemorrhage, pulmonary haemorrhage and bleeding following major trauma. Factors associated with serious bleeding are severe thrombocytopenia ($<20x10^9$/L), trauma, exposure to antiplatelet drugs (e.g., aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs) or anticoagulant medication (e.g., heparin and warfarin) and pronounced mucosal bleeding ('wet' purpura)[3].

The history of a child suspected of having ITP should aim to exclude other differential diagnoses (Table 3) and possible secondary causes (Table 2). A past history of similar episodes or a family history of bleeding disorders indicates congenital thrombocytopenia or coagulopathy. Non-specific symptoms like malaise, lethargy, fatiguability, exercise intolerance, and breathlessness indicate involvement of red blood cell lineage, and recurrent infections indicate involvement of white blood cell lineage; both of which would indicate sinister pathologies like aplastic anaemia or leukaemia. History of photosensitivity, hair loss, joint pain and oral ulcers indicate secondary causes for ITP like systemic lupus erythematosus (SLE). A detailed drug history is important to identify medications responsible for drug-induced thrombocytopenia.

Physical examination of a child with ITP is unremarkable except for evidence of bleeding. The presence of lymphadenopathy, hepatomegaly and significant splenomegaly may indicate haematological malignancy. Malar skin rash and arthritis are suggestive of SLE.

Severity grading

Based on the location and the severity, bleeding episodes of ITP are categorised into five grades (Table 4)[2].

Table 3: ***Causes of persistent thrombocytopenia in children***

Category of disease	Causes/diseases
Bone marrow failure	Fanconi anaemia Congenital amegakaryocytic thrombocytopenia Acquired aplastic anaemia
Haematological malignancy	Acute leukaemia
Congenital thrombocytopenia	Wiskott-Aldrich syndrome Thrombocytopenia absent radius (TAR) syndrome Bernard-Soulier syndrome DiGeorge syndrome
Thrombotic microangiopathies	Thrombotic thrombocytopenic purpura
Other coagulopathies	Von Willebrand disease type 2b
Drug exposure	Heparin Valproate Phenytoin

Table 4: ***Bleeding severity scale***

Severity grade	Features
Grade 0	No bleeding
Grade 1 (minor)	Few petechiae (≤100 total) and/or ≤5 small bruises/ecchymoses (≤3 cm in diameter), no mucosal bleeding
Grade 2 (mild)	Many petechiae (>100 total) and/or >5 large bruises/ecchymoses (>3 cm in diameter), no mucosal bleeding
Grade 3 (moderate)	Overt mucosal bleeding
Grade 4 (severe)	Mucosal bleeding leading to a decrease in haemoglobin >2 g/dL or suspected internal haemorrhage

Investigations

Full blood count, blood picture and coagulation profile are the initial investigations indicated in a child with a bleeding disorder. In ITP, full blood count is normal except for thrombocytopenia (platelet count $<100x10^9$/L). Over 75% of patients have a platelet count $<20x10^9$/L at presentation. Abnormalities in haemoglobin, red blood cells (except for mild microcytic anaemia), or white blood cells indicate a pathology other than ITP[3].

A blood picture would confirm thrombocytopenia with normal-sized platelets and some large platelets. Blood picture is a crucial investigation in children with ITP to exclude other pathologies like leukaemia, which is suspected in the presence of blast cells. Predominantly, very large or small platelets suggest inherited thrombocytopenia syndromes (large platelets - Bernard-Soulier syndrome; small platelets - Wiskott-Aldrich syndrome). The coagulation profile, including prothrombin time, international normalised ratio and activated partial thromboplastin time, is normal in ITP.

Bone marrow examination is not routinely indicated in children with ITP before commencing treatment. However, the presence of atypical clinical features such as lymphadenopathy, hepatomegaly, splenomegaly, or bone pain; full blood count evidence of involvement of other cell lineages except for microcytic anaemia, or suspicious blood picture features, indicate the need for bone marrow examination at a lower threshold. Also, bone marrow examination is indicated in children with ITP who do not respond to standard first-line treatment. When bone marrow examination is performed, it should ideally include bone marrow aspiration, trephine biopsy, flowcytometry, and cytogenetics. Bone marrow examination is normal in patients with ITP except for an increased number of megakaryocytes, which may appear large and immature.

