A STUDY ON DEMOGRAPHY, CLINICAL CHARACTERISTICS, MANAGEMENT PRACTICE AND OUTCOME OF CHILDHOOD IMMUNE THROMBOCYTOPENIA (ITP) IN KELANTAN

By

DR. ROZAIDAHANIM BINTI DAUD

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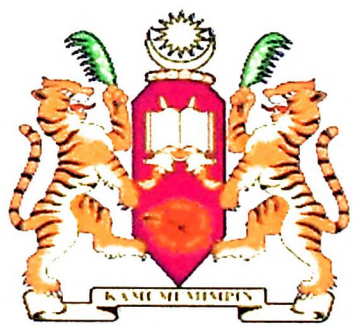

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ABBREVIATIONS

AGE	Acute gastroenteritis
AIHA	Autoimmune hemolytic anemia
BMA	Bone marrow aspiration
FBP	Full blood picture
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
HRPZ II	Hospital Raja Perempuan Zainab II
Hospital USM	Hospital Universiti Sains Malaysia
ICH	Intracranial hemorrhage
IQR	Interquartile range
ITP	Immune thrombocytopenia
IVIg	Intravenous immunoglobulin
IWG	International Working Group
MMR	Measles, Mumps, Rubella
MOH	Ministry of Health
NIH	National Institutes of Health
SD	Standard deviation
SLE	Systemic lupus erythematosus
TIBC	Total iron binding capacity
UK	United Kingdom
URTI	Upper respiratory tract infection

ABSTRAK

Penyakit "Immune Thrombocytopenia" (ITP) di kalangan kanak-kanak adalah masalah darah yang mempunyai pelbagai sejarah semula jadi. Cara perawatannya yang berbeza di seluruh dunia telah menjadi topik perdebatan.

OBJEKTIF:

Untuk menilai demografi, ciri-ciri klinikal, amalan perawatan dan kesan penyakit ITP di kalangan kanak-kanak di Kelantan serta meneroka faktor-faktor yang membawa kepada penyakit ITP kronik.

KAEDAH:

Kajian retrospektif melalui rekod pesakit ini telah dijalankan di dua hospital utama di Kelantan. Ianya melibatkan semua kes ITP baru di kalangan kanak-kanak berumur 6 bulan hingga 18 tahun mulai Januari 2001 hingga September 2012.

KEPUTUSAN:

Terdapat 90 kes ITP baru yang memenuhi kriteria kajian dengan median umur 5.4 tahun dan pengagihan jantina yang sama rata. Kes ITP memuncak dalam tempoh 3 bulan selepas musim hujan, iaitu dari bulan Februari hingga April. Kes paling rendah direkodkan dari Mei hingga Julai, iaitu pada musim kemarau. Sebanyak 53.3% kes mempunyai sejarah penyakit berjangkit yang baru berlaku. Sebanyak 53.3% daripada kes mempunyai manifestasi pendarahan kulit manakala 46.7% mempunyai pendarahan mukosa atau kedua-duanya sekali. Tiada pendarahan intrakranial atau kematian direkodkan dalam tempoh 6 bulan pertama diagnosis. Median bagi kiraan platelet semasa diagnosis adalah 10 x 10^9 / L dengan 50% daripada pesakit mempunyai

platelet gergasi pada gambaran darah lengkap. Aspirasi sum-sum tulang telah dilakukan ke atas 12 pesakit. Sebanyak 85.6% (n = 77) daripada pesakit telah menerima rawatan aktif iaitu rawatan dengan ejen spesifik, transfusi platelet atau kedua-duanya sekali. Terdapat 14.4% (n = 13) pesakit yang hanya diberi pemerhatian sahaja dalam tempoh 6 bulan pertama. Walau bagaimanapun, rawatif aktif didapati tidak mempengaruhi kesan akhir bagi penyakit ITP. Daripada 90 pesakit, 66.7% adalah akut, 24.6% adalah kronik, dan 8.9% lagi tidak dapat ditentukan. Jantina perempuan dan kehadiran platelet gergasi di dalam gambaran darah lengkap dibuktikan dapat membawa kepada penyakit ITP kronik.

KESIMPULAN:

Penyakit ITP di kalangan kanak-kanak mempunyai kesan klinikal yang baik dan rawatan aktif tidak mempengaruhi kesan akhir bagi penyakit ini. Jantina perempuan dan kehadiran platelet gergasi dapat meramalkan penyakit ITP kronik.

ABSTRACT

INTRODUCTION:

Childhood ITP is a hematological disorder with a diverse natural history. The management differs worldwide and has been a topic of debate.

OBJECTIVES:

To evaluate the demographic, clinical characteristics, management practice and outcome of childhood ITP in Kelantan and explore the factors associated with development of chronic ITP.

METHODS:

This study was conducted via retrospective record review in 2 major tertiary centres in Kelantan. It involved all newly diagnosed ITP cases aged 6 months to 18 years from January 2001 till September 2012 who met all the study criteria.

