

Review Article

Childhood immune thrombocytopenia: Clinical presentation and management

Mohamed El Faki Osman

Department of Pediatric, King Khalid university hospital and College of Medicine, King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Immune thrombocytopenia (ITP) is an acquired hematological disorder that is developed secondary to the production of auto-antibodies against platelets leading to isolated thrombocytopenia, in the absence of other causes of thrombocytopenia such as drugs, infections, malignancy, or other autoimmune diseases [1-6]. ITP commonly affects children between one and seven years of age. Severe life threatening bleeding is rare (0.2-0.9%) [7-12]. Childhood primary ITP usually runs a benign, self-limiting course, with or without treatment. Complete remission occurs within six months from diagnosis, commonly within 6-12 weeks, in the majority of children with the diagnosis of ITP. However, 20–30% of children will continue to have persistent low platelets count with bleeding symptoms beyond six months from diagnosis [4, 12–18]. The diagnosis of ITP in children is essentially one of exclusion. The child is usually one to seven years old, develops skin bruises, petechiae, or

mucosal bleeding, who is otherwise healthy and having no lymphadenopathy or organomegally. Full blood count reveals isolated thrombocytopenia with normal hemoglobin (Hb) level, white blood count (WBC) and normal peripheral blood smear. Initial management options for newly diagnosed childhood ITP include; observation only, the use of intravenous immunoglobulin (IVIg), steroids, anti-D immunoglobulin, each alone or in combination [6, 19.] Children who develop chronic ITP may benefit from splenectomy [19, 20-24]. Rituximab, a chimeric monoclonal antibody (anti-CD20), may lead to complete remission, and defers the need for splenectomy [25-27]. Recently, the thrombopoietin (TPO) agonists (Romiplostim and Eltrombopag) produced very good response in adult and pediatric patients with severe chronic ITP [28-30].

Key words: Immune thrombocytopenia, childhood ITP, platelets, purpura.

Correspondence to:

Dr. Mohamed El Faki Osman

Assistant Professor & Consultant Pediatric Hematologist / Oncologist

Department of Pediatrics, College of Medicine, King Khalid university hospital & King Saud University, P.O. Box 2925, Riyadh 11461 Saudi Arabia.

E-mail: moothman@ksu.edu.sa

elfakiosman@hotmail.com

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Definition and historical landmarks of ITP

ITP is an acquired hematological disorder that is developed secondary to the production of auto-antibodies against platelets leading to isolated thrombocytopenia, in the absence of other causes of thrombocytopenia such as drugs, infections, malignancy, or other autoimmune diseases [1-6].

A report on standardization of terminology, definition and outcome of ITP was published recently in Blood by International Working Group (IWG) [6]. The group found that the term purpura is not accurate, because many patients do not present with bleeding symptoms and even thrombocytopenia could be discovered incidentally during routine clinic visit. However, the Acronym ITP will continue to be used and will stand for the new proposed name (Immune Thrombocytopenia). The platelet count threshold to establish the diagnosis was set at a new level (100×10^3), instead of the previous limit of (150×10^3). The report proposes further definitions to the phases of the disease as follows: Newly diagnosed ITP (within 3 months from diagnosis), persistent ITP (between 3 to 12 months from diagnosis; this includes patients that do not reach spontaneous remission or do not maintain complete response off therapy), and chronic ITP (lasting for more than 12 months). Severe ITP is defined as presence of bleeding symptoms at presentation that mandate treatment or occurrence of new bleeding requiring new therapies like platelet enhancing agents or increasing the doses of previously used medication [6].

