Impact of splenectomy on the management of Immune Thrombocytopenia (ITP) in adults: The Chris Hani Baragwanath Academic Hospital Experience

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment for the requirements of the degree of Master of Medicine (Internal Medicine)

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DECLARATION

I, Toyin Raheem Abdulraheem, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine (Internal Medicine) to the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University

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Dr Toyin Raheem Abdulraheem

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Date

DEDICATION

To my wife, Ayeesha for her patience and support

and,

My extended family for their support over the years

ETHICS COMMITTEE APPROVAL

This research was approved by the Human Research Ethics Committee (HREC), University of the Witwatersrand (Clearance Certificate number: M150920). (see Appendix A)

ABSTRACT

Background

Immune thrombocytopenia (ITP) is an acquired, autoimmune disorder where antiplatelet antibodies are directed to both platelets and megakaryocytes resulting in increased platelets destruction and inadequate platelet production. T-cells also play a role in autoantibody production as well as in direct lysis of platelets (cytotoxic T-cells).

The presentation of adult ITP may be acute or insidious in onset. Most cases go on to develop chronic ITP. Primary ITP accounts for approximately 80% of the patients and secondary ITP for 20%. However, in South Africa, there is a paradigm shift with an increasing number of patients with secondary ITP, contributed to mainly by human immunodeficiency virus (HIV) infection.

Splenectomy is the most definitive therapy for ITP. It has the highest likelihood of all the current treatment options of producing a cure. The overall response rate is 70-90% (CR 50-60%, PR 20-30%, relapse rate 15%). It is effective for persistent and chronic ITP after failure of corticosteroid therapy. It is recommended that splenectomy be delayed for at least six months (and preferably 12 months) from diagnosis due to the chance of a spontaneous remission (5-11%). Although open splenectomy and laparoscopic splenectomy have similar efficacy, laparoscopic splenectomy has fewer surgical complications, including less postoperative pain, earlier general diet tolerance and shorter hospital stay.

There is a paucity of data with regard to ITP, and more specifically, looking at the efficacy and safety of splenectomy in the South African context. Furthermore, in view of the increased prevalence of HIV as the most common cause of secondary ITP, it is important to ascertain the feasibility, safety and efficacy of splenectomy in secondary ITP.

Therefore, the current study aimed at exploring the impact of splenectomy as a therapeutic option in ITP, in adults at CHBAH over a period of 29 years (01/01/1986-31/12/2014).

Patients and Methods

This is a retrospective review of the records of ITP patients who had a splenectomy, during the aforementioned study period at the Clinical Haematology unit, Chris Hani Baragwanath Academic Hospital.

The aim of the study was to study the impact of splenectomy as a therapeutic modality in patients with ITP, specifically looking at the indication, timing, outcome, response, duration of response and complications of splenectomy in ITP. The efficacy and safety of laparoscopic versus open splenectomy in ITP was assessed as well as a comparison of the efficacy, safety and outcome of splenectomy in primary and secondary ITP.

Results and Discussion

A total of 56 splenectomised ITP patients' records were reviewed. Of these, 43 were female (77%) while 13 were male (23%). The median age of the patients was 29 years, with a range of 18- 53 years.

Majority of the patients had primary ITP (n=42, 75%), and the remaining (n=14, 25%) had secondary ITP. Of the fourteen patients with secondary ITP who had a splenectomy, 11 had an underlying autoimmune aetiology. Nine patients (82%) were diagnosed with SLE while concomitant auto-immune haemolytic anaemia (Evan's syndrome) and mixed connective tissue disease accounted for 1 each (18%), of the remaining patients, respectively.

In this study, there were three HIV positive patients who had a splenectomy accounting for 5.4% of all splenectomised patients with ITP.

The surgery of choice in this study was open splenectomy (n=51, 91%). Only five patients underwent laparoscopic splenectomy of which two were later converted to open splenectomy because of complications.

Failed corticosteroid (CS) therapy (98.2%) was the commonest indication for splenectomy in this study. These patients were either steroid dependent or showed only a partial response. Similarly, they also experienced disabling side effects from high doses and/or prolonged use of CS therapy. One patient had splenectomy as a result of poor compliance (1.8%).

In the splenectomised patients, platelet counts one year post splenectomy (mean = 231.19 x 10^9/l ± 162.643) were significantly higher than the platelet counts prior to splenectomy (mean = 26.22 x 10^9/l ± 31.552 and p-value= 0.00).

Three patients (5.4%) experienced infections requiring hospitalization. Two patients had thrombotic complications, while five patients had bleeding manifestations up to the time of the last visit.

Overall, 37 patients (66%) had a complete remission, while seven patients (12.5%) had a partial remission. Six patients (10.8%) showed no response to splenectomy. In four patients (7%), the outcome was unknown. Two patients (3.6%) died, one patient from a complication of surgery and the other patient from sepsis four years post splenectomy.

Conclusion

The role of splenectomy in ITP continues to be reassuring, particularly in our setting where the 'newer' agents, such as rituximab (used as an off-label indication in ITP), and thrombomimetics, which are not yet accessible due to high cost, are challenging the role of splenectomy. Splenectomy is the preferred second line therapy after the patient has failed CS therapy. Although the minority of the patients had a laparoscopic splenectomy, with time and experience, laparoscopic splenectomy should become the procedure of choice, especially in conditions such as ITP, where the spleen is not enlarged, and the procedure is highly technically feasible. Furthermore, the outcome for primary versus secondary ITP was equally favourable.

However, there were significantly less number of secondary ITP patients in this study.

The findings in this study are limited by its retrospective nature. For some patients data was missing and the files could not be reviewed. Ideally, a larger sample size would have added to the strength of this study. Nevertheless, we believe that the findings are a fair representation of the role of splenectomy in ITP, in the public sector South African context, based on this retrospective review from a large single centre, over a period of 29 years. Therefore, splenectomy remains a therapeutic modality of choice in this setting, particularly in patients with persistent and chronic ITP, who have failed prior CS therapy.

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ALPS-Autoimmune lymphoproliferative syndrome

APL-Anti-phospholipid syndrome

ATG-Anti-thymocyte globulin

cART-Combination anti-retroviral therapy

CHBAH-Chris Hani Baragwanath Academic Hospital

CR-Complete response

CS Therapy-Corticosteroid therapy

CLL-Chronic Lymphocytic leukaemia

CVID-Common variable immunodeficiency

EBV-Epstein Barr virus

GP–Glycoprotein

HAART-Highly active antiretroviral treatment

H. pylori-Helicobacter pylori

HCV-Hepatitis C Virus

HIV-Human immunodeficiency virus

IgG-Immunoglobulin G

ITP-Immune thrombocytopenia

IVIg -Intravenous Immunoglobulin

IWG –International working group

LPD-Lymphoproliferative disorders

MCT-Mixed connective tissue disease

OPSI-Overwhelming post -splenectomy infection

PR-Partial response

SLE-Systemic Lupus erythematosus

TPO-RAs-Thrombopoietin receptor agonists

VTED-Venous thromboembolic disease

VZV-Varicella zoster virus

CHAPTER 1: LITERATURE REVIEW

1.1 Introduction

Immune Thrombocytopenia (ITP) is an acquired, autoimmune disorder where antiplatelet antibodies are directed to both platelets and megakaryocytes resulting in increased platelets destruction and inadequate platelet production. T-cells also play a role in autoantibody production as well as in direct lysis of platelets (cytotoxic T-cells).[1,2,3]

1.2 Historical Background

The classical clinical description of ITP was first reported in 1735 by a German physician, Paul Gottlieb Werlhof, in a young girl who presented with epistaxis, hematemesis and purpura.[4] This was long before platelets were described by Max Schultze in 1865 and later by William Osler in 1874, as a distinct cellular constituent of blood.[5,6] It was only in 1883 that the link between thrombocytopenia and purpura was established by Brohm.[7] This observation was supported by Denys in 1887, when he noted that platelets were reduced during the active phase of purpura and increased when bleeding stopped.[8,9] The following century witnessed the search for the pathogenic mechanisms of ITP. While there was an ongoing debate among the earlier researchers on the pathogenesis of ITP, a breakthrough came in the management of the disease in 1916 when Paul Kaznelson, a Polish medical student reported the benefit of splenectomy in this disorder. He noted that platelet counts increased significantly in a young woman with ITP, post splenectomy.[9,10]

1.3 Epidemiology

The incidence of newly diagnosed primary ITP is approximately 3 - 4.5 /100 000 /year. There is a higher prevalence of chronic ITP which is 10 - 25/100 000/year.[11,12,13,14] The true incidence of newly diagnosed ITP in South Africa is unknown, but it is estimated to be approximately 1 - 2 / 100 000 /year.[15,16] ITP (primary) is a disease predominantly affecting young females. This is based on two local South African studies where the median ages were 31 years (with a female to male ratio of 4.1:1), and a mean age of 34 years (with a female to male ratio of 5.2:1).[15,16] However, in a population based European study, the median age is approximately two decades later (approximately 57 years), with an increasing incidence with advancing age (>60 years). The gender difference of a female predominance in young and middle aged individuals is also less marked in patients above the age of 60 years.[11,13,14]

Primary ITP accounts for approximately 80% of the patients and secondary ITP for 20%. However, in South Africa, based on a recent review, there is a paradigm shift with an increasing number of patients with secondary ITP, contributed to mainly by human immunodeficiency virus (HIV) infection.[16]In this review secondary ITP accounted for 50% of cases of which 40% of this were attributed to HIV infection.