Other investigations routinely indicated in newly diagnosed ITP are direct agglutination test (DAT) and reticulocyte count to look for associated autoimmune haemolytic anaemia (Evans syndrome). Testing for platelet glycoprotein-specific antibodies is not recommended as the presence of these antibodies is neither specific nor sensitive in diagnosing ITP.

Children with chronic ITP should undergo investigations to rule out the secondary causes of ITP. These include anti-nuclear antibodies and antiphospholipid antibodies to exclude SLE and autoimmune disorders, serum immunoglobulin (IgG, IgA and IgM) levels to exclude immunodeficiency, screening for hepatitis C, cytomegalovirus, and HIV, and thyroid function tests. These investigations are also indicated in a newly diagnosed patient of ITP with clinical features suggestive of a secondary cause.

Diagnosis

ITP is predominantly a clinical diagnosis made in the presence of laboratory confirmation of thrombocytopenia. The diagnosis of ITP could be made with very high certainty if a child with mucocutaneous bleeding and isolated thrombocytopenia (platelet count $<100x10^9$/L) appears well without other systemic signs or symptoms and with no abnormalities in the blood picture. In addition, response to the standard treatment with intravenous immunoglobulin helps to confirm the diagnosis[7].

Treatment of newly diagnosed ITP

Figure 1 is a suggested guideline for management of paediatric immune thrombocytopenia in Sri Lanka.

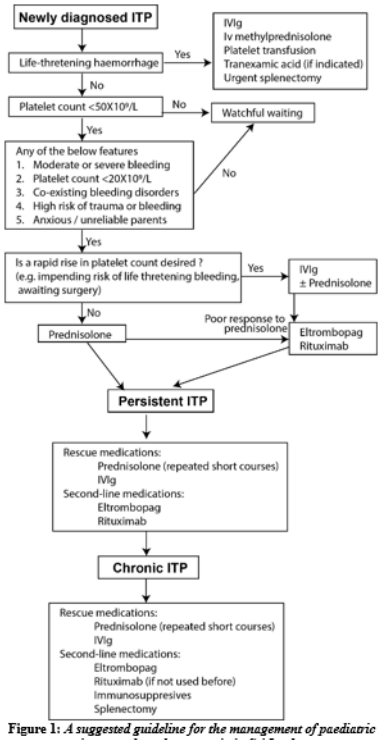

Figure 1: ***A suggested guideline for the management of paediatric immune thrombocytopenia in Sri Lanka***

There are several management options available for newly diagnosed ITP. They are 'watchful waiting' or first-line therapies such as glucocorticoids, intravenous immunoglobulins (IVIG), and anti-D immunoglobulin. The option for each patient is individualised and depends on the severity of bleeding, risk factors for bleeding, platelet count, quality of life, and socio-economic factors. Children with mild ITP with a platelet count >$20x10^9$/L can be managed as outpatients. However, it is advisable to admit children with moderate to severe bleeding (grade 3-4) or platelet count <$20x10^9$/L during initial management[8].

General measures: All children with ITP and their parents should be advised on the importance of avoiding trauma and taking necessary measures to minimise the risk of bleeding. Children with platelet count <$30x10^9$/L should avoid contact sports and restrict activities with a substantial risk for injury. They should avoid taking antiplatelet drugs (e.g., non-steroidal anti-inflammatory drugs like ibuprofen and aspirin) and anticoagulant medicines (e.g., warfarin) that increase bleeding. Paracetamol and opioids can be safely used as analgesics. The risk of epistaxis can be reduced by avoiding nose picking. In post-menarcheal girls, menorrhagia is controlled by hormonal therapy with oral contraceptive pills or norethisterone. All patients and their parents should be educated about the nature, likely course and prognosis of the disease[9].

