A retrospective descriptive review of children diagnosed with Henoch Schönlein purpura at Red Cross War Memorial Children's Hospital over a 5-year period (2015-2019)

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List of abbreviations

EULAR/PRINTO/PRES:	European League Against Rheumatism/Paediatric Rheumatology International Trials Organization/Paediatric Rheumatology European Society
HIC:	High income countries
HSP:	Henoch–Schönlein purpura
IgA:	Immunoglobulin A
IgAV:	Immunoglobulin A Vasculitis
LMIC:	Low-to-middle-income countries
RCWMCH	Red Cross War Memorial Children's Hospital

Chapter One: Publication ready Manuscript

A retrospective descriptive review of children diagnosed with Henoch Schönlein purpura at Red Cross War Memorial Children's Hospital over a 5-year period (2015-2019)

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Abstract

Background: IgA vasculitis, formerly known as Henoch-Schönlein Purpura, is the most common primary vasculitis in childhood. The prevalence, variation in clinical features, and outcomes of IgA vasculitis in low-to-middle income countries are poorly understood, due to a lack of published research. This study aimed to provide a comprehensive description of IgA vasculitis cases encountered at a South African children's hospital.

Methods: A retrospective folder review of all children with a discharge diagnosis of IgA vasculitis at (RCWMCH) a tertiary children's hospital between January 2015 and December 2019 was performed. Patient demographics, clinical characteristics, laboratory findings, management and short-term outcomes were summarised; conventional descriptive and inferential statistical methods were used to analyse the dataset.

Results: Forty-nine children were eligible for inclusion in the analysis, mean age was 6 years and 5 months, male-to-female ratio was 1:1. Rash was the presenting symptom in 48 (97%) children; arthralgia 41 (84%), abdominal pain 18 (37%); oedema manifested as scrotal oedema in 1 (2%) and angioedema in three (6%) children. Kidney involvement was evident in twenty-five (51%) children with proteinuria and or haematuria, while isolated microscopic haematuria occurred in six (12%). Complications were infrequent, five (10%) patients had IgA nephritis on biopsy and one (2%) had a gastrointestinal bleed. The mean length of hospital stay was 1.6 (SD 2) days. At one year of follow-up, two (4%) children had persistent proteinuria and only one patient (2%) still had haematuria.

Conclusion: The clinical course of IgA vasculitis in this cohort of South African children was mostly self-limiting, consistent with international literature. However, patients with persistent haematuria or proteinuria require longer-term follow-up. Collaborative studies within South Africa and sub-Saharan Africa may provide a more accurate picture of the epidemiology of childhood HSP and its complication rates.

Word count: 289

Keywords

IgA Vasculitis, Henoch Schönlein purpura, HSP, children, proteinuria, Africa

Introduction

Since its initial description in the early 1800s, immunoglobulin-A (IgA) vasculitis has rapidly become recognised as the most prevalent vasculitis of childhood, currently having a steady annual incidence rate of 3–27 cases per 100.000 [1]. The classification of IgA vasculitis has undergone multiple revisions since the 1990 version set by the American College of Rheumatology. The most recent classification, referred to as the EULAR/PRINTO/PRES 2010 classification [2], has been reinforced by a 2019 update from the European single hub and access point for paediatric Rheumatology in Europe (SHARE)[3].

IgA vasculitis is a systemic small vessel vasculitis of unknown aetiology, that classically presents as a triad of palpable purpura, arthralgia, abdominal pain and sometimes haematuria and may be present in children. Atypical presentations are rare, and often reflect a complication of the disease course [4]. The hallmark of IgA vasculitis is the deposition of IgA1-predominant immune deposits within affected vessel walls in the skin, gastrointestinal mucosa, joints, and glomeruli of the kidneys. Other areas of the body may also rarely be affected. To date, no genetic mutations have shown to be causative of IgA vasculitis, however genetic mapping of patients suggest strong involvement of the HLA-DQA1/DQB1 region [5]. Age less than 10 years and a preceding upper respiratory tract infection are consistent risk factors for IgA vasculitis even though the mechanism of contribution to pathogenesis has yet to be comprehensively defined[6]. IgA vasculitis predominantly follows a self-remitting course, typically occurring between the ages of two and ten years, long term complications are rare and almost exclusively due to kidney involvement [7]. The degree of kidney involvement with proteinuria and/or haematuria differs between cohorts, often ranging from 30 to 50%. However there is a less than 1% progression to permanent kidney involvement but this has prognostic importance [8].

There does not appear to be a great variation in the clinical course of IgA vasculitis between high- and low-middle-income countries, limited literature suggests IgA vasculitis may present with more severe symptoms in low- to middle-income countries (LMICs) and be more common in European and Asian populations. Owing to the scarcity of data in the LMICs, especially in South Africa, it is difficult to demonstrate this prevalence [9] . In South Africa, most epidemiological data of IgA vasculitis and associated complications, have been somewhat inferred from studies looking at the prevalence of kidney failure or kidney biopsy reviews [10, 11]. A recent publication by Scott and colleagues highlighting the lack of data on paediatric rheumatological conditions in LMICs; also reported that among childhood vasculitis, IgA vasculitis remains the most common. LMIC settings have resource

constraints and socioeconomic challenges which differ from those in HIC settings, this may be of importance if disease complications may extend into chronicity and further strain health resources. The aim of the study was to address a knowledge gap by describing the epidemiology and short-term outcomes of children with IgA vasculitis at a large public quaternary children's hospital.

Methods

Study design

The study was a retrospective observational study with case folder review at Red Cross War Memorial Children's Hospital (RCWMCH).

The study population

RCWMCH is a quaternary hospital that provides dedicated child and adolescent health care to a wide population of children in the Western Cape province of South Africa, most of the children accessing or referred for care at the study site come from low socioeconomic urban and peri-urban communities. However, patients may also come more widely from all nine provinces in South Africa and neighbouring countries, providing comprehensive dedicated paediatric services with a focus on sub-specialities. Most children in the study were managed through the general paediatric service component at RCWMCH.

Inclusion criteria

The hospital information system database known as Clinicom® was used to identify eligible patients by their discharge international coding diagnosis-10 (ICD-10) coding for IgA vasculitis between 1 January 2015 and 31 December 2019 for all new patients seen (inpatients and outpatients) at RCWMCH during that period. Children were included if they met the EULAR/PRINTO/PRES 2010 classification for IgA vasculitis on a folder review.

Exclusion criteria

Children were excluded if records were unavailable for review or vasculitis was not due to HSP upon folder review.

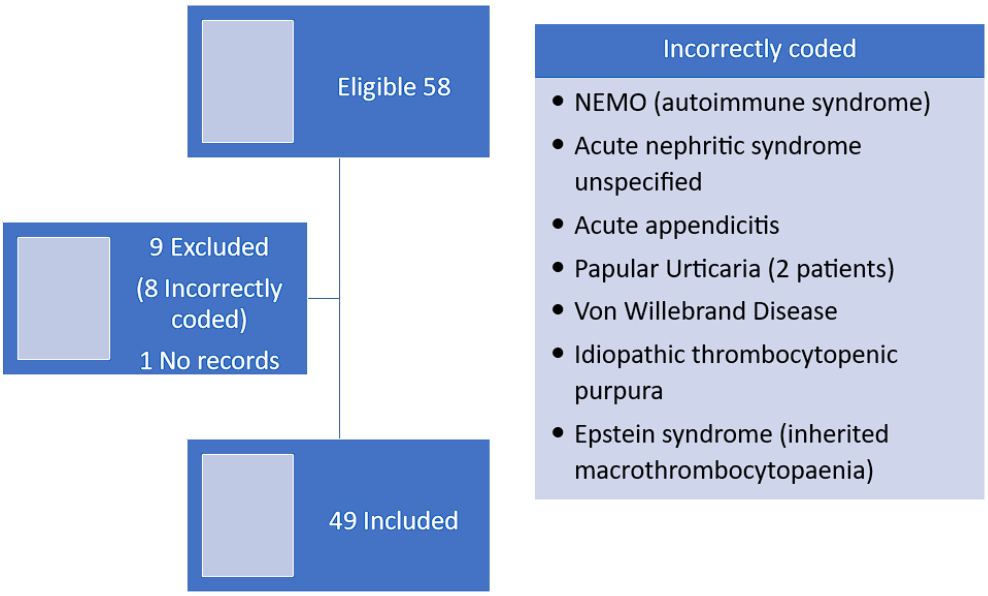

Figure 1: Flow diagram of study participant recruitment

Definitions

For the purposes of this study kidney involvement included those with:

- haematuria was defined as a bedside urinary dipstick test revealing anything from a minimum of 1+ (corresponds to 30mg/dL) upwards to 3+ haematuria; and
- proteinuria from a minimum of 1+ (corresponds to 30mg/dL) upwards to 3+ proteinuria on bedside dipstick urinalysis.
- Acute kidney injury is defined according to the kidney disease: Improving Global Outcomes (KDIGO) 2021 guidelines for IgA nephropathy (IgAN) in children [12]. In these guidelines, Stage 1 is described as a serum creatinine increase of ≥0.3 mg/dL (26.5 µmol/L) or an increase of ≥1.5 to 1.9 times the baseline level. Stage 2 is defined as an increase in serum creatinine to 2.0 to 2.9 times the baseline level.

