Immune Thrombocytopenia at Chris Hani

Baragwanath Academic Hospital

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A dissertation submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfilment for the requirements of the degree of Master of Medicine

Johannesburg, 2014
DECLARATION

I, Firdous Variava declare that this report is of my own work. It is being submitted for the degree of Master of Medicine in the department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand. It has not been presented for any other degree at any other University.

__________________  ____________________
Dr Firdous Variava MBCh (Wits) FCP (SA)  Date
DEDICATION

To my amazing husband, Mohammed

for his infinite support, patience,

assistance and encouragement

and

to my family

for their patience and support
This research was approved by the Ethics Committee for Research on Human Subjects, University of the Witwatersrand (Clearance Certificate number: M120412).
ABSTRACT

Background

Immune thrombocytopenia (ITP) is an auto-antibody mediated platelet disorder associated with thrombocytopenia with/without the presence of mucocutaneous bleeding. Primary ITP is a diagnosis of exclusion. A variety of identifiable causes of ITP contribute to the increasing number of patients with secondary ITP. The management of ITP includes identification and removal of any secondary cause/s and institution of therapy for symptomatic patients (evidence of bleeding), who generally have a platelet count of < 30 X 10^9/l. After stabilization, treatment with corticosteroids is the initial therapy of choice, with clearly defined indications for other treatments including splenectomy, rituximab, thrombopoietin mimetics and other agents.

There is a paucity of data with regard to ITP in South Africa and this study attempts to address this gap and define the changing pattern of ITP in a series of public sector patients diagnosed and managed at a large tertiary hospital over a 25 year period.

Patients and Methods

This study is a retrospective review of adult patients seen at the Clinical Haematology Unit, Department of Internal Medicine at Chris Hani Baragwanath Academic Hospital during the period 01/01/1987 to 31/12/2011. The aim of the study was to determine the profile of patients with ITP, in particular to assess the demographics, clinical presentation, aetiology and management of patients with ITP. In addition, the presentation and outcome of HIV positive versus HIV negative patients was assessed.
Results and Discussion

A total of 243 adult patients with a diagnosis of ITP who presented to the Clinical Haematology Unit, Department of Medicine, CHBAH, during the period 01/01/87 – 31/12/11 were analysed. The median age at presentation was 32 years, with female to male ratio of 4.2:1. The median platelet count at presentation was $10 \times 10^9/l$, with a median of 14 days to platelet recovery of $> 100 \times 10^9/l$.

Primary and secondary ITP was responsible for 48% and 50% of the patients respectively. Secondary ITP increased over the years with important contributions from HIV (40%) and pregnancy (16.8%). Mucocutaneous bleeding remained the predominant clinical manifestation.

Twenty percent of the patients in the study were HIV positive with a female predominance of 3:1. The average CD4 count was 145/ul, with 33% of patients on cART at the time of diagnosis. It was demonstrated that 61.3% of the patients achieved a complete response following initial treatment with corticosteroids and antiretroviral therapy. In general, the response to treatment was greater in HIV negative patients versus HIV positive patients and HIV positive patients took a longer time to achieve a complete response.

Splenectomy was performed in 19% of the patients. 69% of these patients had primary ITP and the remainder (i.e. 31%) had secondary ITP. The most common post surgical morbidity was sepsis.

There was no significant differences in outcomes between primary and secondary ITP.
Conclusion

ITP in South Africa is predominantly a disease of young females. Over the years, there has been a paradigm shift, with an increase in secondary ITP. HIV is the most important defined secondary cause. The presentation in our patients is with severe symptomatic thrombocytopenia (median platelet count of 10 X 10^9/l), with mucocutaneous bleeding requiring immediate therapeutic intervention. Oral corticosteroids are the mainstay of initial treatment. However, a significant number of patients require ongoing long term steroid therapy to maintain the platelet count in a safe range without bleeding. HIV seropositivity was associated with a lower response rate and a longer time to platelet recovery, compared to HIV seronegativity. Splenectomy was performed in approximately one fifth of the patients. It is the most definitive and only curative therapy in ITP. The response rate to splenectomy was 84% (62% CR and 22% PR). Splenectomy is feasible in both primary and secondary ITP, including patients with HIV. After corticosteroids, azathioprine is the most commonly used agent in our patients. Very few patients received rituximab and thrombopoietin mimetics were not used in view of their prohibitive cost. Overall, the outcome in our patients is similar to that described in the literature.
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The patients, without whom this study would not be possible.
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<td>APLS</td>
<td>Antiphospholipid Syndrome</td>
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<tr>
<td>cART</td>
<td>Combination Anti-Retroviral Therapy</td>
</tr>
<tr>
<td>CD</td>
<td>Cluster of Differentiation</td>
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<tr>
<td>CHBAH</td>
<td>Chris Hani Baragwanath Academic Hospital</td>
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<tr>
<td>CLL</td>
<td>Chronic Lymphocytic Leukaemia</td>
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<tr>
<td>DIC</td>
<td>Disseminated Intravascular Coagulopathy</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HL</td>
<td>Hodgkin Lymphoma</td>
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<td>HUS</td>
<td>Haemolytic Uraemic Syndrome</td>
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<td>IgG</td>
<td>Immunoglobulins</td>
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<td>ITP</td>
<td>Immune Thrombocytopenia</td>
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<tr>
<td>IVIG</td>
<td>Intravenous Immunoglobulin</td>
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<td>NHL</td>
<td>Non-Hodkin Lymphoma</td>
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<td>SLE</td>
<td>Systemic Lupus Erythematosus</td>
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<td>TTP</td>
<td>Thrombotic Thrombocytopenic Purpura</td>
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CHAPTER 1: Literature Review

1.1 Introduction

In a recent report by the International Working Group, it is now recommended that the acronym ITP (previously known as immune or idiopathic thrombocytopenic purpura) should be used for Immune Thrombocytopenia (1). The term "immune" was chosen instead of "idiopathic" to highlight the autoantibody-mediated destructive nature of the disease (1).

Immune thrombocytopenia is a disease that has transcended through the ages. It was initially described in 1735 by a German physician and poet Paul Gottlieb Werlhof in his book ‘De Variolis et Anthracibus’ and provided the most complete initial report of immune thrombocytopenia prior to the discovery of platelets (2). Platelets were initially identified in the early 18th century by Addison and Bizzozero and its link to purpura was highlighted in the 1880's. The relationship between the role of platelets and the entity described by Werlhof was described in the late 18th century (2). Not only did the 19th century contribute to the identification of megakaryocytes, but it also provided a breakthrough in the management of the disease, when a Polish medical student Kaznelson identified a response in platelet counts to splenectomy (3). Splenectomy remained the modality of treatment until the introduction of steroids in the 1950's (4). The measurement of platelet-associated IgG, first performed by Dixon et al (1975), gave premise to the presence of an immunological pathogenesis of immune thrombocytopenia (5).

Platelets are small, irregular, anuclear cell fragments with a half-life of 7 to 10 days. They are produced in the bone marrow by the fragmentation of megakaryocytes. Each megakaryocyte gives rise to 1000 - 5000 platelets. Thrombopoietin, which was only identified in the early 1990's, is a
major regulator of platelet production, maturation and function (6). Platelets play an important role in haemostasis, especially in clot formation and respond to vascular injury by platelet adhesion, activation, aggregation and the formation of a platelet plug. Any abnormalities in the quantity or activity of platelets may result in disturbances in haemostasis contributing to bleeding.

Thrombocytopenia refers to a reduction in the platelet count below the normal reference range. Normal platelet counts in a healthy adult range between 150 - 400 X 10^9/l. However, clinical thrombocytopenia is diagnosed with a platelet count < 100 X 10^9/l (1). Thrombocytopenia can occur as a result of reduced platelet production due to decreased megakaryopoiesis (e.g. congenital, aplastic anaemia, bone marrow infiltration, etc.) or ineffective megakaryopoiesis (e.g. megaloblastic anaemia, alcohol, HIV, myelodysplastic syndrome, etc.) or it could be due to reduced platelet survival via splenic sequestration, increased consumption (e.g. DIC, TTP/HUS, pre-eclampsia, etc.), loss of platelets due to haemorrhage or immune destruction such as ITP (7).

1.2 Pathogenesis

Immune Thrombocytopenia was initially described as a disease of peripheral platelet destruction. Its immune mechanism of platelet destruction was supported in the Harrington–Hollingsworth experiment described in the 1950’s where thrombocytopenia developed in healthy individuals after the passive transfer of plasma from patients with ITP (8). The measurement of platelet-associated IgG, first performed by Dixon et al (1975), confirmed the prevalence of an immuno-pathogenic component of ITP (5, 9). The platelet destruction occurs secondary to immune or auto antibody (IgG type) mediated binding to platelet membrane glycoproteins with subsequent destruction of antibody coated platelets by Fcγ receptors expressed on splenic macrophages as well as liver kupffer cells.
The concept of ITP being predominately autoantibody mediated has undergone transformation, as other factors of reduction in platelet production as well as changes in T-cell mediated immunity have come to light. Suppression of megakaryopoiesis may also play a role in the pathogenesis of ITP. Relatively low levels of thrombopoietin, a growth factor for platelets has been implicated in contributing to low platelet counts (10). Intramedullary destruction of platelets by macrophages within the bone marrow is also a contributing factor (11).

More recently, as indicated above, T-cell immunity has also been implicated in the development of thrombocytopenia (12). T-cell mediated cytotoxicity has been shown to contribute to platelet destruction in ITP (13). Semple et al, described in 1996 that qualitative changes in the T-cell activation of natural killer cells, cytokines as well as Th0/Th1 ratio disturbances contributed to the immuno-pathogenic mechanism of the disease and hence platelet destruction (14). T-cell immunity is responsible for the development of T-helper cells which play a role in the development of autoantibodies. Immune dysregulation in ITP is due to loss of tolerance by T-cells to self antigens (12). In addition, patients have an increase in anti-platelet T-cell reactivity where acute presentations were associated with increased IL-2 cytokine activity and in chronic patients, platelet HLA-DR expression correlated inversely with the platelet count (14). Transforming growth factor-B1, a pleiotropic cytokine contributes to T-cell activity and its levels inversely correlate with platelet counts (14). Enhanced expression of apoptotic genes result in increased numbers of auto reactive T-cell clones which enhance platelet destruction and suppress megakaryocyte production (15). In addition, it was recently recognised that inherited polymorphisms within platelet membrane glycoprotein genes also alter the antigenicity of platelet membranes and may regulate their expression levels and modulate their functional expression (16).
Immune thrombocytopenia is primarily a disease of low platelets, associated with mucocutaneous bleeding. The definition of primary ITP according to the International Working Group requires a patient to have a thrombocytopenia with a platelet count of < 100 X 10⁹/l with no obvious cause for the condition (1). ITP may occur as a primary or secondary condition. The distinction between the two is important because of their difference in presentation, pathogenesis, disease progression and management. Primary ITP is an autoimmune disorder of unknown aetiology associated with an isolated thrombocytopenia (1). It is a diagnosis of exclusion. It occurs classically in young-middle aged females in response to an unknown stimulus.

1.3 Secondary ITP

Secondary causes of ITP are well recognised and include all forms of ITP except primary ITP (1). In the past and in the Western world, it accounts for less than 10% of patients diagnosed with ITP (17). Secondary causes include autoimmune diseases (e.g. SLE, APLS, auto-immune hepatitis), viral infections (e.g. HIV, Epstein-Barr virus, Cytomegalovirus, Hepatitis, Varicella, Helicobacter pylori), parasitic infections (e.g. malaria), drugs (e.g. heparin, rifampicin, quinine, penicillin) as well as lymphoproliferative conditions (e.g. CLL and Lymphoma) (18).