RESULTS:

There were 90 patients included in this study with the median age at diagnosis of 5.4 years old and equal gender distribution. A peak incidence of children with ITP was observed within 3 months after rainy season, from February to April. The lowest case recorded was from May to July, the driest months of the year. History of recent infectious illness was detected in 53.3% of cases. A total of 53.3% of cases presented with cutaneous bleeding manifestation while 46.7% had mucosa or mucocutaneous bleeding. No intracranial bleeding or death documented in the first 6 months of diagnosis. The median platelet count at diagnosis was 10 x 10^9/L with 50% of patient had giant platelets in FBP. BMA was performed in 12 patients. There were 85.6% (n=77) of patients who received active medical interventions either with specific agent, platelet

transfusion or both while the remaining were managed expectantly during first 6 months of diagnosis. Active medical intervention did not affect the final outcome for these patients. Of these 90 patients, 66.7% were acute, 24.6% were chronic, and 8.9% were undetermined. Female gender and the presence of giant platelet in the FBP were shown to be associated with the development of chronic ITP.

CONCLUSIONS:

Generally, childhood ITP has a good clinical outcome and active medical intervention has not been shown to influence the final outcome of the disease. Female gender and presence of giant platelet are significant predictors towards chronic ITP.

CHAPTER 1

INTRODUCTION

1.1 Immune thrombocytopenia (ITP)

Immune thrombocytopenia (ITP) is a new nomenclature for a disorder formerly known as idiopathic or immune thrombocytopenic purpura. It was introduced in conjunction with standardization of terminology, definitions and outcome criteria of ITP for both adults and children during Vicenza Consensus Conference by the International Working Group (IWG) of recognized experts in ITP in October 2007. The panel preferred 'immune" as opposed to "idiopathic" to emphasize the immune-mediated mechanism of the disease. The term "purpura" was not included because bleeding symptoms were absent or minimal in the majority of cases (Rodeghiero *et al.*, 2009). However, the well known acronym, ITP was preserved taking into account its utility for literature searches.

ITP is a childhood hematological disorder characterized by isolated thrombocytopenia in an otherwise well child resulting in spontaneous bruising, purpuric or petechial rash and mucosal bleeding. The incidence of childhood ITP from various reports ranges from 1.9 to 6.4 per 100,000 children/year (Terrell *et al.*, 2010). The mean age at diagnosis is 6.2 years with equal gender distribution (Glanz *et al.*, 2008). The overall prognosis for ITP is excellent with low morbidity and mortality. Majority of children with acute ITP will recover within weeks to months without serious bleeding complications. Approximately 20% of children develop chronic ITP. In general, the risk of severe bleeding in ITP is about 3-4% (Bolton-Maggs, 2007) while

intracranial hemorrhage (ICH) is rarely seen, with an estimated incidence around 0.19% to 0.78% (Psaila *et al.*, 2009).

Some of the new terminology, definitions and outcome criteria for ITP provided by the IWG panel are included here for our knowledge. One of the major changes is the cutoff point for the diagnosis of ITP which is now taken as platelet count less than 100 x 10^9/L, instead of less than 150 x 10^9/L in the past. This value was taken based on 3 considerations:

- Recognition that in non-western populations, platelet count in healthy individuals may be between 100 and 150 x 10^9/L.
- A study showing that otherwise healthy subjects with borderline thrombocytopenia (platelet count between 100 and 150 x 10^9/L) have only 6.9% chance of developing a persistent thrombocytopenia of less than 100 x 10^9/L over 10 years follow-up, indicating that the chances are small that a person with an isolated borderline thrombocytopenia will develop ITP (Stasi *et al.*, 2006).
- To avoid inclusion of women with pregnancy-related thrombocytopenia.

The IWG panel had standardized the terminology, definitions and outcome criteria for ITP to ease the development of clinical trials of high scientific quality in future. They had divided ITP into two major diagnostic categories; primary and secondary ITP. The "primary" ITP had replaced the term "idiopathic" to describe the absence of any obvious initiating and/or underlying cause that might be associated with thrombocytopenia. Primary ITP accounts for the majority of cases in most studies. All forms of immune-mediated thrombocytopenia other than primary ITP will be known as secondary ITP. Causes of secondary ITP are as the following:

- connective tissue disease: SLE, antiphospholipid syndrome, Evans syndrome
- immune deficiencies: common variable immune deficiency, Wiskott-Aldrich syndrome
- infections: cytomegalovirus, *Helicobacter pylori*, hepatitis C, HIV, varicella zoster
- vaccination side effect: MMR
- drug administration side effect: heparin-induced thrombocytopenia
- lymphoproliferative disorder

The phases of ITP were divided into 3 categories to facilitate management decisions; newly diagnosed ITP, persistent ITP and chronic ITP. Because of its vagueness and retrospective definition, the term "acute" ITP was no longer used. The "newly diagnosed ITP" refers for all cases with no reliable clinical or laboratory parameters of disease duration at diagnosis and within 3 months from diagnosis. A new category, "persistent ITP" refers to ITP patients during a period of 3 to 12 months from initial diagnosis, and includes patients who have not reached spontaneous remission or not maintaining complete response to therapy. The term "chronic ITP" is preserved, but the duration of thrombocytopenia is extended to more than 12 months. This is following few studies in the past that have shown high rates of spontaneous recovery from ITP even after 6 months of diagnosis (Imbach *et al.*, 2006; Donato *et al.*, 2009). Severe ITP is defined by bleeding at presentation sufficient to mandate treatment, or by the occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dosage of a current agent. Refractory ITP should be reserved for patients who fulfill 2 criteria. First, they should have failed splenectomy or have relapsed thereafter. Second, they should either manifest severe ITP or have a bleeding risk which requires therapy in the opinion of the attending doctor.

