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Descriptive study of biopsy proven IgA and Henoch-Schonlein purpura nephropathy in two government hospitals in Johannesburg (South Africa)

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Descriptive study of biopsy proven IgA and Henoch-Schonlein Purpura Nephropathy in two government hospitals in Johannesburg (South Africa).

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements of the degree in Master of Medicine in the branch of Paediatrics

Johannesburg 2010

Declaration

I Jennifer Gwen Mitchell declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

3rd Day of May, 2010.

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Abstract

IgA (Immunoglobulin A) nephropathy is reported as the most common form of primary glomerulonephropathy worldwide. Despite this there is limited research on IgA nephropathy in African children. This study reviewed IgA and Henoch-Schonlein Purpura (HSP) nephropathies, as it is believed that they are variants of the same pathological process.

This study hypothesized that IgA and HSP nephropathies occur in South African black children and that disease progression is worse in this population group and compares them to their international counterparts.

Methods: The study was a retrospective review of the records of children that presented to the paediatric renal clinics at two academic hospitals in Johannesburg. It reviewed the epidemiology and progression in South African children. These results were then compared to appropriate international reviews. There were a total of 1835 paediatric renal biopsies between 1985 and 2008. Of these 51 were confirmed to be IgA nephropathy (3%) of which one was excluded. Children were reviewed as a whole and then divided into a HSP and an IgA nephropathy group.

Results: The average age at presentation was 9.5 years old. There was a male predominance with a male to female ratio of 2.2:1. Racial differences were noted, and when reviewed in the light of the demographics of the area, there was a higher "prevalence" in Caucasian and Indian patients.

The most common presenting symptom in the study population was haematuria. Nephrotic range proteinuria occurred in more than half of all patients. Presentation in acute renal

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dysfunction was uncommon. Predictors of a poor prognosis were found to be nephrotic range proteinuria, and a lower GFR at presentation.

The study hypothesis that black African children with IgA or HSP nephropathy have a poorer prognosis than other children with similar presentations, was disproved.

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Introduction

Background

IgA (Immunoglobulin A) nephropathy is reported as the most common form of primary glomerulonephropathy worldwide[1]. It is a leading cause of Chronic Renal Disease (CRD) and End Stage Renal Failure (ESRF) in adults [2]. Despite this there is limited research on IgA nephropathy (previously known as Berger's disease[3]) in African children. The purpose of this study is; therefore, to describe IgA Nephropathy in South African Children.

IgA nephropathy is characterised by deposition of IgA containing immune complexes and complement within the renal mesangium[5].

Henoch Shonlein Purpura (HSP) is defined as "a vasculitis with IgA dominant immune deposits affecting small vessels and typically involving skin (leukocytoclastic rash), gut and glomeruli and is associated with arthralgia or arthritis". It can also affect the brain, lungs and scrotum. HSP nephropathy is characterised by deposition of IgA containing immune complexes and complement within small vessels of the renal mesangium.[5-6] Renal involvement occurs in 10 – 60% of patients with HSP and is reported mainly as a mild disease[6].

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The diagnostic criteria for HSP require 3 of the following criteria[6]:

(i) Palpable purpura (compulsory)

(ii) Angina of the bowel

(iii) Gastrointestinal bleeds

(iv) Haematuria

(v) Age < 20

(vi) No history of medication.

This review includes IgA nephropathy and HSP nephropathy, so as to compare and contrast them, as their histological pictures are the same.

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Literature review

IgA nephropathy was first described in 1968 by Jean Berger[3].

Pathogenesis

IgA is present in two forms, secreted from mucous membranes, namely IgA1 and IgA2[3]. IgA1 is secreted, in part, from the tonsillar region[7]. Patients with IgA nephropathy have increased IgA production by lymphocytes, decreased mesangial clearance of IgA and the presence of IgA associated factors[8]. This results in increased IgA concentrations in the serum, with HSP having larger sized IgA molecules[7]. IgA has a hinge region on the peptide, called O-glycosylation, which is abnormal[9]. Abnormal glycosylation suggests a genetic basis for IgA nephropathy[3].

Damage can be done to the kidney affecting the mesangium and the tubulointerstitium. Crescent formation and fibrin deposits can also occur. There is no evidence that mesangial IgA deposition occurs through classical Antigen Antibody reactions[9] and no specific viral or gastrointestinal tract antigens are associated with IgA nephropathy[10]. It is thought, instead, that mesangial cells have specific receptors that bind to IgA containing complexes (IgA, C_3a, C_4, C_3d with or without IgM and IgG, which in higher in HSP)[5,9,11]. IgA binding to mesangial cells results in the release of cytokines, complement and angiotensin II[12]. The cytokines then cause proliferation of mesangial cells and attract polymorphonuclear cells and monocytes as well as causing an overproduction of extracellular matrix[5].

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There are three types of mesangial changes (that progress from 1 to 3)[13]:

(1) Hypercellularity predominates over an increase in matrix

(2) Hypercellularity and matrix increase is equal

(3) Matrix increase predominates over hypercellularity.

Crescents can be seen in some patients and arise from capillary wall destruction. They are associated with endothelial proliferation and sub-endothelial deposits; which is more common in HSP[5].

HSP nephropathy almost always has glomerular fibrin deposits compared to IgA nephropathy[5]. Sub-endothelial deposits of IgA cause stimulation of endothelial cells to express Von Willebrand factor[5]. This then initiates the coagulation cascade and results in glomerular fibrin deposits[5]. The fibrin deposits then attract macrophages which release cytokines and induce epithelial cell proliferation[5].

Tubulointerstitial injury occurs in 3 phases[12]:

(1) Synthesis of IgA

(2) Mesangial IgA deposition and mesangial inflammatory injury, and finally

(3) Tubulointerstitial injury.

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This injury can occur by 4 different mechanisms namely[12]:

(1) Monocytic/macrophage infiltrate

(2) Proteinuria which activates cells in the proximal tubule

(3) Direct inflammatory effect of IgA

(4) Glomerulotubular cross talk.

The increase serum IgA concentration correlates well with an increased in haematuria[11]. The pathological process is systemic; as demonstrated when the kidney of a patient with IgA nephropathy is transplanted into a normal patient, the IgA deposits resolve[12].

Epidemiology

Although IgA nephropathy is reported as the most common form of glomerulonephropathy worldwide, this is not true across all racial groups. For example; FSGS and lupus nephritis are more common in childhood in Australia[14]. FSGS is also more common in African American patients, while IgA nephropathy is more common in young white and Hispanic patients[15]. There is some opinion that the incidence of IgA nephropathy in African American as compared with Caucasian children and adolescents is equal in certain areas (eg. Shelby county, Tennesee, USA)[16]. In Asia; half of the glomerular diseases seen, are IgA nephropathies. This compared to 10 – 30% in Europe and 10 – 15% in the United States of America[17].

The annual incidence of IgA or HSP nephropathy differs across the world. In Italy it is quoted as 0.5/100 000 whereas in Australia it is quoted as 10.5/100 000[14]. This incidence is, however, increasing[15]. The frequency of IgA nephropathy in all renal biopsies is also widely

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variable and reported as between 4 and 44%[6]. International research reports the incidence of HSP as 14 per 100 000[18] and reports HSP as the most common vasculitis in children[6].

The prevalence of IgA nephropathy is highest in Asia (especially Japan and Korea[3]), followed by Mediterranean Europe, Northern Europe and Australia with the lowest in North America. This may be as a result of differing criteria for the performance of renal biopsies.[10,19] IgA nephropathy is rare in black patients (African American patients or black patients in Africa)[5,15,20,21,22]. The prevalence in black patients is approximately the same as that in coloured patients[21]. In summary the prevalence of IgA nephropathy is lower in black compared to Caucasian children and highest in Asian children.

The peak age of presentation of HSP is 5 to 15 years old which is younger than in IgA nephropathy[14]. A male predominance exists in IgA and HSP nephropathies with a male to female ratio that varying between 1.2:1 to 2:1 in international literature[5,14,17,20,23].

Presentation

Presenting complaints are similar in the two diseases as would be expected. Children can present with a wide range of symptoms, none of which are pathognomonic[24]. The disease may present similarly to an acute post streptococcal glomerulonephritis, with haematuria 1 – 2 days following an upper respiratory tract infection[3,25]. Approximately 30 – 40% of IgA nephropathy patients are diagnosed after routine urine analysis (i.e. are asymptomatic). Other presentations include haematuria with or without proteinuria, nephritic/nephrotic syndrome or renal failure[24].

60% of IgA nephropathy patients present with haematuria, 45% with nephrotic syndrome and 5% with heavy proteinuria (there is a certain amount of overlap between these

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presentations)[13,21,24]. Microscopic haematuria and mild proteinuria are more common presentations in Asia where there are school screening programs, compared to gross haematuria which is more common in America as compared to Europe[19].

30% of patients have extra renal symptoms such as arthralgia, abdominal pain or an atypical rash[8]. Patients with HSP present with a typical rash, approximately 75% have joint involvement, and approximately 50% have oedema, abdominal pain and or renal disease[6]. Nephrotic/nephritic syndrome is more common presentation in HSP nephropathy[5].