The identification of the causes of secondary forms of the disease is important as the pathogenic mechanisms differ among these secondary causes and hence targeted treatment directed against the underlying disorder will result in improvement in the platelet counts.
1.3.1 ITP and SLE

Immune Thrombocytopenia, being a predominant autoimmune condition, plays a role in systemic auto-immune conditions. Thrombocytopenia occurs in about 25% of patients with SLE (19). Thrombocytopenia in SLE can be multifactorial with ITP being responsible for 15 - 20% percent of the patients (20). The mechanism of thrombocytopenia in SLE is due to auto-antibodies mediated against platelet glycoproteins, membrane substances as well as against CD40 ligands (21). The clinical presentation is worsened in the presence of other immune mediated conditions that occur in SLE such as vasculitis, thrombotic microangiopathy as well as marrow damage secondary to treatment (22). Reduced platelet counts are associated with a decreased probability of survival in SLE (19). Conversely, SLE develops in 2 - 5% of patients with ITP, where a positive anti-nuclear antibody may be the earliest and only indicator of disease at presentation (22).

1.3.2 ITP and APLS

Antiphospholipid syndrome (APLS) is a condition associated with clinical or radiological evidence of arterial and/or venous thrombosis, associated pregnancy morbidity as well as the presence of laboratory criteria, namely anticardiolipin antibodies, anti-B2- glycoprotein-1 antibodies or lupus anticoagulant. Immune thrombocytopenia occurs in about a third of patients with APLS (22) and 10 - 70% of patients with ITP have one or more antiphospholipid antibodies (23). However, the presence of antiphospholipid antibodies do not alter response to therapy in ITP (23). These patients do require increased platelet counts to prevent bleeding consequences, however, there is an associated increased risk of thrombosis (22). Mechanisms of immune thrombocytopenia in antiphospholipid syndrome include antibody binding to membrane phospholipids and phospholipid receptors (22).
1.3.3 ITP and HIV

Prior to the HIV pandemic, most patients presented with primary ITP with fewer patients presenting with secondary causes. Now in the era of the HIV pandemic, HIV has become the most important contributing cause to secondary ITP (unpublished local data).

Immune Thrombocytopenia has increased in incidence with the HIV pandemic. According to UNAIDS report 2009, 5.6 million people are living with HIV in South Africa (24). An early study in 1982, proposed that thrombocytopenia was seen in 40% of patients with HIV (25). ITP was initially described in 5 - 30% of ARV naive individuals (26). Thrombocytopenia was seen as the initial manifestation of HIV in 10% of cases (27). Its incidence is associated with increased frequency in individuals with advanced retroviral disease (28). The frequency of the disease is increased in patients with a lower CD4 count and increased viral loads of HIV (29). The mechanisms by which HIV contributes to ITP include increased platelet destruction secondary to auto antibodies (30), increased platelet clearance, reduced platelet production as well as platelet destruction secondary to reactive oxygen species (31). Reduced platelet production occurs as a result of cytopathic infection of megakaryocytes resulting in reduced platelet production (32). HIV is associated with enhanced platelet activation as well as the release of platelet derived factors such as CD 154 which has been shown to be directly involved in the development of ITP (22). Patients infected with Hepatitis as well as HIV had greater incidence and severity of thrombocytopenia (33).

Combination anti-retroviral therapy (cART) is an important component of the management plan in ITP (34). Prior to ant-retroviral therapy, the incidence of HIV and ITP was between 10 - 30% and as a result cART is shown to improve platelet counts as well as disease severity in ITP (35). Zidovudine was shown to improve platelet production (36). Thrombocytopenia in some individuals may persist despite cART and optimum therapy (37). This may occur as a result of concurrent hepatitis C.
infection, liver cirrhosis and HIV viral resistance (38). Interferon alpha was shown to be a safe and highly effective treatment in individuals with persistent thrombocytopenia resistant to Zidovudine (39). Splenectomy is still a potentially safe option in refractory ITP in HIV positive patients (40).

1.3.4 ITP and Helicobacter pylori

Helicobacter pylori infection, commonly associated with gastric pathology, has also been associated with ITP. The prevalence of helicobacter pylori infections in patients with ITP is equivalent to its presence in the general population of a region (41). Eradication of helicobacter pylori is associated with improvement in platelet counts particularly in countries with a high prevalence of helicobacter pylori infection (42). Platelet response to documented bacterial eradication ranges from 0 - 7% in two American series to 100% in one Japanese series (42). These differences in response may be attributed to prevalence differences, but can also be as a result of variations in helicobacter pylori genotypes. A study by Asahi et al (2008), observed that helicobacter pylori eradication lowered phagocytic capacity and elevated inhibitory FcγRIIB expression of monocytes in helicobacter pylori positive ITP patients (43).

1.3.5 ITP and Hepatitis C

Hepatitis C is a common chronic viral infection. It is associated with positive viral serology in 20% of patients with ITP (26). Mechanisms by which ITP occur may be explained by auto-antibody production, some molecular mimicry to membrane glycoproteins (33) as well as reduced production of thrombopoietin with advanced hepatitis infection. Corticosteroids should be avoided in patients with ITP and concurrent hepatitis infection as they will increase hepatitis viral loads which can subsequently reduce platelet counts and increase predisposition for liver dysfunction (44). Initial treatment includes antiviral therapy with interferon and ribavirin. However, it must be noted that thrombocytopenia is a recognised side effect of interferon (45). As a result, antiviral agents such as
interferon alpha in combination with newer modalities of treatment such as thrombopoietin mimetics (eltrombopag), have shown promise in the management of these patients (46). Patients with Hepatitis C can develop other causes of non-immune mediated thrombocytopenia such as portal hypertension with hypersplenism, reduced thrombopoetin production as a result of cirrhosis or bone marrow suppression. These causes need to be excluded.

1.3.6 ITP and Malignancy
The association between malignancy, particularly haematological malignancies and ITP has also been reported. In the multicenter GIMEMA study, it was shown that ITP has an increased incidence in patients with B-cell CLL. Approximately 15% of patients presented with auto-immune thrombocytopenia in advanced stages of disease (47). The incidence is increased in patients with advanced age as well as more severe disease (47). The pathogenesis of ITP in CLL is unknown but could be related to abnormal B-cell function as well as failure of regulatory T-cell function (48). ITP may occur at any time during the course of the disease but tends to occur at a median of thirteen months from the time of diagnosis of CLL (49). ITP can occur as a result of the CLL itself or could be related to the treatment of CLL, using drugs such as fludarabine (48). Management of ITP in CLL is less responsive to first line therapy (48) and these patients have a poorer prognosis (49).

Apart from CLL, ITP also occurs in HL as well as NHL. According to the British Lymphoma Investigation Registry, the incidence of ITP occurred at an approximate median time of 23 months (50). ITP occurred in HL with an incidence of 0.2 - 1% (51), while the incidence in NHL is 0.76% of patients with a male to female ratio of 1.75:1 (52). ITP is potentially life threatening in these patients and as a result, chemotherapy is the main modality of treatment (52).
The other secondary causes of ITP tend to occur less commonly. However, in general, it is important to identify secondary causes and treat them to facilitate optimal recovery in patients with secondary immune thrombocytopenia.

1.4 Clinical Presentation

The diagnosis of immune thrombocytopenia is suspected when a full blood count shows an isolated thrombocytopenia or the severity of the thrombocytopenia is out of keeping with the other cytopenias. Anaemia may occur if the patient has had substantial blood loss as a result of the thrombocytopenia or chronic iron deficiency (which may/may not be related to the thrombocytopenia in a young female).

Immune Thrombocytopenia is a diagnosis of exclusion, therefore other causes of thrombocytopenia such as DIC, TTP, aplastic anaemia, haematological malignancies, etc, need to be excluded. If secondary causes are suspected then a bone marrow aspirate and trephine biopsy should be performed. A bone marrow aspirate and trephine biopsy is indicated in patients over the age of 60 when the risk of malignancies, myelodysplastic syndromes and secondary causes become more frequent. It is also indicated if there is a poor response to therapy or patients are refractory to medical treatment (17). The measurement of platelet associated antibodies is unnecessary and not useful in differentiating immune versus non-immune ITP (53). In addition, a negative test cannot be used to exclude ITP (54).

The thrombocytopenia is responsible for the clinical presentation. Symptoms and signs can range from the individual being asymptomatic to mucocutaneous bleeding (petechiae, purpura, ecchymoses, epistaxis, menorrhagia, haematuria or gum bleeding) or less commonly to severe
complications such as internal bleeding (intracerebral haemorrhage or catastrophic gastrointestinal bleeding) (55). Major internal bleeding usually occurs in individuals with platelet counts < $30 \times 10^9$/l (17). Patients over the age of 60 or those with a previous history of intracerebral haemorrhage are at an increased risk for severe haemorrhage (56). In a meta-analysis of 17 studies, the age-adjusted risk of fatal haemorrhage at platelet counts persistently < $30 \times 10^9$/l was estimated to be 0.4%, 1.2%, and 13% per patient per year for those younger than 40, 40 to 60, and older than 60 years of age, respectively (57). Predicted 5-year mortality ranged from 2.2 - 47.8% (57).

Immune thrombocytopenia can be categorised into newly diagnosed ITP, persistent ITP and chronic ITP. Newly diagnosed ITP refers to the initial presentation within 3 months of the diagnosis, while persistent ITP refers to patients with ITP lasting between 3 to 12 months from diagnosis. Chronic ITP is the term used for patients with ITP that persists or if present for more than 12 months (1).

### 1.5 Epidemiology

The Intercontinental Cooperative ITP Study Group (ICIS) has estimated the incidence of ITP in children to be approximately 1.9 to 6.4 cases per 100,000 per year and for adults 3.3 per 100,000 per year (58). In a study of 120 patients at CHBAH presenting with thrombocytopenia, it was shown that primary ITP was responsible for 10 percent of the presentations of thrombocytopenia (59).

Age and gender also affect the predisposition to ITP and these demographics have undergone transformation over the years. In the mid 19th century, ITP was identified as a disease of children with no gender preferences. In a study done at CHBAH, chronic ITP particularly occurred in females, with a female to male ratio of 5.2:1 predominantly in the third decade of life (60). Some reports suggest an increasing incidence of ITP with increasing age (61). Gender disparity is reduced with
increasing age (62). In a population based cohort study of 245 patients in 2003, it was shown that absolute incidence was similar for both sexes except in the mid adult years (30-60), in which the disease has an increased incidence in females (63). The female to male ratio has been reported to be 1.7:1 (61). Genetic susceptibility to ITP is not well documented. Immune Thrombocytopenia is not a inheritable condition but its prevalence is increased in families with a genetic susceptibility to increased auto antibody production (64).

1.6 Management of ITP

The management of ITP has also changed over the decades and centuries. In 1775, Werlhof recognised that blood-letting (phlebotomy) which was a common choice of treatment in that century was contra-indicated in the condition that he had described (2). In the 18th century, the main treatment for Immune thrombocytopenia, known then as Maculosis Haemorrhagicus was good food, exercise and wine (9). A hallmark in the treatment of this condition was made in Prague in 1916 by a Polish student, Kaznelson, who discovered the role of splenectomy in improving platelet counts (3). Steroids became an important role player in the management of ITP from the 1950s (9). In the last 2 -3 decades, the management of ITP became a platform for the use of newer immunosuppressants, biological and immunomodulatory agents.

The primary aim in the management of ITP is to provide a safe platelet count to prevent major bleeding, rather than to normalise the platelet count. The response to treatment is based on platelet counts and can either be partial or complete. Partial response is defined as a platelet count > 30 X 10^9/l and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions greater than 7 days apart and the absence of bleeding (1). A complete response is defined as a platelet count > 100 X 10^9/l on two occasions greater than 7 days apart and the absence of
bleeding(1). No response is defined as a platelet count \( < 30 \times 10^9/l \) or less than the doubling of the baseline count (1).

Conventional modalities of treatment are aimed at reducing the platelet destruction, suppressing autoantibody production, regulating T-cell responses and treating the relevant underlying causes, where evident. Management of these patients should be initiated promptly, particularly with severe thrombocytopenia. The management includes resuscitation in the event of severe bleeding and supportive measures such as blood and platelet transfusions, where appropriate.