Watchful waiting: Patients with no, minor or mild bleeding (grades 0-2) with platelet count >$20x10^9$/L (approximately 20%-30% of all ITP) can be managed by 'watchful waiting'. These patients are not started on treatment and are monitored for bleeding episodes and platelet count. It is advisable to monitor the platelet count initially once or twice a week, which can later be spaced out if the platelet count remains stable or is rising. 'Watchful waiting' is justified as several studies have shown that the treatment of ITP is not curative and does not impact the duration of the disease or prognosis.

Glucocorticoids: The most widely used first-line treatment is glucocorticoids. Oral prednisolone, the preferred drug for children, is given in a dose of 1-2mg/kg/day (maximum 80mg/day) for two weeks, followed by rapid tapering off over 1-3 weeks or 4mg/kg/day (maximum 120mg/day) for four days with abrupt cessation. The response to oral prednisolone is demonstrated by a rise in platelet count 3-14 days after starting treatment. Intravenous methylprednisolone 30mg/kg/day (maximum 1g) for 3-4 days can be used as an alternative to oral prednisolone. Intravenous methylprednisolone 30mg/kg/day is also indicated as a combination therapy with intravenous immunoglobulin (IVIg) in life-threatening haemorrhages. The frequent side effects of glucocorticoids are hypertension, increased appetite, weight gain, hyperglycaemia, sleep and mood disturbances, gastric irritation or ulcer formation, immune suppression, cataracts, glaucoma, myopathy and osteoporosis[10].

Intravenous immunoglobulin: IVIg is equally effective as glucocorticoids and has the advantage of rapid onset of action; however, it is an expensive alternative. IVIg is indicated when a rapid rise in platelet count is desired or in life-threatening haemorrhages. The recommended dose is 1g/kg for 1-3 days. The platelet count rises within 1-4 days of the infusion, but the effect lasts only 1-2 weeks. The common adverse effects of IVIg are allergic reactions, anaphylaxis, headache, abdominal pain, fatigue, myalgia, aseptic meningitis, thromboembolic events and renal impairment.

Anti-D immunoglobulin: This is given intravenously and is as effective as IVIg and glucocorticoids; however, it can be used only in Rhesus-positive, DAT-negative, non-splenectomised patients with a haemoglobin ≥9g/dL. The standard dose is 75µg/kg/day. The most important side effect of anti-D immunoglobulin is severe intravascular haemolysis.

Platelet transfusion: This is not routinely indicated in ITP even if the platelet count is extremely low, as transfused platelets would also undergo rapid destruction due to platelet antibodies. The only indication for it is acute life-threatening haemorrhage, to urgently arrest bleeding. The platelet dose is 10-30mL/kg, which is generally higher than the dose for other conditions. The aim is to immediately raise the platelet count to haemostatic levels (>$50x10^9$/L).

Antifibrinolytic agents: Tranexamic acid is an antifibrinolytic agent that can be used as an adjunct therapy for mucosal bleeding like epistaxis, gum bleeding, menorrhagia and gastrointestinal bleeding except in haematuria where it is contraindicated. The standard dose is 15-25mg/kg 2-3 times a day, and the treatment is continued until bleeding is stopped. There is no place for prophylactic use of tranexamic acid.

Disease course

Approximately 75%-90% of patients with newly diagnosed ITP who require treatment respond to treatment with first-line therapies. Thrombocytopenia is resolved within three months in a majority of cases. However, the effect of the treatment would wean off with time, and the platelet count could drop after stopping treatment in one-third to one-half of patients. Those who were managed by watchful waiting will have a fluctuating course and may require treatment with glucocorticoids, IVIg or anti-D immunoglobulin at later time points[11].