For this study, we had decided to use the traditional terminology and definition for ITP to avoid any confusion as it was conducted retrospectively. Furthermore, almost all references and literature reviews in this study were still using the older terminology and definition. Therefore, a platelet count of less than 150 x 10^9/L was taken as the threshold for diagnosis of ITP. ITP was classified into 2 groups; acute and chronic ITP. Acute ITP was defined as the duration of thrombocytopenia of less than 6 months following initial diagnosis with or without treatment. Persistence of thrombocytopenia for 6 months or more following initial diagnosis defined chronic ITP (George *et al.*, 1996a).

For the management section including in the diagnosis of ITP, we used the American Society of Hematology (ASH) 2011 evidence-based practice guideline for immune thrombocytopenia (Neunert *et al.*, 2011a). This guideline was chosen because it was the latest guideline available at the moment and provided the most comprehensive evidence-based approach in managing ITP patients. It used evidence-based treatment recommendations using GRADE system in areas where such evidence exists, according to a number of recent, consensus-based recommendations. Besides that, we also included some recommendations from the updated version of Paediatric Protocols for Malaysian Hospitals Third Edition 2012. There might be some contradictions among the two guidelines, but the final decision in the management depended on the physician's best judgement and patients (or parents') stated preference.

1.2 Pathogenesis of ITP

The increased platelet destruction and thrombocytopaenia in ITP may result from several complex mechanisms. The main pathologic process in ITP is related to immune-mediated platelet destruction due to circulating platelet autoantibodies (usually to glycoproteins IIb/IIIa, Ib/IX or Ia/IIa) which coated the platelets in ITP plasma, causing them to be prematurely destroyed via phagocytosis in the mononuclear phagocytic system, in particular, the spleen (van Leeuwen *et al.*, 1982; Cines and Blanchette, 2002). These platelet autoantibodies not only involve in platelet destruction, but may also contribute to the inhibition of platelet production by megakaryocytes (Chang *et al.*, 2003). Furthermore, thrombopoietin levels do not increase appropriately in many patients with ITP suggesting thrombopoietin deficiency may involves in the pathophysiology (Kosugi *et al.*, 1996). Recent works also reveal that the immune system may be dysregulated in many other ways; disturbed antigen presentation, cytotoxic T cells, production of idiotypic antibodies, changes in complement pathways and abnormal apoptosis all of which may be implicated. These mechanisms may explain why some patients with ITP do not have a demonstrable autoantibody (Bolton-Maggs, 2007).

The degree of thrombocytopenia in each patient therefore depends on the balance between the quantity of antibody produced, the rate of platelet removal and the bone marrow's compensatory ability to produce platelets from megakaryocytes.

The development of ITP has been attributed to the post viral phenomena where approximately two-thirds of children with ITP had a preceding febrile illness (Cines and Blanchette, 2002). Childhood ITP is acute and generally seasonal in nature, suggesting that infectious or environmental agents may trigger the immune response to produce platelet-reactive

autoantibodies 4 to 8 weeks following an infection (Nugent, 2002). It occurs most commonly in the winter and fall, and least in summer (Nugent, 2006). ITP also has been known to be associated with MMR vaccination in young children, occurring in 1 in 40 000 doses (France *et al.*, 2008). A recent study noted that the incidence of ITP is unlikely related to early childhood vaccines other than MMR, but there is a possible association of ITP with hepatitis A, varicella, tetanus-diphtheria-acellular pertussis vaccines in older children, which requires further investigation (O'Leary *et al.*, 2012).

1.3 Clinical manifestation and diagnosis

The onset of ITP is usually acute. The clinical manifestation varies from an asymptomatic state, cutaneous and/or mucosal bleed, to the most serious complication like intracranial hemorrhage. However, the typical bleeding manifestations are petechiae, bruising, epistaxis and gum bleeding. Physical examinations are usually unremarkable except in atypical cases, where lymphadenopathy and hepatosplenomegaly may be present.

ITP is a diagnosis of exclusion by carefully ruling out alternate causes of thrombocytopenia (e.g; pseudothrombocytopenia, secondary ITP, malignancy and congenital or hereditary ITP). Obtaining a thorough history and physical examination, review of the full blood count and full blood picture remain the key components of the diagnosis of ITP. If all components are typical of ITP, no further testing is needed (Neunert *et al.*, 2011b).

The presence of thrombocytopenia in the full blood count should be confirmed with full blood picture. This is because both very large and very small platelets may be under reported by automated cell counters because of the preset particle size (Drachman, 2004). The classic

description of ITP from the full blood picture is an isolated thrombocytopenia with larger-than-usual platelets and a normal RBC morphology without any immature WBC series. Abnormalities in RBC or WBC series are unusual in children with standard ITP.