Kidney biopsy result grading utilised the International Study of Kidney Disease in Children (ISKDC) grading classification [8]:

Grade I: Minimal mesangial proliferation without crescents or necrosis

Grade II: Mesangial proliferation with focal crescents and/or necrosis involving <50% of glomeruli

Grade III: Mesangial proliferation with diffuse crescents and/or necrosis involving >50% of glomeruli

Grade IV: Global sclerosis involving >50% of glomeruli.

Data collection

The hospital information system database known as Clinicom® was used to identify eligible patients by their discharge international coding diagnosis-10 (ICD-10) coding for IgA vasculitis between 1 January 2015 and 31 December 2019 for all new patients seen (inpatients and outpatients) at RCWMCH during the study period. The search was broadened to look for the diagnosis under its alternative name, Henoch Schönlein purpura. All identified files were then retrieved from the hospital's medical records department and hand-written clinical notes assessed for the 2010 EULAR criteria. Files that met the 2010 EULAR Criteria for IGA vasculitis were then included in the analysis. A data capture sheet with patient demographics (including sex, age, and nutritional status), clinical features at presentation, dates of admission and discharge for length of hospital stay, investigations performed, treatment given, complications and follow-up outcomes were used to capture data on each study patient.

Statistical analysis

The collected data were then entered into an excel spreadsheet and then imported into and analysed using STATA Statistical software, release 16, (College Station, Texas, USA).
Patient demographics, clinical characteristics, laboratory findings, management and short-term outcomes were summarised and presented in tables. Conventional descriptive and inferential statistical methods were used to analyse the dataset. Normality was evaluated using the Shapiro-Wilks method for continuous variables. Continuous variables were expressed as means or medians with standard deviations (SD) and interquartile ranges (IQR) as appropriate. Categorical variables were expressed as proportions and percentages and associations between categorical variables were explored using the Chi square and Fisher's Exact testing as appropriate. For the purposes of this study, significance was set at a p-value of <0.05.

Ethical considerations

Given the inherent challenge of obtaining individual consent retrospectively, an institutional waiver was sought and granted from the hospital research committee. Nevertheless, stringent measures were implemented to anonymize patient data and ensure confidentiality. The collected data was recorded in a Microsoft Excel spreadsheet and securely stored on encrypted university OneDrive storage, accessible only to the researchers. There was no harm to

The study was approved by the Health Sciences Faculty Human Research Ethics Committee of the University of Cape Town (HREC REF: 652/2021) and the Research Committee of RCWMCH and the Department of Health, South Africa (RXH-RCC 312 WC_202111_015).

Results

Demographic data

A summary of the study children's demography is depicted in **Table 1**. The most common age category was the 5 to 10-year-old age group. Forty-one (84%) study participants with weight documentation had a normal weight-for-age classification, no participants were undernourished. The 49 children included in the study had a similar male-to-female distribution.

Table 1: Demographic data of the study children with IgA vasculitis (N=49)

VARIABLE	n (%)
Sex	
Male	24 (48%)
Female	25 (52%)
Age categories	
1-5 years	15 (30%)
5-10 years	28 (57%)
>10 years	6 (13%)
Mean age in months (SD, range)	77 months (31, 30 to 155*)
Nutritional status by WHO WFA z-scores	(n=44)
Mean WAZ (SD, range)	- 0.13 (1.32, -3 to 2.9)
Mean hospital LOS in days (SD, range)	1.6 (SD 2)

IgA- immunoglobulin A; WHO- World Health Organization; WFA: weight-for-age; LOS- length of stay; WAZ: weight-for-age z-score; SD-standard deviation

* Hospital admission policy at time of study, only new patients less than 13 years of age were seen at the study site.

Clinical features at presentation

The main clinical features are represented in **Table 2**. Almost all patients had palpable purpura, (n=48, 97%) at presentation, 41 of the 49 (84%) patients had laboratory testing for thrombocytopenia. Joint involvement was the second most common manifestation in 41 (84%) patients at presentation followed by gastrointestinal complaints of abdominal pain and vomiting.

Fifteen (30%) children had the complete triad of purpura, abdominal pain, and arthritis at presentation. Oedema was an uncommon finding, one patient had scrotal oedema while three patients had associated angioedema of the forehead. Six (12%) children had isolated microscopic haematuria at presentation. A six-year-old child had gastrointestinal bleeding, he presented with a typical rash, abdominal pain, angioedema of the forehead, and passing scanty bloody mucoid stools. As his admission progressed, he also developed arthritis and haematuria. This patient had not received any nonsteroidal anti-inflammatory drugs.

Table 2: Clinical features of IgA vasculitis in the study children (N=49)

Clinical feature	n (%)
Preceding URTI	20 (41%)
Fever	6 (12%)
Skin manifestation	
Palpable purpuric rash	48 (97%)
Joint involvement	
Arthritis/Arthralgia	41 (84%)
Abdominal symptoms	
Abdominal pain	18 (37%)
Gastrointestinal bleed	1 (2%)
Nausea/vomiting	11 (23%)
Kidney involvement	
Haematuria (isolated)	6 (12%)
Proteinuria (isolated)	6 (12%)
Proteinuria and microscopic haematuria	6 (12%)
Localised oedema	4 (8%)
Angioedema	3 (6%)
Scrotal oedema	1 (2%)

IgA-immunoglobulin A; URTI- upper respiratory tract infection; AKI-acute kidney injury

Twenty-six (53%) patients had kidney involvement in the form of proteinuria and or haematuria on bedside dipstick urinalysis during the study period.

At initial presentation, 35 of the 49 (71%) patients required hospital admission, of whom 31 (88%) were treated in the paediatric short stay ward, two (6%) in the paediatric nephrology ward due to kidney involvement, and two (6%), one severe abdominal pain and one severe arthritis, in the

paediatric surgical ward. The study patients who were not admitted were managed in the paediatric medical outpatient's department.

Investigations performed

Six patients had abdominal ultrasound scans of whom two also had abdominal x-rays; all imaging findings were within normal limits. The investigations were ordered at the discretion of the attending physicians. **Table 3** summarises the laboratory findings in those patients where blood tests were done. Some children 12 (25%) had complement C3 and C4 levels done. White cell counts were not elevated, and thrombocytopenia was not seen- the mean platelet count was 428 in our cohort.

Table 3: Laboratory findings of the study children with IgA vasculitis (N=49)

Laboratory finding parameter	
Mean white blood cell count x 10^9 /L (n=41)	10.7 (SD 3.7)
Mean platelet count x 10^9/L (n=41)	428 (SD 99)
Mean urea in mmol/L (n=40)	3.9 (SD 1)
Mean creatinine in mmol/L (n=41)	32 (SD 7.5)
Mean serum complement C3 in mmol/L(n=12)	1.5 (SD 0.37)
Mean serum complement C4 in mmol/L (n=10)	0.28 (SD 0.11)
Acute Kidney Injury	
KDIGO* stage 1	2

Legend: IgA immunoglobulin A. SD- Standard deviation; * kidney disease: Improving Global Outcomes (KDIGO) Stage 1 serum creatinine increase of ≥0.3 mg/dL (26.5 µmol/L) or an increase of ≥1.5 to 1.9 times the baseline level.

