

https://dspace.org/

An audit of biopsy proven minimal change nephrotic syndrome in children at Chris Hani Baragwanath academic hospital

Parbhoo, Kaajal

2016
http://hdl.handle.net/10539/22312

Downloaded from a DSpace repository. https://dspace.org/

An audit of biopsy proven minimal change nephrotic syndrome in children at Chris Hani Baragwanath Academic Hospital

Dr Kaajal Parbhoo

A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree

Of

Master of Medicine

Johannesburg, 2016

DECLARATION

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



02/11/2016

Dr Kaajal Parbhoo MBBCh (Wits) FCPaed (SA)

DEDICATION

To

My parents who believed in me every step of the way.

ABSTRACT

Objective: To evaluate the clinicopathological features, response to treatment and outcomes in children presenting to Chris Hani Baragwanath Academic Hospital with biopsy proven minimal change nephrotic syndrome.

Methods: A retrospective record review was conducted. Available records of children, between the ages of 1 and 14 years, who had nephrotic syndrome clinically and who were proven to be minimal change nephrotic syndrome on renal biopsy, were studied. Children who presented from January 1996 to December 2010 were included. Their demographics, clinical features on presentation, biopsy results, management and outcomes were studied.

Results: In the 15 year period there were 129 (29% of all NS) children with minimal change nephrotic syndrome. Seventeen patients were excluded because 4 were not biopsied and 13 patients' records could not be traced. The remaining 112 patients were included in the study. Ages ranged from 1 year to 13.6 years with a median age of 3.8 years (IQR 2.6-5.9). There was a male predominance, with 72 males and 40 females (1.8:1). The majority of the children studied were Black African (89.3%). On presentation 68.8% had microscopic haematuria. Although 59.8% had a blood pressure at presentation which was above the 95th centile for gender, height and age, only 33.9% had sustained hypertension. On initial biopsy, 34% were found to have the mesangial hypercellular variant of minimal change disease and 6% had the IgM variant of minimal change disease. Two patients went into spontaneous remission. The remainder, were treated with oral corticosteroids. Of those treated, 58.9% were steroid responsive, 19.6% were steroid resistant and 8.9% were initially responsive but subsequently became steroid resistant. Of the sample, 22.3% were

steroid dependent and 16.1% were frequent relapsers. Second line immunosuppressive therapy was needed in 38 (33.9%) patients. The three second line immunosuppressant agents used were intravenous pulsed cyclophosphamide (28.5%), intravenous pulsed methyl prednisolone (9.8%) and mycophenolate mofetil (MMF) (7.1%). Repeat biopsies were performed on 22 children (19.6%). Four of the 22 repeat biopsies showed focal segmental glomerular sclerosis (FSGS).The average length of follow up was 4.86 years (median 3.58). At the last visit, 75.9% of the study group was in remission. During the course of follow up, 41.1% were admitted to hospital for a suspected bacterial infection. A high proportion of patients were lost to follow up (62%). The mortality rate was 1.8%.

Conclusion: At Chris Hani Baragwanath Academic Hospital, all children with nephrotic syndrome are biopsied prior to initiating steroid therapy due to the high prevalence of tuberculosis infection and poor compliance in our population. This practice has highlighted differences between the children in our population with minimal change disease compared to that reported by the International Study of Kidney Disease in Children (ISKDC). In our study there were a higher proportion of children with initial hypertension and haematuria, and fewer children that responded to steroid therapy. This differs from the ISKDC findings in 1978. Their study had predominantly Caucasian children, and our study had predominantly Black African children. These differences in ethnicity may account for the differences.

ACKNOWLEDGEMENTS

I would like to thank my family, friends and teachers for their unwavering support. I would also like to thank my supervisor Prof Udai K. Kala for his advice, assistance, support and patience.

TABLE OF CONTENTS

DECLARATION II

DEDICATION III

ABSTRACT IV

ACKNOWLEDGEMENTS VI

TABLE OF CONTENTS VII

LIST OF TABLES XII

LIST OF FIGURES XIII

ABBREVIATIONS XIV

CHAPTER 1. LITERATURE REVIEW 1

1.1 Historical Perspective 1

1.2 Definition of nephrotic syndrome 2

1.3 Epidemiology of nephrotic syndrome 2

1.4 Minimal Change Disease 3

1.4.1 Aetiology 3

1.4.2 Presentation 4

1.4.3 Histological findings 4

1.4.4 Treatment 5
1.4.4.1 Symptomatic treatment 5
1.4.4.2 Steroid therapy 7
1.4.5 Complications 8
1.4.5.1 Infections 8
1.4.5.2 Thrombosis 9
1.4.5.3 Dyslipidaemia 9

1.5 Aims and Objectives 9
1.5.1 Aims 9
1.5.2 Objectives 10

CHAPTER 2: METHODS 11

2.1 Study Design 11
2.1.1 Inclusion criteria 11
2.1.2 Exclusion criteria 11

2.2 Ethics 12

2.3 Data collection and analysis 12

2.4 Definitions of outcomes measured 12

CHAPTER 3: RESULTS 15

3.1 Patient characteristics at presentation 15
3.1.1 Study population and demographics 15
3.1.2 Blood pressure at presentation 18

3.1.3 Urinalysis at presentation 18
3.1.4 Blood results on presentation 19
3.1.5 Urine results on presentation 19
3.1.6 HIV and tuberculosis co-morbidity 20

3.2 Renal biopsy results 21
3.2.1 Initial biopsy 21
3.2.2 Repeat biopsies 22

3.3 Treatment 22
3.3.1 Steroid therapy 22
3.3.1.1 Oral corticosteroids 22
3.3.1.2 Intravenous methylprednisolone 23
3.3.2 Adjunctive therapy 23
3.3.2.1 Anti-tuberculosis treatment 23
3.3.2.2 Spironolactone 23
3.3.2.3 Antiplatelet agents 24
3.3.2.4 Lipid lowering agents 24
3.3.2.5 Antihypertensive agents 24
3.3.3 Second line immunosuppressant agents 24

3.4 Outcomes 25
3.4.1 Response to steroid therapy 26
3.4.2 Duration of steroids 26
3.4.3 Relapses 26
3.4.4. Response to Intravenous Cyclophosphamide and MMF 27
3.4.5 Complications 27

3.4.5.1 Admission for Infections 27
3.4.5.2 Chronic Kidney Disease 28
3.4.5.3 Hypertension 28
3.4.5.4 Death 28
3.4.6 Follow up 28

CHAPTER 4: DISCUSSION 30

4.1 Background 30

4.2 Patient characteristics at presentation 31
4.2.1 Demographics 31
4.2.2 Clinical features 32

4.3 Treatment 34
4.3.1 Steroids 34
4.3.2 Other immunosuppressant agents 35
4.3.2.1 Intravenous cyclophosphamide 35
4.3.2.2 Other agents 35

4.4 Biopsy Results and Outcomes 36

CHAPTER 5: CONCLUSION 39

CHAPTER 6: REFERENCE LIST 40

CHAPTER 7: APPENDIX 48

Appendix A: Ethics clearance certificate 48

Appendix B: Data Collection Sheet 49

Appendix C: Turnitin 51

LIST OF TABLES

Table 1: Demographics of patients with MCNS 16

Table 2: Creatinine and estimated GFR 19

Table 3: Biopsy results 21

Table 4 : Repeat biopsy results 22

LIST OF FIGURES

Figure 1: Study Sample 15

Figure 2: Age distribution of children in the study (n=112) 16

Figure 3: Race of patients with minimal change disease (n = 112) 17

Figure 4: Gender of patients with minimal change disease (n=112) 17

Figure 5: Microscopic haematuria on urine dipstick 18

Figure 6: Tuberculin skin test results 20

Figure 7: Flow Chart of outcomes according to histological variants 25

ABBREVIATIONS

ACE	Angiotensin converting enzyme
ACTH	Adrenocorticotropic hormone
C3	Complement component 3
CHBAH	Chris Hani Baragwanath Academic Hospital
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GN	Glomerulonephritis
HIV	Human Immunodeficiency Virus
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
IgA	Immunoglobulin A
IgM	Immunoglobulin M
INS	Idiopathic Nephrotic Syndrome
IQR	Interquartile range
ISKDC	International Study of Kidney Disease in Children
MCD	Minimal change disease
MCNS	Minimal change nephrotic syndrome
MMF	Mycophenolate mofetil
NS	Nephrotic syndrome

CHAPTER 1. LITERATURE REVIEW

1.1 Historical Perspective

Nephrotic syndrome is one of the commonest causes of renal disease in children (1). Proteinuria as a cause of oedema was recognized by Hippocrates over 2000 years ago (2). There were many other descriptions of nephrotic syndrome over the years (2) and in 1929 Henry Christian introduced the term nephrotic syndrome (1). Previously, many patients with nephrotic syndrome developed chronic renal failure or died from infections, but a few improved spontaneously (3). With the introduction of various antibiotics the mortality rate dropped from 48% to 19% (4). With the use of corticosteroids it has dropped further to 9% (5). The ISKDC (International Study of Kidney Disease in Children) reported a mortality rate of 2.5% post corticosteroid era in children with minimal change nephrotic syndrome (6).

Initially, the management of nephrotic syndrome was focused on treating the oedema (4). Mercury containing agents were used as a diuretic (4). These compounds are nephrotoxic and their use was discontinued (3). Later, induction of measles (4) and malaria (5) were used to treat nephrotic syndrome. Infusion of albumin was used to correct the albumin and treat the oedema, and diuretics were used to help control the oedema (7). The use of ACTH therapy and later cortisone significantly improved outcomes in nephrotic syndrome (8, 9).