Diagnosis

Diagnosis is based on renal biopsy as there are no confirmatory serological tests[25]. The serum levels of IgA may be elevated, but this is not consistant enough to be the basis of a diagnosis[3].

The biopsy findings show deposition of IgA containing immune complexes and complement within the renal mesangium demonstrated by immunoflourescence[5]. There is focal or diffuse mesangial hypercellularity which is accompanied by an increase in the mesangial matrix[3]. Some biopsies may show endocapillary proliferation, sclerosis or a crescenteric type glomerulonephritis[3]. Children with progressive disease may have tubular injury[3]. Dense deposits in the mesangium are seen on electron microscopy[3]. Histological findings of glomerulosclerosis, crescents, interstitial fibrosis or tubular atrophy indicate a poorer prognosis[3].

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Natural history

The course of HSP and IgA nephropathies are variable, but most often believed to be benign[6,17] with complete remission in approximately 25% of patients[17]. The disease progression is variable, with 20 – 50% of adults progressing to renal failure[26].

There are 3 main contributors to the extent and rate of progression of the disease, namely[24]:

(i) Synthesis, release and persistence of circulatory IgA

(ii) "Reactivity" of the glomerular mesangium, and

(iii) Renal factors that influence immune reaction to the disease.

Recurrent episodes of macroscopic haematuria are usually self limiting and provoked by mucosal infections, commonly by respiratory tract infections. Patients presenting with microscopic haematuria with no proteinuria (or mild proteinuria) will require prolonged follow up and monitoring of renal function, but may not require any specific treatment. Although the crescenteric form of IgA nephropathy is uncommon, the outcome is worse when compared to other forms of crescenteric disease; chronicity may have an influence here.[24]

The histological lesions progress from an early lesion with predominant mesangial proliferation to a predominance of matrix proliferation[27]. As stated earlier the rate of progression is variable[28], with a rate of Glomerular filtration Rate (GFR) decrease of approximately 1 to 3ml/min/1.73m^2/year if the GFR was normal at presentation and up to 9ml/min/1.73m^2/year if the patient presented with nephrotic syndrome[17].

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Children may rarely present with acute renal dysfunction, as a result of acute severe immune and inflammatory injury resulting in crescent formation[24]. The renal failure may also be as a result of mild glomerular injury with heavy haematuria, resulting in tubular occlusion and damage (this being reversible)[24]. Renal failure develops in 10% of IgA nephropathy patients after 20 years, and 20% of HSP nephropathy patients after 20 years[5].

Long term outcome, for IgA nephropathy[28] and HSP nephropathy[29], are documented as in table 1.1 (a single patient may fall into more than one category):

Table 1.1 Frequency of long term outcomes for IgA nephropathy[28] versus HSP nephropathy[29]

	IgA nephropathy	**HSP nephropathy**
No abnormality or clinical signs of disease	53%	69%
Minor urinary abnormalities	47%	7%
Proteinuria	35%	5%
Hypertension	9%	6%
Decreased Glomerular Filtration Rate or Chronic renal failure	3%	9%

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Poor prognostic features

Although many features are associated with a poor prognosis, none of them can be used to reliably predict outcome in a single patient.

Suggested features associated with a poor prognosis include:

(i) Older age at presentation (age > 9 years)[6,12,17,27,31].

(ii) Heavy proteinuria (considered by some, the most important indicator of poor outcome)[12,17,28,31-35].

(iii) Hypertension[12,17,31-33,35]

(iv) Altered renal function[12,17,31,32,34,35]

(v) High histological grade[12,17,33-35]

(vi) Long duration of preceding symptoms[24], and

(vii) Increased body mass index[31].

Goto et al suggests 6 predictors of poor outcome including[33]:

(i) Severe proteinuria on dipsticks (as the most important indicator)

(ii) Hypoalbuminaemia

(iii) Mild haematuria with or without severe proteinuria

(iv) Low total protein level

(v) Raised diastolic blood pressure

(vi) High histological grade.

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There are many varying histological grading classifications, but until recently they have not been adequately reproducible or reliable to be an independent predictor of outcome. The Oxford classification has now been developed that is both reproducible and can accurately predict the risk of progression of renal disease in IgA nephropathy in children as well as adults.[34,35] The classification looks at 6 variables namely:[35]

(i) Mesangial cellularity score

(ii) Segmental sclerosis

(iii) Endocapillary hypercellularity

(iv) Cellular / fibrocellular crescents

(v) Percentage of interstitial fibrosis / tubular atrophy

The literature also suggests that follow up proteinuria may be more helpful than proteinuria at presentation[28].

A good prognosis is suggested by recurrent episodes of macroscopic haematuria[24]. Gender, ethnicity, and serum IgA levels have been found to have no impact on prognosis[24].

In the search for a marker of poor prognosis; activated complement C_3 ($actC_3$) has been found to be promising (in adult patients). $ActC_3$ is formed by C_3 breakdown products after activation. $ActC_3$ levels are increased in patients with increased proteinuria / haematuria. The concentration of $ActC_3$ is significantly higher in patients with IgA nephropathy as compared to HSP nephropathy. This level, of $ActC_3$, reflects active renal disease and correlates, with significance, to the rate of renal function loss. Unfortunately it appears to be non-specific.[38]

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Treatment

The accepted treatment is a combination of anti-inflammatory treatment (e.g. Corticosteroids (referred to from here onwards as steroids) and immunosuppressive therapy) and antisclerogenic drugs[1]. The anti-inflammatory arm is used to fight systemic immune reaction and renal histological activity[1]. Steroids decrease proteinuria, and may protect against renal dysfunction[39]. The antisclerogenic drugs inhibit progressive renal fibrosis[1]. Another important arm of treatment is the maintenance of blood pressure using Angiotensin Converting Enzyme (ACE) Inhibitors[24].

The treatment regimes for IgA nephropathy have been extensively researched, but still treatment guidelines are not well recognised. There are many differing and conflicting ideas on the ideal treatment protocol.

While long term treatment with steroids and / or immunosuppressive agents does not confer any benefit in adult patients[26], a short course of corticosteroids (6 months) has been shown to be effective and safe, long term, in a subgroup of paediatric patients[28,39-41].

The mechanism of action of corticosteroids has two arms namely[40]:

(i) Anti-inflammatory action by modifying inflammatory cell function, and

(ii) Vaso-active by modifying glomerular micro dynamics and influencing renal blood flow.

Immunosuppressive treatment should be considered as part of a combination including steroids, in patients with severe disease or in those that do not show improvement with steroid and supportive treatment alone [2,26,39,40]. Some of these drugs are: Cyclophosphamide (used in the UK in adult patients and in Johannesburg, South Africa), Azathioprine,

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Mycophenolate Mofetil (MMF) (conflicting data on efficacy). Cyclosporine is not recommended due to the increase in serum creatinine after use, neither is Leflunomide recommended.[42] Intravenous immunosuppressive treatment is normally given monthly (for 3 to 6 months) and followed by steroid therapy alone or combined with an oral immunosuppressive drug (such as azathioprine) for 2 years[42]. The use of Cyclophosphamide as the immunosuppressive agent for 6 months followed by corticosteroids alone thereafter does show clinical improvement, however post treatment biopsies still showed chronic disease. Follow up of these children at 5-6 years showed worsening of their proteinuria.[3]

ACE inhibitors are widely used to control blood pressure in children with these diseases[17,32,40, 42, 44, 45]. Ace inhibitors are known to have an antiproteinuric effect on the glomerulus and significantly improve renal survival[32]. The effect of ACE inhibitors on proteinuria appears to be independent from its effect on blood pressure, and for this reason it is recommended, by some, as a first line treatment regardless of the patient's blood pressure[32]. The addition of an ACE inhibitor to steroids adds an additional benefit[44,46].

Anticoagulation and antiplatelet drugs such as warfarin, heparin and dipyridamole have been shown to inhibit some of the mediators of renal damage[26] by decreasing proteinuria in mild disease[2]. Dipyridamole may also prevent hypertension secondary to steroid use[2].

Other forms of treatment include tonsillectomy, which can be performed in patients with mild to moderate disease and recurrent episodes of tonsillitis[7,40,42,47,48]. Treatment with omega 3 fatty acids has been suggested; however there is limited evidence for this recommendation[3]. Supportive management for underlying conditions such as obesity and dyslipidaemia is also recommended[42].

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Renal transplantation

Renal transplantation is an appropriate treatment for any nephropathy with end stage renal disease[49]. This modality of treatment is offered at one of the two hospitals in the study and patient transfer between hospitals is encouraged and efficient, as both paediatric renal clinics act as one unit. The recurrence rate of IgA deposits (not necessarily disease) in the grafted kidney is reported at 40 – 60%[50], HSP being equal to IgA nephropathy[5]. This rate is increased in related live donors[49]. The disease recurrence in the transplanted kidney is 13% with 5% loss of the transplanted kidney over 5 years[50].