Platelet transfusions are utilised in patients who are actively bleeding with a very low platelet count at initial presentation. Platelet transfusions result in a temporary, small increase in platelet counts and contribute to the cessation of bleeding (65). The increase in platelet count post transfusion is related to the dose of platelets infused as well as the patient's body surface area. This is measured by a standardized equation known as the corrected platelet count increment (66). Platelet transfusion increases the post-transfusion platelet count by more than \( 20 \times 10^9/l \) in 42% of bleeding ITP patients and may reduce bleeding (67). The combination of a platelet transfusion together with intravenous immunoglobulins are associated with good responses such as resolution of bleeding, ability to safely undergo procedures and rapid restoration of adequate platelet counts with minimal side effects (68).

Treatment is rarely required if the platelet count is \( > 50 \times 10^9/l \), however if the individual has associated platelet dysfunction, trauma, surgery, lifestyle predispositions to bleeding, then, treatment should be considered for optimisation and to reduce the risk of catastrophic bleeding (69). Therapeutic agents are divided into those used in the emergency setting and those used to
maintain the increased platelet counts (70). Combination therapy is associated with a better response than single agent therapy (70).

1.6.1 Corticosteroids

Specific management includes first line treatment with corticosteroids (oral prednisone 1-2mg/kg or oral dexamethasone 40mg daily for 4 days or intravenous methylprednisolone 1g daily for three days), or other variations in doses mentioned in the literature (18, 71).

Corticosteroids are synthetic glucocorticoids. The use of steroids in ITP was initiated in the 1950's (4). The pathways by which steroids improve outcomes in ITP occur by a variety of mechanisms. The mechanisms by which corticosteroids improve platelet counts was elucidated in a study carried out on ITP-prone mice which indicated that platelet counts improved due to the suppression of reticulo-endothelial phagocytic function (72). Steroids also aided in reducing consumption of antibody coated platelets in the spleen and bone marrow (73). They also play a role in the suppression of antibody production and improvement of vascular integrity (72). They reduce bleeding by means of a direct effect on blood vessels (74). Steroids inhibit cytokine pathways, promote T-cell apoptosis and inhibit T-cell proliferation and signalling pathways (75).

Duration of treatment with corticosteroids is not definitive and is individualised. It should be continued until platelet response is sustained. Corticosteroid dependence refers to the need for ongoing or repeated doses of corticosteroids for a period of at least two months to maintain a platelet count of > 30 X 10^9/l and/or to avoid bleeding (1). Response rates vary from 50 to 90% depending on intensity and duration of therapy and remission is achieved in only 10 to 30% if therapy is tapered or stopped (17).
Intravenous high dose methylprednisolone has shown successful results with response rates of 80%, however this response is unsustained and requires maintenance therapy with oral prednisone. Hence it can be used in the acute phase for a rapid response in platelets thus facilitating a reduction in bleeding risk (76).

Long term use of corticosteroids, as may be necessary in certain patients, is associated with adverse effects. Side effects due to prolonged use of steroids include cushingoid symptoms and signs, weight gain, fluid retention, osteoporosis, mood changes, skin changes, electrolyte abnormalities and increased risk of infections. They have being associated with an increased predilection to the development of metabolic diseases such as hypertension, diabetes as well as hepatic steatosis. The most serious side effect is an adrenal crisis which occurs if steroids are withdrawn abruptly without tapering the dose.

Single agent use is associated with response rates of approximately 30%, therefore steroids should be considered in conjunction with other agents (70). In some centres, intravenous immunoglobulins are used together with corticosteroids in patients as an emergency treatment, in acute non-responders or to facilitate optimisation in pregnant patients.

1.6.2 Intravenous Immunoglobulin

Intravenous immunoglobulin is a preparation of pooled, human polyclonal IgG immunoglobulins extracted from the plasma of thousands of healthy donors. It is associated with the most rapid onset of action when compared to the other agents. Its key efficacy was demonstrated in 1979, in a children’s hospital in Berne, Switzerland in a 12 year old boy with severe haemorrhagic chronic ITP,
who as a result of long-term steroids and vincristine became hypogammaglobulinaemic. In an attempt to correct the hypogammaglobulinaemia, intravenous immunoglobulins were given which showed a co- incidental increase in the platelet count (9). Intravenous immunoglobulins have shown initial responses comparable to corticosteroids with a shorter time to response (77). Its use is favourable and highly effective in the acute stage in patients at high risk of bleeding as 85% of patients achieve a safe but transient platelet count of >50 X 10^9/l (78). It is used in conjunction with corticosteroids but is also recommended in cases unresponsive or poorly responsive to steroids. It has positive outcomes in younger patients as well as female patients (79). Its use increases platelet numbers but the mechanisms by which this occurs has remained unclear. Mouse models with ITP have shown that intravenous immunoglobulins may exert immunomodulatory effects reducing phagocytosis of platelets by blockade of macrophage Fc receptors (80). They also contain antiidiotypic antibodies that neutralise specific auto-antibodies and reduce antibody production against platelets (81). Kessel et al (2007), recently discovered that IVIG increases T regulatory cells and their suppressive functions (82). Its use in conjunction with steroids reduce the risks of transfusion reactions as well as aseptic meningitis and enhances the response to the intravenous immunoglobulins. Disadvantages of this treatment include its short half life of about three weeks, its high cost and being a blood product, its risk of transmission of infective diseases (83).

Second line treatment options include splenectomy, immunosuppressives such as Azathioprine, Danazol, Vincristine, Rituximab (anti – CD20 monoclonal antibody) and anti-D immunoglobulin.

1.6.3 Azathioprine
Azathioprine is a purine analogue immunosuppressive drug. Azathioprine acts at the level of the T-cell to prevent the production of auto-reactive T cell clones. Azathioprine showed a response in about 40-60% of patients refractory to corticosteroids (84). Median time to achieve a response is
approximately 4 months and relapse may occur once the dose is tapered or reduced (84). Side effects include leucopenia as well as hepatotoxicity. Azathioprine may be used as a steroid sparing agent.

1.6.4 Cyclosporin A

Cyclosporin A is an immunosuppressant drug derived from a fungus. It acts directly on T-cells (85). Cyclosporin A was associated with good clinical outcomes in more than 80% of patients resistant to first–line therapy, with 42% achieving a complete response (86). Side effects associated with cyclosporine use includes renal insufficiency, hypertension, gout, gastro–intestinal disturbances, hirsutism, gum hypertrophy and neuropathy (86).

1.6.5 Cyclphosphamide

Cyclophosphamide is a nitrogenous mustard alkylating agent with immunomodulatory effects. It can be given intravenously or orally. It offers an additional means of therapy in patients who fail splenectomy (87). Responses typically require 1 to 3 months of treatment (17) but a response may be seen in 2-10 weeks and is dependant on duration of therapy as well as duration of disease (88). A duration of disease of less than one year is associated with a better response to therapy (88). It has however, been used with caution as there are reports of the development of acute leukaemias in patients with ITP treated with cyclophosphamide (89). Side effects include immunosuppression, haemorrhagic cystitis, infertility, carcinogenicity and teratogenicity.
1.6.6 Danazol

Danazol is a derivative of the synthetic steroid ethisterone which is a modified testosterone which were initially used in the treatment of endometriosis. Its uses in haematological disorders was later discovered. In a small trial of patients with chronic ITP, it was found that the platelet counts and bleeding manifestations improved in most of the patients. Danazol induces a response within three months (90). The platelet factor 3 availability and circulating immune complexes level normalised in the majority of patients (91). Its mechanism of action is not fully understood, however it is thought that it may play a role in the inhibition of immunological pathways involved in platelet destruction. Response rates of 60 - 67% have been shown (71). Response to Danazol is influenced by the gender, age as well as presence or absence of a spleen. Response is best seen with advancing age and in female nonsplenectomized patients (90). Side effects include masculinization due to its androgenic effects as well as hepatotoxicity and skin rashes. The longer the duration of treatment with Danazol, the better the responses. Relapse is more frequent in individuals that are treated with Danazol which is discontinued within 6 months (90).

1.6.7 Dapsone

Dapsone is derived from the anti-bacterial prontosil red. Dapsone may delay splenectomy for up to 32 months in patients who have not responded to first-line corticosteroid therapy, however, splenectomized patients have a lower response rate (92). Side effects include haemolysis, hepatotoxicity, rashes and hypersensitivity reactions. Caution should be observed in patients with G6PD deficiency as it predisposes to haemolysis (93).
1.6.8 Mycophenolate Mofetil

Mycophenolate mofetil is an immunosuppressive drug. It is a reversible inhibitor of inosine monophosphate dehydrogenase in the synthesis of guanine which plays a role in the development of T-cells and B-cells. MMF should be used in combination with other agents as individual therapy with MMF does not appear to be highly effective. Response rates were seen in 39% of patients, particularly those with a shorter duration of illness, but the increase in platelet counts were unsustained (94). Side effects include myelosuppression, electrolyte abnormalities, hyperglycaemia and an increased risk of developing neoplasia.

1.6.9 Vincristine

Vincristine is a vinca alkaloid from the periwinkle plant and has a role in cancer chemotherapy. It inhibits microtubule assembly thus inhibiting mitosis in metaphase. It is cytotoxic to macrophages, decreasing phagocytosis thus reducing platelet clearance (95). The thrombocytotic effect can also be due to the increased megakaryopoetic endomitosis thus increasing platelet counts (95). The frequency of responses is 60% (96). Limitations of its use include its side effect profile, particularly the neurotoxicity (97). As a result, it is shown that vincristine is advantageous in the treatment of refractory ITP.

1.6.10 Rituximab

Rituximab is a chimeric monoclonal antibody against CD 20 which is found on all mature B cells. It results in B cell destruction. It has been shown to produce effective results in improving platelet counts (98). Possible mechanisms of cell lysis include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and induction of apoptosis. Hence Rituximab is highly effective for in vivo depletion of B cells thus eliminating auto reactive B-cell clones (99).
In patients in whom Rituximab has been used, 62% of patients responded with 46% achieving a complete response (100). Response times vary from 1-2 weeks to 6 - 8 weeks (101) with a median duration to response of 5,5 weeks. The response is maintained from 2 months in some patients to as long as 5 years or longer in 15 - 20% of patients but the median duration of a response is 10,5 months (100). Due to its favourable effects, it should be considered as part of management in refractory ITP (102).

Side effects of Rituximab are mostly related to the first infusion (fever, chills, hypotension, bronchospasm, etc). Profound and prolonged peripheral B-cell depletion is universal, but serious infection other than reactivation of hepatitis B in chronic carriers is rare and generally seen only in the context of additional immunosuppression (17). Treatment with Rituximab is also associated with the risk of progressive multifocal leukoencephalopathy (103).

1.6.11 Anti-D Immunoglobulin

Anti-D immunoglobulin consists of IgG against the RhD antigen on red blood cells. It is prepared from the plasma of RhD negative individuals immunized against the D antigen. It was first introduced by Salama et al in 1984 as part of the treatment of ITP (104). Anti-D immunoglobulin antibody coated red blood cells block sequestration of antibody coated platelets by the reticulo-endothelial system by competitive inhibition, thereby preventing phagocytosis of platelets and thus improving platelet counts (105). It is considered to be effective with a positive increase in 70% of RhD positive, non-splenectomized patients and the effects last for greater than 21 days in 50% of responders (106). Patients with ITP after splenectomy have minimal or no response to intravenous anti-D immunoglobulin (106). Side effects include intravascular haemolysis, therefore caution is advised in patients with anaemia secondary to bleeding (107). More recently there has been difficulty in obtaining anti-D for therapeutic uses in ITP.
While some patients with ITP may be refractory to all treatment, failure to respond to 3-4 drug regimes may warrant further investigation of another diagnosis other than ITP (70). If ITP remains the diagnosis, splenectomy should be considered or the much newer modalities of treatment.

1.6.12 Splenectomy

Splenectomy was introduced by Kaznelson as a modality of treatment in the early 19th century (3) and has remained the ultimate treatment of choice for refractory ITP. The spleen plays a crucial role in the haematopoietic as well as immune systems. It plays an important role as one of the largest filters of blood, maintaining the integrity of red blood cells and is responsible for pooling of about one third of normal platelets. The spleen also contains lymphoid tissue and is thus able to initiate adaptive immune responses especially immune responses to encapsulated organisms. The spleen also serves as a site of production of antibodies directed against platelets and hence its role in ITP (108). The mechanism by which splenectomy improves platelet counts is by removing the auto antibodies responsible for platelet destruction, reducing the platelet pooling in the spleen as well as improving platelet survival times (73).