1.2 Definition of nephrotic syndrome

Nephrotic syndrome is characterized by heavy proteinuria (>40mg/m^2/hour), oedema, hypoalbuminaemia and hyperlipidaemia (1). It is divided into congenital, idiopathic (primary) and secondary nephrotic syndrome (7). Congenital or infantile nephrotic syndrome, presenting before 1year of age, has a poorer prognosis and is caused by certain gene mutations affecting components of the glomerular filtration barrier (10). Secondary nephrotic syndrome is due to an underlying systemic disease such as systemic lupus erythematosus, IgA Nephropathy, HIV associated nephropathy and diabetic nephropathy (7). Idiopathic nephrotic syndrome is the largest group. It includes; minimal change disease (MCD), focal segmental glomerular sclerosis (FSGS) and diffuse mesangial proliferation (10, 11). Some authors consider these 3 different types to be part of the same spectrum of disease, however, other authors feel that they are distinct entities (10). Membranous nephropathy is also included in idiopathic nephrotic syndrome (12). Most patients with idiopathic nephrotic syndrome have minimal change disease (13).

1.3 Epidemiology of nephrotic syndrome

The prevalence of idiopathic nephrotic syndrome is about 16 per 100 000 population (14). The incidence varies amongst different populations and seems to be higher in children of African and Asian descent (15). There is an overall male predominance with a male to female ratio approaching 2:1 in younger children (15). Many studies have shown ethnic differences in histological types and response to treatment (11, 16, 17). Internationally, as reported by the ISKDC in 1978, the majority of children (77%) with primary nephrotic syndrome had minimal change nephrotic syndrome (MCNS). They also found that 93% of

children with MCNS were steroid responsive and, MCNS could be identified by typical clinical features at presentation such as: absence of haematuria or hypertension, age of presentation younger than 6 years but older than 1 year, normal C3 level, and normal renal function, together with responsiveness to steroid therapy. (13) In South Africa, studies have shown that MCNS is not the commonest histological type of nephrotic syndrome in Black African children. However, Indian and Caucasian children from South Africa seem to follow what was described by the ISKCD. (18-20)

1.4 Minimal Change Disease

1.4.1 Aetiology

There has been a lot of research into the underlying cause of idiopathic nephrotic syndrome (INS) in the last few decades. Researchers are looking to identify the underlying cause and thus, facilitate the development of better, targeted therapeutic agents. (21) There are many theories but no one cause has been identified. Some researchers feel there is an immune abnormality related to T cell dysfunction (3). Others suggest that there may be circulating factors that cause injury to the podocytes (21-23). There is also research into genes that code for certain proteins like nephrin and podocin that have been implicated in certain forms of steroid resistant nephrotic syndrome (24).

1.4.2 Presentation

The majority of children with MCNS will present before the age of 6 years (13). They have the typical features of nephrotic syndrome; oedema, proteinuria, hypoalbuminaemia and hyperlipidaemia. They are often intravascularly depleted in the face of severe oedema. (6) These children may have respiratory compromise secondary to pleural effusions or pulmonary oedema. Some children may have complications such as venous thrombosis or severe sepsis at presentation. (12) According to the ISKDC, in children with MCNS, only 23% have haematuria at presentation and 21% have a high blood pressure at presentation (13). In a previous study from Johannesburg it was found that 84% of children with MCNS had microscopic haematuria at presentation and 13.4% had hypertension (25). Children with MCNS generally have normal renal function or mild pre-renal dysfunction. They also have high cholesterol and triglyceride levels, which generally resolves once the child is in remission. (26)

1.4.3 Histological findings

In the majority of children with MCD there are normal glomeruli with no abnormalities on light microscopy and foot process effacement on electron microscopy (27). Some patients may have mild mesangial hypercellularity which is regarded as a variant of MCD (28). Some studies report that this variant may have a poorer prognosis but others have failed to confirm this (27, 28). IgM nephropathy is another variant of MCD with mesangial IgM deposits associated with either minimal change or mesangial hypercellularity. This variant has been shown to have a poorer prognosis and a higher rate of steroid dependence and steroid resistance when associated with mesangial hypercellularity. MCNS with IgM

deposits and no mesangial hypercellularity, has been shown to behave the same as minimal change disease.(29-31) Some authors argue that these are separate entities and not variants of MCD due to the differences in presentation and outcome (27, 32)

1.4.4 Treatment

Based on the results from the ISKDC, the current recommendations (33) are that in children with nephrotic syndrome, once secondary causes have been ruled out (by detailed history, examination and blood results) and the presentation is typical of MCD (no haematuria, normal blood pressure, normal C3 and age between 1 and 6 years (13)), then a trial of steroids should be started with no need for a renal biopsy. If the patient responds to steroids and does not have frequent relapses then they are presumed to have MCD (6) and treatment and follow up are continued as such.

1.4.4.1 Symptomatic treatment

A low salt diet and mild fluid restriction may be used to manage the oedema (26). Protein intake should be slightly higher than age recommendations (10) with less saturated fat (26, 34). Some children with MCD may need diuretic therapy to treat the oedema if it is severe, and albumin to treat the hypovolaemia (34). However, routine use of diuretics and albumin is not recommended due to the potential complications such as intravascular volume depletion, worsening renal function and electrolyte abnormalities with diuretics and congestive cardiac failure with albumin. (14, 26)

Dyslipidaemia does not require routine treatment as the levels return to normal once the child is in remission (26). However, in children with steroid resistant disease, the risk of atherosclerosis is increased and warrants dietary modifications and lipid lowering therapies such as HMG-CoA reductase inhibitors (14).

Maintenance of normal intravascular volume, avoidance of bed rest and early recognition and management of infections are necessary to prevent the formation of thrombi (10). Routine use of anticoagulants for primary prophylaxis is not recommended (26, 34). Some authors suggest antiplatelet agents such as low dose aspirin may be useful in patients with steroid resistant nephrotic syndrome or underlying hypercoagulable states (14).

Antihypertensive agents, such as calcium channel blockers or β adrenergic antagonists can be used to manage high blood pressure (34). For chronic hypertension however, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers are preferred as they also decrease proteinuria (14, 26).

Infections need to be treated early as they are an important contributor to morbidity (26). Antibiotics used should cover Streptococcus pneumoniae and gram negative organisms until culture results are available as these are the most commonly identified bacterial causes of sepsis (26, 34). There is no good evidence for prophylactic penicillin use (14) but some authors feel that there is still a place for prophylaxis due to the overwhelming number or infections caused by Streptococcus pneumoniae (26). Routine administration of the Influenza virus vaccine, the Varicella zoster virus vaccine and the Pneumococcal vaccine is important to prevent infections (26). In developing countries tuberculosis is an important

consideration as the rate of pulmonary tuberculosis is higher in children with nephrotic syndrome (35). Current recommendations from India state that children without evidence of tuberculosis and a positive Mantoux test should get 6 months of isoniazid therapy and those with evidence of active disease should be treated with standard regimens (34).

1.4.4.2 Steroid therapy

Initially, before corticosteroids became available, ACTH therapy was used to treat nephrotic syndrome and it improved outcomes in these patients (8). Corticosteroids were later introduced and they were thought to suppress an immune mediated process that was damaging the glomerular filtration barrier (24). Recent studies have shown that steroids actually affect podocyte function directly (3, 21, 24).

Based on the ISKDC recommendations, subsequent studies done by the Arbeitsgemeinschaft fur Padiatrische and various Cochrane reviews, the current recommended schedule is 2mg/kg/day (maximum 60mg) of prednisone for 4 - 6 weeks followed by 1.5mg/kg (maximum 40mg) every alternate day with weaning of the dose over 2 to 5 months.(14, 33, 36)

Based on the regimen suggested by Mendoza for the treatment of steroid resistant nephrotic syndrome due to FSGS (37), pulsed intravenous methyl prednisolone has been used together with intravenous cyclophosphamide to induce remission in steroid resistant

nephrotic syndrome with MCD, as well (38). The KDIGO guidelines however state that cyclophosphamide can be used in frequently relapsing and steroid dependent nephrotic syndrome(39), however, based on a Cochrane review of a few small randomized control trials, they recommend that cyclophosphamide not be used in steroid resistant nephrotic syndrome(40) as one study showed that cyclosporine achieved remission in more patients than cyclophosphamide and two studies showed that it was no more effective than steroids alone. These studies were all reported as having low or very low quality evidence due to various reasons, one of them being small numbers. (41)

1.4.5 Complications

Complications of nephrotic syndrome are well documented (1, 10, 12). They are divided into complications of the disease and complications of treatment. Some complications are caused by both the disease process and the treatment.

1.4.5.1 Infections

Children with nephrotic syndrome are predisposed to infections because of the disease itself and the various treatment modalities that affect the immune system. The commonest infections are peritonitis, cellulitis, pneumonia and urinary tract infections. (14, 26, 34) Respiratory tract infections, which are usually viral, and urinary tract infections are the commonest infections which trigger a relapse (42). Prompt treatment of infections and appropriate adjustment of steroid therapy is necessary during these episodes (36, 42).