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Hypothesis and Aims

This study reviewed South African children presenting to the dedicated paediatric nephrology units in the Wits complex of Charlotte Maxeke Johannesburg Academic (CMJA) and Chris Hani Baragwanath (CHB) hospitals. These sites were chosen as they are the two, public sector, tertiary hospitals in the area and have children referred to them from other smaller primary and secondary hospitals in the areas that they serve. CMJA serves the greater Johannesburg area (higher proportion of white patients) and CHB serves Soweto and its surrounding areas (higher proportion of black patients) and can therefore be called representative of the government hospitals in Gauteng, South Africa. They also serve as referral hospitals for the smaller, and poorer, surrounding provinces, in particular the North West province (Klerksdorp Hospital where an outreach program is run jointly by both hospitals).

There is limited data describing the clinical course and outcomes of IgA nephropathy in black South African children, this study describes these features; in addition to this, the clinical outcomes in South African children were compared to outcomes seen in children from other countries reported in the literature.

This study hypothesized that black South African children diagnosed with IgA nephropathy present with more severe disease and have a worse outcome despite standard therapy.

The study highlights similarities and differences in the South African population compared to their international counter parts.

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Specifically, this study;

(1) Describes the clinical features at presentation and follow up of South African children diagnosed with biopsy-proven IgA and HSP nephropathy

(2) Describes the epidemiology (age, gender, race) of South African children diagnosed with either nephropathy

(3) Determines the association between presenting features, renal function (represented by GFR) and clinical outcome

(4) Compares treatment options (including need for dialysis and renal transplant)

(5) Compares presenting clinical features, treatment modalities and clinical outcomes in South African children and their international counterparts.

This study serves as a description of IgA nephropathy for South African children.

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Materials and Methods

The study was a retrospective review of the records of children that presented to the paediatric renal clinics at the Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Hospital. Due to the small numbers of IgA and HSP nephropathy the study was a review of all adequate records, at the relevant hospitals, of children with biopsy proven IgA or HSP nephropathy who presented between January 1985 and December 2008 (23 year period).

Inclusion Criteria:

(1) Children were defined as less than 16 years of age.

(2) IgA or HSP nephropathy was diagnosed on biopsy.

(3) Presentation between 1 January 1985 and 31 December 2008 to one of the two clinics.

(4) Patient records were available and had adequate information.

The records were found in the two relevant clinics where all clinic patient records, past and present, are kept.

IgA nephropathy was defined as a positive Immunofluorescence for IgA (with or without C_3) in glomerular mesangial areas, sometimes associated with IgA deposits in other areas of the glomeruli on renal biopsy[3]. If more than one immunoglobulin stain was positive, then IgA was predominant.

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HSP nephropathy has the identical histological features, but also has systemic features described in the introduction.

Biopsy samples were taken under sedation with a core biopsy needle, or true cut biopsy needle, under sterile conditions. A core of renal tissue was removed and examined by a medical technologist, who was present at the time of the biopsy. The technologist examines the core sample, to determine whether it is kidney and whether it is an adequate sample, using a dissecting microscope.

The sample for light microscopy has to contain approximately 10 glomeruli to be adequate. The sample for immunofluorescence needed 8 glomeruli and electron microscopy sample required 1-2mm portions containing 2-3 glomeruli. Renal cortex was required (juxta-medulla). Tissue samples are then placed into the relevant fixatives as soon as possible to prevent deterioration. Formalin, or a mixture of formalin (corrosive) and mercuric chloride, is used for light microscopy. A transport medium (Zeuss medium) is used for the sample for immunofluorescence and a gluteraldehyde solution is used for the electron microscopy sample.

Light microscopy specimens were returned to the laboratory and processed through ascending grades of alcohol to chloroform and embedded in wax (blocked). Thin sections were then cut and stained routinely with Haematoxylin and Eosinophil and special stains. Slides were then given to the pathologist for diagnosis.

Immunofluorescence specimens were prepared for frozen sections. They were rinsed in a buffer solution and placed on a "multi-well" slide. A range of antisera were then diluted according to optimization (albumin, IgG, IgM, IgA, C_3, fibrinogen). These have fluorescent

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markers for diagnosis under the fluorescent microscope. Following this, the individual dilutions were placed in the marked "wells". On completion of the procedure, the slides were mounted on suitable mounting media under a cover slip and observed for Immunofluorescence under a fluorescent microscope. This was done as soon as possible, at longest a week.

The last sample was sent for electron microscopy.

Biopsy specimens were processed by the staff in the renal histology laboratory at Charlotte Maxeke Johannesburg Academic Hospital. A report was then issued from the histology department to the relevant clinic. Fifty-one children were identified as having IgA nephropathy on their biopsy results. Of the fifty one children, one file was found to be incomplete and was excluded from the study.

The records were kept up to date by the doctors that saw the children at their scheduled clinic visits. At each visit weight, height and blood pressure were recorded by the clinic sister. A relevant history and examination were documented by the attending doctor. All blood tests, including Urea and Electrolytes and Creatinine, were recorded on a flow sheet in each child's file and updated regularly. These blood tests were done at the discretion of the attending doctor. The creatinine values, from these tests, were used to calculate the GFR (using the Schwartz formula[53]), on admission, and at their last test recorded (used for follow up GFR).

Presenting symptoms were defined as the complaints the child had on arrival at hospital and those features found by the doctor on his/her first assessment of the child. The histological grading of each biopsy was done, according to Haas[50], using the histological report sent from

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the renal histopathology laboratory. The oxford classification of IgA nephropathy was, unfortunately not yet published at the time of data collection.

This was done at the time of data collection according to the following grading system (designed by Haas)[50]:

I	minimal or no mesangial hypercellularity without glomerulosclerosis
II	focal and segmental glomerulosclerosis without active cellular proliferation
III	Focal proliferative glomerulonephrosis
IV	Diffuse proliferative glomerulonephrosis (with or without crescents)
V	Any biopsy with ≥ 40% globally sclerotic glomeruli and/or ≥ 40% estimated cortical tubular atrophy or loss.

For the purposes of this study the following definitions were made:

Nephritic syndrome was defined as micro/macroscopic haematuria, oedema and hypertension. Nephrotic syndrome was defined as a proteinuria of 2+ or more on dipsticks[51]. Mild proteinuria was defined as 1+ proteinuria on dipsticks. Hypertension was defined as a systolic blood pressure greater than the 95th centile on blood pressure for height charts[52].

GFR was calculated according to the Schwartz formula for children[53]:

GFR (ml/min/1.73m^2) = k X height (cm) / Creatinine (mg/dl)

Where K = 0.33 in preterm infants

0.45 in term infants to 1 year of age

0.55 in children to 13 years of age

0.55 in adolescent females

0.70 in adolescent males

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A conversion factor of 88.3 was used to convert µmol/l to mg/dl.

Acute renal dysfunction was defined as a GFR less than 60ml/min/1.73m^2.

Data was collected on a data collection form, under the following headings (see data collection sheet):

1. Gender -male or female
2. Race
3. Age at presentation
4. Growth parameters evaluated using z scores according to the WHO growth charts[54]
5. Presenting symptoms (including hypertension)
6. Renal function at presentation, and follow up, as determined by Glomerular Filtration Rate (GFR)
7. Histological grade of renal biopsy
8. Treatment received
9. Outcome and length of follow up.

A normal weight was defined, in accordance with the WHO guidelines (2003)[54], as a z-score between +2 and -2. Overweight was any z-score greater than +2, and underweight was any z-score less than -2. As a measure of outcome the progression of the disease at the last clinic visit was reviewed as well as the follow up GFR (calculated using the creatinine from the latest blood results recorded and the height of the child at that time using the Schwartz formula[53]). The disease progression was divided into categories namely: active disease, recovery and death. Active disease was defined as: "active" urine on dipsticks, i.e. a positive dipsticks for blood and or protein. Recovery was defined as: loss of urinary symptoms on

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dipsticks, i.e. neither blood nor protein on dipsticks. Death was defined as: death due to renal disease, (all children that died, died as a result of their renal disease). Children for whom a follow up appointment was made, but not kept or rescheduled, were deemed to have been lost to follow up regardless of their disease state.

The sample population was analyzed as a whole group and then subdivided into two smaller groups, a HSP group and an IgA group. The HSP group included all those patients who were diagnosed clinically as having HSP; the IgA group included those children who did not clinically fulfil the criteria for HSP. These subgroups were then compared to each other to look for any differences in presentation or outcome.

Statistics

Categorical variables were analysed, with the help of a statistician using Pearson chi squared and Fisher's exact method. A "p" value of less than 0.05 was taken as statistically significant. Averages and 95% confidence intervals were performed on data with continuous variables, such as age and GFR values. A linear regression study was done to assess the influence of presenting symptoms on outcome and diagnostic testing was performed on this model to ensure its accuracy. The linear regression was done using the R-squared test for reliability. Diagnostic tests that were performed included the Ramsey Reset test using powers of fitted values for follow up GFR, and the Skewness/Kurtosis test for normality. During the linear regressional analysis those patient that had died were excluded, as there were only three children in that group and therefore they were confounding the statistics. A statistician was consulted for the more complicated calculations and the simpler calculations were done using Microsoft © Excel.