1.4 Definitions and Terminology

The normal platelet count ranges between 150 - 400 x 10^9/l. Local South African studies have shown some variability in the level of the platelet counts, including studies performed by Tikly et al, 1987 and Lawrie et al, 2009, who found the

following normal ranges (M: 164 – 396 x 10^9/l; F: 191 – 442 x 10^9/l) and (M: 171 - 388 x 10^9/l; F: 186 - 454 x 10^9/l), respectively.[17,18] Despite the lower limit of normal being well above 100 x 10^9/l, platelet counts below the lower limit of normal and above 100 x 10^9/l are generally not associated with any clinical manifestations. Therefore, the threshold for ITP and indeed for clinical thrombocytopenia is defined as a platelet count of < 100 x 10^9/l.[19]

Due to the difficulty posed by lack of standardization of clinical criteria for the diagnosis and management of ITP in clinical practice and in research, the International Working Group (IWG) on ITP in 2007, came up with a document or proposal to address this problem. Their recommendations have been widely adopted by many clinical guidelines. ITP now refers to **I**mmune **T**hrombocyto**p**enia (**ITP**) and no longer to terminologies such as immune or idiopathic thrombocytopenic purpura.[19]

Primary immune thrombocytopenia is a diagnosis of exclusion once all other causes are excluded. This requires detailed history – including family history, prior history of bleeding and bleeding after haemostatic challenges, drug history and complete physical examination). Thereafter, other known causes of immune mediated thrombocytopenia referred to as secondary ITP should be excluded. This includes drugs such as rifampicin, quinine and heparin, infections such as HIV, autoimmune disease including systemic lupus erythematosus (SLE) and lymphoproliferative disorders (LPD) such as chronic lymphocytic leukaemia (CLL) and lymphoma.

Table 1.1 Causes of secondary ITP

1. Infections	HIV, hepatitis C, EBV, Malaria, VZV, H. Pylori
2. Drugs	Heparin, rifampicin, quinine, quinidine, penicillin, ATG, captopril etc.
3. Lymphoproliferative	CLL, Lymphoma
4. Auto-immune	SLE, APLS, auto-immune hepatitis, auto- immune thyroiditis
5. Other	Evans syndrome, Auto-immune lymphoproliferative syndrome, CVID

EBV- Epstein Barr Virus; VZV- Varicella Zoster Virus; H. Pylori- Helicobacter Pylori; ATG- Anti-thymocyte globulin; HIV- Human Immunodeficiency Virus. CLL- Chronic lymphocytic leukaemia; APLS- Auto-immune lymphoproliferative syndrome; CVID- Common variable immunodeficiency

There are no specific clinical or laboratory parameters to establish the diagnosis, and the diagnosis remains one of exclusion. Abnormal clinical features such as lymphadenopathy or hepatosplenomegaly (in the absence of bleeding) should suggest another cause of thrombocytopenia or a secondary cause of ITP.

Furthermore, three distinct phases of the disease are recognized in primary ITP:

I. Newly diagnosed (from diagnosis to 3 months)
II. Persistent (from 3 to12 months)
III. Chronic (>12 months)[19]

The International Working Group (IWG) also recognizes the platelet count as a surrogate measure of important clinical end points such as bleeding and quality of life, with regard to determining response to therapy.

Different categories of response are defined:

i. Complete response (CR) is defined as a platelet count equal to or more than 100 x 10^9/l,
ii. Response (R) is defined as any platelet count between 30 and 100 x 10^9/l and at least doubling of the baseline count, and
iii. No Response (NR) is defined as any platelet less than 30 x 10^9/l or less than doubling of the baseline count.

1.5 Aetiopathogenesis

Since 1951, when Harrington et al, demonstrated that ITP is characterized by reduced platelet survival due to a humoral factor, much has been gained in our understanding of the pathogenic mechanisms of ITP.[20]

Immune Thrombocytopenia (ITP) is an autoimmune disease resulting from an interaction between a possible genetic predisposition and an environmental trigger with subsequent immune dysregulation involving humoral and T- cell immune dysfunction. The trigger varies from an unknown cause to a wide range of factors such as infections. In the end, a combination of both increased platelet destruction and inadequate production is responsible for ITP.[21] A number of factors have been identified culminating in low platelet counts. These include loss of immune tolerance to autoantigens with antibody production and subsequent destruction of platelets by the reticuloendothelial system, direct lysis of platelets, suppression of

megakaryocytes and reduction in thrombopoietin secretion. This multiplicity of mechanisms or pathways explains the heterogeneous pattern of clinical presentation and response to therapy observed in ITP patients.[22]

1.5.1 Antiplatelet auto-antibodies in ITP

The hallmark of the diagnosis in ITP is the presence of autoantibodies directed against platelets. Earlier studies in the 1970s showed increased production of antibodies, mainly of the Immunoglobulin G (IgG) class in about 90% of ITP patients.[23] However, with the newer more sensitive tests, autoantibodies are detected in only 60% of patients.[24] This finding underscores the success of immunosuppressive therapy such as corticosteroids and splenectomy in the management of this disorder. Specifically, the autoantibodies are directed against platelet glycoprotein (GP)IIb/IIIa, GPIb/IX and others like GPIa/IIa, GPIV, and GPV.[21] It has also been shown that megakaryocytes are a target of these autoantibodies in studies by McMillan et al, Rabellino et al and Vinci et al in the 1970s.[25,26,27] The observation that platelet production is not increased in the face of accelerating platelet destruction gives further credence to the fact that megakaryocytes are also suppressed.[22]

1.5.2 T- cell dysfunction in ITP

The suspicion that T -cell dysfunction may play a role in the pathogenesis of ITP had initially been reported by different study groups but it was only in 2003, that the study by Olsson et al demonstrated a cytotoxic T lymphocyte mediated thrombocytopenia in ITP patients in whom autoantibodies were not detected. They observed in an in

vitro study that patients with active disease had peripheral blood T-cells that could bind to platelets resulting in their destruction.[3,28,29]

In addition, T cells are also implicated in antibody production via CD4 Th0/ Th1 activation, associated with reduced peripheral Th2 and T-regulatory cells and impaired susceptibility to apoptosis. The net effect is promotion of antigen presentation and perpetuation of the pro-inflammatory milieu with cell-mediated and complement-fixing IgG responses. Loss of immune tolerance by T-cells to autoantigens is the basis for immune dysregulation in ITP.[3,21,22,30,31]

1.5.3 Defective Thrombopoiesis in ITP

Studies by Emmons et al and Kosugi et al in 1996, independently observed that thrombopoietin levels are normal or slightly increased in ITP in contrast to the expected elevated levels, if the only mechanism was peripheral destruction, implying a defective thrombopoiesis in this condition.[32,33]

Endogenous thrombopoietin (TPO) which is produced primarily in the liver is the main regulator of megakaryocytopoiesis and platelet production.[34] As TPO is being produced, it is constantly used up by megakaryocytes and platelets. Thrombopoietin deficiency can either be primary where there is decreased production from liver disease or a functional deficiency resulting from rapid clearance by megakaryocytes and platelets.[35] The lower-than-expected level of TPO observed in ITP is thought to be due to a functional TPO deficiency.[36-39]

This discovery paved way to the development of thrombopoietin receptor agonists (TPO-RAs) which have proven effective in the management of ITP.[40]

1.5.4 Variable pathogenesis of thrombocytopenia in secondary ITP

The potential to initiate an autoimmune response and antibody production in secondary ITP results from different mechanisms. A common mechanism relating to most infectious causes of secondary ITP such as HIV, HCV and helicobacter pylori is as a result of production of cross reactive antibodies. This mechanism is otherwise known as molecular mimicry. The inciting organism shares similar antigenic proteins with some surface receptors on platelets such as GPIIb/IIIA, resulting in the production of antibodies against the inciting agent binding to platelets.[41-46]

The mechanism in autoimmune diseases such as SLE, Antiphospholipid syndrome and Evans syndrome is de novo autoantibodies cross reacting with platelets.[47-50] Furthermore, certain haematological disorders associated with immunodeficiency (e.g. CLL, CVID and ALPS) produce antibodies that cause platelet destruction.[51-54]

Non immunologic mechanisms also contribute to thrombocytopenia in some cause of secondary ITP. This includes cytopathic destruction of megakaryocytes by HIV and inadequate thrombopoietin secretion in chronic liver disease from viral hepatitis C infection.[34,45] In both instances, the result is impaired platelet production.

