Management of Paediatric Immune Thrombocytopaenia in a South African centre from 1991-2011

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DECLARATION

I, *Shehnaaz Akhalwaya*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abbreviations

American Society of Hematology	ASH
Antibody	Ab
Antigen presenting cells	APC
Bone marrow aspirates	BMA
British Society for Haematology	BSH
Chronic ITP	cITP
Fragment crystallisable	Fc
Haemoglobin	Hb
Immune Thrombocytopenia	ITP
Immunoglobulin G	IgG
Inter quartile range	IQR
Intercontinental Childhood ITP Study Group	ICIS
International Working Group	IWG
Intracranial Haemorrhage	ICH
Intravenous immunoglobulin	IVIG
Mean corpuscular volume	MCV
Measles-Mumps-Rubella	MMR
Red Cross War Memorial Children's Hospital	RCWMCH
T helper	Th
Thrombopoeitin receptor agonists	TPO-RA
United Kingdom	UK

ABSTRACT

Management of Paediatric Immune Thrombocytopenia at a South African centre from 1991-2011

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Three hundred and seventeen patients meeting the diagnostic criteria for immune thrombocytopenia presented to Red Cross War Memorial Children's Hospital between 1991 and 2011. We retrospectively reviewed these patients in order to describe patient demography, the natural history of the disease, and different approaches to diagnosis and management. There were 162 males and 155 female patients. The median age of onset was 3.48 years old (IQR 1.66-6.36). In the 4 weeks preceding presentation, 98 (31%) patients had a viral illness. The median presenting platelet count was 7 x 10^9/L (IQR 3-14.5). Petechiae were the most common clinical sign at presentation (58%; 184/317). None of the patients presented with intracranial haemorrhages. The majority of patients in the study were admitted (234/317; 74%) with a median stay of 4 days (IQR 0-6). Bone marrow aspirates (BMA) were performed in 188 patients (59%). There was a reduction in BMA from 1991-2000 to 2001-2011 ($p<0.001$). There was an increase in the percentage of patients treated from 1991-2000 (77/170; 44%) to 2001-2011 (99/147, 67% $p< 0.001$). Resolution occurred in 75% of patients with a median time to resolution of 31 days (IQR 11-73 days). When we analysed the "survival estimate" from the 2 decades, despite differing rates of BMA, treatment rates and regimens, there was no statistical difference in resolution.

Chapter 1: Literature Review

Immune Thrombocytopenia (ITP) or Immune Thrombocytopenic Purpura, also known as Idiopathic Thrombocytopenic Purpura is one of the commonest causes of thrombocytopenia (low platelets) in children. This condition has seen vast changes in definition, management options and treatment strategies in the last 10 years. As research has led to a better understanding of ITP, the need for standardisation has become more apparent, leading to international collaboration with regard to recommendations and building registries of patients.

Thus far most of the work has been spearheaded by developed countries namely United States of America, the United Kingdom (UK) and Nordic countries. Our place as a developing country in Sub-Saharan Africa, with perhaps different needs, demographics and resources has not been examined. The aim of the study is to review patients presenting to Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, to understand the local demographic and the natural history of the disease, and to examine our position in the diagnostic and management debate.

The literature review which was done in June 2013 and repeated in November 2015, was done using Pubmed, Ebscohost,The Cochrane library and Web of science. The terms of the search included MeSh words: [ITP] [Child] [paediatric/pediatric] [immune/idiopathic thrombocytopenia] [Africa] and free text. The bibliographic references of relevant articles were also hand-searched for additional publications

Definition

ITP is a well recognised cause of thrombocytopenia in children, defined as a platelet count less than < 100 x 10^9/l. This threshold was established by the International Working Group (IWG) at the Vicenza Consensus Conference, held in Italy in 2007.[1] The previous cut-off of <150 x 10^9/l was no longer recommended for 2 reasons. Studies from Iran and Uganda found that frequently in healthy people the platelet count ranged from 100-150 x 10^9/l.[1,2,3] Furthermore, a cohort prospective study in healthy individuals with platelet counts between 100-150 x 10^9/l found that the 10 year probability of developing severe thrombocytopenia was only 6.9% (with a 95% CI of 4-12%).[4]

The nomenclature of ITP changed at the conference. Previously the term “Idiopathic” Thrombocytopenia was used; the expert panel preferred to encourage the use of “Immune” Thrombocytopenia thereby stressing the pathophysiology of the disease.[1] The IWG also described 2 forms of ITP i.e. primary and secondary ITP; “Primary” denoting the absence of an underlying cause, and therefore being a diagnosis of exclusion. “Secondary” ITP are those diseases which have an immune mechanism as well as another causative stimulus e.g. drugs, systemic lupus erthymatosus.[1,5]

Different phases and severities of ITP were proposed. All new cases of patients with ITP were to be labelled as a “Newly Diagnosed ITP”. In the event that symptoms persisted, or recurred after 3 months (to a maximum of 12 months) then the new nomenclature would be “Persistent” ITP. Were the disease process to continue for more than 12 months, the patient was then to be categorised as having “Chronic” ITP.

Response to treatment or resolution was also defined. The IWG did acknowledge that while the clinical picture of the patient and his/her symptomatology was crucial

to assess response/remission, for the sake of uniformity cut-off values needed to be included. If a patient's platelet count was greater than 100 x 10^9/l with no bleeding, then they were said to have attained a "Complete Response". Response was defined by a platelet count between 30 and 100 x 10^9/l as well as doubling of the baseline count. If a patient had neither the count between the stated range or the count had not doubled from baseline, then they were said to have "No response".[1]

Refractory ITP was been defined in adults as failure to achieve response, or loss of response after a splenectomy. However in children, a splenectomy was often delayed and thus the IWG did not reach agreement on the definition of refractory ITP in children.[1]

Pathogenesis

The pathogenesis of ITP is complex. It is an immune mediated disorder, characterised by the loss of self tolerance. ITP is caused by autoantibodies, usually IgG, that are directed against platelet membrane antigens e.g. glycoprotein IIb and IIIa. These antibody coated platelets trigger a premature destruction of the platelets, by the reticuloendothelial system (mainly in the spleen). The antibodies also have an effect against glycoproteins on the surface of megakaryocytes. These combine to upset the balance between production and destruction of platelets.[6, 7, 8]

Antigen presenting cells (APC) are the key players in the pathway that leads to loss of self-tolerance. Their purpose is to internalise and break down proteins that are seen as antigens and then present them to T cells.[7,9,10] Usually aberrant APCs that recognise "self" as antigenic are themselves destroyed. Some studies have shown that the APCs create "cryptic epitopes" that make them capable of escaping negative selection.[7, 9]

T cells become activated upon recognition of platelet specific antigens on APCs.[8] The T cells release cytokines that result in antigen specific B cells. Some studies have shown that there is an increase ratio of Th1/Th2 cells which favours "autoreactive B cell development".[7,11] Some research proposes that a novel T cell, Th 17 produces cytokines e.g. Interleukin 17 that further favour the imbalance between Th1 and Th2 cells, and then also drives autoimmunity.[10] The dysregulation of self-tolerance is further promoted by impaired T-regulatory cells, whose function is to decrease cell-mediated and antibody-mediated response.[7, 9, 10]

Once the B cell has been induced, it produces autoantibodies to glycoproteins on platelets and megakaryocytes. These antibody-platelet complexes are then removed by Fc receptors on phagocytes, predominantly in the spleen.[8] The megakaryocytes with bound antibody either undergo phagocytosis, or apoptosis-like programmed cell death.[7, 8]

Triggers

The cause of ITP is often unknown, however certain intrinsic (e.g. gene mutations affecting immune response, ethnicity) and extrinsic factors (e.g. infectious disorders, recent vaccines or drugs) may contribute.

In a cohort study by Kühne *et al*. data was collected from two cohorts within the same time period - 90 Asian (Vietnamese) and 89 European (German and Swiss) children over a two year period. The sex and age distribution were similar, but there was a substantial difference in the rate of infection which preceded the onset of ITP. Infection was categorised as occurring within 14, 21 or more than 21days before the onset of ITP. It was non-specific in its definition including fever, upper respiratory tract, gastrointestinal tract or "any specific infection and immunisation". Sixteen

percent of the children in Vietnam had a preceding infection as compared to 66% in the European cohort ($p < 0.001$). This may support the theory that certain environmental or ethnic factors play a role in ITP.[12]

A systematic review of literature around vaccines, specifically looking at the Measles-Mumps-Rubella (MMR) vaccine, was conducted. The time after exposure in the studies that were included was either not stated or between 35 days to 182 days. The findings were that of a low incidence of MMR–associated ITP (0.0087 to 4 cases per 100 000 vaccine doses). It was found that the "MMR-associated ITP is rare, self-limiting and non-life threatening".[13] It has been reported as safe to repeat doses of MMR in a patient with either vaccine-related or non-vaccine related ITP, as long as the platelet count is normal.[14,15]

Epidemiology

Research

In 1996, when researchers from the American Society of Haematology (ASH) published recommendations on managing ITP, the overall consensus was that the recommendations were lacking in clinical data and research.[5,16] Soon afterwards the Intercontinental Childhood ITP Study Group (ICIS) in 1997 was formed. The group was established to promote research in the field and share patient data, thus increasing the pool of patients to be analysed. The group was renamed in the early 2000s to the International Cooperative Study Group to include both paediatric and adult haematology. The group developed registries to study the epidemiology of patients with ITP, the natural history and differences in outcome based on management and/or interventions. The first registry was started in 1997 and "closed"

in 2000. The ICIS Registry 1 looked at the epidemiology of ITP. Registry 2 (2002-2004) focused on bleeding as an outcome in ITP, and examined the platelet count as a risk factor for bleeding. Two current registries that are being collated are the PARC-ITP i.e. Paediatric and Adult Registry on Chronic ITP and The Splenectomy Registry.[5]

Incidence

A critical review paper estimates the incidence of ITP in children and adults at 1.9 to 6.4 x 10^5 children per year based on statistical analysis of recent studies.[17]

They reviewed studies in the Medline database where estimates of the incidence of ITP were published. Eight studies were identified, and 4 out of 8 studies were determined to have the most accurate estimates, based on the method of patient identification and study design.[17] The lowest estimated incidence was 2.2 per 10^5 children/year and the highest incidence estimate was 5.3 per 10^5 children/year. The 4 studies that were cited were from Norway,[18] Scandinavia (Nordic study),[19] Britain (UK audit) [20] and Germany[21]. It is unknown whether interpretation of the data is applicable to a southern African setting.