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Ethics

Ethics approval was granted by the Human Research Ethics Committee of the University of Witwatersrand. Ethics clearance number: M090209.

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Results

There were a total of 1835 biopsies, for children under the age of 16, during the study period. Of these 1835 biopsies, 51 were predominantly IgA positive on immunoflourescence (giving a prevalence of 3%). The records were found in the archives of the two clinics; where one record was found to be incomplete and therefore excluded from the study, leaving a study population of 50 children.

The whole group consisted of 50 children and was divided into a HSP group and an IgA group as per figure 4.1.

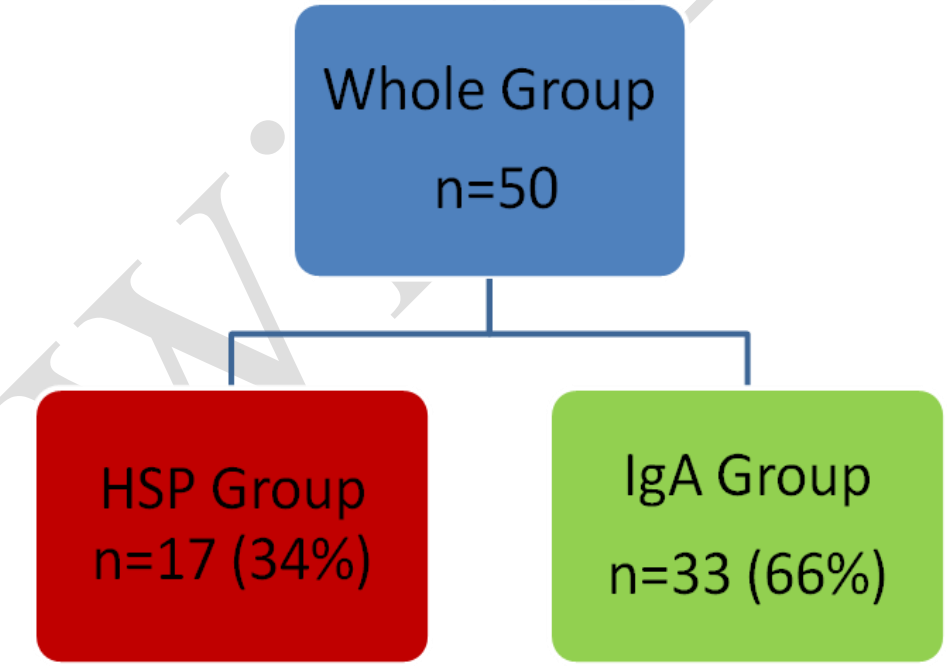

Figure 4.1 Division of the whole group into subgroups HSP and IgA.

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The excluded child was diagnosed, on biopsy, with IgA nephropathy and underwent renal transplantation. He was a male child who presented at 12 years of age. He received a related live donor kidney and appeared to be well post renal transplant with a good follow up GFR. He was transferred to the adult renal clinic after being followed up for 5 years in the paediatric clinic. Unfortunately his first visit notes were missing from the file, thus excluded from the analysis.

The final results, after analysis, are as follows.

The average age at presentation was 9.5 years old, with two peaks of presentation at 8 and 13 years of age. The 95% confidence interval for presenting age was 8.8 to 10.3 years of age. The HSP group had an average age of 8.6 years with a peak at 10 years, and the IgA group had an average age of 10 years with a peak at 13 years.

There was a male predominance as shown in table 3.1. This predominance was shown in both subgroups, but more prominent in the HSP subgroup. The male to female ratio for the study population was 2.2: 1.

Racial differences were noted with a predominance of black patients in the whole group and the IgA group. The study demographics are summarized in table 4.1.

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Table 4.1 Demographic profiles of HSP and IgA nephropathy patients

		Whole Group No (%)	**HSP Group No (%)**	**IgA Group No (%)**
Gender	Male	34 (68)	13 (76)	21 (64)
	Female	16 (32)	4 (24)	12 (36)
Age	0 – 2 years	0 (0)	0 (0)	0 (0)
	2 – 5 years	3 (6)	1 (6)	2 (6)
	5 – 10 years	21 (42)	9 (53)	12 (36)
	➢ 10 years	26 (52)	7 (41)	19 (58)
Race	Black	28 (56)	7 (41)	21 (64)
	White	15 (30)	7 (41)	8 (24)
	Coloured	3 (6)	2 (12)	1 (3)
	Indian	4 (8)	1 (6)	3 (9)
	Other	0 (0)	0 (0)	0 (0)

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This racial difference must be viewed in the context of the population that the clinics serve. Table 4.2 summarizes the area population[55,56] and corrects the study demographics in relation

to the population served to allow better interpretation of the data. The "Average number in area population during study period" was calculated by averaging the total population in the clinics' drainage areas, according to the 1996[55] and 2001[56] South African national censuses. This shows a higher "incidence" of the diseases in white and Indian children.

Table 4.2 Breakdown of populations into racial groups

Racial Group	Number in study population			Average number in area population during study period[55,56]	Number per 100 000 of area population		
	Whole Group	HSP Group	IgA group		Whole Group	HSP Group	IgA Group
Black	28	7	21	3291656	0.90	0.21	0.64
White	15	7	8	705714	2.22	1.00	1.13
Coloured	3	2	1	246777	1.27	0.81	0.4
Indian	4	1	3	183072	2.47	0.55	1.64
Total	50	17	33	4198593	**1.19**	**0.40**	**0.79**

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The growth parameters showed that the majority of children (82%) presented with a normal weight, i.e. z-scores between -2 and +2, and a normal Body Mass Index (BMI). The BMI was calculating using the recorded height and weight of each child. This is demonstrated in figure 4.2.

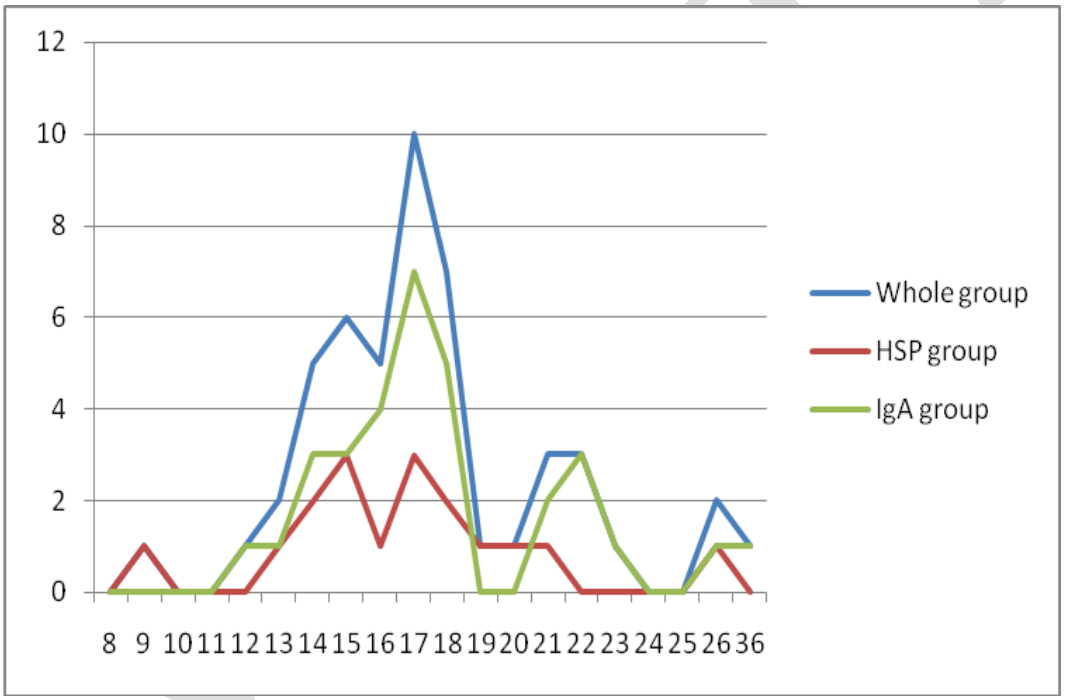

Figure 4.2 Graph to show Body Mass Index

The most common presenting symptom in the study population was haematuria, macroscopic more common than microscopic. Nephrotic range proteinuria occurred in more than half of all patients regardless of which group they were in (see figure 4.3). Acute renal dysfunction at presentation was seen in 11 patients (22%), of which the majority were children with IgA nephropathy (10 in the IgA group versus 1 in the HSP group). Arthritis was only found in the HSP group, as would be expected by the definition of HSP. Abdominal pain and a preceding upper respiratory tract infection were found with similar frequencies in both groups (the HSP group having only a slightly higher incidence).