Kidney involvement

Overall, during the study period 26 (53%) of children had evidence of kidney involvement in the form of haematuria and or proteinuria, all these children were also followed up. Two had transient acute kidney injury which resolved during admission, while one child progressed to chronic kidney disease currently with an estimated glomerular filtration rate (eGFR) of 50-60ml/min/1.73m^2 being followed up by the nephrology service. Fifteen children who were seen in the outpatient clinic for routine follow up, were referred to the paediatric nephrology service because of persistent haematuria and or proteinuria. Five children underwent kidney biopsies due to persistent proteinuria and haematuria. Additionally, two of these children also had hypertension. The timing of the kidney biopsies varied in the study period with the minimum time of four months and maximum of four

196 years. The results are outlined in Table 4 based on the International Study of Kidney Disease in
197 Children (ISKDC) grading classification.

198 ## Table 4: Kidney biopsy results in 5 of 49 study children with IgA vasculitis

Age (years)	sex	Diagnosis time	Biopsy date	Biopsy result*	Proteinuria/haematuria#	Complications	Status at last follow up
10	Male	August 2018	June 2020	Grade I	2/2	Hypertension	3+ proteinuria
7	Male	January 2018	April 2018	Grade IV	2/2	Hypertension	Recovered
6	Female	January 2019	May 2019	Grade I	2/3		Transferred to private facility
8	Male	June 2015	August 2018	Grade II	2/2		2+ proteinuria
5	Male	November 2016	November 2020	Grade III	3/3		Recovered

199 Legend: IgA immunoglobulin A.* International Study of Kidney Disease in Children (ISKDC) grading
200 classification [12]: Grade I: Minimal mesangial proliferation without crescents or necrosis Grade II:
201 Mesangial proliferation with focal crescents and/or necrosis involving <50% of glomeruli Grade III:
202 Mesangial proliferation with diffuse crescents and/or necrosis involving >50% of glomeruli Grade IV:
203 Global sclerosis involving >50% of glomeruli. # bedside urinary dipstick test 1+ (corresponds to
204 30mg/dL) for haematuria and 1+ (corresponds to 30mg/dL) for proteinuria

205 ## Treatment received by study children during the acute phase of admission in short
206 ## stay ward

207 **Analgesia**

208 Most patients received simple analgesia for joint and or abdominal pain; 36 patients (74%) received
209 paracetamol; 21(43%) patients received ibuprofen as add-on analgesia. There were three patients
210 (6%) who received a weak opioid with tilidine and one (2%) who received a stronger opioid with oral
211 morphine.

212 Immunosuppressants

Six patients managed by the paediatric nephrology service received some form of immunosuppression other than steroids during their clinical course, the indication for all patients was for IgA nephritis or persistent haematuria. The most common immunosuppressant used was mycophenolate mofetil which was administered to five patients, tacrolimus was used as a second agent in two cases. **Table 5**

Table 5: Immunosuppressant therapy received by children with IgA vasculitis (N=49)

Immunosuppressant used	Number (%)	Dose/ formulation
Prednisone (oral)	16 (33%)	1- 2mg/kg
Betamethasone (topical)	1 (2%)	0.1%
Hydrocortisone (topical)	1 (2%)	1%
Topical fluocinolone (0.05%)	8 (16%)	0.05%
Mycophenolate mofetil (oral)	5	
Tacrolimus (oral)	2	

Legend: IgA immunoglobulin A

Follow up period

The mean length of hospital stay was 1.6 (±SD 2) days, however 10 (20%) patients required readmission, the mean time to readmission was 3.8 (SD 2.4) days. In most cases the reason for re-admission was moderate to severe abdominal pain and/or arthritis. There were no deaths among the study children died. At one-year follow-up after discharge, nine children were monitored: two had persistent proteinuria, one with persistent haematuria, and six had recovered fully. Among the five children diagnosed with IgA nephritis on kidney biopsy, two had persistent proteinuria, two had recovered and one had persistent haematuria.

Statistical analysis

Because kidney involvement is the most serious complication of IgA vasculitis, an analysis was performed to explore associations. The Chi-square test was applied to assess the significance of associations between categorical variables, such as rash, abdominal pain, arthritis, and kidney involvement. The results are summarized in the following table.

Table 6: Associations between clinical features and kidney involvement in children with IgA vasculitis (N=49)

Clinical features	No Kidney Involvement	Kidney Involvement	p-value
Rash	23	25	1.000
Abdominal Pain	5	13	0.041
Arthritis	23	26	1.000
All Three clinical features	34	15	0.205

Legend: IgA immunoglobulin A

Analysis revealed a statistically significant association between abdominal pain and kidney involvement (p = 0.041); however, no significant associations were found between the presence of a rash (p = 1.000), arthritis (p = 1.000), or the combination of rash, abdominal pain, and arthritis (p = 0.205) with kidney involvement.

Discussion

Our study from a large LMIC public quaternary children's centre show that IgA vasculitis is a relatively common paediatric condition, the annual incidence of cases varied between 0.4/100 000 and 3.6/100 000 new patient visits over the course of the study period at our institution. We believe that this is one of the few epidemiological reports on IgA vasculitis in African children, it is an important condition due to the uncommon complication of long-term kidney disease that may require additional resource allocation. There are no comparable data on annual incidence in LMIC, however data from HICs show annual population incidence rates of 3.5 in Japan and 26.7 in Scotland per 100 000 with the highest rate reported between 4 and 6 years in the United Kingdom of 70.3 per 100 000 [13]. In contrast to most studies that showed a male predominance, our study of 49 children with IgA vasculitis showed an even male-to-female ratio[14]. The mean age of study participants was in keeping with high-income countries, with 87% of our study population being less than 10 years of age, no patient was below the age of two years in our study [9]. Data on IgA vasculitis in the African Continent are scarce [15], there is a need for epidemiological data on the prevalence of IgA vasculitis and associated risk factors for complications, as most data are inferred from studies looking at prevalence of kidney failure or kidney biopsy review (Mitchell, 2010; Sinclair, 2010). One study in a

university hospital in Tunisia by Naija et al. found 68 cases of IgA vasculitis over a 15-year period; they described IgA nephritis in 34 patients of whom 14 had biopsy confirmation [16].

Bacteria, viruses, and protozoa have all been implicated as triggers for IgA vasculitis especially Group A Streptococci and Parvovirus B [6] . Acute upper respiratory tract infection as a potential trigger for IgA vasculitis is suggested in our study with 41% of our study participants having had a documented history of preceding URTI in keeping with literature on IgA vasculitis; in a study of 219 Italian children by Coppo and colleagues, they found 41% of children to have had a preceding upper respiratory tract infection [17], data from the systematic review by Hetland et al., also concluded that upper respiratory tract infection precedes a majority of IgA vasculitis cases.[9].

Joint manifestation remained the second most common clinical feature of IgA vasculitis occurring in 41 (84%) of our patients. A recent publication by Breda et al., of 280 children in Italy over a 16-year period also demonstrated joint involvement as the second most common feature [1] which is also in keeping with American literature where a review by Reamy et al found that up to 75% of children develop arthritis [18]. The available literature reports that 5 – 25% of patients with IgA vasculitis may have joint manifestation preceding rash [14]. Interestingly in our cohort, one patient presented with joint involvement only, which contributed to diagnostic uncertainty until the development of the typical rash.

Gastrointestinal symptoms account for the third most common feature and along with joint pain have high acute morbidity; abdominal pain tends to be colicky in nature and may be associated with vomiting and can even mimic an acute abdomen in its severity [9, 18]. Intestinal complications such as gastrointestinal haemorrhage is rare but has been reported; intussusception can also occur with a mural haematoma serving as the lead point [9, 18]. In our study 18 (37%) patients had abdominal pain; there was one patient with gastrointestinal bleeding, thought to be superficial mucosal bleeding; no incidence of intussusception occurred. These children were more likely to receive steroid therapy. Literature recommendations for immunosuppressant with corticosteroids is based on a robust randomised controlled trial and is for the reduction of the intensity and duration of joint and abdominal pain and not recommended for the prevention of kidney disease [18]. In a meta-analysis by Han Chan et, al. including thirteen studies with 2398 children from Japan, Korea, Spain, Brazil, Finland, Iran, and Thailand found a significant association with abdominal pain and kidney involvement (defined as presence of proteinuria, haematuria and or blood cell casts) [19]. Our study from Sub-Saharan Africa also found a significant association between abdominal pain and kidney involvement.

