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A 10 YEAR REVIEW OF IDIOPATHIC NEPHROTIC SYNDROME IN CHILDREN: A SINGLE-CENTRE EXPERIENCE, JOHANNESBURG, SOUTH AFRICA.

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Dissertation submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree
of
Master of Science in Medicine

Johannesburg, 2016

DECLARATION

I, Dr Yassir Mahgoub Bakhiet declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine, in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature of candidate: _____

18th January, 2016

DEDICATION

I dedicate this humble effort to children with kidney disease.

ABSTRACT

Background: Idiopathic nephrotic syndrome (INS) is the commonest type of nephropathy seen in children. The histopathological types and steroid response patterns of INS have been changing over the years and this has been attributed to differences in ethnicity and geographical location. The aim of this study was to determine the steroid response pattern, renal histopathology and complications in a cohort of the children treated for INS by the Division of Paediatric Nephrology, CMJAH, Johannesburg, South Africa between 2004 and 2013.

Method: A retrospective study was carried out to review the records of 163 children between the ages of 2 and 16 years managed for INS over a 10 year period.

Results: The majority (111) of the 163 children were of the black racial group. There were 97 boys and 66 girls. The mean age of onset was 5.3 years ± 2.8, with the highest rate of INS seen in the 2-6 year age group (71.2%). Only 132/163 had a renal biopsy performed (MCD 52.3%, FSGS 43.2%, MesPGN 4.5%). The black race had a similar rate of MCD (38.8%) and FSGS (37.8%), while the white race had a higher rate of MCD (64.3%) when compared to FSGS (14.3%). Ninety four (57.7%) patients were steroid sensitive (SSNS) while 69 patients (42.3%) were steroid resistant (SRNS). Minimal change disease was the most common histopathological type seen in SSNS (60%), while FSGS was the most common observed in patients who had SRNS (65.2%). There was a statistically significant association between the various steroid response patterns and the different histopathological types. The highest rate of resistance to all treatment after a mean follow up of 60 months was seen among children of the mixed race and black racial groups (50.0% and 40.5% respectively). Stunted growth (52.1%), hypertension (47.2%) and reduced eGFR (25.8%) were the most common complications observed.

Conclusions: There appears to be an increase in the rate of FSGS in all the racial groups, and an increase in the rate of MCD in the black race group, when compared to previous South African studies. Furthermore, steroid response was also observed to have increased significantly among the black racial group when compared with previous studies. Although hypertension was the most common complication observed in our cohort, a very high rate of stunted growth was also observed. This may be due to the significant number of patients with reduced eGFR, SRNS and FSGS in our cohort. The use of long term steroid therapy may have contributed to this high rate.

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NOMENCLATURE

Anti-ds DNA	Anti-double stranded DNA
AKI	Acute kidney injury
ANA	Antinuclear antibody
APN	Arbeitsgemeinschaft für Pädiastrische Nephrologie
Chlor	Chlorambucil
CP	Cyclophosphamide
CyA	Cyclosporine A
eGFR	Estimated glomerular filtration rate
ESKD	End stage kidney disease
ESR	Erythrocyte sedimentation rate
FRNS	Frequently relapsing nephrotic syndrome
FSGS	Focal segmental glomerulosclerosis
HAART	Highly active antiretroviral therapy
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
IFRNS	Infrequently relapsing nephrotic syndrome
IgG	Immunoglobulin G
INS	Idiopathic nephrotic syndrome
ISKDC	International Study of Kidney Disease in Children
KDIGO	Kidney Disease Improving Global Outcomes
LDL	Low density lipoprotein
LRTI	Lower respiratory tract infection

MCD	Minimal change disease
MMF	Mycophenolate Mofetil
MesPGN	Mesangial proliferative glomerulonephritis
NOS	Not otherwise specified
NS	Nephrotic syndrome
PTB	Pulmonary tuberculosis
RTI	Respiratory tract infection
SDNS	Steroid dependent nephrotic syndrome
SRNS	Steroid resistant nephrotic syndrome
SSDs	Steroid sparing drugs
SSNS	Steroid sensitive nephrotic syndrome
Tacro	Tacrolimus
TEP	Thromboembolic phenomenon
uPCR	Urinary protein/creatinine ratio
URTI	Upper respiratory tract infection
UTI	Urinary tract infection

1. INTRODUCTION

Approximately 90% of children presenting between the ages of two and ten years with nephrotic syndrome (NS) will be diagnosed as having idiopathic nephrotic syndrome (INS). (1-3) Most cases of NS that present in the first year of life are diagnosed as congenital NS, and above the age of ten years most of the cases will be diagnosed as having secondary NS. (1,2,4)

The spectrum of INS in African countries seems to be different from other parts of the world suggesting that an interaction of genetic and environmental factors plays an important role in the pathogenesis of INS. (5-8)

A significant number of cases of INS are usually steroid sensitive, while some cases will be diagnosed as having steroid unresponsive disease. (1,9)

The histopathological pattern of presentation, its changing pattern and advances in the treatment of childhood INS have been reported widely. (10-16) Childhood INS is most commonly caused by one of several idiopathic diseases: Minimal-change disease (MCD), focal segmental glomerulosclerosis (FSGS) and, less commonly, mesangial proliferative glomerulonephritis (MesPGN). (1,2,17) These various histopathological features have been strongly associated with differences in response to corticosteroid therapy, subsequent clinical course and prognosis. (9,18,20)

Many authors feel that the histopathological pattern of INS has been changing despite a stable incidence of the disease in the last 30 years. This is as noted by the increasing reported incidence of FSGS. (14,15,20)

Although the use of corticosteroids as initial therapy for INS is accepted internationally, steroid sparing drugs (SSDs) are indicated in steroid resistant nephrotic syndrome (SRNS),

frequently relapsing NS, in cases with severe side effects of steroid therapy, in children at risk for toxicity and in patients with poor compliance. (18,21)

Various complications have been attributed to INS and as a result of adverse effects of treatment. (1,22) These include infections, thromboembolic phenomenon (TEP), acute kidney injury (AKI), hypertension and declining renal function. Common side effects such as the development of cushingoid features and obesity, hypertension, growth retardation, ophthalmologic disorders, behavioral changes and osteoporosis may also be seen as a result of corticosteroid therapy. (22-24)

A better understanding of the presentation, the steroid response pattern and the histopathological pattern of childhood INS is very important in determining future guidelines for effective management of the disease.

1.1 Literature Review

Idiopathic nephrotic syndrome (INS) is the commonest type of nephrotic syndrome (NS) seen in children. (18,25) It is characterized by a combination of NS with non-specific histopathological abnormalities seen on renal biopsy (1).

While INS develops in the absence of an underlying etiology, many conditions have been reported to be associated with INS. These include, for example, upper respiratory tract infections (URTI), allergic reactions, malignancies, and Eosinophilic Lymphoid Granuloma. (25-27) However, the question still remains as to whether these factors are real causes, or just precipitating agents, of the disease.

Idiopathic nephrotic syndrome has been reported as being fifteen times more common in children than adults. (28) The male to female ratio is usually around 2:1 among younger children and then becomes closer to 1:1 in adolescence. The most common age of presentation is 2-6 years. (1,2,9)

The reported incidence of INS varies with the ethnic origin and different geographical locations of the different cohorts studied (5,29,30) and, although the worldwide incidence of INS has been stable for the last 30 years, many authors feel that the histopathological pattern has been changing as noted by the increasing reported incidence of FSGS. (10-12) The annual incidence of INS in the USA and Europe is 1-3 cases per 100 000 children, with a prevalence of 16 per 100 000 children. (29,30) Similar findings were reported from New Zealand. (17)

In a report from the United Kingdom, INS was 6 times more common in children of Asian origin than in those of European origin (13). This finding was supported by a study from India. (31) In the United States a recent review of children with INS in Houston, Texas revealed that race had an important impact on the histological lesion seen in INS. (11) They

found only 11% of the Hispanic population, and 18% of Caucasians, had FSGS compared with African American children (47%). (11) The spectrum of INS in African countries seems to be different from the other parts of the world which suggests that the interaction of genetic and environmental factors play an important role in the pathogenesis of INS. (5-8)

1.1.1 Pathogenesis

The pathogenesis of INS remains unclear, however evidence suggests that a defect in the immune system plays an important role. (32,33)