Splenectomy has long been considered the gold standard of therapy for patients who require treatment for chronic ITP. Splenectomy is recommended in individuals who do not have a sustained response in platelet counts and those who cannot tolerate first and second line therapy as a result of side effects, or inefficacy (17). The initial response to splenectomy resulted in a stable response in 60 - 70% of patients (109). 85% of patients attain a haemostatic response after splenectomy and two thirds achieve a durable response (109). Relapse has been reported in 15 - 25% of patients within 10 years (110). It can be performed as an open or laparoscopic surgical procedure. Mortality rates for open and laparoscopic splenectomy are 1.0% and 0.2%, respectively (109). The decision to perform a
splenectomy should not be hastened within the first 6 months unless strong indications are present, as 10% of patients with ITP may undergo spontaneous remission (111).

Time to splenectomy indicates the time (usually in months) between the date of diagnosis and the date of splenectomy. Time to splenectomy failure indicates months between the date of splenectomy and a decrease in the platelet count to < $30 \times 10^9/l$ (112).

Post splenectomy thrombocytosis has been associated with long term remission. Age less than 40 years is seen as a positive predictor for long term response to splenectomy (113). Patients refractory to multiple forms of treatment as well as those with secondary ITP have poorer outcomes to splenectomy (109). Post splenectomy patients are at an added lifelong risk for sepsis and opportunistic infections particularly secondary to encapsulated organisms such as pneumococcal, meningococcal as well as haemophilus sepsis (114). Other complications of splenectomy include bleeding as a result of the surgical procedure as well as a predisposition to thromboembolic events.

Patients that do not respond to splenectomy are at greatest risk of mortality, but in some of these individuals, spontaneous remissions do occur (115). Splenectomy failure could be due to the presence of an accessory spleen. This can be suspected if the blood smear does not show typical post splenectomy features such as Howell Jolly bodies and less frequently Heinz bodies and leucocytosis. This can be confirmed by an MRI scan or technetium scan.

Patients are said to have refractory chronic ITP if they do not respond to splenectomy (platelet count after splenectomy either did not reach $30 \times 10^9/l$ or, after an initial increase, fell below $30 \times 10^9/l$)
and require additional therapy for symptomatic thrombocytopenia (112). ITP in adults cannot be said to be refractory unless a splenectomy has been performed (1). The main goal of therapy in refractory ITP is to provide a safe platelet count in order to prevent catastrophic haemorrhages with the least drug toxicity (116).

In a study carried out by McMillan and Durette in 2004, 75% of patients with refractory ITP eventually achieved remission, although it took a long duration to attain this response, while the other 25% who did not achieve remission suffered significant morbidity and mortality (112).

1.6.13 Thrombopoietin Mimetics

Newer modalities of treatment such as thrombopoietin receptor agonists are becoming available for refractory cases (3). Thrombopoietin analogues were initially purified in 1994 and in 2008, drugs that mimic the action of thrombopoietin were first discovered. Romiplostim is a thrombopoietin mimic that activates the thrombopoietin receptor directly while eltrombopag is a thrombopoietin mimic that activates the receptor by binding to the trans-membrane domain (117). They induce megakaryocyte and platelet production via JAK-2 and STAT-5 kinase pathways (118). Thrombopoietin receptor agonists should be considered for patients at risk of bleeding who relapse post splenectomy or individuals who have a contra-indication to splenectomy or who are refractory to the above treatment options (18). Side effects include rebound thrombocytopenia, other cytopenias secondary to reticulin fibrosis, exacerbation of thrombotic tendencies, hepatotoxicity, and cataracts (119).

An overall platelet response rate was observed in 79% of patients on romiplostim (120). These responses were sustained for up to 4 years on continuous therapy, with most patients able to
decrease or discontinue concurrent corticosteroid therapy (120). 59% of eltrombopag-treated patients achieved a platelet response (121). These agents, however do not induce cure and require continuous use.

1.6.14 Novel therapies

Novel therapies such as the orally available Syk-kinase inhibitor R406 are effective in increasing and maintaining platelet counts in 50% of patients with refractory ITP (122). It was shown that this agent blocks signalling from antibody sensitised pathways (122). Side effects include gastro intestinal complications, including liver derangements. More research is needed with this agent which could contribute to the management of ITP in the future.

Other treatment options for patients with refractory ITP, i.e. patients that have failed splenectomy include, Campath-1H, combination chemotherapy or stem cell transplantation. However, accessory splenic tissue should be sought in patients who relapse post splenectomy. Campath-1H is associated with severe immunosuppression and a high risk of infections. Haematopoetic stem cell transplantation should be used as a last resort in refractory patients with ITP who have persistent bleeding complications.

1.7 Outcomes

While ITP can usually be controlled as a chronic disease, it can be fatal in a small percentage of patients. Mortality rates range from 2% in patients under the age of 40 to 48% in older patients (57). Most fatal accounts of bleeding have been reported in adult patients with platelet counts < 30 × 10^9/l (57). The mortality of patients with ITP is mainly due to fatal intracranial haemorrhage. The risk
increases with age and in patients refractory to therapy (4). Spontaneous remission occurs in more than 80% of cases in children but is less common in adults.

Future therapeutic options for the management of ITP may include other anti-CD 20 ligands, Syk inhibitors or FcRn blockade may assist with autoimmunity and reduce levels of autoantibody. All these agents are still being investigated.

1.8 Conclusion

Immune Thrombocytopenia is a disease that has transcended through the ages. Its pathogenesis and newer immunological avenues are still to be elucidated. Newer studies exploring the pathogenesis of the disease will add to the already evolving future management of ITP and thus facilitate improved outcomes.

1.9 Objectives of the study

• To assess:
  o Demographics
  o Clinical presentation
  o Causes of ITP
  o Management of ITP

• Compare presentation and outcomes between HIV positive and HIV negative subjects

• To describe the impact of splenectomy in ITP

• To describe the impact of different treatment modalities in the management of patients with ITP
CHAPTER 2: Patients and Methods

2.1 Study Design

A single centre retrospective review of adult patients seen at the Clinical Haematology Unit, Department of Medicine, Chris Hani Baragwanath Academic Hospital from the period 01/01/1987 to 31/12/2011.

2.2 Sample Population

The sample population identified by the Clinical Haematology Unit included approximately 300 patients but only 231 detailed patient records were found in both the Clinical Haematology Unit and the Chris Hani Baragwanath Academic Hospital record section.

2.2.1 Inclusion criteria

- All adult patients over 18 years of age with a diagnosis of ITP
- Secondary causes of ITP were included

2.2.2 Exclusion criteria

- All patients with non-immune thrombocytopenia
2.3 Data Collection

Retrospective data was collected on all patients that were diagnosed with ITP from 01/01/1987 – 31/12/2011. Permission was obtained from the Clinical Haematology Unit, Department of Medicine and CHBAH authorities. The information was obtained from files kept at the Clinical Haematology Unit as well as the CHBAH records section. Data collection included a case record analysis using a prepared data collection sheet (see appendix A).

The following information was obtained:

- Demographics: age, gender

- Platelet count at diagnosis: ITP was diagnosed when the full blood count demonstrated a thrombocytopenia with the exclusion of non-immune causes of thrombocytopenia such as microangiopathic haemolytic anaemias, aplastic anaemia, haematological malignancies or bone marrow infiltration.

- Type of ITP: Primary ITP was diagnosed if secondary causes such as SLE, pregnancy, drugs, HIV, Hepatitis B and C (based on serology), malaria (based on malaria antigen positivity or smear positivity for plasmodium falciparum), other infections and lymphoproliferative disorders (based on histology or laboratory confirmation) were excluded.

- Clinical presentation based on documented history and examination.

- HIV status based on rapid testing with confirmation using ELISA testing. The CD4 count at diagnosis in retroviral positive patients and whether the patient was on anti-retroviral treatment was also documented.

- Management of ITP including drugs, number of treatments, doses and duration of treatment was obtained from the haematology files.

- Information concerning splenectomy including time to splenectomy, demographics, type of splenectomy, vaccination, antibiotic prophylaxis as well as complications were obtained from the haematology files. No surgical notes were studied.

- Outcomes were defined as follows:
Partial response is defined as a platelet count of > 30 X 10^9/l and a greater than 2-fold increase in platelet count from baseline and the absence of bleeding (1).

A complete response is defined as a platelet count of > 100 X 10^9/l on two occasions greater than 7 days apart and the absence of bleeding (1).

No response is defined as a platelet count < 30 X 10^9/l or less than the doubling of the baseline count (1).

Death as a consequence of ITP or complication of treatment.

Lost to follow up occurred if no further information could be obtained.

The patients’ names and personal details were kept confidential. The file numbers were given a numerical coding system in order to maintain confidentiality. The information on the data collection sheet was then captured onto the REDCap research database. REDCap is a research database that has been approved by the University of the Witwatersrand, that allows efficient capture of data electronically utilising an electronic replica of the data collection sheet and assists with instantaneous exportation of information to a statistical program of choice. It is a web based program and allows for easy access if internet is available, however it is secure as it is protected by a personalised security password for which only the researcher has access. It facilitates confidentially by utilising the password system but also by creating a numerical code for each data collection sheet.

2.4 Data Analysis

Once the data was collected on the REDCap system, verification of the data was done utilising software that was provided within the REDCap system. The collected data, once verified, was exported to Microsoft Excel for analysis. Statistical analysis was performed within the Microsoft Excel program. Descriptive statistical analysis (mean, median) was utilised for demographic statistics and the degree of spread using standard deviations or range for continuous variables. Mean and
standard deviations were employed for parametric data. Median with interquartile ranges were utilised for non-parametric data. Frequency distribution tables were employed for categorical data as well as pie and bar charts. Graph pad instat was utilised for further statistical analysis.

Bivariate analysis for pairs of categorical data was done, employing contingency tables with the Fisher’s Exact method or chi-square method when appropriate. Unpaired, non parametric data was analysed using the Mann-Whitney test whilst paired parametric data was analysed with the paired t-test. Statistical significance was ascertained at a p value of <0.05. A statistician was consulted to verify the methods used.

2.5 Ethics

Ethics approval was granted unconditionally by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (Clearance Certificate number: M120412). No informed consent was needed from the patients due to the retrospective nature of the analysis.
CHAPTER 3: Results

3.1 Demographics of patients with ITP

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<th></th>
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<th>Primary</th>
<th>Secondary</th>
<th>Unknown</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N=243</td>
<td>N=118</td>
<td>N=121</td>
<td>N=4</td>
</tr>
<tr>
<td>AGE (years)</td>
<td>32(18-90)</td>
<td>31(18-64)</td>
<td>33(18-90)</td>
<td>38(24-55)</td>
</tr>
<tr>
<td>(median±IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENDER - Male</td>
<td>47(19%)</td>
<td>23(19.5%)</td>
<td>23(19%)</td>
<td>1(25%)</td>
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<tr>
<td></td>
<td>196(81%)</td>
<td>95(80.5%)</td>
<td>94(81%)</td>
<td>3(75%)</td>
</tr>
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<td>F:M RATIO</td>
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<td>4.1:1</td>
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<td>PLATELET COUNT ( X 10^9/l) (median±IQR)</td>
<td>10 (0-233)</td>
<td>9(1-233)</td>
<td>11(0-179)</td>
<td>26(4-42)</td>
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<tr>
<td>TIME TO PLATELETS &gt; 100 X 10^9/l (days) (median±IQR)</td>
<td>14(3-545)</td>
<td>13(3-370)</td>
<td>18(4-230)</td>
<td>20(7-37)</td>
</tr>
</tbody>
</table>

Table 1: Demographics of patients with ITP

In the period under review, a total of 254 records were reviewed from the Clinical Hematology Unit, Department of Medicine, Chris Hani Baragwanath Academic Hospital. 11 records were excluded from data analysis as the age was <18 years. A total of 243 patients were analyzed for the period January 1987 to December 2011 (25 years).
243 patients were analyzed of which 47 (19%) were male and 196 (81%) were female (see figure 1). The female to male ratio was 4.2:1. Both primary and secondary ITP had a female gender predominance of 80.5% and 81% respectively (see figures 2 and 3 respectively). The median age of presentation for the whole group was 32 years (range: 18 – 90 years).