Age

The mean age of onset with children registered in the ICIS Registry 1 was 5.7 years (in girls 5.9 years and boys 5.5 years.)[5] The peak age distribution was between 1-6 years old. Similarly in the Nordic study nearly 80% of the children were less than 8 years old[19] and in a UK study, using the UK Childhood ITP registry, the majority were between 2 and 5 years old.[22]

Gender distribution

Most studies have shown that in the younger age groups i.e. 1-5 years old, boys predominated over girls,[5,21,22,23] with a UK report approximating a ratio of 1.8:1 (males to females),[22] 1.5:1 in a German survey[21] and 1.4:1 in the Nordic study[19]. The older children either had an equal representation of boys to girls[19,21] or a slight predominance of girls (0.8:1[20]). A retrospective chart review from The Children's Hospital in Alabama reported no difference in the gender distribution between girls and boys.[24] They did not stratify the children into age categories and this may explain why their findings differed from other studies.

Seasonal Variation

There is conflicting data with regard to seasonal variation.

In the Nordic[19] (n=385) and German studies[21] (n=323), a peak incidence in winter was seen. Zeller *et al*[19] ascribes this to the increased incidence of infections in winter, thus increasing the number of post-infectious cases of ITP.

An observational study using the Intercontinental Cooperative ITP Registry (n=2190) reported a peak occurrence during spring/early summer and a nadir in autumn. The authors did not explain these findings.[23]

Preceding infections

Infections are known to be one of the triggers for ITP.[12] Various studies use different time frames for the time before onset of ITP; Grainger *et al* used a cut off of 6 weeks prior to onset of ITP, and reported that in 47% of cases (n=104/220), that there was a preceding history of a viral infection.[22] The Nordic study group (n=292/501) reported an incidence of infection of 57.7% 4 weeks before the diagnosis of ITP.[19]

Similarly, a study from The Hospital for Sick Children in Toronto revealed that 57% of their participants had a recent upper respiratory tract infection. The time period was unspecified.[25] There are few data from developing countries with regard to the relationship between infections and the onset of ITP, although one may expect the incidence to be higher. Interestingly Kühne *et al* showed a low incidence of infection (15%) preceding the onset of ITP, in a Vietnamese population group (n= 82).[12]

A retrospective study from Nigeria reported all patients (children and adults) who presented with ITP over an 11 year period. None of their patients had a preceding infection. There were only 11 patients (in total) making it neither statistically, nor clinically significant, because the majority of the patients were adults (n=7).[26] This highlights the need for larger studies in the developing world. It is important to mention that it is difficult to draw specific conclusions when comparing different countries/ populations as the term "viral infection" or upper respiratory tract infection is not standardised.

Presentation

Platelet count at diagnosis

Various reports reveal that the mean platelet count at diagnosis can range from 7,3-24 x 10^9/l.[12,19,21-25] More than half of the patients in two studies, had platelet counts less than 10 x 10^9/l.[19,21] Age, gender and race was not shown to have a significant effect on the presenting platelet count.[19]

Presenting complaints

Multiple studies have shown that the most common manifestation of ITP is cutaneous bleeding (i.e. bruising and petechiae), followed by mild

epistaxis.[19,21,22,24,27,28] The frequency of severe bleeding is reported at around 3%,[22] with the risk of intracranial haemorrhage (ICH) reported to be lower than 1% (0.1-1%).[22-24,29]

Lilleyman *et al* reported the incidence of ICH over a 20 year time period in a UK survey. Fourteen children were identified, and the circumstances around the diagnoses were analysed. The group reported an extrapolated annual incidence of 0.1% in children with ITP. The platelet count of all patients was below <20 x 10^9/l. The study also revealed that 50% of the patients' intracranial bleeds occurred more than 1 month after diagnosis, refuting previous thinking that the greatest risk for ICH is shortly after diagnosis. Additionally 50% of the patients had another contributory risk factor which may have precipitated the ICH.[29]

The Relationship of the Platelet Count to symptomology

Table1, adapted from a graph from a study published in the Lancet,[20(fig 2)] shows that despite having platelet counts less than 10 x 10^9/l, the majority of patients in this group still only have mild symptoms (180 out 425). Mild symptoms account for more than 70% of all "platelet count groups".

Table 1. Platelet count to severity in UK

Platelet count	**No symptoms**	**Mild**	**Moderate**	**Severe**
	1.9%*	**74.5%**	**20.4%**	**3.2%**
<10 x 10^9/l.	0.2%	42%	15%	3%
10-19 x 10^9/l.	0.5%	19%	4%	0.2%
20-50 x 10^9/l.	0.2%	10%	1%	0
51-100 x 10^9/l	1%	3%	0.4%	0
>100 x 10^9/l.	0	0.5%	0	0

*adapted from bar graph showing numbers of patients in each category; percentages calculated from n=425

The severity of presentation of the disease has previously been measured by the degree of thrombocytopenia, however, it has been agreed upon by the ICIS group that severity should rather be correlated with bleeding symptoms.[1,5]

Thus far, no standardised tool has been recommended. A novel bleeding severity tool used in the UK audits characterised bleeding as 'Mild', 'Moderate', 'Severe' and 'Life threatening or ICH'. (Table 2)[22]

Table 2. Severity of bleed

Mild	Few petechiae and small (< 5cm) bruises; Epistaxis stopped with applied pressure.
Moderate	Numerous petechiae and large (>5 cm) bruises; Epistaxis longer than 20min. Intermittent bleeding from gums, lips, buccal, oropharynx or gastrointestinal tract. Hypermenorrhagia, haematemesis, haematuria, malaena without hypotension and falling of Hb <2g/dl.
Severe	Epistaxis requiring nasal packing or cautery. Continuous bleeding from gums, buccal, oropharynx. Suspected internal haemorrhagia (lung, muscle, joint, others). Hypermenorrhagia,

	haematemesis, haematuria, malaena without hypotension and falling of Hb >2g/dl.
Life threatening or intracranial haemorrhage(ICH)	Intracranial haemorrhage or continuous or high-volume bleeding resulting in hypotension or prolonged capillary refill and requiring fluid resuscitation or blood transfusion (>10ml/kg)

Based on this scoring tool, the UK audit (n=203) showed that 54% of patients studied were classified as mild, 42% as moderate and 4% as severe. The children with mild ITP had less bleeding sites as compared to the moderate and severe group. In the "severe group "(8 children), only 1 child had an ICH.[22]

Chronic ITP

Chronic ITP (cITP) has a reported incidence of between 24- 31%.[19,23,24] No factors have been shown to predict chronicity, however, factors such as an insidious onset, lack of preceding viral infection and an older age at presentation (i.e. >7 years), have been reported to have an association with cITP.[19,24]

Diagnosis and investigations

American (ASH) and British (BSH) guidelines take a similar approach to the diagnosis of ITP. [16,,30-31] The British Society for Haematology (BSH), make the diagnosis of ITP a diagnosis of exclusion, when history, examination and investigations do not suggest an alternate diagnosis.[31-32] ASH updated their 1996

guideline in 2011 dispensing with the requirement for a bone marrow aspirate. They recommend diagnosing ITP in children with suggestive histories, examination findings of a petechial rash/purpura in an otherwise normal child, isolated low platelet count or sparse platelets on smear. If there are any atypical findings or suspicion of another disease process, then the diagnostic approach includes imaging, further laboratory tests and a bone marrow aspirate.[30]

Bone marrow aspirates (BMA)

Bone marrow aspirates (BMA) do not, in most instances, aid in the diagnosis of ITP.[30] Calpin et al[33] reviewed 484 patients that had BMAs to confirm ITP. No diagnoses of leukaemia were made post-BMA in the 332 children with typical heamatologic features of ITP. In the 152 with the provisional diagnosis of ITP with "atypical features" (152 children) 3 had leukaemia and 7 had aplastic anaemia. On review of the clinical presentation in the children with leukaemia, it was found that they had inconsistent features of ITP; and the patients with aplastic anaemia had other abnormal parameters on their blood film. The risk of missing the diagnosis of leukaemia in the setting of typical findings of ITP is less than 1%. Another study showed that it is unlikely for a child with leukaemia to present with only an isolated thrombocytopenia (0 cases in 2239 cases).[34] Therefore both the American and British guidelines suggest BMA only in those patients that have an atypical course, are unresponsive to drug therapy or have other features making another diagnosis likely.[30-32]