Studies on children with INS have found increased cytokines (IL1, IL2, IL4, IL12, IL13, IL18, and tumour necrosis factor alpha (TNFα)) in the serum, which may all directly act on the glomerular capillary wall. (32)

There is also evidence for a glomerular permeability factor produced by T cells. (33) Also, INS patients have been found to have high levels of circulating B lymphocytes, IL2, soluble IL2 receptor and interferon gamma levels during a relapse episode. (34,35)

All of these observations point to the role of the immune system in the pathogenesis of INS, however the exact mechanism which affects the immune system, and how the cells are involved (cytokines or immunological factors), is still unknown. (36)

Additional evidence that NS has an immunological basis is the beneficial effect of immunosuppressive drugs in INS patients. (36,37)

1.1.2 Clinical presentation and complications of NS

INS is often preceded by an upper respiratory tract infection (URTI) followed by the sudden onset of periorbital swelling. (23,29) Anasarca may develop with ascites, pleural and pericardial effusions. (1) Oedema of the scrotum, penis and labiae may also be seen. (1,2) Abdominal pain is often an associated feature and may be as a result of a bacterial peritonitis, visceral oedema, gut ischaemia and rarely pancreatitis and even renal vein thrombosis. (29,38) Severe intravascular hypovolemia secondary to the sudden fall of plasma albumin may cause acute kidney injury (AKI). (2) Gross haematuria is not a feature of INS unless there has been a renal vessel thrombosis, although microscopic haematuria may be seen up to 23% of patients with MCD and even more than that in patients with other histopathological types. (18) Hypertension may be present with INS. (1,2,18) Thromboembolic phenomenon (TEP) such as deep vein or arterial thromboses and pulmonary embolism may also occur during the first attack or during a relapse. (1)

Although all the drugs used in the management of INS have known side effects, because of their ubiquitous use in INS, those of the glucocorticoid group deserve special mention. These include the development of cushingoid features and obesity (42%), hypertension (10%), growth retardation (8%), ophthalmologic disorders including posterior subcapsular cataracts and raised intraocular pressure (6%), behavioral changes including aggression, inattention, hyperactivity and sleep disturbances (4%) and osteoporosis (2%). (22-24)

1.1.3 The clinical course of INS

The clinical course of INS is described according to the level of steroid responsiveness. One third of patients will experience a single attack and are cured after a course of corticosteroid. (24,29) About 10% - 20% of INS children will suffer a relapse several months after stopping

the treatment. (39) In these patients cure usually takes place after three or four of these episodes, which all respond to a standard course of corticosteroids. These patients are described as having infrequently relapsing NS, (IFRNS). (39) The remaining 40–50% of children with steroid sensitive NS will relapse frequently (FRNS) and some may even become steroid dependent (SDNS) and will be at risk for steroid toxicity. Patients who continue to respond to steroids have a minimal risk of developing chronic renal failure. (24,39)

In INS, patients with FSGS on biopsy have been reported as having the highest risk for steroid resistance (SRNS), although a minority of steroid resistant patients will have MCD on biopsy. (40,41)

The prognosis of SRNS is poor and these patients have a high risk for developing disease related complications and progression to chronic kidney disease. Steroid resistant nephrotic syndrome (SRNS) accounts for 10%–20% of end-stage kidney disease (ESKD) in children and has a high recurrence rate after kidney transplantation. (41,42)

1.1.4 Laboratory evaluation

a. Urinalysis:

   All cases of suspected NS should have a urine dipstick test performed. The finding of more than 3+ protein on dipstick test is highly suggestive of significant proteinuria and the urine should then be sent for an early morning urinary protein/creatinine ratio (uPCR) estimation with the nephrotic range reported as 0.2–0.4 g/mmol. (43)

b. Blood chemistry:

Serum proteins are markedly reduced and the serum albumin concentration usually falls below 20 g/l. (1) Serum lipids are usually increased. Total cholesterol and LDL cholesterol are elevated while HDL cholesterol remains unchanged or low. (44) This results in an increased LDL:HDL cholesterol ratio. (44)

Serum electrolytes are usually within the normal range although the serum sodium may be decreased (pseudohyponatraemia). (1) Serum potassium may be high in oliguric patients. Serum calcium is consistently low but the ionized calcium is usually normal and serum calcitriol is normal. (1,2) Blood urea nitrogen and creatinine concentrations are usually within the normal range. (2)

c. Haematology:

Haemoglobin and haematocrit are often increased due to plasma volume contraction. (1) Thrombocytosis may be seen in children with INS. (2)

d. Serology:

C3 and C4 complement level, antinuclear antibody (ANA) and anti-double stranded DNA (Anti-ds DNA) are all important tests to perform in INS to exclude secondary causes of NS. (1, 2)

e. Virology screening:

Hepatitis B, C and HIV antibody testing is also recommended as all of these viruses can cause secondary NS. In addition, the immunosuppressive therapy used in INS may result in a flare of the viral activity. (1, 2) Some centers obtain a Varicella IgG titer too, to allow for pre therapy immunization with Varicella-Zoster Virus vaccine in unexposed patients.

f. Tuberculosis screening is also often performed prior to initiating immunosuppressive therapy. (1, 2)

Histopathology

Although different units have different protocols for performing renal biopsies in children with INS, most units would agree with the following indications and would perform a renal biopsy in the following group of patients (1,2,21):

1. Children with NS in whom the onset of the disease occurs before the age of 1 year and after the age of 10 years.
2. Children who remain unresponsive to an initial course of corticosteroid therapy of more than 6 weeks, or who develop secondary steroid resistance (SRNS).
3. Children who respond to corticosteroid therapy but then go on to develop more than three relapses over a one year period (FRNS).
4. Children who have atypical features of NS at the time of diagnosis (macroscopic haematuria, hypertension, persistent renal insufficiency, and low C3 component of complement).

Childhood INS is most commonly caused by one of two idiopathic diseases: Minimal change disease (MCD) is the most common histopathological lesion seen and accounts for 85% of INS. More than 95% of these cases respond to steroid therapy and will not need a renal biopsy. (1,14,45) Minimal change disease shows normal glomeruli with normal capillary walls and normal cellularity on light microscopy. (1) The second most common histological type of INS is FSGS. (1,2,29) This presents as a heterogeneous disease, with both immune and non-immune causes, and has been reported to be less frequent in young children (20 %). (1,2,46) FSGS implies an irreversible scarring process taking place in the glomeruli. (46,47) There are five histological variants of FSGS (collapsing, cellular, glomerular tip, perihilar and not otherwise specified (NOS)) which may have clinical impact on response to treatment and prognosis. (48,49) For example, glomerular tip lesions appear to have better outcomes

than the collapsing glomerulopathy type which predominates in black patients. (48,49) Recent genetic studies highlight the fact that FSGS is associated with several genes that may play a critical role in podocyte function and the glomerular filtration barrier. (50-52) However a mechanism for the glomerular abnormalities in MCD, and idiopathic FSGS with relapse, remains unknown. (53) A third distinct type, mesangial proliferative glomerulopathy (MesPGN) is rare in children. (1,2)

In all cases of INS no significant deposition of immunoglobulin or complement is noted in the kidney tissue. (1)

1.1.6 Treatment

The initial protocols emphasizing the role of corticosteroids in inducing remission of INS were established between 1967 and 1974 by the International Study of Kidney Disease in Children (ISKDC), and were subsequently modified by the Arbeitsgemeinschaft für Pädiastrische Nephrologie (APN). (3,54,55) Although the use of corticosteroids as initial therapy for INS is accepted internationally there are many areas of uncertainty in the management of INS. Two American surveys demonstrated wide practice variation in all aspects of INS treatment and many clinical practice guidelines for management of childhood INS have been published over the years e.g. France (2008), North America (2009), and India (2008). (56-60)

In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) published an international clinical practice guideline for the management of INS. (21) The goal of this guideline was to improve quality of care by helping clinicians to know and understand the evidence that determines practice. However, many reports in the literature suggest that actual

clinical practice deviates from what the evidence recommends partly due to the absence of a systematic approach when it comes to translating existing evidence into practice. (56,57,61,62)

1. **Symptomatic treatment**

   Children with INS may develop significant complications and therefore therapy is also aimed at reducing complications. The use of antimicrobial prophylaxis, treatment of infection, immunization, antithrombotic therapy, antihypertensive therapy, conservative management of oedema and management of dyslipidaemia may all be indicated for symptomatic treatment. (63)