As demonstrated in figure 4, primary ITP accounts for 48% of presentations to hospital. Secondary causes for ITP were identified in 50% of patients. 2 % of the cohort could not be identified as primary or secondary due to a lack of information on analysis of the patient’s records and hence were referred to as unknown.

The median platelet count at presentation for all patients with ITP was 10 X 10^9/l. In primary and secondary ITP, the platelet counts at presentation were similarly low at 9 X 10^9/l and 11 X 10^9/l respectively.

The duration for platelet recovery independent of other factors and treatment options showed that the median days to platelet recovery > 100 X 10^9/l was 14 days. Primary ITP showed a quicker recovery of platelets to > 100 X 10^9/l compared to secondary ITP by 5 days (i.e. 13 versus 18 days).
Figure 1: Gender distribution in ITP

Figure 2: Gender distribution in Primary ITP

Figure 3: Gender distribution in Secondary ITP
3.2. Timeline of ITP at Chris Hani Baragwanath Academic Hospital

The prevalence of primary compared to secondary ITP have shown a difference from 1987 to 2011. The 1987-1992 group showed a substantially higher frequency of primary ITP compared to the later
years. The subsequent increase from 34 to 57.5% in secondary ITP is seen when comparing the 1987-1992 group to the 2005-2011 group with a trend close to statistical significance (p value =0.0676).

### 3.3 Secondary causes of ITP

![Secondary Causes of ITP](image)

Figure 6: Secondary causes of ITP

A secondary cause of ITP was established in 121 patients (50%). The leading causes were an ANA positivity and HIV with 42.1% and 40% respectively. Out of the 51 patients that displayed ANA positivity, 18 patients (35%) were documented to have SLE. The ANA positive group in this review were not analyzed further (with regard to this study), for fulfillment of criteria for SLE. Out of the 4 patients with confirmed antiphospholipid syndrome, 3 had concurrent ANA positivity and were followed up at Rheumatology with the presumptive diagnosis of SLE/APLS overlap. Of the 121 patients analysed, 23 patients were identified to have more than one secondary cause for ITP.
The third most common cause of secondary ITP was pregnancy associated ITP, which accounted for 16% of the secondary causes of ITP. 8 individuals were noted to have drug induced ITP, of which NSAIDS accounted for 37.5% of the drug induced causes. Other drugs that were identified as the cause of secondary ITP included thiazide diuretics (HCTZ), penicillin, bactrim and ciprofloxacin.

Infective causes other than HIV were noted in very small proportions. These were confirmed by serological testing. These included hepatitis B, hepatitis C and malaria which accounted for 0.82% of patients each. Non specific viral infections were responsible for two patients (1.65%) and this diagnosis was suspected on clinical presentation.

A lymphoproliferative disorder was diagnosed in one patient.

Other causes include Evans syndrome, mixed connective tissue disease, scleroderma, bilharzia, alcohol and herbal intoxication with a frequency of 0.82% each.
3.4 Clinical presentation at diagnosis

The sites of bleeding identified on history were evaluated. Each patient may have had more than one site identified at diagnosis. Figure 7 and 8 summarize the sites of bleeding based on history and clinical examination. Hundred and sixteen (48%) and 107 (44%) patients respectively out of the total of 243 patients presented with skin bleeding and epistaxis. Intracerebral bleeds accounted for 2% of all the clinical presentations.
### Clinical Examination

<table>
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<th>Frequency</th>
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</tr>
<tr>
<td>Haematuria</td>
<td>4</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>4</td>
</tr>
<tr>
<td>Hepatomegaly</td>
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</tr>
<tr>
<td>ICB</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
<tr>
<td>Subconjunctival</td>
<td>10</td>
</tr>
<tr>
<td>Not stated</td>
<td>11</td>
</tr>
<tr>
<td>GIT</td>
<td>15</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>26</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>33</td>
</tr>
<tr>
<td>Gum bleeds</td>
<td>54</td>
</tr>
<tr>
<td>Haem bullae</td>
<td>55</td>
</tr>
<tr>
<td>Pallor</td>
<td>95</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>97</td>
</tr>
<tr>
<td>Skin bleeds</td>
<td>195</td>
</tr>
</tbody>
</table>

Figure 8: Frequency of clinical features found on examination (ICB = intracerebral bleed, GIT = gastrointestinal tract, Haem bullae = haemorrhagic bullae)

Figure 8 shows the features that were identified on clinical examination. Most patients had more than one site of bleeding detected clinically. Skin bleeding occurred in 195 patients (80%). Other common associated clinical features include epistaxis (39%), pallor (39%), haemorrhagic bullae (22%) and gum bleeding (22%). Thirty three patients (13.5%) were also identified as having lymphadenopathy and 8 patients (3%) had associated intracranial bleeding at the time of presentation. In 11 patients, the clinical features were not adequately documented in the patient’s records.
Lymphadenopathy  |  Splenomegaly |  Hepatomegaly |
--- | --- | ---
Primary ITP (N=118) | 9 | 1 | 1
Secondary ITP (N=121) | 25 | 3 | 4

Table 2: Frequency of lymphadenopathy, splenomegaly and hepatomegaly

The table above indicates that 7.6% of patients with primary ITP had associated lymphadenopathy, while only 0.8% of patients with primary ITP were found to have splenomegaly and hepatomegaly. Patients with secondary ITP were more likely to have lymphadenopathy, splenomegaly or hepatomegaly attributable to their underlying aetiologies.

3.5 HIV and ITP

3.5.1 Demographics of HIV positive patients with ITP

<table>
<thead>
<tr>
<th></th>
<th>HIV +</th>
<th>HIV -</th>
<th>HIV status unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=48</td>
<td>N=171</td>
<td>N=24</td>
</tr>
<tr>
<td>AGE (years)</td>
<td>33 (18-74)</td>
<td>31 (18-90)</td>
<td>33 (18-64)</td>
</tr>
<tr>
<td>GENDER* - Male</td>
<td>12 (24%)</td>
<td>29 (17%)</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>Female</td>
<td>36 (76%)</td>
<td>142 (84%)</td>
<td>17 (71%)</td>
</tr>
<tr>
<td>PLATELET COUNT</td>
<td>12 (1-233)</td>
<td>12 (0-179)</td>
<td>11 (4-40)</td>
</tr>
<tr>
<td>(median±IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIME TO PLATELETS &gt; 100 X 10^9/l (days)**</td>
<td>31 (3-545)</td>
<td>13 (3-379)</td>
<td>11 (3-153)</td>
</tr>
<tr>
<td>(median±IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Demographics of patients with ITP and HIV status

*p value=0.2139 (Fisher analysis)

**p value=0.0115 (Mann-Whitney)
The demographics of patients with HIV were evaluated and are presented in Table 3. Twenty percent of patients were noted to be HIV positive. The HIV status of 24 patients was unknown. Females accounted for 76% of patients with ITP and HIV, compared to 84% in the HIV negative group. The female to male ratio is 3:1. There was no statistical significance in gender amongst HIV positive and HIV negative patients.

The platelet count at presentation was similar in both groups, with a median platelet count at presentation of $10 \times 10^9$/l of blood in the HIV positive group.

The time to platelet recovery of $>100 \times 10^9$/l was also measured. HIV positive individuals with ITP took on average 18 days longer to achieve platelet counts of $>100 \times 10^9$/l when compared with their HIV negative counterparts. This was statistically significant with a p value of 0.0115 (see Table 3).

### 3.5.2 Recovery of platelets related to HIV status

<table>
<thead>
<tr>
<th></th>
<th>HIV Positive (N=48)</th>
<th>HIV Negative (N=171)</th>
<th>HIV unknown (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>34 (71%)</td>
<td>152 (89%)</td>
<td>18 (75%)</td>
</tr>
<tr>
<td>NO</td>
<td>12 (25%)</td>
<td>10 (6%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>2 (4%)</td>
<td>9 (5%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

Table 4: Recovery of platelets $>100 \times 10^9$/l in HIV positive and HIV negative groups

p value =0.0004 (using Fisher analysis)

Table 4 shows the number of patients that achieved a complete response (with platelet recovery of $> 100 \times 10^9$/l). Eighty nine percent of HIV negative patients achieved a complete response as
compared to 34 (71%) of the HIV positive patients. This was statistically significantly different with a p value of 0.0004.

### 3.5.3 ITP in HIV positive patients and cART status

<table>
<thead>
<tr>
<th></th>
<th>All HIV Positive</th>
<th>On cART</th>
<th>Not on cART</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>48</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td><strong>CD4 COUNTS</strong> (median±IQR)</td>
<td>145(2-1427)</td>
<td>215(74-820)</td>
<td>147(2-800)</td>
</tr>
<tr>
<td><strong>RECOVERY OF PLATELETS &gt; 100 X 10⁹/l</strong>*</td>
<td>Yes</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>TIME TO PLATELETS &gt; 100 X 10⁹/l (days)</strong></td>
<td>Median</td>
<td>31(3-545)</td>
<td>33(7-545)</td>
</tr>
</tbody>
</table>

Table 5: HIV positive patients on cART and relationship with CD4 counts, recovery of platelets >100 X 10⁹/l and time to platelets >100 X 10⁹/l

* p value = 1.0000 (Fisher analysis)

** p value=0.0889 (Mann-Whitney)

The cART status of patients with ITP was also evaluated. 16 (33%) patients were noted to be on cART at the time of diagnosis, whilst 23 (48%) of patients were not on cART at the time of diagnosis. The cART status of the remaining 18% of patients was not known. The median CD4 count of patients on cART at time of diagnosis was 215/ul. This was substantially higher when compared to patients not on cART with a median of 147/ul. However, there was no statistical difference (p value = 0.0889) when assessing time to recovery of platelets > 100X 10⁹/l in patients who were receiving or not receiving cART.
The timeframe for platelet recovery to > 100 X 10^9/l of blood was also evaluated. The median time for patients on cART at time of diagnosis was 33 days compared to 18 days for patients not on cART at the time of diagnosis.

### 3.5.4 Outcomes of HIV positive versus HIV negative patients

<table>
<thead>
<tr>
<th></th>
<th>HIV Positive (N=48)</th>
<th>HIV Negative (N=171)</th>
<th>HIV Unknown (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPLETE</td>
<td>26 (54%)</td>
<td>109 (64%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td>PARTIAL ON TX</td>
<td>8 (17%)</td>
<td>16 (9%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>DEATH</td>
<td>2 (4%)</td>
<td>7 (4%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>LOST TO FOLLOW UP</td>
<td>12 (25%)</td>
<td>39 (23%)</td>
<td>4 (17%)</td>
</tr>
</tbody>
</table>

Table 6: Final outcomes in HIV positive and HIV negative patients (TX = treatment)

(Chi =2.46 df=3; p value=0.48)

The final outcomes in HIV positive patients versus HIV negative patients was assessed. Table 6 demonstrates the 4 outcomes observed which included complete response, partial response, death and lost to follow up. Overall, 22% of patients were lost to follow up and 61.3% of patients achieved complete response. Of the HIV positive patients, 54% achieved complete response, while 64% of HIV negative patients showed a complete response to treatment. There were however no statistically significant differences in the outcomes of HIV positive versus HIV negative patients.

Complete response was higher in the HIV negative group while partial response was higher in the HIV positive group (although this was not statistically significant). Mortality in both the groups was the same.
3.6 Splenectomy and ITP

![Pie chart showing splenectomy performed of total number of patients (N=243)](figure9)

Figure 9: Splenectomy performed of total number of patients

3.6.1 Splenectomies performed according to timeframes

A review of all splenectomies done for patients with ITP were evaluated. Forty five patients (19%) had a splenectomy performed during the years 1987-2011 (see figure 9).