The incidence of BMA varies from 13-72%.[21- 25, 35] The low rate of "13% BMA" is due to deliberate attempts by British centres to adopt a more conservative approach on the basis that BMAs do not aid in the diagnosis. Analysis from the UK Registry

comparing ‘proportion of children undergoing bone marrows’ from 1995 to 2000 to 2009 showed a reduction from 40% to 18% to 13% respectively.[21]

A study in Alabama, where 72% of patients (n=409) had bone marrow biopsies, reported that the bone marrow biopsy result did not alter the diagnosis or management of the patients.[24] Similarly, a study in Ontario where 64% of patients (n=74) had bone marrow aspirates revealed that the diagnosis was not altered in any of the patients, even in those who had “Atypical ITP” (53% of those who had BMA).[12]
A survey in 2008 by the Department of Paediatrics and Child Health at Tygerberg polled 101 doctors around South Africa in respect of their management approach to acute ITP in children. A large proportion of responders would first do a bone marrow aspirate before initiating steroid therapy and some would do one even if they were not considering steroids. Between 30-50% of responders would do a bone marrow aspirate; 30% for mild ITP and around 50% for moderate ITP (epistaxis, bleeding from oropharynx).[36] Recommendations from the Indian Society of Haematology advocate a BMA before steroid initiation, as follow-up of patients cannot be certain in their social demographic.[37]

Management

Management options in the acute phase vary from expectant management (due to the high rate of spontaneous remission as well as rarity of serious bleeds[38]) to emergency interventions such as platelet transfusions (for life-threatening bleeds), or definitive treatments such as corticosteroids and immunoglobulins.
A review by Cooper[39] examined studies from different countries and the variability of treatment rates between countries. South Africa’s treatment rate was at 81%,

exceeded only by Canada at 90%. The UK's rates were 16% in 2011, compared to previous rates of 61% in 1995, and 38% in 2003.[32]

The dilemma to treat or to "watchfully wait" is often guided by the fear of ICHs.[39] More research is changing the previous non-evidenced based model, and as shown above, the UK is on a downward trend with regard to treating patients. Newer data has shown that "eventual normalisation of the platelet count happens regardless of the management chosen".[23,32,40-41] A multicentre study by the NOPHO-ITP Study Group showed that having policies that actively treat patients with "newly diagnosed ITP", accelerated the platelet recovery, however it did not have any effect on the development of cITP or the morbidity at follow-up.[42]

ASH recommendations have had a notable change from the 1996 ASH guideline. There has been a move away from treatment based on the platelet count. This is in keeping with data that suggests that despite the presentation, platelet count and treatment most children do not experience severe bleeding.[30,38] The BSH guidelines acknowledge that many children with very low platelet counts have minimal symptoms and usually have spontaneous remission within a few weeks. The guidelines also note that life-threatening haemorrhage is rare in children with ITP, regardless of the platelet count, and is not necessarily prevented by drug treatment. Therefore, children with acute ITP are managed expectantly. Mild cases are not admitted, but educated about the disease and the warning signs, and are informed to return at any time should the parents be concerned. The full blood count is repeated with 10 days to ensure a more serious disease process is not missed. The first line treatment of acute ITP with bleeding symptoms is oral corticosteroids.[31,32]

<u>Hospitalisation</u>

The Intercontinental Childhood ITP registry reported that the average rate of hospitalisation was 73%. In the patients who were “untreated”, 47% of these cases were still admitted for observation, and in the “treated” group, 85% of cases were admitted.[23] The UK reported a lower rate of hospitalisation. In 2009, 43% of the children were admitted, with a median stay of 1-5 days.[22]

Treatment

The aim of treatment is to reduce the risk of serious bleeding, without engendering treatment-related risks.[39]

ASH suggests observation alone for children with mild bleeding. In children with mild bleeding where follow-up is uncertain, the child comes from far away, rest and low activity cannot be assured or there is an upcoming invasive procedure, treatment may be warranted.[30,]

Parental anxiety and patient anxiety, as well as the psychosocial impact sometimes also affect practice.[43]

- First-line therapy:
  - Corticosteroids:

Steroids are considered first line therapy.[39,44]

Their mechanism of action is thought to be threefold. They inhibit phagocytosis and antibody synthesis, they improve platelet production and increase stability of the microvasculature.[45]

The Intercontinental Childhood ITP registry observational study showed that 33% of the patients treated received steroids. Corticosteroids have been shown to have a response rate of 70-80%.[7,30,]

There is still debate with regard to dosing, however, shorter duration of steroids is now recommended. With prolonged use, the side effects of corticosteroids often outweigh their benefits. To avoid these complications, prednisone should always be rapidly tapered and stopped after a maximum of 4 weeks of therapy. The traditional regimen has been two milligrams per kilogram per day over 21days.[30,44]

Four milligrams per kilogram per day for four days was shown to be more common practice in a Canadian study[25]. The International consensus report recommends prednisone to be used only to maintain a haemostatic platelet count, and for as short a time as possible. They report that the higher dose regimen (4mg/kg) has shown that 72% to 88% of children raise their platelet count to > 50 10^9/L within 72 hours.[44]

- IVIG:

Intravenous immunoglobulin (IVIG) is also considered part of the first-line therapy for ITP. It acts on both humoral and cellular immunity. They block the Fc receptors of macrophages in the reticulo-endothelial system thereby slowing the clearance of antibody-coated platelets.[7,37,45] They also exert an effect by arresting maturation of dendritic cells, decreasing interleukin-12 production and increasing interleukin-10 production.[7,45]

The recommended dose ranges from 0.8-1g per kilogram per day as a single dose. The efficacy of IVIG is reported to be between 70-90%.[7,30] The rise in platelets is rapid (rise within 24-48 hours). The Intercontinental Childhood ITP registry observational study showed that 29% of the patients treated received IVIG.

Interestingly, in a Nordic study IVIG was used as the first line therapy over corticosteroids. Fifty one percent of treated cases received IVIG, compared to 5% of those who received corticosteroids. One percent of cases used both IVIG and

steroids. Similarly, Sutor *et al* reported a preference for IVIG. Sixty one percent of patients received IVIG, 19% corticosteroids, 6% both IVIG and corticosteroids and 14% no treatment.[21]

An audit by Bolton-Maggs and Moon in 1995 in the UK showed a discrepancy between published guidelines in 1992[46] and clinical practice. Amongst these was that IVIG was used commonly as first line therapy (23%), almost equivalent to corticosteroids (24%).[21] A follow up audit was done in 2009 and showed that of those who received platelet-raising therapy, corticosteroids was the first line therapy (48%), then IVIG (28%) and combination therapy (24%). It also showed a high rate of expectant management (80%).[20-22]

Among more common, non-life threatening side effects IVIG has been shown to have serious life-threatening side effects like anaphylaxis. In addition, it is costly and requires hospitalisation for infusion.

- Anti-D immunoglobulin

Anti-D used to be available as a front-line agent for the treatment of ITP.[32]

Since 1996, numerous studies have examined the use of Anti-D vs. IVIG. In a randomised prospective study by Tarantino *et al,* a single dose of Anti-D (50 µg/kg or 75 µg/kg), was compared to 0.8mg/kg IVIG. The data showed that a dose of 75µg/kg was superior to the lower dose of 50µg/kg. However, this came at the expense of additional side effects. There was equivalent efficacy between Anti-D and IVIG; patients who received Anti-D, had a response rate of 71% within 24hours, and 98% within 72hours. Similarly patients receiving IVIG, had a response rate of 78% within 24hours and 90% within 72hours.[47]

Common side effects of Anti-D include headaches, chills, nausea, vomiting and anaemia. Serious side-effects can occur. The FDA has issued a black box warning due to an increased risk of haemolysis and renal failure.[30,32,37,39]

ASH recommends Anti-D, only in patients who are D- positive, who have a negative direct antiglobulin test (Coombs) and who have not undergone splenectomy.[30]

- Second-line therapy:

  - Rituximab

Rituximab is a second line agent that is used in the treatment of ITP. It is an anti-CD20 monoclonal antibody that targets and destroys CD20+ B-lymphocytes.[7,37,39,48-49] Its Fc domain facilitates both complement and Ab-mediated clearance. It alleviates disease burden by removing or reducing the level of autoreactive B antibodies.[48]

A few studies have shown that the use of rituximab does show a response in the treatment of ITP. A systematic review of observational studies (n=323) showed a complete response (platelet count > 100 x 10^9/l) in 39% of patients, and a partial response (>30 x 10^9/l) in 68%.[49]

Patel *et al* examined selected responders to rituximab to assess the duration of response 5 or more years from initial treatment. The sustained response to rituximab was estimated as 26% at 5-years.[39,48]

Rituximab is shows potential as a "splenectomy sparing" drug [49] but there is a paucity of randomised control trials to help direct clinical practice.