There are no specific biomarkers for the diagnosis of IgA vasculitis, however efforts have been made to identify a biomarker that can stratify patients at risk for kidney complications [20]. The degree of kidney involvement that has been reported varies between 20% and 80% in the literature [9], increasing the need to identify suitable biomarkers for risk stratification. Pillebout et al., looked at multiple markers such as immunoglobulins, hypogalactosylation in IgA1, IgA receptors, pro-inflammatory cytokines and neutrophil gelatinase-associated lipocalin (NGAL) to identify biomarkers that can predict kidney involvement at diagnosis; however, these markers are laborious to measure and with varying levels of kidney involvement among cohorts, may be impractical. However future studies are needed to determine clinical utility [20]. Our study was unable to address this due to these tests not being routinely available in our centre.

Regarding complications, kidney impairment which can lead to kidney failure remains a key prognostic indicator for morbidity in IgA vasculitis, Narchi et al., estimated that the presence of both proteinuria and haematuria may indicate a 15% risk, whereas the combination of nephritic-nephrotic syndrome carries a higher risk of 50% for progressing to kidney failure [21] . Emphasis is thus placed on closely monitoring patients with IgA vasculitis to identify those with kidney involvement who may require referral to the paediatric nephrology service. The Single Hub and Access point for Paediatric Rheumatology in Europe (SHARE) recommends monitoring children through blood pressure measurements, early morning urinalysis, and assessment of renal function via estimated glomerular filtration rate [3].

In 2019, SHARE issued consensus recommendations regarding the criteria for undergoing a kidney biopsy in cases of IgA Vasculitis with kidney involvement. A kidney biopsy is advised if a patient has severe proteinuria (exceeding 250 mg/mmol) for a minimum of four weeks. However, even a shorter duration of severe proteinuria is considered a relative indication for biopsy. Additionally, a biopsy is recommended for patients with sustained moderate proteinuria (ranging from 100 to 250 mg/mmol) or impaired eGFR less than 80 ml/min/1.73 m2[3].

Overall, in our cohort there were twenty-five (51%) children who had kidney involvement as defined by the presence of microscopic haematuria at presentation; similarly, Breda et al., reported thirty-seven (18%) children in a cohort of 208 Italian children with a mean age of 6.44 years to have kidney involvement. In contrast to both our study population and the cohort by Breda et al, Pillebout et al., reported thirty-three (66%) of a cohort of fifty children with IgA vasculitis were found to have kidney involvement with similar criteria [20]. Sinclair conducted a review of seven kidney biopsies of IgA nephritis at RCWMCH study site between 2005 to 2010, seven cases of IgA nephritis were found; six of the seven cases had a biopsy by 6 months, at that time, there was no standardised

immunosuppression regimen [10]. An extensive systemic review by Narchi which included twelve studies of 1133 children found that no long-term kidney impairment occurred in those with a normal urinalysis at six months, hence recommending that urinalysis testing needs to continue for six months in those that have a normal urinalysis at presentation [21]. The excellent prognosis in our cohort of children strongly recommend a follow up period not longer than 6 months in those patients with no kidney involvement.

Treatment regimens in IgA vasculitis has remained controversial, there are few randomised controlled trials, in the absence of complications or kidney involvement, treatment is for symptomatic relief of pain [9]. The is no consensus on treatment in IgA nephritis and thus is centre dependant, the decision for a kidney biopsy prior to treatment is on a case by case basis influenced by factors such of severity of IgAV nephritis, acute kidney injury, nephrotic syndrome and/or initial response to treatment[22]. In the case of IgA vasculitis-associated nephropathy, the drug of choice is difficult to determine due to a substantial proportion of children with a favourable prognosis and unpredictable response to immunosuppressive therapy in individual children [8]. Most literature on IgA vasculitis-associated nephropathy is limited to retrospective studies with a lack of meticulously designed randomised controlled trials. Treatment may be individualised according to severity of disease, presence of underlying medical conditions and the local availability of specific immunosuppressive therapeutic agents [8]. Table 6 depicts some of the immunosuppressive agents utilised in the study period.

The use of corticosteroids in the symptomatic relief of abdominal and joint pain has been extensively documented in the treatment of IgA vasculitis [23]. Frequent use of steroids was observed in our study with almost half (n=23, 47%) of patients having received oral prednisone at a dose of 1-2mg/kg. There is limited evidence on the utility of topical steroid in IgA vasculitis for pruritic rash or joint pain with a single published case report showing good outcomes in the case of presentation with haemorrhagic bullae [24]; we however observed significant use of topical steroids (n=10, 20% of patients). There was no recorded case of dapsone use in our study, an anti-inflammatory drug that has also been described in individual cases in literature for chronic skin lesions [25].

Adjuvant symptomatic relief of pain with simple analgesia was adequate for almost all patients with only one patient requiring a stronger opioid such as morphine for relief of pain.

The limitations of this descriptive retrospective study include the lack of comparison with other LMICs and the limited data on the annual incidence of IgA vasculitis in Africa. The small sample size

of 49 children from a single centre may not be representative of the larger population, and the study's findings may not be generalizable to other populations or settings. Furthermore, because IgA vasculitis is generally considered a benign condition, some children may have been either missed/gone undiagnosed if seen and discharged at primary care level, or even managed by district level paediatricians. The absence of a control group and the lack of randomization in the study design limit the ability to establish causality and make definitive conclusions about the risk factors for IgA vasculitis. Additionally, the reliance on medical records for data collection may have introduced potential bias or incomplete information. Study participants were recruited by ICD 10 coding discharge data at RCWMCH, there may be cases of IgA vasculitis not accounted for in the study duration due to under reporting [26].

However, the strengths of this study were that it was conducted in a quaternary hospital with a comprehensive paediatric service, which provides a wide population of children and adolescents in the Western Cape province of South Africa; further, a standardized data capture sheet was used ensuring consistent and accurate data collection. The study had a lengthy follow-up duration of up to one year, which is longer than most IgA vasculitis studies, allowing for a more comprehensive analysis of outcomes. Our study adds to the limited literature on IgA vasculitis in low- and middle-income countries, specifically in South Africa, by describing the epidemiology and short-term outcomes of children with IgA vasculitis at a large quaternary African children's hospital, allowing comparisons with descriptions of IgA vasculitis from high-income and LMIC settings. We found that most patients presented with the classic triad of symptoms, and kidney involvement was common, but most cases were self-remitting without long-term complications. Our findings also concur with other studies which show that kidney involvement is the most serious long-term outcome and reinforces the practice of prioritising children with kidney involvement for longer term follow up.

Conclusions

Our findings suggest that the clinical course of IgA vasculitis in South Africa is similar to that reported in other countries. However, further research is needed to fully understand the disease's pathogenesis and risk factors for kidney involvement in this population. Our study also highlights the importance of continued research and surveillance of IgA vasculitis in low- and middle-income countries to improve diagnosis, management, and outcomes for affected children.

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The authors are grateful to the Information Management Unit and Hospital Medical Records Department, the doctors and nurses who care for the children at Red Cross Children's Hospital, and most importantly to our pediatric patients from whom we learn so much.

Declarations

Ethical approval and consent to participate.

The study was approved by the Health Sciences Faculty Human Research Ethics Committee of the University of Cape Town (HREC REF: 652/2021) and the Research Committee of RCWMCH and the Department of Health, South Africa (RXH-RCC 312 WC_202111_015). Due to the retrospective nature of the study a waiver for individual consent for files to be analysed was granted by the Health Sciences Faculty Human Research Ethics Committee of the University of Cape Town.

Availability of data and materials

All the datasets used and/or analysed during the current study are available within the manuscript.

Competing interests

The authors declare that they have no competing interests.

Financial disclosure statement

The author(s) received no specific funding for this work

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Chapter two: Appendices

Appendix A: Study Protocol

Research Study

Single center experience of children with Henoch Schönlein purpura

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Table of Contents

Research Title

Single center experience of children with Henoch Schoenlein purpura in South Africa.

A retrospective descriptive review of all children diagnosed with HSP at Red Cross War Memorial children's hospital over a 5-year period.

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Background

Worldwide Henoch Schönlein Purpura (HSP) is one of the most common primary vasculitis of childhood however the clinical course in low and middle income countries such as South Africa are poorly characterized [9]. It is uncertain if there is a significant difference in prevalence or ethnic distribution of HSP in our local setting.