There is a continuing debate regarding indication of BMA in ITP patients. The ASH guideline 2011 recommends that BMA is not necessary in children and adolescents with the typical features of ITP (grade 1B) and in those who fail IVIg therapy (grade 1B). It suggests that BMA is also not necessary in similar patients before initiation of treatment with corticosteroids or before splenectomy (grade 2C).

According to the Paediatric Protocols for Malaysian Hospital 3rd Edition, the threshold for performing a BMA is low. The indications are usually as follows:

- before starting steroid therapy
- when there is failure to respond to immunoglobulin therapy
- when there is persistent thrombocytopenia of more than 6 months
- when thrombocytopenia recurs after initial response to treatment

Bone marrow aspiration in acute ITP usually reveals normal or increased numbers of megakaryocytes. Previously, bone marrow aspiration is often obtained to exclude the possibility of acute leukemia, which might enter a temporary remission or trigger an unrecognized tumour lysis syndrome with steroid treatment. A retrospective cohort of BMA samples collected to confirm provisional diagnoses of acute ITP from 332 children with typical hematological features of ITP found that none had diagnoses of leukemia and only one case of bone marrow aplasia (Calpin *et al.*, 1998). A larger retrospective sample review from records of 2239 children

with acute lymphoblastic leukemia (ALL) also revealed that none had significant thrombocytopenia alone when they were first seen by the hematologist (Dubansky *et al.*, 1989).

Other tests like reticulocytes count, erythrocyte sedimentation rate, antinuclear antibodies, blood group, Coomb test (positive in Evans syndrome) and Epstein-Barr viral serology may be needed in selected cases depending on associated symptoms (Warrier and Chauhan, 2012). Platelet antibody testing is not indicated as it may be positive or negative (Bolton-Maggs, 2007). Therefore, the most important measure in managing childhood ITP is a close and continued monitoring of clinical and hematological status.

1.4 Management of ITP

There have been numerous advances in the management of ITP in the recent years. Previously, platelet count (which is often extremely low in ITP) has been made as a sole determinant of bleeding risk even though life threatening or fatal bleeding is rare. Almost all of the randomized clinical trials conducted in childhood ITP only focused on platelet counts as the solitary outcome measure. Other factor also should be considered in clinical decision making like assessment of bleeding tendency (Buchanan and Adix, 2001). The goal of treatment is now directed towards achieving a platelet count that is associated with adequate hemostasis, rather than a normal platelet count (Neunert *et al.*, 2011a). The hemostatic system in ITP patients may give adequate protection from bleeding complications, even when the platelet counts are less than 20 x 10^9/L (Bolton-Maggs and Moon, 1997; Medeiros and Buchanan, 1998). Besides that, an increased number of large and reticulated platelets in ITP have been shown to promote adhesion and aggregation more effectively than in thrombocytopenia caused by bone marrow failure (Saxon *et al.*, 1998).

One should also realize that none of the treatment modality decreases mortality or alters the risk of the disease process from becoming chronic. Severe bleeding and ICH often are unpredictable in ITP. It can occur at any stage of the disease and is not necessarily prevented by any treatment. Therefore, the mode of treatment is best personalized based on platelet count, severity of bleeding, age, duration of illness, social issues (including lifestyle, distance from hospital and economic considerations), cost and side effects of treatment, anticipated surgical procedures, and also, the parents, patient or physician concerns.

In general, management of ITP can be divided into four categories; observation alone, first-line pharmacological management, second-line pharmacological management, blood product transfusion such as platelet transfusion and splenectomy.

1.4.1 Observation alone

A majority of ITP cases remits spontaneously and the risk of serious bleeding is low. One study showed 80% of children recovered within 6 weeks with no treatment (Bolton-Maggs *et al.*, 2001) and in another study, 67% recovered within 4 weeks (Rosthøj *et al.*, 2003).

In the United Kingdom (UK), many choose not to treat children with clinically mild ITP (bruising and purpura only) even with profound thrombocytopenia (platelet counts less than 10 to 20 $\times$ 10^9/L). The proportion of UK children receiving platelet-raising treatment was noted to decrease from 61% in 1995 to 38% in the year 2000. The current UK 2009 registry practice has shown a continued reduction in the number of children receiving treatment in comparison with historical international practice from 69% to 16% of cases. Data collection from 225 children with a new diagnosis of acute ITP through a national UK Childhood ITP registry started in

January 2007 noted that 54% had clinically mild, 42% moderate and 4% severe disease. There was no case of ICH. The mean platelet counts at diagnosis for these groups were 14, 8 and 6 × 10^9/l respectively (Grainger *et al.*, 2011).

This watchful waiting strategy also has been implemented in Denmark since early 2000s without adverse effects seen in the duration or the morbidity of ITP. Medical records review for children with ITP presenting with a platelet count less than 30 x 10^9/L in the 1990s (n = 22) and in the 2000s (n = 47) found that the rate of initial treatment with IV immunoglobulin (IVIg) or steroids was reduced from 64% in the 1990s to 15% in the 2000s. (Bekker and Rosthoj, 2011).

Therefore, patients with no bleeding or mild bleeding symptom (involving cutaneous manifestations only without any mucosal bleeding) can be managed with observation alone regardless of platelet count (grade 1B).