The ASH updated guideline recommends that it be considered in children where conventional treatment has failed, and who have ongoing, significant bleeds and/or to improve quality of life.[30] Clinicians must always be mindful of the adverse effects

which include hypotension, rash, sore throat, fevers, rigors, neutropenia, long-term immunosuppression from hypogammaglobulinaemia and the potential for haematological malignancies.[39,48-,49]

- Thrombopoeitin receptor agonists

Thrombopoeitin receptor agonists (TPO-RA) are novel agents in the treatment of refractory ITP. They are considered game-changers in the treatment of chronic ITP. They stimulate the production of platelets but also are thought to have some immune modulating effect. They are believed to increase total circulating 'transforming growth factor' and reduce interleukin-2-producing CD4 cells. This in turn re-establishes immune tolerance.[39,49]

There are two TPO-RAs registered. The first, romiplostim, is a synthetic recombinant protein- classified as a peptibody. This induces activation of the thrombopoeitin receptor. The second, eltrombopag, is a small molecule that binds to the transmembrane domain, and not at the receptor site. It does not compete with TPO.. In early studies, Romiplostim was compared to placebo; there was a 88% response rate in the first study, and a 83% response rate in the second study.[50-51] In both studies patients on the TPO-RA treatment arms had no side effects but the study sample was very small (n=22 and n=18 respectively).[50-51] A randomised controlled, double blinded, placebo controlled study (n=62) was conducted by Tarantino et al.[52] They found that Romiplostim induced a high rate of platelet response as compared to placebo that was statistically significant and that the drug was safe in children. [52]

Eltombag has also been licensed for use in children with chronic ITP. It has been shown in a multi-country randomised controlled trial (PETIT2) to be effective in maintaining a platelet response with a safe side effect profile. The most common

side effect was raised hepatic aminoacid transferases. There were more adverse events in the placebo group than the treatment arm.[53]

Splenectomy

The spleen is the main site where platelets are consumed by antibody recognition of the Fc receptor on macrophages within the reticuloendothelial system. Splenectomy in patients with cITP removes the mechanism of platelet destruction as well as a large source of antibodies.[7,30,44]

Both the international consensus paper by Provan *et al* 2010,[44] and the updated ASH evidence-based guideline 2011 by Neunert *et al*,[30] agree that a splenectomy, with appropriate previous vaccination, is an effective treatment modality in chronic refractory ITP. Five studies over the last 20 years have shown an overall response of 71.5%.[39]

However the decision to undertake a splenectomy in a child must not be taken without careful consideration. ASH recommends that splenectomy be reserved for children with significant or persistent bleeding who have failed to respond to other treatments.[30] Provan *et al* argues that splenectomy is "rarely recommended in children because risk of death from ITP in childhood is extremely low (0.5%)" and the risk of post-operative sepsis outweighs the benefit.[44]

Conclusion

The approach to the diagnosis and management of ITP has undergone considerable change over the last two decades. Nomenclature has changed and the management

now tends to follow evidence-based practice. New scientific research has also offered novel agents that can be used in patients with chronic disease.

The ITP Working Group is collaborating to increase the number of study patients, to improve future practice and to standardise treatment protocols.

The Haematology-Oncology Service at the Red Cross Children's War Memorial Hospital has always advocated a more conservative approach akin to that adopted by the BSH. Local considerations have informed this approach. Poor social circumstances and lack of private transport frequently mandate admission in well patients but this has allowed clinicians to 'watch and wait' in many cases.

A review of patients presenting to RCCWMH would be helpful to understand the local demography of patients with ITP, the natural history of the disease, and to situate us in the diagnostic and management debate.

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Chapter 2: Publication ready manuscript

Management of Paediatric Immune Thrombocytopenia at a South African centre from 1991-2011

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ABSTRACT

Management of Paediatric Immune Thrombocytopenia at a South African centre from 1991-2011

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Three hundred and seventeen patients meeting the diagnostic criteria for immune thrombocytopenia presented to Red Cross War Memorial Children's Hospital between 1991 and 2011. We retrospectively reviewed these patients in order to describe patient demography, the natural history of the disease, and different approaches to diagnosis and management. There were 162 males and 155 female patients. The median age of onset was 3.48 years old (IQR 1.66-6.36). In the 4 weeks preceding presentation, 98 (31%) patients had a viral illness. The median presenting platelet count was 7 x 10^9/L (IQR 3-14.5). Petechiae were the most common clinical sign at presentation (58%; 184/317). None of the patients presented with intracranial haemorrhages. The majority of patients in the study were admitted (234/317; 74%) with a median stay of 4 days (IQR 0-6). Bone marrow aspirates (BMA) were performed in 188 patients (59%). There was a reduction in BMA from 1991-2000 to 2001-2011 ($p<0.001$). There was an increase in the percentage of patients treated from 1991-2000 (77/170; 44%) to 2001-2011 (99/147, 67% $p< 0.001$). Resolution occurred in 75% of patients with a median time to resolution of 31 days (IQR 11-73 days). When we analysed the "survival estimate" from the 2 decades, despite differing rates of BMA, treatment rates and regimens, there was no statistical difference in resolution.

Management of Paediatric Immune thrombocytopenia at a South African centre from 1991-2011

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Introduction

Immune Thrombocytopaenia (ITP) is an immune mediated disorder, characterised by loss of self tolerance. ITP is defined as a platelet count less than < 100 x 10^9/l, and is caused by autoantibodies, usually IgG, directed against platelet membrane antigens e.g. glycoprotein IIb and IIIa.[1-3] Autoantibodies may be directed against megakaryocytes as well reducing platelet formation. There is also evidence of T-cell cytotoxity in the pathogenesis of ITP. [3]

A common cause of isolated thrombocytopenia in childhood, ITP has seen vast changes in definition, diagnosis and management in the last decades. As research has enabled us to understand more about ITP, the need for standardisation has become apparent.

The incidence of ITP is estimated at between 1.9 to 6.4 per 10^5 children per year.[4] The mean age of onset with children registered in the ICIS Registry 1 was 5.7 years

(5.9 years for girls, 5.5 years for boys)[5] and the mean platelet count at presentation ranged from 7.3-24 x 10^9/l.[6-12] The most common manifestation is cutaneous bleeding, followed by mild epistaxis.[7-9,11,13,14] The frequency of severe bleeds is around 3%,[20] with a risk of intracranial haemorrhage (ICH) at lower than 1% (0.1-1%). [9-11,15]

A diagnostic approach emphasises the clinical picture in a context of isolated thrombocytopenia.[16] Both the updated American (ASH) and British Society for Haematology (BSH) guidelines suggest that bone marrow biopsies (BMA) are only necessary in those patients that have an atypical course, are unresponsive to drug therapy or have features making another diagnosis likely.[16-17] Despite this the incidence of BMA in newly diagnosed ITP varies from 13-72%.[8-12,18]

Acute management options vary from expectant management (due to the high rate of spontaneous remission as well as rarity of significant bleeding) to emergency interventions such as platelet transfusions (for life-threatening bleeds), or treatments such as corticosteroids and immunoglobulins. The dilemma to treat or to “watchfully wait” is often guided by the fear of ICHs.[19,20]

ASH recommendations have had a notable change from the 1996 ASH guideline. There has been a move away from treatment based on the platelet count. This is in keeping with data that suggests that despite the presentation, platelet count and treatment most children do not experience severe bleeding. ASH suggests observation alone for children with mild bleeding..[16] Similiarly, the BSH guidelines acknowledge that many children with very low platelet counts have minimal

symptoms and usually have spontaneous remission within a few weeks. Since life-threatening haemorrhage is rare in children with ITP, regardless of the platelet count, and is not necessarily prevented by drug treatment, most children with acute ITP can be managed expectantly.[17]

To date, most of the guidelines for ITP have been written by and for developed countries. The place of a developing country in Sub-Saharan Africa, with potentially different needs, demographics and resources has not been addressed. The aim of this study was to review patients presenting to the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, to determine the patient demography and the natural history of the disease, as well as to examine our approach to diagnosis and management.

Methodology

This was a retrospective document review. Prior to the research, ethics approval was obtained from the University of Cape Town Human Research Ethics Committee. (623/2013)

The RCWMCH is the only children's hospital in southern Africa, and is one of two tertiary referral sites for paediatric patients in Cape Town, Western Cape. The population in the city of Cape Town is 3 740 026. In 2015, it was estimated that 26% of children in the Western Cape live under the poverty line (less than ZAR671 per month i.e. less than USD50 per month).[21,22] The gross national income per capita of South Africa is USD 6050 as compared to the United States at USD 54960 and the

United Kingdom at USD 43340.[23] Most cases of ITP are referred to the Haematology Oncology service at RCWMCH from primary and secondary level hospitals in the state sector, or from private practitioners. Once the diagnosis is made and management initiated these patients are usually down referred to their closest point of care, but may be referred back if complications occur.

The institutional database of all patients with ITP since 1951 to present was searched. All patients diagnosed with ITP from 1991 to 2011 were examined and audited. All patients were given numerical identifiers to maintain patient confidentiality. Data was entered into a Microsoft Access™ database, and included identifying data, co-morbidities, clinical information around bleeding, full blood count at presentation, platelet counts at various intervals, treatment and outcome. (Appendix 1)

Complete resolution was defined as a platelet count > 100 x 10^9/l. Chronic ITP (cITP) was defined as persistence of thrombocytopenia greater than 12 months (this definition has been changed from 6 months by the International ITP working group because there is still a good chance of spontaneous resolution after 6 months).[24] Relapse was defined as a platelet count >100 x 10^9/l but relapsing to a count less than 100 x 10^9 /l within 12 months. The administered dose of steroid was either stated as mg/kg/day or was calculated.

This was a descriptive study. Success of treatment outcomes were analysed using Statistica™. Children treated for ITP at the RCWMCH were divided into two cohorts: 1991 to 2000 and 2001 to 2011. Where the 2 groups or treatments were compared

the log-rank test or Chi-squared test was used, with a p-value of 0.05 being regarded as significant.