1.4.5.2 Thrombosis

There is an increased incidence of venous and rarely arterial thrombosis in children with nephrotic syndrome (14, 26). There are multiple reasons why children with nephrotic syndrome are at increased risk for development of thrombi. Hypovolaemia and increased blood viscosity, hyperlipidaemia, immobility, loss of anticoagulant proteins and side effects of the medication all contribute to the risk of thrombosis formation. (12, 26)

1.4.5.3 Dyslipidaemia

At presentation children with nephrotic syndrome have raised cholesterol and triglyceride levels. This improves without treatment once they go into remission. (26) Children with steroid resistant nephrotic syndrome have persistent dyslipidaemia and may need HMG CoA reductase inhibitors to treat the dyslipidaemia (14).

1.5 Aims and Objectives

1.5.1 Aims

To determine the profile of paediatric patients presenting to Chris Hani Baragwanath Academic Hospital with Minimal Change Nephrotic Syndrome over a 15 year period.

1.5.2 Objectives

a. To determine the percentage of children presenting with nephrotic syndrome who have minimal change disease on renal biopsy.
b. To describe the demographics of children with minimal change disease.
c. To determine the rate of response to steroid therapy, dependence on steroid therapy and the need for additional immunosuppressive therapy.
d. To ascertain whether there is an association between variants on light microscopy and immunofluorescence staining (mesangial hypercellular variant and IgM nephropathy) and failure to respond to steroid therapy.
e. To determine the rate of focal segmental glomerulosclerosis on repeat biopsy.
f. To determine the length of follow up and the outcome of these patients.

CHAPTER 2: METHODS

2.1 Study Design

A retrospective record review was conducted. Records of patients who presented to the Nephrology Unit at Chris Hani Baragwanath Academic Hospital between January 1996 and December 2010 were analysed. Data was collected from the Nephrology Clinic files and some missing data was collected from inpatient files and laboratory records.

2.1.1 Inclusion criteria

All children aged 1 year to 14 years presenting to Chris Hani Baragwanath Academic hospital with nephrotic syndrome who were proven to have minimal change disease on biopsy were included.

2.1.2 Exclusion criteria

Patients with suspected nephrotic syndrome who did not consent to biopsy or those who were not biopsied for other reasons were excluded. Those with inadequate biopsies were also excluded.

2.2 Ethics

The University of the Witwatersrand Ethics Committee granted ethics approval unconditionally at a meeting on 4th May 2012 (clearance certificate M120468 – Appendix A). All patients were allocated a study number and their names and hospital numbers were not recorded on the data collection sheet.

2.3 Data collection and analysis

Data was collected manually on the data collection sheet and then captured into Microsoft Excel (see Appendix B for data collection sheet). All descriptive statistics such as means, medians, frequencies, percentages as well as standard deviations and interquartile ranges were obtained using Microsoft Excel. Graphs such as pie charts, frequency distribution tables were drawn in Microsoft Excel. The remaining statistical analysis was done using Statistica. Chi-squared, Fisher exact and ANOVA tests were used to determine significance. Statistical significance was measured at a level of 5% (p-value<0.05).

2.4 Definitions of outcomes measured

High blood pressure on presentation was determined using age, gender and length or height centiles according to charts published in the fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents from 2004 (43). A blood pressure above the 95th centile was assessed as high.

Haematuria was regarded as significant if there was 1+ or more red blood cells detected on urine dipstick. This was based on recommendations of significant microscopic haematuria from a British research group. Formal urine microscopy is more reliable than urine dipstick findings. (44) However, the results of formal urine microscopy, to assess number of red blood cells per high power field, red cell morphology and the presence of casts, was not available on most patients and thus not included in the study.

The glomerular filtration rate (GFR) was calculated using the modified Schwartz bedside calculation (GFR = 0.413 x height (cm) / serum creatinine (mg/dl) or GFR = 36.5 x height (cm) / serum creatinine (µmol/l)) (45, 46)

Response to treatment was defined as follows: (6)

- **Remission** – trace or 1+ protein on urine dipstick for 3 consecutive days with resolution of oedema
- **Responded** – went into remission within 8 weeks of daily, high dose steroid therapy
- **Resistant (non-responder)** – not in remission after 8 weeks of high dose steroid therapy
- **Initially responsive then resistant (late non-responder)** – initially went into remission within 8 weeks but later relapsed and did not respond to steroids

Outcomes were defined as follows: (6, 33)

- **Steroid sensitive nephrotic syndrome:** responds to corticosteroids by achieving complete remission.
- **Frequent relapsing nephrotic syndrome:** has 2 or more relapses in the first 6 months or 4 or more relapses in a 12 month period

- **Steroid dependent:** responded to treatment but relapses on weaning steroids or within 2 weeks of stopping steroids.
- **Transfer to adults:** once patients were older than 14years they were eligible for transfer to adult nephrology services.
- **Death**: The patient demised during follow up.
- **Loss to follow up**: patients who did not return for follow up at any point in the course of follow up

CHAPTER 3: RESULTS

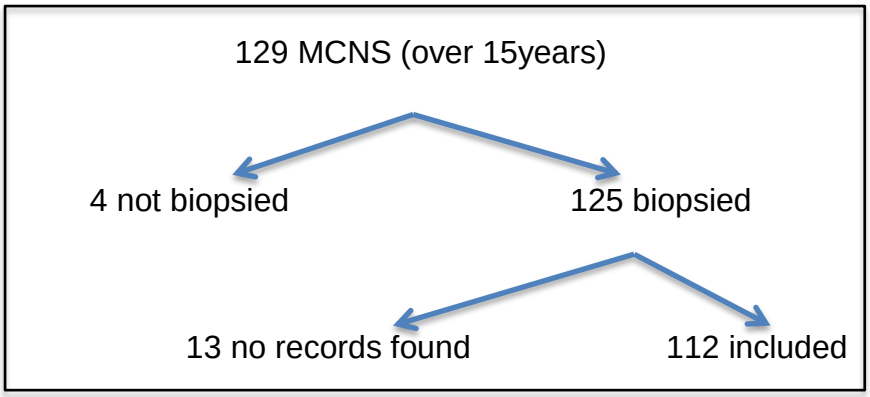
3.1 Patient characteristics at presentation

3.1.1 Study population and demographics

The study included patients that presented to the Paediatric Nephrology Unit from January 1996 to December 2010. Only patients with biopsy proven minimal change disease were included.

During this 15 year period there were a total of 440 children with idiopathic nephrotic syndrome. Of these 129 (29%) patients had minimal change nephrotic syndrome, 4 of these patients were not biopsied and 13 patients' records could not be traced. The remaining 112 patients were included.

Figure 1: Study Sample



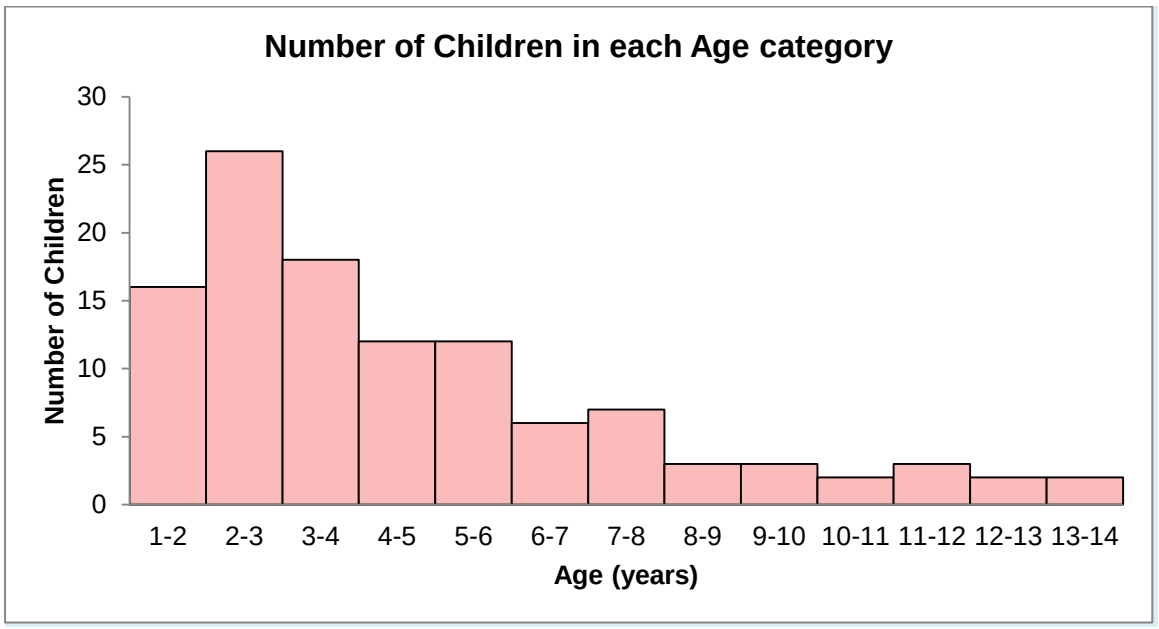
The table below shows the demographics of the patients included in the study.