1.6 Clinical presentation

The clinical presentation in adults may be acute or insidious in onset. About 80% of patients go on to develop chronic ITP. Spontaneous remissions occur in 5 - 11% of adults, mostly in the first year after diagnosis.[55,58] In general, there is an inverse

relationship between remission and the duration of the disease, so that the chances of remission decline as the disease progresses.[56]

Immune Thrombocytopenia (ITP) can be asymptomatic with no clinical features of bleeding in 20-40% of patients.[9,13,21] This is because bleeding is uncommon when platelet counts are above 30 x 10^9/l.

The most frequent hemorrhagic manifestation in ITP is purpura. Purpura broadly encompasses any kind of mucocutaneous bleed, i.e. skin and/or mucous membrane. Thus epistaxis, gum bleeding and sub-conjunctival bleeding are all considered as purpura according to IWG. The presence of any bleeding necessitating treatment in ITP patients is now regarded as severe ITP. Terminologies such as mild or moderate ITP have been discarded.[57]

The incidence of major bleeding events such as intracranial hemorrhage is low; being 1.6% in one long term observational study.[58] The platelet count remains the best known predictor of bleeding events in ITP.

1.7 Management

The decision to initiate treatment is primarily based on whether the patient is symptomatic (bleeding) and the level of the platelet count (< 30 x 10^9/l). The goal of treatment is to stop the bleeding and increase the platelet count to a safe level and not necessarily to achieve a normal platelet count.

Newly diagnosed ITP refers to disease from diagnosis to 3 months. In this phase of the disease, corticosteroids (CS) are the mainstay of treatment. Corticosteroids act

by suppressing antibody production and reticuloendothelial phagocytic function in the spleen and bone marrow. They also improve vascular integrity by acting directly on blood vessels[93]. Corticosteroids used in ITP include: prednisone, dexamethasone and methylprednisolone. Prednisone is the preferred initial treatment, at a dose of 1-2 mg/kg/day x 10-14 days (up to 21 days). Prednisone is then tapered over the next 4 to 6 weeks. Alternative treatments include dexamethasone – 40 mg daily orally/IVI x 4 days or methylprednisolone – 1g daily IVI x 3 days. Platelet transfusions are reserved for patients with severe/very severe thrombocytopenia who are actively bleeding or who have recent onset 'red purpura' such as oral haemorrhagic bullae.

For emergency treatment, intravenous immunoglobulin (IVIg) and IVI/oral CS should be used in combination. Platelet transfusions should be administered (1 unit single donor apheresis platelets) in the bleeding patient with severe thrombocytopenia. Another option that may be considered where the patient continues to have active bleeding despite the above measures (i.e. CS, IVIg, platelet transfusion), is an emergency splenectomy. However, this is rarely necessary.

Persistent ITP refers to disease that persists beyond 3 months up to 12 months. Treatment should be considered in symptomatic patients and if the platelet count is $<30 \times 10^9$/l. Treatment options include CS or IVIg if used successfully previously. CS are preferred over IVIg, as the benefit of IVIg is likely to be temporary (short-lived) and at a much higher cost. Second line immunosuppressive agents (such as azathioprine and mycophenolate mofetil), should be considered as steroid sparing agents. If the above therapy proves unsuccessful, other second line agents such as cyclophosphamide, danazol, vincristine etc. may be considered. Rituximab and TPO-

receptor agonists (TPO-RAs) used as bridging therapy are further options if not prohibited by cost considerations. It is preferable to defer splenectomy to beyond 6 months and ideally to beyond 12 months, as a small proportion of patients may achieve spontaneous remission during the persistent phase of disease. The choice of second line therapies is based on the experience of the clinician, efficacy and safety of the drug, availability, cost and patient preferences.[59,60]

Chronic ITP refers to disease that persists/continues for more than 12 months. It is likely that the patient may have been on intermittent CS, and/or other immunosuppressive or second line therapy, with a variable clinical response. The three major treatment options for chronic ITP include TPO-RAs, rituximab and splenectomy. Each of these options has advantages and disadvantages and treatment must be tailored and individualized to the patient with chronic ITP.

1.7.1 Thrombopoietin receptor agonists (TPO –RAs)

Two TPO-RAs are available for use in ITP, romiplostim and eltrombopag. They bind to the thrombopoietin receptor causing proliferation and differentiation of megakaryocyte progenitor stem cells similar to the action of endogenous thrombopoitin.[61,62] Romiplostim is available as a weekly subcutaneous injection at a dose of 3-10ug/kg, while eltrombopag is an oral agent taken daily at a dose of 30-50mg.

These agents are effective in both splenectomised and non-splenectomised patients with a response rate of up to 88%. However, the response is delayed for at least 2 weeks and an indefinite duration of treatment is required to achieve a durable

response.[62,63] In one randomized controlled trial, patients treated with romiplostim had a higher quality of life with less bleeding and fewer transfusions compared to the standard first line medical care[94]. The most feared complication of TPO-RA is progressive bone marrow fibrosis but clinical trials suggest that the incidence is low. Other complications include, headache, rebound thrombocytopenia following abrupt discontinuation of drug, increased incidence of arterial and venous thrombosis and with the use of eltrombopag, there is a risk of hepatotoxicity.[64-67]

1.7.2 Rituximab

Rituximab is an anti-CD20 monoclonal antibody used as an 'off- label' indication in patients with ITP. Rituximab targets CD-20 positive B-cells, resulting in B-cell depletion. From the experience of its use in lymphoma and ITP trials, it is a safe and relatively well tolerated drug. Rituximab induces a one year CR in 44% of patients with a single course of treatment (375mg/m^2 weekly for 4 weeks).[68-73]

Its efficacy is not reduced with repeated use in patients who previously responded and those who have had a splenectomy, making it a useful option not only in persistent and chronic ITP, but also in refractory ITP.[31,74] The predictors of response as suggested in the literature include young patients, prior response to CS therapy and early use of rituximab in the course of ITP. Also, the combination of rituximab with high dose dexamethasone has shown improved response rates of 71% and a durable response of 57%.[74-76]

The most common complication of rituximab is the first infusion reaction seen in 10-15% of patients. This can be prevented by pre-medication with diphenhydramine and paracetamol, as well as a slow infusion rate, over several hours. Rarely, the use of

rituximab has been associated with life threatening infections such as fulminant hepatitis B infection, pneumocystis jirovecci pneumonia, parvovirus B19 infection and progressive multifocal leukoencephalopathy.[77] A mortality rate of 2.9% was reported in one study mostly related to infections. However, many of these patients were on prior immunosuppressive therapy which may have confounded this finding.[75] In general, rituximab is considered a safe and effective drug for ITP.

1.7.3 Splenectomy

Splenectomy is the most definitive therapy for ITP. It has the highest likelihood of all the current treatment options of producing a cure. It is effective for persistent and chronic ITP after failure of CS therapy. It is recommended that splenectomy be delayed for at least 6 months (and preferably 12 months) from diagnosis due to the chance of a spontaneous remission – 5-11%.[55,58]

The overall response rate is 70-90% (CR 50-60%, PR 20-30%, relapse rate 15%).[58] Open splenectomy and laparoscopic splenectomy have similar efficacy. One disadvantage of laparoscopic splenectomy is inability to look for accessory splenectomy at surgery, however, it has fewer surgical complications, including less postoperative pain, earlier general diet tolerance and shorter hospital stay.[77,78] The risk of OPSI (overwhelming post-splenectomy infection) is 1.4-fold increased in the first year after splenectomy.[77] Vaccination against *S. pneumoniae, N. meningitides* and *H. influenza* are recommended two weeks prior to the procedure.[79] If relapse occurs post-splenectomy, accessory splenic tissue (splenunculi) should initially be sought and excluded.

