A RETROSPECTIVE DESCRIPTIVE STUDY OF DEMOGRAPHICS, TREATMENT MODALITIES AND OUTCOMES OF CHILDHOOD IMMUNE THROMBOCYTOPENIA AT A TERTIARY HOSPITAL IN SOWETO, SOUTH AFRICA

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DECLARATION

I, Gcebile Mahlalela, student no. 0705527N, declare that this Research Report is my own work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

Signature of candidate

11 day of December 2023

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ABBREVIATIONS

ITP-immune thrombocytopenia

IVIG-intravenous immunoglobulin

RCT-randomised controlled trial

HRQoL-health-related quality of life

CHBAH-Chris Hani Baragwanath Academic Hospital

CI- confidence interval

Hb-haemoglobin

SD-standard deviation

IQR-interquartile range

DEFINITIONS

ITP: Platelet count <50x10^9/L

Acute/Newly diagnosed ITP: first 3 months.

Persistent ITP: ITP lasting between 3 and 12 months.

Chronic ITP: ITP lasting for more than 12 months.

Remission: platelet count of ≥50x10^9/L in the absence of any treatment for ITP.

Relapse: recurrence of symptoms after remission sustained without any treatment.

ABSTRACT

Background: Primary immune thrombocytopenia (ITP) is an autoimmune mediated disorder and is the most common cause of acquired thrombocytopenia in childhood. Many children will recover spontaneously but treatment may be required to prevent life threatening bleeding. There are controversies regarding treatment options, response rates and predictors of remission in childhood ITP.

Objectives: A retrospective review of demographics, treatment modalities and outcomes of children diagnosed with immune thrombocytopenia at a tertiary hospital

Methods: Patient records of children between the ages 0-16 years, diagnosed with ITP at Chris Hani Baragwanath Academic Hospital from 01 July 2010 to 30 June 2020 were retrieved. Data on demographics, clinical presentation, treatments, and outcomes were collected. Outcomes were measured at 1, 3- and 12-months follow-up. Statistica software was used to perform descriptive statistics, and bivariate analyses and logistic regression.

Results: 80 files were reviewed but 5 patients were lost to follow-up at 1 month. At 12 months, many patients had been lost to follow-up, with only 35 patients remaining. The mean age at diagnosis was 6.3 years, with 80% of patients less than or equal to 10 years of age. In the study group, 16.3% patients did not receive pharmacologic treatment, and all of these went into remission except one patient lost to follow-up. Younger age, ≤ 10 years was associated with higher rates of remission for all 3 follow-up intervals. Corticosteroids was the most common treatment used and a large proportion of the patients in remission at 1, 3 and 12 months received corticosteroids. The likelihood of remission with a preceding illness in the whole study group was higher, with odds ratios of 2.81, 2.03, and 2.97 at 1, 3, and 12 months respectively. Platelet count, sex and haemoglobin at diagnosis had no significant association with remission.

Conclusions: A strategy of watchful waiting can be used in the management of childhood ITP. Younger aged patients with a preceding illness had the highest likelihood of remission, while other predictors showed no significant association with remission. There are no significant differences between our population and the population described in the literature.

SUBMISSIBLE PAPER

A RETROSPECTIVE DESCRIPTIVE STUDY OF DEMOGRAPHICS, TREATMENT MODALITIES AND OUTCOMES OF CHILDHOOD IMMUNE THROMBOCYTOPENIA AT A TERTIARY HOSPITAL IN SOWETO, SOUTH AFRICA

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1. BACKGROUND

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by a low platelet count in the absence of underlying disease.[2] It is a diagnosis of exclusion in individuals who are otherwise healthy, with no other abnormalities on physical examination except haemorrhage and an isolated thrombocytopenia without other changes in the full blood count. ITP is the most frequent childhood autoimmune cytopenia, affecting 2.2–5.3 per 100,000 children aged 18 years or less every year. [2] Acute ITP in children is likely to have a post-infectious cause, [6] and many children go into remission with or without treatment. [1] Life-threatening or severe bleeding is rare, with reported rates between 0.5- 2.9% of children experiencing major haemorrhage. [16,17] Approximately 20–30% of children with ITP will develop chronic thrombocytopenia, lasting beyond 12 months. [1,8,13] While many children with ITP can be safely observed, treatments are often needed to decrease bleeding, or to improve health-related quality of life (HRQoL). [7] Identified predictors of a short duration of illness include abrupt onset of less than 2 weeks, age of less than or equal to 10 years, preceding infection, platelet count of less than 5x10^9/L, wet purpura, and the male gender. [3] There are controversies regarding the need for treatment, treatment options, the timing of treatment and response rates. [4] Predictors of remission from ITP in children are not well understood. [1,13] Identifying predictors of recovery would be beneficial for improving treatment decisions and quality of life for children and their families. [3] Identifying whether specific treatments modify the clinical course would be useful for treatment decisions that impact outcomes [1], and several studies have attempted to identify clinical and laboratory features that predict the disease course in paediatric ITP. [1] Whilst the standard initial treatment for ITP is corticosteroids, IVIG and anti-D, [12] further studies are required to determine the most appropriate agent to use as a second line in children, including the use of thrombopoietin receptor agonists. [9]

This retrospective descriptive study was aimed at highlighting the demographics and clinical presentation of childhood ITP at a tertiary hospital in South Africa. It looked at response rates and outcomes of the different treatment modalities used at this hospital, identified risk factors for chronicity and predictors of remission, and searched for similarities and differences in the outcomes described in published literature from other geographical settings.