Purpura denotes a reddish-purple lesions caused by bleeding under the skin. Purpura is a word of Latin origin meaning "purple". As a clinical symptom, purpura was recognized by the ancient Greek and Roman (Hippocrates and Galen) who described it as red "eminence" associated with plaque (pestilential fevers) [31,32]. In the 10th century the Muslim philosopher and physician Abu Ali Al-Hussain, Ibn

Abdullah Ibsina (Avicenna) (980-1037) described a chronic form of purpura that matches the diagnosis of ITP [32]. In 1735, the German Poet and physician Paul Gottlieb Werlhof (1699-1767) gave classical description of ITP. He described a disease in a 16 years old girl who had cutaneous and mucosal bleeding and called it "morbus maculosus haemorrhagicus". The condition was then called after him as Werlhof disease [31, 32]. Werlhof disease was then given the name (purpura simplex). Many milestones followed during the years including the discovery of platelets and megakaryocytes by the end of the 19th century. In 1916, Paul Kaznelson, who was still a medical student in Prague, assumed that the spleen was the site of platelet destruction and convinced his tutor, Professor Doktor Schloffer, to perform the first splenectomy ever in ITP for a 36-year old lady, who had a disease which fits our definition of chronic ITP. Splenectomy was followed by significant rise in platelets count [31, 32]. The immune nature of ITP was first demonstrated in 1951 by William J Harrington, who infused normal volunteers with plasma extracted from ITP patients. This resulted in severe drop in platelet counts [1]. In 1951, Evans was able to identify the plasma factor as antiplatelet antibody [33]. In the same year, Wintrobe was the first to use steroids for the treatment of ITP [34]. In 1981, Imbach et al, reported the successful use of intravenous immunoglobulin (IVIG) in treating ITP [35] and in 1983, the use of anti-D in ITP was described by Salama et al [36]. The use of rituximab was introduced by the end of 20th century for the treatment of patients with chronic and refractory ITP [25-27]. Recently the use of thrombopoietin (TPO) agonists to enhance platelets production showed promising results in severe refractory chronic ITP [28-30]

Epidemiology of childhood ITP

The incidence, prevalence, and natural history of ITP in children differ significantly from adult ITP.

Childhood ITP has an estimated incidence of 4.0–5.3 per 100,000 [4-13], while adult ITP has lower incidence of 1.6 - 2.6 per 100,000. ITP in children affects males and females equally, but in infancy males are affected more frequently than females [38-42]. Childhood ITP has an acute abrupt onset and is commonly preceded few weeks earlier by a viral illness or immunization, such as mumps, measles and rubella (MMR) vaccine [43-45]. Fernington et al, estimated the risk to be 1 in 24,000 doses of MMR vaccine [46]. In a large multi-center study by the International Childhood ITP Registry (ICIS), data was collected from 2031 children with ITP. There were 136 centers from 38 countries participating in the study. Frequency of ITP reached a peak during spring and a nadir during autumn [42]. ITP resolves within 6 months in up to 85 % of children with or without drug treatment. However, 25% of children may continue to have symptomatic ITP [4, 12-18]. The role of *Helicobacter pylori* (*H pylori*) infection in the causation of chronic ITP in children is not established. In one controlled study, the prevalence of *H pylori* in children with chronic ITP was similar to general population, and eradication of *H pylori* from children with chronic ITP did not enhance recovery compared to children in whom *H pylori* was not eradicated [47]. Hence the recommendation is against routinely testing for *H pylori* in children with chronic ITP [48].

Pathophysiology of ITP

Platelet destruction:

The debate, whether platelet destruction or impaired production was the cause of thrombocytopenia in ITP, started since the early years of the 20th century and continued till early 1950s. Harrington and coworkers, in their famous experiment in 1951, provided the first direct evidence that an anti-platelet factor was the cause of platelet destruction in ITP. He infused plasma from ITP patients into normal volunteers, which resulted in profound thrombocytopenia in eight