![Bar chart showing splenectomy performed according to years](figure10)

Figure 10: Splenectomy performed according to years

Splenectomies were evaluated according to timeframes (see figure 10). Nineteen percent of the total number of patients underwent a splenectomy. Twenty five percent of patients diagnosed with
ITP during the period 1987-1992 had a splenectomy as opposed to 14% of patients during the period 2006 - 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Days to Splenectomy (median±IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987-1992</td>
<td>167(37-2667)</td>
</tr>
<tr>
<td>1993-1998</td>
<td>210(10-1829)</td>
</tr>
<tr>
<td>1999-2005</td>
<td>223(7-2982)</td>
</tr>
<tr>
<td>2006-2011</td>
<td>220(12-1250)</td>
</tr>
</tbody>
</table>

Table 7: Median days to splenectomy from diagnosis of ITP according to year breakdown

The same timeframes were used as in figure 10 and the median days to splenectomy were evaluated. The 1987-1992 period had a median duration of 167 days to splenectomy from diagnosis. The longest median duration to splenectomy occurred in the period of 1999-2005 with a median time of 223 days. Of note, the shortest duration of splenectomy from time of diagnosis was 7 days. In each timeframe the longest wait were all greater than 1250 days with one individual having a splenectomy after 2982 days.
### 3.6.2 Summary of patients that underwent splenectomy

<table>
<thead>
<tr>
<th>Age (median±IQR)</th>
<th>29(18-54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender - Male</td>
<td>10(22%)</td>
</tr>
<tr>
<td>Female</td>
<td>35(78%)</td>
</tr>
<tr>
<td>Type of ITP – Primary</td>
<td>31(69%)</td>
</tr>
<tr>
<td>Secondary</td>
<td>14(31%)</td>
</tr>
<tr>
<td>HIV status – Positive</td>
<td>3(7%)</td>
</tr>
<tr>
<td>Negative</td>
<td>35(78%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7(15%)</td>
</tr>
<tr>
<td>Time to Splenectomy (days) (median±IQR)</td>
<td>201(7-3650)</td>
</tr>
<tr>
<td>Type of Splenectomy – Open</td>
<td>43(96%)</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>2(4%)</td>
</tr>
<tr>
<td>Vaccination – Yes</td>
<td>45 (100%)</td>
</tr>
<tr>
<td>Antibiotics after splenectomy – Yes</td>
<td>45(100%)</td>
</tr>
<tr>
<td>Complications after splenectomy – Yes</td>
<td>9(20%)</td>
</tr>
<tr>
<td>No</td>
<td>27(60%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9(20%)</td>
</tr>
</tbody>
</table>

Table 8: Summary of patients that underwent splenectomy (N=45)
Forty five patients underwent splenectomy during 1987-2011. The mean age of this group of patients was 32 years with a female predominance of 78%. Thirty one (69%) of patients had primary ITP. Only 3 patients were confirmed HIV positive.

The median time to splenectomy was 201 days. An open surgical procedure was performed in 96% of patients. Hundred percent of patients received vaccinations (pneumococcal vaccine) prior to the surgical procedure. Antibiotics prophylaxis post splenectomy was provided to all patients for at least two weeks after the procedure. In these adults, it was not routine policy to continue antibiotics for 2 years post-splenectomy or longer, except for selected patients who had recurrent/frequent infections.

### 3.6.3 Complications post splenectomy

![Complications Post splenectomy](image)

Infection was the predominant post surgical morbidity. Twenty percent of patients undergoing splenectomy developed infections post surgery, despite antibiotic prophylaxis and vaccination. 1 patient demised post surgery.
3.6.4 Drug used prior to splenectomy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PRED ONLY</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2 DRUGS</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3 DRUGS</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>4 DRUGS</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&gt;5 DRUGS</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 9: Drugs used prior to splenectomy (N=43)

Splenectomy is often considered for refractory ITP or with early failure of medical treatment. Table 8 shows the number of drugs used prior to splenectomy and are grouped according to previous timeframes used. In the period from 1987 – 1992, the majority of patients were on 1-2 drugs prior to the decision for splenectomy. This is in contrast with the 2006-2011 group where 9 out of the 13 patients that had a splenectomy had 3 or more drugs used and 5 of the 13 patients had 4 or more drugs used prior to a decision to undertake splenectomy.

3.6.5 Response to splenectomy

![Graph showing response to splenectomy](image)

Figure 12: Response of patients that underwent splenectomy
62% of patients that underwent splenectomy showed a complete response to this modality of treatment. Ten patients (22%) had a partial response. Only 3 patients (7%) remained refractory to splenectomy (see figure 12)

3.7 Medical treatment of ITP

Various drugs have been used in the medical treatment of ITP. The most commonly used drug and first line option was Prednisone.

Two hundred and thirty three patients out of the 243 (96%) patients analysed were given Prednisone.

![Dose of Prednisone (N=233)](image)

Figure 13: Dose of prednisone used

The majority of the patients were started on 60mg to 80 mg of prednisone (+1mg/kg/day). Higher doses of up to 120 mg were used in 26 patients (11%).

The average duration of the initial dose of prednisone (60 to 80mg) that was used, was 16 days.

Corticosteroid’s (prednisone) dose was gradually tapered once the platelet count was > 100 X 10^9/l.
Figure 14 shows the total duration of uninterrupted oral steroid use in patients with ITP from the time of diagnosis. Of the 233 patients known to be on oral steroids, retrospective analysis only assisted in providing time frames on 128 patients and hence the remainder were not included in the analysis. Of these patients, 52% of patients were continued on varying doses of steroids (dependant on their platelet counts) for greater than 731 days. With regards to steroid use, 16.4% of patients continued with steroids for 366-730 days. Only 3% of patients were weaned off the steroids within a period of less than 3 months and 22.6% within 6 months.
Various other drugs were also used in the treatment of ITP. In addition to the initial prednisone, this includes intravenous corticosteroids such as methylprednisolone as well as other immunosuppressive agents such as azathioprine, intravenous immunoglobulin and danazol. Chemotherapeutic agents such as vincristine as well as newer monoclonal antibodies such as rituximab were also used in the cohort.

![Other drugs used](chart.png)

**Figure 15: Frequency of other drugs used in the treatment of ITP**

The most commonly utilized drugs in addition to prednisone were azathioprine and methylprednisolone with 82 and 74 patients been put on these treatments respectively. Danazol was used in 20 patients. Intravenous immunoglobulins, vincristine and rituximab were used as alternative options in patients refractory to standard therapy in 11, 8 and 6 patients respectively.
Hundred and twenty patients (51%) were only given prednisone. The remaining 49% received more than one drug. Sixty six patients (28%) received 2 drugs whilst 50 patients (21%) received 3 or more drugs. Four percent of patients were on 5 or more drugs during the course of treatment. Methylprednisolone was regarded in this study as an additional drug to the prednisone as it was only used in a selected number of patients who were already on prednisone.

Figure 16: Number of drugs used

<table>
<thead>
<tr>
<th>Number of Drugs</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral pred</td>
<td>120</td>
</tr>
<tr>
<td>2 drugs</td>
<td>66</td>
</tr>
<tr>
<td>3 drugs</td>
<td>28</td>
</tr>
<tr>
<td>4 drugs</td>
<td>13</td>
</tr>
<tr>
<td>&gt;5 drugs</td>
<td>9</td>
</tr>
</tbody>
</table>

(N=236)
3.8 Outcomes

The final outcomes of patients with ITP were analysed based on their platelet counts. The major outcomes include:

- Complete response – platelets > 100 X 10^9/l
- Partial response – platelets between 30 – 99 X 10^9/l
- Death
- Lost to follow up

3.8.1 Outcomes based on medical treatment

<table>
<thead>
<tr>
<th></th>
<th>PRED ONLY (N=120)</th>
<th>2 DRUGS (N=66)</th>
<th>3 DRUGS (N=28)</th>
<th>4 DRUGS (N=13)</th>
<th>5 OR MORE DRUGS (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPLETE</td>
<td>78(65%)</td>
<td>43(65%)</td>
<td>14(50%)</td>
<td>9(70%)</td>
<td>4(45%)</td>
</tr>
<tr>
<td>PARTIAL ON TX</td>
<td>5(4%)</td>
<td>10(15%)</td>
<td>8(29%)</td>
<td>2(15%)</td>
<td>3(33%)</td>
</tr>
<tr>
<td>DEATH</td>
<td>8(7%)</td>
<td>3(5%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>1(11%)</td>
</tr>
<tr>
<td>LOST TO FOLLOW UP</td>
<td>29(24%)</td>
<td>10(15%)</td>
<td>6(21%)</td>
<td>2(15%)</td>
<td>1(11%)</td>
</tr>
</tbody>
</table>

Table 10: Final outcomes versus number of drugs used in ITP patients (N=236) (TX = treatment)

Outcomes were also analyzed based on the number of drugs utilized in the treatment of ITP. Two hundred and thirty six patients were reviewed (instead of 243 patients as 7 patients had inadequate data regarding treatment) and the breakdown of their responses are depicted in table 10.

In the prednisone only group, 78 patients (65%) showed a complete response while mortality was recorded at 6%. A total of 65% patients achieved a complete response while receiving 2 drugs.
14 patients (50%), 8 patients (69%) and 4 patients (44%) had a complete response when receiving 3
drugs, 4 drugs and 5 or more drugs respectively.

<table>
<thead>
<tr>
<th></th>
<th>PRED ONLY (N=72)</th>
<th>2 DRUGS (N=29)</th>
<th>3 DRUGS (N=8)</th>
<th>4 DRUGS (N=6)</th>
<th>5 OR MORE DRUGS (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPLETE</td>
<td>48 (67%)</td>
<td>23 (79%)</td>
<td>3 (37.5%)</td>
<td>4 (67%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>PARTIAL ON TX</td>
<td>3 (4%)</td>
<td>1 (3%)</td>
<td>4 (50%)</td>
<td>1 (16.5%)</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>DEATH</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>LOST TO FOLLOW UP</td>
<td>19 (26%)</td>
<td>5 (18%)</td>
<td>1 (12.5%)</td>
<td>1 (16.5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 11: Final outcomes versus number of drugs in Primary ITP (N=118)
(TX = treatment)

<table>
<thead>
<tr>
<th></th>
<th>PRED ONLY (N=45)</th>
<th>2 DRUGS (N=38)</th>
<th>3 DRUGS (N=20)</th>
<th>4 DRUGS (N=7)</th>
<th>5 OR MORE DRUGS (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPLETE</td>
<td>29 (64%)</td>
<td>20 (53%)</td>
<td>11 (55%)</td>
<td>5 (71%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>PARTIAL ON TX</td>
<td>2 (4%)</td>
<td>8 (21%)</td>
<td>4 (20%)</td>
<td>1 (14%)</td>
<td>1 (16.6%)</td>
</tr>
<tr>
<td>DEATH</td>
<td>4 (9%)</td>
<td>3 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (16.6%)</td>
</tr>
<tr>
<td>LOST TO FOLLOW UP</td>
<td>10 (22%)</td>
<td>7 (18%)</td>
<td>5 (25%)</td>
<td>1 (14%)</td>
<td>1 (16.6%)</td>
</tr>
</tbody>
</table>

Table 12: Final outcomes versus number of drugs in Secondary ITP (N=116)
(TX = treatment)

The final outcomes assessed separately with regard to the type of ITP are depicted in table 11 and
12. In the prednisone only group, similar outcomes were observed for complete recovery in primary
versus secondary ITP with 67% and 64% having a complete response respectively. Lower complete
response rates are observed in secondary ITP with regard to use of 2 drugs, with 53% of secondary
ITP showing a complete response compared to 79% of primary ITP patients. However, this is
different when comparing primary and secondary ITP and use of 3, 4 and 5 drugs or more. Secondary
ITP achieved a better response rate to 3 drugs, 4 drugs and 5 or more drugs when compared to the primary ITP group.