HSP classically presents as palpable purpura, arthralgia, abdominal pain and often hematuria in children. Atypical presentation is rarely seen in children but include frank hematuria, altered mental status or seizures.

Potential differential diagnoses in an acute rash such as that of HSP include life threatening meningococcemia and other connective tissue diseases, progression of HSP can also rarely lead to chronic renal disease warranting renal transplant. When these are coupled together especially in the hands of inexperienced staff, there is potential for a multitude of unwarranted investigations, treatment arrays and extended hospital stay. Diagnostic confusion also occurs when the presentation is atypical particularly if the rash is absent at disease onset [4]. Although short & long-term outcomes are excellent there may be considerable morbidity. Morbidity in the short term is associated with pain most commonly secondary to gastrointestinal manifestations such as bleeding, intussusception or rarely bowel wall ischemia. Long term morbidity is almost always due to renal disease with the degree of subsequent renal impairment correlating with the extent of renal involvement at presentation. Mortality is rare in children with IgA vasculitis and is usually associated with complications such as pulmonary hemorrhage, Intestinal perforation, and end stage renal disease of IgA nephritis*. Adult-onset IgA vasculitis has an increased risk of complications and mortality when compared to childhood onset.

Red Cross Children's Hospital (RCCH) is a quaternary hospital that provides a dedicated child and adolescent health service for a wide population in the Western Cape but also receives referrals from all nine provinces in South Africa and Sub-Saharan Africa.

Due to limited publications on HSP in children in a setting such as that of South Africa it is important to understand the clinical course of this disease in this population to develop optimal management protocols and identify areas of research interest for preventative or definitive treatment.

Literature review

A systemic search of the Medline/PubMed, Web of Science and Scopus databases was performed on articles up to 28/05/2020.

With a filter of publication year 2010 until 2020 and the MeSH term Henoch Schoenlein purpura 5359 articles were retrieved; this was reduced 10 hits when "South Africa" was added. A search from Web of Science revealed 4292 results and reduced to 75 articles with South Africa and a similar 2010 to 2020 filter applied. The Scopus database yielded the maximum number 18 878 results using variations of keywords: "Henoch", "Henoch Schoenlein purpura". "Schoenlein purpura" & "IgA

Vasculitis" with only 394 results obtained with "IgA vasculitis South Africa" & "Henoch Schoenlein purpura South Africa".

Of note this review included two systemic reviews, a systemic literature review of HSP by Hetland et al performed in 2017 that reviewed literature published 2011 to 2016 and that of Narchi et al published in 2005 that looked at the risk of long-term renal impairment along with the recommended follow up period in HSP.

Epidemiology of HSP

IgA Vasculitis (IgAv) or as more widely known; Henoch Schoenlein Purpura (HSP) remains the most common vasculitis of childhood outside of China and some parts of Asia where Kawasaki Disease is more prevalent [9, 27]. Much progress in the pathology and treatment of HSP has been made since it's recognition in the early 1800's; however, the diagnostic criteria remain largely clinical and unchanged [28].

It is estimated that HSP affects 10-20 children per 100 000 per year, of which over 90% are less than 10 years [9].

In South Africa there is a need for epidemiological data on prevalence of HSP and associated risk factors for complications as most data is somewhat inferred from studies looking at prevalence of end stage renal disease or renal biopsy review[10, 11].

Diagnosis

The diagnosis is mainly on clinical criteria, the revised EULAR guidelines published in 2010 have excellent sensitivity and good specificity, one study found it to be 100% and 87% respectively [9].

Table I. Diagnostic criteria for Henoch-Schönlein purpura (HSP), as developed by EULAR/PRINTO/PRES

Criterion	Description
Mandatory criterion	Purpura or petechiae with lower limb predominance
Minimum 1 out of 4 criteria	1. Diffuse abdominal pain with acute onset 2. Histopathology showing leukocytoclastic vasculitis or proliferative glomerulonephritis, with predominant immunoglobulin A (IgA) deposits 3. Arthritis or arthralgia of acute onset 4. Renal involvement in the form of proteinuria or haematuria

Table 6 EULAR/PRINTO/PRES: the European League Against Rheumatism, the Paediatric Rheumatology International Trials Organization, and the Paediatric Rheumatology European Society

Pathogenesis of HSP

The current body of evidence in HSP research have yet to establish a direct casual pathogenic mechanism in HSP, however Heineke & Ballering propose an elaborate multi-hit model to explain the systemic features arising from IGA vasculitis.

IgA immune complex deposition in the vasculature accompanied by complement factors and large neutrophil infiltrates are the hallmark feature of IgA vasculitis [6].

The multi-hit hypothesis proposes that IgA vasculitis stems from the interaction between IgA and cell surface antigens that result in the formation of auto-antibodies likely under the influence of certain factors such as infections, genetics and complement proteins [6].

Immunoglobulin A

Immunoglobulin A provides immune modulation binding to pathogens in a manner that it is repelled by mucosal surfaces, activates complement and neutralizes bacterial products. IgA can activate multiple receptors to achieve these functions for instance binding of IGA with CD71 a universally expressed transmembrane glycoprotein can potentiate IgA deposition in IgA nephritis. IgA exists in the circulation as one of two subtypes the abundant IgA1 or IgA2, evidence suggests that the IgA1 subtype is most involved in the immune interactions in IgAv. The FcαRI receptor has been proposed as the archetypal receptor for IgA as the pro-inflammatory immune effects in IgAv result from the interactions of IgA immune complexes with the FcαRI receptor. The FcαRI receptor can be found as a transmembrane receptor on myeloid cells and as a soluble form (sCD89).

Henieke & Ballering (2017: 1246–1253) on IgA and FcαRI interactions

“Binding of IgA immune complexes to FcαRI on neutrophils induces activating Immunoreceptor Tyrosine-based Activation Motif signaling (ITAMs). Cross-linking of FcαRI results in multiple pro-inflammatory functions, such as phagocytosis, production of reactive oxygen species (ROS), release of granules containing toxic molecules such as lactoferrin, cytokine and chemokine secretion, antibody-dependent cellular cytotoxicity (ADCC) and the release of neutrophil extracellular traps (NETs). Furthermore, FcαRI triggering induces the release of chemoattractant LTB4, resulting in neutrophil migration.”

Anti-endothelial cell antibodies (AECA)

These are a heterogeneous group of antibodies against poorly characterized antigens of human tissue, IgA from patients with IgA vasculitis can bind human endothelial cells. There is often a history of a recent respiratory illness preceding HSP, it is thought that some microorganisms have similar antigenic structures as the vessel wall. This can lead to the production of cross reactive AECA, commonly associated pathogens include Streptococcus, Influenza, and Parvo B virus although no single pathogen has been inextricably linked to HSP. AECA promote vascular damage via a cytokine and a complement dependent cytotoxicity pathway. IgA AECA can induce endothelial cells to produce cytokines such as TNF-α (which has the effect of enhancing endothelial binding to ACEA) and IL-8. It has not been established how IgA ACEA activate complement but it has been shown in vitro. This inflammatory process is then greatly aided by neutrophil activation by IgA through the FcαRI receptor which will lead to further neutrophil infiltration and subsequent tissue damage.

Genetics

No mutations have been directly shown to cause HSP however multiple genes have been implicated For instance, a genome wide association study conducted by Raquel López-Mejías et al in a European and Spanish cohort strongly suggests that HSP is an archetypal HLA Class II mediated immune mediated condition, genetic mapping of 285 HSP patients matched to 1006 healthy controls demonstrated a strongly significant involvement of . It is therefore suggested that HSP may share a pathophysiological origin with other vasculitides such as Giant cell arteritis [5]. Genome wide sequencing have also yielded positive results in the increasingly recognized field of epigenetics, Luo et al found a significant increase in H3 acetylation and H3K4 methylation in Peripheral Blood Mononuclear Cells (PBMNCs) of patients with IgAv in contrast with healthy controls and also showed

that this increase correlated positively with disease activity in the IgAv patients with renal involvement[29].

Clinical Manifestations of HSP

The classic tetrad of HSP is purpura, arthralgia, abdominal pain and hematuria, symptoms can occur simultaneously or in any sequence [4, 9].

Rash

Rash is the most common manifestation; cutaneous lesions tend to be distributed in dependent area and/or overlying contact pressure points especially the lower extremities and buttocks. Lesions begin as maculopapular or urticarial eruptions in crops that rapidly progress to palpable purpura and/or petechiae [9, 30].