2. METHODS

2.1 Study Design

This was a retrospective, descriptive study reviewing patient records of children diagnosed and treated for ITP at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, from July 2010 to June 2020. Data was collected from patient files stored in the haematology-oncology clinic filing room.

2.2 Study Population

Files of patients meeting the following criteria were reviewed and the data were entered on to a data collection tool: (i) children between the ages of 0 and 16 years; (ii) males and females; (iii) all races, ethnicities, and nationalities, and (iv) a confirmed diagnosis of ITP made at CHBAH or referred from other institutions. The diagnosis of ITP was based on a presentation of bleeding associated with low platelet counts in an otherwise healthy individual, with normal red and white blood cell counts, normal smear and a normal or low haemoglobin level secondary to bleeding. Most of the patients' diagnoses were also confirmed with a bone marrow aspirate and trephine.

2.3 Measures

Information collected included age at presentation, sex, presenting complaint, preceding illness or vaccination, platelet count at diagnosis, haemoglobin level at diagnosis, treatment modality and outcome. The presenting complaint looked at the type of bleeding such as epistaxis and/or mucocutaneous bleeding, to use this information to grade the severity of bleeding using a bleeding severity score such as the Modified Buchanan and Adix bleeding score. [18] Most patient records did not have adequate information to be able to use a scoring system and therefore the haemoglobin level was used as a surrogate marker of bleeding severity. Treatment was classified as follows: Observation only, intravenous immunoglobulin (IVIG), or corticosteroids only, and a combination of corticosteroids and IVIG. The following outcomes were reviewed at 1 month, 3 months and 12 months follow-up: remission/recovery, relapse, chronic ITP, death, and loss to follow-up. Remission was defined as a platelet count of ≥50x10^9/L in the absence of any bleeding. Relapse was defined as the recurrence of symptoms after remission without any treatment. Chronic ITP was a platelet count of < 50x10^9/L at 12 months.

2.4 Statistical Analyses

Analyses were performed using Statistica software, version 14.0.0.15. Descriptive statistics such as means, standard deviations, frequencies and percentages were calculated to describe the patient demographics. A Mann-Whitney U test was used to perform a bivariate analysis of the outcome of remission at 1, 3 and 12 months. A p-value of ≤ 0.05 was considered statistically significant. To examine the predictors of remission, non-parametric tests were done using logistic regression to calculate odds ratios.

2.5 Ethics

The retrospective study was conducted on data that were readily available and data were kept anonymous. There were no additional study investigations or risks involved for the patients and therefore informed consent was not obtained. Approval for the study was given by the institution's research committee and clearance from the University of the Witwatersrand Human Research Ethics Committee was granted, clearance number M211047.

3. RESULTS

There were 80 files reviewed of patients diagnosed with ITP from July 2010 to June 2020, who were seen and/or admitted by the haematology unit or discussed telephonically. 78 patients had the diagnosis of ITP confirmed on bone marrow aspirate, which indicated that the cause of thrombocytopenia was most likely immune-mediated. The other 2 patients' diagnoses were made on clinical suspicion of ITP secondary to a preceding viral illness. The demographic and clinical characteristics of the patients are shown in Table 1. At 1 month, 5 patients were excluded as they did not follow up and therefore data for 75 patients was available for further analysis. The patients lost to follow up included the telephonic consults. A further 25 of these patients were lost to follow-up by 3 months, and therefore data for 50 patients was available for analysis. At 12 months follow-up, a sizeable number of patients had been lost to follow-up, with 35 patients' data available for review. The details of patient enrolment, follow-up and outcomes are shown in Figure 1.

Table 1. Demographic and Clinical Characteristics of Sample Population

Characteristics	
N	80
Age at diagnosis-years (mean±SD)	6.3 ±4.1
(median/IQR)	4/ 3-10.5
Gender; male n (%)	42 (52.5)
Female n (%)	38 (47.5)
Platelet count at diagnosis-10^9(mean±SD)	8.7 ± 9.6
(median/IQR)	8.9/ 6.7-11.6
Hb at diagnosis-g/dL (mean±SD)	8.8 ± 3.1
(median/IQR)	4.5/ 2.5-9.5
Preceding illness n (%)	23 (28.8)
Treatment at diagnosis;	
Observation n (%)	13 (16.3)
Corticosteroids n (%)	58 (72.3)
Prednisone	55 (68.8)
Dexamethasone	2 (2.5)
Methyl-prednisone	1 (1.25)
IVIG n (%)	2 (2.5)
Corticosteroid & IVIG n (%)	7 (8.8)