The advantages and disadvantages of splenectomy are tabulated in Table 1.2 and a check list is also included where splenectomy is contemplated/indicated or has been performed –(see Table 1.3 on page 16).[77]

Table 1.2 Advantages and disadvantages of splenectomy as a therapeutic option in ITP

	ADVANTAGES	**DISADVANTAGES**
Splenectomy	- Effective, tried and tested therapy - Most definitive therapy in ITP - May be curative - Response rate 70-90%; CR 50- 60%; PR 20-30% - Approximately 60% of patients remain in remission 5-10 years after splenectomy – an outcome that is not superseded by any other therapy - High response rate confirmed in local studies[16,80] - Recommended for adults Who have failed CS therapy - No major cost consideration - No further therapy required in complete responders - A safe option in responding patients who contemplate pregnancy - Suitable in young, middle-aged adults	- Removal of relatively 'healthy' organ - Irreversible - Response may be unpredictable - Relapse rate: up to 15% - Surgery - related mobidity and mortality (less with laparoscopic splenectomy) – includes bleeding, infections and thrombosis - OPSI (overwhelming post splenectomy infection) in small minority of patients - Increased risk of thromboembolic events - Other adverse events include: Pulmonary hypertension <u>Caution / ?contraindications</u> - Significant co-mobidities that increase risk of complications - Elderly patients have a higher rate of complications, e.g. VTED - Increased risk of infection in Patients with immunodeficiency states e.g. CVID, Hepatitis C, HIV (however, successful splenectomy has been performed in carefully selected patients locally and elsewhere)

Table1.3 Check list for splenectomy patients

A. Before splenectomy	**Intervention**
Education regarding procedure and possible complications. Discuss laparoscopic versus open splenectomy	Consider antibiotic cover for *S. peumoniae* and *H influenza* if clinically indicated. Use augmentin or a cephalosporin or a quinolone
Vaccination	Vaccination against *S. pneumonia, N. meningitides* and *H. influenza* type b, ideally 14 days before scheduled splenectomy
Elevation of platelet count	Increase platelets to >50x10^9/l by using CS, IVIg, other treatment. This may not always be necessary, depending on the surgeon. Procedure can be safely performed at lower platelet counts with platelet transfusion administered at time of clamping the splenic vessels
Thrombosis risk	Consider appropriate thrombo-prophylactic measures
Imaging/platelet sequestration studies	^{111}In-labelled platelet sequestration studies if available [81]
B. After splenectomy	**Intervention**
Antibiotic prophylaxis	Postoperative antibiotic prophylaxis for 2 weeks or until the risk of infection is abated. In younger individuals, long-term antibiotic prophylaxis may be considered up to the age of 21. Antibiotics may also be considered in adults for the first two years post-splenectomy. Patients should be educated about infections/OPSI, and encouraged to wear a bracelet indicating 'splenectomy' Where long term antibiotic prophylaxis is not used, patients should be provided with a short course/supply of antibiotics which could be used at

	home at the earliest onset of fever/infection, prior to seeking further medical attention
Thrombo-prophylaxis	Good hydration, early mobilization, mechanical prophylaxis (IPC). Consider anticoagulants (LMWH) once platelet count has increased (haemostasis secured/no bleeding) if any risk factors for thrombosis are present or there is a rapid increase of the platelet count into the thrombocytosis range
Discontinuation of other treatments	Gradual tapering of CS, tapering and discontinuation of TPO-RA
Revaccination	Annual 'flu' vaccine. Booster vaccine for *S. pneumonia* every 5 years
Relapse after splenectomy	Look for accessory spleen – technetium scan
Regular follow up	Monitor platelet counts post-surgery: every few days in the first week to 10 days; then 2 weekly x 1 month, monthly x 3 months, 3 monthly x 1 year and at least 6-12 monthly thereafter. Check platelet count at any time in symptomatic or bleeding patients

A number of factors have been described in the literature as predictors of outcome following splenectomy. Younger patient have the best response to splenectomy with the lowest complication rates compared to elderly individuals who usually have associated co-morbidities. A high platelet count in the first 10-14 days after splenectomy also confers a favourable response. Prior poor response to multiple agents, longer duration of disease and secondary ITP are associated with poorer outcomes.[58,82-89]

The type of splenectomy procedure impacts on the morbidity and mortality following splenectomy. A series by Kojouri et al, reported a complication rate of 12.9% with laparotomy (open splenectomy) and 9.6% with laparoscopic splenectomy. However, mortality was significantly low (1% for laparotomy versus 0.2% for laparoscopic splenectomy).[58] The complications include intra-operative complications such as bleeding and injury to internal organs, infections (including OPSI) and post splenectomy thrombotic events.

Infections caused by encapsulated organisms are always a concern following splenectomy. In a retrospective study of 9976 ITP patients (splenectomised and non-splenectomised), the cumulative incidence of sepsis in patients who had a splenectomy was 11.1% versus 10.1% in non-splenectomised patient.[90] This study, together with the study by Vianelli et al, reported a very low mortality rate from infection, with the latter study showing zero mortality from infection.[82,90]

A potential concern in our setting is the perceived increased risk of infections following splenectomy in HIV sero-positive patients. Studies that looked at response and complications following splenectomy showed no significant difference between HIV positive and HIV negative patients.[16,79,92]

Patients who have refractory ITP, having undergone splenectomy carry a poorer prognosis, although some of these patients may eventually achieve remission in the long term. Mortality is related to both complications of splenectomy and toxicity of therapy.[90,91]

1.8 Aims and objectives of the study

1.8.1 Aims

To study the impact of splenectomy as a therapeutic modality in patients with ITP

1.8.2 Objectives

a. To assess the impact (specifically the indication, timing, outcome - response and duration of response, complications etc.) of splenectomy in ITP

b. To compare the efficacy and safety of laparoscopic versus open splenectomy in ITP

c. To compare the efficacy, safety and outcome of splenectomy in primary and secondary ITP

CHAPTER 2: PATIENTS AND METHODS

2.1 Study Design

This is a retrospective study of all splenectomised patients with ITP who were diagnosed and managed at the Clinical Haematology unit, Department of Medicine, Chris Hani Baragwanath Academic Hospital, between 01/01/1986 and 31/12/2014 (29 years).

2.2 Study Population

The study included all patients that had a splenectomy for ITP and where sufficient data was available for review of the patients. There were 64 patients, of whom 56 were evaluable.

2.3 Inclusion Criteria

Patients > 18 years of age who were diagnosed with ITP and who have had a splenectomy

2.4 Exclusion Criteria

a. Patients < 18 years of age

b. Patients who have missing and/or incomplete records/data

2.5 Description of Methodology

A retrospective review of records of patients who had a splenectomy for ITP, during the aforementioned study period was performed. Permission was obtained from the Clinical Haematology Unit, the Department of Medicine and the CHBAH authorities.

A standardised questionnaire (see Appendix B) was used to document the following characteristics, on each of the patients:

a. Demographics
b. Diagnosis–primary or secondary ITP and cause of secondary ITP
c. Indication for splenectomy
d. Timing of splenectomy (i.e. time from diagnosis to splenectomy)
e. Type of splenectomy–open or laparoscopic
f. Details of treatment and number of lines of treatment pre-splenectomy
g. Clinical and laboratory parameters prior to and post-splenectomy
h. Specific preparation of patients prior to splenectomy (re: target platelet counts, vaccination, platelet transfusion during procedure)
i. Peak post-splenectomy platelet count and response in the immediate post-splenectomy period (10-14 days)
j. Antibiotics peri and post-splenectomy
k. Therapies used peri and post-splenectomy (e.g. corticosteroids, IVIg)
l. Thrombo-prophylaxis
m. Complications – immediate and delayed (intra-operative, post-operative – sepsis, bleeding, thrombosis, and relapse)
n. Outcome (based on response criteria)
o. Mortality related to splenectomy or other reasons for mortality

The response criteria in ITP are as defined in Table 2.1 below.

Table 2.1 Response criteria in ITP

a. Complete response (CR)	Platelet count ≥ 100 x 10^9/l and absence of bleeding
b. Partial response (PR)	Platelet count ≥ 30 x 10^9/l and at least 2 - fold increase of the baseline count and absence of bleeding
c. No response (NR)	Platelet count < 30 x 10^9/l, or less than 2-fold increase of the baseline count or bleeding
d. Loss of CR or R	Platelet count below 100 x 10^9/l or bleeding (from CR) or below 30 x 10^9/l or less than 2-fold increase of the baseline count or bleeding (from response)
e. Time to response	Time from starting treatment to time of achievement of CR or R
f. Duration of response	Measured from the achievement of CR or R, to loss of CR or R
g. Refractory ITP	Failure to achieve R or loss of response after splenectomy; ongoing need of treatment to minimize the risk of clinically significant bleeding

The patient's name and personal details were kept confidential. The file numbers were given a numerical coding system in order to maintain confidentiality.