Table 1: Demographics of patients with MCNS

Total Number	112
Age - range (years)	1 to 13.6
- median (IQR)	3.8 (2.6 to 5.9)
Gender - Males	72 (64.3%)
- Females	40 (35.7%)
Race - Black African	100 (89.3%)
- Caucasian	3 (2.7%)
- Mixed Race (Coloured)	4 (3.6%)
- Indian	5 (4.5%)

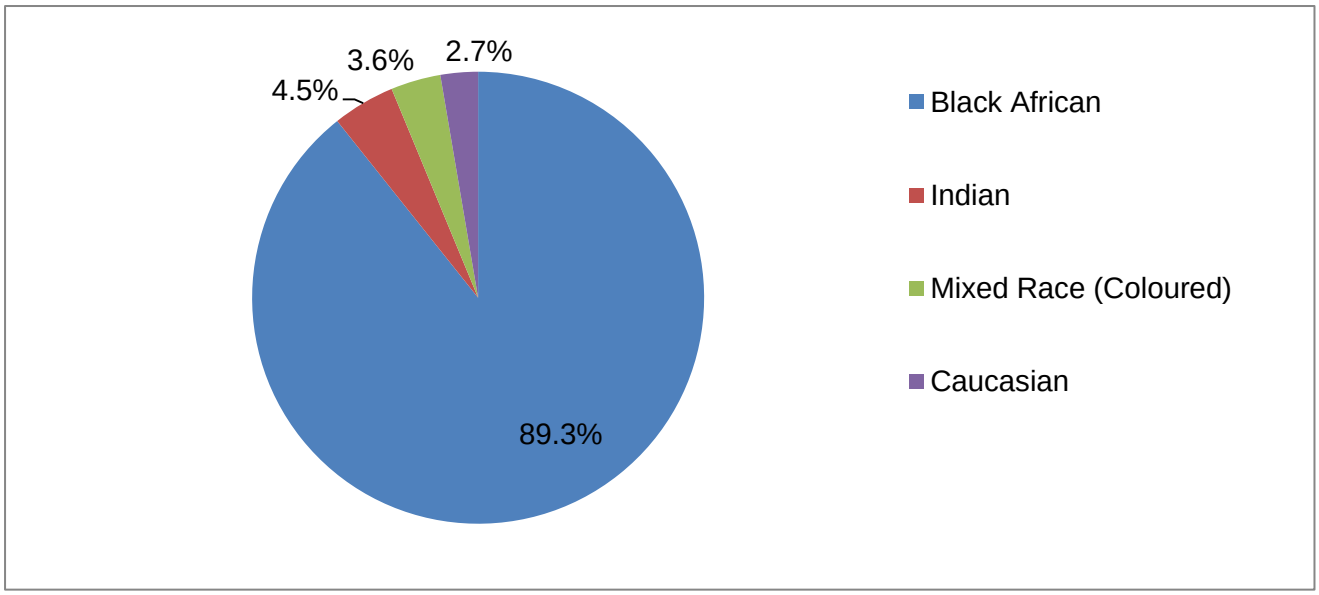
The age of patients ranged from 1 year to 13.6 years with and interquartile range of 2.6 to 5.9 years. The figure below shows the age distribution of the study sample.

Figure 2: Age distribution of children in the study (n=112)



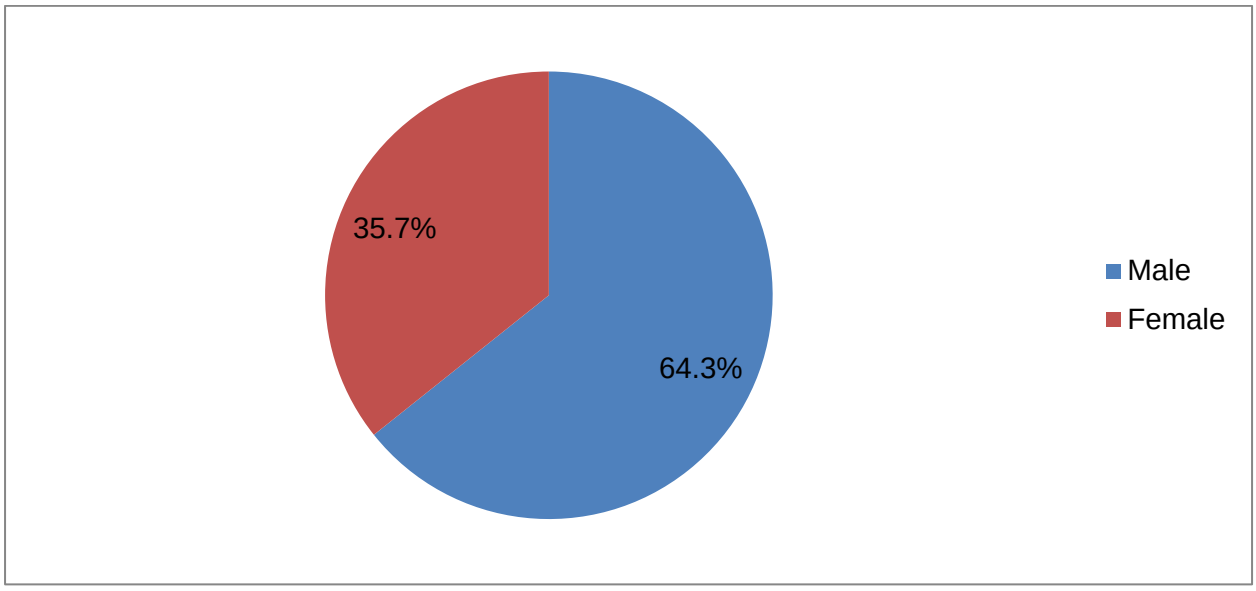
The majority of the patients that present to CHBAH are Black African. A small number of Caucasian, Indian and Mixed Race (Coloured) patients also presented to the unit.

Figure 3: Race of patients with minimal change disease (n = 112)



There was a male predominance with a male : female ratio of 1.8:1.

Figure 4: Gender of patients with minimal change disease (n=112)



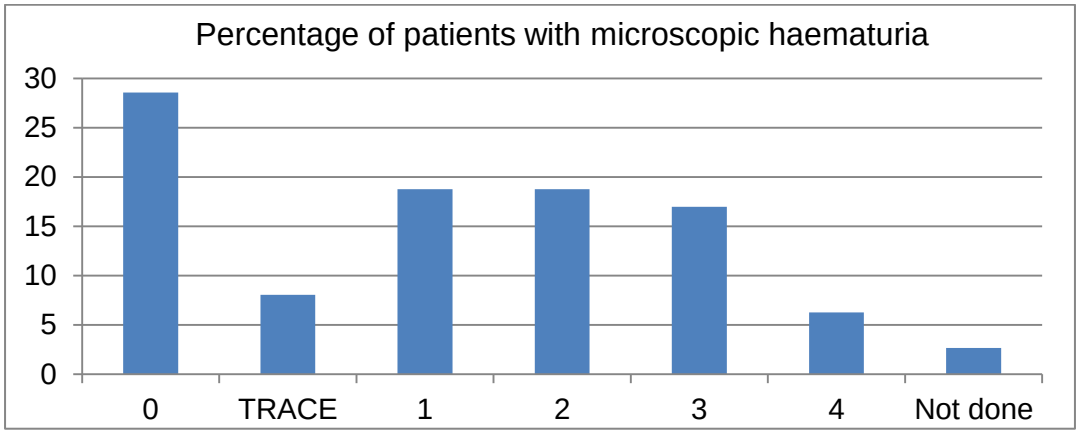
3.1.2 Blood pressure at presentation

The mean systolic blood pressure was 108mmHg (standard deviation = 15mmHg). At presentation 59.8% (67) had a high blood pressure (either systolic or diastolic that was above the 95th centile for gender, age and height). On follow up only 38 patients (33.9%) had hypertension and needed treatment. There was no significant association between blood pressure at presentation and biopsy results (p=0.17), response to treatment (p=0.25) or number of relapses (p=0.53).

3.1.3 Urinalysis at presentation

Urine dipstick analysis was performed on all patients at presentation. In 3 patients the result was not documented. Of the rest, 68.8% had 1+ or more haematuria on dipstick. When evaluating the association between haematuria and minimal change variants on biopsy there was no significant difference (p=0.69). There was also no significant association between haematuria at presentation and response to steroids (p=0.79) or number of relapses (p=0.86).

Figure 5: Microscopic haematuria on urine dipstick



3.1.4 Blood results on presentation

Serum cholesterol, albumin, urea and creatinine on presentation were analyzed. The cholesterol levels were very high with a median of 11mmol/l (IQR 8.4 – 13.4). Eighty-eight percent of the study sample had a total cholesterol level above 6.4mmol/l(250mg/dl) at presentation. The urea levels were closer to the upper limit of normal with a median of 4.2mmol/l (IQR 2.8 – 5.6). The creatinine levels however were mostly normal with a normal estimated GFR as demonstrated in the table below.