Results

Three hundred and fifty three folders were evaluated. (Figure 1) Thirty six patients were excluded from analysis because they had non-immune forms of thrombocytopenia or secondary immune thrombocytopenia (28), inadequate records (6), or were involved in a clinical trial (2) (Appendix 2). A total of 317 patients were included in the analysis. The median age of onset in the study group was 3.48 years (IQR 1.66-6.36). The majority of children (72%) were less than 6 years old. There were 162 males [median age 3.4 (IQR 1.42-6.55)] and 155 females [median age 3.54 (IQR1.77-6.32)]. When stratified into those under 5 years old and those older than 5, the gender distribution was not statistically different.

A large number of patients had co-morbidities (92/317; 29%). Nineteen had iron deficiency anaemia, which was presumed when a patient had a haemoglobin (Hb) of < 11 g/dl and MCV <75 fL (Appendix 3). In the 4 weeks preceding presentation, 98 (31%) patients had a viral illness. Only 6 patients (2%) had received vaccinations before the onset of illness.

On presentation, the median platelet count was 7 x 10^9/l (IQR 3-14.5), with a median Hb of 11.2g/dl (IQR 9.9-12). Most patients (196/317) had platelet counts below 10 x 10^9/L. Table 1 summarises the patient characteristics, management and outcome

between the two decades. In the second decade 2001-2011, patients presented with lower platelet counts with a median of 5 x 10^9/L (IQR 3-12 p=0.002).

More than half the patients (58%; 184/317) presented with petechiae. Fourteen percent (45/317) presented with epistaxis; 5% (15/317) with gastrointestinal bleeds and 4% (12/317) with haematuria (macroscopic). None of the patients presented with ICH. Nineteen percent (61 patients) presented with "other" symptoms; mouth bleeds (16/317, 5%) were the most common presentation followed by trauma (7/317, 2%), sub-conjunctival bleeds (5/317, 1.6%) and in 4 patients (1.2%) ITP was an incidental finding.

When bleeding (during the course of the patients' illness) was classified according to the bleeding severity tool suggested by Bolton-Maggs,[25] mild bleeds were seen as the most prevalent (Table 2). When platelet count was compared to severity the majority of patients with platelets <10x10^9/l were mild or moderate (Table 3). In the case of life threatening bleeds (5/317); 3 patients were less than 5 years old: 1 had a GIT bleed and 1 presented in shock with a purpuric rash. The third patient (2 years old) presented with epistaxis and lobar pneumonia. Her profound thrombocytopenia resolved within a month but she relapsed 9 months from diagnosis and developed an ICH 2 months after the relapse. She was found to have a right temporal haemorrhage, which she survived. She did not have any long term neurological sequelae. She was treated with IVIG, pulsed with methylprednisone and received a platelet transfusion. The other 2 patients were both 11 years old; 1 had haematuria, and the second, who had initially presented with petechiae and mild bleeding, presented 7 months later with an ICH. Imaging revealed a temporal intra-cerebral

bleed. The patient survived with a mild residual right hemiplegia. She was treated with 4mg/kg of oral prednisone, IVIG and received a blood and platelet transfusion.

The majority of patients in the study were admitted to hospital (234/317; 74%) with a median admission stay of 4 days (IQR 0-6). BMA were performed in 188 patients (59%). Of those (188 patients), 82% were admitted and 60% received treatment. BMA were done with greater frequency in patients with lower platelet counts, lower haemoglobin, in those with co-morbidities which includes patients with iron deficiency anaemia (Table 4). BMAs were also more often performed in those with increased 'severity of bleed' score (Table 2). When looking at 1991-2000 as compared to 2001-2011 there has been a reduction in the number of BMAs which shows statistical significance (Table 1 -2).

More than half the children in the cohort (175/317; 55%) were treated. In the "untreated" group 71% were admitted and in the "treated" group 77% of cases were admitted. Patients were treated in accordance to their bleeding score as seen in Table 2. All patients that had life-threatening bleeds were treated. There was an increase in the percentage of patients treated from 1991-2000, (68/156; 43%) as compared to 2001-2011 (107/161; 67%, $p< 0.001$) (Table 1).

The most common treatment modality used was oral steroids (162/175; 91%) and of those (where the oral dose administered is known [n=153]) 52% (79/153) received a dose of 4mg/kg for 4 days and 48% (74/153) received 2mg/kg for 2 weeks. Four patients received intravenous steroids (methyl-prednisone, dexamethasone or hydrocortisone). When we looked at the difference in dosage per decade, we found

that 90% of patients that received 2mg/kg were in 1991-2000, whereas 73% of patients received 4mg/kg in 2001-2011 ($p<0.001$). Sixteen children received IVIG (11 of whom also received steroids) and 1 received rituximab. This patient had 22q deletion syndrome with T-cell deficiency and rituximab was given during the chronic phase of his disease with no response to other modalities.

Six percent of all patients (9/317) required a blood transfusion, and 7 percent (23/317) required a platelet transfusion; in all cases for severe or life-threatening haemorrhage.

The outcome of 7 patients was unknown as 5 were lost to follow up and 2 were transferred (Figure 1). Resolution of ITP within 1 year occurred in 75% of the patients (237/317 patients) with a median time to resolution of 31 days (IQR 11-73 days). Figure 2 shows the rise in platelet count over time, until complete resolution. As seen in the Figure 3-A, there was no statistical difference in time to resolution between those patients that had “no treatment” (median of 34 days) as compared to those who received treatment (median of 27 days) ($p=0.3$). More patients that did not receive treatment [79% (112/142)] resolved, as compared to those [62% (109/175)] that received treatment, although this was not statistically significant. In each of the bleeding score categories the proportion of cases that resolved was: Mild 71% (121/171), Moderate 67% (83/123), Severe 89% (16/18) and Life Threatening 20% (1/5). There was no difference in time to resolution if a patient presented with a platelet count of less than 10×10^9/L (Figure 3-B).

Thirty-one patients relapsed (7%) with a median time to relapse of 231 days (IQR: 109-303). Approximately two thirds of these the patients (20) went on to become

chronic, with 11 resolving. There was no difference in BMA rates in those who had relapsed and those who did not. There was a difference ($p<0.001$) in the rate of relapse between the two decades (Table 1).

Out of the total of 317 patients, 93 patients (29%) went on to become chronic. In the chronic ITP cohort, the mean age was 4.35 years old (IQR 2.47-8.44). There was no difference in gender distribution in this group of patients. Patients with chronic ITP (cITP) were less likely to present with a preceding viral illness ($p<0.001$). The platelet count (11 x 10^9/L, IQR 5-20) on admission was noted to be higher than those with acute ITP (6 x 10^9/L, IQR 3-12; $p<0.001$). Figure 2 shows the difference of "rise in platelets over time" as compared to those who resolved. BMA were done in 74% of patients ($p=0.001$) and 72% of patients (65/93) with cITP received treatment.

Refractory ITP was seen in 27 patients. Refractoriness was defined as no response to steroids and/or IVIG. A total of 19 patients underwent splenectomies (17 had refractory ITP; $p<0.001$). The time to splenectomy was a median of 796 days; with a response rate of 53% (10/19). Response to splenectomy was defined as a platelet count of > 100 x 10^9/l . The median age at splenectomy was 8.76 years old (IQR 6.37 to 11.65). There was no statistical difference in the age of responders to non-responders.

Overall when we analysed the "survival estimate" from the two decades, despite differing rates of BMAs, treatment rates and regimens, there was no statistical difference in resolution of platelet count (Figure 3-C).

Discussion

The mean age of onset with children registered in the ICIS Registry 1 was 5 years 8 months old.[5] The peak age distribution was between 1 to 6 years old. Other studies have reflected similar demographics.[7,9] The patients that are seen at Red Cross War Memorial Children's Hospital reflect that of the findings of the ICIS registry regarding age.

Most studies have shown that in younger age groups i.e. 1 to 5 years old, boys predominated over girls.[5,8-10] The older children either, had an equal representation of boys to girls,[7,8] or a slight predominance of girls (0.8:1).[9] We found no difference between the incidence of girls and boys even when we stratified for age.

Infections are known to be one of the triggers for ITP.[6] There is little data from developing countries with regard to infection rates, and one might expect the incidence to be higher, but a study of Vietnamese children (n=82) showed a low incidence of infection (15%) preceding the onset of ITP.[6] In our cohort 98 out of 317 had preceding viral illnesses (31%) which is higher than the Vietnamese study but lower than Canadian studies (57%).[12]

The mean platelet count on presentation in our cohort was 12.6 x 10^9/l, however the median count was 7 x 10^9/l, better reflecting the large number of patients who have very low counts on presentation. The literature similarly shows a mean platelet count ranging from 7.3-24 x 10^9/l.[6-12] More than half the patients in 2 large studies had platelet counts less than 10 x 10^9/l.[7,8]

When our patients were classified according to the bleeding severity score tool proposed by Bolton Maggs[9] mild bleeds were the most prevalent (54%) even in

those with low platelet counts (Table 3), but less common than in the UK where 75% of patients presented with mild bleeds; less than 6% with severe bleeds and none with an ICH as a presenting symptom. We had a higher incidence of moderate (39%) and severe bleeds (5.5%) in comparison to the UK data (20% and 3% respectively) and 5 patients (1.5%) had life threatening bleeds (Table 2-3, Table 5 adapted from graph from the Lancet[13,25 (fig 2)]). Interestingly, of the patients that had life-threatening bleeds, 4 out of the 5 went on to become cITP and 3 required splenectomies. Two of the patients had ICHs, 8 and 10 months into the course of the disease. Fortunately, they were not left with significant morbidity.