Management of persistent ITP

Children who continue to have thrombocytopenia beyond three months of initial diagnosis are classified as persistent ITP. These children should be carefully followed up as outpatients. Their management should be individualised based on the duration of ITP, frequency of bleeding episodes requiring hospitalisation, or medication, comorbidities, cost and availability of treatment options, treatment adherence, medical and social support networks, and patient preferences. Watchful waiting would be all that is required for a majority of patients. During bleeding episodes, if treatment is indicated, they should be managed similarly to children with newly diagnosed ITP with short courses of oral prednisolone and/or repeated doses of IVIg or anti-D immunoglobulin. Second-line treatment options available for this group, and for those who are resistant to first-line therapies, are thrombopoietin receptor agonists and rituximab.

Thrombopoietin receptor agonists: Oral eltrombopag or subcutaneous romiplostim are thrombopoietin receptor agonists used to stimulate platelet production to counteract

the increased platelet destruction of ITP[12]. Oral eltrombopag is used in a dose of 25-50mg (maximum 75mg) once daily, and 60%-80% of patients show an initial response to the drug. It can be used long-term, and the minimum required dose to maintain a haemostatic platelet count (>$50x10^9$/L) is continued. The important adverse effects of eltrombopag are transaminitis, drug-induced hepatitis, thrombosis and headache.

Rituximab: This is a human anti-CD20 monoclonal antibody that targets auto-antibody-producing B lymphocytes. It is given intravenously 375mg/m^2 weekly for four weeks. Due to the risk of reactivation, it is important to exclude the hepatitis B carrier state by doing hepatitis B surface antigen before commencing rituximab. The response rate to rituximab is reported as 40%-50%. Urticaria, headache and serum sickness are important adverse effects of rituximab.

Management of chronic ITP

Approximately 10-20% of children with ITP develop chronic ITP. The risk factors for the development of chronic ITP are older age, insidious onset, lack of mucosal bleeding and less severe thrombocytopenia at presentation. Treatment of chronic ITP is challenging and is based on symptom frequency and severity[13]. Those who maintain a platelet count >$20x10^9$/L with no or mild bleeding episodes can continue to be managed without treatment while monitoring their platelet count. Patients who respond to glucocorticoids would benefit from repeated courses of oral glucocorticoids to maintain their platelet count >$20x10^9$/L. However, continuous long-term oral glucocorticoid treatment for over 1-2 months is discouraged. Similarly, children who respond to eltrombopag can be managed with long-term therapy. The maximum safe duration of eltrombopag treatment is still unknown. Patients who do not respond to glucocorticoids and eltrombopag, who are glucocorticoid dependent, or who later show a poor response to first-line treatment, require immunosuppressive medication or splenectomy[14].

Immunosuppressive medication: Mycophenolate mofetil, azathioprine, 6-mercaptopurine, cyclosporin, sirolimus, cyclophosphamide, and dapsone have been used to treat chronic ITP with variable success rates. The risks of medication should be carefully weighed against its benefits before commencing immunosuppressive medication.

Splenectomy: Splenectomy is rarely used as a treatment for ITP and is reserved for chronic ITP in patients older than five years, who are refractory to medical treatment. In addition, urgent splenectomy is indicated to rapidly increase the platelet count in life-threatening haemorrhages (at any stage of ITP) when all other measures, including IVIg, intravenous methylprednisolone, and platelet transfusions, have failed. Splenectomy removes the site of platelet destruction and offers the greatest likelihood of sustained remission. It is important to adequately prepare a child before splenectomy by vaccinating against encapsulated organisms. Polysaccharide pneumococcal, meningococcal and haemophilus influenzae type b vaccines are recommended at least two weeks before the splenectomy. All children should be given antibiotic prophylaxis with oral penicillin for life post-splenectomy. Post-splenectomy sepsis and risk of thrombosis are the important long-term complications of splenectomy,

Prognosis

Approximately 80% of children with newly diagnosed primary ITP remit within 3-12 months of initial diagnosis. Among children with chronic ITP, spontaneous remission is seen in 30% in two years and 50% in five years. The chance of spontaneous remission is higher in younger children and children with relatively higher platelet counts. Patients who do not respond to first- and second-line medical treatment and splenectomy are diagnosed as chronic refractory ITP. This entity needs specialised management with multiple agents and expertise.

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