2. **Specific treatment**

   Although remission without treatment may occur within 1 or 2 weeks in up to 5% of cases, corticosteroid therapy is recommended as the initial treatment for all children who meet the criteria for INS. (64) It is important to remember that any underlying infection must be treated before starting corticosteroids to prevent the risk of overwhelming sepsis during treatment. (3,59) It should also be kept in mind that an occult infection may be responsible for steroid resistance. (1)

   a. **Treatment of the initial episode:** The ISKDC has reported that approximately 90% of responders will go into remission within 4 weeks after starting corticosteroids and that less than 10% will go into remission after 6–8 weeks of a daily regimen. (3) The standard regimen according to KDIGO 2012 consists of prednisone, 60 mg/m^2/day or 2 mg/kg/day (up to a maximum of 60 mg/day), in divided doses for 4 weeks followed by 40 mg/m^2/dose or 1.5 mg/kg/dose (up to a

maximum of 40 mg/day on alternate days) in a single dose for 4 weeks and continued for 2-5 months with tapering of the dose. (21)

The duration of the corticosteroid course has come under debate recently. The APN and other several controlled studies documented that the relapse rate was reduced with longer courses of corticosteroid therapy. (55,65,66) However, a recent multicenter randomized placebo controlled trial showed that although extending the initial prednisone treatment from 3 to 6 months may delay the first relapse, it does not appear to have an impact on the occurrence of frequent relapses nor alter the course of the disease. (67)

b. **Treatment of relapses:** The risk for a relapse is higher in male children and in those aged less than 5 years at onset. (1) Corticosteroid therapy should be started immediately if proteinuria recurs, and then persists for more than 3 days, to avoid any associated complications. (3) The KDIGO has proposed that infrequent relapse episodes should be treated with daily prednisone 60 mg/m^2/day or 2 mg/kg/day (up to a maximum of 60 mg/day) until the child has been in remission for 3 days, followed by prednisone 40 mg/m^2/dose or 1.5 mg/kg/dose (up to a maximum of 40 mg/day) on alternate days for at least 4 weeks. (21) Treatment of frequent relapses and SDNS consists of daily prednisone (60 mg/m^2/day) until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 months, then decreasing doses until a dose of 10-30 mg/m^2/dose or 0.3-1 mg/kg/dose has been reached, on alternate days or as daily dosing in cases where alternate-day prednisone therapy has not been effective. (21) Another option available for the treatment of frequent relapses and SDNS is the use

of steroid sparing drugs (SSDs), particularly where patients have developed steroid related adverse effects. (21)

c. **Treatment of steroid resistant INS:** The treatment of SRNS remains a difficult challenge. Most children with SRNS have received intensive treatment regimens and many of them have been over treated. (8,40,41) There is no diagnostic marker that can be used as a predictor for steroid responsiveness or resistance in INS. (8,41) SRNS patients with FSGS on biopsy, and who have not had genetic screening performed, may respond to cyclosporine. Complete remission may be achieved in 31%, and partial remission in 38%, during a 6 month course of therapy. (68-70) Cyclophosphamide use in SRNS has not been shown to have any effect on inducing remission. (1,2,40) The use of methylprednisolone in SRNS is controversial. Mendoza *et al*. found a high rate of remission and a reduction in the incidence of end-stage kidney disease from 40% to 5% using historical controls, when he administered methylprednisolone in SRNS patients. (71) Despite this finding, Waldo *et al*. found that pulse methylprednisolone was not effective in inducing remission in black patients. (72) The rate of remission is higher in patients with late onset SRNS who have responded to a steroid sparing agent compared with those who have SRNS from the outset. (8) Tacrolimus has also been shown to be effective for children with SRNS with a complete remission rate of 81%, and a partial remission rate of 13%, described. (73,74)

d. **Steroid sparing drugs (SSDs):** The indications to use SSDs in children with INS include; severe side effects of corticosteroid therapy, children at risk for toxicity, multiple severe relapses and poor compliance. (21) These drugs include: Levamisole, alkylating agents (Cyclophosphamide, Chlorambucil), calcineurin

inhibitors (Cyclosporin, Tacrolimus), antiproliferative agents (Azathioprine, Mycophenolate Mofetil (MMF)) and Rituximab.

In conclusion, INS remains an important cause of childhood glomerulopathy. Its different patterns of presentation, different types of histopathology and different responses to treatment are attributed to ethnic and geographical variation. Recent studies indicate an increasing incidence of steroid resistance in children with INS and these patients have a high risk for developing disease related complications and progression to chronic kidney disease. A better understanding of the disease along with improved management may transform the outcome of childhood INS.

1.2 Justification for the study

Idiopathic NS makes up a significant number of children treated in our clinic, and the progression of the disease in black South African children is still not fully understood. Data from units in Sub-Saharan Africa suggests that INS is less common among black African children and also that the clinical behavior and response to therapy appears to be different when compared with children in the western world. These data suggest that genetic and environmental factors are important in the pathogenesis of INS. (5-8)

A study from Durban, South Africa found that, in black South African children, the glomerular proliferative change was the commonest lesion seen and that corticosteroids were found to be ineffective. (5) Our impression is that the clinical picture of our patients is different from that reported in previous studies on African children. (5-7,10) In addition, although much research has been done on INS in the past, there are still gaps in our knowledge of this disease especially with regards to our unique patient population. It is for these reasons that we have undertaken to perform this study.

We planned to undertake this research to try to increase our knowledge of this condition, especially as it pertains to our patient cohort. We hoped that the findings of this study would give us more information on this topic and might enable us to identify new prognostic indicators and perhaps enable us to develop better approaches to the management of this condition, specifically for our patients.

1.3 Aim

To determine the steroid response pattern, renal histopathology and complications in a cohort of children treated for INS by the Division of Paediatric Nephrology, CMJAH, Johannesburg, South Africa between 2004 and 2013.

Specific objectives

(1) To determine the rate of the different renal histopathological patterns seen in the study cohort on renal biopsy.

(2) To determine the rate of the different steroid response patterns of the study cohort.

(3) To determine if there is any association between the racial groups in the study cohort and objectives 1 and 2.

(4) To document any complications that might have developed namely hypertension, infections, thromboembolic phenomena (TEP), acute kidney injury (AKI), hypothyroidism, psychosis, obesity, cataracts, stunted growth and a reduced eGFR.

2. MATERIALS AND METHODS

The study was carried out in the Division of Paediatric Nephrology of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The Division provides a comprehensive tertiary and quaternary paediatric nephrology service primarily to children referred from Gauteng and its surrounding provinces.

2.1 Study design

The study was a descriptive retrospective cohort study.

2.2 Study population

All patients between 2 and 16 years of age with Idiopathic Nephrotic Syndrome treated by the Division of Paediatric Nephrology at CMJAH between January 2004 and December 2013.

2.3 Selection criteria

2.3.1 Inclusion Criteria

1. Only children between the ages of 2 and 16 years were included in the study
2. Only children who had at least 6 months of follow up after onset of the disease were included in the study
3. Only children who fulfilled all the criteria for INS at the initial presentation (generalized oedema, hypoalbuminaemia (serum albumin < 25 g/l), significant proteinuria (uPCR > 0.2 g/mmol) with, or without, hypercholesterolemia (serum cholesterol > 5.2 mmol/l)) were included in the study

2.3.2 Exclusion Criteria

1. Any files with absent or incomplete data
2. Patients with systemic diseases or infections known to cause secondary nephrotic syndrome
3. Children with congenital nephrotic syndrome (onset <3 months of age)
4. Children with evidence of chronic renal impairment prior to the diagnosis of INS (estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2)
5. Children with a family history of nephrotic syndrome or chronic kidney disease

2.4 Sample size

The files of 180 patients with INS were identified from the clinic data base.

Only 163 of these patients met all the study selection criteria.

Seventeen patients were excluded from the data analysis (8 were above the age of 16 years and had been transferred to adult unit, 2 files had incomplete data and 7 children were still within the 6 month period post onset of the disease)

2.5 Study procedure

The individual patient records of the Division of Paediatric Nephrology of CMJAH are kept in patient files in a secure filing room in the division. These files were screened for patients who fulfilled the selection criteria. Data was then extracted from the patient files that met the study criteria by the primary investigator and entered onto a data capture sheet. (Appendix A).

Information extracted included the following clinical information: anthropometry (weight and height), blood pressure, the presence of oedema, ascites, pleural and/or pericardial effusions, the presence of infection (URTI, LRTI, UTI, peritonitis) and the presence of TEP. The dipstick urinalysis was used to document the presence of haematuria.