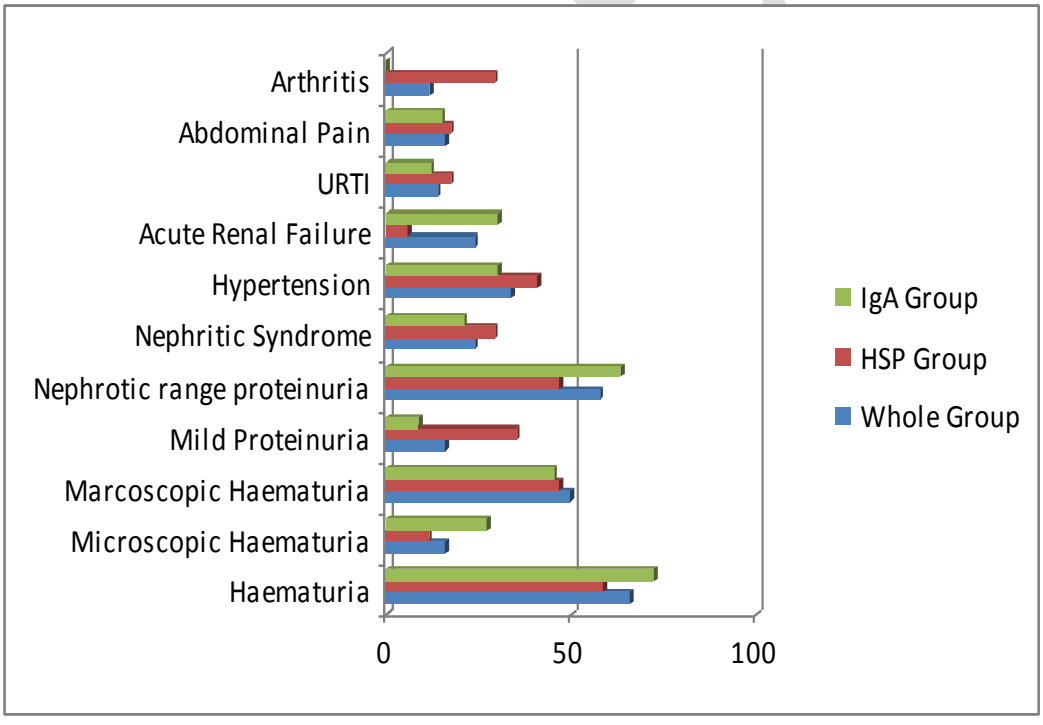

Figure 4.3 Presenting symptoms (shown as percentages).

The average GFR at presentation was 100ml/min/1.73m^2, with a 95% confidence interval of 84 to 117ml/min/1.73m^2. Figure 4.7 Shows and compares the GFR values and standard deviations.

The histological grading of each renal biopsy showed most children presented with a histological grade between I and III[50]. The breakdown of each grade is shown in figure 4.4. Although this distribution is similar for both subgroups, the HSP group had a slightly higher percentage with a histological grade II (35%) and the IgA group had a slightly higher percentage with histological grades I and III (28% in each). Grade IV and grade V were rare findings on renal biopsy regardless of the group.

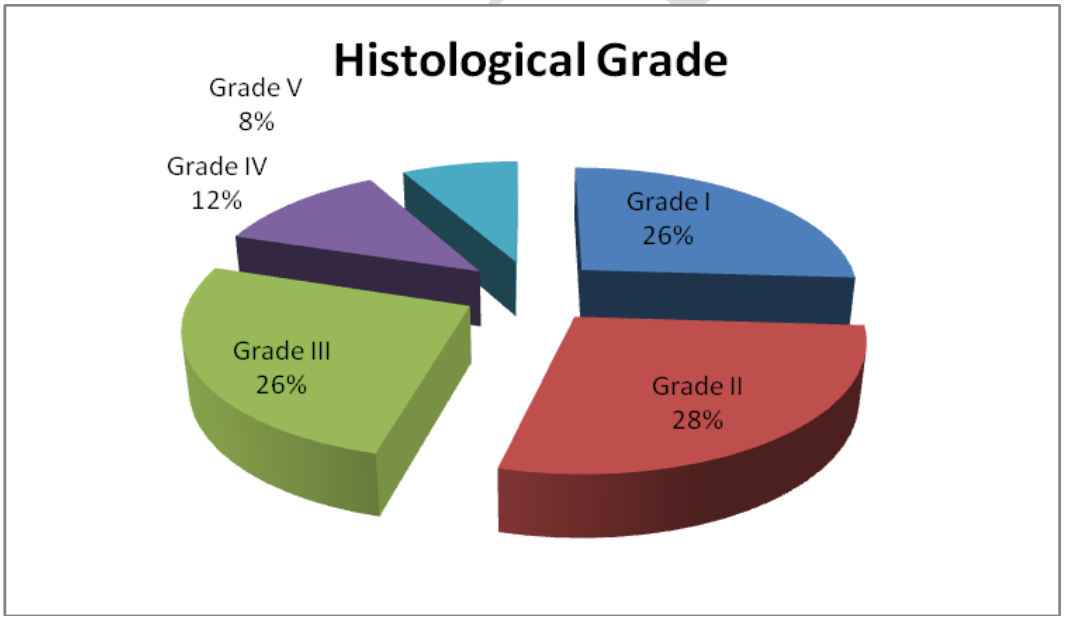

Figure 4.4 Histological grading of whole group.

Treatment regimes between the groups were similar, with small percentages receiving no treatment and the majority of children receiving corticosteroids given orally in the form of prednisone (see figure 4.5). The most commonly used antihypertensive drugs used in these patients were nifedipine, enalapril, captopril, amlodipine, metoprolol, doxazosin. Of these enalapril and captopril are classed as ACE inhibitors. All the children that received immunosuppressive therapy also received prednisone therapy (i.e. no child received immunosuppressive therapy, other than steroids, alone). The immunosuppressive drug of choice for these two hospitals was intravenous cyclophosphamide given monthly over 3 to 6 months, depending on the dose strength. There was no follow up medication, after the intravenous immunosuppressive therapy, with an oral, non-steroidal, immunosuppressive drug.

Two children received renal transplantation.

The first child presented at age 11 years with chronic renal failure. She had a GFR at presentation of 9ml/min/1.73m^2. She was started on dialysis while awaiting a donor kidney for transplantation to become available. She then received a cadaveric kidney and her renal function improved. She appeared to be doing well, but then unfortunately missed several clinic appointments. Unfortunately the transplanted kidney was rejected, most likely due to non-compliance of her immunosuppressive treatment post transplant. She then underwent haemodialysis again, but continued to deteriorate and finally died as a result of her renal disease.

The second child to receive a renal transplant presented at age 6 years. He presented with acute renal dysfunction and was started on haemodialysis. He received his first renal transplant at age 7 years. He appeared to do well after this transplant, and his renal function

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improved well. Unfortunately he had recurrence of IgA nephropathy in the transplanted kidney. His renal function deteriorated and he received a second transplant at 13 years of age. After his second transplant he appeared to do well with a much improved renal function. Unfortunately due to social problems he became non-compliant and required a third transplant at 17 years of age. He was transferred to another province, where he had better social support, and where he was looked after at another paediatric renal clinic in a tertiary hospital.

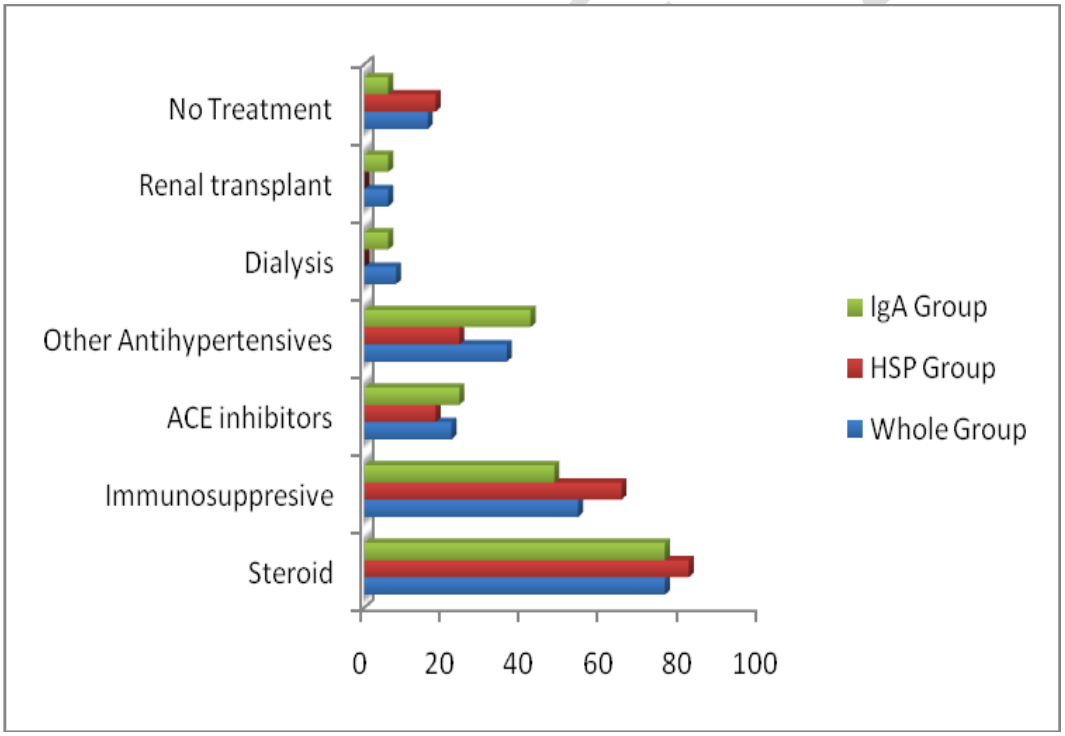

Figure 4.5 Treatment (shown as percentages).