Table 5: Platelet count to severity in UK (n=425)

Platelet count	**No symptoms**	**Mild**	**Moderate**	**Severe**
	1.9%*	**74.5%**	**20.4%**	**3.2%**
<10 x 10^9/l.	0.2%	42%	15%	3%
10-19 x 10^9/l.	0.5%	19%	4%	0.2%
20-50 x 10^9/l.	0.2%	10%	1%	0
51-100 x 10^9/l	1%	3%	0.4%	0
>100 x 10^9/l.	0	0.5%	0	0

*adapted from bar graph showing numbers of patients in each category; percentages calculated from n=425

It would seem that the patients seen at our institution are clinically more severe than those managed in the UK. A possible explanation for this is that, the referral pathway over the last decade has changed where clinicians in secondary hospitals and private facilities manage mild cases of ITP, thus skewing the distribution of patients seen at our facility. The difference in certain intrinsic (e.g. gene mutations affecting

immune response, ethnicity) and extrinsic factors (e.g. infectious disorders, recent vaccines or drugs) may also contribute.[6]

The Intercontinental Childhood ITP registry reports that the average rate of hospitalisation is 73%. In the patients that were “untreated”, 47% of these cases are still admitted for observation, and in the “treated” group 85% of cases are admitted.[10] The UK has a lower rate of hospitalisations. In 2009, 43% of the children were admitted, with a median stay of 1.5 days.[9] The rate of admission in our cohort of patients was 70%. This is higher than the UK rates but aligns with the Intercontinental Childhood Registry. This may be as a result of us seeing patients that are clinically more severe based on the comparison of “bleeding score” as mentioned earlier. Social reasons also contribute to our higher admission rates. Our patients have poorer access to healthcare and education, are multi-lingual which creates potential language barriers and have poorer access to reliable transport and are therefore frequently admitted as a precautionary measure in case they suffer severe haemorrhage in the acute phase.

It is worth noting that there are important differences in methodology between Intercontinental Childhood Registry[5], UK review[9] and this study. The Intercontinental Childhood Registry namely Registry I was the first project of ICIS. Coordinators and investigators from across the world were recruited. Newly diagnosed patients were registered by their institution on a case by case basis. Once patients were registered, then the investigators were sent questionnaires that looked at presentation of ITP, demographics, natural history and nature of disease.[5]

The UK study by Grainger et [9] extracted data from the UK Childhood ITP registry, and compared the results to an audit in 1995 and 2000. Those audits were conducted by postal questionnaire. The classification of 'severity of bleed' was made by the reporting clinician not by the data analysts as is the case in this study.

The incidence of bone marrow aspiration varies from 13-72%.[8-12,18] Analysis from the UK Registry comparing 'proportion of children undergoing BMA' from 1995 to 2000 to 2009 showed a reduction from 40% to 18% to 13% respectively.[8] This reduction reflects a more conservative approach because it has been shown to be unnecessary.[26] US studies show a different approach but no added benefit from doing BMA more frequently.

A study from Alabama where 72% of 409 study patients had BMA, reported that the bone marrow aspirate result did not alter the diagnosis or management of the patients.[11] Similarly a study in Ontario[12] with 74 patients, 64% had BMA. The diagnosis was not altered in any of the patients, even in those who had "Atypical ITP" (53% of those who had BMA).

We have performed BMAs in 188 cases (59%). This is more than the patients in the UK registry but less than the patients reported in Northern American series. The patients presenting with low haemoglobins are a reflection of the high incidence of iron deficiency anaemia in our population, rather than bleeding on presentation or chronic blood loss. A study in 2002 reported the prevalence of anaemia between 64% - 83% of children. Iron-deficiency anaemia was found in 32%-46%.[27] It was found that in this group of patients more BMA were performed (22.8% vs. 13.2%). It may suggest that BMA are performed more readily as the clinician had a heightened

concern for a secondary cause when two or more haemopoetic “cell lines” were affected. Patients with platelet counts less than 10 x 10^9/L, and with co-morbidities were also more likely to have BMA performed. However these did not show not statistical significance. We observed that BMA frequency increased with severity of bleeding, and this did show statistically significance (p=0.008) (Table 4).

Despite the higher numbers of BMA performed at RCWMCH compared to the UK, there has been a reduction over time. The haematology oncology service at RCWMCH has endeavoured to align itself with a more conservative approach by minimising “unnecessary” invasive procedures and this is reflected in the study. In the years 1991-2000 61.7% of patients underwent BMA compared to 2001-2011 when the proportion fell to 38% (p<0.001).

Chronic ITP in our study was present in 29% of patients. This is in line with studies that show an incidence of between 24- 31%.[7,10,11] We found that our patients were less likely to present with a preceding viral illness (p<0.001) and also had a higher platelet count on presentation. The age of presentation was not in keeping with previous studies that showed an association with older age (i.e. >7 years).[7,11]

A review article in The British Journal of Haematology examined studies from different countries, and the variability of treatment rates between countries. The treatment rate reported for South Africa was 81%,[28] exceeded only by Canada at 90%. The UK’s rates were 16% in 2011, compared to previous rates of 61% in 1995, and 38% in 2003.[20] The rate for South Africa was based on a single institution study

at Tygerberg Hospital in Cape Town which reviewed 106 patients over 10 years from 1996 to 2006.[28]

The findings of our study show that over the last 20 years we have a considerably lower treatment rate of around 55%. But it must be said that our rates of treatment increased from 44% in 1991-2000 to 67% in 2001-2011. ($p<0.001$) There was no difference in admission rate, and the patient profile was similar (Table 1).

Looking at treatment modalities, 166 (95%) of the 175 children who were treated received steroids and 16 (9%) received IVIG, including 11 who received both.

The Intercontinental Childhood ITP registry observational study showed that 33% of the patients treated received steroids with a response rate of 70-80%.[2,16,19] The traditional regimen has been 2mg/kg per day over 10-14days.[16,19] Four mg/kg per day for 4 days was described in a Canadian study[12] and is now the recommended approach. This higher dose regimen is effective in that 72% to 88% of children raise their platelet count> 50 10^9/l within 72 hours.[29] and is intended to limit the window of exposure to steroids and their side effects (hypertension and glucose intolerance). From 2001 the use of the higher dose prednisone regimen (4mg/kg for four days) became common practice at RCWMCH. It was used in 72% of cases, whereas in 1991-2000 90% of patients received the 2mg/kg/day regimen. There was no difference in resolution rates between the two dosages ($p=0.6$). There has been no evidence to support either dosing regimen over the other.[8,16,30]

In the 2009 UK survey by Grainger, corticosteroids are used most commonly as first line therapy (48%), followed by IVIG (28%). Expectant management in the survey was at 80%.[9] By comparison, Nordic[18] and German[8] studies showed IVIG used as

the first line therapy over corticosteroids. The preference for IVIG is due to a more rapid rise in platelet count (often within 24 hours) with equal efficacy of between 70-90%. [2,19]

Albeit an effective agent in the management of ITP, IVIG is not without potential side effects some of which may be potentially life-threatening viz. anaphylaxis. Considering the huge differential in cost between oral prednisone and IVIG and the fact that in our setting extreme cost of drugs can be prohibitive, we have historically been judicious with its use, in the face of a much cheaper alternative. In addition to cost, it also requires hospitalisation for administration. Consequently only 16 of our patients received IVIG.

When looking at the relapse rate, there was a statistical difference between the two decades with less patients relapsing from 2001 onward. The time to response as well as percentage of children that reached complete resolution did not change between the two decades further emphasising that despite treating a higher percentage of patients there was no change in the time to resolution. This is a reassuring finding which supports an approach of “watchful waiting”. We have observed that ITP is a benign, self limiting disease. We have had no deaths, and even with the severest complication of ICH both patients survived with minimal morbidity.

Conclusion:

This study has allowed us to better understand the demography of patients seen at RCWMCH. We have shown that key patient characteristics are similar to those reported in the literature. We have shown that lower platelet counts should not be the only factor taken into account when deciding on treatment, but that the severity of bleeding can also be therapeutically instructive.

It appears that we fall in the middle of the management divide between the American and British guidelines. Our higher admission rates mostly speak to our patient demographic who have poorer access to reliable transport, resources and healthcare. We are reassured that we are keeping abreast with international guidelines of adopting a more conservative approach to BMA, thereby minimising patient discomfort, procedural risks and reducing costs without compromising outcome. Unexpectedly we found that our treatment rates have risen and this may be accounted for by severity in bleeding due to changes in referral pathways. Our data supports the contention from other sources that a “watchful waiting” has similar outcomes to patients receiving treatment. The favourable outcomes seen in patients with ITP, despite very low platelet counts and even moderate to severe bleeding, reinforces the idea that this condition is largely self-limiting, and empowers us to confidently reassure parents.

Authorship

S.A designed the research, collected data, analysed and interpreted data, and wrote the manuscript; A.D designed the research, interpreted data and edited the manuscript; A.v.E edited the manuscript; and M.H edited the manuscript.

Conflict of- interest disclosure: The authors declare no conflict in interest.