In addition, all pertinent laboratory data were interpreted and captured where relevant as follows; remission, relapse, the presence of infection, hypercholesterolaemia, haematuria, hyperglycaemia, hypothyroidism, acute kidney injury, reduced eGFR, etc.

Additional information recorded on the data capture sheet included the age of the child at the time of data capture, the age at presentation, sex, race, the follow up period (the period from the date of onset of the disease up to the time of data collection), the steroid response pattern of INS (SSNS and SRNS), the number of relapses per year (FRNS and IFRNS), the use of steroid sparing drugs (SSDs), the type of SSDs (alkylating agents [cyclophosphamide or chlorambucil], calcineurin inhibitors [cyclosporine or tacrolimus], Mycophenolate mofetil [MMF] and rituximab), the presence of other complications (e.g. hypertension, growth stunting, psychosis, obesity, cataracts and TEP), and the outcome to treatment (sustained remission without steroid, in remission with a small dose of steroid, in remission with steroids and SSDs, FRNS, SRNS and resistance to all treatment). In cases which had a renal

biopsy performed the histopathological type of INS was documented (MCD, FSGS, MesPGN).

All the relevant information was then entered into an Excel database.

Strict patient confidentiality was maintained. All patients were allocated a study number and no patient was identified by name or hospital number on the database.

2.6 Definition of terms

1. Follow up period: The period from the date of the onset of disease up until the time of data collection.
2. Steroid response pattern (21):
    a. Steroid sensitive nephrotic syndrome (**SSNS**) (initial responder): Attainment of remission within initial 4 weeks of corticosteroid therapy.
    b. Steroid dependent nephrotic syndrome (**SDNS**): Two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy.
    c. Steroid resistant nephrotic syndrome (**SRNS**) (initial non responder/steroid resistance): Failure to achieve complete remission after 8 weeks of corticosteroid therapy.
3. Remission (21): Urine protein/creatinine ratio (uPCR) < 200 mg/g (< 0.02 g/mmol) or <1+ of protein on urine dipstick for 3 consecutive days.
4. Relapse: Urine PCR ≥ 2000 mg/g (≥ 0.2 g/mmol) or ≥ 3+ protein on urine dipstick for 3 consecutive days (21):
        a. Infrequently relapsing nephrotic syndrome (**IFRNS**): One relapse within 6 months of initial response, or one to three relapses in any 12 month period.

b. Frequently relapsing nephrotic syndrome (**FRNS**): Two or more relapses within 6 months of initial response, or four or more relapses in any 12 month period.

5. Types of steroid sparing drugs (SSDs):
    - CP - Cyclophosphamide (Cytoxan®)
    - Chlor - Chlorambucil (Leukeran®)
    - CyA - Cyclosporine (Neoral®)
    - Tacro - Tacrolimus (Prograf®)
    - MMF - Mycophenolate mofetil (Cellcept®)
    - Other – SSD e.g.: Levamisole, Rituximab.
6. Hypertension (75): A blood pressure greater than the 95th percentile for sex, age and height using standard charts or any patient on antihypertensive treatment.
7. Stunted growth (76): A height that is 2 standard deviations (SD) or more below the mean for children of that sex and chronologic age. This corresponds to a height that is below the 3rd percentile.
8. Estimated glomerular filtration rate (eGFR) (77): The eGFR was calculated using the new "bedside" Schwartz equation eGFR = 36.5 x Height (cm)/Serum Creatinine (mmol/l). Reduced eGFR was defined as an eGFR less than 90 ml/min/1.73m^2. The Siemens Advia 1800 enzymatic technique was used for the serum creatinine assay.
9. Hypercholesterolaemia (78): serum total cholesterol and triglyceride levels were greater than or equal to the 95th percentile for age and sex. (Total serum cholesterol > 5.2 mmol/l).
10. Hyperglycaemia (79): A blood sugar level greater than 11.1 mmol/l (200 mg/dl).

2.7 Ethics and permission

The study was conducted in full conformance with the principles of the Declaration of Helsinki, Good Clinical Practice and within the laws and regulations of South Africa. Consent was obtained from the head of the institution where the study data was collected. A submission to the Postgraduate Committee at the University of Witwatersrand and the Human Research Ethics Committee was made in order to obtain clearance for this study to take place and a clearance certificate was obtained (M150234). (Appendix B)

2.8 Data Analysis

All data were collated, checked and analysed using a computer based statistical package STATA version 13.1. The statistical analysis was performed by the primary investigator and the results were checked by a statistician. Continuous parameters were reported as mean and standard deviation while categorical variables were presented as percentages, bar charts and pie charts. Most variables were categorical due to the nature of the study design. These were reported using the proportion of total respondents. Associations between groups were determined using chi-square testing and bilateral Fisher's exact tests. A confidence interval of 95% was used and a p value < 0.05 was regarded as statistically significant.

3. RESULTS

A total of 163 children who met the study criteria were recruited. There were 97 (59.5%) males and 66 (40.5%) females with a male to female ratio of 1.46:1. (Table I) The mean age of the children at the time of presentation was 5.3 years ± 2.8.

The mean follow up period (the period from the date of the onset of disease up until the time of data collection) was 60 months ± 36.9.

At presentation, the majority of the patients were in the 2 to 6 year age group (71.2%). (Table I) The majority of the patients in the cohort were of the black race (68.1%) and also the black race made up the highest number in all the age groups. (Table II)

At initial presentation, 122 (74.8%) of the children had hypercholesterolaemia, 77 (47.2%) had hypertension, 32 (19.6%) had haematuria and 59 (36.2%) had an infection (respiratory tract infection 35, peritonitis 21 and UTI 3).

3.1: The histopathological patterns of the disease

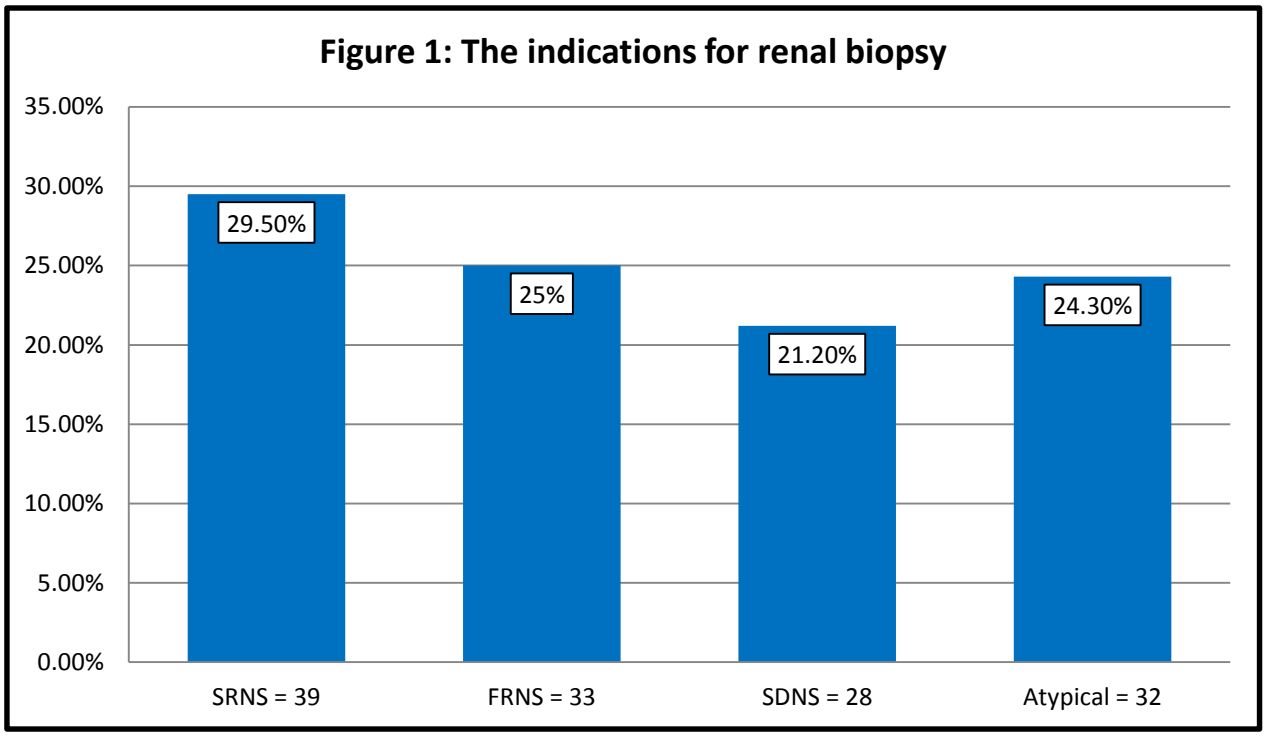
Only 132 (80.9%) of the patients underwent a renal biopsy. The majority of the biopsies (90) were performed among the age group 2 to 6 years as shown in Table III. The most common indications for renal biopsy were steroid resistance (29.5%) and an atypical presentation such as the presence of hypertension, haematuria on presentation, or age greater than, or equal to, 10 years (24.3%). (Figure 1)

The biopsy rate was similar in the Black, White and Mixed racial groups (81.1%, 85.7% and 87.5% respectively), while the Asian racial group had the lowest rate (72.7%).