Abdominal pain

Abdominal pain ranges from mild colicky pain to an acute abdomen but usually resolves within a few days, other gastrointestinal manifestations include blood in stools, intussusception, and rarely intestinal perforation. Nausea and vomiting often accompanies abdominal pain [9].

Arthralgia & Arthritis

Joint involvement is typically symmetrical ankle and/or knee involvement, sometimes hip joints may be involved. Manifestation may be both joint pain and swelling that can limit mobility but typically nondestructive [14, 31].

Renal involvement

Renal involvement is predominantly limited to microscopic hematuria that follows the rash within 1 to 4 months, however there is a spectrum of presentation from microscopic hematuria and mild proteinuria, nephrotic syndrome, acute nephritic syndrome, hypertension and or renal failure [9].

In one of the most extensive reviews Narchi et al reviewed twelve studies involving 1133 children with HSP that had a wide follow up range depending on the study. It found that about 34% of children had proteinuria and/or hematuria of which only about one fifth were associated with nephritic or nephrotic syndrome, permanent renal impairment only occurred in 1.6% of those with isolated urinary abnormalities but up to 19.5% of those with nephritic or nephrotic syndrome [21]. Interestingly about 85% of children who developed nephritic or nephrotic syndrome were diagnosed within four weeks of initial HSP diagnosis[21]. No long term renal complications occurred in those patients with a normal urinalysis [21].

Other presentations though less common

Angioedema can present in the scrotum, eyelids, forehead, sacrum, hands and/or feet, it is more common in young children and toddlers [9, 30].

Low grade fever is occasionally reported[9].

Focal seizures, altered mental state are some unusual nervous system manifestations due to vasculitis [14, 30].

Laboratory makers for HSP

No diagnostic serum markers although serum IgA levels are typically elevated. Antistreptolysin O can be elevated (suggesting a preceding streptococcal infection) [9].

By diagnostic criteria of HSP, thrombocytopenia excludes HSP however thrombocytosis may be seen [9, 30].

Histologic evidence of predominant IgA deposition in cutaneous lesions or on renal biopsy with proliferative glomerulonephritis are part of diagnostic criteria [28].

Radiographic studies

No routine imaging is necessary, ultrasound or abdominal CT are sometimes performed for evaluation of abdominal compilations. There are no pathognomonic features of HSP [9].

Treatment

Since no treatment modality has yet been shown to prevent renal complications current therapy depends on whether there is renal involvement at presentation [9, 21]. In the absence of renal involvement treatment is symptomatic for example, adequate pain medication and rehydration as needed.

Corticosteroids have been shown to ameliorate abdominal pain (when used without renal involvement) in HSP but did not have benefit in reducing relapse or progression to renal involvement [9].

Protocols for treatment of patients with renal complications remain institutionally based as there is still lack of consensus on exact immunosuppressive and immunomodulatory treatment. Various agents such as Cyclosporine A, Dapsone, Mycophenolate mofetil, Rituximab have reported efficacy in small RCT and case series [9]. In a Cochrane review of two studies of cyclophosphamide therapy in HSP associated kidney disease it was found to have no significant difference in the risk of persistent kidney disease at follow up when compared to supportive therapy in one and no benefit to cyclophosphamide plus corticosteroids when compared to corticosteroid monotherapy [32].

Prognosis

In general prognosis for HSP is excellent in childhood with the rate of complications significantly increasing with age at diagnosis. Most children show resolution within 2 weeks, few develop isolated hematuria or mild proteinuria that resolves and rarely have complications [14, 21, 30].

A meta-analysis involving 2398 children found, male gender, age over 10 years at presentation, severe gastrointestinal symptoms, arthralgia, persistent purpura or relapse, complete blood count (CBC) greater than $10x10^9$/l, platelets > $500x10^9$/l and low C3 to be all associated with chronic kidney disease [33]. It's unclear the extent each of these contributed to risk of chronic kidney disease due to limitations of the studies reviewed [33].

Morbidity can result from relapse or complications of disease. Relapse is often milder and of shorter duration however some children have more than 1 relapse episode [14, 33]. Complications are mostly related to renal disease, however some children present with atypical course of the disease with CNS involvement such as focal neurological deficits cause morbidity [34]. Typically there is a less than 1% risk of progression to end stage renal disease [35].

Mortality may result from gastrointestinal complications (e.g. intestinal perforation), end stage renal disease, rarely pulmonary hemorrhage or intracranial bleeding [7, 35].

Research question

What are the clinical presentation, characteristics, and short-term outcomes of children with Henoch Schönlein Purpura at Red Cross Children's Hospital.

Aims

To describe epidemiology and short-term outcomes of children with HSP at RCCH over a 5-year period.

Objectives

To document the number of all children with Henoch Schoenlein purpura at RCCH over a 5-year period

To determine the presenting features of HSP at RCCH

To describe the demographics of the Children with HSP at RCCH during the study period

To document and describe the special investigations performed

Study Methods

Study settings

Red Cross Children's Hospital is the largest children's hospital in Sub-Saharan Africa and provides all levels of multidisciplinary care along with several paediatric specialist services. It is a tertiary hospital that is affiliated to the University of Cape Town caring for children primarily up to the age of 13 years. Found in Rondebosch Cape town, it has a diverse local catchment area excluding direct referrals from other parts of South Africa from all 9 provinces or neighbouring regions in Sub-Saharan Africa as of 2015/2016 there were about 260000 patient visits each year.

Study design

Retrospective descriptive observational study

Recruitment and enrolment

Inclusion Criteria

All patients that had a discharge diagnosis of HSP on the hospital information system database (Clinicom®)) from 01/01/2015 until 31/12/2019 will be reviewed and those that meet the 2010 European League against Rheumatism (EULAR) classification for HSP will be included.

Children identified from the renal biopsy registrar with IgA nephropathy and skin biopsy result with IgA whose folder review meet the EULAR diagnostic criteria for HSP will also be included.

Exclusion Criteria

Records unavailable for review

Vasculitis not due to HSP

Sampling

All patient folders that meet EULAR criteria for HSP recruitment criteria for the specified period will be included in the review.

Data collection methods

Each file identified by the hospital information system database- Clinicom by discharge ICD-10 coding and/or the hospital Renal biopsy register for the specified year will be obtained from the medical records department and analysed.

A data collection sheet will be created to capture the following

Age

Sex

Self-reported race/ethnicity

Nutrition status- weight-for-age z-score; height-for-age and weight-for-height will be desirable and captured where the data are available

Any preceding illness e.g. upper respiratory tract infection

Duration of symptoms prior to presentation

Specific presenting symptoms and signs

Temperature on presentation

Presence of atypical features/ systems complications

Haematuria detected during presentation or follow-up

Proteinuria detected during presentation or follow-up

Hypertension as a complication

Number intussusception on ultrasound

Number had renal or skin biopsy

Other

Laboratory results where available including:

White cell count, haemoglobin & platelet count on admission

Urea & Creatine range on admission

Urine microscopy

IgA levels

Serum complement levels

HIV status

Biopsy results

Treatments given

Length of hospital stay

Document follow up arrangements where known (short-term outcomes)

Long-term outcomes where available from the hospital records

Data safety and monitoring

Data will be stored on university cloud accessed Microsoft OneDrive that is encrypted with a strong password that only the researcher is aware of.

Data analysis

Patient demographics, clinical characteristics, laboratory findings, management and short-term outcomes will be summarised and presented in tables and graphs with categorical variables expressed as proportions and percentages and continuous variables expressed as means or medians with standard deviations and interquartile ranges as appropriate. Associations between categorical variables will be explored using chi-squared or Fisher's Exact testing as appropriate. There may be need for further testing for strength of associations if any factor associations have p values <0.1 e.g. parametric testing (T-test) for normally distributed continuous data and rank-sum testing for skewed.

Ethical considerations

This research will be guided by the principles of the Declaration of Helsinki in 2013.

Description of risks and benefits

There will be no direct interaction with patients only the records, potential harm if a patient's folder is currently being analyzed for research purposes and patient presents to the hospital seeking health care, possible delay in treating clinician receiving full patient history.

This potential harm will be minimized by ensuring that folders are always analyzed within reach of the hospital record keeping system (i.e. not to leave the hospital) the researcher to within reach when analyzing patient files.