out of ten recipients [1]. In the same year, Evans et al, suggested that the anti-platelet factor was an anti-platelet antibody [33]. In 1965, Shulman et al, were able to show that the anti-platelet antibody was in the immunoglobulin G-rich serum, and could be absorbed by and reacted with the patient's own platelets [49]. It was in 1975 when Dixon and Rosse were able to quantify the platelet associated IgG antibodies [50]. Eventually, the anti-platelet antibodies were identified to be specifically against individual platelet glycoproteins (GPs). In 1982, van Leeuwen et al, by using the platelet immunofluorescent test (PIFT), were able to demonstrate auto-antibodies against GP 11a/11Ib. These antibodies were able to adhere to platelets from normal individuals but not to platelets from patients with Glanzmanns disease, who lack platelets GP11a/11Ib [51]. Other antiplatelet antibodies often demonstrated in severe cases of chronic ITP are directed against multiple glycoproteins (GPs) on the platelets surface, namely, anti-GP 1a/11a and anti-GP 1b/IX antibodies [12,52-61]. The antibodies bind to their target glycoprotein molecules on the platelet surface by the variable portion (Fab) leaving the constant portion (Fc) exposed. The reticuloendothelial system (RES) phagocytic cells, (monocytes/macrophages) express Fc γ receptors (Fc γ R) on their surface which recognize and bind to the Fc portion of the antibodies on the platelet surface, thus leading to their rapid removal by phagocytosis [52-62]. The spleen is very rich in Fc γ R-bearing phagocytic cells and is the main site for the destruction of the antibody-coated platelet [52,62]. The phagocytic cells in the RES express three classes of (Fc γ Rs), Fc γ R1 is high-affinity receptor binds both monomeric IgG and immune-complex IgG. Fc & R11A and Fc γ R111A are both low-affinity receptors and bind only immune complex Ig γ G [54]. The therapeutic effect of IVIG in ITP is proposed to be due to competitive inhibition of Fc γ R on phagocytic cells in the RES [36,63].

The production of antiplatelet autoantibodies was explained by the theory of molecular mimicry. An environmental antigen like those on infectious agents, resemble the host self-antigenic structure (platelet glycoproteins), stimulates B-cells to produce antibodies against the host own platelets. To do so, B-cells require the help of CD4 positive T-cells. The role of helper T-cell in the pathogenesis of ITP has been established by many investigators in the recent years [64-66]. These studies also suggested direct cytotoxic effect of T-cells on platelets in ITP.

Impaired platelet production

For about 60 years, autoimmune platelets destruction and compensatory increase in megakaryocyte production in the bone marrow is considered to be the hall mark of ITP. Recently, the rate of thrombopoiesis in ITP is shown to be inadequate to compensate for the peripheral platelets destruction. There is substantial evidence in the scientific literature showing that impaired thrombopoiesis is in fact a contributory factor to the low platelet count in ITP. The anti-platelets antibodies against GP1b/IX and GP11b/111a complex also act against the same glycoprotein molecules on the surface of megakaryocytes [12, 23, 52, 57, 58, 60]. Chang et al in 2003 found that plasma from ITP children containing anti-platelets antibodies inhibits megakaryocyte proliferation in vitro [67]. McMillan et al in 2004, demonstrated that megakaryopoiesis was suppressed by plasma containing autoantibodies taken from adult patients with ITP [68]. Ultrastructural studies of megakaryocytes from ITP patients showed features of apoptosis and para-apoptosis [69]. Thrombopoietin (TPO), the main haematopoietic growth factor that enhance megakaryocyte development and platelets production, is known to be low or normal in ITP patients and does not correlate with the low platelet level [70-72]. The theory of impaired platelet production is further supported by the fact that TPO

receptors agonists, romiplostin and eltrombopag, enhance platelets production and increase platelets count to a safer level in a significant number of both adult and children patients with ITP [28-30].