There were no children in the study population that received tonsillectomy or omega 3 fatty acids.

The average period of follow up was approximately 3 years with a range of 1 – 12 years. Unfortunately there were a large proportion of children lost to follow up (51%), this occurring mostly, but not exclusively, after a short follow up.

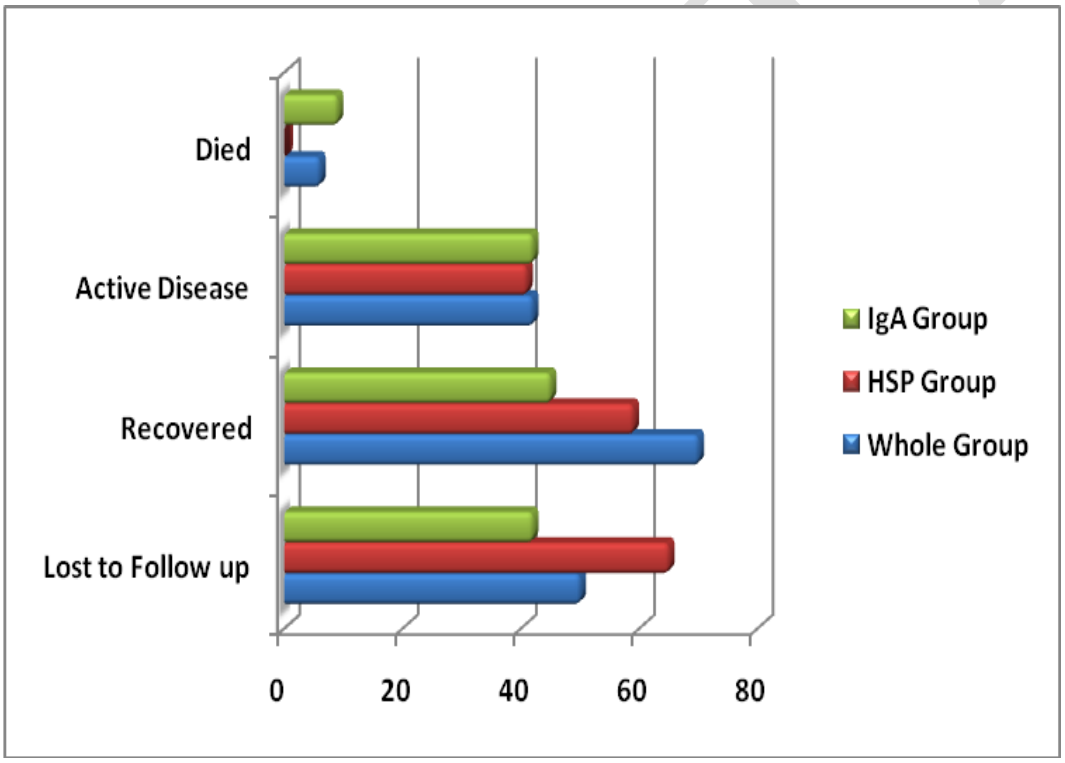

Figure 4.6 Outcomes (shown as percentages).

There were only 3 deaths in the study population.

The first death was the child described above.

The second death was a child, who was autistic, whose parents elected for her not to receive a renal transplant, but rather to receive supportive therapy only. Her renal function deteriorated slowly over time and she underwent peritoneal dialysis. Her deteriorating renal function resulted in her death after 5 years of attending the paediatric renal clinic.

The last patient that demised in the study was seen at the paediatric renal clinic, for four years, where he received peritoneal dialysis after developing renal failure. He was then transferred to the adult clinic at 17 years of age, where he deteriorated over time and finally demised as a result of his renal failure. Figure 4.6 summarizes patient renal outcomes.

The children who received renal transplantation or who demised are summarised in table 4.3.

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Table 4.3 Children who were Dialysed, received Renal Transplant or Demised. (A child may fall into more than one category, i.e. may have been transplanted and then demised.)

		Dialysed (%)	Transplanted (%)	Demised (%)	Total (%)
Sex	**Male**	3 (60)	0 (0)	1(33)	3 (50)
	Female	2 (40)	2 (100)	2 (67)	3 (50)
Age	**0 – 10**	1 (20)	1 (50)	0 (0)	1 (17)
	10 – 16	4 (80)	1 (50)	3 (100)	5 (83)
Race	**Black**	4 (80)	1 (50)	2 (67)	4 (66)
	White	0 (0)	0 (0)	1 (33)	1 (17)
	Coloured	1 (20)	1 (50)	0 (0)	1 (17)
	Indian	0 (0)	0 (0)	0 (0)	0 (0)
	Other	0 (0)	0 (0)	0 (0)	0 (0)
Disease	**IgA**	5 (100)	2 (100)	3 (100)	6 (100)
	HSP	0 (0)	0 (0)	0 (0)	0 (0)
Total		5	2	3	6
Demised		2 (40)	1 (50)	3 (100)	3 (50)

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The average follow up GFR was 117ml/min/1.73m^2, with a 95% confidence interval of 116.4ml/1.73m^2/min to 117.5ml/1.73m^2/min, with an average change in GFR of 22.6ml/1.73m^2/min (95% confidence interval of 22.2ml/1.73m^2/min to 23ml/1.73m^2/min).

Figure 4.7 summarizes the GFR values.

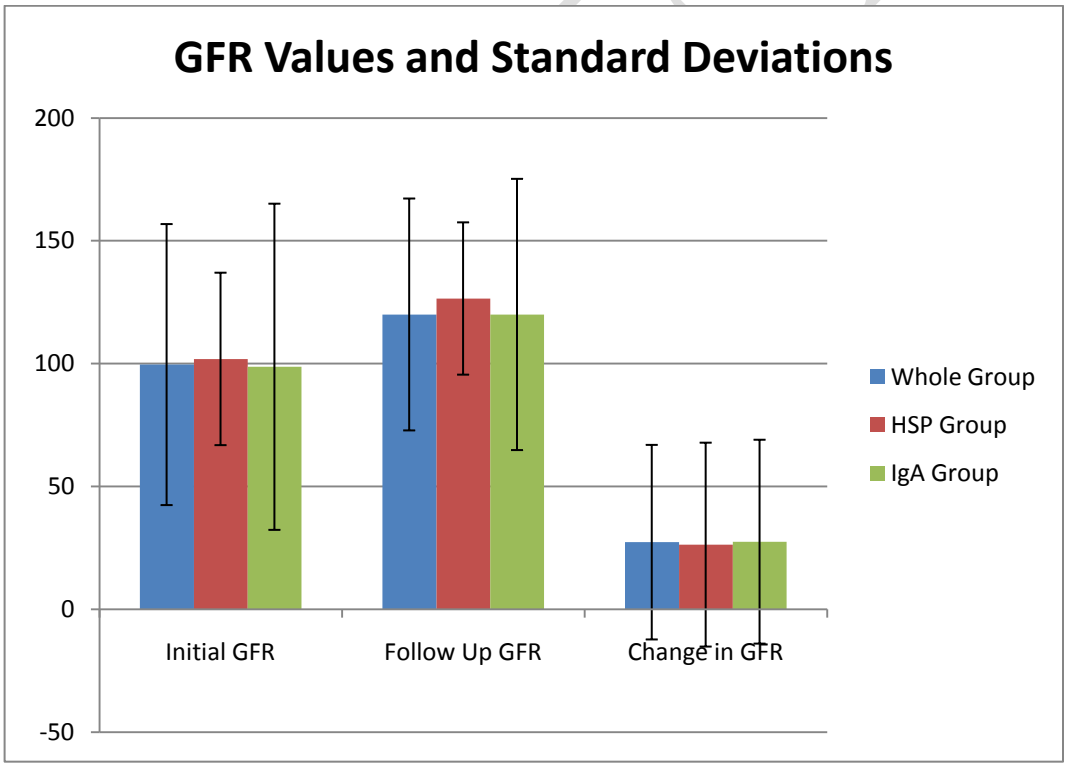

Figure 4.7 Graph showing GFR values and standard deviations

The measure of disease activity showed that the majority of patients recovered, despite the large percentage that were lost to follow up.