Table 2: Creatinine and estimated GFR

	Median	**Interquartile Range**
Creatinine(µmol/l)	34	27 – 44
GFR (ml/min/1.73m^2)	105	87 – 145

3.1.5 Urine results on presentation

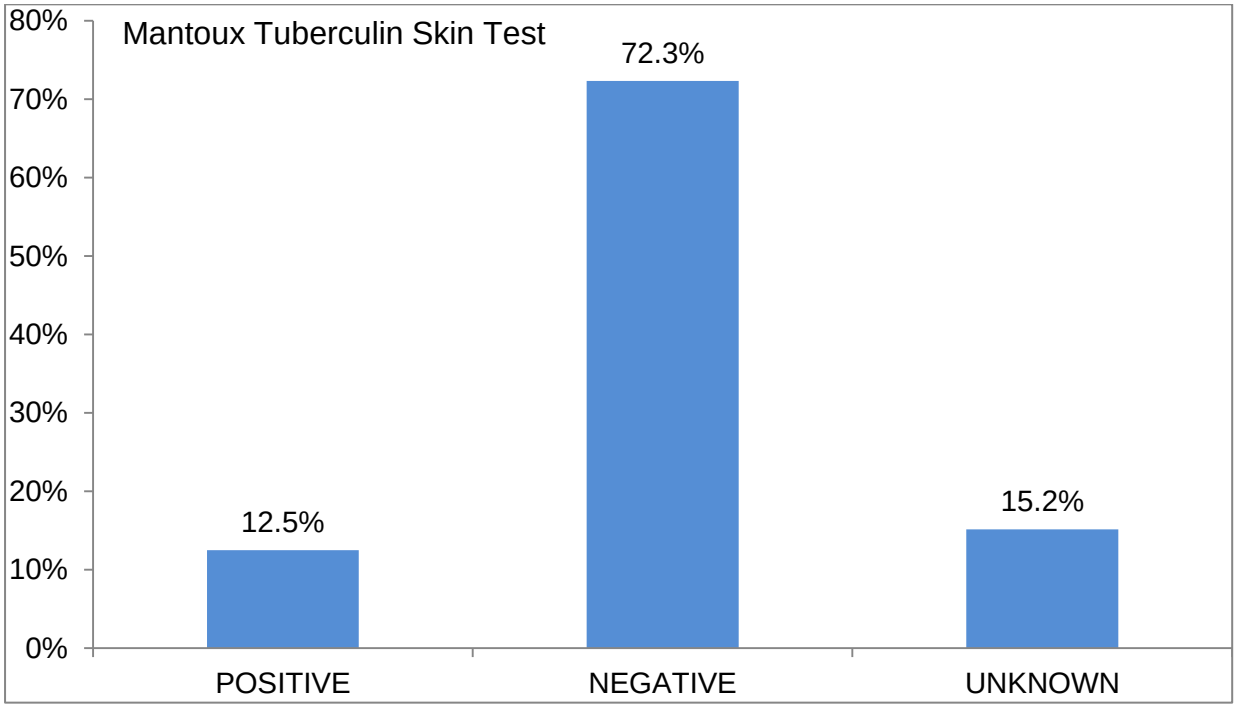
Only a spot urine specimen was sent for urine analysis. A protein : creatinine ratio was done on these specimens. The median was 1.04 g/mmol (IQR 0.64–1.73). Twenty-four hour urine specimens were not sent, therefore urine protein losses could not be quantified in terms of grams/day.

3.1.6 HIV and tuberculosis co-morbidity

From the patients included in the study, 78.6% were HIV negative. The remaining 21.4% did not have a documented HIV results. There were no known HIV infected children in this study.

Fourteen patients had a positive Mantoux tuberculin skin test. Of the remainder, 17 did not have a tuberculin skin test result documented and the rest (81) had no reaction or a reaction smaller than the recommended cut off. Anti-tuberculosis treatment was started on 25 patients (22.3%).

Figure 6: Tuberculin skin test results



3.2 Renal biopsy results

3.2.1 Initial biopsy

All the patients were biopsied at presentation. In one patient, the initial biopsy was inadequate and a repeat was done a few weeks later. All specimens were sent for light microscopy, immunofluorescence staining and scanning electron microscopy. Of the 112 patients, 54% (61) did not have electron microscopy performed because the pathologist felt the light microscopy and immunofluorescence were conclusive.

The results of the initial biopsies are shown in the table below. Just under half of the patients had a variant of minimal change disease. The commonest variant was the mesangial hypercellular variant. There were only 7 patients with IgM nephropathy.

Table 3: Biopsy results

Initial Biopsy (112)	Number	Percentage
Minimal Change	67	60%
Mesangial hypercellular variant	38	34%
IgM nephropathy	7	6%

3.2.2 Repeat biopsies

Repeat biopsies were performed in 22 children. Eighteen of the 22 had either steroid resistant, steroid dependent or frequently relapsing nephrotic syndrome. The other 4 did not fit any of the above definitions but were difficult to wean off steroid therapy. There was no difference in the median length of initial steroid therapy between the initial cohort and those requiring repeat biopsies. The results of the repeat biopsies are shown in the table below. Only 4 patients with repeat biopsies showed progression to FSGS.

Table 4 : Repeat biopsy results

Repeat (22)	Number	Percentage
Minimal Change	10	45.4%
Mesangial hypercellular variant	8	36.4%
FSGS	4	18.2%

3.3 Treatment

3.3.1 Steroid therapy

3.3.1.1 Oral corticosteroids

Oral corticosteroid therapy was commenced once the biopsy results were obtained in 98% (110) of the patients. The remaining 2 patients had gone into spontaneous remission prior

to the initiation of steroids. The initial dose of oral prednisone used was 2mg/kg/day as a daily dose up to a maximum of 60mg per day. The median duration of daily high dose oral corticosteroids was 8 weeks (IQR 4 – 12). Once the patient was in the remission the dose was weaned to an alternate day dose.

3.3.1.2 Intravenous methylprednisolone

In 9 patients, high dose, pulsed, alternate day intravenous methylprednisolone was used to induce remission in steroid resistant nephrotic syndrome. In 8 of these patients it was followed by intravenous pulsed cyclophosphamide therapy.

3.3.2 Adjunctive therapy

3.3.2.1 Anti-tuberculosis treatment

Treatment for pulmonary tuberculosis was started in 25 patients based on symptoms together with either chest X-ray findings or tuberculin skin test results.

3.3.2.2 Spironolactone

Most patients (83%) were started on spironolactone therapy. Spironolactone therapy is used by our renal unit for its diuretic effects and for its effect on preventing renin driven sodium and water retention.

3.3.2.3 Antiplatelet agents

Antiplatelet agents such as aspirin or dipyridamole were used in 93 (83%) patients for primary prevention of thromboembolic complications. Initially dipyridamole was preferred.

3.3.2.4 Lipid lowering agents

Statins were used in 26 patients (23%). Of the 26 children that were started on lipid lowering agents, 11 were either steroid resistant, steroid dependent or frequent relapsers.

3.3.2.5 Antihypertensive agents

ACE Inhibitors were used in 45 (40%) patients. It was used to treat hypertension and to decrease proteinuria in steroid resistant patients.

3.3.3 Second line immunosuppressant agents

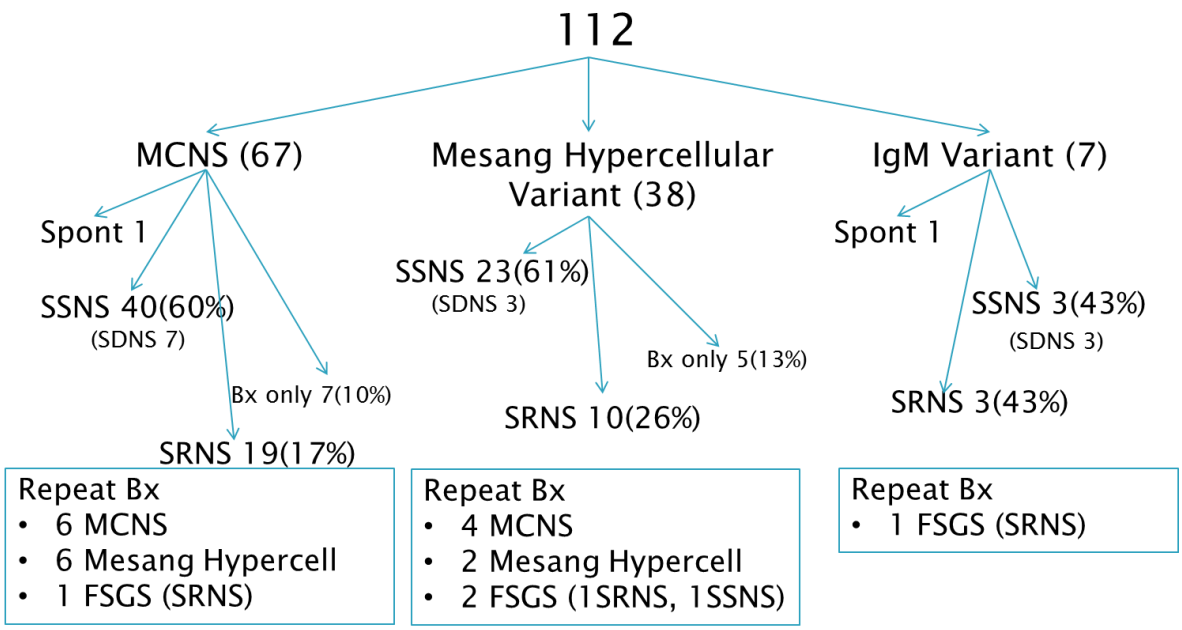
During the study period only 2 second line agents were used. A total of 34 patients required a second line agent. Twenty of the 34 were resistant to steroid therapy, 11 were steroid dependent and/or frequent relapsers. The remaining 3 patients were labelled as either steroid dependent or frequent relapsers, but did not fit the definition per se. In 32 patients, a pulsed, monthly dose (500mg/m^2/dose) of intravenous cyclophosphamide was used for 6 months. In 6 of those 32 patients mycophenolate mofetil (MMF) was added if they did not respond to the oral corticosteroids and intravenous cyclophosphamide. In 2 patients MMF was used alone as a second line immunosuppressant agent. In our unit intravenous

cyclophosphamide is preferred to oral cyclophosphamide as compliance is a problem in our patient population. A monthly intravenous dose, results in better compliance, and we have noted minimal side effects.

3.4 Outcomes

The flow diagram below shows the outcomes according to biopsy results.