Clinical presentation of childhood ITP

ITP in children typically affects a previously healthy young child who is between two to seven years of age. Males and females are equally affected. However, recent studies reported a higher male/female ratio during infancy with a decreasing trend toward older age [38-42]. The disease onset is abrupt with bruises and petechial rashes affecting almost all patients. Epistaxis may occur in about one third of patients and hematuria is uncommon. In about two thirds of patients, the disease onset is preceded by an infection in the previous few days to several weeks. The infection is most often an upper respiratory tract viral infection and the interval between the infection and the ITP onset is in the range of two weeks [3-5, 7-12, 16, 19]. Clinical examination reveals a healthy child who only has bruises and petechiae as manifestation of the low platelet count. There should be no organomegaly and no lymphadenopathy. In very rare occasions, the tip of the spleen may be felt. The diagnosis of ITP in children is essentially one of exclusion. The CBC shows isolated thrombocytopenia with normal WBC and normal Hb levels. The peripheral blood smear shows no evidence of abnormal cells.

Differential diagnosis of ITP in children

The diagnosis of ITP in children is essentially one of exclusion. In order to differentiate ITP from other conditions, medical history should include type and severity of bleeding, systemic symptoms, history of respiratory infections, recent live viral vaccine, medications, presence of bone pain, and family history of bleeding disorders. Clinical examination should include observation for any dysmorphic features, especially skeletal anomalies, and the

presence or absence of hepatosplenomegaly and/or lymphadenopathy [19]. When the history and/or the clinical examination are atypical, the following conditions should be considered:

1. In an infant:
 - Bernard Soulier syndrome
 - Wiskott Aldrich syndrome
 - Unspecified congenital thrombocytopenia
2. In an older child:
 - Von Willebrand disease type 11B
 - Fanconi anaemia
 - Aplastic anaemia
 - Acute leukaemia
 - Other autoimmune conditions like systemic lupus erythematosus (SLE) and Antiphospholipid syndrome
 - Common variable immune deficiency (CVID)
3. If the young child is sick and febrile, the possibility of an infection should be considered especially meningococcal disease or HIV.

Laboratory investigations in ITP

1. Complete blood count and peripheral blood smear are essential to establish the diagnosis of ITP. CBC shows isolated thrombocytopenia with normal WBC and normal Hb levels. Anaemia is present only if there is severe bleeding [16, 19, 48, 73,74] .
2. Bone marrow aspiration (BMA) is not required to establish the diagnosis of ITP and also is not necessary prior to steroid treatment in typical cases of ITP. However, BMA should be done if there is bone pain, lymphadenopathy, hepatosplenomegaly, anaemia that is not explained by blood loss, or abnormally high or low WBC [16, 19, 73, 74].
3. Antiplatelet antibodies measurement does not assist in the diagnosis of ITP and therefore should not be routinely performed.

4. Coagulation screening does not help in the diagnosis of ITP, and should be done only if infection or inherited bleeding disorders are considered.
5. Test for Antinuclear Antibodies (ANA) could be performed in older children with ITP or those who have a chronic form of the disease. ANA testing is not required in children newly diagnosed with primary ITP,.
6. Immunoglobulin level should be done only if common variable immune deficiency (CVID) is suspected.
7. Thrombopoietin level does not help in the diagnosis of ITP and therefore should not be routinely performed [16,19,48,73,74].

Management of childhood ITP

The rationale for treating children with ITP is to increase platelet count to a safer level and prevent serious bleeding, mainly intracranial haemorrhage (ICH) [16, 19, 59, 73, 74]. Severe bleeding symptoms, like gastrointestinal bleeds or severe epistaxis, in children with ITP are very rare, up to 4%, in most of the published data. The incidence of ICH is less than 1% of cases in many studies across the globe [7-12]. Kuhane et al in 2003, reported ICH in 3 out of 2540 children (0.17%) with ITP from the Intercontinental Childhood ITP Study Group (ICIS) [42]. In a multicentre study from Argentina, ICH was reported in 0.2% (3 out of 1682 children with ITP). In this study there were 505 children with platelet counts below 20,000, none of them presented with severe bleeding symptoms, however, 3 (0.6%) developed severe bleeding during the subsequent 28 days [39]. The course of ITP in children is benign and self-limiting in up to 85% of newly diagnosed cases [16,19,48,74,77]. In a prospective study by (ICIS), 863 children with ITP were evaluated for severity of bleeding symptoms at diagnosis and during the following four weeks. Only 25 children