Table I: The general characteristics of children with INS	
Sex	**n = 163 (%)**
Male	97 (59.5)
Female	66(40.5)
Race	
Black	111 (68.1)
Asian	22 (13.5)
Mixed	16 (9.8)
White	14 (8.6)
Age group at presentation (years)	
2 – 6	116 (71.2)
7 – 10	36 (22.1)
11 – 16	11 (6.7)
Follow up period (months)	
6 – 48	78 (47.8)
49 – 84	37 (22.7)
85 – 120	48 (29.5)

Table II: The age group distribution according to the racial groups

	Racial group n (%)				
Age group	**Black**	**Asian**	**Mixed Race**	**White**	**Total**
2 – 6	71 (61.2) (64.0)	20 (17.2) (90.8)	14 (12.1) (87.5)	11 (9.5) (78.6)	116 (100) (71.2)
7 – 10	30 (83.3) (27.0)	1 (2.8) (4.6)	2 (5.6) (12.5)	3 (8.3) (21.4)	36 (100) (22.1)
11 – 16	10 (90.9) (9.0)	1 (9.1) (4.6)	0 (0.0) (0.0)	0 (0.0) (0.0)	11 (100) (6.7)
Total	111 (68.1) (100)	22 (13.5) (100)	16 (9.8) (100)	14 (8.6) (100)	163 (100) (100)



The different histopathological types of INS seen according to the different racial groups are summarised in Table IV.

There were no documented complications arising from the procedure noted in the medical records of these patients.

132 patients underwent a renal biopsy. The most common histopathological lesion observed was MCD (52.3%) and the least common lesion observed was MesPGN (4.5%). (Figure 2)

The mean age at presentation of MCD and FSGS was similar, 64.5 months ± 28.3 and 67.0 months ± 39.8 respectively. The mean age at presentation for MesPGN was higher (94.0 months ± 28.6) when compared to the others.

The black race had a similar incidence of MCD (38.8%) and FSGS (37.8%) while the white race had a higher incidence of MCD (64.3%) when compared to FSGS (14.3%). (Table IV)

Mesangial proliferative glomerulonephritis was almost exclusively seen in the black race.

When comparing the different racial groups with regards to the different histopathological types of INS, no significant statistical difference was detected (p=0.604). (Table IV)

Figure 2: The histopathological types of INS (n=132)

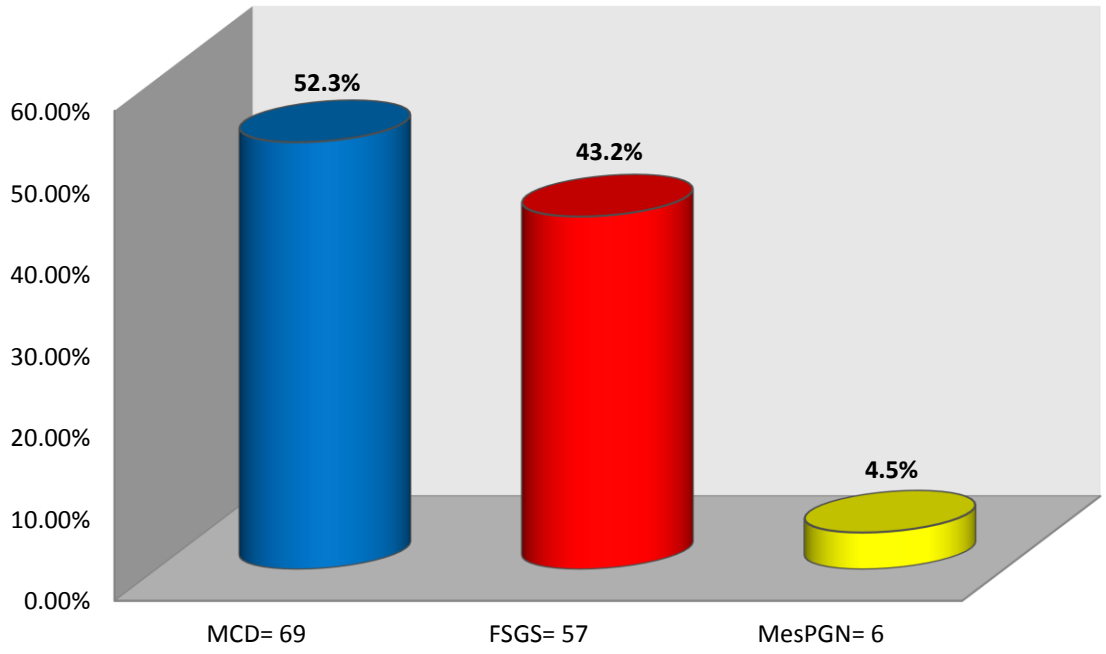


Table III: The histopathological types of INS according to age group

Age group (year)	Histopathological types of INS n (%)				
	No Biopsy	**MCD**	**FSGS**	**MesPGN**	**Total**
2 – 6	26 (22.4) (83.9)	50 (43.1) (72.5)	37 (31.9) (64.9)	3 (2.6) (50.0)	116 (100) (71.2)
7 – 10	4 (11.1) (12.9)	17 (47.2) (24.6)	13 (36.1) (22.8)	2 (5.6) (33.3)	36 (100) (22.1)
11 – 16	1 (9.1) (3.2)	2 (18.2) (2.9)	7 (63.6) (12.3)	1 (9.1) (16.7)	11 (100) (6.7)
Total	31 (19.0) (100)	69 (42.3) (100)	57 (35.0) (100)	6 (3.7) (100)	163 (100) (100)

Fisher's exact, p = 0.116

Table IV: The histopathological types of INS according to racial distribution					
Race	**Histological type n (%)**				
	No biopsy	**MCD**	**FSGS**	**MesPGN**	**Total**
Black	21 (18.9) (67.7)	43 (38.8) (62.4)	42 (37.8) (73.7)	5 (4.5) (83.3)	111 (100) (68.1)
Asian	6 (27.3) (19.3)	9 (40.9) (13.0)	7 (31.8) (12.3)	0 (0.0) (0.0)	22 (100) (13.5)
Mixed	2 (12.5) (6.5)	8 (50.0) (11.6)	6 (37.5) (10.5)	0 (0.0) (0.0)	16 (100) (9.8)
White	2 (14.3) (6.5)	9 (64.3) (13.0)	2 (14.3) (3.5)	1 (7.1) (16.7)	14 (100) (8.6)
Total	31 (19.0) (100)	69 (42.3) (100)	57 (35.0) (100)	6 (3.7) (100)	163 (100) (100)

Fisher's exact, p = 0.604

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3.2: The steroid response pattern

All 163 patients of the cohort received prednisolone 2 mg/kg as a daily dose for at least 4 weeks.

The steroid response pattern was as follows; 94 (57.7%) patients had SSNS, and SRNS was present in 69 patients (42.3%). (Figure 3)

Children with SSNS were further classified into frequent relapsers (≥2 relapses/6 months) and infrequent relapsers (<2 relapses/6 months).