Figure 7: Flow Chart of outcomes according to histological variants



Spont – went into spontaneous remission

SSNS – Steroid sensitive nephrotic syndrome

SRNS – Steroid resistant nephrotic syndrome

Bx only – only initial presentation and biopsy results are available (there is no follow up data)

There was no significant difference in the response to steroid treatment, between the minimal change group and the mesangial hypercellular variant group (p=0.62). The IgM

nephropathy variant had a poorer response to treatment with 43% being steroid resistant but this difference is not statistically significant (p=0.67), possibly, due to the small number in that subset.

3.4.1 Response to steroid therapy

Seventy-six patients (67.8%) initially responded to steroids, 10 of the 76 later became steroid resistant. Twenty-two patients (19.6%) were resistant to steroids initially. Two percent went into spontaneous remission. The remainder defaulted follow up and their initial response to steroid therapy is unknown. There were 25 patients (22.3%) that had steroid dependent nephrotic syndrome. On follow up 16 of the 25 remained steroid dependent at their last visit. Overall at the end of follow up, 59% of patients had steroid sensitive nephrotic syndrome and 28.5% of patients had steroid resistant nephrotic syndrome.

3.4.2 Duration of steroids

The median duration of steroid treatment was 8 weeks with an interquartile range of 4 to 12 weeks. There was a significant association between a shorter duration of initial steroid therapy and developing frequently relapsing nephrotic syndrome (p=0.021)

3.4.3 Relapses

Of the 112 patients in the study, 64 had at least 1 relapse. The median number of relapses was 1. The highest number of relapses was 18 in 1 child. Overall, 18 patients (16%) had frequently relapsing nephrotic syndrome.

3.4.4. Response to Intravenous Cyclophosphamide and MMF

Of the 32 patients treated with cyclophosphamide, 23 responded and went into remission. Eleven of the twenty-three continued to have multiple relapses and some remained steroid-dependent. Only 9 patients (28%) did not respond to cyclophosphamide. Six of these nine patients had repeat biopsies done. Two showed FSGS, one showed mesangial hypercellular variant, one showed IgM nephropathy with mesangial hypercellularity and two showed minimal change only.

Of the 8 patients treated with MMF, 6 had steroid resistant nephrotic syndrome and 2 had steroid dependent nephrotic syndrome. Only 2 of the 6 patients with steroid resistant nephrotic syndrome went into remission.

3.4.5 Complications

3.4.5.1 Admission for Infections

During the course of follow up, 46 (41%) patients required admission for treatment of a suspected bacterial infection. These infections included peritonitis, pneumonia, septicaemia and urinary tract infections. Two of these patients died during their admission from sepsis related complications. These were the only 2 known deaths that occurred in the study population.

3.4.5.2 Chronic Kidney Disease

Three patients developed chronic kidney disease during follow-up. Two of these patients had steroid resistant nephrotic syndrome but repeat biopsies were not done. The third patient had a repeat biopsy, due to steroid resistance, which showed FSGS.

3.4.5.3 Hypertension

As mentioned before 34 % of the patients had hypertension requiring treatment.

3.4.5.4 Death

There were 2 known deaths in the study population. The one had IgM nephropathy and was a frequent relapser. He died 5years and 4 months after presentation. At the time of his death he was admitted for streptococcal septicaemia. The second child also died from sepsis. She was steroid resistant and had developed renal failure. She died a year and 2 months after presentation.

3.4.6 Follow up

The median duration of follow up was 3.6 years (IQR 0.7 to 7.7 years). There was a 62% (69) loss to follow up. Thirty-two of the 69 patients (29% of the total) defaulted within the first year, of those 12 (11% of the total) were started on steroids but never returned after the biopsy. Seven patients were transferred to the adult nephrology services and 4 patients

were transferred to other hospitals. The remaining 40 patients still attend the Paediatric Nephrology Clinic at CHBAH.

CHAPTER 4: DISCUSSION

4.1 Background

Idiopathic nephrotic syndrome is the commonest form of nephrotic syndrome in children (12). The majority of children with idiopathic NS have minimal change disease on biopsy and most children with MCD have a favourable response to steroid therapy (3, 13). Congenital or infantile nephrotic syndrome is usually genetic in origin (10) and thus children under the age of 1 year were excluded from this study.

The present study differs from other studies as only patients with biopsy proven minimal change nephrotic syndrome were included. Most recent studies on nephrotic syndrome in children, either study idiopathic nephrotic syndrome in general, steroid sensitive nephrotic syndrome (presumed to be MCD) or steroid resistant nephrotic syndrome (15-17, 47-50). International practice, based on current recommendations, is not to routinely biopsy children who are steroid sensitive, with typical features of MCD. (33, 47) The current practice at Chris Hani Baragwanath Academic hospital is to biopsy all children presenting with nephrotic syndrome prior to the initiation of treatment due to the high prevalence of tuberculosis, poor compliance and higher rates of steroid resistance. This puts us in a unique position. We are able to describe MCD in our population and see how it differs from the population group described by the ISKDC study (13). It does, however, make the comparison between our findings and recent literature very difficult.

In a predominantly Caucasian and Asian population, the internationally reported proportion of children with nephrotic syndrome who have MCD is 77% (13). However in a mixed

population with more African-American and Hispanic patients the proportion is much lower (55% presumed and biopsy proven) (11). Even in a European population from Croatia, the proportion of children with nephrotic syndrome, who had presumed or biopsy proven MCD was 53.5% (49). In the period studied (1996 – 2010), MCD only made up 29% (129/440) of all children presenting to Chris Hani Baragwanath Academic hospital with nephrotic syndrome. This hospital was the only hospital serving Soweto and its' surrounding regions at the time of the study with the majority of the patients seen coming from this area. It is also a referral hospital to other level 1 and 2 hospitals in the southwestern parts of Gauteng and to the entire North West province. Thus there may be a slight selection bias but not enough to explain the massive difference in the proportion of children with nephrotic syndrome that have MCD. This difference may be a result of the difference in the ethnicity, and thus the genetics, between the children studied by the ISKDC study (Caucasian and Asian predominantly) (13) and our population (predominantly Black African) (11, 16, 17).

4.2 Patient characteristics at presentation

4.2.1 Demographics

Our study population was predominantly African (89%) with just over 10% being made up of a combination of Caucasian, Indian and Mixed Race (Coloured) children. This is different to the population studied by the ISKDC group. Their population was predominantly Caucasian and Asian (13). Many authors have reported that ethnicity has an impact on the proportion of children with idiopathic nephrotic syndrome who have minimal change disease and their response to steroid therapy. (11, 16-18, 20, 50) This difference may explain the difference

in response to steroids and the higher percentage of steroid resistance and dependence seen in our population.

Most studies have shown a clear male predominance in children with nephrotic syndrome (15-17, 20, 50). The male to female ratio in this study is 1.8:1 which is in keeping with that reported for children with minimal change disease by the ISKDC study (1.9:1) (13).

The median age of children in this study is 3.8years (IQR 2.6 to 6years). This is similar to the figure reported by ISKDC study of 79% of children with MCNS presenting under the age of 6 years(13).

4.2.2 Clinical features

Based on published data from the ISKDC, certain clinical features are thought to be predictive of MCNS. These are: age of presentation after 1 year but before 6 years of age, absence of haematuria, normal C3, normal blood pressure and being steroid responsive. (6, 13) In our study a high percentage (68.8%) of children presented with microscopic haematuria on urine dipstick. This is much higher than that reported in children with MCNS by the ISKDC group (23%) (13) but in keeping with a previous study done at the same hospital (25). Our study also showed a much higher percentage of children with a high blood pressure at presentation (59.8%) compared to the ISKDC population (20.7%) (13). This finding is not in keeping with a previous study from this same population group that reported a much lower percentage (13%) (25). This discrepancy is difficult to explain and is an area that needs to be investigated further. There is however a study from Germany that reports 95% of children with MCNS had a high blood pressure at presentation. The same

study also reported that only 19% remain hypertensive once in remission. (51) In our study, 33.9% of patients were reported to be hypertensive on follow up. A review by Gipson et al reported that hypertension occurred in 13 to 51% of children with idiopathic nephrotic syndrome (14).

Blood results on presentation showed a serum cholesterol level above 6.4mmol/l in 88% of patients. This is in keeping with the definition of nephrotic syndrome (1) and slightly lower than ISKDC report that 95% of children had a cholesterol level above 250mg/dl (6.4mmol/l) (13). Only 23% of patients needed a lipid lowering agent due to persistently high cholesterol levels. The American Association of Pediatrics recommends a low fat diet and treatment with a lipid lowering agent if the fasting LDL cholesterol is greater than 4.1mmol/l (26). Others recommend treatment with HMG CoA reductase inhibitors in children with steroid resistant nephrotic syndrome and persistent dyslipidaemia (14).

Creatinine values and calculated GFR were normal in our study but urea values were mildly elevated suggesting mild intravascular volume depletion which can be present in children with nephrotic syndrome (26).