(2.9%) had severe bleeding symptoms at diagnosis [75]. Therefore, there are two main questions the pediatrician will face when dealing with a newly diagnosed young child with ITP, whose platelet count is very low, and yet having no or very mild bleeding symptoms:

1. To treat or not to treat?
2. What treatment to use?

The majority of the existing clinical practice guidelines (CPGs) for the treatment of ITP, recommend not to treat the platelet count alone, and to follow “watch and wait policy” especially if the child has bruising, scattered purpura and petechiae only. However, if the child has more bleeding symptoms, especially mucous membrane bleeding, and, in addition, if the platelet count is less than 10,000 then treatment is recommended [16,19,48,73,74].

The therapeutic agents used for the treatment of ITP are generally divided into three types based on the mechanism of action:

1. Inhibit antibody production.
2. Inhibit Fc& receptors (Fc& R) function.
3. Stimulate platelet production.

There are three main options for the initial pharmacologic treatment of ITP:

1. Corticosteroids
2. Intra venous immunoglobulin (IVIG)
3. Anti-D immunoglobulin.

The definition of response of ITP to therapy by the international working group (IWG) is as follows:

A. Complete response (CR) means platelet count of 100,000 or more measured on two occasions, seven days apart, and no bleeding. Loss of CR is present when platelet count drops to less than 100,000 on two occasions one day apart.

B. Response (R) platelet count 30,000 or more and platelet count more than two fold of baseline on two occasions, seven days apart, and no bleeding.

Loss of response is present when platelet count drops to less than 30,000 on two occasions one day apart.

C. No response (NR) is platelet count less than 30,000 or less than two fold increase from base line measured twice one day apart and presence of bleeding [6].

I. Treatment of newly diagnosed children with ITP

8. Corticosteroids:

Corticosteroid is used effectively, since it was first introduced for the treatment of ITP in the 1950s. Corticosteroids produce its effects by reducing the production of anti-platelet antibodies and by decreasing clearance of opsonized platelets. Steroids also increase vascular stability in ITP. Prednisone is used in different doses and regimens. There is no advantage of one regimen over the other. It is commonly used as 1-2 mg/kg/day for up to 2 weeks and discontinued by the third week. [2,5,10,16,19,73,74]. Other regimens use prednisone in a higher dose (4 mg / kg/day) initially and taper to discontinue by the third week. This regimen raises the platelet count to more than 50,000 by day seven of treatment. To avoid steroids use for a longer durations, and to minimize side effects, other investigators used prednisone [4 mg/kg/day) for four days only without tapering and produced similar results to other regimens. High dose methylprednisolone (30mg/kg, maximum one gram) is used in emergency situations.

9. Intra venous immunoglobulin (IVIG):

Since the introduction of IVIG for the treatment of children with ITP by Imbach et al, IVIG is shown to be very effective in raising platelet counts in more than 80% of patients, and it does so faster than steroids [35]. IVIG is a pooled blood product, and its mechanisms of action in ITP is likely to be through occupation of the Fc γ receptors (Fc γ Rs) on the phagocytic cells in the RES, resulting in increased opsonized platelet's survival. The pooled IVIG contains anti-idiotypic antibodies, which bind to the circulating anti-platelet

antibodies making them unable to bind platelets. A third mechanism of action of the IVIG is suppressing antibody production by B-cells [36,63]. The usual dose of IVIG is 0.8gm—1gm/kg/day to be infused over 6---10 hours, to minimize the side effects, and can be repeated twice. Side effects may develop in up to 75% of patients, especially severe headache, fever and vomiting. Aseptic meningitis is a well known complication as well. IVIG raises platelet counts faster than any other therapeutic agent, thus is used as the first line drug in ITP, when there is a desire to raise platelet counts more rapidly [13-15,16,19,48,53,73,74].