When analyzed by the statistical methods referred to in chapter 3, the following observations can be made:

(i) Neither the race nor the sex of the child indicated a poorer prognosis (sex p=0.74, race p=0.67-0.96). Indian patients appeared to have a better prognosis, but the number of Indian patients in population (4) limits the significance of this (p=0.09).

(ii) There was no statistical significance in the difference in outcomes of the HSP group compared to the IgA group (p = 0.384).

(iii) There was also no correlation between presenting symptoms and outcomes based on disease activity, however this did not hold true when outcome was assessed according to GFR at follow up.

(iv) Histological grade at the time of biopsy showed conflicting results, with a histological grade of IV being predictive of a good outcome (p=0.02).

(v) Treatment regimes of each child revealed no statistical significance between the different treatment regimes when correlated with disease activity.

Diagnostic testing was performed on the statistical model referred to above to ensure its accuracy in modelling these diseases. These tests all showed that the model is accurate and can be used to predict future disease profiles. Figure 4.8 shows these diagnostic test results.

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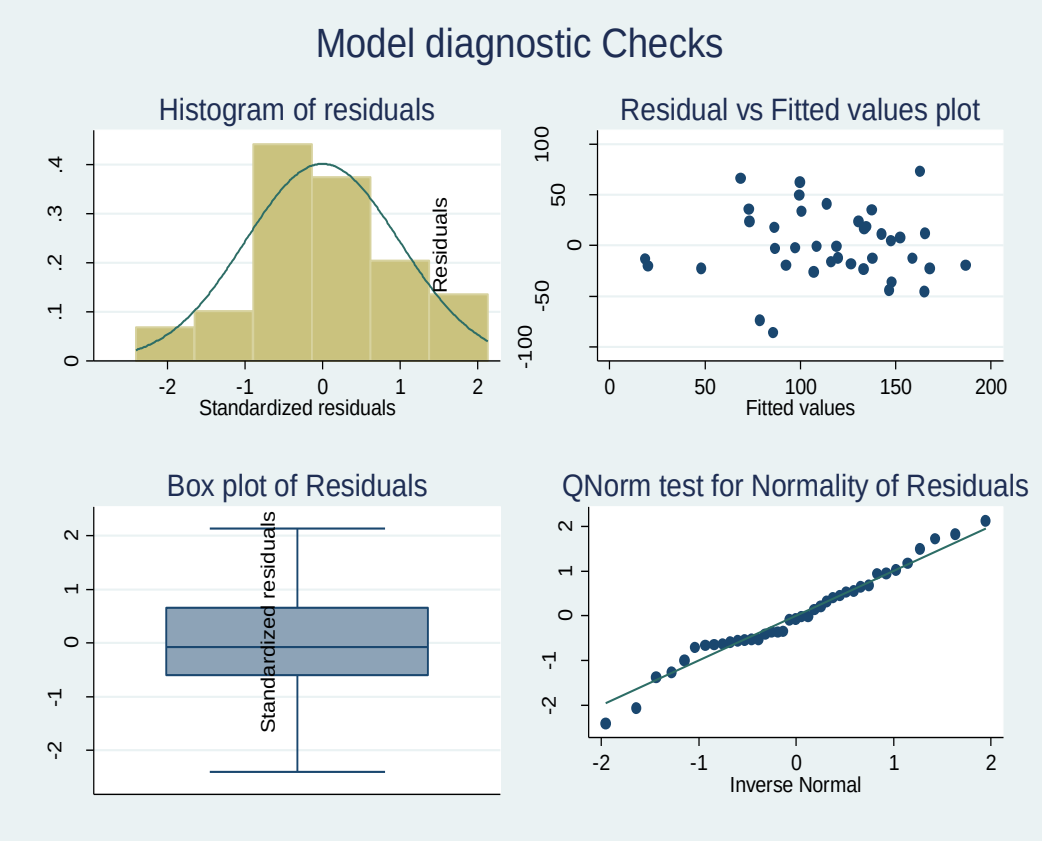

Figure 4.8 Graphs of diagnostic tests to prove accuracy of the statistical model.

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Discussion

This study reviewed of IgA nephropathy and Henoch-Schonlein Purpura (HSP) nephropathy. The study hypothesized that IgA and HSP nephropathy occurs in South African black children and that the overall outcome is worse in these patients when compared to other racial groups. This study shows that, while IgA does occur with a higher frequency than previously thought in black children, it does not hold a poorer prognosis. The study highlights similarities and differences in the South African population compared to their international counter parts.

The study reviewed South African children who presented to the paediatric nephrology units in the Wits complex of Charlotte Maxeke Johannesburg Academic (CMJA) and Chris Hani Baragwanath (CHB) hospitals between 1 January 1985 and 31 December 2008 with biopsy proven IgA or HSP nephropathy.

The total number of children included in the study was relatively small when viewed from a statistical stand point; however in a disease with a low prevalence these numbers are, in fact, significant.

The "prevalence" of IgA and HSP nephropathy, in the context of all paediatric renal biopsies, was 3% (51 out of 1835 biopsies), 2% for IgA and 1% for HSP. This implies the "rarity" of the disease in this setting.

The average age at presentation was 9.5 years old, with the HSP group having an average age that was younger (8.6 years) than that in the IgA group (10 years). This age at presentation compares well with international studies[14].

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There was a male predominance in this study with a male to female ratio of 2.2:1 (a slightly higher incidence of males than reflected in international data[5,14,17, 20,22]).

The predominance of black patients, when reviewed in the knowledge of the surrounding population, was a false reflection. The true reflection shows that Indian children (in IgA nephropathy) and white children (in HSP nephropathy) have a higher "incidence" in the study population, which correlates with international literature[15,17]. However IgA nephropathy does have a higher incidence in the black population than previously suggested by South African literature[22] which agrees with more recent evidence from the USA[16].

The "incidence" of the whole study group is 1.19/100 000 population. International literature gives the incidence of IgA nephropathy, as 0.5/100 000 people (Italy) to 10.5/100 000 people (Australia)[14]. These quoted incidences are, however, for IgA nephropathy excluding HSP nephropathy. Therefore the comparison must be made with the IgA group only. The "incidence" of IgA group was 0.79/100 000 population, falling at the lower end of the international range. The "incidence" quoted for the study is, however, not the true incidence of the disease, as the population demographics include people of all ages and the study population includes only children less than 16 years old. Children taken to private hospitals are also not included in this study population. The "incidence" reported by the study is, however, a reflection of what the true incidence may be. The data for HSP may be more accurate than that for IgA, as HSP is a disease of childhood and rarely occurs in adults[6,14]. The reported incidence of HSP vasculitis is 14/100 000 people[18], but this number reflects all patients with HSP and not only those with HSP nephropathy, as the study reports. The incidence of HSP nephropathy can be estimated by acknowledging that 10 to 60% of children with HSP develop renal disease[6]. This would result in an incidence of HSP nephropathy of

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around 1.4 to 8.4 /100 000 people. The study's approximate incidence was 0.4/100 000 much lower than that estimated.

Most of the children in the study presented with a normal weight and normal BMI.

The most common presenting symptom in the study was haematuria, which is the same as the international literature reports. More than half of all the study children presented with nephrotic range proteinuria, this was true in both subgroups. Unfortunately the other criteria needed to diagnose nephrotic syndrome, such as serum levels of cholesterol, were not collected in this study. After nephrotic range proteinuria, hypertension was the next most common presenting features. This is in keeping with international studies[13,21,24,25]. Although acute renal dysfunction (GFR <60) was a common presenting feature in the IgA group, it was the least common presenting feature in the HSP group. This can be explained by the fact that systemic, and more often skin features, of HSP bring children to seek medical attention (and thereafter monitoring) earlier. Despite the monitoring of children with HSP before renal disease is identified, it is interesting to note that more children presented with microscopic haematuria in the IgA group than in the HSP group. Females appear to have a lower presenting GFR, but this was not proven in the linear regression.

The histological grading of each renal biopsy showed that most children presented with a histological grade between I and III. Children with higher histological grades were not found to be of an older age group, as would be suggested by international literature (the histology progresses over time[13]). It is important to mention here that, although renal biopsy reports follow standard guidelines, the individual renal biopsies were not seen by the same histologist and therefore may not have been uniform.

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Treatment regimes were started and altered according to the discretion of the attending doctor, most often in consultation with a paediatric nephrologist. When reviewed in a linear regression for outcome, there was no statistically significant difference between treatment regimes. This is by no means suggesting that a child will have the same, or similar, outcome if treated aggressively with antihypertensive and immunosuppressive therapy, including, among others, steroids, versus no treatment at all. The lack of statistical significance can be explained by the fact that the sicker children received a more aggressive treatment regime than the less sick children. The improvement is comparable across all treatment regimes suggesting that the treatment was equally effective for each disease severity and grade.

The average follow up period was approximately 3 years with a range of 1 – 12 years. Unfortunately there were a large proportion of children lost to follow up (51%). This could inhibit the significance of a linear regressional analysis, but the diagnostic tests performed to ensure the model was accurate enough to draw conclusions from, suggests that the model can be used to draw conclusion. Those children lost to follow up did not come back to either clinic and so an argument can be made to presume they have done well. However, no attempt was made in the study to contact these children or their families. It was feared that the assumption that these children did well may skew the data, and their "outcome" was taken as their clinical assessment at their last clinic visit.