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Figure 1. Consort diagram of patients with ITP from 1991-2011

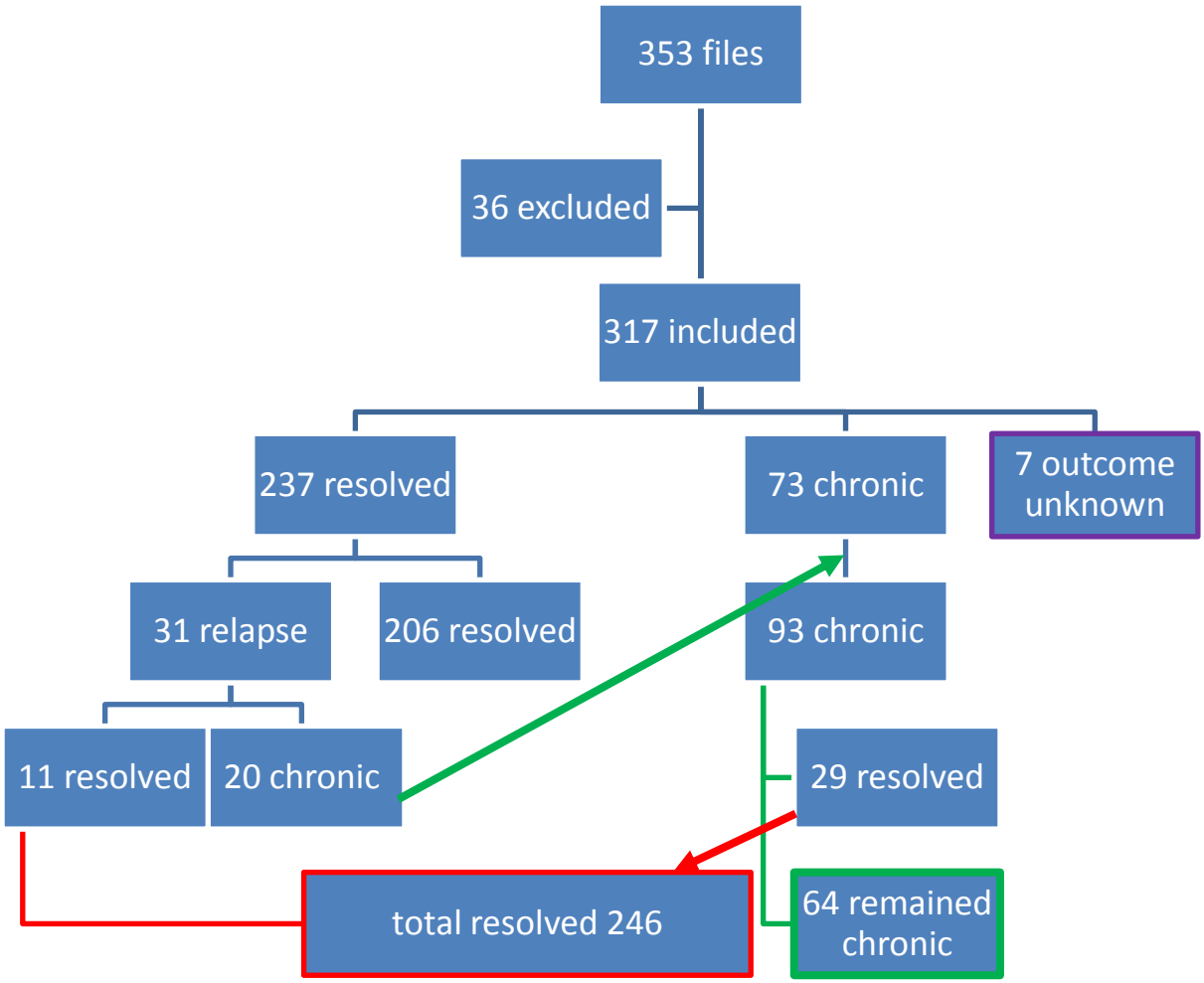


Figure 2. Rise of platelet count at varying time intervals.
Chronic patients shown on the left; Patients that resolved on the right

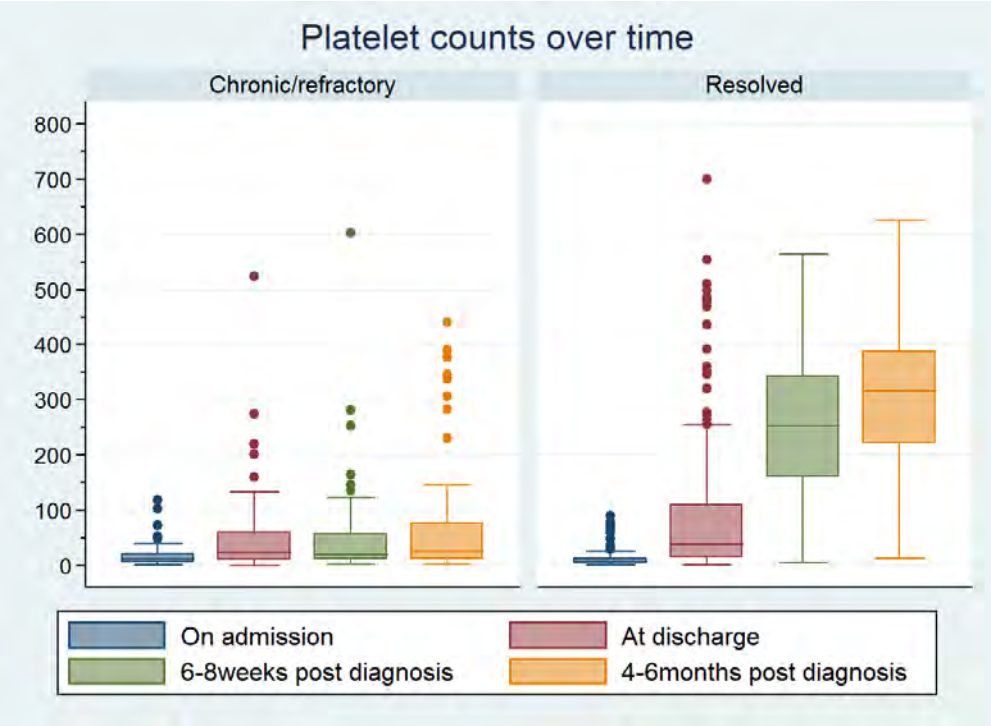
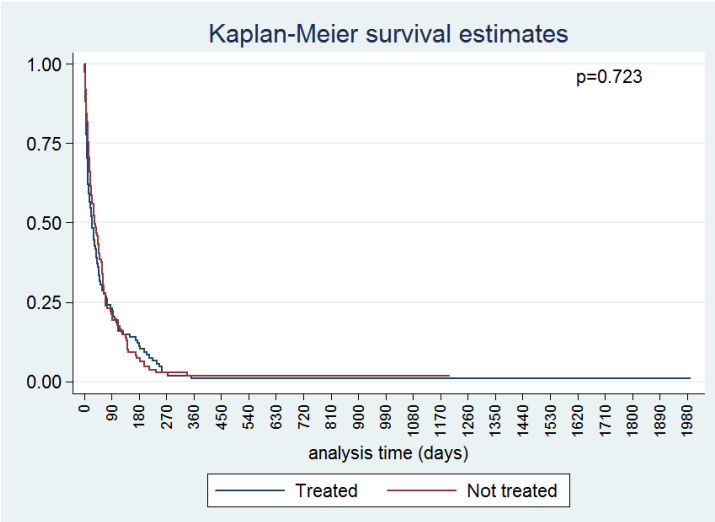
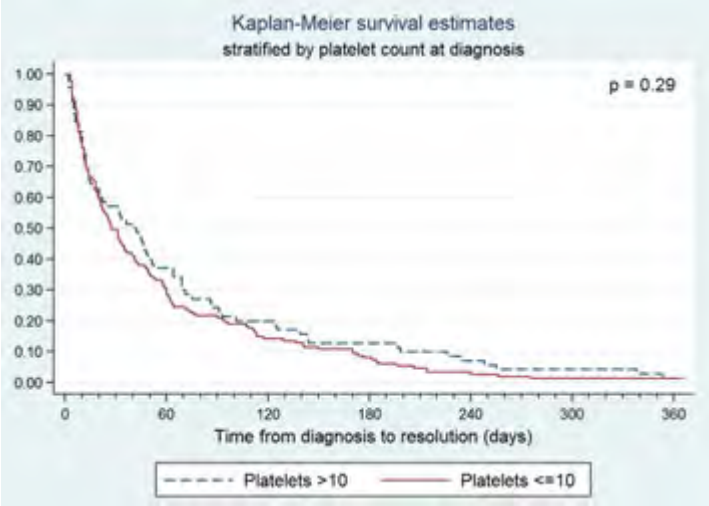


Figure 3. Kaplan Meier Survival Estimates (A) Time to resolution comparing treatment vs. no treatment. (B) Time to resolution when comparing platelet count above and below 10x 10^9/L. (C) Time to resolution comparing decades