10. Anti-D immunoglobulin:

Anti-D immunoglobulin, like IVIG, is a pooled blood product. It is licensed for treating ITP patients who are blood group D positive, non-splenectomized and who have normal Hb level. Anti-D immunoglobulin exerts its effects in ITP by sensitizing the D positive red blood cells (RBCs) which in turn bind to the macrophages Fc receptors leading to their blockade and increase the survival of the opsonized platelets. It causes a rapid rise in platelet count comparable to IVIG response [79-80]. Anti-D immunoglobulin is given at a daily dose of 45-50mcg/kg/day as a short intravenous infusion, thus can be used on outpatient basis. It also causes side effects like fever, chills and headache but less frequent than IVIG. One of its most serious side effects is severe haemolysis [16, 19,48]. For this reason anti-D is not recommended when the Hb level is on the lower side. It is to be used in patients with high Hb level and when there is a need to raise the platelet counts more rapidly than steroid.

II. Treatment of persistent ITP, chronic ITP and non-responders:

In these patients, and in the presence of bleeding symptoms, the use of second line therapy is needed:

1. Rituximab:

Rituximab is a chimeric anti-CD20 monoclonal antibody consisting of human immunoglobulin constant region Fc and murine variable region Fb. Rituximab binds to CD20, which is expressed on the surface of premature and mature B-Cells, leading to the death of these antibody-producing cells [25-27]. When administered at a dose of 375mg/m² once weekly intravenously, for 4 weeks, it depletes the circulating B-cells to undetectable level for up to 6-12 months. Many published studies used rituximab in the above regimen, to treat children with severe chronic and refractory ITP. Response rate to rituximab varies among these studies, but the long lasting remission was reported in one third of patients and is similar in most of these studies. It was used as monotherapy or in combination with other medications including IVIG and steroids. It is recommended to be used as splenectomy sparing agent in chronic ITP [81-85]. Serious side effects are rare and include hypotension during the infusion, severe anaphylaxis, serum sickness, and thrombocytosis. Infectious complications are particularly rare. The long term safety of rituximab has been well established, however, recently there are some reports of long-term complication of progressive leukoencephalopathy [86].

2. High dose dexamethasone:

Dexamethasone has been used in small trials in a high dose (0.6 mg/kg daily for four days) and repeated every 4 weeks for duration of six months in patients who failed to respond to other therapies. High dose pulse dexamethasone produced less response in children compared to adults patients with ITP. Dexamethasone pulses were used in combination with IVIG in an effort to avoid splenectomy [87,88].

3. Thrombopoietin (TPO) receptor agonists:

These are new agents that stimulate platelet production by a mechanism similar to endogenous TPO. Two

agents (Romiplostim and Eltrombopag) are approved for the use in adult patients with ITP, in Europe, USA, Japan and other countries [29]. Romiplostin is Fc-fusion protein, which stimulates platelet production by a mechanism similar to the endogenous TPO. It is used in adult ITP patients in a dose of 1 mcg-10mcg/kg subcutaneously once every week. An increase in platelet count to more than 50,000 was reported to follow a single dose, and the response was maintained for up to two weeks [29,30,89-94]. The most commonly reported side effect was headache followed by nasopharyngitis, and fatigue. Serious side effects were rare, such as increase in bone marrow reticulins, congestive heart failure, and thrombotic complication [29,30].

In a recent randomized, double-blind, placebo study in pediatric patients with ITP for more than six months, romiplostim increased platelet count to more than 50,000 in 88% (15/17) of patients compared to no patients in the placebo group ($P=0.0008$). The most common reported side effects were headache and epistaxis [30]. The doses used in the study ranged between 2mcg-5mcg/kg once a week. The authors concluded that, romiplostim is effective and apparently safe to be used in children with ITP. To the best of my knowledge, this is the only published randomized study in children, and of a small sample size.