It is interesting to note that none of the children that fell into the HSP group developed renal failure, despite the international literature reporting a higher rate of progression to renal failure in people with HSP as compared to IgA nephropathy (20% compared to 10% after 20 years). This may be due to the fact that this study did not follow up children once they had moved on to the adult renal clinic.

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To review the clinical relevance of the presenting features, a linear regression was used to highlight which, if any, of those features present at presentation could be used to predict prognosis.

As previously stated there were a large number of children that were lost to follow up, this fact impacts on the reliability of the data collected. The three categories of disease progression, when reviewed, were not as useful as previously anticipated, and a better guideline of a child's condition was his/her GFR at follow up. This may be due to a child responding to treatment first by increasing GFR and only then losing urinary symptoms after some time. Those children lost to follow up may also have impacted less on the follow up GFR than on a disease progression category. This was due to the fact that a change in GFR, up or down may be small, but still recognized as deterioration or improvement, whereas a small change in a clinical picture may not be reflected in such broad categories as those defined for disease progression. The broad categories of disease progression also made it difficult to distinguish severe disease (i.e. needing dialysis and or renal transplant) from mild disease, as was possible using GFR. For the reasons listed above GFR was used as the end point for the regressional analysis.

As in international literature, neither the race nor the sex of the child indicated a poorer prognosis. The outcomes of the HSP group when compared to the IgA group were similar.

Predictors of a poor prognosis were found to be nephrotic range proteinuria and a lower GFR at presentation. This correlates well to international data[12,17,28,31-33,36,37]. Unlike international reports[6,12,17,27,31], this study did not find a significant difference in outcome according to age. This may be due to the study population being in an older age group. International data

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reports that a child presenting after the age of 9 years has a poorer prognosis[6,12,17,27,31], but in this study the average age of presentation, for IgA, was 10 years, with 13 years being the most common presenting age, and the majority of children presenting after the age of 9 years. Neither the race nor sex of the child had an influence on prognosis, disproving the study hypothesis that black children have a poorer prognosis than children in other racial groups with a similar presentation.

Although the literature states that a higher histological grade represents a poorer prognosis[12,17,33,36,37], the results from this study do not correlate. A histological grade of grade IV at the time of biopsy proved to be predictive of a good outcome. This however may not be reliable due to the small numbers in this group as well as the fact that a more aggressive treatment regime was started as soon as crescents were seen on renal biopsy. Crescents are not seen in the lower histological grades, but are a prominent feature in histological grades IV and V[50].

The treatment of each individual child was based on that child's presentation and special investigations, including blood results and renal biopsy. This influences the outcome for each treatment, as those that were started on immunosuppressive drugs (cyclophosphamide in most cases) had a more severe disease at presentation, or on review. This implies that the comparison of treatment regimes in this study does not lead to an unbiased result and therefore cannot be commented on. It is, however, worth mentioning that most children were treated with steroids as a first line treatment and cyclophosphamide was added later depending on the disease severity or lack of improvement of activity markers. It is also worth noting that only 67% of children, who were hypertensive, were started on an ACE inhibitor. No children who were normotensive were started on an ACE inhibitor. This differs

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from international literature that recommends starting an ACE inhibitor (even when the blood pressure is normal[32]).

The average GFR for the study children showed a GFR improvement from 100ml/min/1.73m^2 to 117ml/min/1.73m^2. There is an average of 23ml/min/1.73m^2 improvement for GFR.

The "outcome" measured by disease activity (as determined by dipsticks) showed most children's disease resolved; this despite the large loss in follow up. This correlates with international literature which states; most children have a benign course of illness and the disease resolves[6,17]. In the study, those children that still had active disease (by dipsticks) at their last clinic visit may also have resolved before their follow up, and that may have been the reason for defaulting clinic visits. This, however, can only be speculation as those children were not contacted and hence the true reason for defaulting is not known.

When reviewing those children that received dialysis, renal transplant and those that demised, the data shows an equal male to female ratio. However all those needing renal transplant and 67% of those that demised were female. This in the context of a majority male disease suggests a poorer prognosis for females. All those children requiring dialysis, renal transplantation or who demised, suffered from IgA nephropathy and not HSP nephropathy. This suggests that IgA nephropathy has a poorer prognosis than HSP. The racial distribution of these children shows a majority black distribution in each of the subgroups. Once compared to the racial distribution of the IgA group (as all these children came from the IgA group) this data changes. 18% of children with IgA nephropathy needed either dialysis, renal transplant or demised (19% of black children, 12.5% of white children and 100% of coloured

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children). Statistically there was only 1 coloured child and therefore not significant. Despite this when a linear regression was performed on the whole group neither sex, race nor disease (IgA vs. HSP) was shown to indicate a poorer prognosis with statistical significance.

Negative predictive factors suggested by this study are:

(i) Nephrotic syndrome at presentation (p=0.02).

(ii) Low GFR on presentation (p=0.00).

(iii) Presentation with acute renal dysfunction for IgA nephropathy only (p=0.042).

In summary; this study describes the average child with IgA or HSP nephropathy in Johannesburg, South Africa, is a very diverse population.

It occurs in all the racial groups and the hypothesis of a decreased occurrence and an increased severity in the black child is not valid. Thus the only poor prognostic indicators were presentation in nephrotic syndrome and a low GFR at presentation which conforms with most literature[12,17,31-33,36,37].

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Conclusion and Recommendations

This study was a retrospective review of the records of children that presented to the paediatric renal clinics at the Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Hospital. It hypothesized that IgA and HSP nephropathy occurs in South African black children and disease progression is worse in this group of children. It went on to describe the differences and similarities of South African children when compared to their international counterparts.

This study reviewed incidence, gender, presenting symptoms, treatment and outcomes in South African children. These results were then compared to appropriate international reviews. This study not only reviewed IgA nephropathy but also Henoch-Schonlein Purpura (HSP) nephropathy as it is believed to be a variant of the same pathological process[4,5].

This study reviewed records from the two government referral hospitals (i.e. tertiary hospitals) for Johannesburg with specialised paediatric nephrology services. In order to have sufficient number of children in the study, the study reviewed records up to 23 years old, with differing clinical practices over time and noting that not all the files had recent blood chemistry and creatinine results. The study does, despite the above, give a good picture of the presentation of IgA and HSP nephropathy in children in Johannesburg, South Africa. The study hypothesis; black children have a poorer prognosis than other children with a similar presentation, was disproved.

The clinical significance of these observations will enable doctors in the future to asses which patients are more likely to have IgA or HSP nephropathy. They will also have an

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indication on which children will potentially have a poorer prognosis and require more aggressive treatment and stricter follow up conditions.

Treatment regimes used in these two hospitals differ from those used internationally only in a few aspects. These differences are:

(i) ACE inhibitors were not used as extensively in the study children as literature recommends.

(ii) Intravenous cyclophosphamide infusions was, commonly, used as the immunosuppressive drug of choice for severe disease, followed by steroid therapy without azothioprine (an oral immunosuppressive agent) as recommended in the literature[43].

The recommendations after this study would therefore be:

The use of ACE inhibitors as the first line antihypertensive drug of choice should be recommended, even in children who are normotensive (if the disease is progressive).

The question of whether the use of cyclophosphamide, without a follow up period of azothioprine is effective needs to be evaluated. This study suggests that it is an effective alternative in the short term, but patients were not followed up for long enough to be definitive.

Studies of the reliability of substances such as $ActC_3$ (in adults) could be investigated to evaluate the accuracy at which they predict outcomes in our paediatric population.

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The limitations of this study are as follows:

(i) This was a retrospective study and therefore has certain limitations such as

a. The accuracy of the records that were kept by differing doctors during the study period

b. The differing views of the doctors, despite being overseen by a paediatric nephrologist

c. The poor follow up of children after 2 years, despite having been given follow up dates.

(ii) The grading of each child's biopsy was done based on a report issued by the histologist and not done at the time of the histology report. The grading was done by a single doctor, making it more reliable than it would have been had many doctors been involved, however the grading was not done by the histologist who saw the biopsy. Some details that may have influenced histological grading may have been omitted from the report, causing an inaccurate histological grade to be assigned to the child. This is unlikely, but a possibility.

(iii) The study, when compared to other studies in Asia had a relatively small number of children due to the high incidence of the disease in areas such as Asia.

(iv) There was no set protocol used at either clinic. The decision to use treatment such as immunosuppressant therapy (e.g. Cyclophosphamide) was based on the paediatric nephrologists' interpretation of results and clinical presentation of the individual child.

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(v) Missing data from some files made the collection and analysis of data more difficult.

(vi) There is no international population group that accurately represents the population group seen in South Africa, thus making it difficult and complicated comparing South African and international data. At least now we have some documentation and a basis for ongoing study of IgA and HSP nephropathies in South African children.

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