However, the Malaysian Paediatric Protocol outlines that careful observation and monitoring of platelet count, without specific treatment, might be more appropriate for patients with platelet count more than 20 x 10^9/L without bleeding and for those with platelet count more than 30 x 10^9/L with only cutaneous purpura. A repeat blood count must be done within the first 7 to 10 days to ensure that there is no serious evolving marrow condition.

The conservative approach must be discussed in details with the family and appropriate anticipatory guidance should be given to monitor and prevent bleeding. For example, they should be well informed regarding the need to avoid injury, contact sports and drugs that interfere with platelet function, in particular aspirin and other non-steroidal anti-inflammatory drug which could add more risk for bleeding in patients with ITP. If any bleeding occurs, they should seek

medical treatment immediately. If a female patient enters menarche, the physician should explain what the expected menstrual blood loss to be and what features would be considered as excessive and warranted treatment.

1.4.2 First-line pharmacotherapy

The first line pharmacotherapy includes corticosteroids, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin (anti-D). The basic mechanism of action for drugs in this category is by blocking the destruction of antibody-coated platelets by the mononuclear phagocytes. First-line pharmacotherapy is usually effective to transiently raise the platelet count but does not provide long term responses. In all trials, there was a consistent trend to support the conclusion that the average time for the platelet count to rise is shortest using IVIg or high dose steroids, next shortest using conventional dose steroids (or anti-D) and slowest on no treatment (Lilleyman, 1999).

ASH 2011 guideline recommends a single dose of IVIg (0.8 to 1 g/kg) or a short course of corticosteroids to be used as a first - line treatment (grade 1B). The Paediatric Protocols for Malaysian Hospitals Third Edition 2012 recommends treatment for ITP in the following conditions:

- in a life threatening bleeding episode regardless of platelet count
- platelet count less than 20 x 10^9/L with mucosal bleeding
- platelet count less than 10 x 10^9/L with any bleeding

The choice of treatment are either oral Prednisolone 2 mg/kg/day for 14 days then taper off, oral prednisolone 4 mg/kg/day for 4 days or a single dose of IVIg 0.8 g/kg/dose.

1.4.2.1 Corticosteroids therapy

The mechanism of action of corticosteroids in ITP is to increase platelet lifespan by inhibiting phagocytic activity and suppressing the platelet autoantibody synthesis. However, the evidence to determine its benefit in populations perceived to be at higher risk of bleeding compared to observation alone is still lacking. The ASH guideline 2011 stated that there is also no evidence to support any one dose, or dosing regimen which is superior over the others. Many physicians still consider corticosteroid therapy for children with a platelet count less than 10×10^9/L or those with mucosal bleeding.

If corticosteroids are chosen as an initial treatment, long term use should be avoided in children with ITP due to its side effect. Some of the common complications associated with corticosteroid treatment are cushingoid facies, acne, weight gain, hypertension, diabetes mellitus, growth retardation, gastritis, myopathy, osteoporosis, personality changes and opportunistic infections.

1.4.2.2 IVIg therapy

There are multiple complex mechanisms of how IVIg works in ITP. Among the most accepted mechanisms are the inhibition of Fc-receptor mediated platelet phagocytosis, suppression of anti-platelet antibody production and anti-idiotypic inhibition of anti-platelet antibodies. New research also suggests that a significant portion of IVIG benefit may be due to IVIG-mediated acceleration of the elimination of anti-platelet antibodies (Hansen and Balthasar, 2004).

A single dose of IVIg (0.8 – 1.0 g/kg) is recommended if a more rapid increase in the platelet count is desired (grade 1B). The response is usually seen within 24 to 48 hours. This

effect is particularly useful for patients with severe ITP and those who is undergoing interventional procedure or surgery. Although IVIg is more expensive, comparatively it may be more cost effective as the duration of hospitalization may be shortened compared to other treatment modalities.

Some common adverse effects related to IVIg infusion are nausea, headache, fever and chills. Other serious but rare side effects include thromboembolic events, aseptic meningitis, renal impairment and anaphylaxis especially in IgA-deficient patients. IVIg also has all the potential problems of a large pool blood product like transmission of hepatitis C and Parvovirus B19, eventhough now it has been reduced through a three-fold strategy which consists of donor selection, testing of donor plasma, viral removal and viral inactivation (John Looney and Huggins, 2006).

1.4.2.3 Anti-D therapy

Anti-D therapy is not advisable in children with low hemoglobin due to bleeding or with evidence of autoimmune hemolysis (grade 1C). A single dose of anti-D is suggested as first-line therapy in Rh-positive, non-plenectomized children requiring treatment (grade 2B). Anti-D is ineffective in Rh-negative patients or those who have undergone splenectomy. Anti-D works by binding to Rh-positive red blood cells, and these opsonized RBCs in turn compete with opsonized platelets in the spleen for sequestration. Eventhough the red cells are destroyed, the benefits usually outweigh the risks because there are many more red cells than platelets in the circulation.

There are 2 different doses of anti-D used in previous studies; either 50 ug/kg or 75 ug/kg given intravenously, but at this point, there is no solid evidence to recommend a specific dose of anti-D immunoglobulin.