Figure 3: Pie chart showing distribution of steroid response patterns

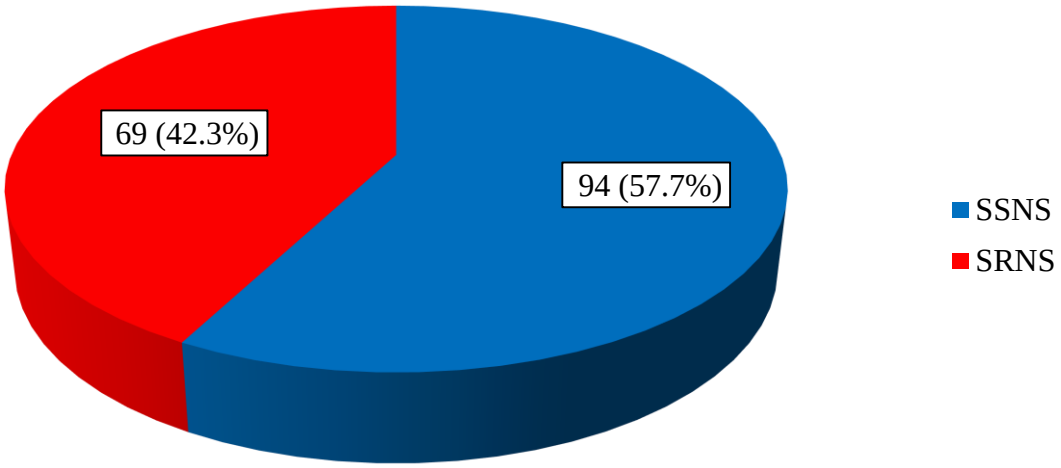

Table V: The distribution of the different response patterns to steroid therapy

Response pattern	(n)	%
IF	55	33.7
FR	10	6.1
SDNS	29	17.8
SRNS	69	42.3
Total	163	(100)

Table VI: The steroid response patterns according to the histopathological types of INS

Clinical type	Histological type n (%)				
	No Biopsy	**MCD**	**FSGS**	**MesPGN**	**Total**
SSNS	20 (30.8) (64.5)	39 (60) (56.5)	6 (9.2) (10.5)	0 (0.0) (0.0)	65 (100) (39.9)
SDNS	5 (17.2) (16.1)	18 (62.1) (26.1)	6 (20.7) (10.5)	0 (0.0) (0.0)	29 (100) (17.8)
SRNS	6 (8.7) (19.4)	12 (17.4) (17.4)	45 (65.2) (79.0)	6 (8.7) (100)	69 (100) (42.3)
Total	31 (19.0) (100)	69 (42.3) (100)	57 (35.0) (100)	6 (3.7) (100)	163 (100) (100)

Fisher's exact, $p < 0.001$

Table VII: The relationship between the racial groups and the steroid response patterns

Race	Steroid response pattern (%)			
	SSNS	**SDNS**	**SRNS**	**Total**
Black	39 (35.1) (60.0)	21 (18.9) (72.5)	51 (46.0) (73.9)	111 (100) (68.1)
Asian	13 (59.1) (20.0)	3 (13.6) (10.3)	6 (27.3) (8.7)	22 (100) (13.5)
Mixed	6 (37.5) (9.2)	2 (12.5) (6.9)	8 (50.0) (11.6)	16 (100) (9.8)
White	7 (50.0) (10.8)	3 (21.4) (10.3)	4 (28.6) (5.8)	14 (100) (8.6)
Total	65 (39.9) (100)	29 (17.8) (100)	69 (42.3) (100)	163 (100) (100)

Fisher's exact, $p = 0.434$

Ninety four (57.7%) patients responded to their first steroid course and, of those, 55 (33.7%) turned out to be infrequent relapsers and 10 (6.1%) became frequent relapsers. (Table V)

Twenty nine (17.8%) of the group of patients who were initially steroid sensitive later became steroid dependent, while 69 (42.3%) of the patients were steroid resistant from the outset. (Table V)

Table VI shows the various steroid response patterns of INS according to the different histopathological types. Minimal change disease was the most common type (60%) seen in SSNS, while FSGS was the most common type (65.2%) observed in patients who had SRNS.

There was a statistically significant association between the various steroid response patterns and the different histopathological types.

Six patients (8.7%) of the SRNS group were not biopsied. All six defaulted from follow up and subsequently presented at a later stage to our division with severe renal dysfunction requiring renal replacement therapy. (Table VI)

Table VII shows the relationship between the different racial groups and the various steroid response patterns. SSNS was seen more in the Asian (59.1%) and white groups (50%) while the mixed race and black racial groups had a higher incidence of SRNS (50% and 46%respectively). (Table VII)

There was no statistically significant association seen between the various racial groups and the different steroid response patterns (p=0.434).

Table VIII: The relationship between steroid response patterns and outcome of INS at 60 months mean follow up period

	Sustained remission without any treatment	Remission on steroid treatment alone	Remission on SSDs and steroid treatment	FRNS	Resistant to all treatment	Total
SSNS	53 (81.5) (100)	1 (1.5) (3.6)	0 (0.0) (0.0)	10 (15.5) (83.3)	1 (1.5) (1.6)	65 (100.0) (39.9)
SDNS	0 (0.0) (0.0)	27 (93.1) (96.4)	2 (6.9) (22.2)	0 (0.0) (0.0)	0 (0.0) (0.0)	29 (100.0) (17.8)
SRNS	0 (0.0) (0.0)	0 (0.0) (0.0)	7 (10.1) (77.8)	2 (2.9) (16.7)	60 (87.0) (98.4)	69 (100.0) (42.3)
Total	53 (32.5) (100.0)	28 (17.2) (100.0)	9 (5.5) (100.0)	12 (7.4) (100.0)	61 (37.4) (100.0)	163 (100.0) (100.0)

Fisher's exact, $p < 0.001$

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Table IX: The relationship between racial groups and outcome of INS at 60 months mean follow up period

Race	Sustained remission without any treatment	Remission on steroid treatment alone	Remission on SSDs and steroid treatment	FRNS	Resistant to all treatment	Total
Black	34 (30.7) (64.2)	22 (19.8) (78.6)	5 (4.5) (55.6)	5 (4.5) (41.6)	45 (40.5) (73.8)	111 (100.0) (68.1)
Asian	11 (50.0) (20.8)	2 (9.1) (7.1)	1 (4.6) (11.1)	3 (13.6) (25.0)	5 (22.7) (8.2)	22 (100.0) (13.5)
Mixed	3 (18.7) (5.7)	1 (6.3) (3.6)	2 (12.5) (22.2)	2 (12.5) (16.7)	8 (50.0) (13.1)	16 (100.0) (9.8)
White	5 (35.7) (9.3)	3 (21.4) (10.7)	1 (7.2) (11.1)	2 (14.3) (16.7)	3 (21.4) (4.9)	14 (100.0) (8.6)
Total	53 (32.5) (100.0)	28 (17.2) (100.0)	9 (5.5) (100.0)	12 (7.4) (100.0)	61 (37.4) (100.0)	163 (100.0) (100.0)

. . Fisher's exact, $p = 0.135$

Steroid sparing drugs (SSDs) were used in patients who were steroid dependent and steroid resistant. Nine of the SRNS patients were able to achieve remission with the use of SSDs. Seven of these remained in remission afterwards on SSDs and corticosteroid treatment, while two developed a frequently relapsing picture while on SSDs and corticosteroid treatment. (Table VIII)

The highest rate of resistance to all treatment after a mean follow up of 60 months was seen among children of the mixed race and black racial groups (50.0% and 40.5% respectively). (Table IX)

3.3: The complications from the disease and/or the treatment

The most common complications observed were stunted growth (52.1%), hypertension (47.2%), reduced eGFR (25.8%), peritonitis (12.9%) and pulmonary tuberculosis (8.6%). Other complications such as thromboembolic phenomenon (TEP), AKI and hypothyroidism were less common. (Table X)

A more detailed breakdown of the group with a reduced eGFR can be seen in Figure 4.

Hypertension, peritonitis, reduced eGFR and stunted growth were most commonly seen in patients with FSGS, and there was a statistically significant association between the presence of these complications and the various steroid response patterns and different histopathological types. (Table XI and XII)

Hypertension, peritonitis, reduced eGFR and stunted growth were most common in black children with INS when compared to the other racial groups but, of these complications, only hypertension showed any statistically significant association when comparing the different racial groups. (Table XIII)

Table X: The complications of INS		
		n (%)
Hypertension		
	Yes	77 (47.2)
	No	86 (52.8)
Peritonitis		
	Yes	21 (12.9)
	No	142 (87.1)
Reduced estimated glomerular filtration rate (eGFR)*		
	Yes	42 (25.8)
	No	121 (74.2)
Thromboembolic phenomenon		
	Yes	4 (2.5)
	No	159 (97.5)
Acute kidney injury		
	Yes	1 (0.6)
	No	162 (99.4)
Hypothyroidism		
	Yes	1 (0.6)
	No	162 (99.4)
Stunted growth		
	Yes	85 (52.1)
	No	78 (47.9)
Pulmonary tuberculosis		
	Yes	14 (8.6)
	No	149 (91.4)
Hyperglycaemia		
	Yes	4 (2.5)
	No	159 (97.5)
Psychosis		
	Yes	2 (1.2)
	No	161 (98.8)
Chicken pox		
	Yes	1 (0.6)
	No	162 (99.4)
Obesity		
	Yes	1 (0.6)
	No	162 (99.4)
Cataract		
	Yes	1 (0.6)
	No	162 (99.4)

* See Figure 4 for the breakdown of reduced eGFR.