2.6 Data Analysis

Data was captured on an Excel spreadsheet and exported into SPSS version16.0 (originally, Statistical Package for the Social Sciences and renamed Statistical Product and Service Solutions) software.

Descriptive statistics such as the frequency distribution, median and standard deviation were used to transform the raw data into a form that is easy to understand and interpret. Frequency distributions were presented graphically as either pie or bar charts for categories such as patient gender with only male and female categories. In cases where there were more categories such as site of bleeding, bar graphs were used to present the results graphically.

A paired sample t-test was conducted to assess whether there was a significant difference between the highest platelet counts 14 days post splenectomy and the platelet counts prior to splenectomy as well as the difference between the platelet counts one year post splenectomy and the platelet counts prior to splenectomy. The paired t-test examines if the mean of the differences is different from zero (no difference). If the p-value of the t-test is less than 0.05 (the significance level), then the difference between the two samples is considered to be significant. If the p-value is greater than 0.05 then the null hypothesis cannot be rejected and it is concluded that there is no difference between the two means.

2.7 Ethics Approval

Ethics approval was granted by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (Clearance Certificate no. M150590). Informed consent was not needed from the patients due to the retrospective nature of the study.

CHAPTER 3: RESULTS

3.1 Demographics

Of the 56 splenectomised ITP patients, 77% were females (n=43) and 23% were males (n=13).

The median age of the patients was 29 years with a median age of 29 with a range of 18-53 years.

The ethnic breakdown of the patients was as follows: The vast majority of the patients were Blacks (n=49, 87.5%), while (n=4, 7%) were Whites, a smaller number (n=2, 3.6%) were of Indian origin and (n=1,1.8%) patient was of Mixed race (coloured). The demographic profile table is shown below.

Table 3.1: Demographic profile

Demographics	Frequency	Percent
Gender		
Male	13	23%
Female	43	77%
Ethnicity		
Black	49	87.5%
White	4	7%
Indian	2	3.6%
Mixed race	1	1.8%

3.2 Clinical Presentation

Bleeding manifestations constituted the most common clinical presentation (n=45, 80%) on admission. This decreased to (n=35, 62.5%) prior to splenectomy and further to (n=4, 7.7%) 1 year post-splenectomy. The site of bleeding was mainly cutaneous (32 of 45, 71%) at presentation, and (27 of 35, 77%) prior to splenectomy. None of the splenectomised cohort had lymphadenopathy, hepatomegaly or splenomegaly.

Table 3.2: Clinical features according to timelines

		First Presentation	**Prior to Splenectomy**	**1-year Post-Splenectomy**
Bleeding	n=	56	56	52
		45 (80.4%)	35 (62.5%)	4 (7.7%)
	asymptomatic	11 (19.6%)	21 (37.5%)	46 (88.5%)
Site of Bleeding		45	35	4
	skin	32 (71%)	27 (77%)	4(100%)
	sub-conjunctival	1 (3.1%)	0 (0.0)	
	epistaxis	7 (15.6%)	5 (14.3%)	
	gum	1 (3.1%)	0 (0.0%)	
	menorrhagia	3 (6.7%)	1 (2.9%)	
	haematuria	1 (3.1%)	0 (0.0%)	
	ICB	0 (0.0%)	2 (5.7%)	
Fever	n=	56	56	52
		2 (3.6%)	1 (1.8%)	0 (0.0%)
Anaemia	n=	56	56	52
		12 (21.4%)	7 (12.5%)	0 (0.0%)

ICB- Intra-cerebral bleed

Of the 56 patient, three patients (5.4%) were HIV sero-positive, while one patient (1.8%) had mixed mitral valve disease. Eleven patients (19.6%) had an underlying autoimmune disease. Of these 11 patients, nine were diagnosed with systemic lupus erythematosus (SLE), 1 patient had an auto-immune Haemolytic anaemia (Evan's syndrome) and another patient had mixed connective tissue disease (MCTD). None of them had a lymphoproliferative disorder or Tuberculosis (TB).

Table 3.3: Co-morbid diseases

		Frequency	**Percent**
TB		0	0.0
HIV	positive	3	5.4
	negative	53	94.6
Auto immune Disease		11	19.6
Type of Auto immune Disease	SLE	9	81.8
	AIHA	1	9.1
	MCTD	1	9.1
LPD		0	0.0
Mixed Mitral Valve disease		1	1.8

HIV- Human Immunodeficiency Virus; LPD- Lymphoproliferative disorder; SLE- Systemic Lupus Erythematosus, AIHA- Autoimmune Haemolytic Anaemia; MCTD- Mixed Connective Tissue Disease

Prior to splenectomy, all the 56 patients (100%) were on prednisone, 11 patients (19.6%) had received IV immunoglobulin, 35 patients (62.5%) were treated with azathioprine and only 5 patients (9%), received rituximab.

A year post splenectomy, the number of patients receiving prednisone decreased to 14 patients (26%), 8 patients (14.8%) were still on azathioprine, with only 2 patient on rituximab as a result of poor response to splenectomy (partial or no response).

Table 3.4: Drug history prior to splenectomy and 1 year after splenectomy

	Drugs Prior to Splenectomy	**Drugs 1-yr Post-Splenectomy**
Prednisone	56	54
	56 (100%)	14 (26%)
Solumedrol		
	20 (35.7%)	-
Danazol	56	54
	11(19.6%)	-
Azathioprine	56	54
	35 (62.5%)	8 (14.8%)
Rituximab	56	54
	5 (9%)	2 (3.7%)

3.3 Types of ITP

Most of the patients who had a splenectomy were diagnosed with primary ITP (n=42, 75%), while secondary ITP was encountered in the remainder (n=14, 25%).

Of the 14 patients that had secondary ITP, 11 patients (79%) had an underlying autoimmune disease, while 3 patients (21%) were sero-positive for HIV.

Table 3.5: Secondary ITP

		Frequency	**%**
Cause of secondary ITP	Auto-immune	11	79
	HIV	3	21

In ‘classical’ primary ITP, a bone marrow aspirate and trephine (BMAT) is not always performed. However, in this study, forty-seven patients (84%), had a (BMAT).

3.4 Time to splenectomy

It took on average, 27.9 months from the diagnosis of ITP to splenectomy (range: 1 month - 156 months). Half of the patients took 12 months or longer to splenectomy (median = 12 months). Fourteen patients, constituting 25% of the total, had their splenectomy after 24 months.

Table 3.6: Time to splenectomy according to intervals in months

Interval (months)	Frequency	%
0 - 3 months	8	14.3
3 - 6 months	4	7
6 - 9 months	10	17.9
9 - 12 months	10	17.9
18- 24 months	10	17.9
> 24 months	14	25
Total	56	100.0

3.5 Types of splenectomy

Open splenectomy was performed in the vast majority of patients (91%). Three patients had a laparoscopic procedure, while 2 patients had their laparoscopic surgery later converted to open splenectomy due to complications.

Table 3.7: Types of splenectomy

Types of splenectomy	Frequency	%
Laparascopic	3	5.4
Laparascopic/ Open	2	3.6
Open	51	91
Total	56	100.0

3.6 Number of classes of treatment used prior to splenectomy

In this study, most patients received up to three different classes with a minority receiving a fourth or fifth drug class prior to splenectomy (see Table 3.10 on page 34).

Table 3.8: Number of classes of treatment used prior to splenectomy

Variable	Classes	Number	%
Classes of treatment prior to splenectomy	1	22	39.3%
	2	18	32.1%
	3	10	17.9%
	4	4	7.1%
	5	2	3.6%

3.7 Indication for splenectomy

The indication for splenectomy was mainly due to poor response to medical therapy (partial and no response, relapse, steroid dependency with side effects in order to maintain platelet count above 30 x 10^9/l) in 55 patients (98.2%). In 1 patient, the indication was due to poor compliance to therapy. The breakdown of indication for splenectomy as relates to CS therapy is shown in figure 3.6 below.