Some of the common side effects related to anti-D infusion are fever, chills and headache. In addition, the Food and Drug administration (FDA) has provided a warning and specific monitoring requirements as there had been reports of fatal intravascular hemolysis reported with anti-D. One of the cautions is that patients who receive anti-D should remain in a health care setting for 8 hours after treatment, although most cases of intravascular hemolysis occur within 4 hours. Patients with intravascular hemolysis may have back pain, chills and rigors, fever and hemoglobinuria. Usually the fall in hemoglobin due to hemolysis is not more than 2 g/dL, but in rare cases, it can be severe resulting in renal failure and disseminated intravascular coagulation.

1.4.3 Second-line pharmacotherapy

The medications in this category are high-dose dexamethasone and rituximab. Rituximab is a humanized monoclonal antibody against the CD20 antigen on B lymphocytes that can temporarily deplete the blood of B-cells that produce autoantibodies. Rituximab is effective in patients with or without a spleen.

High-dose dexamethasone and rituximab are reserved for children with significant ongoing bleeding unresponsive to first-line pharmacotherapy (grade 2C). They may be considered as an alternative to splenectomy in children and adolescents with chronic ITP or in patients who do not respond favourably to splenectomy (grade 2C). They may be used as

necessary to prevent bleeding, especially during the first 12 months of persistent disease while waiting for a possible spontaneous remission.

There was one retrospective analysis done in adult ITP patients that showed initial treatment with high-dose dexamethasone produced a longer response duration compared to a conventional dose of prednisone (Teramura, Ishiyama et al. 2012). So far, there were no such studies done in children with ITP. However, pulses of steroids, IVIg or anti-D have been tried in the past for children with chronic symptomatic ITP who have not reached the stage where splenectomy is being considered and who genuinely need treatment for the relief of symptoms. The pulse steroids can be high-dose prednisolone, methyl prednisolone or dexamethasone, given via oral or intravenous administration. There is no evidence that any particular schedule is more or less effective than any others. The duration and extent of response are variable, depending more on the patient than on the treatment (Lilleyman, 1999). Another randomized controlled study comparing IVIg and high-dose dexamethasone therapy for children with chronic ITP concluded that treatment with pulsed high-dose dexamethasone is not always effective in children with chronic ITP, but it is worth trying in severe symptomatic chronic childhood ITP (Hedlund-Treutiger *et al.*, 2003).

Potential drawbacks of rituximab include its cost as well as the risk of first-infusion reactions, which may be severe or, rarely, fatal. Other rare side effects of rituximab include progressive multifocal leukoencephalopathy, the potential for neutropenia and reactivation of chronic infections such as tuberculosis.

1.4.4 Other medications for ITP

Data regarding the use of other medications like azathioprine, danazol, interferon, mycophenolate mofetil, cyclosporine, anti-CD52 monoclonal antibody or combination of agents for the treatment of ITP in children is still lacking for specific recommendations. However, one single agent that could be considered for patients who fail steroid therapy is dapsone.

Dapsone (also called diphenylsulfone, DDS, or avlosulfon) is an anti-infective sulfone drug. It has been used for the treatment of leprosy, pemphigoid, SLE and rheumatoid arthritis. The exact mechanism of action for dapsone in ITP is unclear. One retrospective study involving dapsone as a treatment for 35 children with chronic ITP and a platelet count of less than 50 x 10^9/L demonstrated a response rate of 65.7% and continuous complete response rate (maintenance of a platelet count more than 50 x 10^9/L with or without dapsone) of 31% (Damodar *et al.*, 2005).

The current thought in ITP is the use of new classes of therapeutic agent, thrombopoietin receptor agonists in children and adolescent. Rather than inhibit platelet destruction, as do all the other ITP therapies, they act by increasing platelets production by the bone marrow. However, there was no recommendation made in the ASH guideline 2011 regarding the usage of thrombopoietin receptor agonists in children and adolescent as studies are ongoing and no results had been published at that time. Two drugs in this class (Romiplostim and Eltrombopag) are currently available for treating chronic ITP in adults who have had an insufficient response to corticosteroids, IVIg and splenectomy.

Romiplostim is given subcutaneously once a week while Eltrombopag is taken orally once daily. The first randomized clinical trial to determine safety and efficacy of Romiplostim in children with ITP by Bussel, Buchanan et al. (2011) showed that it was effective to increase platelet counts in 88% of children with ITP compared to placebo. It was well-tolerated and apparently safe. A randomized clinical trial of efficacy, safety and tolerability of Eltrombopag in children with previously treated chronic ITP (PETIT2) is currently in progress. Adverse effects of thrombopoietic agents include headache, nasopharyngitis and fatigue (with Romiplostim), nausea, vomiting and hepatotoxicity (with Eltrombopag), rebound thrombocytopenia, bone marrow fibrosis and thrombosis.

1.4.5 Splenectomy

Splenectomy is one definitive form of therapy for ITP which usually promotes long-term and sustained responses. This is because the spleen is the major site for both autoantibody production and platelet destruction. Splenectomy is recommended for children and adolescents with chronic or persistent ITP who have significant or persistent bleeding, and lack of responsiveness or intolerance of other therapies and/or who have a need for improved quality of life (grade1B). However, splenectomy is suggested to be delayed for at least 12 months, unless accompanied by severe disease as defined by the IWG as unresponsive to other measures or other quality of life expectations (grade 2C) considering the relatively high rate of spontaneous remission.