Figure 4: Breakdown of group with a reduced eGFR (ml/min/1.73m^2)(n=42)

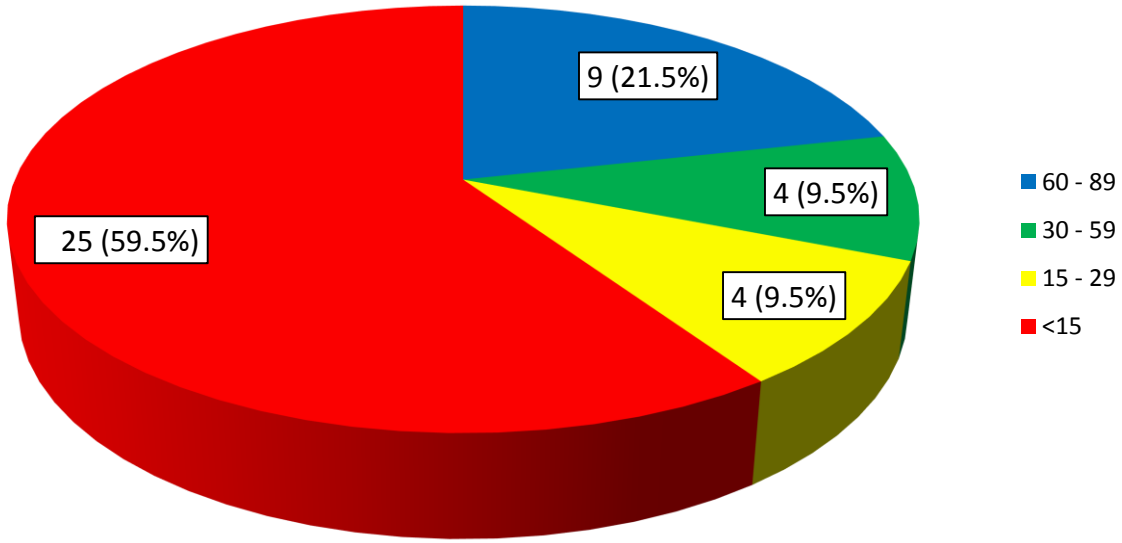

Table XI: The relationship between the common complications of INS and the histopathological types

Complications	Histopathological types = n (%)			
	MCD (n=69)	**FSGS (n=57)**	**MesPGN (n=6)**	**P value**
Hypertension	14	46	5	<0.001
Peritonitis	6	12	2	0.044
Reduced eGFR	6	24	5	<0.001
Stunted growth	25	43	5	<0.001

Table XII: The relationship between the common complications of INS and the steroid response patterns

Complications	Steroid response pattern			
	SSNS (n=65)	SDNS (n=29)	SRNS (n=64)	P value
Hypertension	12	6	59	<0.001
Peritonitis	2	3	16	<0.001
Reduced eGFR	4	2	36	<0.001
Stunted growth	20	11	54	<0.001

Table XIII: The relationship between the common complications of INS and the different race groups

Complications	Race group = n (%)				
	Black (n = 111)	Asian (n = 22)	Mixed (n =16)	White (n = 14)	P value
Hypertension	59	8	8	2	0.030
Peritonitis	15	2	3	1	0.795
Reduced eGFR	34	3	4	1	0.143
Stunted growth	60	12	7	6	0.778

4. DISCUSSION

In this single centre study, we did a 10 year review of children with idiopathic nephrotic syndrome (INS). One hundred and sixty three children met the selection criteria and their records were reviewed.

The study found a male preponderance with a male: female ratio of 1.46:1 which is similar to various studies done elsewhere. (5,6,12,41,45) The mean age at presentation was 5.3 years ± 2.8. This finding is lower than that described by Bhimma *et al* in Durban (6.2 years) and other studies reported from India (7.9 years), New Zealand (6.1 years) and Pakistan (7.26 years). (5,12,17,80) A study from the USA reported a similar age at presentation (5.3 years) to our study, (11) while studies from Iran and Turkey reported a lower age at presentation of 4.9 years and 4.6 years respectively. (9,45) These differences in the age of presentation may be due to ethnic differences in the patient demographics of the various studies mentioned above. In the case of the studies from India, Pakistan and New Zealand, the majority of the patients were Asian, whereas the study from the USA had a much more diverse patient group in terms of ethnicity than the other studies. Although we expected our study cohort to have a similar age of presentation to that of the Durban study, the Durban study had a higher percentage of Asian patients in their cohort than we had in ours and it is possible that this made their mean age of presentation closer to that observed in the studies from India, Pakistan and New Zealand than to that of our study.

Our study found the highest rate of INS in the age group 2 to 6 years. This is similar to that which has been reported from Pretoria, Iran and New Zealand and other Western countries. (1,6,9,17)

In our study, black children made up the predominant race group (68.1%). This is in keeping with the racial distribution of the general population of Johannesburg. Similarly, the study from Pretoria also reported a cohort made up predominantly of black patients (77.7%). (6) The study from Pretoria had only two racial groups in the study, white and black, and this may explain the greater percentage of black patients reported in their findings as compared to our study. On the contrary, the study from Durban reported the Indian (Asian) race to be the predominant group (52.5%), with the black race representing only 43.3% of the patients. (5)

There were various indications for renal biopsy in our group of patients; the most common were steroid resistance (29.5%), a frequently relapsing picture (25%) and an atypical presentation (24.3%). Other studies have also documented these same reasons as the most frequent indications for biopsy. (9,11,12,17,41,45,80) Some units in South Africa had a policy to biopsy all patients from the black race group, however this policy was not followed in our unit. (5,6)

Minimal change disease (MCD) accounted for the most common histopathologic variant observed in our cohort (52.3%). This is similar to the report from Pakistan where MCD accounted for 51.2%. (80). Other studies, including previous South African studies, have reported a much lower rate of MCD (<36%). (5,6,12,41,45) It is possible that these apparent differences in the rate of MCD in children may be due to variations in the indications for biopsy in the different studies (where the most common indication was steroid resistance) rather than actual differences in the rate of MCD in the various population groups studied.

Focal segmental glomerulosclerosis (FSGS) was found to have a rate of 43.2% in our study which is higher than the rates reported in previous South African studies namely 28.5% in the Durban study, 25% in the Pretoria study and 31.3% in a study from Johannesburg. (5,6,10) One

possible reason for this finding may be the decline of infection related nephrotic syndrome (NS) which up until now was one of the most common causes of NS in children and presented as other histopathological subtypes such as Membranous Nephropathy (MN) and Membranoproliferative glomerulonephritis (MPGN). (5) Other possible reasons include the postulation that suggests the transition of MCD to FSGS in selected cases, although this has yet to be proven, and the very real possibility of misdiagnosing FSGS as MCD due to technical challenges or sampling error. (1,2)

As has been also noted in previous studies, in our cohort, the age of presentation of FSGS was most common in the age group of 2-6 years. (5,45)

Mesangial proliferative glomerulonephritis (MesPGN) was the least common histopathologic variant observed in our study (4.5%). Even though higher rates have been reported from India (11.4%), Turkey (17%) and the US (25%), our findings are in keeping with rates reported in previous South African studies. (5,6,11,12,45)

Ethnicity has been implicated in playing a role in the histopathological types of INS. Studies with diverse patient cohorts have reported a higher rate of FSGS in the black race group. (5,6,11) Similarly, in our group FSGS made up a larger proportion of cases in the black race group when compared to the other race groups.