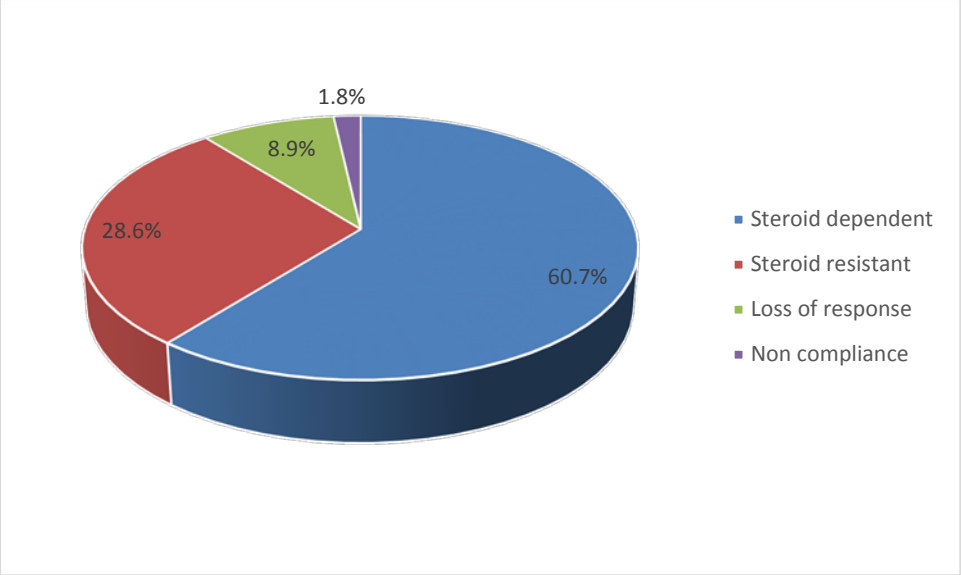

Figure 3.6: Indication for splenectomy as relates to CS therapy

3.8 Preparation for splenectomy

Most of the patients (87.5%) had a platelet transfusion peri-splenectomy (i.e. shortly before or during the procedure) as shown in the table below.

Table 3.9 Peri-operative measures

Antibiotics peri-splenectomy and up to 2 weeks post splenectomy	56	100%
Pneumococcal vaccination	56	100%
Platelet transfusion	49	87.5%
Thrombo-prophylaxis	0	0

Table 3.10: Number of splenunculi detected intra-operatively

	Frequency	**%**
Splenunculi	3	5.4

The table below show various complications recorded from splenectomy including the mortality.

Table 3.11: Complications

	Perioperative		**Non-operative**	
	n	**%**	**n**	**%**
Infection	2	3.6	9	16.1
Bleeding	1	1.8	4	7.1
Thrombosis	0	0	2	3.6
Death	1	1.8	1	1.8

3.9 Response to splenectomy

The mean platelet counts response according to timelines is summarized below.

Table 3.12: Platelet count response according to timelines

Mean platelet counts-at presentation	12 x 10^9/l
Mean platelet counts-pre-splenectomy	26 x 10^9/l
Mean platelet counts-14 days post- splenectomy	347 x 10^9/l
Mean platelet counts-1-year post-splenectomy	231 x 10^9/l

A paired sample t-test was conducted to compare the platelet count 14 days post splenectomy and the platelet count prior to splenectomy. The results are shown on page 32.

Table 3.16: Paired sample t-test for highest platelet count 14 days post-splenectomy against the platelet counts prior to splenectomy

Paired Sample Statistics				Paired Sample t-Test	
	Mean	**Number**	**Standard deviation**	**t-value**	**p-value (2 Sided)**
Highest platelet count 14 days post splenectomy	347.2	56	177.7	10.8	0.000
Platelet count prior to splenectomy	26.2	56	31.6		

It was noted that the highest platelet count 14 days post splenectomy were on average 347.2 ± 177.7, compared to 26.2 ± 31.6 prior to splenectomy. The difference between the two is significant with a p-value = 0.00

A paired sample t-test was also conducted to compare the platelet count one year post splenectomy and the platelet count prior to splenectomy. The results are shown in table 3.14.

Table 3.14: Paired sample t-test for platelet count one year post splenectomy against the platelet count prior to splenectomy

Paired Sample Statistics				Paired Sample t-Test	
	Mean	**Number**	**Standard Deviation**	**t-value**	**p-value (2 Sided)**
Platelets counts one year post splenectomy	231.2	56	162.6	7.4	0.00
Platelet counts prior to splenectomy	26.2	56	31.6		

The result shows that the platelet counts one year post splenectomy (mean = 231.2 ± 162.6) were significantly higher than the platelet counts prior to splenectomy (mean = 26.2 ± 31.6). The difference between the two is significant with a p-value of 0.00

The status of disease at the last visit is depicted in Figure 3.2 on page 34. Thirty seven patients, 66% were in complete remission, 7 patients (12.5%) had a partial remission while there was no response and loss of response in 3 patients each. Two patients died (3.6%) and in 4 patients (7.1%), the response was unknown.

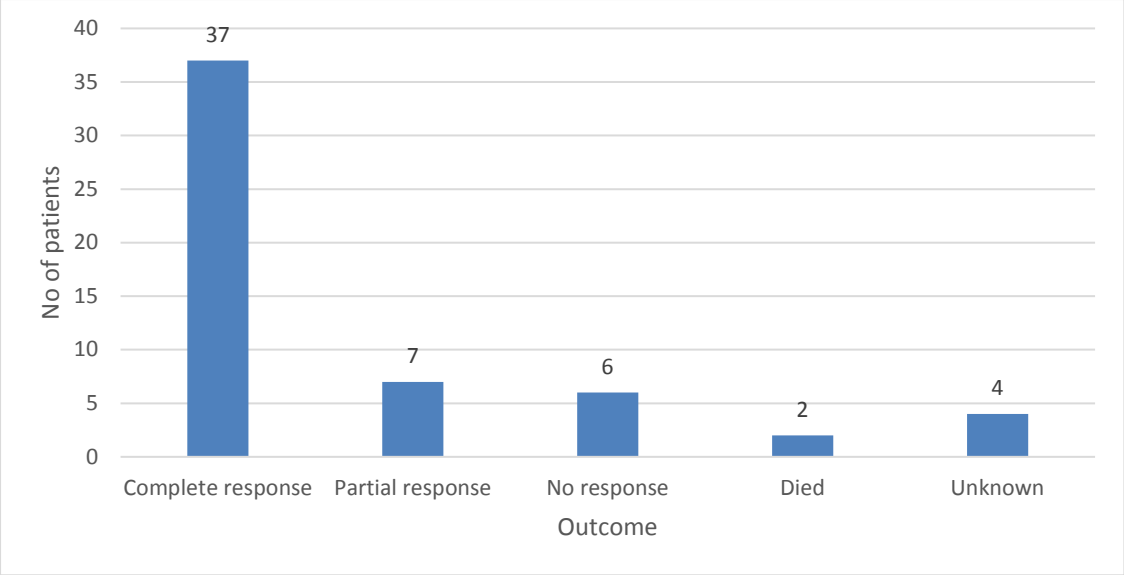

Figure 3.2 Status of disease at last visit

CHAPTER 4: DISCUSSION

4.1 Introduction

Splenectomy was the first, definitive, recognized therapeutic modality in ITP, several years before the discovery of corticosteroids in the 1950s.[9] The role of splenectomy as a treatment option has evolved over the last century and it is currently regarded as a second line treatment option.

To this effect, the current retrospective study was performed, to assess the impact of splenectomy on the management of ITP, in patients at Chris Hani Baragwanath Academic Hospital from 1986 to 2014. Of the 343 patients who were diagnosed with ITP within the study time frame, 64 patients had a splenectomy (64/343=18.6%).

4.2 Epidemiology

Similar to many autoimmune diseases where females are predominantly affected, in this study, the female to male ratio was 3.3:1. This is the same gender ratio reported in the Cape Town splenectomised cohort (Female=56, Male=17)[79]. The female preponderance is also in keeping with the gender distribution of ITP in our institution as observed in a recent study by Variava, in which 80% were females, with a female to male ratio of 4.2:1.[16] The gender differences of ITP were less marked in two international studies where the female to male ratio were 1.7:1 and 1.2:1[95,96]. This disparity may be ascribed to the increasing number of secondary ITP due to HIV infection which is mostly prevalent among women between the ages of 15 and 49 in South Africa.[97]

The mean age of these patients was 31 years, in keeping with local South African studies.[15,16] However, ITP is now being increasingly seen in older patients in the Western world with estimated average age of 60 years. The gender difference of a female predominance in young and middle aged individuals is also less marked in the elderly.[13,14]

4.3 Clinical Presentation

The majority of our patients presented with bleeding. Eleven patients (19.6%) were asymptomatic at first presentation, having been diagnosed after incidental review of their blood counts. Similar to the reports in the literature, the commonest bleeding manifestations were mucocutaneous bleeds[57]. Eighty percent of our patients had skin bleeds (n=45), followed by epistaxis (n=7, 15.6%) and menorrhagia (n=3, 6.7%). Two patients (3.6%) had an intra-cranial bleed of all the clinical presentations in this series of splenectomised patients and 2% of all cases of ITP at our institution as reported by Variava[16]. Both figures are higher than in the US series where the incidence of intra-cranial bleed was less than 1%[98].