As splenectomy increases the risk of infection especially by encapsulated organisms, all patients should be vaccinated with pneumococcal, *Haemophilus influenza* type B, and meningococcal vaccines, preferably at least 2 weeks before surgery to optimize the immune response. This vaccine reduces the risk of overwhelming post splenectomy infection. Daily

prophylactic penicillin or an equivalent antibiotic if the child is allergic to penicillin is indicated for lifelong to prevent pneumococcal sepsis. This is because the currently available vaccines do not cover against all pneumococcal serotypes. Pneumococcal booster should be given to post splenectomy patients for every 5 years. Perioperatively, platelet count can be raised with corticosteroids, IVIg or anti-D. Platelet transfusion should not be given prophylactically but should be reserved for patients with intraoperative bleeding. Finally, both patient and parents should be educated about the lifetime risk of sepsis and they must understand the need for prompt medical evaluation for all febrile illnesses.

1.4.6 Emergency treatment of ITP

For the emergency treatment of ITP, IVIg should be considered along with corticosteroids with the aim of increasing the platelet count (grade 2B). IVIg is proven to have the most rapid onset of action. Platelet transfusions have been reported to be effective in the treatment of bleeding. These can be given ranging from every 30 minutes to 8 hourly transfusion or given together with continuous infusion of IVIg. These actions can result in a rapid reduction in bleeding and/or improvement in the platelet count. However, the effect of platelet transfusion on the platelet count is short-lived.

Treatment options in this situation according to the Malaysian Paediatric Protocol include the following:

- high dose IV Methylprednisolone 30 mg/kg/day for 3 days
- IVIg 0.8g - 1g/kg as a single dose
- combination of IVIg and methylprednisolone in life threatening conditions

- platelet transfusion in life threatening haemorrhage: 8 - 12 units/m2 body surface area (2 to 3 folds larger than usual units)

Recombinant factor VIIa may be added for ITP patients who are unresponsive to other modalities if an immediate response is necessary, such as in the case of ICH. Precaution is needed when using recombinant factor VIIa due to risk of thrombosis. Other agents that have been used as an adjunct therapy in ITP include antifibrinolytic agents (aminocaproic acid and transxenamic acid) and desmopressin acetate. However, the efficacy of these agents has not been proven.

The final measure in truly life threatening bleeding is emergency splenectomy with or without IVIg and/or corticosteroids, in conjunction with platelet transfusion. This approach is considered high risk given the dangers of unplanned surgery, lack of immunization and the associated risk of bleeding either pre, intra or post-operatively.

1.4.7 Platelet transfusion in ITP

Routine use of platelet transfusion in ITP is not recommended, either at diagnosis or later if the disease becomes chronic. Despite this, the practice depressingly continues (Bolton-Maggs & Moon, 1997). Conventional doses of platelets offer risk without benefit since the transfused platelets are rapidly cleared from the circulation. This is because the underlying autoimmune mechanism that destroyed the patient's platelets will also destroy the donor platelets.

As mentioned before, the only extraordinary circumstances where platelet transfusions are appropriate are true life threatening haemorrhage, for example, ICH, severe epistaxis or gastrointestinal bleeding causing a drop in hemoglobin. However, the dose should be massive as

the platelets will be consumed by the haemorrhage to form blood clots and will reduce further circulating platelets. This is analogous to the 'swamping' dosages of factor VIII used in haemophiliacs with inhibitors (Lilleyman, 1999).

One study has been conducted to evaluate the efficacy of platelet transfusion alone in patients with refractory ITP. Ten patients with refractory ITP and bleeding or a high bleeding risk were consecutively transfused with apheresis platelet concentrates (APC) without the administration of other drugs. Platelet transfusion resulted in an increase in the platelet count to 84 to 157 x $10^3/\mu l$, and the cessation of bleeding in all patients without any serious adverse effects. Although platelet counts gradually decreased within a few days post-transfusion, the bleeding had stopped in all cases. These findings indicate that consecutive platelet transfusion using APCs was a rapidly effective emergency treatment in patients with refractory ITP (Salama *et al.*, 2008).

1.4.8 Surgery in the Patient with ITP

Risk of bleeding during or following surgery in ITP patients is a major concern. Fortunately, the incidence of serious bleeding is uncommon. A normal platelet count of more than 150 x 10^9/L is not required to prevent bleeding and promote healing. For major surgeries, a platelet count of 50 x 10^9/L is acceptable in combination with other surgical techniques to minimize the bleeding. A platelet count of 20 to 30 x 10^9/L is usually adequate for minor surgeries such as tooth extractions, repair of lacerations, biopsies of lumps or hernia repairs. However, for any delicate operations involving the eye, heart or brain where even a slight amount of excessive bleeding is harmful, a platelet count of more than 100 x 10^9/L is required, at least transiently during the procedure.

Treatment should be considered in patients with baseline platelet counts that are lower than what has been deemed necessary for the operation. These consist of cortisosteroid, IVIg or anti–D. Oral steroid can be started one week prior to surgery to promote an increase in platelet count, which can be confirmed three or four days later. IVIg can be used as an alternative if the platelet count does not rise satisfactorily or if the patient is already known to be refractory to steroids. Platelet transfusion can be given right at the beginning of the surgery if the platelet counts are very low or the patient is planned for a delicate surgery. Other general measures to reduce the risk of bleeding include cessation of drugs that impair platelet function, measures to minimize trauma, use of fibrin glue to manage dental extractions and tranexamic acid for surgical procedures that involve the mucosa such as mouth or urinary tract.