A



B



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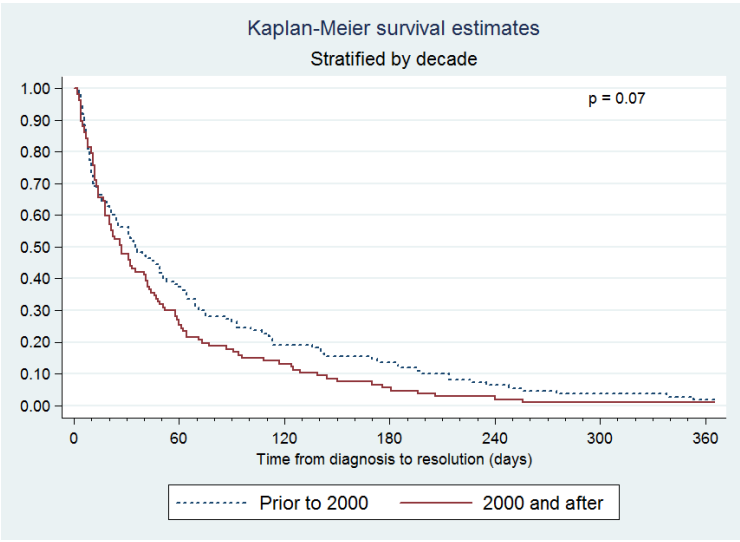

Table 1. Patient Characteristics comparing 1991-2000 to 2001-2011

	Decade prior to 2000 N=156 (%)	Decade 2001 and after N=161 (%)	p-value
Baseline characteristics:			
Male Sex	79 (49.4)	79 (50.6)	0.87
Age (years)	3.8 (1.7–6.5)	3.1 (1.6–6.1)	0.22
Viral illness	50 (32.1)	48 (29.8)	0.67
Platelet count on diagnosis	10 (4–17)	5 (3–12)	0.002
Management:			
Admitted	118 (75.6)	116 (72.1)	0.47
Received treatment	68 (43.6)	107 (66.5)	<0.001
· **Steroids**	63 (40.4)	103 (64.0)	<0.001
· **IVIG**	8 (5.1)	8 (5.0)	0.95
Platelet transfusion	6 (3.9)	17 (10.6)	0.02
Blood transfusion	10 (6.4)	9 (5.6)	0.76
Bone marrow biopsy	115 (73.7)	73 (45.3)	<0.001
Splenectomy	8 (5.1)	12 (7.5)	0.72
***Outcomes*:**			
Resolved (within one year)	113 (72)	124 (78)	0.28
Relapse	20 (13)	11 (6.8)	<0.001
Refractory ITP	7 (4.5)	20 (12.4)	0.01
Chronic ITP	54 (35)	39 (24)	0.01

Table 2. Severity of bleed looking at presenting platelet count, treatment and BMA

Severity of bleed	Proportion of child with bleed severity n=317	Mean platelet count x 10^9/l	Proportion receiving treatment	Proportion undergoing BMA
Mild	n=171, 54%	14.18	n=82, 48%	n=87, 51%
Moderate	n=123, 39%	11.2	n=72, 59%	n=83, 67%
Severe	n=18, 5.5%	10.7	n=15, 83%	n=14, 72%
Life-threatening	n=5, 1.5%	5.8	n=5, 100%	n=5, 100%

Table 3. Platelet count related to severity of bleeding symptoms

Platelet count	Mild	Moderate	Severe	LifeThreatening
X 10^9/L	n=171	n=123	n=18	n=5
< 10 n=188	n=96 (30%*)	n=73 (23%)	n=15 (5%)	n=4 (1.3%)
10-19 n=71	n=38 (12%)	n=31 (9.8%)	n=2 (0.6%)	0
20-50 n=45	n=27 (8.5%)	n=17 (5.4%)	0	n=1 (0.3%)
>50 n=13	n=10 (3.2%)	n=2 (0.6%)	n=1 (0.3%)	0

*percentages calculated from total patients (n=317)

Table 4. Bone Marrow Aspirates

N=317	Biopsy Total 188	No Biopsies 129	
Plts < 10	121 (64.4%)	75 (58.1%)	P=0.263
Hb <10	64 (31.9%)	20 (14.7%)	P<0.001
>/= moderate bleeds	101(53.7%)	45 (34.9%)	p=0.008
Co-morbidities	63 (33.5%)	29(22.5%)	p=0.034
Iron def Anaemia	43 (22.8%)	17 (13.2%)	p=0.030
1991-2001 **2001-2011**	115 (73%) 73 (45%)	41 (27%) 88 (55%)	p<0.001

Appendices

Appendix 1: Data sheet

ID		
Folder number	number	
Name	text	
Surname	text	
Date of birth	date	
Date of diagnosis	date	
Age at Diagnosis	DoD - DoB	
Sex code	number	1-male 2-female
Preceding viral illness	Yes/no	
Recent Immunisation	Yes/no	Within 14 days
Co-morbidity	text	
PRESENTATION:		
Presenting symptom	text	
Platelet count	number	
Hb	number	
MCV	number	
WCC	number	
Severity of bleeds [20]	number	1-mild Few petechiae and small (<5 cm) bruises. Epistaxis, stopped by applied pressure
		2-moderate Numerous petechiae and large (>5 cm) bruises. Epistaxis longer than 20 min. Intermittent bleeding from gums, lips, buccal, oropharynx or gastrointestinal tract.
		3-severe Epistaxis requiring nasal packing or cautery. Continuous bleeding from gums, buccal, oropharynx. Suspected internal haemorrhage (lung, muscle, joint, others).
		4-life threatening or inter cranial bleed Intracranial haemorrhage or continuous or high-volume bleeding resulting in hypotension or prolonged capillary refill and requiring fluid resuscitation or blood transfusion (>10 ml/kg)
MANAGEMENT		
Admission	Yes/No	
Bone marrow biopsy	Yes/No	
No treatment	Yes/No	
Steroid	Yes/No	
Type of steroid	Text	
Dose of steroid	number	mg/kg
Anti-D	Yes/No	
Rituximab	Yes/No	
Blood transfusion	Yes/No	
Platelet transfusion	Yes/No	
Days of admission	number	
OUTCOME		
Platelet count at diagnosis	Number	
Platelet count in 2 weeks	number	

Platelet count in 4 weeks	number
Platelet count in 6 weeks	number
Platelet count in 6 months	number
Date of resolution	Date
Days to complete resolution	DoRes-DoD
Relapse	Yes/no
Date of Relapse / Date Last Seen	Date
Time to Relapse / Time without Relapse	DoRel-DoD
Refractory ITP	Yes/no
Chronic ITP	Yes/no
Required splenectomy	Yes/no
Date of splenectomy	Date
Timing of splenectomy	DoS-DoD
Response to splenectomy	Yes/no
Death	Yes/no

Appendix 2:

Diagnoses excluded from analysis	Number
File not found/incomplete	6
Tuberculosis	14
Part of clinical trial	2
Hepatitis B	2
Human immunodeficiency viral infection	2
Von willebrand disease	1
Diagnosis outside of the 20 year study range	1
Bernard soulier syndrome	1
Cytomegalovirus infection	1
Hepatitis A	1
Hereditary thrombocytopenia	1
Post transplant	1
Systemic lupus erthymatosus	1
Thrombocytopenia absent radii syndrome	1
Vasculitis	1

Appendix 3:

Co-morbidities	
Iron deficiency anaemia	60
Asthma	8
Acute gastro enteritis	5
Lower respiratory tract infection	4
Impetigo	3
Mumps	3
Epilepsy	2
Tuberculosis exposed	2
Otitis media	2
Allergic Rhinitis	2
Ventricular-Peritoneal shunt-hydrocephalus	1
Upper respiratory tract infection, diarrhoea and vomiting	1
Upper airway obstruction	1
Tonsillitis	1
Tinea capitis	1
Congenital bilateral ptosis	1
Trisomy 21, Gastro-oesophageal reflux disease	1
Spastic quadriparesis	1
Scalp infection	1
Scabies	1
Rheumatic heart disease	1
Q22 deletion, Cerebral-vascular accident, T-cell immunodeficiency	1
Pelvi-ureteric junction obstruction with UTI	1
Previous tuberculosis	1
Pre septal cellulitis	1
Physical abuse	1
Parasuicide	1
Chronic gastroenteritis	1
Obese	1
Axillary abscess	1
Lice	1
Left renal agenesis, maternal chronic ITP	1
Kwashiorkor , Seizure	1
Atopy, eczema	1
Insulin dependent diabetes mellitus, hay fever, spasmodic croup annually	1
Herpes stomatitis	1
Heterozygous haemoglobin E	1
Gingivitis	1
Foetal alcohol syndrome	1
Escherichia coli (E.Coli) urinary tract infection	1
Dysmorphic, Patent ductus arteriosus	1
Dog bite	1
Developmental delay, social problems	1
Dilated cardiomyopathy, Molluscum	1
Chronic suppurative otitis media	1
Constipation	1

Appendix 4: Authors guideline “Blood”

- Authorship Contributions
- Disclosure of Conflicts of Interest
- References
- Tables
- Figure Legends
- Figures

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Other article types

Review Articles

Review articles are welcomed by the Journal and are generally solicited by the Editor-in-Chief; authors wishing to submit an unsolicited Review Article are invited to contact the Editor-in-Chief prior to submission in order to screen the proposed topic for relevance and priority, given other review articles that may already be in preparation. Review articles should focus on recent scientific or clinical advances in an area of broad interest to those in the field of hematology. Such articles must be concise and critical and should include appropriate references to the literature. All Review Articles, including those solicited by the Editors, are rigorously peer reviewed before a final publication decision is made.

Review articles should not exceed 4,000 words in length; the abstract must not exceed 250 words; we recommend a limit of 100 references. These articles should have no more than 3 authors. Permission to include more than 3 authors must be granted by the Editor-in-Chief. The use of tables and color figures to summarize critical points is encouraged; the Journal offers assistance with preparation or improvement of figures by professional illustrators, once the article is accepted.

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