Eltrombopag is the second TPO receptors agonist approved for use in adult ITP patients. It differs significantly from romiplostim. It is small, non-peptide organic molecule and described as a TPO non-peptide mimetic [29,89,90,94]. It is the first oral TPO agonist. In the first randomized study, eltrombopag was given in three different doses of 30mg, 50mg, and 75mg once daily for six weeks, and the fourth group was given placebo. The platelet count of 50,000 or more on day 43, was seen in 28%, 70%, and 81% respectively

in the different eltrombopag groups, and in only 11% of the placebo group [95]. The commonest side effect reported was headache, in addition to transient increase in bilirubin and alanine transferase (ALT) in few patients. There is no published study in pediatric population.

4. Splenectomy for persistent, or chronic ITP, or ITP not responding to therapy:

Splenectomy is known to be effective in curing ITP. Kaznelson in 1916 assumed that platelet destruction in ITP takes place in the spleen analogous to the destruction of red blood cells in immune hemolytic anaemia. He performed splenectomy in one ITP young lady with good response. Splenectomy removes the main site of platelet destruction and antibody production. Firkin and coworkers in 1969 showed that platelet destruction was due to phagocytosis by splenic macrophages [62]. It is a common practice in adult patients with ITP, who failed the first line therapy. It is effective in curing ITP in up to 75% of patients. In the rest of patients who do not respond to splenectomy, platelet destruction may take place in other sites of the reticuloendothelial system (RES) especially the liver. Vianelli et al in 2005 reported the outcome of 402 patients who underwent splenectomy for chronic ITP. Eighty six percent (345/402) had good response, 66% achieved complete remission, and 20% achieved partial remission [96]. Elective splenectomy is indicated in children who have chronic ITP with troublesome or persistent bleeding symptoms, and who failed other options of medical therapy including, IVIG, steroids, rituximab, and other immune suppressive therapy [20-23]. It is recommended to delay splenectomy in children for up to 12 months from diagnosis because spontaneous remission may still occur [16,19,48]. Overwhelming sepsis is a real threat in splenectomized children, so patients should be prepared for splenectomy by receiving immunization against streptococcus

pneumonia, neisseria meningitidis and haemophilus influenza and should be started on penicillin prophylaxis [16,19,48]. Splenectomy may be performed laparoscopically when feasible.

5. Other immune suppressive therapies:

There is a group of ITP patients who do not respond to the above first and second line therapies. In these patients, other therapeutic options involve agents that were used in very small numbers of patients or single case reports. Therefore, there is not enough data for evidence-based recommendations. Examples for these agents include vincristine, vinblastine, cyclophosphamide, azathioprine, cyclosporine, mycophenolate mofetil, alpha-interferon, and dapsone. Most of these agents have significant side effects [97-101].

III. Emergency management of intracranial hemorrhage (ICH) and life threatening bleeding:

In patients who present with ICH, all efforts should be taken to raise the platelet count as fast as possible to a safe level that could stop the bleeding. Infusion of large amount of platelets should be started immediately; this may not raise the platelet counts but rather platelets will be recruited at the site of the bleeding and may stop the bleeding. Methylprednisolone at a dose of 30mg/kg (maximum 1000mg) should be given immediately over 30 minutes. IVIG usually infused at a dose of 1gm/kg, along with iv methylprednisolone [59,73,76]. These steps may be repeated as long as it is clinically indicated. Emergency splenectomy may be considered if there is no response to the above therapy and may be performed at the same time if the patient needs emergency evacuation of the intracranial bleeding [59]. Recombinant VIIa has been used and proved very effective in stopping the bleeding in different platelet disorders, including ITP, and may be given at a dose of 90mcg/kg every 2-3 hours [102]. The antifibrinolytic agents, tranexemic

acid and aminocaproic acid, are used as adjunct to the above therapy.

IV. Management of MMR-associated ITP:

If a child develops ITP following MMR vaccine, the vaccine titers should be checked. If the child is fully immunized then no need for further MMR vaccination. However, if the vaccine titers are not adequate, the child should receive the rest of the vaccine doses as scheduled, because the possibility of developing ITP with wild infections is higher than with the vaccine [45,48,].

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