SD; standard deviation

IQR; interquartile range

IVIG; intravenous immunoglobulin

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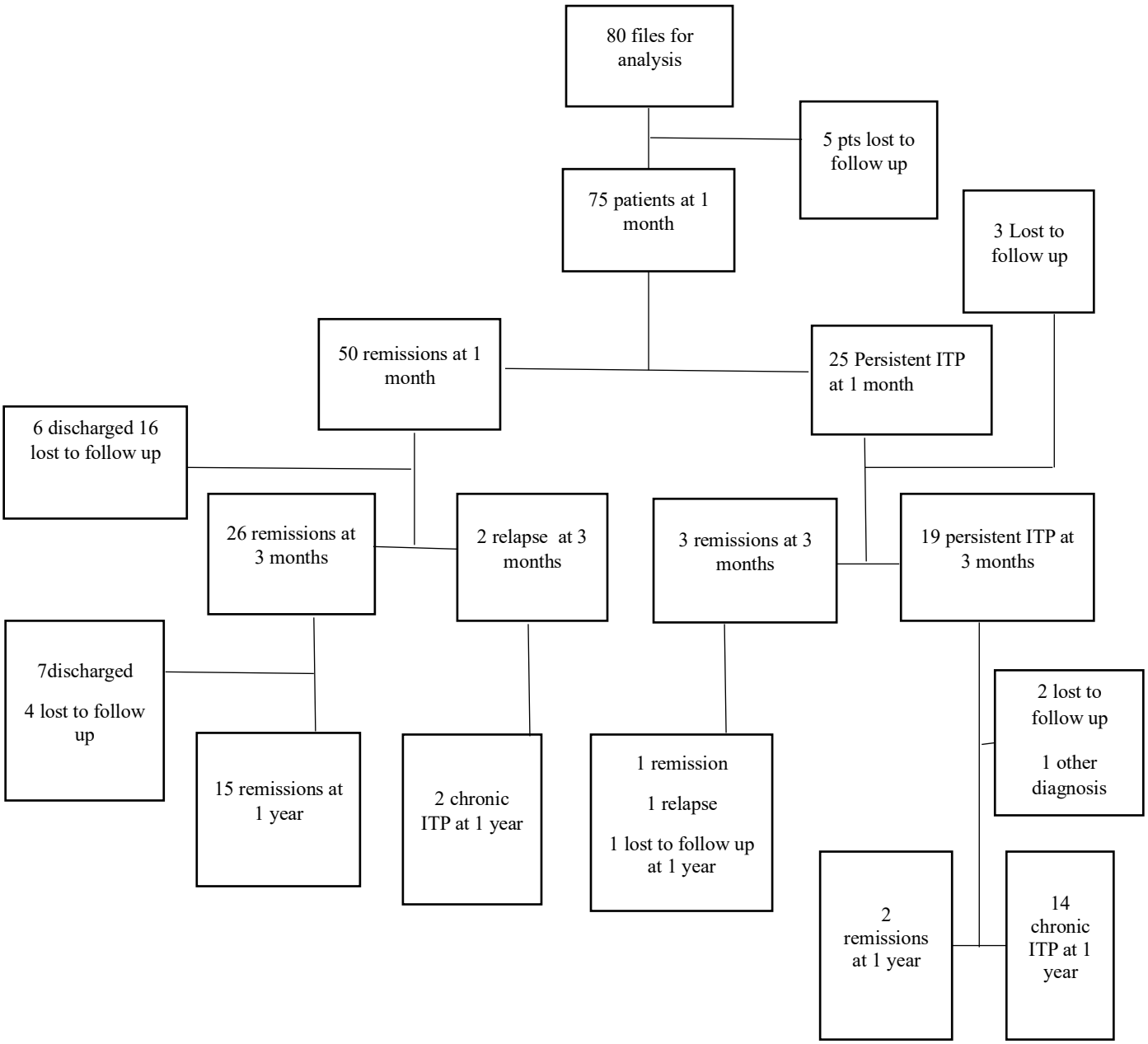
Figure 1. Patient enrolment, follow up and outcomes.



Note: Lost to follow-up indicates patients who did not come for subsequent visits.

Many of the patients lost to follow-up did not honour their follow-up appointments, whilst some of the patients who were in remission were discharged from the haematology unit before completing a year of follow-up. One patient was referred to rheumatology at 1-year follow-up with a possible diagnosis of an underlying rheumatology condition. In this study, 16 out of the 35 (46%) patients seen at 12 months had chronic ITP. A large proportion of patients who were not in remission by 1 month of follow-up became chronic ITP patients. This group consisted of 14 out of 16 chronic ITP patients noted on the flow diagram, Figure 1.

The mean age at diagnosis was 6.3 years, with 80% of patients less than 10 years of age. There were 52.5% males in the study, and 28.8% of the patients had a preceding illness. 72.5% of our patients presented with epistaxis with or without associated mucocutaneous bleeds. Haemoglobin level was used as a surrogate marker for severe bleeding and 28% of patients presented with a haemoglobin level <7g/dl, which might be an indication that many of the patients presented with mild to moderate bleeding. Observation alone without pharmacologic treatment was used in 16.3% of patients, who all achieved remission except one patient whose outcome is not known as the patient was lost to follow-up. The most common pharmacological treatment used was corticosteroids at 72.3%, mainly oral prednisone at 68.8%. Only 2 patients received dexamethasone and 1 patient received intravenous methylprednisolone. Two patients were treated with intravenous immunoglobulin and 7 patients were treated with a combination of corticosteroids and IVIG.

Remission was achieved in 50 of the 75 patients seen at 1 month, in 29 of the 50 patients seen at 3 months and in 18 of the 35 patients seen at 12 months. This showed remission rates of 66.6%, 58% and 51% at 1, 3 and 12 months respectively. Sixteen patients had chronic ITP at 12 months follow-up.