3.8.2 Outcomes of primary versus secondary ITP

<table>
<thead>
<tr>
<th></th>
<th>PRIMARY (N=118)</th>
<th>SECONDARY (N=121)</th>
<th>UNKNOWN (N=4)</th>
<th>ALL ITP (N=243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPLETE</td>
<td>79</td>
<td>68</td>
<td>2</td>
<td>149</td>
</tr>
<tr>
<td>PARTIAL ON TX</td>
<td>11</td>
<td>16</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>DEATH</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>LOST TO FOLLOW UP</td>
<td>26</td>
<td>28</td>
<td>1</td>
<td>55</td>
</tr>
</tbody>
</table>

Table 13: Final outcomes of Primary versus Secondary ITP

(TX = treatment)

(The 6.241 df=5; p value=0.1005)

The final outcomes were based on the best documented outcome at the last visit and were analyzed in this cohort of 243 patients and sub-categorized into primary and secondary ITP. Seventy nine patients with primary ITP showed a complete response compared to 68 patients with secondary ITP.

Nine deaths occurred in the secondary group compared to primary ITP which accounted for 2 deaths. A significant proportion of patients in both primary and secondary ITP were lost to follow up at time of analysis. There were no statistically significant differences in outcomes between primary and secondary ITP.
CHAPTER 4: Discussion

4.1 Introduction

Immune thrombocytopenia was initially described in the 17th century and its understanding has evolved over the years (2). It is primarily an immune mediated disorder associated with low platelets and manifests predominantly with mucocutaneous bleeding. A retrospective study of ITP was undertaken in order to analyse the patterns of the disease and the potential impact of the increasing number of patients with secondary ITP, particularly with regard to the influence of HIV. In our study, we analysed 243 patients with ITP at Chris Hani Baragwanath Academic Hospital from 1987 to 2011.

4.2 Epidemiology

The median age of diagnosis in our patients was 32±14 years. This is in keeping with a previous study carried out at CHBAH, which found that ITP occurred predominantly in females in the third decade of life (60). A study carried out in Denmark, showed that the median age of diagnosis for patients with ITP was 56 years, with an increased incidence with increasing age (61). A prospective study carried out in the United kingdom also showed an increased incidence of ITP in patients over the age of 60 (123). These differences in age between our study and the Western world could be attributed to a number of factors, including i) younger age structure of our population, ii) higher incidence of secondary causes such as HIV and other infections and iii) the more frequent association with pregnancy. In addition, patients in the Western world are more likely to be affected by conditions that commonly affect middle aged and the older populations, such as haematological malignancies (e.g. lymphoproliferative disorders) and drug related effects due to polypharmacy in the elderly population.
The gender differences were also quite marked. Although the female to male ratio is 4.2:1, which is slightly lower than in another South African series where the ratio was 5.2:1 (60). This is contrary to other studies which demonstrated a less marked female to male ratio of 1.7:1 and 1.2:1 (61, 123). Overall, the disease is more prevalent in females due to its link with autoimmunity and possibly other factors which are not entirely clear.

4.3 Clinical Presentation

Thrombocytopenia is associated with mucocutaneous bleeding. The lower the platelet count, the more likely that the patient will bleed spontaneously. The median platelet count at presentation in our patients was $10 \times 10^9/l$, with minimal variation between primary and secondary ITP.

In view of such low platelet counts (grade 4/severe thrombocytopenia), spontaneous bleeding was found in the majority of patients at diagnosis. In keeping with the literature, mucocutaneous bleeding was the main clinical presentation, with 48% of our patients presenting with skin bleeding, 44% with epistaxis and 34% with gum bleeding. Only 3% of patients presented with an intracerebral haemorrhage. In the United States, the incidence of ITP with intracerebral haemorrhage occurs in 0.19 to 0.78% of cases (124). These differences could be attributed to logistical factors such as higher thresholds in our population to health seeking behaviour, the possibility that complex ITP patients are referred to this tertiary hospital, later presentations to hospital as well as severe thrombocytopenia at initial presentation. As noted earlier, patients may be symptomatic or asymptomatic.

Splenomegaly is an uncommon presentation in patients with primary ITP. It can occur in secondary ITP due to SLE, HIV, or portal hypertension secondary to chronic hepatitis infection. Splenomegaly
was found in 0.8% of patients with primary ITP. This is in keeping with the literature where < 3% of patients present with splenomegaly (125). This is contrary to the paediatric population in which 10% of children with primary ITP presented with a mild splenomegaly at diagnosis (126). There are no documented cases of isolated hepatomegaly in primary ITP, however 0.8% of our patients with primary ITP had hepatomegaly. Hepatomegaly can be associated with secondary ITP especially in patients with HIV, SLE, hepatitis and lymphoproliferative disorders.

4.4 Primary versus Secondary ITP

The frequency of primary versus secondary ITP was 48% and 50% respectively. In a study by Cines et al in 2005, secondary causes of ITP accounted for less than 10% of all patients diagnosed (17). In a later study in 2009, secondary ITP accounted for 20% of the cohort of which SLE was the most common cause accounting for 5% of the patients presenting with ITP, while HIV was responsible for 1% of the patients studied (22). This is contrary to our population in which a higher prevalence of secondary ITP could be attributed to the higher prevalence of HIV infection which accounted for 40% of the patients with secondary ITP. In the study by Cines et al in 2005, lymphoproliferative disorders and immunodeficiency syndromes played a greater role in secondary ITP (17) as opposed to our study, in which HIV positivity, ANA positivity/SLE/APLS, pregnancy and other infections such as hepatitis B, hepatitis C and malaria have had a greater contribution to secondary aetiologies.

The overall incidence of ITP has increased over the years. This can be attributed to increased availability of automated platelet counts, facilitating easier diagnosis of ITP itself, changes in referral patterns with the establishment of dedicated departments as well vigilant surveillance resulting in increased identification of secondary contributing causes. The overall prevalence of secondary ITP increased from 34% to 57.5% in later years in our study. This can be attributed to an increased
prevalence of HIV infection as well as better screening methods for other autoimmune conditions and other secondary contributing factors.

4.5 SLE and ITP

Immune Thrombocytopenia being an immune mediated condition, plays a role in systemic autoimmune conditions. ANA positivity was seen in 42.1% of patients with secondary ITP with 15% of patients diagnosed with SLE. Patients diagnosed with ITP and ANA positivity, should be monitored for features of SLE, as evolution to SLE can occur in 2-5% of patients with ‘primary ITP’ several years later (22). In addition, since ITP is a diagnosis of exclusion, other causes of thrombocytopenia in SLE such as TTP, overlap APLS, DIC, hypersplenism, hypoplastic anaemia, haemophagocytic syndrome or treatment related complications need to be excluded.

4.6 Pregnancy and ITP

Thrombocytopenia is a complication in 10% of pregnancies and ITP accounts for 5% of cases of pregnancy associated thrombocytopenia (127). ITP is a diagnosis of exclusion and conditions such as gestational thrombocytopenia, pre-eclampsia, HELLP syndrome and microangiopathic haemolytic anaemias (DIC secondary to placental abruption, intra-uterine fetal deaths or TTP) need to be excluded prior to diagnosing ITP in pregnancy. Differentiating ITP from gestational thrombocytopenia can pose a diagnostic dilemma, however, gestational thrombocytopenia is associated with mild thrombocytopenia with no impact on the maternal and fetal health and resolves post delivery as opposed to ITP which is associated with platelet counts lower than 50 X $10^9$/l of blood (17). In our study, 15% of patients with secondary ITP were pregnant with 80% of patients requiring treatment for thrombocytopenia post delivery. The median platelet count of secondary ITP due to pregnancy in our study was $16 \times 10^9$/l (range: 2 -91) with 95% of patients
having a platelet count < 50 X 10^9/l. Caution needs to be exercised with medical treatment taken during pregnancy as adverse effects of medication, such as the corticosteroids, is amplified during the pregnancy and the physician needs to monitor for complications such as gestational diabetes, pregnancy induced hypertension, accelerated osteoporosis, placenta abruption and prematurity (128). Medical treatment is limited to steroids and IVIG due to the teratogenic effects of the other drugs. Splenectomy can be considered for patients that fail the above medical treatment and this should preferably be performed during the second trimester. Another consideration, is that ITP in pregnancy can be associated with fetal thrombocytopenia as maternal platelet antibodies can cross the placenta and cross react with fetal platelets. In a review by Fujimura et al (2002), in presenting mothers with ITP, 22.6% of their babies developed neonatal thrombocytopenia (128).

4.7 HIV and ITP

Thrombocytopenia in HIV can be multifactorial, therefore bone marrow suppression, drugs used in the treatment of HIV, HIV associated malignancies and nutritional deficiencies need to be excluded. An association between HIV and ITP was first described in 1982 (25). ITP has increased in incidence with the HIV pandemic with 5-10% of patients with HIV developing ITP (129). The trend can be seen in figure 5 where the incidence of secondary ITP has increased over the years and this has been influenced by an increased prevalence of HIV infection. HIV was responsible for 40% of cases of secondary ITP and 20% of all cases of ITP in our study. Demographics such as gender, in terms of female predominance remained consistent despite HIV infection. The clinical presentation of patients with HIV and ITP did not deflect from patients with primary ITP or other causes of secondary ITP. The median age of ITP in patients with HIV infection was similar to the age in the HIV negative population. This correlates with the predominant diagnosis of HIV being in the second to third decade of life (130). In a study by Ambler et al (2012), the median age of diagnosis of ITP with
HIV was 37 (range 27 – 66) years (131). A study done in Nova Scotia, supports our findings and suggests that the diagnosis of HIV infection may parallel the increases in the diagnosis of ITP (132).

Duration to platelet recovery was prolonged in patients that were HIV positive (average of 31 days to platelet recovery > 100 X 10^9/l), while patients on cART had a longer duration to platelet recovery than patients not on cART by 15 days (see table 5). The median CD4 count of our population in this study was 145/ul, which increased to a median count of 215/ul if the patients were on cART. In a study by Ambler et al (2012), the median count in the HIV positive patients with ITP was 260/ul (131). It is difficult to explain this phenomenon in our patients, as despite the patients being on cART, it took a longer duration of time to platelet recovery. Physiologically, immunoregulatory T cells (CD4) play a role in the regulation of self tolerance. These cells are proposed to play a role in autoimmunity by preventing the amplification of autoreactive T cells (133). In ITP the ratio of CD4:CD8 is reduced but improves with disease course and remission (134).

The management of patients with HIV and ITP is similar to those patients that are HIV negative. Splenectomy is effective in patients with HIV associated ITP that have not responded to medical treatment (40). As described in the literature, initially zidovudine monotherapy was instituted as part of the treatment and facilitated an increase in platelet counts in 60-70% of patients with HIV associated ITP (135). This set the footpath for the early initiation of cART in patients diagnosed with HIV associated ITP. Use of cART facilitates sustained platelet responses and recovery due to reduction in viral load and HIV mediated pathogenic mechanisms on platelet function (35). Therefore cART plays an important role in the management of patients with ITP (136). In our study, response to treatment whether, partial or complete, was similar in both the HIV positive and HIV negative groups with an overall response of 70%.
4.8 Splenectomy and ITP

Splenectomy is seen as the gold standard of treatment and was first described in the early 19th century (3). In our study population, 19% of patients underwent splenectomy. Splenectomy is recommended in patients who are refractory to medical treatment or those who have unsustained responses to treatment, requiring ongoing medical therapy (17). According to Srinavasan et al (2003), splenectomy should also be considered in patients with a history of non-compliance to medical treatment, or those that develop complications to medical treatment such as Cushings syndrome secondary to prolonged steroids, hypertension or diabetes (137). A systematic review of patients that underwent splenectomy for ITP, highlighted that two-thirds of patients achieved a complete response post surgery (109). In a study by Supe et al (2009), complete response was seen in their study population in 60 % of patients and a partial response was seen in close to 40% (138). These response rates correlate with our findings, in which a response was seen in 84% of patients, with 62% being a complete response. 6% of patients were refractory to splenectomy and in 10% of the patients, the response was unknown (due to lack of ongoing follow up). In a study by McMillan et al in 2004, 75% of his study population that underwent splenectomy achieved a complete or partial response (112). Factors documented in the literature that may contribute to sustained responses to splenectomy include thrombocytosis post surgery, younger age of presentation and fewer drugs prior to surgery (109).