All the patients satisfied the requirement of initiating treatment for ITP, based either on the severity of bleeding or a significant thrombocytopenia (levels < $30x10^9$/l).

The mean platelet count prior to splenectomy was 26 $x10^9$/l, as opposed to 12 x 10^9/l at presentation. The higher mean platelet count prior to splenectomy is a reflection of patients being on treatment and the indication for splenectomy not only being a low platelet count, but other factors such as steroid dependence with intolerable or unacceptable side-effects.

None of the patients had lymphadenopathy, splenomegaly or hepatomegaly. Thus, the diagnosis of ITP could be made with a high degree of probability on clinical grounds alone. Nonetheless, 84% of the patients (n=47) subsequently underwent a bone marrow examination to further strengthen the diagnosis and exclude other causes of ITP.

Of the 14 patients (25%) with secondary ITP who had a splenectomy, 11 patients had an underlying autoimmune disease (9 patients had SLE while concomitant autoimmune haemolytic anaemia and mixed connective tissue disease was present in 1 patient each, respectively). In this study, the number of HIV sero-positive patients who had a splenectomy was low (n=3, 5.4% of all splenectomised patients with ITP) compared to what would have been expected with the change in the pattern of the aetiopathogenesis of ITP in South Africa. Human immunodeficiency virus infection has increasingly become a major cause of secondary ITP. In our experience at CHBAH as observed in the study by Variava, secondary ITP accounted for 50% of all cases of ITP, of which 40% of cases were due to HIV infection. The lower than the expected number of HIV associated ITP requiring splenectomy may be attributed to a favourable response to HAART and medical therapy or possibly to the concern of increased morbidity, particularly in relation to infection, in the setting of splenectomy in HIV seropositive patients.

4.4 Splenectomy and ITP

Having failed CS, either alone or in combination with other agents, such as second line immunosuppressive therapy or IVIg, patients with persistent and chronic ITP typically require one of three second line therapies, viz: splenectomy, rituximab and

TPO-RAs (e.g. eltrombopag, romiplostim). Of these three modalities, splenectomy has the highest efficacy in relation to achieving a cure (based on a sustained, complete remission). Up to 90% of patients will show a response to splenectomy, and up to two thirds of patients will achieve a complete and durable remission.[58]

Our study showed a similar outcome with 66% (n=37) achieving a complete remission and a further 12.5% (n=7) showing a partial response. There was no response or loss of response (relapse) in 10.7% (n=6) of the patients.

The mean platelet count of 231.9 X 10^9/l, one year post splenectomy was statistically significantly higher than the mean platelet count prior to splenectomy (26 X 10^9/l), with a p-value = 0.00.

In those who have a complete and sustained response to splenectomy, splenectomy is regarded as being curative, with no need for further therapy. By extension, it is therefore cost effective, compared to the newer agents, especially the TPO-RAs, which need to be given for a prolonged period of time, prior to possible discontinuation.

In the Western world, there is a progressive decline in the rate of splenectomy, where cost may not be a limiting factor and where patient preferences play a significant role.[77] In addition, although splenectomy is a relatively safe procedure, it is not without complications. Given the paradigm shift, with ITP occurring in older patients in the Western world, there is also a concern about the increased risk of thrombotic manifestations post-splenectomy.[58]

Failed CS therapy was the commonest indication for splenectomy in this study in keeping with the literature where remission is only expected in 10 to 30% of cases[99]. All of the patients were on CS therapy prior to splenectomy with 22 patients on CS therapy alone (39.3%), while the remaining patients had additional therapies. Up to 5 classes of treatment were used prior to splenectomy. Steroid dependence and steroid resistance were noted in 34 and 16 patients, respectively, while 5 patients had a relapse or loss of response to CS. The majority of these patients also experienced disabling side effects from high doses and prolonged use of CS.

Six patients (10.7%) did not respond to oral and/or IV CS and IV immunoglobulin, necessitating splenectomy within a period of three months. Three of these 6 patients (5.4% of all splenectomised patients) underwent emergency splenectomy. The indication for emergency splenectomy was an intracranial bleed in 2 patients, while the third patient had severe, ongoing, active bleeding which did not respond to supportive and specific measures, including CS, IV immunoglobulin and platelet transfusions. All of these patients had a favourable outcome, following emergency splenectomy.

Only one patient underwent splenectomy due to poor compliance to treatment. Incidentally, this patient was also diagnosed with mixed mitral valve disease that required surgery and anticoagulation.

The average time to splenectomy in this study was 27.9 months. This is significantly longer than the previous recommended period of > 6 months from diagnosis. In the

newer guidelines, there is a trend to delay splenectomy to more than one year, as a small proportion of patients (5-11%) may achieve a spontaneous remission up to 1 year from diagnosis. This observation is important as it is well documented that time to splenectomy is an important predictor of response. The further splenectomy is delayed from the diagnosis of ITP, the poorer the response.[55,58]

The delay to splenectomy in this study may be attributed to the perceived danger and complications of surgery, and the removal of an 'organ' of the body, which is irreversible.

Age at splenectomy is considered to be an independent and consistent predictor of response to splenectomy.[83] The mean age of the patients prior to splenectomy was 31 years. Eight patients were older than 40 years of age, and none were older than 60 years. Only one patient in the age group > 40 years had a poor response to splenectomy, as opposed to the observation in the systematic review by Kojouri et al, where poor outcomes were reported in patients older than 40 years, in many of the case series that were reviewed.[58] However, there was lack of standardization of variables such as age-group and response to therapy in this reported series.[58] More so, the age distribution of newly diagnosed chronic ITP in South Africa is clearly opposite to that seen in the Western world, where the mean age of presentation is 57 years.[11-14] The younger age at presentation of ITP in our patients (mean of 31 years) is consistent with a more favourable response to splenectomy.

Another suggested predictor of response is the post splenectomy platelet count, within the first 4 weeks after surgery. Five out of the six patients who did not respond

to splenectomy had a platelet count < 60 X 10^9/l, four weeks post- surgery, in contrast to the responders in whom the lowest platelet count was 150 X 10^9/l and the highest count was 606 X 10^9/l.[58,82]

Contrary to preference of laparoscopic splenectomy over open laparotomy in most centres including the Cape Town study by Antel et al where 62% of their patients had laparoscopic surgery,[58,79] In this study the surgical procedure of choice was open splenectomy. Ninety-one percent of patients (n=51), had an open splenectomy. Only three patients had a laparoscopic splenectomy. Two other patients who initially had laparoscopic surgery were converted to open surgery due to suspected intra-abdominal sepsis. However, this study is unable to comment on laparoscopic surgery in view of the small numbers that were exposed to this procedure. Nevertheless, the literature suggests that where the expertise is available, laparoscopic splenectomy is a better option with less complications and early hospital discharge.[77,78]

The complications recorded in this study were classified as perioperative or non-operative complications. Three patients (5.4%) had perioperative complications, defined as complications related to surgery up to the time of discharge. Of these patients, one patient had operative bleeding while the other 2 patients had intra-abdominal sepsis due to bowel perforation. The non-operative complication rate was 27% in 15 patients. Nine of these patients (16.1%) had infections, of which 3 required hospitalization. Two patients (3.6%) had thrombotic manifestations, while 4 patients had mucocutaneous bleeds. The overall complication rate in our study was 32.2%. This is much higher than what the literature suggested. The combined complication rate for open and laparoscopic splenectomy reported by Kajouri et al

was 22.5% (open splenectomy=12.9%, Laparoscopic=9.6%), while Antel et al reported a complication rate of 16%.[58,79] These differences may be attributed to lack of standard definition of what was regarded as a complication across these series especially in relation to infections (mild versus severe sepsis) in the follow up period. Secondly, the high rate of infections recorded in our study could have been confounded by the ongoing need for CS therapy and immunosuppressive agents in some patients.