The prevalence of HIV and tuberculosis is very high in Sub-Saharan Africa (52). In our study 22.3% of children with MCNS were started on treatment for tuberculosis. This is higher than the percentage of children with MCNS and tuberculosis reported in a previous study from Soweto (35). Gulati et al reported that 9%(28/300) of children with nephrotic syndrome had tuberculosis in their study (53). Due to the high HIV prevalence, the incidence of tuberculosis has increased in both HIV infected and uninfected individuals (52). There were no known HIV infected individuals in this study. A study from India showed that

MCNS does occur in HIV infected individuals as well, and not all proteinuria in HIV infected individuals is due to HIV-associated nephropathy. They had 1 patient, out of 27 adult patients with renal dysfunction or nephrotic range proteinuria that had biopsy proven MCD. (54)

4.3 Treatment

4.3.1 Steroids

Oral corticosteroid therapy (prednisone) was used at an initial dose of 2mg/kg/day up to a maximum of 60mg/day in 98% of patients. This dose is in keeping with international recommendations (33). The median initial duration of high dose steroids was 8 weeks with an interquartile range of 4 to 12 weeks after which steroids were weaned over a variable period. The KDIGO guidelines suggest 4 to 6 weeks of high dose steroids followed by alternate day steroids to be tapered over 2 to 5 months (33). This is similar to what is practiced elsewhere, except some use a shorter tapering period of 6 weeks (3, 14) based on the modified ISKDC regimen. A 2015 Cochrane Review on steroids therapy for nephrotic syndrome in children found that 3 newer well designed studies did not show any benefit from using a total of 5 to 6 months of steroid therapy versus a shorter 3 month course even though previous studies had shown that a longer course decreased the risk of relapses. In our study we found a significant association with shorter duration of steroids and the development of frequently relapsing nephrotic syndrome. This is in keeping with older studies and contrary to the findings of the Cochrane review published in 2015. The reason for this difference is unclear but it may be due to the difference in response to steroids in a different ethnic population. They also recommended using steroids during episodes of viral

illnesses to decrease the risk of relapse in children with frequently relapsing nephrotic syndrome instead of a longer duration of initial steroids. (55)

4.3.2 Other immunosuppressant agents

4.3.2.1 Intravenous cyclophosphamide

In our study there was a good response to monthly pulsed intravenous cyclophosphamide. Most patients who were previously resistant went into remission. The ISKDC reported on the efficacy of oral cyclophosphamide (56) in frequently relapsing nephrotic syndrome. A recent review reports that cyclophosphamide is still commonly used in frequently relapsing and steroid dependent nephrotic syndrome as a steroid sparing agent (36). Pulse intravenous cyclophosphamide is reported to be more effective than oral cyclophosphamide with fewer side effects in steroid resistant minimal change nephrotic syndrome (57).

4.3.2.2 Other agents

The only other agent used was oral MMF. Other centers are currently using calcineurin inhibitors like tacrolimus and rituximab, a monoclonal anti-CD20 antibody, as initial second line therapy and have shown better remission rates with them, but both these drugs are not easily available in our setting (36, 58).

4.4 Biopsy Results and Outcomes

Biopsy results showed that 34% had mesangial hypercellular variant of MCD and 6% had IgM nephropathy. These were the only 2 variants reported on in our study, and thus the only 2 variants that were analysed. The ISKDC divided minimal change disease into 6 histological subtypes, based on light microscopy. There was a significant difference in initial response to steroids between the “nil” disease, mild mesangial hypercellularity and diffuse mesangial hypercellularity but no difference in long term response to steroids at 2 years. (28) In this study there was no significant difference in the proportion of children with steroid sensitive nephrotic syndrome between the children with the mesangial hypercellular variant and those with just MCD (“nil” disease). Two further variants based on immunofluorescence, IgM nephropathy and C1q nephropathy, were initially thought to have a poorer prognosis than immunofluorescence-negative MCD, however, a recent study has shown that there is no difference in outcomes in their group of patients. (31) Both C1q and IgM nephropathy have been reported in a broad spectrum of glomerular diseases. (29, 31) In our study no patients were reported to have C1q deposits on immunofluorescence and 6% of patients had IgM nephropathy. The group with IgM nephropathy seemed to have a higher rate of steroid-resistant nephrotic syndrome (43%) however, this difference was not significant. The lack of a significant difference may be due to the small number in this group.

Overall the initial response to steroids was poorer than the ISKDC reports with only 67.8% responding to initial steroid therapy compared to 93% in their study (6). Two other South African studies reported an initial response rate of 68% (25) and 66% (20). There was a difference in the response rates between Caucasian and Black African children (81% vs

56%) in a study done in Pretoria (20). Other studies report on steroid response in idiopathic nephrotic syndrome as a whole group, which is not comparable to our study. On long term follow up, 28.5% of patients had steroid-resistant nephrotic syndrome, 22.3% had steroid dependent nephrotic syndrome and 16.1% were frequent relapsers compared to 17% reported previously in the same population. There is some overlap between the groups as some patients may have fitted into different definitions at different points in the course of their disease.

Twenty-three of 32 patients (72%) that were treated with intravenous cyclophosphamide went into remission. Of the 23, 11 continued to have relapses but they were less frequent. In the Indian study by Elhence et al, a 100% of the children with steroid resistant minimal change nephrotic syndrome went into remission with intravenous cyclophosphamide. The numbers in this study were small and thus difficult to compare. (57) MMF has only been available more recently and thus there were only 8 patients treated with MMF. Only 50% of patients treated with MMF went into remission. An American study reported a response rate of 63% in steroid sensitive, frequently relapsing nephrotic syndrome and only 45% in steroid resistant nephrotic syndrome in a center where MMF is used as the initial second line agent (58) this is similar to the rate we found. The same study found a better response to tacrolimus (a calcineurin inhibitor) and rituximab but a poor response to cyclosporine (a calcineurin inhibitor) (58). Another study reported that MMF may not be as effective as calcineurin inhibitors in frequently relapsing nephrotic syndrome (36).

A serious bacterial infection requiring hospital admission occurred in 46 patients (41%). This rate of infection is similar to the rate of infection (48%) found in a study done in Pretoria (20) looking at all children with nephrotic syndrome, and slightly higher than the

rate (39%) in an Indian study which also looked at all children with nephrotic syndrome (53).

There were 2 (1.8%) patients that demised. The ISKDC reported an overall mortality rate of 2.5% in children with MCD. This was higher in non-responders (steroid-resistant children) compared to responders. (28). In our study one death occurred in the child with steroid resistant nephrotic syndrome and the second child was a frequent-relapser.

The rate of loss to follow up was very high in this study. Twenty-nine percent defaulted follow up within the first year. This may affect the study findings.

CHAPTER 5: CONCLUSION

In our 15 year retrospective review we found some differences between our population of children with minimal change disease and those in the rest of the world, particularly the western world.

The most striking differences were found in the higher proportion of children with haematuria and high blood pressure at presentation. There was also a poorer response to steroid therapy with a lower proportion of steroid responsive patients.

Intravenous pulsed cyclophosphamide with or without intravenous pulsed methyl prednisolone was predominantly used as a second line regimen in our study. MMF was used in very few patients. This is different to the trend in most first world centers where tacrolimus and rituximab are gaining more favour.

Poorer long term outcomes were predicted by steroid response rather than by histological variants. This seems to be in keeping with findings elsewhere.

The differences between our population, which is predominantly Black African and the population described by most western literature, could be explained by underlying genetic factors which have yet to be identified. Further research is needed in this field.

CHAPTER 6: REFERENCE LIST

1. Kher KK, Schnaper HW, Makker SP. Clinical pediatric nephrology. Abingdon, Oxon [UK]; Boca Raton, FL: Informa Healthcare ; Distributed in North America by Taylor & Francis; 2007.

2. Cameron JS. Five hundred years of the nephrotic syndrome: 1484-1984. The Ulster Medical Journal. 1985;54(Suppl):S5-s19.

3. Srivastava RN. 50 years of nephrotic syndrome in children, and hereafter. Indian pediatrics. 2013;50(1):107-10.

4. Barness LA, Moll GH, Janeway CA. Nephrotic syndrome I. Natural history of the disease. Pediatrics. 1950;5(3):486-503.

5. Arneil GC. 164 children with nephrosis. Lancet. 1961;2(7212):1103-10.

6. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. The Journal of pediatrics. 1981;98(4):561-4.

7. Arneil GC. Management of the nephrotic syndrome. Archives of disease in childhood. 1968;43(228):257-62.

8. Metcoff J, Rance CP, Kelsey WM, Nakasone N, Janeway CA. Adrenocorticotrophic hormone (ACTH) therapy of the nephrotic syndrome in children. Pediatrics. 1952;10(5):543-66.

9. Arneil GC. Treatment of nephrosis with prednisolone. Lancet. 1956;270(6920):409-11.

10. Avner ED. Pediatric nephrology Berlin: Springer; 2009 [Available from: http://dx.doi.org/10.1007/978-3-540-76341-3.

11. Bonilla-Felix M, Parra C, Dajani T, Ferris M, Swinford RD, Portman RJ, et al. Changing patterns in the histopathology of idiopathic nephrotic syndrome in children. Kidney international. 1999;55(5):1885-90.

12. Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet. 2003;362(9384):629-39.

13. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney international. 1978;13(2):159-65.

14. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, et al. Management of childhood onset nephrotic syndrome. Pediatrics. 2009;124(2):747-57.

15. El Bakkali L, Rodrigues Pereira R, Kuik DJ, Ket JC, van Wijk JA. Nephrotic syndrome in The Netherlands: a population-based cohort study and a review of the literature. Pediatric nephrology (Berlin, Germany). 2011;26(8):1241-6.

16. Zhou TB, Lin N, Qin YH, Liu YG. Distribution of pathological finding in the children with nephrotic syndrome from Guangxi. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2014;25(3):684-8.

17. Obiagwu PN, Aliyu A, Atanda AT. Nephrotic syndrome among children in Kano: a clinicopathological study. Nigerian journal of clinical practice. 2014;17(3):370-4.

18. Bhimma R, Coovadia HM, Adhikari M. Nephrotic syndrome in South African children: changing perspectives over 20 years. Pediatric nephrology (Berlin, Germany). 1997;11(4):429-34.