Despite the inhomogeneous nature of our cohort, we observed an initial response rate to steroid therapy of 57.7% and a steroid resistance rate of 42.3%. This is almost similar to the steroid response pattern reported from Pakistan, even though they had a much more homogeneous cohort. (80) Studies from New Zealand and Iran reported much higher steroid response rates of 80.4% and 75.2% respectively. (9,17)

A similar rate of frequent relapse (10.6%) and steroid dependence (17.8%) was observed in our steroid sensitive group of patients to that which was reported in the study from New Zealand. (17)

Although we observed a high rate of steroid resistance among the black racial group in our study, this group also had a high rate of steroid sensitivity (35.1%). This is contrary to reports from previous South African studies and the traditional belief that most black children are steroid resistant. (5,6,10)

We also observed that the mixed racial group exhibited a similar steroid response pattern to the black racial group.

A small fraction of the MCD group was steroid resistant (17.4%), and likewise a small fraction of the FSGS group was steroid sensitive (21%). These findings are in keeping with findings reported elsewhere. (9,12,17,45,80)

Unexpectedly, we did not find any significant statistical association between racial distribution and the histopathological types, or any association between racial distribution and steroid response pattern.

Various complications were observed in our cohort; these were due to the disease itself and also related to adverse effects of the treatment administered to the patients. The most common complication observed was hypertension which was found in 47.2% of the patients. This finding is similar to the rate reported by the study from Pretoria (47.8%). (6) High rates of hypertension were seen mostly in patients with FSGS (46/57), SRNS (59/64) and in those of the black and mixed race racial groups (59/111 and 8/16 respectively). In addition, we also found a statistically significant association between hypertension and racial group. The Durban study reported a very

low rate of hypertension (2.2%). We believe that this is because, in that study, hypertension was only mentioned in the context of steroid related complications, whereas in our study we reported on hypertension as a complication across the board. (5)

Peritonitis is a common complication seen in INS. In our study, 12.9% of the patients had one or more episodes of peritonitis. This rate is higher than what has been reported in previous South African studies where the reported rate was closer to 7%. (5,6)

Previous reports have noted a reduced eGFR (<90ml/min/1.73m^2) in patients with SRNS. These patients are at risk of progression to ESKD (<15ml/min/1.73m^2). (6,41) At least a quarter of our patients (25.8%) had a reduced eGFR but this rate is lower than what was reported in the study from Pretoria (35.8%). (6) Among our cohort with reduced eGFR (42/163), 25 (59.5%) were already in ESRD. We also observed that six patients with steroid resistance, who defaulted at some point from follow-up, were amongst the group with ESRD.

A high rate of stunted growth was observed in about half of our cohort (52.1%). This very important finding was observed as a late outcome of the disease or treatment. The finding may be partly explained by longer courses of steroids given to patients with SRNS, in an attempt to effect remission, and also because of the high rate of a reduced eGFR in our cohort. Furthermore, in our centre, patients are maintained on low dose steroid therapy even when in remission or on steroid sparing drugs.

Thrombo-embolic phenomena were observed in only four children in our cohort (2.5%), a rate similar to that noted in reports from elsewhere. (6,17) This low rate may be due to the routine use of low dose aspirin in our patients with INS.

It is often difficult in children to obtain a confirmatory diagnosis of pulmonary tuberculosis (PTB) due to the low yield from specimens (sputum and blood) sent for laboratory investigation. For this reason most diagnoses are made based on clinical suspicion and then a response to empirical treatment. In our cohort 14 children (8.6%) were treated for PTB based on clinical signs. None had sputum positive PTB. This rate is much lower than what has been previously reported in South Africa. (7) Possible reasons for this difference may include an overall improved health status of the indigent community in South Africa, better detection and treatment of PTB in the general community and the increased use of HAART in the general population. (81) It is also possible that the authors of the previous study may have had a much higher index of suspicion for PTB than did our unit. (7)

5. CONCLUSIONS

Our cohort demonstrated the same age pattern at presentation of INS as has been documented previously, with the age group 2-6 years being the most common age of presentation, and the racial distribution observed in our study is in keeping with that of the general population pattern of Johannesburg.

We found higher rates of MCD, and also of favourable steroid response patterns, in our black race group than have been previously reported from South Africa.

Of concern is our finding of an increase in the rate of FSGS in all the racial groups when compared to previous studies and we are not sure if this represents a new trend that FSGS is increasing in our population. If our finding of an increase in the rate of FSGS when compared to previous South African studies is real, this may mean that in the future we might begin to see an increase in the rate of steroid resistance among South African children with INS.

In our study the highest rates of a reduced eGFR were observed among those patients with SRNS and among those with FSGS. Given the high rate of SRNS and FSGS in our group of black patients, there is concern that this group would be at a high risk of going on to develop a reduced eGFR in the future.

Even though hypertension was the most common complication observed in our cohort, a very high rate of stunted growth was also observed. Based on this we will be limiting the routine use of long term steroid therapy in our steroid resistant patients in the future.

We hope that the results of this research will be useful in improving the care of children with INS in our unit.

6. RECOMMENDATIONS

Our study did not include patients from the private sector who are on medical aids. It is possible that these patients, who are more likely to come from better socio economic circumstances, may have a slightly different spectrum of disease than that seen in our cohort. Also, another limitation of our study is that it is of a retrospective nature. In light of the above, we would suggest that the time has come for a prospective, multicentre, national study on childhood INS in South Africa. Specific factors to be addressed might include a careful documentation of the clinical presentation and histopathological findings of the disease, genetic evaluation, and then an assessment of the steroid response patterns to strict study protocols. A study of this nature will give us a clearer of picture of the rate of FSGS and steroid responsiveness in South Africa, and will also enable us to tailor treatment regimens unique to our patients.

Unfortunately, the nature of our data was such that we could not compare the response rates of our patients to the other agents used in SRNS. We would suggest that this be taken into account when planning further research on this topic.

In view of the high rates of short stature observed in our study we will be adjusting our treatment regimes to shorter and lower dose courses for steroid responsive INS, and will be withdrawing steroids sooner in patients who have shown themselves to be steroid resistant. The question of how long one should persist with steroid therapy, and at what dose, in South African children with SRNS has not yet been clearly answered, hence our recommendation for the performance of a multicentre national trial.

APPENDIX A: Data collection sheet

1. General information

Study number	
Enrolment date	
Date of birth	
Age (years)	
Sex	☐ Male ☐ Female
Race	☐ Black ☐ White ☐ Mixed ☐ Asian

2. Medical history

Age at diagnosis (years)	
Follow up period (months)	
Atypical presentation	☐ Haematuria ☐ Hypertension
Steroid response	☐ SSNS ☐ SRNS
Relapse	☐ FRNS ☐ IFRNS ☐ SDNS
Renal biopsy	☐ Yes ☐ No
Histopathological report	☐ MCD ☐ FSGS ☐ MesPGN
Steroid sparing drugs (SSDs)	☐ yes ☐ no
Type of SSDs	☐ Cyclophosphamide ☐ Chlorambucil ☐ Cyclosporine ☐ Tacrolimus ☐ MMF ☐ Others
Renal biopsy	☐ Yes ☐ No

Comments:

3. Outcome of treatment

Sustained remission without any treatment	☐	Remission on only steroid treatment	☐
Remission on SSDs and steroid treatment	☐	Frequent relapse to all treatment	☐
Resistant to all treatment	☐		

4. COMPLICATIONS

Hypertension	☐ Yes ☐ No
Stunting	☐ Yes ☐ No
Infection	☐ Yes ☐ No
Types of infection	☐ RTI ☐ Peritonitis ☐ PTB ☐ Chicken pox ☐ Others
Reduced eGFR (<90 ml/min/1.73m^2)	☐ Yes ☐ No
Breakdown of eGFR <90 ml/min/1.73m^2	☐ 60-89 ☐ 30-59 ☐ 15-29 ☐ <15
Hyperglycaemia	☐ Yes ☐ No
Thromboembolic phenomenon	☐ Yes ☐ No
Acute kidney injury	☐ Yes ☐ No
Hypothyroidism	☐ Yes ☐ No
Psychosis	☐ Yes ☐ No
Obesity	☐ Yes ☐ No
Cataract	☐ Yes ☐ No

APPENDIX B: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Yassir Mahgoub Bakhiet

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150234

NAME: (Principal Investigator)	Dr Yassir Mahgoub Bakhiet
DEPARTMENT:	Paediatrics and Child Health Paediatric Nephrology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A 10 Year Review of Idiopathic Nephrotic Syndrome in Children; A Single Centre Experience, Johanneburg, South Africa
DATE CONSIDERED:	27/02/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Cecil Levy

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 02/03/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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