Another precaution stands for those on steroid therapy. This type of patients may need extra doses of steroids during and following surgery to avoid Addisonian crisis especially if they have been on it for a long time (http://www.itpsupport.org.uk).

1.4.9 Alternative therapy (papaya leaf extract)

Antioxidants are believed to play a role in ITP patients. One example is papaya leaf extract that might increase the platelet count. Traditionally, papaya leaves extract has been used by some population to help in digestion and skin healing.

The leaves of papaya have been proved scientifically to contain many active components that can increase the total anti-oxidant activity in blood and reduce lipid peroxidation level. Thus, it may potentially provide the means for the treatment and prevention of selected human diseases such as cancer, various allergic disorders and may serve as immunoadjuvant for vaccine therapy

(Otsuki *et al.*, 2010). Recent studies also showed that the papaya leaf extract could significantly increase the platelet count, maintain stability of the hematocrit in the normal level, shorten hospitalization and accelerate the increased in platelet count in dengue fever patients compared with control group (Yunita, Hanani et al. 2012).

However, with regards to ITP, there is no scientific evidence available at this moment to advocate its use for our patients.

1.4.10 BMA or treatment refusal among parents of ITP patients and its impact

The problem of BMA refusal among the Malay community in Kelantan is well acknowledged. The reasons that we frequently encountered in practice includes the false belief that BMA will result in paralysis, fear because it is a painful procedure and some parents just simply refused.

Important aspects in managing such cases include a straightforward and direct discussion regarding the ITP management, including the potential complications related to missed diagnosis or treatment. If possible, try to explore the reason for refusal, correct any misconception if present and give an overview regarding the procedure itself.

It is undeniable that the bone marrow aspiration is a painful and stressful procedure. In practice, we often administer general anaethesia for the children while sedatives plus local anaesthesia may be adequate for adolescent patients to alleviate the pain and provide some relaxation. Bone marrow aspiration is regarded a very safe procedure and adverse events following bone marrow biopsy are rare. The latest annual UK survey documented 15 adverse events, representing 0.07% of all 20323 reported procedures. Hemorrhage remains the single most common and most serious adverse event. Other complications are persistent pain, collapse

related to previously undiagnosed severe aortic stenosis, anaphylactic reaction and fracture at the site of the biopsy in a patient with osteoporosis (Bain, 2006).

The same approach goes for those who refuse medical treatment. The options of therapy should always be discussed between the patient, parents and attending doctor. All the related side effects and benefits of treatment should be explained in details including what to expect from treatment. Parental preference for treatment or no treatment after being presented with the facts should always be taken into account in managing our patients.

After all, if the parents are still concerned about the use of human blood product, eg; IVIg and refuse BMA for their own reason, perhaps one might think the use of steroid is justified in this situation as we are not going to go against the parents' wishes. However, parents need to be emphasized that steroid could mask the appearance of a more serious condition like acute leukemia as it has the role of killing or depressed the cancerous cells.

1.5 Place of Study

Hospital Universiti Sains Malaysia (Hospital USM) in Kubang Kerian and Hospital Raja Perempuan Zainab II (HRPZ II) in Kota Bharu are the two tertiary care centres in Kelantan. Hospital USM is also one of the main teaching hospitals for the undergraduates and postgraduate students in Malaysia. It offers 723 beds for inpatients. HRPZ II is a government hospital that was built since the British era in 1920s and now, it has become the biggest hospital in Kelantan with 920 beds available for inpatients. Both hospitals provide multiple clinical sub-specialities, together with clinical and non-clinical support services.

Kelantan is one of the thirteen states in Malaysia and her capital city is known as Kota Bharu. It is situated in the northeast of Peninsular Malaysia. It is bordered by Narathiwat Province of Thailand in the north, Terengganu in the east, Perak in the west, Pahang in the south and South China Sea in the northeast of Kelantan.

The weather in Kelantan is characterized by two monsoon regimes, namely, the Northeast Monsoon and the Southwest Monsoon. The Northeast Monsoon from November to March brings heavy rainfall, which often causes severe floods. The Southwest Monsoon from late May to September normally signifies relatively drier weather. The transition period in between the monsoons is known as the intermonsoon period. Over the East Coast states including Kelantan, the months with maximum rainfall are November, December and January while June and July are the driest months in most districts (http://www.met.gov.my).

The people here are predominantly Malays (95%), followed by other races like Chinese, Indian, Siamese and Orang Asli. The population estimates based on the adjusted population and housing census of Malaysia in 2010 was around 1.6 million.

1.6 Rationale of this study

To date, to the best of our knowledge, there are no local data regarding childhood ITP. It is proposed by many workers in different places that ITP has got different treatment approach, geographical and seasonal variation. Therefore, it is hoped that this study would aid practicing pediatrician in Malaysia to better understand the natural history of childhood ITP in our country and generate future research in managing children with this disorder.