There was no difference in the efficacy, safety and outcome of splenectomy between primary and secondary ITP in this study. The majority of the splenectomised patients had primary ITP (75%), while the remaining 25% were diagnosed with secondary ITP. This is in contrast to the increasing number of secondary ITP patients at our hospital, as observed in the study by Variava, where a secondary cause of ITP was reported in 50% of the patients, mostly due to HIV infection (40% of all secondary ITP).[16] The 3 HIV sero-positive patients who had a splenectomy, had a favourable outcome. Their CD4 counts were 118/ul, 240/ul and 328/ul, respectively. Although this number is very small, our findings are consistent with other studies that looked at splenectomy in HIV sero-positive patients versus HIV sero-negative patients, where there was no significant difference in mortality post splenectomy.[79,92] In the study at Groote Schuur Hospital in Cape Town by Antel et al, splenectomy was shown to be effective, irrespective of the HIV status. The complications, morbidity and mortality in association with splenectomy in this study, were not statistically significantly different in the 12 HIV sero-positive patients, compared to the 44 HIV sero-negative patients.[79]

Two patients died in this study (3.6% mortality rate). This is higher than the 1% mortality rate quoted in the literature.[58] As indicated earlier, the first patient was one of the two patients that developed sepsis from gut perforation following laparoscopic splenectomy. The indication for splenectomy in her was lack of response to corticosteroids, including IV Solumedrol and also IV immunoglobulin. She had a good platelet count rise post splenectomy (platelet count of 238 on day 11 post-splenectomy, from a platelet count of 10, prior to splenectomy), with no evidence of bleeding. Extended spectrum beta-lactamase producing Escherichia coli (ESBL - E.coli) was cultured in her blood, and she unfortunately succumbed to septicaemia on day 11, post-surgery.

The second mortality from this study was a woman with refractory ITP requiring additional CS therapy and azathioprine. She had a splenectomy 4 years earlier with variable platelet counts post-splenectomy and no bleeding manifestations. She developed nosocomial pneumonia after being discharged from the hospital 2 weeks before, with salmonella sepsis. She also had a significant co-morbidity, having been diagnosed with chronic thromboembolic pulmonary hypertension. The cause of her death was sepsis. Both patients had primary ITP and were HIV sero-negative.

4.5 CONCLUSION

The role of splenectomy in ITP continues to be reassuring, particularly in our public sector setting, where the newer agents, such as the thrombomimetics, are not yet available due to their high cost, and rituximab is used as an off-label indication, after failure of CS and immunosuppressive therapy. Splenectomy is the preferred second line therapy after the patient has failed CS therapy. Although the minority of the

patients had a laparoscopic splenectomy, with time and experience, laparoscopic splenectomy should become the procedure of choice, especially in conditions such as ITP, where the spleen is not enlarged, making the procedure highly technically feasible. Furthermore, the outcome for primary versus secondary ITP was equally favourable. However, it must be noted that there were significantly lesser numbers of secondary ITP patients in this study.

We believe that the findings are a fair representation of the role of splenectomy in ITP, in South Africa, based on a retrospective review from a large single centre, over a period of 27 years. This is further corroborated by the findings of the recent publication from Cape Town, by Antel et al.

Therefore, splenectomy remains a feasible and appropriate second-line therapeutic modality in ITP. In our setting, it is arguably the second-line treatment of choice, and must be considered for patients with persistent and chronic ITP, who have failed prior CS therapy.

4.6 LIMITATIONS

The findings in this study are limited by its retrospective nature. For some patients data was missing and files could not be reviewed. Ideally, a larger sample size would have added to the strength of this study. In addition, this is a single centre study carried out at Chris Hani Baragwanath Academic Hospital, South Africa, therefore the findings may not necessarily be applicable to other populations.

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APPENDIX A

R14/49 Dr Toyin Raheem Abdulraheem

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150920

NAME: (Principal Investigator)	Dr Toyin Raheem Abdulraheem
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Impact of Splenectomy on the Management of Immune Thrombocytopenia (ITP) in Adults: The Chris Hani Baragwanath Academic Hospital Experience
DATE CONSIDERED:	02/10/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Moosa Patel and Mohammad Waja
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/11/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature Date 10/11/2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B

DATA COLLECTION SHEET

A. DEMOGRAPHICS

Study Number: _____

Gender: Male ☐ Female ☐

Date of Birth: | D | D | | M | M | | Y | E | A | R |

Date of Diagnosis: | D | D | | M | M | | Y | E | A | R |

Ethnic Group: Black ☐ White ☐ Coloured ☐ Asian ☐ Other: ☐

B. HISTORY

AT PRESENTATION	**PRIOR TO SPLENECTOMY**	**1 YEAR POST-SPLENECTOMY OR AT LAST VISIT (IF < 1 YEAR POST-SPLENECTOMY)**
Bleeding Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Sites of Bleeding Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
_____	_____	_____
_____	_____	_____
Symptoms of anaemia Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
_____	_____	_____
_____	_____	_____
History of fever/infections Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
_____	_____	_____
_____	_____	_____

Past or known history of:

1. TB Yes ☐ No ☐
2. HIV Yes ☐ No ☐
3. SLE Yes ☐ No ☐
4. LPD Yes ☐ No ☐

5. Other comorbid diseases

_____

AT PRESENTATION	**PRIOR TO SPLENECTOMY**	**1 YEAR POST-SPLENECTOMY OR AT LAST VISIT (IF < 1 YEAR POST-SPLENECTOMY)**
Is patient on any medication Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
List of medications		

C. EXAMINATION

AT PRESENTATION	**PRIOR TO SPLENECTOMY**	**1 YEAR POST-SPLENECTOMY OR AT LAST VISIT ((IF < 1 YEAR POST-SPLENECTOMY)**
Pallor Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Jaundice Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Lymphadenopathy Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Hepatomegaly Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Splenomegaly Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Active bleeding Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Petechiae Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Purpura Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Ecchymoses Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Haematomas Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Other bleeding Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐

Any other relevant clinical features related to:

I. Secondary ITP
II. Complications of ITP
III. Comorbid disease

C. DIAGNOSIS

1^{O} ITP Yes ☐ No ☐

2^{O} ITP Yes ☐ No ☐

If 2^{o} ITP – cause of 2^{o} ITP _____

Was BMAT done ? Yes ☐ No ☐

Was any abnormality detected? Yes ☐ No ☐

Details of abnormality _____

D. SPLENECTOMY

Date of diagnosis of ITP: _____

Date of splenectomy: _____

Number of lines of prior treatment used: _____

Prior treatments used: _____

Name	Dose	Route	Duration	Response

Indication for splenectomy: _____

Type of splenectomy: Open: _____ Laparoscopic: _____

Antibiotics used peri/post-splenectomy: Yes ☐ No ☐

If yes: Duration of use: 2 weeks only ☐ 2 years ☐ Lifelong ☐ Other ☐

Vaccination peri/post- splenectomy: Yes ☐ No ☐

If yes: Type of Vaccination/ Time prior to or after splenectomy

Pneumococcal _____

Meningococcal _____

Therapies used immediately prior to splenectomy

Corticosteroids Yes ☐ No ☐

(type/dose/duration/route) _____

IVIg Yes ☐ No ☐_____

Other Yes ☐ No ☐_____

Platelet transfusions used: Yes ☐ No ☐_____

Platelet counts: 1 week prior to splenectomy _____

Day of splenectomy _____

Highest count in the first two weeks post-splenectomy (count; day)_____ day:__

Was thromboprophylaxis used? Yes ☐ No ☐

If yes, type of thrombo-prophylaxis:

Mechanical only ☐ Aspirin ☐ Heparin (LMWH) ☐ Other ☐

_____

When was thrombo-prophylaxis used?

Peri-splenectomy ☐ Peri and post-splenectomy ☐ Post-splenectomy ☐

Duration of thrombo-prophylaxis _____

Were splenunculi/accessory spleens detected at surgery Yes ☐ No ☐

Number and location of splenunculi/accessory spleens, if detected ?

At surgery: Bleeding _____

Infection_____

Post surgery: Wound sepsis _____

Infection _____

OPSI/other infections_____

Thrombosis post-splenectomy _____

Other complications post-splenectomy _____

Platelet count at 1 year post-splenectomy _____

Platelet count at last visit (duration from date of splenectomy): _____

Response to splenectomy: CR _____

PR_____

NR _____

Duration of response: _____

Outcome

Date: _____

Alive ☐ Deceased ☐ Lost to follow up ☐

If deceased:

Cause/s of death: _____

_____

_____

Survival time (date of diagnosis – date of death and date of splenectomy to date of death) in

months: _____ ; _____

If lost to follow up:

Date last seen: _____

Status of disease at last visit (e.g. remission, relapse): _____