Informed consent process

Approval to wave individual informed consent will be sought from the Human Ethics Research Committee of the University of Cape Town

Permission will be sought from Red Cross Children's hospital to access clinical folders

Privacy and confidentiality

No patient identifiable data such as name and folder numbers will be published

Reimbursement for participation

Not Applicable

Emergency care and insurance for research-related injuries

No injuries are anticipated as research will be limited to a folder record review

Strengths and Limitations

Strengths

Potential to provide new insights in disease presentation in this specific population

Estimated low cost audit of a common South African paediatric problem

Limitation

Availability of folder records

Patients not appropriately coded on ICD coding may lead to not identifying cases

Lack of follow up may impair ability to assess short to intermediate outcomes.

Communication and Dissemination

The study results will be presented to the Department of Paediatrics at one of the Annual Research Day events and will likely be submitted for publication in an open access, peer-reviewed scientific journal for dissemination.

Study Timelines

Research Item	Deadline
Research proposal	31 May 2020
Departmental Research committee review (Approval from Department of Child and Adolescent Health)	August-September 2020
Department of Human Research Ethics of UCT approval	August-september 2020
Approval from the RXH Research Committee	August-september 2020
Data collection	Oct - December 2020
Data analysis	31 January 2021
Dissertation write up	31 March 2021
Dissemination	30 April 2021

Budget

The study will be self-funded, anticipated costs include the following:

	Item description	Cost
	Stationery	R350
	Statistician	University allocated session =0
	Editor	University writing centre = 0

Total Project Cost		R350

What happens at the end of a study?

Knowledge and insights gained from the study will be made freely available to all interested parties and presented at one of the departmental academic meetings and submitted to an open access peer-reviewed journal for publication.

An attempt will be made to produce a primary care guideline for management of HSP and provide a strict criterion for tertiary care referral.

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Appendix B: Data Capture sheet

Baseline Characteristics

Study No:		Folder no:		DOB (D/M/Y):		
DOA (D/M/Y)		DOD(D/M/Y)				
Actual weight:		Actual height:				
Sex	Female (0)		Male(1)			

Hiv Status	Exposed neg (0)	Unexpose neg (1)	Positive (2)	Exposed unknown status (3)	Unexposed unknown status (4)	Unknwon status (5)

Presenting Features

URTI in past 2 weeks	Yes (1)	No (0)
Rash	Yes (1)	No (0)
Arthralgia/Arthirits	Yes (1)	No (0)
Abdopain	Yes (1)	No (0)
Haematuria	Yes (1)	No (0)
Fever	Yes (1)	No (0)
Nausea/vomitting	Yes (1)	No (0)
Other (complication)		

Investigations

	Actual value			
WCC				
Plt				
Urea				
Creat				
C3				
C4				
Asot				
IGA				
INR				

Proteinuria	0(0)	1+(1)	2+(2)	3+(3)
Haematuria	0(0)	1+(1)	2+(2)	3+(3)

Imaging

Abdo xray	not perfomed (0)	Normal (1)	Bowel wall thickening (2)	Bowel obstruction (3)	Bowel perforation (4)			
Abdo uss	not perfomed (0)	Normal (1)	Echogenic kidneys (2)	Free peritoneal fluid (3)	Target, donut sign, intussuception(4)	Scrotal oedema (5)	Appendicitis (6)	Other diagnosis (6)
CT resu	not perfomed (0)	Normal (1)	Bowel wall thickening (2)	lymphadenopathy (3)	mesenteric edema (4)	vascular engorgement (5)	Intussusception (6)	Other diagnosis (7)

Biopsy Result

Renal Date:	not perfom (0)	Gr1 (1)	Gr2 (2)	Gr3 (3)	Gr4 (4)	Gr5 (5)	Gr6 (6)
Skin Date:	not perfomed (0)	LccVascul+ Fibrinoidnecros (1)	Lccvascu no fibrine (2)	Perivac, IgA depos (3)			

Treatment

Steroid	None(0)	Prednisone (1)	Betamethasone (2)	Methylprednisone (3)	Dexamethasone (4)	Hydrocortisone (5)	Top Fluocinolon 0.025% (6)	Top Clobestol Propion 0.05% (7)
Steroid dose	Not given (0)	0.5mg/kg (1)	1mg/kg (2)	2mg/kg (3)	3mg/kg (4)	4mg/kg (5)	5mg/kg or > (6)	Topical preparation (7)
Steroid start (D/M/Y)				Steroid stop (D/M/Y)				
Antibiotic	None (0)	Amoxil (1)	Co-Amoxicla (2)	Penicillin Vk (3)	Other (4)			
Antibiotic days								
Analgesia	None (0)	Paraceta (1)	Brufen(2)	Tilidine(3)	Morphin(4)	Other(5)		
Immunomodulation	None (0)	Cyclophosp (1)	Rituximab (2)	Mycophenmofet (3)	Tacroliumus (4)		Other (5)	
Immun Start (D/M/Y)				Immun Stop (D/M/Y)				

Complications

0 None	1 Glomerulonephritis	2Hemorrhagic cystitis	3 Nephrotic syndrome	4 Renal failure
5Ureteral obstruction	6Bowel infarction	7Bowel perforation	8Duodenal obstruction	9Gastrointestinal hemorrhage
10Intestinal stricture	11Intussusception	12Alveolar hemorrhage	13Interstitial infiltrate	14Pulmonary effusion

15Aphasia	16Ataxia	17Cerebral hemorrhage	18Chorea	19Cortical blindness
20Neuropathy	21 Paresis	22 Seizure	23Anterior uveitis	24Myocarditis
25 Myositis	26 Orchitis	27Scrotal edema	28Testicular torsion	29 Angioedema
30 Hypertension				

Follow UP

Date at last Follow up								
Status	0 No follow up	1Recovered & discharged	2Recovered & Scheduled for follow up	3Relapse	4Haematuria	5Proteinuria	6ESRD	7Down referred

Appendix C: UCT Health Sciences Human Research Ethics Committee approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

E-52 Room 45- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 October 2021

HREC REF: 652/2021

Dr H Buys
Division of Paediatrics & Child Health
Room 508, 5th Floor, ICH Building-Red Cross Hospital
Rondebosch
Email: heloise.buys@uct.ac.za
Student: MKHMPH020@myuct.ac.za

Dear Dr Buys

PROJECT TITLE: A RETROSPECTIVE DESCRIPTIVE REVIEW OF CHILDREN DIAGNOSED WITH HENOCH SCHÖNLEIN PURPURA AT RED CROSS WAR MEMORIAL CHILDRENS' HOSPITAL OVER A 5-YEAR PERIOD (2015-2019)-MMED CANDIDATE-DR MPHO MAKHWARENE

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020; 06 July 2020 & 01 July 2021.

Approval is granted for one year until the 30 October 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Mpho Makhwarene will also be involved in this study.

Please quote the HREC REF 652/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/5/2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	11/5/2023

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

HUMAN RESEARCH ETHICS COMMITTEE
10 MAY 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)			
HREC REF Number	652/2021	Current Ethics Approval was granted until	30-10-2022
Protocol title	A retrospective descriptive review of children diagnosed with Henoch Schönlein Purpura at Red Cross War Memorial children's hospital over a 5-year period (2015-2019)		
Principal Investigator	A/Prof Heloise Buys		
Department / Office Internal Mail Address	Paediatrics and Child Health		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☑	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	
Only current MMED project- final write up stage	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		49
Total number of records or specimens collected, reviewed or stored since last progress report		49
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☑ No

4. Signature

Signature of PI		Date	09/05/2023

UNIVERSITY OF C

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS011: Study deviation

HREC office use only (FWA00001637; IRB00001938)			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature/ Designee		Date	11/5/23

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

HUMAN RESEARCH ETHICS COMMITTEE
10 MAY 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	09/05/2023
HREC REF Number	652/2021
Project Title	A retrospective descriptive review of children diagnosed with Henoch Schönlein Purpura at Red Cross War Memorial children's hospital over a 5-year period 2015-2019)
Protocol number	
Principal Investigator	A/Prof Heloise buys
Department / Office Internal Mail Address	Paediatrics & Child Health

2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.
The study approval renewal was not completed timeously and the approval lapsed 30/10/2022- huge apologies- distracted by other events within the clinical department- exams and heavy clinical load in the EC. Will not happen again!