19. Thomson PD. Renal problems in black South African children. Pediatric nephrology (Berlin, Germany). 1997;11(4):508-12.

20. van Biljon G. Nephrotic Syndrome in Children-Studies from South Africa: INTECH Open Access Publisher; 2011.

21. Chugh SS, Clement LC, Mace C. New insights into human minimal change disease: lessons from animal models. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;59(2):284-92.

22. Cara-Fuentes G, Wasserfall CH, Wang H, Johnson RJ, Garin EH. Minimal change disease: a dysregulation of the podocyte CD80-CTLA-4 axis? Pediatric nephrology (Berlin, Germany). 2014.

23. Machado JR, Rocha LP, Neves PD, Cobo Ede C, Silva MV, Castellano LR, et al. An overview of molecular mechanism of nephrotic syndrome. International journal of nephrology. 2012;2012:937623.

24. Davin JC, Rutjes NW. Nephrotic syndrome in children: from bench to treatment. International journal of nephrology. 2011;2011:372304.

25. Kala U, Jacobs DWC. Minimal Change nephrotic syndrome - a 12 1/2 year review at Baragwanath Hospital (abstract). Kidney international. 1995;48(3):910.

26. McCaffrey J, Lennon R, Webb NJ. The non-immunosuppressive management of childhood nephrotic syndrome. Pediatric nephrology (Berlin, Germany). 2015.

27. Fogo AB. Minimal change disease and focal segmental glomerulosclerosis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2001;16 Suppl 6:74-6.

28. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A Report of the International Study of Kidney Disease in Children. Kidney international. 1981;20(6):765-71.

29. Vanikar A. IgM nephropathy; can we still ignore it. Journal of nephropathology. 2013;2(2):98-103.

30. Mubarak M, Kazi JI, Shakeel S, Lanewala A, Hashmi S, Akhter F. Clinicopathologic characteristics and steroid response of IgM nephropathy in children presenting with idiopathic nephrotic syndrome. APMIS : acta pathologica, microbiologica, et immunologica Scandinavica. 2011;119(3):180-6.

31. Vintar Spreitzer M, Vizjak A, Ferluga D, Kenda RB, Kersnik Levart T. Do C1q or IgM nephropathies predict disease severity in children with minimal change nephrotic syndrome? Pediatric nephrology (Berlin, Germany). 2014;29(1):67-74.

32. Shakeel S, Mubarak M, Kazi JI, Lanewala A. The prevalence and clinicopathological profile of IgM nephropathy in children with steroid-resistant nephrotic syndrome at a single centre in Pakistan. Journal of clinical pathology. 2012;65(12):1072-6.

33. Group KDIGOKGW. KDIGO Clinical Practice Guidelines for Glomerulonephritis. Kindey International Supplements. 2012;2(2):139 - 274.

34. Bagga A, Ali U, Banerjee S, Kanitkar M, Phadke KD, Senguttuvan P, et al. Management of steroid sensitive nephrotic syndrome: revised guidelines. Indian pediatrics. 2008;45(3):203-14.

35. Kala U, Milner LS, Jacobs D, Thomson PD. Impact of tuberculosis in children with idiopathic nephrotic syndrome. Pediatric nephrology (Berlin, Germany). 1993;7(4):392-5.

36. Larkins N, Kim S, Craig J, Hodson E. Steroid-sensitive nephrotic syndrome: an evidence-based update of immunosuppressive treatment in children. Archives of disease in childhood. 2015.

37. Tune BM, Mendoza SA. Treatment of the idiopathic nephrotic syndrome: regimens and outcomes in children and adults. Journal of the American Society of Nephrology : JASN. 1997;8(5):824-32.

38. Sinha A, Bagga A. Pulse steroid therapy. The Indian Journal of Pediatrics. 2008;75(10):1057-66.

39. Lombel RM, Gipson DS, Hodson EM. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatric nephrology (Berlin, Germany). 2013;28(3):415-26.

40. Lombel RM, Hodson EM, Gipson DS. Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO. Pediatric nephrology (Berlin, Germany). 2013;28(3):409-14.

41. Hodson EM, Willis NS, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. The Cochrane database of systematic reviews. 2010(11):Cd003594.

42. Uwaezuoke SN. Steroid-sensitive nephrotic syndrome in children: triggers of relapse and evolving hypotheses on pathogenesis. Italian journal of pediatrics. 2015;41(1):19.

43. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114(2 Suppl 4th Report):555-76.

44. Arm JP, Peile EB, Rainford DJ, Strike PW, Tettmar RE. Significance of dipstick haematuria. 1. Correlation with microscopy of the urine. British journal of urology. 1986;58(2):211-7.

45. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. Journal of the American Society of Nephrology : JASN. 2009;20(3):629-37.

46. Staples A, LeBlond R, Watkins S, Wong C, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatric nephrology (Berlin, Germany). 2010;25(11):2321-6.

47. Andolino TP, Reid-Adam J. Nephrotic syndrome. Pediatrics in review / American Academy of Pediatrics. 2015;36(3):117-25; quiz 26, 29.

48. Banaszak B, Banaszak P. The increasing incidence of initial steroid resistance in childhood nephrotic syndrome. Pediatric nephrology (Berlin, Germany). 2012;27(6):927-32.

49. Batinic D, Milosevic D, Coric M, Scukanec-Spoljar M, Konjevoda P, Batinic D, et al. Idiopathic nephrotic syndrome in children: review of 282 Croatian cases. Clinical nephrology. 2012;78(2):116-21.

50. Bircan Z, Yavuz Yilmaz A, Katar S, Vitrinel A, Yildirim M. Childhood idiopathic nephrotic syndrome in Turkey. Pediatrics international : official journal of the Japan Pediatric Society. 2002;44(6):608-11.

51. Kuster S, Mehls O, Seidel C, Ritz E. Blood pressure in minimal change and other types of nephrotic syndrome. American journal of nephrology. 1990;10 Suppl 1:76-80.

52. Corbett EL, Marston B, Churchyard GJ, De Cock KM. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. Lancet. 2006;367(9514):926-37.

53. Gulati S, Kher V, Gulati K, Arora P, Gujral R. Tuberculosis in childhood nephrotic syndrome in India. Pediatric nephrology (Berlin, Germany). 1997;11(6):695-8.

54. Vali PS, Ismal K, Gowrishankar S, Sahay M. Renal disease in human immunodeficiency virus - Not just HIV-associated nephropathy. Indian J Nephrol. 2012;22(2):98-102.

55. Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. The Cochrane database of systematic reviews. 2015;3:Cd001533.

56. Prospective, controlled trial of cyclophosphamide therapy in children with nephrotic syndrome. Report of the International study of Kidney Disease in Children. Lancet. 1974;2(7878):423-7.

57. Elhence R, Gulati S, Kher V, Gupta A, Sharma RK. Intravenous pulse cyclophosphamide--a new regime for steroid-resistant minimal change nephrotic syndrome. Pediatric nephrology (Berlin, Germany). 1994;8(1):1-3.

58. Kim J, Patnaik N, Chorny N, Frank R, Infante L, Sethna C. Second-line immunosuppressive treatment of childhood nephrotic syndrome: a single-center experience. Nephron extra. 2014;4(1):8-17.

CHAPTER 7: APPENDIX

Appendix A: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Kaajal Parbhoo

CLEARANCE CERTIFICATE	M120468
PROJECT	An Audit of Biopsy Proven Minimal Change Nephrotic Syndrome in Children at Chris Hani Baragwanath Academic Hospital
INVESTIGATORS	Dr Kaajal Parbhoo
DEPARTMENT	Department of Paediatrics Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED	04/05/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 17/07/2015 CHAIRPERSON .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof U Kala

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix B: Data Collection Sheet

Study No:

Sex:

Age at presentation: date of presentation: date of birth:

Race:

Clinical features at presentation: Weight: Height/length: HIV: PPD:
Haematuria:

Hypertension (BP):

Investigations at presentation
Urine protein:creatinine ratio:

Serum albumin: Cholesterol

Renal function & GFR:

Date of initial biopsy:

Biopsy result:

Histological Variant on electron & immunofluorescence microscopy
IgM nephropathy:

C1q nephropathy:

Mesangial proliferation:

Initial Therapy:
- Steroid therapy □
- Cyclophosphamide □
- ACE / ARB □
- Spironolactone □
- Salicylates / dipyridamole □

Duration of steroid treatment: Relapses:

Response to steroid therapy:
- Responsive □
- Dependent □
- Resistant □

Second line therapy used:
- IVI cyclophosphamide infusion □
- Additional IVI methyl prednisolone □
- Oral MMF □

Repeat biopsy performed: Y / N

Date of repeat biopsy:

Result of repeat biopsy:

Follow up:

Outcome at 1 year:

Length of follow up:

In remission Y/N

Steroid dependence Y/N

Renal Failure Y/N

Other complications:
- Hypertension: Y/N
- Infections (pneumonia/ peritonitis/ septicaemia/ other): Y/N
- Cataracts

Lost to follow up: Y/N

Appendix C: Turnitin

Submission Info

SUBMISSION ID	660587344
SUBMISSION DATE	17-Apr-2016 10:57AM
SUBMISSION COUNT	1
FILE NAME	Kaajal_Parbhoo_02031…
FILE SIZE	874.44K
CHARACTER COUNT	54689
WORD COUNT	9613
PAGE COUNT	63
ORIGINALITY	
OVERALL	7%
INTERNET	6%
PUBLICATIONS	8%
STUDENT PAPERS	2%