Table 2 shows a bivariate analysis of remission at 1, 3 and 12 months. Younger age was associated with higher rates of remission for all 3 follow-up intervals, with rates of 82%, 76% and 83% at 1,3 and 12 months for the age group of 0 to 10 years, however, this age group had the largest number of patients, and these figures were not statistically significant due to the small total number of patients. Gender and platelet count at diagnosis was not significantly associated with remission, with marginal differences noted in the remission rates between the comparative groups. Remission rates were higher amongst patients with a haemoglobin level

(Hb) greater than 7g/dl at all 3 intervals, however most of the patients presented with a haemoglobin above 7g/dl. All but one of the 13 patients observed were in remission at one month. Many of these patients were lost to follow-up in the following months. Most patients received corticosteroids (72.3%) and made up a large proportion of the patients in remission at 1, 3 and 12 months.

Table 3 demonstrates an analysis of the association of remission with age, gender, preceding illness, platelet count, haemoglobin, and treatment at diagnosis. The table indicates that there was no significant association of remission with age, gender, platelet count and haemoglobin at diagnosis. There was an increased likelihood of remission with preceding illnesses, with odds ratios of 2.81, 2.03, 2.97 at 1, 3, and 12 months respectively, but these were also not statistically significant. There was a high association between observation and remission which showed that patients who had not received pharmacological treatment also had high chances of remission. The table shows no statistically significant association between all pharmacological treatments and remission at 1, 3 and 12 months.

Table 2. Bivariate Analysis of Remission at 1, 3 and 12 months

	Numbers at diagnosis (n=80)	Remission at 1 month (n=50)	Remission at 3 months (n=29)	Remission at 12 months (n=18)
Age at diagnosis		**p-value 0.35**	**p-value 0.03**	**p-value 0.30**
0-10 years n (%)	**60**	41 (82)	22 (76)	15 (83)
11-16 years n (%)	**20**	9 (18)	7 (24)	3 (17)
Gender		**p-value 0.78**	**p-value 0.65**	**p-value 1.00**
Male n (%)	**42**	22 (44)	13 (45)	9 (50)
Female n (%)	**38**	28 (56)	16 (55)	9 (50)
Platelet count at diagnosis		**p-value 0.26**	**p-value 0.30**	**p-value 0.26**
<5x10^9 n (%)	**40**	28 (56)	15 (52)	8 (44)
≥5x10^9 n (%)	**40**	22 (44)	14 (48)	10 (56)
Haemoglobin at diagnosis		**p-value 0.54**	**p-value 0.57**	**p-value 0.25**
Hb<7g/dl n (%)	**22**	13 (26)	3 (10)	3 (16)
Hb≥7g/dl n (%)	**58**	37 (74)	26 (90)	15 (84)
Treatment at diagnosis:				
Observation n (%)	13	12 (24)	4 (14)	3 (16)
Corticosteroids n (%)	55	33 (66)	22 (76)	14 (78)
IVIG n (%)	2	2 (4)	1 (3)	-
Corticosteroids & IVIG n (%)	7	3 (6)	2 (7)	1 (6)

P values are in bold italics and a statistically significant p-value is p<0.05

Table 3. Analysis of predictors of remission at 1, 3 and 12 months

	Remission at 1 month (n=50) Odds ratio (95% CI) *P value*	Remission at 3 months (n=29) Odds ratio (95% CI) *P value*	Remission at 12 months (n=18) Odds ratio (95% CI) *P value*
Age at diagnosis			
0 -10 years	1.06 (0.85-1.31) ***0.63***	0.85 (0.68-1.06) ***0.15***	1.10 (0.87-1.40) ***0.43***
11-16 years	2.34 (0.83-6.59) ***0.11***	0.82 (0.31-2.18) ***0.70***	0.73 (0.14-3.82) ***0.71***
Gender			
Male	1.45 (0.58-3.60) ***0.42***	0.91 (0.36-2.31) ***0.85***	0.88 (0.28-2.79) ***0.84***
Female	Reference	Reference	Reference
Preceding illness			
Yes	2.81 (0.92-8.62) ***0.07***	2.03 (0.73-5.63) ***0.18***	2.97 (0.81-10.8) ***0.10***
No	Reference	Reference	Reference
Platelet count at diagnosis			
<5x10^9 n (%)	0.80 (0.42-1.51) ***0.49***	0.96 (0.53-1.70) ***0.87***	0.86 (0.45-1.66) ***0.65***
≥5x10^9 n (%)	1.02 (0.96-1.08) ***0.56***	1.00 (0.39-1.06) ***0.96***	1.03 (0.95-1.11) ***0.50***
Haemoglobin at diagnosis			
Hb<7g/dl n (%)	1.02 (0.55-1.89) ***0.94***	0.99 (0.46-2.15) ***0.99***	0.57 (0.23-1.44) ***0.24***
Hb≥7g/dl n (%)	0.86 (0.66-1.11) ***0.26***	0.90 (0.70-1.16) ***0.42***	1.20 (0.86-1.65) ***0.28***
Treatment at diagnosis:			
Observation	9.16 (1.13-74.5) ***0.05***	0.71 (0.19-2.61) ***0.61***	6.60 (0.63-68.8) ***0.11***
Corticosteroids	0.54 (0.19-1.51) ***0.24***	1.99 (0.71-5.64) ***0.19***	1.08 (0.28-4.22) ***0.92***
Corticosteroids & IVIG	0.41 (0.09-2.00) ***0.27***	0.57 (0.10-3.16) ***0.52***	0.34 (0.04-3.17) ***0.34***

Results of the bivariate analysis are provided as odds ratio and 95% confidence interval (95% CI)

P values are in bold italics and a statistically significant p-value is p<0.05

4. DISCUSSION

ITP in children generally has a good prognosis. A strategy of watchful waiting can be implemented in the management of children experiencing no or mild bleeding symptoms despite low platelet counts. [5]

All but 2 patients in this study had a bone marrow aspirate done to confirm the diagnosis although not recommended as a routine diagnostic test for children with a typical presentation of ITP. [12] The decision to perform bone marrow examinations in these patients may have been due to factors such as patient likelihood to follow-up and experience of the clinician. In this study, 16.3% of the patients did not receive pharmacological treatment and they all were in remission at one-month follow-up, except one patient who was lost to follow-up.

The use of a score such as the Buchanan and Adix bleeding score provides a grading system in which the severity of bleeding symptoms, in conjunction with other risk factors such as planned procedure likely to induce blood loss, platelet count <30x10^9, a very active lifestyle and access to medical care influence the decision to treat or not to treat. Selection criteria for observation alone could not be deduced in this study as bleeding severity scores were not used to stratify patients into low or high risk and guide treatment strategies.

It is not clear from this study why only a small number of patients were managed by observation only, but this could be an indication of the severity of symptoms at presentation, or the reluctance of healthcare practitioners to withhold pharmacological treatment. The risk of bleeding in untreated children with severe thrombocytopenia and restriction to activities of daily living may contribute to the decision to give pharmacologic treatment.

One significant challenge was the large number of patients lost to follow-up, especially at 3 and 12-month follow up. This is not unique to this study as multiple other studies have cited this as a particular problem. This is most likely due to disease resolution and patients not seeing the need for follow-up. Some patients, 21of 80 in this study, treated at this institution are referrals from hospitals outside Johannesburg, which could be contributing to the number of patients lost to follow-up.

Higher remission rates were noted in the younger age group compared to the older age group. This is in keeping with reports from other studies, although regression analysis in this study did not yield a positive association between younger age and remission, and this was most likely due to the small sample size that produced statistically insignificant results.

Associations between remission and gender, platelet count and haemoglobin at presentation could not be demonstrated. The study did however demonstrate a high likelihood of remission in patients with preceding illness. It is also noted in this study that patients who did not go into remission within a month of treatment were more likely to progress to chronic ITP, as 14 out of the 16 patients who developed chronic ITP had not achieved remission in the first month of follow-up.

Several ITP studies have been able to show a positive association between predictors of remission, such as younger age, low platelet count at diagnosis, male gender, preceding infection, and bleeding severity but conflicting evidence remains regarding these predictors. [1,2] In this study a strong correlation between preceding illness and remission was demonstrated, and higher remission rates among younger children. This was also demonstrated by the larger proportion of chronic ITP patients in the older age group, which is in keeping with the literature, [10] and that none of the chronic ITP patients had a preceding illness before presentation. [15] Other previously mentioned factors were not predictive of remission.

In this study, corticosteroid treatment was the most common form of treatment, with very few patients receiving immunoglobulin or a combination of treatments. This is contrary to other studies that used intravenous immunoglobin as often as corticosteroids. Intravenous immunoglobulin could have been used less frequently in this setting due to cost implications and the difficulty of acquiring IVIG in public state hospitals.

This study had a small sample size which negatively affected statistical measurements. The small sample size was due to difficulties in obtaining patient records from the archiving room because of poor record keeping and an old paper-based system of record keeping. The use of electronic record keeping should be implemented in the future.

This study was conducted at a tertiary hospital which poses a bias for more severe cases. The outcomes may therefore not be generalizable for less severe cases. Bleeding severity scores were not used in this study as not enough information had been documented about the clinical presentation and bleeding characteristics to be able to use any bleeding severity score and due to the retrospective nature of the study, this information could not be obtained. Haemoglobin level was used as a marker for the severity of bleeding, with a haemoglobin level of less than 7g/dl, indicating severe bleeding and the need for blood transfusion on presentation. Bleeding severity scores are used in making decisions to treat or monitor, in cases of watchful waiting.

These could have been used in this study to identify the reason many patients were treated pharmacologically and not observed.

At present, several studies and literature reviews have been carried out to try and comprehend the differences in presentation, treatment responses and outcomes in children with ITP, but no conclusive evidence has been demonstrated to assist healthcare providers with the management of these patients. [8,11] More research work in the form of large randomised controlled (RCT) trials can be done to compare the different treatment modalities and prospective studies to better understand the predictive factors of remission and chronicity in children with ITP.

5. CONCLUSIONS

In summary, this study supports the evidence that watchful waiting or observation can be used in the management of children with ITP as deemed appropriate by the treating clinician. Classification of bleeding severity using a score such as the Buchanan and Adix bleeding score is necessary to guide treatment choices. The use of such a score provides a grading system in which the severity of bleeding symptoms, in conjunction with other risk factors, guide the decision to treat or not to treat. Most patients with mild or no bleeding symptoms can be managed with watchful waiting. The study also indicates that children with a preceding infection and younger age are more likely to go into remission. Other key predictive factors of remission could not be demonstrated in this study and thus further research is required to enhance our approach to the management of these children and to improve outcomes.

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APPENDICES

Appendix A: Instructions for authors

Author Guidelines

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

To submit a manuscript, please proceed to the *SAJCH* Editorial Manager website: Editorial Manager

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc.) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAJCH* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, radiographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAJCH*.

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Material submitted for publication in the *SAJCH* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAJCH* does not hold itself responsible for statements made by the authors. The corresponding author should also indicate if the research forms part of a postgraduate short report, dissertation or thesis.

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Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that it is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAJCH is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *Satch*els publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Editorials, Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAJCH is a Journal on child health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 6 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out

- **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

***Scientific letters*/short reports**

These include case reports, side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Review articles should always be discussed with the Editor prior to submission.

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a precis of reviews published in the international literature

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.

- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the SAJCH or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not**1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx/doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)
Rex v Jopp and Another: Name of the parties concerned
1949: Date of decision (or when the case was heard)
(4): Volume number
SA: SA Law Reports
11: Page or section number
(N): In this case Natal - where the case was heard. Similarly, (C) wood indicate Cape, (G) Gauteng, and so on.
NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the *SAJCH* requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Author Agreement form [forthcoming]
  - Manuscript

- Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for external peer review. Each manuscript is reviewed by either one or two reviewers selected on the basis of their expertise in the field. A double blind review process is followed at SAJCH.

Authors are expected to receive feedback from reviewers and an editorial decision within approximately 6 weeks of submission. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.

Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise and resubmit will be sent for a second round of peer review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion.

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Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is currently applicable. Queries can be directed to Dianes@hmpg.co.za or Claudian@hmpg.co.za

Production process

The following process should usually take between 4 - 6 weeks:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

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Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

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- DOAJ
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo
- EBSCO
- EMBASE

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Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

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Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted as 'supplementary files' (not in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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Appendix B: Research Protocol

A RETROSPECTIVE DESCRIPTIVE STUDY OF DEMOGRAPHICS, TREATMENT MODALITIES AND OUTCOMES OF CHILDHOOD MMUNE THROMBOCYTOPENIA AT A TERTIARY HOSPITAL IN SOWETO, SOUTH AFRICA.

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ABBREVIATIONS

ITP-immune thrombocytopenia

IVIG-intravenous immunoglobulin

RCT-randomised controlled trial

ICIS-Intercontinental Childhood ITP Study

CHBAH-Chris Hani Baragwanath Academic Hospital

HIV- Human Immunodeficiency virus

HAART- highly active antiretroviral therapy

MMR- measles, mumps, rubella

CI- confidence interval

HDMP- high dose methyl prednisone

ICH- intracranial haemorrhage

TPO- thrombopoeitin

DEFINITIONS

Primary ITP: patients without a known aetiology or trigger for thrombocytopenia

Secondary ITP: triggered by disease or drugs.

Newly diagnosed ITP: first 3 months

Remission: platelet count of ≥50x10^9/L in the absence of any treatment for ITP.

Persistent ITP: ITP lasting between 3 and 12 months.

Chronic ITP: ITP lasting for more than 12 months.

Relapse: recurrence of symptoms after remission sustained without any treatment

Refractory ITP: failure to achieve remission after splenectomy.

1. BACKGROUND

1.1 Epidemiology

Immune thrombocytopenia is the most common cause of acquired thrombocytopenia in childhood. (1) The incidence of ITP in children for studies done in Europe reported an incidence of 4.6 to 5.3 cases per 100000, (15) with a peak in incidence between the ages of 2 and 5, and adolescence. It is estimated that approximately 60% of children diagnosed with ITP have a preceding history of viral illness within the past month. (14) (2,7)

In infants and young children, ITP occurs more often in boys, but no gender difference has been noted in school going children and adolescents. A history of infection or vaccination 21 days prior to presentation was found in 50% of children who went into remission in a study by the ICIS group. (3)

1.2 Pathophysiology

Primary immune thrombocytopenia is an acquired autoimmune mediated disorder, characterised by isolated thrombocytopenia. It is defined as a peripheral blood platelet count less than 100 000 platelets per microlitre, in the absence of an underlying cause of the thrombocytopenia. (9) In ITP, autoantibodies, most commonly IgG, against platelet membrane antigens such as glycoprotein IIb/IIIa complex, coat platelets, which shortens their half-life because of accelerated clearance by macrophages. These antibodies may also inhibit platelet production. (4) On the contrary, autoantibodies are not detected in one third of patients. (14) There is also a small risk of developing ITP following vaccination, particularly with measles, mumps, rubella (MMR) and varicella vaccines. Upper respiratory tract and gastrointestinal tract infections are often seen days or weeks before ITP in children.(14)

1.3 Clinical Manifestations

Clinical manifestations of ITP include cutaneous bleeding such as petechiae, purpura, ecchymoses in an otherwise healthy child. Bleeding is graded according to severity. Mucocutaneous bleeding is minor, mucocutaneous plus one other bleeding site is moderate, mucocutaneous plus more than one site of bleeding or intracranial haemorrhage is severe. (4) There is no clear evidence of a direct correlation between the degree of thrombocytopenia and bleeding. (1) Serious bleeding episodes with platelets < 20x10^9 were found in < 10% of cases in a 5 year follow up study by Rosthoj et al, 2012 and events leading to hospitalisation occurred in less than 50% of cases. (10) Demircioglu F et al noted that 60-80% of patients recover in weeks to months, while 20% become chronic. (4)

1.4 Diagnosis

Primary ITP is a diagnosis of exclusion. A platelet count threshold of <100x10^9/L forms the diagnosis of ITP. It is diagnosed in children who are otherwise healthy, with no other abnormalities on physical examination except haemorrhage. The full blood count is normal except platelets or a low haemoglobin secondary to bleeding. The blood smear is normal and large platelets can be observed. Bone marrow examination should only be performed if there is any doubt in the diagnosis of primary ITP or ITP persists without prior treatment response.

(14) Tests to exclude various infectious diseases may be indicated if there is clinical suspicion or high prevalence of such infections. Antinuclear and anti-phospholipid antibodies, lupus anticoagulant and serum immunoglobulins may also be investigated where appropriate. (14)

1.5 Management

Treatment is not indicated for newly diagnosed ITP with no or mild bleeding, that is, skin manifestation only (1). Corticosteroids are the preferred first line therapy unless a rapid increase in platelets is needed or contraindications to corticosteroids are present (2). Majority of children with ITP have a short duration of disease, (4) and increased likelihood of spontaneous recovery and so receive a shorter course of corticosteroids, (1) but the reduced quality of life due to risk of bleeding and restrictions imposed on daily activities to avoid trauma is a cause for concern for families and physicians (4). Intravenous immunoglobulin and anti-D have been reported to show a more rapid response. (1) In a randomised controlled trial by Zaja et al, 2010, combination therapy of dexamethasone and Rituximab was shown to be more effective in preventing chronic disease (p-value 0.004, 95% CI 0.079-0.455), although an increase in adverse events was also noted. (1) In the study by Dermircioglu F et al, the treatment options used were observation, HDMP, IVIG, and splenectomy in chronic ITP patients older than 5 years and refractory to pharmacological treatment. Immunosuppressants are also used as second line therapy for children. Supportive management includes restriction of physical activity and avoiding head and abdominal trauma. (4)

1.6 Outcomes

Infants have been found to have higher rates of recovery and the disease process is usually self-limiting. A recovery rate of 77% was found in ICIS I group study and 89.8% recovery rate in a study by Donato et al, on children. The recovery rate is lower amongst adolescents, 32-53%. Early age of onset and initial IVIG therapy are associated with shorter duration of ITP. 25-30% will become chronic. (2,5) Splenectomy is associated with complete remission in >75% of children with ITP. (2). In a study done by the ICIS group, there were no statistical differences in outcomes between children who were treated and those not treated implying that current available therapies do not affect the resolution or persistence of ITP in children. (3) In the study by Demircioglu F et al, there was also no statistical significance between HDMP and IVIG in treatment response. (4) In the study by Gungor T et al, 2018, remission rate was 71.6% and 28.4% chronicity. 66.7% of patients treated with methyl prednisone achieved complete response, 60.3% responded to IVIG and 72% responded with observation only. Relapse or recurrence rates were 46.9%, 31.9% and 40% for methyl prednisone, IVIG and observation, respectively. (5) In a study by Bennett et al, remission was significantly associated with a younger age and bleeding at diagnosis, with a remission rate of 59% at 12 months. (6). Initial treatment strategies have been noted not to affect outcomes. (8) Persistent and chronic ITP are managed like acute ITP. The recommended treatment options are dexamethasone (80% platelet response), HDMP (60-100% response), Rituximab (31-79% response), combination therapies with varying response, splenectomy (60-70% response) and thrombopoietin receptor agonists, but no finalised studies have been done in children regarding TPO receptor agonists. (9). Major haemorrhage from persistent or chronic ITP is uncommon and children eventually undergo remission despite prolonged ITP course. (11).

The aims of treatment are to prevent life threatening bleeding, stabilise and reduce bleeding and increase health-related quality of life (HR-QoL). (14)

1.7 Justification of the study

There are controversies regarding treatment options for ITP, timing of treatment and response rates. This study will add on to the much-needed evidence for the best management approach for ITP. Majority of studies on ITP have been done in developed countries and not in Africa and so this study is aimed at highlighting differences in the demographics, clinical presentation, response rates and outcomes to the different treatment modalities used at this tertiary hospital in South Africa. The findings of this study will also help improve the management strategies used by the hospital for better outcomes in the future.

2. STUDY AIMS AND OBJECTIVES

I. To describe the demographics of children diagnosed with ITP at CHBAH.

II. To review the different management and treatment modalities used on children with ITP.

III. To measure the outcomes of the various treatment modalities

IV. To compare the outcomes to those described in other geographical groups or settings.

3. METHODS

3.1 STUDY DESIGN

This will be a retrospective, descriptive study reviewing patient records of children diagnosed and treated for ITP at CHBAH from June 2010 to June 2020.

3.2 STUDY POPULATION

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Children between the ages of 0 and 16 years • Males and females	• Alternative cause of thrombocytopenia identified. • Patients outside the stipulated age group

• All races, ethnicities and nationalities • Confirmed diagnosis of ITP • Children diagnosed at CHBAH or referred from other institutions.	• Cases with missing information

3.3 STUDY SETTING

Information will be collected from paper-based patient records kept at the haematology/oncology clinic at CHBAH. Patient records are kept in files that contain information about first presentation, admissions, follow up appointments and final outcomes. This is a tertiary hospital that manages local cases, referred cases from other institutions and more often manages more severe cases of ITP.

3.4 PROCEDURE

Paper based records in the form of files of patients that fulfil the inclusion criteria will be retrieved and reviewed. The necessary data will be collected from each file, as indicated on the data collection tool (Annexure A).

3.5 MEASUREMENT

Variables: Age at presentation, gender, presenting complaint, preceding illness or vaccination, platelet count at diagnosis, treatment modality (Observation only, IVIG, corticosteroids, anti-D immunoglobulin, Rituximab, Thrombopoietin agonists, splenectomy).

Outcomes: Remission/recovery, Relapse, Chronic ITP, Death, loss to follow up.

3.6 SAMPLE SIZE

In order to ensure that the study is comprehensive and can be used to draw an accurate conclusion, we anticipate reviewing at least 100 patient files. The haematology/oncology unit at CHBAH sees approximately 10 to 15 patients a year with ITP, thus the reason to date the study 10 years in retrospect in order to obtain adequate numbers.

4. DATA ANALYSIS

The following variables will be analysed:

1. Age

   The age at presentation of all cases identified will be used and entered onto a statistical software to be able to deduce an association of age to the different outcomes.
2. The percentage number of patients presenting with preceding illness or vaccination will be measured.
3. The ethnicity of patients will be documented.
4. The complaint and platelet count at presentation will be noted and their significance to the different outcomes will be measured.
5. The haemoglobin level at presentation will be documented and used as an objective measure of the severity of bleeding.
6. The rates of remission, relapse, chronic ITP and death following the different treatment modalities will be measured and expressed in percentage and frequencies. The different treatment modalities to be measured are observation, IVIG, steroids, Rituximab, Thrombopoietin agonists and splenectomy.

The Statistical Product and Services Solutions (SPSS, IBM, USA) software will be used to define variables, enter and analyse data and draw informed conclusions. Categorical variables will be described using frequencies and percentages and compared using the Chi-square test. Continuous variables will be compared using the analysis of variance (ANOVA) tool to determine statistically significant differences between variables. A Mann-Whitney U Test will be used to compare continuous variables of not normally distributed data. A p-value will be used for statistical significance with a p-value of ≤ 0.05 considered to be statistically significant.

5. LIMITATIONS

- The study is a retrospective audit of an existing database which may pose a challenge of missing data and incomplete records.
- The study will be conducted at a tertiary hospital which poses a bias of severe cases. The outcomes may therefore not be generalizable for less severe cases.

6. ETHICS

This is a retrospective study of data that is already available and therefore will not require informed consent. The data will be kept anonymous, patient names or hospital numbers will be kept confidential. There will be no additional study investigations or risks involved for the participants. Data collection will begin once the CHBAH Research committee has given authorisation and clearance from the University of Witwatersrand ethics committee has been obtained. The protocol will be submitted to the ethics committee by 31 July 2021.

7. SCHEDULE

	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar
Literature review												
Preparing protocol												
Protocol assessment												
Ethics Application												
Collecting data												
Data analysis												
Writing up report												
Writing up paper												
Submit for publication												

The protocol will be submitted for assessment by the end of June 2021, then the application for ethics approval will be submitted in July 2021. Collection of data will begin as soon as approval has been granted by the ethics committee and should be complete by end of March 2022. The aim is to have submitted for publication on or before October 2022.

8. FUNDING

All costs incurred during this study will be funded by the researcher. The anticipated costs include:

ITEM	**AMOUNT**
Printing	R 200
Transport/Petrol	R 2000
Stationery	R 100
Internet Data	R 500
TOTAL	R 2800

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Appendix A

DATA COLLECTION SHEET

Age	
Gender	Male ☐ Female ☐
Race	African ☐ Caucasian ☐ Asian ☐ Coloured ☐
Presenting complaint	Cutaneous bleed ☐ Cutaneous and mucosal bleed ☐ Haematuria ☐ Gastrointestinal bleed ☐ ICH ☐ Other:
Onset and duration of symptoms	
Bleeding history	YES ☐ NO ☐ If yes, type of bleed: No. of episodes:
Family history of bleeding disorders	YES If yes, which condition
Co-morbidities	
Platelet count at diagnosis	
Haemoglobin level at diagnosis	
Preceding illness 1 month prior	YES ☐ NO ☐ If yes, what was the preceding illness?
Vaccination 1 month prior	YES ☐ NO ☐ If yes, which vaccine?
Treatment modality:	1) Observation only 2) IVIG 3) Corticosteroids 4) Anti-D Ig 5) Rituximab 6) Thrombopoietin agonist 7) Immunosuppressant 8) Splenectomy 9) Combined treatment namely:
Platelet numbers at	1 month: 3 months: 6 months: 1 year:
Outcomes	1) Remission 2) Relapse 3) Chronic ITP 4) Death 5) Lost to follow up

Appendix C: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: I, **Gcebile Mahlalela** (Student number: **0705527N**), am a student registered for the degree of **MMed (Paeds)** in the academic year **2023.**

I hereby declare the following:

4 - I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

5 - I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

6 - I have followed the required conventions in referencing the thoughts and ideas of others.

7 - I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

8 - I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection)

software indicating the level of plagiarism in my research document.

Signature: _____ Date: 11 December, 2023

Appendix D: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr G Mahlalela

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M211047

NAME: (Principal Investigator)	Dr G Mahlalela
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
PROJECT TITLE:	*A retrospective, descriptive study of demographics, treatment modalities and outcomes of childhood immune thrombocytopenia at a tertiary hospital in Soweto, South Africa*
DATE CONSIDERED:	2021/10/29
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr D MacKinnon
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/01/20

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **October** and therefore reports and re-certification will be due in the month of **October** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date

Appendix E: Turn it in report.

Submissible paper final..docx

ORIGINALITY REPORT

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