3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.
Nil required, other than to aid the MMED student to complete the write up and submit thesis for examination
3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.
Calendar reminders on iPhone

4. Principal Investigator's acknowledgement of responsibility

This signature indicates the PI has reviewed the deviation, taken appropriate follow-up action and implemented or plans to implement preventative steps where possible.			
Signature of PI		Date	09/05/2023

Appendix D: Table data used in manuscript

Table 1: Demographic data of the study children with IgA vasculitis (N=49)

VARIABLE	n (%)
Sex	
Male	24 (48%)
Female	25 (52%)
Age categories	
1-5 years	15 (30%)
5-10 years	28 (57%)
>10 years	6 (13%)
Mean age in months (SD, range)	77 months (31, 30 to 155*)
Nutritional status by WHO WFA z-scores	(n=44)
Mean WAZ (SD, range)	- 0.13 (1.32, -3 to 2.9)
Mean hospital LOS in days (SD, range)	1.6 (SD 2)

IgA- immunoglobulin A; WHO- World Health Organization; WFA: weight-for-age; LOS- length of stay; WAZ: weight-for-age z-score; SD-standard deviation

* Hospital admission policy at time of study, only new patients less than 13 years of age were seen at the study site.

Table 2: Clinical features of IgA vasculitis in the study children (N=49)

Clinical feature	n (%)
Preceding URTI	20 (41%)
Fever	6 (12%)
Skin manifestation	
Palpable purpuric rash	48 (97%)
Joint involvement	
Arthritis/Arthralgia	41 (84%)
Abdominal symptoms	
Abdominal pain	18 (37%)
Gastrointestinal bleed	1 (2%)
Nausea/vomiting	11 (23%)

Kidney involvement	
Haematuria (isolated)	6 (12%)
Proteinuria (isolated)	6 (12%)
Proteinuria and microscopic haematuria	6 (12%)
Localised oedema	4 (8%)
Angioedema	3 (6%)
Scrotal oedema	1 (2%)

IgA-immunoglobulin A; URTI- upper respiratory tract infection; AKI-acute kidney injury

not elevated, and thrombocytopenia was not seen- the mean platelet count was 428 in our cohort.

Table 3: Laboratory findings of the study children with IgA vasculitis (N=49)

Laboratory finding parameter	
Mean white blood cell count x 10^9 /L (n=41)	10.7 (SD 3.7)
Mean platelet count x 10^9/L (n=41)	428 (SD 99)
Mean urea in mmol/L (n=40)	3.9 (SD 1)
Mean creatinine in mmol/L (n=41)	32 (SD 7.5)
Mean serum complement C3 in mmol/L(n=12)	1.5 (SD 0.37)
Mean serum complement C4 in mmol/L (n=10)	0.28 (SD 0.11)
Acute Kidney Injury	
KDIGO* stage 1	2

Legend: IgA immunoglobulin A. SD- Standard deviation; * kidney disease: Improving Global Outcomes (KDIGO) Stage 1 serum creatinine increase of ≥0.3 mg/dL (26.5 µmol/L) or an increase of ≥1.5 to 1.9 times the baseline level.

Table4: Kidney biopsy results in 5 of 49 study children with IgA vasculitis

Kidney biopsy result grading (n=5) *	n
Grade I	2
Grade II	1
Grade III	1
Grade IV	1

Legend: IgA immunoglobulin A.* International Study of Kidney Disease in Children (ISKDC) grading classification [12]: Grade I: Minimal mesangial proliferation without crescents or necrosis Grade II: Mesangial proliferation with focal crescents and/or necrosis involving <50% of glomeruli Grade III:

Mesangial proliferation with diffuse crescents and/or necrosis involving >50% of glomeruli Grade IV: Global sclerosis involving >50% of glomeruli.

agent in two cases. **Table 5**

Table 5: Immunosuppressant therapy received by children with IgA vasculitis (N=49)

Immunosuppressant used	Number (%)	Dose/ formulation
Prednisone (oral)	16 (33%)	1- 2mg/kg
Betamethasone (topical)	1 (2%)	0.1%
Hydrocortisone (topical)	1 (2%)	1%
Topical fluocinolone (0.05%)	8 (16%)	0.05%
Mycophenolate mofetil (oral)	5	
Tacrolimus (oral)	2	

Legend: IgA immunoglobulin A

Table 6: Associations between clinical features and kidney involvement in children with IgA vasculitis (N=49)

Clinical features	**No Kidney Involvement**	**Kidney Involvement**	**p-value**
Rash	23	25	1.000
Abdominal Pain	5	13	0.041
Arthritis	23	26	1.000
All Three clinical features	34	15	0.205

Legend: IgA immunoglobulin A

Appendix E: Turnitin report

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Faculty of Health Sciences

FHS04 - Turnitin plagiarism declaration

Note: This form is completed by **masters' students** and their **supervisors. Masters' students must** submit th form with their dissertation for examination.

Section A: Student and thesis details	
Master's Candidate Full Name	Mpho Makhwarene
Student Number	MKHMPH020
Faculty	Health Sciences
Department	Paediatrics & Child Health
Supervisor/s	A/Prof Heloise Buys
Co-Supervisor	Prof Mignon McCulloch
Dissertation Title	A retrospective descriptive review of children diagnosed with Henoch Schönlein Purpura at Red Cross War Memorial Children's Hospital over a 5-year period (2015-2019)

Note: Please complete and sign the applicable declaration.

Section B: Declaration by student

I, Mpho Makhwarene (**Student's name**)

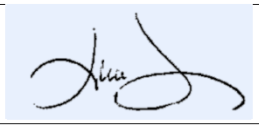
hereby declare that this dissertation has been submitted to the Turnitin module (or equivalent similarity and originality checking software). Plagiarism is to use another's work and pretend that it is one's own and I know that plagiarism is wrong. Please note that the report should be discussed with your supervisor. I confirm that I have discussed and resolved any concerns emanating from the Turnitin report with my supervisor.

Signed (signature image | text)			**Date**	08/06/23

Section C: Declaration by supervisor

I, A/Prof Heloise Buys (**Supervisor's name**)

hereby declare that this thesis/dissertation has been submitted to the Turnitin module (or equivalent similarity and originality checking software). Plagiarism is to use another's work and pretend that it is one's own. I confirm that I have discussed and resolved any concerns emanating from the Turnitin report with my student.

Signed (signature image | text)			Date	8/6/2023

Appendix F: PLosOne journal submission guidelines

Submission Guidelines

Related information for authors

PLOS Writing Center

Submission system

Journal scope and publication criteria

Getting started guide

Guidelines for revisions

Publication fees

APC Support

Style and Format

File format	Manuscript files can be in the following formats: DOC, DOCX, or RTF. Microsoft Word documents should not be locked or protected. LaTeX manuscripts must be submitted as PDFs. Read the LaTeX guidelines.
Length	Manuscripts can be any length. There are no restrictions on word count, number of figures, or amount of supporting information. We encourage you to present and discuss your findings concisely.
Font	Use a standard font size and any standard font, except for the font named "Symbol". To add symbols to the manuscript, use the Insert → Symbol function in your word processor or paste in the appropriate Unicode character.
Headings	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout and spacing	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page and line numbers	Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).
Footnotes	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.

Language	Manuscripts must be submitted in English. You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.
Reference style	PLOS uses "Vancouver" style, as outlined in the ICMJE sample references. See reference formatting examples and additional instructions below.
Nomenclature	Use correct and established nomenclature wherever possible.

Units of measurement	Use SI units. If you do not use these exclusively, provide the SI value in parentheses after each value. Read more about SI units.
Drugs	Provide the Recommended International Non-Proprietary Name (rINN).

Manuscript Organization

Manuscripts should be organized as follows. Instructions for each element appear below the list.

Beginning section	*The following elements are required, in order:* Title page: List title, authors, and affiliations as first page of the manuscript Abstract Introduction
Middle section	*The following elements can be renamed as needed and presented in any order:* Materials and Methods Results Discussion Conclusions (optional)
Ending section	*The following elements are required, in order:* Acknowledgments References Supporting information captions (if applicable)
Other elements	Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figure files are uploaded separately. Tables are inserted immediately after the first paragraph in which they are cited. Supporting information files are uploaded separately.

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Books	Bates B. Bargaining for life: A social history of tuberculosis. 1st ed. Philadelphia: University of Pennsylvania Press; 1992.
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