The time to splenectomy plays a role with regard to response. As the time to splenectomy increases, the rate of response decreases (139). Based on the opinion of some experts, splenectomy is recommended within 3 to 6 months if a patient requires significant medical treatment to maintain a safe platelet response and reduce the bleeding risk (17). However the current guidelines are in favour of deferring splenectomy to > 6 months to > 12 months after diagnosis (18, 71).
The surgical procedure type in 96% patients was open surgery as opposed to laparoscopic surgery. Laparoscopic surgery reduces recovery time and postoperative analgesia requirements and has less intra-operative blood loss as opposed to open surgery. Therefore, laparoscopic surgery is now being preferred to open surgery (140). In our setting, open surgery was considered due to less expertise in the field of laparoscopy and the anticipation of more complications such as bleeding requiring adequate haemostatic control.

Complications post splenectomy include sepsis, particularly with encapsulated organisms, subphrenic abscess formation, bleeding, intra-operative injury to surrounding structures such as the pancreas, bowel, renal structures, as well as increased risk of thrombotic events, such as the increased risk of thrombosis due to reduced mechanical filtering by the spleen resulting in increased platelet activation and thrombus formation (141). In our study, infection was the predominant post-surgical complication and occurred in 20% of patients in the immediate post splenectomy period, despite all the patients who underwent splenectomy, having received pneumococcal vaccination and antibiotic prophylaxis for at least two weeks after the surgery.

Despite newer drug options for the treatment of refractory ITP such as thrombopoietin mimetics and rituximab, splenectomy is still the preferred modality of treatment in our patients. The reason for this can be attributed to logistical factors in obtaining the newer drugs, the cost of which is generally prohibitive.
4.9 Medical Treatment of ITP

The mainstay treatment of ITP is oral corticosteroids, particularly prednisone. This was the drug of choice in 96% of patients in our study (4% of patients were unknown). The effects of steroids in ITP are multifactorial, however long term steroid use is detrimental and can result in Cushing’s syndrome, metabolic consequences such as hypertension, diabetes, increased propensity to sepsis, poor wound healing as well as osteoporosis. Duration of treatment is individualised depending on platelet counts. In our study the timeframes of 128 patients were elucidated of which 52% received uninterrupted steroid use at varying doses, depending on the platelet counts and symptomatology, for greater than 2 years. Complications of long term steroid use were not elaborated in this study. Single agent use has been documented to be associated with complete response rates of 30% (70), which is in keeping with our study.

The outcomes with regard to medical treatment were assessed according to the IWG criteria. Partial response is defined as a platelet count of $> 30 \times 10^9/l$ and a greater than 2-fold increase in platelet count from baseline with the absence of bleeding. A complete response is defined as a platelet count of $> 100 \times 10^9/l$ on two occasions greater than 7 days apart and the absence of bleeding (1).

49% of patients required other treatment in addition to prednisone to sustain or achieve platelet responses. Drugs available at our institution as part of additional treatment included: methylprednisolone, azathioprine, danazol, intravenous immunoglobulin, vincristine, anti-D immunoglobulin as well as rituximab. The commonly used drug, after corticosteroids was azathioprine. The literature describes azathioprine to be associated with responses in 40-60% of patients that are refractory to corticosteroids (84). Rituximab was utilised in 2.4% of our patients particularly those refractory to our other available treatments.
In a study by Boruchov et al (2009), combination therapy utilising intravenous immunoglobulin and intravenous methylprednisolone + anti-D immunoglobulin was effective in elevating platelet counts acutely in 71% of patients that were refractory to oral steroids (70). This combination was also found to be effective in patients with high risk predictors for bleeding as well as HIV associated ITP (70).

72% of patients were found to respond either to single agent or multi-agent therapy. This statistic may underestimate the true response to treatment as 19% of patients in our study were lost to follow up. Complete response to single agent prednisone was similar in both primary and secondary ITP, with 67% and 64% respectively. There were no remarkable differences in the number of drugs utilised and their outcomes in patients with primary versus secondary ITP. The literature suggests that if a patient fails to respond to a combination of 4 drugs, alternative diagnosis for the thrombocytopenia should be sought (71). However in our study, 4% of patients were on 5 or more drugs with no alternative diagnosis identified.

4.10 Conclusion

ITP in South Africa is predominantly a disease of young females. Over the years, there has been a paradigm shift, with an increase in secondary ITP. HIV is the most important defined secondary cause. The presentation in our patients is with severe symptomatic thrombocytopenia (median platelet count of 10 X 10^9/l), with mucocutaneous bleeding requiring immediate therapeutic intervention. Oral corticosteroids are the mainstay of initial treatment. However, a significant number of patients require ongoing long term steroid therapy to maintain the platelet count in a safe range without bleeding. HIV seropositivity was associated with a lower response rate and a longer time to platelet recovery, compared to HIV seronegativity. Splenectomy was performed in approximately one fifth of the patients. It is the most definitive and only curative therapy in ITP. The response rate to splenectomy was 84% (62% CR and 22% PR). Splenectomy is feasible in both
primary and secondary ITP, including patients with HIV. After corticosteroids, azathioprine is the most commonly used agent in our patients. Very few patients received rituximab and thrombopoietin mimetics were not used in view of their prohibitive cost. Overall, the outcome in our patients is similar to that described in the literature.

4.11 Limitations of the study

As a result of the retrospective nature of the study, we relied on aggregated data documented in patient’s records. In some circumstances, these records were not adequately completed and certain information was lacking. In addition, this study was carried out at Chris Hani Baragwanath Academic Hospital and as a result, we are unable to make generalisations that may apply to other populations due to sampling bias. Our cohort was based on referrals to the haematology department, hence there is a selection bias as well as a possible underestimation of the number of cases identified as certain number of patients may have been treated by general physicians. A proportion of patients were non-compliant and lost to follow up and their information could not be included in the study. Despite these limitations, the reasonably large number of patients reviewed in this study over a 25 year period provides a fair estimate and generalisation of ITP in adults in South Africa.
CHAPTER 5: References


Appendix A: Data Collection Sheet

ALLOCATED STUDY NUMBER: ________

AGE: ________

GENDER: ________

DATE OF INITIAL PRESENTATION_____

ITP:

PRIMARY: ________

SECONDARY: ________

INFECTIONS

HIV _____ HEPATITIS _____ CMV _____ EBV _____ OTHER _____

AUTO- IMMUNE DISORDERS

SLE ________ ANTIPHOSPHOLIPID SYNDROME ____________

DRUGS _______________________________________________________________________

LYMPHOPROLIFERATIVE DISORDERS _____________________________________________

OTHER _______________________________________________________________________

PLATELETS AT DIAGNOSIS_____

CLINICAL PRESENTATION

HISTORY

SITES OF BLEEDING

SKIN ________ GUM BLEEDING______ EPISTAXIS ________ HAEMATURIA ________

GASTRO - INTESTINAL _____ MENORRHAGIA______ INTRACRANIAL BLEEDING _____

OTHER _______________________________________________________________________

DRUG HISTORY __________________________________________________________________

OTHER RELEVANT HISTORY __________________________________________________________________

CLINICAL EXAMINATION

PALLOR ____________

LYMPHADENOPATHY ______________________________

SITES OF BLEEDING

SKIN ________ GUM BLEEDING______ HAEMORRHAGIC BULLAE______

EPISTAXIS ________ HAEMATURIA ________ GASTRO - INTESTINAL ________

MENORRHAGIA______ INTRACRANIAL BLEEDING _____ RETINAL BLEEDS ______

SUBCONJUNCTIVAL HAEMORRHAGE ________ OTHER ____________________________

HEPATOMEGALY ________

SPLENOMEGALY ______________________________
OTHER FEATURES RELEVANT TO SECONDARY CAUSES ______________________________

HIV STATUS: ________

CD4 IF HIV POSITIVE: __________________________

IF HIV POSITIVE, IS PATIENT ON cART: ________________

IF ON cART, DATE COMMENCED: ________________

TREATMENT

SUPPORTIVE:

SPECIFY: ________________________________

BLOOD PRODUCTS: __________________________

SPECIFIC INCLUDING DOSE, DURATION (START AND STOP DATES OF INDIVIDUAL TREATMENT) AND ORDER IN WHICH DRUGS INITIATED

CORTICOSTEROIDS ____________________________

INTRAVENOUS IMMUNOGLOBULINS__________

AZATHIOPRINE ______________________________

VINCRIStINE ________________________________

ANTI-D ________________________________

DANAZOL ________________________________

RITUXIMAB ________________________________

TREATMENT OF SECONDARY CAUSES ____________

OTHER ______________________________

SPLENECTOMY __________________________________

TIME OF SPLENECTOMY FROM INITIAL PRESENTATION ________________

TYPE OF SPLENECTOMY ________________________________

RESPONSE TO SPLENECTOMY ________________________________

IF PATIENT REQUIRED FURTHER TREATMENT AFTER SPLENECTOMY ____________

TIME TO PARTIAL RESPONSE FROM INITIAL PRESENTATION DATE (PLATELET COUNT >30,000 PER MICROLITRE OF BLOOD) ________________________________

TIME TO COMPLETE RESPONSE FROM INITIAL PRESENTATION DATE (PLATELET COUNT >100,000 PER MICROLITRE OF BLOOD) ________________________________
WAS RESPONSE SUSTAINED:
YES ________ NO ________

IF NO, HOW LONG AFTER INITIAL TREATMENT THAT PATIENT RELAPSED ____________
THERAPIES USED FOR RELAPSE ____________________________________________
RESPONSE TO THESE THERAPIES _________________________________________

CURRENT STATUS:
COMPLETE RESPONSE ________________________________________________
PARTIAL RESPONSE OFF TREATMENT ____________________________________
PARTIAL RESPONSE ON TREATMENT _____________________________________
DEATH _____________________________________________________________

IF DEATH OCCURRED:
CAUSE OF DEATH ____________________________________________________
SURVIVAL (DATE OF DIAGNOSIS TO DATE OF DEATH) ______________________

LOSS TO FOLLOW UP _________________________________________________

IF LOSS TO FOLLOW UP:
LAST DATE PATIENT SEEN ___________________________________________
CLINICAL STATE OF PATIENT AT THAT DATE ______________________________

OTHER RELEVANT INFORMATION AT FOLLOW UP (CO-MORBIDITIES) ____________
______________________________________________________________
Appendix B: Ethics Approval Letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Firdose Variava

CLEARANCE CERTIFICATE M120412
PROJECT Immune Thrombocytopenia at Chris Han Baragwanath Academic Hospital

INVESTIGATORS
Dr Firdose Variava.

DEPARTMENT
School of Medicine/Internal Medicine

DATE CONSIDERED
04/05/2012

DECISION OF THE COMMITTEE*
Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 03/07/2012

CHAIRPERSON
(Professor PE Cleaton-Jones)

*Guidelines for written ‘informed consent’ attached where applicable
cc Supervisor : Prof Moosa Patel

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...
Appendix C: Turnitin Letter from supervisor

26 September 2014

The Chair

Postgraduate Studies Committee

Faculty of Health Sciences

University of the Witwatersrand

Re: Turn-it-in report: Dr. Firdous Variava – MMed: ‘Immune Thrombocytopenia at Chris Hani Baragwanath Academic Hospital’

I have reviewed the Turn-it-in report of Dr. Variava’s MMed dissertation. The report identifies a similarity index of 12%. Much of this similarity relates to definitions which are standardized. The other information which bears a similarity has been appropriately referenced.

Thank you

Yours sincerely

Moosa Patel MBChB, FCP(SA), MMed(Wits), FRCP(Lond.), PhD(Wits)

Supervisor of the above study

Professor and Head of Clinical Haematology, Department of Medicine, Chris Hani Baragwanath Academic Hospital and the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa