ACUTE POST STREPTOCOCCAL GLOMERULONEPHRITIS AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL, CAPE TOWN, SOUTH AFRICA - A FIVE-AND HALF-YEAR DESCRIPTIVE REVIEW

Master of Philosophy in Paediatric Nephrology

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Date of Submission 18th of October 2021

Declaration

I, Khadija Ali Mohamed Abugrain declare that

(i) The research reported in this dissertation is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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Dedication

In dedication to my parents. I take this opportunity to express my gratitude for their care and support over the years, and to thank them for instilling me with a strong passion for learning and for doing everything possible to put me on the path to success.

And to my husband for all his kindness and endless support in reaching my achievement.

It is my genuine gratefulness and warmest regard that I dedicate this work to International Paediatric Nephrology Association for funding me with a scholarship for the successful fulfilment of my paediatric nephrology training program.

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Abstract

Background: Acute post streptococcal glomerulonephritis (APSGN), although not a common cause of progressive kidney failure, is an important cause of paediatric hospital admission, parental worry, and acute kidney injury (AKI). In well-resourced settings, there has been a decline over the last three decades in the incidence of APSGN in children with this condition almost disappearing in Central Europe. However, this is not the case in less privileged countries such as in South Africa (SA) where APSGN is still a major public health problem and a frequent cause of paediatric hospital admission and AKI. Nevertheless, APSGN in South Africa has not been studied adequately in recent times and not currently addressed as an important public health issue.

Objectives: In this retrospective study we describe the occurrence of APSGN, the aetiology, clinical presentation, and complications among children (<14years) admitted to the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, SA from January 2015 to June 2020.

Methods: The hospital electronic database with recorded ICD-10 coding was used to identify potential cases of acute nephritic syndrome. Children were included if they presented with at least two signs of acute nephritis, associated with evidence of activation of an alternative pathway complement system (low C3 serum level) or clinical and serological evidence of previous or current streptococcal infection. Demographic, clinical features, investigations, management, and outcome data were collected. Data were presented as median and interquartile ranges (IQR) or means and standard deviation (SD) depending on normality of data while proportions of categorical data were presented as percentages. Population incidences were calculated from the four major health districts within the drainage areas for RCWMCH. This study was conducted in accordance with the 2013 Declaration of Helsinki and was approved by RCWMCH administration and the University of Cape Town's Human Research Ethics Committee, (HREC: 623/2020).

Results: There were 157 children with suspected acute nephritic syndrome (haematuria, oedema, oliguria and hypertension), of whom 96 met the inclusion criteria and were recruited. Of the 96 children included in the study, 89 (93%) cases had confirmed APSGN, and seven (7%) children had a clinical diagnosis of rapidly progressive glomerulonephritis (RPGN), with positive streptococcal serology and crescentic glomerulonephritis in the kidney

biopsy. APSGN occurred in 61 (63%) children aged five to ten years with 62 (65%) males (ratio of 1.9:1). APSGN was more often associated with streptococcal skin infections (55%). The majority 95 (99%) of cases presented with haematuria, while proteinuria was noted in 85 children. Seventy-one (74%) children presented in stage 2 hypertension, with 10 (10%) presenting with hypertensive seizures. Serum C3 levels were low in 83 (87%) children. 90 (94%) children had elevated anti-deoxyribonuclease B antibodies (anti-DNase-B) levels, and 77 (80%) also had elevated anti-streptolysin O titres (ASOT) titres at presentation. Eighty-eight (92%) children received a diuretic agent, 60 (63%) required an anti-hypertensive agent, and 90 (94%) received a penicillin antibiotic for 10 days. The median length of hospital stay was five (IQR 3-6) days. There were no deaths. Eighty-one (85%) children with APSGN recovered. Five (5%) progressed to end stage kidney disease (ESKD). A percutaneous kidney biopsy was indicated in eleven (11%) children. Seven (64%) biopsies confirmed type II crescentic glomerulonephritis, and four (36%) biopsies showed histological features of post-infectious nephritis.

Conclusion: APSGN during childhood remains an important health problem in SA and commonly follows streptococcal skin infection. The outcome is favourable in most children; however, our study revealed an important sub-group with crescentic glomerulonephritis who progressed to ESKD. We recommend active case seeking at primary care level by checking urine dipstick, blood pressure and serum creatinine and better post-discharge follow up.

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Abbreviations

APSGN	Acute post streptococcal glomerulonephritis
AGN	Acute glomerulonephritis
ESKD	End stage kidney disease
GAS	Group A beta haemolytic streptococci
AKI	Acute kidney injury
PRES	Posterior reversible encephalopathy syndrome
WHO	World Health Organization
RBCs	Red blood cells
RPGN	Rapidly progressive glomerulonephritis
C3	Complement 3
C4	Complement 4

CHAPTER 1

Introduction

Diseases involving the renal glomeruli are encountered frequently in paediatric nephrology clinical practice with glomerulonephritis accounting for 10-15 % of ESKD [1]. Post infectious glomerulonephritis is an immunological response of the kidney following non-renal infection, most commonly secondary to Group A β-haemolytic streptococcus (GAS) [2], and may also result from other infections of the skin or throat. APSGN although not a common cause of progressive kidney failure, is an important cause of paediatric hospital admission, AKI and parental worry because of the accompanying haematuria. APSGN usually occurs one to three weeks post streptococcal skin or throat infection. It predominantly presents between the ages of five and twelve years, with a male to female ratio of 2:1. APSGN is unusual before the age of three years [3]. GAS is an important cause of morbidity and mortality, as indicated in a recent population-based data systematic review to estimate the global burden of GAS disease. There are at least 517 000 deaths each year due to severe GAS diseases. More than 616 million incident cases of GAS pharyngitis and over 111 million prevalent cases of GAS skin infection are estimated to occur each year [4], with a risk of glomerulonephritis after a nephritogenic GAS infection of 10–15 percent [5]. In tropical and subtropical countries, there is a tendency to have skin infection-associated APSGN [6], rather than the pharyngitis-associated APSGN found more predominantly in temperate climate areas [7, 8].

A recent review of the epidemiology of skin infection in children in low income settings by the World Health Organization's (WHO) Department of Child and Adolescent Health and Development, indicated that impetigo and scabies have been considered a major public health problem in low and middle income countries (LMIC) for decades, with little recent progress in their prevention and treatment [9]. The review described the main aetiological factors contributing to the increased prevalence of skin infections in low-middle-income settings, to be that of inadequate hygiene and poor access to water [9]. High interpersonal contact and household density has been also been recognized by the WHO as an aetiological factor increasing the incidence of transmissible skin infections like impetigo and scabies [9].

South Africa has been facing drought for the last 5 years with certain parts of the country consequently being classified disaster regions in 2017. When the drought was at its worst, the use of water was restricted to only 50L per

person daily during 2018 [10]. The situation has persisted with some provinces reporting drought into 2020 [11]. The country faces a global phenomenon where water is constrained in quality and quantity that results in a real concern over public health as 30% of the children in SA have no access to on site water, and 18% live in overcrowded households [12].

In high-income and some low- and middle-income settings, there has been a decline over the last three decades in the incidence of APSGN in children with this condition almost disappearing in Central Europe [13]. However, this is not the case in other low socioeconomic settings, such parts of South Africa, where APSGN is still a major public health problem and a frequent cause of paediatric hospital admission and AKI. Nevertheless, APSGN in South Africa has not been studied adequately in recent times and not currently addressed as an important public health issue. The characteristics of the streptococcal infection involved, and the immunological responses of the patients are unknown. The epidemiology and geographical distribution of streptococcal infection related glomerulonephritis are not well known across the country. However, some provinces like Gauteng reported a decline in the incidence of APSGN in children (personal communication, Petersen K. paediatric nephrologist, Witwatersrand University, Johannesburg, S A ed2020, April 17). While other provinces such like KwaZulu-Natal, Eastern Cape and Western Cape provinces reported a persistent high incidence of APSGN in children. (Personal communication Naicker E. paediatric nephrologist, Inkosi Albert Luthuli Central Hospital, University of Kwazulu Natal, Durban, SA. ed2020, April 9, and Russion D. paediatric nephrologist, Cecilia Makiwane Hospital East London Hospital, Walter Sisulu University of Eastern Cape. ed2020, April 23).

The mortality from APSGN is estimated to be around 1%, either in the acute phase or from long-term kidney failure [4]. Short term fatalities may occur as a result of hyperkalaemia, pulmonary oedema or seizures related to posterior reversible encephalopathy syndrome (PRES) but they are exceedingly rare.

The clinical presentation of APSGN can range from unrecognized, asymptomatic acute glomerulonephritis (AGN) manifesting with microscopic haematuria and a transient decrease in serum complement activity, to full-blown AGN, characterized by red- to brown-coloured urine, proteinuria, oedema, hypertension, and an elevation in serum creatinine [14]. Some children may even present with serious complications such as hypertensive emergency,

congestive cardiac failure with pulmonary oedema, kidney failure, posterior reversible encephalopathy syndrome, and retinopathy [15]. The most constant serological finding is the reduction in serum complement levels that occurs in approximately 90 percent of cases. The activation of the complement system is usually via the alternative complement pathway marked by reduction in serum C3 and CH50. Anti-streptolysin O titre and anti-DNAse B titre tests are widely available and the most frequently elevated antibodies in upper respiratory infections and skin infection, respectively. In one study the sensitivity of ASO, and Anti-DNase B was 78.4% and 64.9% while the specificity was 89.2% and 91.9% respectively [15].

Rapidly progressive (crescentic) glomerulonephritis (RPGN) is a severe form of glomerulonephritis that characteristically presents with a rapid deterioration in kidney function over days, weeks or months. The kidney damage is often severe and irreversible and will often progress to ESKD [3]. Crescentic glomerulonephritis is seen in less than 0.5 percent of APSGN kidney biopsies [7].

There is no specific therapy to cure APSGN, and management is mainly based on eradication of the streptococcal infection and on supportive treatment of symptoms and complications as required [15].

The outcome of APSGN is usually favourable, particularly in children. Most children will have complete clinical recovery with resolution of their disease process beginning within the first two weeks [13]. The long-term prognosis of APSGN has been the subject of many reports. A review of three case series of 229 children with APSGN found that more than 90% had normal or only modestly reduced kidney function five to 18 years after the APSGN episode [13]. A combined analysis of reported data, indicates that 20 % of the children followed up for 10–20 years after APSGN, have an abnormal urine analysis but azotaemia was found in less than 1 % of the patients [13]. Nevertheless, APSGN was significantly correlated with increased incidence of reduced glomerular filtration rate and thus long-term follow-up of hypertension and proteinuria would be recommended.

Ethical considerations

Ethical permission to conduct the study was obtained from: see appendix

The Department of Paediatrics and Child Health Research Committee.

The University of Cape Town Human Research Ethics Committee (HREC: 623/2020).

The RCWMCH Research Committee. (RCWMCH RCC248/ WC _202011_001)

All data has been recorded anonymously with a study number, and only the principal investigator has access to the clinical record numbers of the participant. Data collected were de-identified and saved in a password protected file.

Journal for which the paper has been formatted

The journal chosen for publication of manuscript is the **Journal of the International Paediatric Nephrology Association.**

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CHAPTER 2: PUBLICATION-READY MANUSCRIPT

A Review of Acute Post-Streptococcal Glomerulonephritis at the Red Cross War Memorial Children's Hospital, Cape Town, South Africa

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Abstract

In this retrospective study we describe the occurrence of acute post streptococcal glomerulonephritis (APSGN) among children (<14years) admitted to the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa (SA) from January 2015 to June 2020. There were 157 cases of acute nephritic syndrome (haematuria, oedema, oliguria and hypertension), 96 met the inclusion criteria and were recruited. Demographic, clinical features, laboratory findings, management, and outcome data were collected. Data were presented as medians (IQR) or means (SD), while categorical data were presented as proportions. APSGN was defined based on the clinical presentation of at least two signs of acute nephritis, a low serum complement 3 (C3) level or evidence of a recent streptococcal infection. APSGN was more often associated with streptococcal skin infections (55%). Seventy-one (74%) children presented in stage 2 hypertension, with 10 (10%) presenting with hypertensive seizures. C3 levels were low in 83 (87%) children; 90 (94%) children had elevated anti deoxyribonuclease-B (anti-DNase-B) levels, and 77 (80%) also had elevated anti-streptolysin O titre (ASOT) at presentation. A percutaneous kidney biopsy was indicated in eleven (11%) children. Seven (64%) biopsies confirmed type II crescentic glomerulonephritis, and four (36%) showed histological features of post-infectious nephritis. While 81 (85%) children recovered, five (5%) progressed to end stage kidney disease (ESKD). Childhood APSGN remains an important health problem in SA with favourable outcome in most cases apart from those with crescentic glomerulonephritis who progressed to ESKD.

Keywords: APSGN, Group A streptococci, haematuria, proteinuria, children.

Introduction

Diseases involving the renal glomeruli are encountered frequently in paediatric nephrology clinical practice with glomerulonephritis accounts for 10-15 % of ESKD in children [1]. Post-infectious glomerulonephritis is an immunological response of the kidney following non-renal infection, most commonly secondary to Group A β-haemolytic streptococcus (GAS) [2] and may also result from other infections e.g., *Mycoplasma pneumoniae* and *Staphylococcus aureus*. APSGN, although not a common cause of chronic kidney disease (CKD), is an important cause of paediatric hospital admissions, acute kidney injury (AKI) and parental concern because of the accompanying haematuria and oedema. In high-income country (HIC) and some low and middle-income country(LMIC) settings, there has been a decline over the last three decades in the incidence of APSGN in children, with this condition almost completely disappearing in Central Europe [3]. Information from Africa about APSGN epidemiology in children is scarce. Yet some reports from Nigeria and Ethiopia have confirmed APSGN is still a major public health problem, and a frequent cause of paediatric hospital admission and AKI [4-7]). APSGN in SA has not been studied adequately in recent times and is not currently addressed as an important public health issue. The epidemiology and geographical distribution of streptococcal infection-related glomerulonephritis is not well known across the country and is likely under-reported.

Methods

This retrospective descriptive study was conducted from January 2015 to June 2020 at the RCWMCH, Cape Town, SA. The RCWMCH provides a secondary, tertiary and quaternary level services, offering care for common general paediatric diseases and all major paediatric specialties, and drains a large population base of both urban and semi-urban communities from Western Cape Province. The hospital also serves as a national and international referral hospital for multidisciplinary subspecialty care. The health care system also allows children without complications to be managed at regional centres. The hospital's electronic database with recorded International Statistical Classification of Diseases (ICD-10) discharge codes was used to identify potential cases of acute nephritic syndrome.

Children were included if they presented with at least two signs of acute nephritis syndrome (haematuria, oedema, oliguria and hypertension), associated with evidence of activation of an alternative pathway complement system (low C3 serum level) or clinical and serological evidence of previous or current streptococcal infection (**Table1**). Children found to have causes of acute glomerulonephritis other than APSGN were excluded. The Cape Town Census and Population Statistics 2011 database (*Cape Town census and population statistics*) provided the denominator for estimating population level incidences as adjusted to the risk of increase in population number during study period [8]. The source population (incidence denominator) included the average Cape Town city children (≤ 14 years old) population from the four health districts (Western, Southern, Klipfontein, and Mitchells Plain suburbs) referring to RCWMCH during the study period. Annual incidence per 100 000 calculations were done for the 5-year period 2015 to 2019. The year 2020 only included 6 months data as it was interrupted by the COVID-19 pandemic, hence this year was not included in the incidence calculations, although all patients seen up to end June 2020 were included in the overall descriptive analysis. In a sub-analysis, we looked at the incidence rates per 100 000 children from socio-economically deprived suburbs.

Frequency of APSGN was described by geographical area with respect to socio-economic standards and the availability of access to formal housing, clean water and sanitation. These were seen as potential risk factors contributing to the occurrence of APSGN. Continuous data were presented as median and interquartile ranges (IQR) or means and standard deviation (SD), depending on the normality of data, while proportions of categorical data were presented as percentages. Serological marker levels of streptococcal infection were recorded, along with anti-streptolysin O titres (ASOT) and or anti-deoxyribonuclease B antibodies (Anti-DNase-B). Generic upper limits of normal values defined by the SA National Health Laboratory System using Laser Nephelometry technique (Beckman Coulter) were used. For ASOT, the upper limits of normal values are age-specific and are given as follows: <6 years 100 IU/ml, 6-12 years 250 IU/ml, >12 years 200 IU/ml. According to local laboratory reference ranges, the normal anti-DNase-B reference range for children is < 75 IU/ml. This study was conducted in accordance with the 2013 Declaration of Helsinki and was approved by RCWMCH administration and the University of Cape Town's Human Research Ethics Committee (HREC), (HREC: 623/2020).

Table 1: Operational Definitions

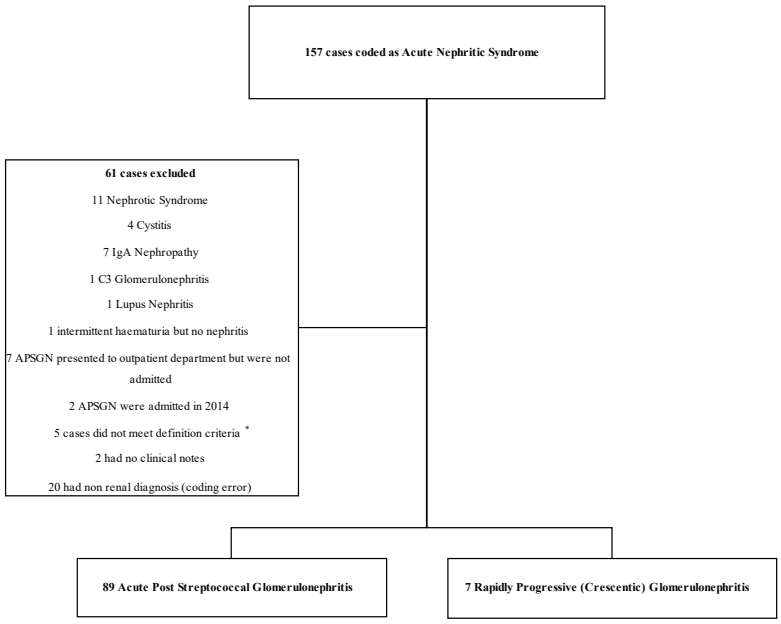
Parameter	Definition
Oliguria	Urine volume less than 0.5 mL/kg/hr.
Clinical oedema	Puffiness of the face, bilateral pitting pedal oedema, and abdominal wall oedema.
Microscopic Haematuria	Blood in the urine that is detectable by a bedside urine dipstick ≥2 +
Macroscopic Haematuria	Frankly blood-stained, visible pink or brown coloured urine owing to the presence of RBC - confirmed by microscopic examination.
Proteinuria	Used normal values of protein excretion as a function of age [9] • Children 1–2 years > 0.04 g Protein/mmol Creatinine • Children 2–3 years > 0.03 g Protein/mmol Creatinine • Children 3–5 years > 0.02 g Protein/mmol Creatinine • Children >5 years > 0.015 g Protein/mmol Creatinine
Nephrotic Range Proteinuria	Spot urine protein/creatinine ratio of > 0.2 g/mmol or 3 + of protein on the urine dipstick [10].
Acute kidney injury (AKI)	Age specific normal ranges of enzymatic creatinine were used to diagnose AKI as per the following references [9]. • Children < 2 years old 9- 32 umol/L • Children 2 to < 5 years old 18-38 umol/L • Children 5 to < 12 years old 27- 54 umol/L • Children > 12 years old 40-72 umol/L
Acute Nephritis	A syndrome of AKI, hypertension, haematuria, proteinuria and fluid overload [11].
Rapidly progressive glomerulonephritis (RPGN)	Glomerular disease (proteinuria, haematuria and red cell cast) accompanied by rapid loss of renal function with rising creatinine over days to weeks [11].

Results

194 During the five and a half-year period under review, 157 children were identified as acute nephritic syndrome by

195 ICD-10 coding in the hospital database, of whom 96 met the inclusion criteria and were recruited (**Figure 1**).

196 **Figure 1: Flow Diagram of Patient Recruitment**



*no known complement level or antistreptococcal serology

Of the 96 children included in the study, 89 (93%) cases had confirmed APSGN, and seven (7%) children had a clinical diagnosis of rapidly progressive glomerulonephritis (RPGN), with positive streptococcal serology and crescentic glomerulonephritis in the kidney biopsy. In this study, the population incidence of APSGN in Cape Town was calculated at 3.6 per 100,000 (**Table 2**). Nevertheless, distribution by communities showed a greater number of cases in communities with a lower socio-economic level and poor access to piped water inside their dwellings; (**Table 3**) shows the incidences from six such areas.

Table 2: Annual incidence of APSGN per 100 000 in children under 14 years of age in Cape Town (2015-2019)

Year	2015	2016	2017	2018	2019	5-Year average
Population size	494 213	501 748	509 097	515 207	519 189	507 891
Cases per year	11	19	23	19	19	18.2
Incidence rate	2.2	3.7	4.5	3.6	3.6	3.6

APSGN: acute post streptococcal glomerulonephritis

Table 3: Cape Town under 14 average incidences of APSGN per 100 000 population by suburb (2015-2019)

Suburb	Cases APSGN (5-year average)	Average population	Incidence rate	Population with access to inhouse piped water
Nyanga	9 (1.8)	17 487	10.3	53.5%
Gugulethu	14 (2.8)	28 215	9.9	47.6%
Philippi	15 (3)	60 480	4.9	26.00%
Manenberg	7 (1.4)	19 282	7.2	89.3%
Langa	4 (0.8)	14 757	5.4	49.6%
Mitchells Plain	5 (1)	94 277	1.06	95.9%
Rest of drainage area*	37 (7.4)	273 393	2.7	Variable

*Children from these areas may have presented to other facilities APSGN: acute post streptococcal glomerulonephritis

Patient characteristic, clinical presentation, diagnosis and laboratory finding summarized in **table 4**. Of the 53 children with identified skin infections, 10 (19%) were treated for scabies and three (6%) were treated for tinea corporis.

Table 4: Patient characteristics, clinical presentation, diagnosis and laboratory findings of the study children

	Clinical presentation	Count	Percent
Age (years)	mean age at presentation	7.7 (SD 3.03)	
Sex	Male to female ratio	1.9:1	
Nutrition[#]	Normal weight-for-age	76	79
	Moderate underweight-for-age	2	2
	Severe underweight-for-age	0	0
HIV infection	Screened for HIV infection	75	
	HIV infected	0	

Clinical presentation with nephritic syndrome	Haematuria	95	99
	Sub-nephrotic range Proteinuria	37	39
	Nephrotic-range Proteinuria	48	50
	Oedema	84	88
	Oliguria / Anuria	29 / 1	30/ 1
	Hypertension Stage 1	7	7
	Hypertension Stage 2	71	74
	Hypertensive encephalopathy	10	10
	PRES on brain imaging	8	8
Source of Streptococcal infection	Skin infection	53	55
	Throat infection	23	24
	Skin and throat infection	9	9
	No source identified	11	12
Serum C3 level	Low C3	83	87
	Normal C3	6	6
	Unknown C3	7	7
Antistreptococcal serology	Elevated anti-DNase-B	90	94
	Elevated ASOT	77	80
	Unknown AS serology	6	6
Diagnosis	APSGN	89	93
	RPGN Crescentic	7	7

C3: complement 3; HIV: human immunodeficiency virus; AS: antistreptococcal serology; APSGN: acute post-streptococcal glomerulonephritis; RPGN: rapidly progressive glomerulonephritis; PRES: posterior reversible encephalopathy syndrome. * Discharge weights after resolution of oedema was used to calculate nutritional status for children using WHO weight-for-age charts.

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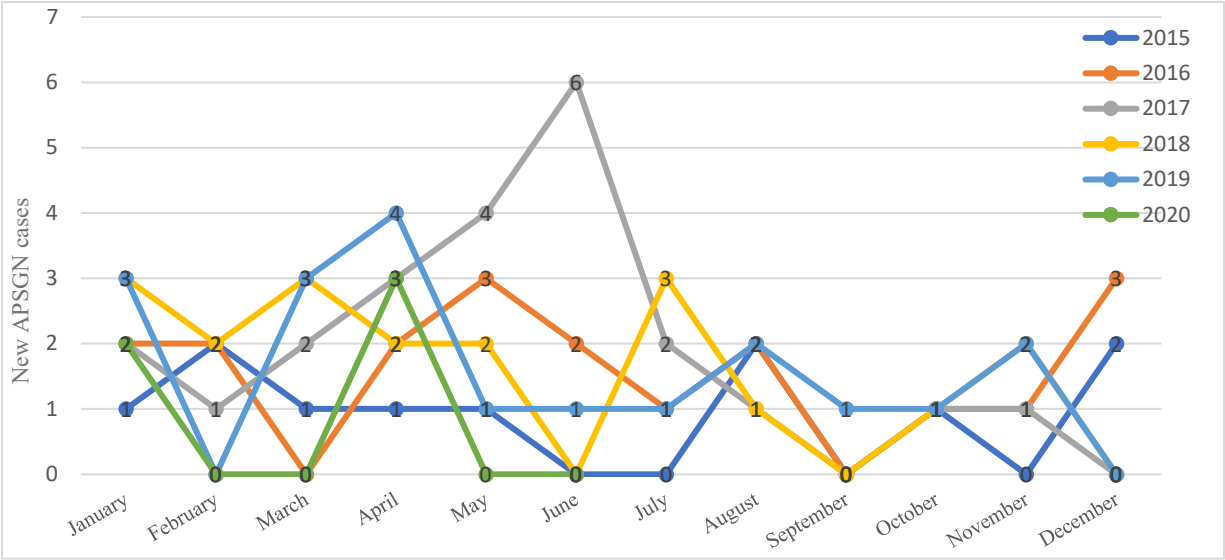
Seasonal pattern and variation: The seasonal distribution pattern during the 66-month study period showed an increased cases of APSGN in autumn (March-May) with 35 (36.5%) cases out of the 96, while the lowest numbers were noted in the spring (September-November) season with 12 (12.5%) cases. The number of cases were 24 (25%) and 25 (26%) in winter and summer, respectively. The highest number of cases (23) were noted in the year 2017 and lowest in 2020 (5 cases) **Figure 2**.

Figure 2: Cases of APSGN per month per year: Jan 2015- June 2020



ASPGN: Acute post streptococcal glomerulonephritis

Diagnosis: The serum complement level was available for 89 (93%) children. Serum C3 levels were found to be low in 83 (87%), and normal in six children at presentation. Anti-streptococcal antibody serology levels measured in 90 (94%) children showed elevated anti-DNase-B levels, whilst 77 (80%) also had elevated ASOT titres at presentation. Six patients had elevated blood cholesterol (>5mmol/L), low serum albumin (<30 g/L) levels, and nephrotic-range proteinuria on presentation. Percutaneous kidney biopsy was performed in eleven (11%) children: four of eleven (36%) biopsies showed histological changes of diffuse exudative proliferative glomerulonephritis on light microscopy, and fibrinogen and C3 on immunofluorescent staining in keeping with post-infectious nephritis glomerular damage; seven of eleven (64%) biopsies confirmed type II (immune complex) crescentic glomerulonephritis.

Management: Fifty-seven (59%) children presented in AKI, and a diuretic (furosemide) was administered to 88 (92%) children; 60 (63%) children required an anti-hypertensive agent in conjunction with the diuretic (25 treated with a single dose of rescue amlodipine for elevated BP and 35 (26%) children received regular amlodipine for more than one day). Ten (10%) cases had severe AKI with persistently rising serum creatinine levels despite fluid restriction to insensible losses and diuretic use. Four of these ten children responded to methylprednisolone (10mg/kg intravenously) pulse therapy, while six needed the addition of cyclophosphamide. Most of the study children, (91%) were treated with a penicillin antibiotic for 10 days. Eight (8%) patients were admitted to the paediatric intensive care unit, of whom, six (6%) were admitted for observation due to recurrent hypertensive seizures, and two (2%) were admitted for cardiorespiratory support due to severe congestive cardiac failure and pulmonary oedema.

Outcome: No deaths occurred during the acute presentation and follow-up period. The median length of hospital stay was 5 (IQR 3-6) days and ranged between 1 and 30 days. Eighty-one children (85%) with APSGN recovered and 6 (6%) of the children did not return for follow-up evaluation. Three (3%) patients had persistent proteinuria after six months from presentation, and one patient had persistent hypertension and was on amlodipine, these three children with persistent proteinuria were lost to follow-up and could not be traced. Outcomes were noted to be unfavourable in the seven children treated for RPCGN, as five (5%) of them progressed to ESKD. Of these five, three required acute haemodialysis, and initiation of chronic intermittent peritoneal dialysis at first presentation, one patient did not require acute haemodialysis, yet still progressed to ESKD and was started on peritoneal dialysis within 6 months of initial presentation, and one child defaulted follow-up after discharge and returned in ESKD three years post discharge (**Table 5**). At the six weeks review visit, 68 (71%) children were seen, all of whom had urine dipstick screening on the review day with only two children having their renal function and complement level checked; 56 (58%) had persistent microscopic haematuria, 15 (16%) had persistent proteinuria, and eight (9%) had persistent hypertension; none had persistent macroscopic haematuria. Follow-up kidney function and complement levels were normal in the two children who had these measured.

Table 5: Outcome of APSGN and RPCGN

Outcome	APSGN	RPCGN	Count (%)
Recovered	81		81 (85)
ESKD		5	5 (5)
Persistent proteinuria longer than six months post episode	2	1	3 (3)
Hypertension on Amlodipine, then lost to follow up	1		1 (1)
Unknown (lost to follow up)	5	1	6 (6)
Grand Total	**89**	**7**	**96**

257

Discussion

258 Our study involving 96 children shows that APSGN is still an important public health problem and a frequent cause
259 of paediatric hospital admission and AKI in the Western Cape, SA, and may be an important contributor to ESKD.
260 Though the incidence of APSGN was found to be high in our study (3.6/100 000), it is still likely to be an
261 underestimate of the true burden of disease in Cape Town, for two reasons- firstly, this study overlooked subclinical
262 cases and only assessed symptomatic patients presenting for medical services; secondly, as this was a retrospective
263 single centre study, it did not count cases who may have presented to other health facilities in Cape Town.

264 In SA, the incidence of APSGN in children is not reported across the country. Anecdotal reports from some
265 provinces such as Gauteng suggest a decline in the incidence of APSGN in children in recent years (personal
266 communication Petersen K. Adjunct Professor. Paediatric Nephrologist, Witwatersrand University, Johannesburg,
267 South Africa ed2020, April 17). Studies on children with APSGN are scarce in sub-Saharan Africa. However, some
268 data from Nigeria, reported an APSGN prevalence of 0.1 per 100 000 children in Sokoto and a prevalence rate of
269 1.3% and 0.8% in Calabar and Benin respectively [5-7].

270 In this study's cohort more than one third of the children presented in the autumn (March-May), with the least cases
271 presenting in spring (Sep-Nov). This differs from findings of a study done in Chile where the seasonal distribution

pattern had a bimodal tendency, with a rise in the autumn (38%) and in spring (30%). The researchers did not note any seasonal variation in terms of preceding skin or throat infection [12].

While most children presented with acute nephritis, more than one third of the children presented with complication of nephritis and or fluid overload complications, which may be reflective of late presentation of those children to a healthcare facility. However, this is a tertiary referral centre where complicated cases are referred for specialist care.

The diagnosis of APSGN is usually not difficult when a classical nephritis clinical presentation (haematuria, oedema, oliguria and hypertension) is associated with serologic evidence of recent streptococcal infection and depressed serum C3 concentration; in this study C3 serum levels were found to be depressed in 86.4 per cent of children. Five children had low C3 and low C4 at presentation, however, none of them had clinical or biochemical evidence suggestive of lupus nephritis. All of these five children had a history of either previous or current throat or skin infections with elevated serum antistreptococcal markers. Rodríguez *et al*., described an activation of classical complement pathway (reduced C4 level) in 15–30 per cent of APSGN children [12]. ASOT and anti-DNase-B titre tests are widely available and the most frequently elevated antibodies in upper respiratory and skin infection, respectively [13]. Yet in this study's cohort almost two thirds of children had preceding skin infections and the anti-DNase-B level was elevated in more than 90 per cent of the children suggesting that APSGN in SA children occurs more commonly secondary to skin infections than pharyngitis. This pattern of infection is similar to that seen in areas with a temperate Mediterranean climate such as is the case in Chile [11]. In contrast, other parts of the world such as Australia and North Africa have reported APSGN to occur more commonly post-pharyngitis with prevalence of 45% and 80%, respectively [15,16]. We have speculated on the role of severe water restriction and overcrowding in maintaining transmission of streptococcal skin infection, this has not been previously reported and our study has not been designed to answer this question, nevertheless, it makes for interesting reflection. In the current study setting, drought is a challenge that SA has been facing for the last five years with certain parts of the country being classified a disaster region in 2017. In this study the annual incidence rate reflected an increased incidence of APSGN during the year of drought in 2017 with an incidence rate of 4.5 per 100 000 children. Public health messaging and strict water restrictions imposed by the South African government during the period of critical

297 water shortage led to many people attempting to comply with the restrictions by reducing handwashing, bathing and
298 resorting to ultrashort shower times. In the Western Cape province in particular, residents were faced with the real
299 threat of a 'day zero' outcome for the province running out of water.[17] This may have had an effect on skin
300 infection control and its spread, particularly in the years 2017 and 2018. Further in this cohort we noted an increased
301 incidence rate in communities with a lower socio-economic level and poor access to piped water inside their
302 dwellings with an incidence rate at 10.3 and 9.9 in Nyanga and Gugulethu respectively as compared to the rest of the
303 drainage area collectively where incidence rate was 2.7 per 100 000 children. Conversely, the authors noted a
304 decrease in the number of APSGN cases during the first 6 months of years 2020 COVID-19 pandemic. This
305 decreased number of APSGN could be an accurate figure reflecting a decrease in the incidence due to the effect of
306 lockdown resulting in reducing the risk of exposure and inter-personal transmission of streptococcal throat and skin
307 infections. On the contrary, it might be an underestimation of the true incidences due to the de-escalation and
308 disruption of healthcare services, lack of access to transport during this period, and fear of exposure to COVID-19 at
309 healthcare facilities on the part of the community. However, incidence rate for year 2020 was not calculated as only
310 6 months were involved in this study period.

311 A kidney biopsy is not routinely indicated in the acute setting for the diagnosis of classical APSGN [13]. In this
312 study's cohort, eleven children required a kidney biopsy because of RPGN, or to exclude crescentic
313 glomerulonephritis, or where the diagnosis of acute nephritis was not certain as they presented atypically with
314 nephritis and nephrotic range proteinuria, hypoalbuminemia, and hypercholesterolemia. Immune complex mediated
315 crescentic glomerulonephritis accounted for 64 per cent of APSGN biopsies and six per cent of the total APSGN
316 cases. This result concurs with what has been described in SA in two separate studies. One study was a ten-year
317 review of native kidney biopsy records at the RCWMCH from 2004 to 2015, and the other was a seven-year review
318 from KwaZulu Natal province between 1981 to 1987, whereby crescentic glomerulonephritis accounted for 5.1 per
319 cent and 5.8 per cent of native kidney biopsies respectively, with almost 60 per cent and 30 per cent of the crescentic
320 glomerulonephritis being of an immune complex mediated subtype due to post-infectious nephritis [18, 19]. The
321 outcome was noted to be poor in children with crescentic glomerulonephritis with more than 50 per cent progressing
322 to ESKD. This is similar to earlier reports from both high and low- middle-income countries[18, 20, 21]. There are

other common paediatric kidney conditions which may present similarly for consideration such as the clinical presentation of minimal change nephrotic syndrome, lupus nephritis and HIV nephropathy however, their histology findings differ significantly from those seen in children with APSGN. Whereas idiopathic nephrotic syndrome will show foot processes effacement on electron microscopy, HIV nephropathy has a specific histological picture of collapsing focal and segmental glomerulosclerosis. On the other hand, lupus nephritis has a very specific histological classification and unique full house pattern on immunofluorescent staining. Hence kidney biopsy is sometimes indicated when the clinical diagnosis is uncertain.

There is no specific therapy to cure APSGN, and management at many institutions is mainly based on the supportive treatment of symptoms and complications as required; eradication of the streptococcal infection is also often used, though this is contentious in some countries where antibiotics treatment is only indicated in case of confirmation of active skin or throat infection[22]. At our institution a 10-day course of penicillin or, in allergic individuals, erythromycin is standard therapy for streptococcal eradication [23]. The reason for this protocol is that treatment of carrier state may prevent spread of infection to household contact and in this study's cohort, almost all children were treated with a 10-day course of a penicillin antibiotic.

The outcome of APSGN in children is usually favourable. In this cohort some children presented with uncomplicated APSGN, these patients were admitted for one day only and were then referred to another healthcare facility for continuation of supportive care. These patients usually did not come to follow-up at RCWMCH; hence the outcome of these patient was not known, however, all children diagnosed with kidney complications are routinely referred to the paediatric nephrology service at RCWMCH, and the service did not note any increase of these cases returning with complications. Thus, we have assumed these patients recovered fully without long term sequelae as this is the usual course of this disease. Five patients progressed to ESKD, three of whom are currently still on peritoneal dialysis, and one has had successful kidney transplantation. Three patients had persistent proteinuria after six months post initial presentation, all of them had nephrotic range proteinuria and AKI on presentation. All the three were lost to follow up and their whereabouts could not be traced. Nevertheless, APSGN was significantly correlated with

increased incidence of a decrease in the glomerular filtration rate and thus long-term follow-up of hypertension and proteinuria would be recommended.

Although this is a report from a single centre, our study has several strengths, - this is a large cohort of children who attended a public children's hospital, and we have been able to show that APSGN is still an important public health condition and this may be related to poverty, overcrowding, infective infestations such as scabies and lack of regular access to piped water. Our study was not designed to prove this hypothesis or explore the associations statistically. Additionally, we have been able to describe important complications of this usually benign condition emphasising the value of specialist referral in a subset of patients. We have also been able to update the SA scientific knowledge base on APSGN in South African children, and we have also been able to describe how the progression of RPGN can be appropriately addressed if patients are referred to the current children's centre, and it is diagnosed timeously and immunomodulator treatment started early. The main limitation of this study comes from the retrospective nature of the study, hence missing data, reliance on accurate coding, and underreporting are to be acknowledged, further we may have missed cases managed at other facilities. We recommend that all children presenting acutely with oedema or haematuria should have their blood pressure and serum creatinine levels measured; from this if the serum creatinine is normal then a favourable outcome is more likely, but a raised serum creatinine may be more ominous, and we recommend that these children be referred for evaluation at a tertiary children's centre. We would also recommend that in addition to ASOT titres which are routinely measured in these cases, Anti-DNase-B levels should also be measured as in our cohort, we described that skin sepsis is a common cause of this condition. We further recommend that all children be followed up at least once at 6 weeks post episode where their blood pressure, urine dipstick, serum complement, and general wellness can be measured. We could also consider supplying families with information leaflets for education and stress at discharge, the importance of follow-up.

Due to the retrospective nature of the study, we noted that the follow-up of about one third of affected children was inadequate, with the majority of patients absconding from follow-up after discharge. Additionally, it would be useful to improve the accuracy of the national statistics on this condition, the recent move to electronic discharge records will go some way to improving the provincial data capturing and should be adopted nationally.

Conclusion

APSGN during childhood continues to be an important health problem in SA, more commonly following skin infection than throat infection. The outcome is favourable in most children, apart from those with crescentic glomerulonephritis who mostly progressed to CKD. Long-term outcome is not addressed adequately, we recommend more attention brought to post discharge follow up and maybe a leaflet to be handed to the patient's care giver to state the importance of adherence to follow up even in the absence of oedema or haematuria.

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CHAPTER 3: APPENDICES

Appendix A: Research Protocol

Title: Acute Post Streptococcal Glomerulonephritis at Red Cross Children's Hospital, Cape Town, South African – a 5-year review

Degree: Master's degree of Philosophy in paediatric Nephrology

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EXECUTIVE SUMMARY

The purpose of this retrospective, descriptive study, is to describe the occurrence of acute post streptococcal glomerulonephritis and to study the aetiology, clinical presentation, and complications among children presenting to a tertiary level children's hospital in Cape Town, South Africa.

List of Acronyms

AGN	Acute glomerulonephritis
AKI	Acute kidney Injury
APSGN	Acute post streptococcal glomerulonephritis
C3	Complement 3
C4	Complement 4
GAS	Group A beta haemolytic streptococci
PRES	Posterior Reversible Encephalopathy Syndrome
RBCs	Red blood cells
RCWMCH	Red Cross War Memorial Children' Hospital
RPGN	Rapidly Progressive Glomerulonephritis
WHO	World Health Organization

Operational Definitions:

1. Acute post streptococcal glomerulonephritis (APSGN) will be diagnosed based on clinical assessment and laboratory test results as per the following criteria:
    - Clinical presentation with acute glomerulonephritis (AGN); oliguria, oedema, hypertension, haematuria, proteinuria, red blood cell casts in urine, and circulatory congestion (pulmonary oedema , congestive cardiac failure).
    - Evidence of recent Group A beta-haemolytic streptococcal pharyngitis or skin infection, based on history, clinical examination and raised antistreptococcal antibody titres. Anti-streptolysin O titre of > 240 iu/ml and Anti-DNase-B antibodies titre of > 640 iu/ml.[1]
    - Evidence of activation of alternative pathway of complement system, low complement-3 of < 0.9 g/L and normal complement-4 ranging 0.1-0.4 g/L blood levels.
2. Oliguria: urine volume less than 0.5 mL/kg/hr.
3. Oedema: puffiness of face, bilateral pitting pedal oedema and abdominal wall oedema.
4. Macroscopic haematuria: visible pink or brown coloured urine owing to the presence of RBC confirmed by microscopic examination.
5. Microscopic haematuria: the presence of more than five red blood cells (RBCs) per high power field in the sediment of 10 mL of centrifuged freshly voided urine sample.
6. Proteinuria: protein in urine will be measured quantitatively and expressed as a protein /creatinine ratio (g/mmol).

Table 1 Normal values of protein excretion as a function of age.[2]

Age	g Protein/mmol Creatinine
6–12 months	0.05
1–2 years	0.04
2–3 years	0.03
3–5 years	0.02
5–7 years	0.015
7–17 years	0.015

7. **Nephrotic Range Proteinuria:** Spot urine protein /creatinine ratio of > 0.2 g/mmol
8. **Stage 1 Hypertension:** an average systolic blood pressure of ≥95th percentile for gender, age, and height. Using the 2017 American Academy of Paediatric BP tables for boys and girls.[3]
9. **Stage 2 Hypertension:** an average systolic blood pressure of ≥95^{th} +12 percentile for gender, age, and height. Using the 2017 American Academy of Paediatric BP tables for boys and girls.[3]
10. **Acute Kidney Injury:** age specific normal ranges of creatinine will be used to diagnose AKI as per the following references:

Table 2 Plasma creatinine reference intervals (2.5–97.5th percentiles)[2]

Age Group	Enzymatic Creatinine Range
Children < 2 years old	9- 32 umol/L
Children 2 to < 5 years old	18-38 umol/L
Children 5 to < 12 years old	27- 54 umol/L
Children > 12 years old	40-72 mol/L

11. **PRES:** Posterior reversible encephalopathy syndrome is a clinico-radiological syndrome characterized by a headache, seizures, altered mental status and visual loss and characterized by white matter vasogenic oedema affecting the posterior occipital and parietal lobes of the brain predominantly.[4]
    Diagnosis of posterior reversible encephalopathy syndrome will be confirmed based on the following criteria:
    - **Severe Hypertension (** ≥ Stage 2 Hypertension) with concurrent seizure.
    - Computerized Tomography scan of brain showing bilateral areas of white matter oedema in the posterior cerebral hemispheres, particularly the parieto-occipital regions.
12. Stages of Chronic Kidney Disease will be based on the KDIGO 2012 clinical practice guideline.[5]
    - G1 – Normal GFR (≥90 mL/min per 1.73 m^2)
    - G2 – GFR between 60 and 89 mL/min per 1.73 m^2
    - G3a – GFR between 45 and 59 mL/min per 1.73 m^2
    - G3b – GFR between 30 and 44 mL/min per 1.73m^2
    - G4 – GFR between 15 and 29 mL/min per 1.73 m^2
    - G5 – GFR of <15 mL/min per 1.73 m^2 (End Stage Kidney Disease)

1. BACKGROUND AND LITERATURE REVIEW

1.1. Defining the Clinical Problem

Diseases involving the renal glomeruli are encountered frequently in paediatric nephrology clinical practice and are the most common causes of end stage kidney disease in children.[6] Post infectious glomerulonephritis is an immunological response of the kidney following non-renal infection, most commonly secondary to Group A β-haemolytic streptococcus,[7] and may also result from other infections of the skin or throat. Acute post streptococcal glomerulonephritis (APSGN), although not a common cause of progressive kidney failure, is an important cause of paediatric hospital admission, parental worry, and acute kidney injury(AKI) because of the accompanying haematuria.

In high income and some low-middle income settings, there has been a decline over the last three decades in the incidence of APSGN in children with this condition almost disappearing in Central Europe.[8] However, this is not the case in other low socioeconomic settings, such parts of South Africa, where APSGN is still a major public health problem and a frequent cause of paediatric hospital admission and AKI. Nevertheless, APSGN in South Africa has not been studied adequately in recent times and not currently addressed as an important public health issue. The characteristics of the streptococcal infection involved, and the immunological responses of the patients are unknown. The epidemiology and geographical distribution of streptococcal infection related glomerulonephritis are not well known across the country.

1.2. The literature review

Introduction:

APSGN is a non-suppurative sequel to specific nephritogenic strains of Group A β-haemolytic streptococcal (GAS) throat or skin infection.[9] The association between streptococcal infection and acute glomerulonephritis (AGN) has been known since 1953 when Rammelkamp established the association between group A beta-haemolytic streptococcus type 12 and AGN.[10] APSGN usually occurs one to three weeks post streptococcal skin or throat infection, predominantly between the ages of five and twelve years, with a male to female ratio of 2:1. APSG is unusual before the age of three years.[9]

GAS is an important cause of morbidity and mortality, as indicated in a recent population-based data systematic review to estimate the global burden of GAS disease, there are at least 517 000 deaths each year due to severe GAS diseases, and more than 616 million incident cases per year of GAS pharyngitis, and over 111 million prevalent cases of GAS skin infection,[11] with a risk of AGN after a nephritogenic GAS infection of 10–15

percent.[12] In tropical and subtropical countries, there is a tendency to have skin infection-associated APSGN,[13] rather than the pharyngitis-associated APSGN found more predominantly in temperate climate areas.[14, 15]

A recent review of the epidemiology and skin infection in children in low income settings by the World Health Organization's (WHO) Department of Child and Adolescent Health and Development, indicated that impetigo and scabies have been considered a major public health problem in middle-low-income countries for decades, with little recent progress in their prevention and treatment.[16] WHO described the main aetiological factors attributing to the increased prevalence of skin infections in low-middle-income settings, to be that of inadequate hygiene and poor access to water.[16] High interpersonal contact and household density has been also recognized by the WHO as an aetiological factor increasing the incidence of transmissible skin infections like impetigo and scabies.[16]

In our setting, drought is a challenge that South Africa has been facing for the last 5 years with certain parts of the country being classified a disaster region in 2017. When the drought was at its worst, the use of water was restricted to only 50L per person daily during 2018. This situation is worsened, and some provinces have reported persistent drought over 2020.[17] The country faces a global phenomenon where water is constrained in quality and quantity that results in a real concern over public health as 30% of the children in SA have no access to on site water and 18% live in overcrowded households.[18]

Epidemiology of APSGN

APSGN is the most common cause of acute nephritis in children globally,[19] with an estimated 470,000 new annual cases of APSGN worldwide.[11] In low-income countries, the annual incidence of APSGN ranges from 9.5 to 28.5 per 100,000 individuals, accounting for 97 percent of the global incidence of disease.[8] However, this incidence rate is likely an underestimate of the true burden of APSGN, as most studies have overlooked subclinical cases and only assessed symptomatic patients presenting for medical services. Subclinical disease is estimated to be four to 19 times more common than symptomatic disease.[19] In high-income settings the

incidence of APSGN in children has continued to decrease and become more common in the elderly (more than 60 years) with comorbidities like diabetes, alcoholism and drug abuse.[20]

In SA, the incidence of APSGN in children is not reported across the country. However, some provinces like Gauteng reported a decline in the incidence of APSGN in children.[21] While other provinces such like KwaZulu-Natal, Eastern Cape and Western Cape provinces reported a persistent high incidence of APSGN in children.[22, 23] The mortality from APSGN is estimated to be around 1%, either in the acute phase or from long-term kidney failure.[11] Short term fatalities may occur as a result of hyperkalaemia, pulmonary oedema or seizures related to posterior reversible encephalopathy syndrome (PRES) but they are exceedingly rare.

Clinical presentation and Diagnosis :

The clinical picture appears characteristic enough to suggest that the diagnosis of APSGN can be made using clinical features combined with the serological confirmation of streptococcal infection.[24] Bacteriological confirmation of GAS skin or throat infection is only achieved in 25% of APSGN children, hence it is not required for confirmation of the diagnosis. Kidney biopsy is not routinely indicated in the acute setting for the diagnosis of APSGN.[9] However, biopsy is indicated in cases of severe kidney impairment requiring dialysis or if the serological testing was not confirmative of the diagnosis.

The clinical presentation of APSGN can range from unrecognized, asymptomatic AGN manifesting with microscopic haematuria and a transient decrease in serum complement activity, to full-blown AGN, characterized by red- to brown-coloured urine, proteinuria, oedema, hypertension, and an elevation in serum creatinine.[24] Some children may even present with serious complications such as hypertensive emergency, congestive cardiac failure, kidney failure, posterior reversible encephalopathy syndrome, and retinopathy.[19]

Rapidly progressive (crescentic) glomerulonephritis (RPGN)is a severe form of glomerulonephritis that characteristically presents with a rapid deterioration in kidney function over days, weeks or months. The kidney damage is often severe and irreversible and will often progress to chronic kidney disease and death.[9] Crescentic glomerulonephritis is seen in less than 0.5 percent of APSGN kidney biopsies.[18]

The most constant serological finding is the reduction in serum complement levels that occurs in approximately 90 percent of the cases. The activation of the complement system is usually via the alternative complement pathway marked by reduction in serum C3 and CH50.

Anti-streptolysin O titre and anti-DNAse B titre tests are widely available and the most frequently elevated antibodies in upper respiratory infections and skin infection, respectively. In one study the sensitivity of ASO, and Anti-DNase B was 78.4% and 64.9% while the specificity was 89.2% and 91.9% respectively.[19]

Treatment and Prevention:

There is no specific therapy to cure APSGN, and management is mainly based on eradication of the streptococcal infection and on supportive treatment of symptoms and complications as required.(14)

Once a diagnosis of APSGN is made, even if infection is not apparent at the time of diagnosis, antibiotic therapy to eradicate streptococcal infection is indicated, as early treatment of streptococcal infection has been reported to prevent or reduce the severity of glomerulonephritis.[8] A 10-day course of penicillin or, in allergic individuals erythromycin, is standard therapy for streptococcal eradication.[25] Preventive antibiotic treatment is indicated in the case of an epidemic situation or for household members of index cases where APSGN is common or when clusters of cases are reported.[8] We don't routinely check siblings for raised streptococcal titres at RCWMCH.

Hospitalization and restriction of fluid and sodium intake are essential for the treatment of patients with AGN. A sodium-restricted diet is recommended to provide the child with approximately 2 to 3 mEq/kg/day of sodium, the amount required for a growing child. Loop diuretics provide prompt diuresis and are indicated for children presenting with significant oedema, hypertension, and circulatory congestion. Diuretic therapy like furosemide 1-2 mg/kg to a maximum of 60 mg facilitates the resolution of oedema and ameliorates the hypertension that is driven by extracellular volume expansion.[9]

Children who present with RPLS due to severe hypertension may require emergency antihypertensive treatment using oral nifedipine (5 mg in children, every 4–6 h) or Amlodipine (0.1-0.2mg/kg/dose 24hrly) or parenteral nicardipine, all of which are usually effective if available.[26]

Children with APSGN have variable reductions in kidney function. Haemodialysis or peritoneal dialysis are infrequently required in the acute episodes for the treatment of hyperkalaemia, uraemia, or severe circulatory congestion unresponsive to medical treatment with diuretics and fluid and sodium restriction.

Prognosis:

The outcome of APSGN is usually favourable, particularly in children. Most children will have complete clinical recovery with resolution of their disease process beginning within the first two weeks.[8]

The long-term prognosis of APSGN has been the subject of many reports. A review of three case series of 229 children with APSGN found that more than 90 percent had normal or only modestly reduced kidney function five to 18 years after APSGN episode.[8] A combined analysis of reported data, indicates that 20 percent of the children followed up for 10–20 years after APSGN, have an abnormal urine analysis but azotaemia was found in less than 1 % of the patients.[8] Nevertheless, APSGN was significantly correlated with increased incidence of decrease in glomerular filtration rate and thus long term follow-up of hypertension and proteinuria would be recommended.

1.3. The research question

What is the prevalence of acute post streptococcal glomerulonephritis managed in a tertiary level children's hospital in Cape Town and how has the period prevalence has changed over the five-year period?

2. AIMS AND OBJECTIVES

Aim: To describe the prevalence and the associated risk factors of APSGN in children presenting to Red Cross War Memorial Children's Hospital (RCWMCH), in Cape Town, South Africa.

Objectives of study:

1. To describe the aetiology and age distribution differences including preceding group A streptococcal skin infection and/or pharyngitis predisposing APSGN.
2. To describe the potential risk factors contributing to occurrence of APSGN in view of geographical area distribution, socioeconomic standards and the availability of access to formal housing, clean water and sanitation among children with APSGN where available.
3. To describe the various clinical presentations of children with APSGN and the standard of care provided to children with APSGN in RCWMCH.
4. To describe the complications resulting from APSGN and the outcome of children with APSGN with identification of those children who may need long-term follow-up.

3. METHODS

This is a retrospective descriptive study to be carried out over a period of 5 and a half years, from January 2015 up to June 2020, at RCWMCH, Cape Town, South Africa.
International Statistical Classification of Diseases (ICD10) discharge codes will be used to identify potential cases of APSGN. Blood and urine test results to be verified on the National Health Laboratory Services (NHLS) system as required for the participants. The clinical notes of patients found to have been diagnosed with APSGN will be retrieved as to extract demographic and clinical information.

3.1. Study design

This is a retrospective cross-sectional study.

3.2. Setting

The study will be conducted at RCWMCH. The hospital was established in 1956 and is the only stand-alone paediatric hospital in the sub-region and serves as one of two referral, public, tertiary level hospitals, offering care in all major paediatric specialties, and drains a large population base of both urban and semi-urban communities from Western Cape Province . The hospital also serves as a national and international referral hospital for multidisciplinary subspecialty care. The Western Cape province is the fourth largest province in South Africa and has an estimated 1.7 million children <14years-of-age. (STATS SA P0302- Mid-year population estimates, 2018).

3.3. Participant selection and sampling strategy

An ICD10-coded discharge database will be used to identify children (less than 14 years old) admitted to the hospital with APSGN over 5 years and 6 months, clinical notes of all the selected cases will be reviewed, Only the children confirmed to have APSGN (as per case definition) will be included in this study, while other children found to have causes of acute glomerulonephritis other than APSGN (e.g. nephrotic syndrome, Henoch Schonlein purpura) will be excluded. The source population (prevalence denominator) will include all medical admission to RCWMCH during the study period.

Cape Town Census and Population Statistics, Statistics South Africa 2011 (Cape Town Census and Population Statistics) database will be used to describe the risk factors contributing to occurrence of APSGN as well as context in view of geographical area distribution, socioeconomic standards and the availability of access to formal housing, clean water and sanitation among children with APSGN. Based on the provided address, patients will be assigned a particular risk profile in light of the information gathered from either the Suburb or Ward Profiles in the Census 2011 documents. All information to be recorded in the study database.

3.4. Data collection and Measurements.

This study will involve a retrospective chart review. After having received the necessary ethical and institutional approvals, the discharge database of RCWMCH will be used and all cases indicating a primary or secondary diagnosis of post infectious glomerulonephritis will be selected. Using this refined list, their respective clinical note files will be retrieved from RCWMCH medical records department. Cases that do not meet the case definition of APSGN as well as any duplication will be discarded and will not be entered into our database. The data collection period will be from Jan 2015 up to June 2020.

Data collected will be de-identified when exported from the online data management software (REDCap) and be saved in a confidential Microsoft Excel files with password protection. Only the PIs and the researcher (MPhil student) will have access to the REDCap database and any other exported datafiles that will be used for analysis purposes.

A questionnaire has been devised for the capture of the relevant data see APPENDIX.

Specific definitions have been set out to define criteria for various categories (see operational definitions). Information collected will include age, sex, suburb, clinical presentation with AGN (haematuria, proteinuria, hypertension, oedema), Hypertension complication, circulatory congestion at time of presentation, Complement 3 and 4, ASOT, Anti DNase B, Cholesterol, Albumin, urea and creatinine, Diuretics, antihypertensives, antibiotics and scabies medication used, ICU admission, duration of hospitalisation and hospital care, complication, outcome.

The primary outcome is the prevalence of APSGN among patients admitted to RCWMCH. Secondary outcome measures the outcome of children with confirmed APSGN, whether they fully recover and retain normal kidney function (Normal Plasma creatinine reference per age group Table 2), normal BP level and normal blood complement level or progress to CKD/ESKD or are ultimately demised in the five year study period.

Prevalence will be calculated using the following formula

$$\text{Prevalence of APSGN in children admitted to RCWMCH during the study period} =$$

$$\frac{\text{number of children confirmed to have APSGN}}{\text{Total number of medical hospital admission during the study period}}$$

3.5. Data management

An online data capturing software (REDCap) will be used in the administration and capture of folder data in this study. This will enable the researcher to have immediate access to the data and troubleshoot if there are any queries. The data set will be cleaned by examining for outlying points during the data cleaning process and exported to Stata v14 (StataCorp, Texas, USA) for analysis.

3.6. Statistical analysis

Data will be presented as median [interquartile ranges (IQR)] or means [± standard deviation (SD)] depending on normality of data while categorical data will be presented as proportions. Since the primary outcome of APSGN is categorical i.e. positive for the condition of interest as per case definition criteria or negative, the Mann Whitney test/T-test will be used to investigate differences with any numerical variables while the Fisher's exact test/ Chi-square will be used for categorical variables. The prevalence of APSGN over the study period will be reported as the number of those with clinically confirmed APSGN as a proportion of medical admission in RCWMCH during the study period.

Objective 1: To describe the aetiology and age distribution differences including preceding group A streptococcal skin infection and/or pharyngitis predisposing APSGN.

- Descriptive statistics for the baseline characteristics including the socio-demographic characteristics and clinical presentation at hospital visit will be presented as proportions for the categorical variables and means (SD)/ median (IQR) for continuous variables.

Objective 2: To describe the risk factors contributing to occurrence of APSGN in view of geographical area distribution, socioeconomic standards and the availability of access to formal housing, municipal water and sanitation among children with APSGN.

- The association between the outcome of ASPGN (positive/negative for the condition) and the predisposing risk factors will be assessed using chi-square/fishers exact test dependent on the assumption of a large sample be fulfilled. The dependent variables to be considered will include area of residence, socioeconomic position and access to formal housing which will be presented in a categorical format.

Objective 3: To describe the various clinical presentations of children with APSGN and the standard of care provided to children with APSGN in RCWMCH.

- Clinical presentation variables to be collected at baseline will include symptoms of glomerulonephritis, complications like presence of cardiac failure and a battery of laboratory investigations that will all be captured in categorical format and presented as proportions. The different variables capturing the standard of care amongst ASPGN positive patients will be reported as proportions.

Objective 4: To describe the complications resulting from APSGN and the outcome of children with APSGN with identification of those children who may need long-term follow-up.

- The different variables capturing the different outcomes (for e.g. CKD staging or persistent proteinuria) in ASPGN positive patients will be reported as proportions.

For all statistical testing, a p-value of <0.05 will be considered significant.

4. ETHICAL CONSIDERATIONS

Ethical permission to conduct the study will be obtained from the Department of Paediatrics and Child Health Research Committee, the University of Cape Town Human Research Ethics Committee and the RCWMCH Research Committee.

4.1. Community Participation

Not applicable as this study is a retrospective descriptive study to analyse stored data.

4.2. Social value

This study will help highlight the high incidence of APSGN, identify high risk geographical suburbs, poverty and overcrowding as well as highlight how drought could lead to an increase in the incidence in the Western Cape province. This may facilitate focused attention for prevention and care for those affected children.

4.3. Scientific value

Very few studies of APSGN are published in literature regarding clinical profile detailing aetiology and complications from hospitals in Cape Town,

APSGN has not been recently adequately studied in Cape Town paediatric population, and the high prevalence of post infectious glomerulonephritis has not been addressed. Thus, the results from this study will help to fill this

knowledge gap and give clinicians information that may be useful when managing children with APSGN in this population.

4.4. Risk/benefit balance

As a retrospective descriptive study. there will be no additional risks nor direct benefits to the patients included in the study.

4.5. Independent ethics review

University of Cape Town, Faculty of Health Sciences. Human Research Ethical Committee.

4.6. Informed consent

No written consent is required as these data are already documented during hospital admission.

4.7. Ongoing respect for participants

All data will be recorded anonymously with a study number, and only the principle investigator will have access to the clinical record numbers of the participant. Data collected will be de-identified and be saved in a confidential file with password protection

5. METHODOLOGICAL CHALLENGES AND STUDY LIMITATIONS

- This is a retrospective chart review and missing data and underreporting is to be acknowledged.
- This is going to be a single center surveillance and might not represent the whole province population/ hence the results may not be generalizable
- The clinical notes are to be retrieved from the medical records department, and there may be a challenge in accessing all notes as some notes may be not available upon request.
- Some APSGN cases may pass unrecognized and may not be presented to hospital, while others may be managed as an out-patient, this may underestimate the prevalence, and this is acknowledged.
- Some required diagnostic laboratory tests may not have been done on admission in all cases.
- Evidence of streptococcal infection will be based on serological antistreptococcal titres and not on proven cultures, as cultures are not routinely done on admission

6. FEASIBILITY

6.1 Timelines and project management.

Literature search, protocol preparation submission and ethical approval 3 months. (June-August 2020)

Recruitment and data collection 2 months (October-November 2020)

Data entry into electronic format 1 month (December 2020)

Statistical analysis and review 1 month (January 2020)

Write up 3 months (February -April 2021)

6.2. Study team, contributors and authorship.

Name	Department	Contribution	Author or acknowledgement
Khadija Abugrain	Paediatric Nephrology School of Child and Adolescent Health University of Cape Town.	MPhil Student	
Heloise Buys	Paediatric Emergency Medicine School of Child and Adolescent Health University of Cape Town.	Supervisor	

Mignon McCulloch	Paediatric Nephrology School of Child and Adolescent Health University of Cape Town.	Co-Supervisor	

6.3. Participating Centres

Red Cross War Memorial Children's Hospital. Cape Town, Western Cape, Republic of South Africa.

6.4 Study Funding and Progress

Not applicable as a retrospective descriptive study.

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Appendix B: Data collection tool

Study Number	
Hospital Number	
Date of birth	DD/MM/YYY
Date at presentation	DD/MM/YYYY
Gender	1. Male 2. Female
Suburb	
Symptom of Glomerulonephritis at presentation	Haematuria 1. Yes 2. No
	Proteinuria 1. Yes 2. No 3. Nephrotic range
	Oedema 1. Yes 2. No
	Oliguria 1. Yes 2. No
	Hypertension

	1. No 2. Stage 1 Hypertension 3. Stage 2 hypertension
complication at presentation	Hypertensive seizures 1. Yes 2. No
	PRES on radio imaging of brain. 1. Yes 2. No
	Cardiac failure 1. Yes 2. No
	Pulmonary Oedema 1. Yes 2. No
Evidence of **current** or **preceding** Streptococcal infection on presentation	1. Skin infection 2. Throat infection 3. No
Low Complement 3 blood level at presentation.	1. Yes 2. No 3. Unknown
Normal Complement 4 blood level at presentation.	1. Yes 2. No 3. Unknown
Elevated ASOT blood level at presentation.	1. Yes 2. No 3. Unknown
Elevated Anti-DNase B antibodies blood level at presentation.	1. Yes 2. No 3. Unknown

Normal Blood Cholesterol level at presentation	1. Yes 2. No
Acute Kidney injury at presentation	1. Yes 2. No
Creatinine level at presentation	…… umol/L
Creatinine level repeat (24-48 hours from admission creatinine)	…… umol/L
CRP level at presentation	1. Not done 2. < 10 (Negative) 3. > 10 4. > 30 5. > 50
Confirmed UTI on presentation	1. Yes 2. No 3. Unknown
Acute Renal dialysis	1. PD 2. HD 3. Nil
Managements and care at hospital	Use of loop Diuretic therapy 1. Yes 2. No
	Use of Antihypertensive agent in conjunction with diuretic therapy 1. Yes 2. No
	Fluid Restriction 1. Yes 2. No

	ICU admission 1. Yes 2. No
	Brain Radio-imaging 1. Yes 2. No
	Required treatment with antibiotics 1. Yes 2. No
	Was renal biopsy required during hospital stay 1. Yes 2. No
	Required treatment with Ascabiol 1. Yes 2. No
Length of hospital admission in days.	
Steroid use (pulse Therapy)	1. Yes 2. No
Cyclophosphamide	1. Yes 2. No
Weight of admission in Kg	…….. KG
Weight on discharge in Kg	…….. KG

What Was the biopsy result	
Outcome	1. Retained normal kidney function. 2. CKD stage 2 3. CKD stage 3 4. CKD stage 4 5. CKD stage 5 6. ESKD on dialysis
6 weeks follow up	Presented to 6 weeks follow up 1. Yes 2. No 3. Still admitted
	Persistence of Haematuria 1. Yes 2. No 3. Unknown
	Persistence of Hypertension 1. Yes 2. No 3. Unknown
	Persistence of Proteinuria 1. Yes 2. No 3. Unknown
	Normal Complement 3 1. Yes 2. No 3. unknown
	Normal Urea and Creatinine 1. Yes 2. No

	3. unknown

Appendix C: UCT Health Sciences Human Research Ethics Committee approval

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

07 October 2020

HREC REF: 623/2020

Dr H Buys
Ambulatory and Emergency Division
Department of Paediatrics
ICH Building, 5th Floor, Rm 508
Red Cross War Memorial Children's Hospital
Email: - heloise.buys@uct.ac.za
Student: -Dr.abugrain@yahoo.co.za

Dear Dr Buys

PROJECT TITLE: ACUTE POST STREPTOCOCCAL GLOMERULONEPHRITIS AT RED CROSS CHILDRENS HOSPITAL, CAPE TOWN, SOUTH AFRICAN-5 YEAR REVIEW-MASTER'S CANDIDATE DR KHADIJA ABUGRAIN

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

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

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

Approval is granted for one year until the 30 October 2021.

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

We acknowledge that the student: Dr Khadija Abugrain will also be involved in this study.

Please quote the HREC REF in all your correspondence.

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

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

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

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

Appendix Cc:Ethical approval

Western Cape Government
Health

DR AN PARBHOO
Manager: Medical Services
Red Cross War Memorial Children's Hospital
Email: Anita.Parbhoo@westerncape.gov.za
Tel: +27 21 658 5430 Fax: +27 21 658 5006/5166

16 November 2020

Dr K Abugrain
Paediatric Nephrology

Dear Dr Abugrain,

RESEARCH: RXH: RCC 248 / WC_202011_001

PROJECT TITLE: Acute Post Streptococcal Glomerulonephritis at Red Cross Children's Hospital, Cape Town, South African – a 5-year review

It is a pleasure to inform you that the hospital Research Review Committee has approved your application to conduct above-mentioned study at Red Cross War Memorial Children's Hospital.

Kindly note that this approval is subject to strict adherence to the HREC recommendations regarding research involving participants during COVID-19, dated 17 March 2020 (UCT HREC notice attached).

Yours sincerely,

DR AN PARBHOO
MANAGER: MEDICAL SERVICES

Appendix D: Turnitin Report

This Turnitin Report has been reviewed and approved by Supervisor A/Prof Heloise Buys
19/10/2021

abgkha001:APSGN_Manuscript_March_KHADIJA_citation_updated.docx

by Khadija Abugrain

Submission date: 13-Mar-2021 07:25PM (UTC+0200)

Submission ID: 1532081217

File name: bd910fe7626_APSGN_Manuscript_March_KHADIJA_citation_updated.docx (80.97K)

Word count: 4706

Character count: 26141

abgkha001:APSGN_Manuscript_March_KHADIJA_citation_upda.

ORIGINALITY REPORT

14%	7%	12%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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2	jfmpc.com Internet Source	1%
3	Edward L. Kaplan, Constance D. Rothermel, Dwight R. Johnson. "Antistreptolysin O and Anti-Deoxyribonuclease B Titers: Normal Values for Children Ages 2 to 12 in the United States", Pediatrics, 1998 Publication	1%
4	Ximena Berr&#65533;os, Ingrid Riedel, Eric Solar, Gloria Sandoval, Beatriz Guzm&#65533;n, Edda Lagomarsino. "Post-streptococcal acute glomerulonephritis in Chile?20&#65533;years of experience", Pediatric Nephrology, 2004 Publication	1%
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Acute Post-Streptococcal Glomerulonephritis (APSGN) at the Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, South African: a Five-Year Review

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Abstract

In this retrospective study we describe the occurrence of APSGN, the aetiology, clinical presentation, and complications among children (<14years) admitted to the Red Cross War Memorial Children's Hospital in Cape Town, South Africa from January 2015 to June 2020, using the discharge database to identify potential cases. There were 157 cases coded as acute nephritic syndrome, of which 96 were included in the study. APSGN was defined based on the clinical presentation of at least two signs of acute nephritis, associated with a low complement 3 serum level and or evidence of a recent streptococcal infection. We found a population incidence of APSGN in Cape Town of 1.7 per 100,000 children. APSGN occurred predominantly in children aged five to ten years (51.46%) with a male-female ratio of 1.9:1. Most patients presented during the fall season, and APSGN was more often associated with streptococcal skin infection (55.21%) compared to a throat infection (23.96%). Proteinuria was noted in 85 children (48 with nephrotic range proteinuria). Most children presented in stage 2 hypertension (71, 73.95%), with 10 (10.4%) presenting with hypertensive seizures. Serum C3 levels were low in 83 (86,4%) children. A percutaneous kidney biopsy was indicated in eleven children. Seven biopsies confirmed type II (immune complex) crescentic glomerulonephritis, and four biopsies showed histological features suggestive of post-infectious nephritis. While 61 children recovered, four progressed to ESKD, two had persistent proteinuria more than six months after acute presentation, and one child had persistent hypertension. The outcome was not measurable in 27 children.

Keywords: APSGN, Group A beta haemolytic streptococci, haematuria, Proteinuria

Introduction

Diseases involving the renal glomeruli are encountered frequently in paediatric nephrology clinical practice and are the most common causes of end-stage kidney disease (ESKD) in children [1]. Post-infectious glomerulonephritis is an immunological response of the kidney following non-renal infection, most commonly secondary to Group A β-haemolytic streptococcus [2] (GAS), and may also result from other infections. Acute post-streptococcal glomerulonephritis (APSGN), although not a common cause of chronic kidney disease (CKD), is an important cause of paediatric hospital admissions, parental worry, and acute kidney injury (AKI) because of the accompanying haematuria.

In high-income and some low-middle income settings, there has been a decline over the last three decades in the incidence of APSGN in children, with this condition almost completely disappearing in Central Europe [3]. However, this is not the case in other low socio-economic settings, such as parts of South Africa (SA), where APSGN is still a major public health problem, and a frequent cause of paediatric hospital admission and AKI. Nevertheless, APSGN in SA has not been studied adequately in recent times and is not currently addressed as an important public health issue. The characteristics of the streptococcal infection involved, and the immunological responses of the patients are unknown. The epidemiology and geographical distribution of streptococcal infection-related glomerulonephritis is not well known across the country.

Method

This retrospective study was conducted from January 2015 to June 2020 at the RCWMCH, Cape Town, SA. International Statistical Classification of Diseases (ICD10) discharge codes were used to identify potential cases of acute nephritic syndrome. Clinical notes of all the selected cases were reviewed, and only the children confirmed to have APSGN (as per case definition) were included in this study, while other children found to have causes of acute glomerulonephritis other than APSGN were excluded. The Cape Town Census and Population Statistics 2011 database was used to describe the potential risk factors contributing to the occurrence of APSGN, as well as the context in view of geographical area distribution, socio-economic standards and the availability of access to formal housing, clean water and sanitation among children with APSGN. Based on the provided address, patients were assigned a particular risk profile in light of the information gathered from either the Suburb or Ward Profiles in the Census 2011 documents. Data were presented as median [interquartile ranges (IQR)] or means [standard deviation (SD)], depending on the normality of data, while categorical data was presented as proportions. The source population (incidence denominator) included average Cape Town city children (≤ 14 years old) in the population during the study period. APSGN was defined based on clinical

presentation of at least two signs of acute nephritis (haematuria, oliguria, oedema and hypertension), associated with evidence of activation of an alternative pathway complement system (low C3 serum level) and or clinical and serological evidence of previous or current streptococcal infection. Serological markers of streptococcal infection were elevated, along with anti-streptolysin O titre (ASO) and or anti-deoxyribonuclease B antibodies (Anti-DNase-B). The generic upper limits of normal (ULN) values were found to correlate with values used by the SA National Health Laboratory System using Laser Nephelometry technique (Beckman Coulter). For ASO, the upper limits of normal values are age-specific and are given as follows: <6 years 100 IU/ml, 6-12 years 250 IU/ml, >12 years 200 IU/ml. The normal anti-DNase-B reference range for children is < 75 IU/ml.

Table 1 Operational Definitions

Parameter	Definition
Oliguria	Urine volume less than 0.5 mL/kg/hr.
Clinical oedema	Puffiness of the face, bilateral pitting pedal oedema, and abdominal wall oedema.
Microscopic Haematuria	Blood in the urine that is detectable by a dipstick >2 +
Macroscopic Haematuria	Visible pink or brown coloured urine owing to the presence of RBC - confirmed by a microscopic examination.
Proteinuria	Used normal values of protein excretion as a function of age [4] • Children 1–2 years > 0.04 g Protein/mmol Creatinine • Children 2–3 years > 0.03 g Protein/mmol Creatinine • Children 3–5 years > 0.02 g Protein/mmol Creatinine • Children >5 years > 0.015 g Protein/mmol Creatinine
Nephrotic Range Proteinuria	Spot urine protein/creatinine ratio of > 0.2 g/mmol or 3 + of protein on the urine dipstick.
AKI	Age specific normal ranges of enzymatic creatinine were used to diagnose AKI as per the following references [4]. • Children < 2 years old 9- 32 umol/L • Children 2 to < 5 years old 18-38 umol/L • Children 5 to < 12 years old 27- 54 umol/L • Children > 12 years old 40-72 umol/L

Results

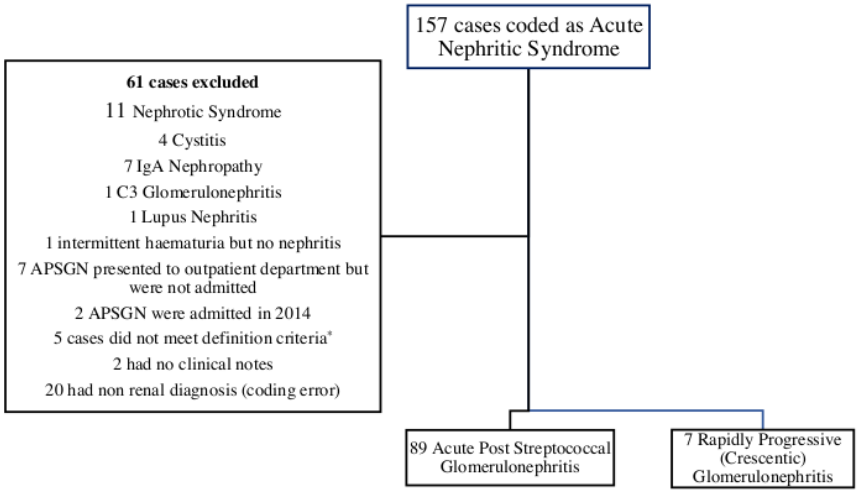

Figure 1 Flow Diagram of Patient Recruitment. (*no known complement level nor antistreptococcal serology)

During the 66 months' study period, 157 cases coded as acute nephritic syndrome, of which 96 cases were included and 61 cases were excluded from the study (figure 1). Of the 96 children included in the study, 89 (92,70%) cases had confirmed APSGN as per the definition criteria, and seven (6,30%) children had a clinical diagnosis of RPGN, with positive streptococcal serology and crescents, and evidence of post-infectious

glomerulonephritis in the kidney biopsy. During the 66 months' study period, 157 cases coded as acute nephritic syndrome, of which 96 cases were included and 61 cases were excluded from the study (figure i). Of the 96 children included in the study, 89 (92,70%) cases had confirmed APSGN as per the definition criteria, and seven (6,30%) children had a clinical diagnosis of RPGN, with positive streptococcal serology and crescents, and evidence of post-infectious glomerulonephritis in the kidney biopsy. The population incidence of APSGN in Cape Town is 1.7 per 100,000.

Table 2 Annual incidences (*the highest incidence noted during the year 2017)

Year	2015	2016	2017	2018	2019	2020	Total
Cases per year	11	19	23	19	19	5	**96**
Incidence rate per 100,000 people	1.07	1.8	2.1*	1.7	1.7	0.9	**1.5**

Table 3 Incidences per Suburb.

Suburb	Count APSGN	≤14 years Population number (2011)	Incidence rate per 100,000	% of population having access to piped water inside dwelling
Nyanga	9	15,840	56.81	53.5%
Gugulethu	14	25,557	54.77	47.6%
Philippi	15	54,783	27.38	26.00%
Manenberg	7	17,466	45.80	89.3%
Langa	4	13,367	29.2	49.6%

The median age of presentation was 7.4 (IQR 5.18-10.25) years, with ages ranging from 1.9 to 15.4 years. Nevertheless, APSGN occurred predominantly in ages between five to ten years (51.46%) (fig ii). A predominance of the male gender was noted with a male to female ratio of 1.9:1. Where discharge weight was known in 78 children, there were no severely malnourished children, as 76 children plotted as normal weight for their age and two children plotted as moderately underweight for their age. Eighty children were tested for HIV infection during their hospital admission with no HIV-positive results documented. Distribution by communities showed a greater number of cases in communities with a lower socio-economic level and poor access to piped water inside their dwellings.

Seasonal pattern and variation: The seasonal distribution pattern during the 66 months' study period showed an increased incidence of APSGN in Autumn (Mar-May) (36.4%), while the lowest incidence was noted in the Spring (Sep-Nov) season (12.5%). Winter and Summer showed an incidence of 25 per cent and 26 per cent respectively.

Clinical presentation: Of the 96 cases, 95 had confirmed haematuria, and one patient presented in ESKD with anuria. Ninety-four children had their urine tested for proteinuria either by using a urine dipstick or by the quantitative measurement of urine protein to creatinine ratio, of which 48 children had a nephrotic range proteinuria, 37 had a sub-nephrotic proteinuria and nine had no proteinuria. Based on clinical examination, clinicians identified oedema in 84 cases on presentation, while 12 cases were assessed as not having oedema. Only 29 children had a clinical record of confirmed oliguria either from a history given by parents or by measured urine output, one patient was anuric, and ten patients had normal urine output. Most children presented with stage 2 hypertension (71 cases), while five children had normal BP on admission. Ten children presented with hypertensive seizures, eight of them had confirmed as Posterior Reversible Encephalopathy Syndrome (PRES) on CT scan of the brain. Additionally, 35.48 per cent of the patients presented with fluid overload complications (cardiac failure and/or pulmonary oedema) (See Table 3).

Table 4 Clinical presentation and diagnosis of APSGN

	Clinical presentation	Count	Percent

Clinical presentation with nephritic syndrome	Haematuria	95	89.9
	Sub-nephrotic Proteinuria	37	38.54
	Nephrotic Proteinuria	48	50.00
	Oedema	84	87.50
	Oliguria / Anuria	29 / 1	30/ 1.04
	Hypertension Stage 1	7	7.29
	Hypertension Stage 2	71	73.95
	Hypertensive encephalopathy	10	10.42
Source of Streptococcal infection	Skin infection	53	55.21
	Throat infection	23	23.96
	Skin and throat infection	9	9.38
	Nil infection identified	11	11.46
Serum C3 level	Low C3	83	86.46
	Normal C3	6	6.25
	Unknown C3	7	7.29
Antistreptococcal serology	Elevated anti-DNase-B	90	93.75
	Elevated ASO	77	80.21
	Unknown AS serology	6	6.25
Diagnosis	APSGN	89	92.71
	RPGN Crescentic	7	7.29

Based on history, clinical examination or investigations, clinicians identified a likely source of infection in 85 cases, of which 23 had a history of current or previous throat infections, 53 had skin infections, and nine patients had both skin and throat infections. Of the 53 children with identified skin infections, ten were treated for scabies skin infection and three were treated for Tinea skin infection.

Diagnosis: The serum complement level was known in 89 subjects. Serum C3 levels were found to be low in 83 (86.4%), and normal in six subjects. Anti-streptococcal serology was known in 90 children, and 90 children had elevated anti-DNase-B, and 77 of them also had elevated ASO at presentation. Six patients had a high blood cholesterol (>5mmol/L) and low serum albumin level (<30 g/L) level at presentation, and all of them had nephrotic range proteinuria on presentation. Percutaneous kidney biopsy was indicated in eleven children. Four biopsies showed a histological change of diffuse exudative proliferative glomerulonephritis on light microscopy, and fibrinogen and C3 on immunofluorescent staining. These finding suggest that events leading to glomerular damage in accordance with post-infectious nephritis. Seven biopsies confirmed type II (immune complex) crescentic glomerulonephritis. Six out of the seven crescentic nephritis cases were treated with three doses of Methyl Prednisone followed by one dose of intravenous Cyclophosphamide, while one child was only treated with Methyl Prednisone with no Cyclophosphamide administered.

Management: The mean length of hospital stay was 5.7 days and the median was five days (the range was from one to 30 days). Eight patients were admitted to ICU, of which, six were admitted for observation due to recurrent hypertensive seizures, and two were admitted for respiratory support due to cardiac failure and pulmonary oedema. Four children were admitted for observation for one day, but they were not fluid restricted and did not receive diuretics nor antihypertensives. Diuretic was administered to 88 subjects, 60 of them required an anti-hypertensive agent in conjunction with the diuretics (25 treated with only a single dose of Rescue for elevated BP and 35 children needed regular Amlodipine for more than one day). Almost all cases were treated with penicillin containing antibiotics for 10 days. Fifty-seven children presented in AKI (as per definition criteria set for AKI). Nevertheless, ten cases had severe AKI with persistently rising serum creatinine levels despite fluid restriction and diuretics use. These ten children were treated as RPGN with four of them responding to Methyl Prednisone (10mg/kg IV) pulse therapy, while six needed the addition of Cyclophosphamide.

Outcome: Most children (61) with APSGN (63.54%) recovered, while three patients had persistent proteinuria after six months from presentation, and one patient had persistent hypertension and was on Amlodipine. Outcomes were noted to be unfavourable in the seven children treated for RPCGN, as four (4.17%) of them

progressed to ESKD (three required acute haemodialysis, and initiation of chronic intermittent peritoneal dialysis at first presentation, and one patient did not require acute haemodialysis, yet still progressed to ESKD and was started on peritoneal dialysis within 6 months of initial presentation) (See Table 5).
At four to six weeks post the acute episode, 68 children presented to follow-up visits. All of them had urine dipstick screening on the review day with only two children having their renal function and complement level checked, both had normal creatinine to age and normal serum complement levels. At six weeks' review, 56 children had persistent microscopic haematuria, 15 had persistent proteinuria, and eight had persistent hypertension.

Table 5 Outcome of APSGN and RPCGN (rapidly progressive crescentic glomerulonephritis)

Outcome	APSGN	RPCGN	Count (%)
Recovered	61		61 (63.54%)
Unknown	25	2	27 (28.13%)
ESKD on PD		4	4 (4.17%)
Persistent proteinuria longer than six months post episode	2	1	3 (3.12%)
Hypertension on Amlodipine, then lost to follow up	1		1 (1.04%)
Grand Total	**89**	**7**	**96**

Discussion

APSGN is a disease spectrum that can range from subclinical to severe disease, with asymptomatic cases estimated to be four to 19 times more common than symptomatic disease [5]. The incidence of APSGN in SA however, is high, it is more likely to be an underestimate of the true burden of disease in Cape Town city, for two reasons. Firstly, is that this study overlooked subclinical cases and only assessed symptomatic patients presenting for medical services, also as this was a single centre study, it did not count cases presented to other health facilities in Cape Town.
With this high incidence rate, APSGN is still a major public health problem and a frequent cause of paediatric hospital admission and AKI is SA. Yet we do not seem to be following the trend of high income and some low-middle income settings. In this setting, drought is a challenge that SA has been facing for the last five years with certain parts of the country being classified a disaster region in 2017. In this study the annual incidence rate reflected an increased incidence of APSGN during the year of drought in 2017 with an incidence rate of 2.1 per 100,000 people. Nevertheless, the authors noted a decrease in the incidence rate of APSGN during the COVID-19 pandemic in 2020 with incidence rates decreasing to 0.9 per 100,000 people. This decreased incidence of APSGN could be an accurate figure reflecting a decrease in the incidence due to the effect of lockdown resulting in reducing the risk of exposure and inter-personal transmission of Streptococcal throat and skin infection. Or it might be an underestimation of the true incidences due to the de-escalation of healthcare services, and lack of access to transport during this period.
In this study most cases presented from areas of low socio-economic status (Philippi, Gugulethu and Nyanga), where on-site water is restricted to 26 per cent, 47 per cent and 53 per cent of the population. Despite their low socio-economic status, most children had normal weight for age parameters, hence APSGN cannot be considered a disease of malnourished children.
Human immunodeficiency virus (HIV) infection can lead to progressive loss of kidney function known as HIV-associated nephropathy (HIVAN). In Cape Town, a ten-year review of a single-centre renal biopsy database showed an increased incidence of HIVAN from 6.6 per cent in 2000 to 25.7 per cent in 2009, with HIVAN found to be the second most common cause of nephrotic range proteinuria in adults [6]. A reassuring finding in this review is that none of the children who presented with APSGN were HIV infected, this might reflect a successful eradication of mother-to-child transfer of the HIV infection.
In this study's cohort more than one third of the subjects presented in the fall season, with the least cases presenting in spring - this is different from the study done in Chile where the seasonal distribution pattern had a

bimodal tendency, with a rise in the autumn (38%) and in spring (30%). The researchers did not note any seasonal variation in terms of preceding skin or throat infection.

Most children presented with acute onset of haematuria, proteinuria, hypertension, oedema, and AKI while oliguria/anuria was only confirmed in 30 children. This is due to the poor recording of urine output, as most clinicians did not ask about oliguria on admission, and not all subjects had their urine output monitored. Also, most children had received a stat dose of diuretics on admission, and this could have resulted in normalisation of urine output. More than one third of the subjects presented with complication of nephritis and or fluid overload complications, which may be reflective of late presentation of those children to a healthcare facility.

Eight out of the ten children presented with hypertensive seizure had confirmed PRES on CT scan of their brain. There were no other pathological findings on the CT scan of their brains. Almost all these children returned to a normal blood pressure on diuretics, with only one child requiring a Labetalol infusion, yet none of these children had their neurodevelopment monitored on the long term.

The diagnosis of APSGN is usually not difficult when a nephritic clinical presentation is associated with serologic evidence of recent streptococcal infection and depressed serum C3 concentration, in this study C3 serum levels were found to be depressed in 86.4 per cent of subjects. This reflects a decreased sensitivity of this test compared to other studies, such as the study conducted in Chile and Sydney where serum C3 levels were depressed in 95 per cent and 100 per cent of subjects [7, 8]. Nevertheless, seven subjects in this study had unknown C3 serum levels, which could have contributed to the decreased sensitivity. Five children had low C3 and low C4 at presentation, however, none of them had clinical or biochemical evidence suggestive of lupus nephritis, and all of these five children had a history of either previous or current throat or skin infections with elevated serum antistreptococcal markers. Rodríguez *et al*. described an activation of classical complement pathway (reduced C4 level) in 15–30 per cent of APSGN subjects [9].

ASO and anti-DNase-B titre tests are widely available and the most frequently elevated antibodies in upper respiratory and skin infection, respectively [5]. Yet in this study's cohort almost two thirds of subjects had preceding skin infections and the anti-DNase-B level was elevated in more than 90 per cent of the subjects. Hence, APSGN in SA occurs more commonly secondary to skin infections than pharyngitis. This pattern of infection is similar to areas with a temperate Mediterranean climate as in Chile [7], nevertheless other parts of the world such as in Australia and North Africa reported APSGN to occur more commonly post-pharyngitis (60% and 80% respectively) [8, 10].

Evidence of a host immune response to group A streptococcal antigen is used for confirmation of streptococcal infections in children. Hence, knowledge of the upper limits of normal antistreptococcal serology by healthcare workers is critical to make an accurate diagnosis. Although there have been updated reports of antistreptococcal serology in different parts of the world [11, 12], the researchers are unaware of any recent similar data from children in SA. Therefore, in this study the researchers used age-related 'normal' values for ASO and anti-DNase-B provided in the package inserts of commercially available kits; however, there are no recent reports to validate such values. This is acknowledged as a limitation in the study.

A kidney biopsy is not routinely indicated in the acute setting for the diagnosis of APSGN [9]. However, a biopsy is indicated in cases of severe kidney impairment requiring dialysis, or if the serological testing was not confirmative of the diagnosis. In this study's cohort, indication for biopsies were presentation with RPGN to confirm or exclude crescentic glomerulonephritis, or in children whom diagnosis of acute nephritis was not certain as they presented with nephritis and nephrotic range proteinuria, hypoalbuminemia, and hypercholesterolemia. Eleven subjects required a kidney biopsy during admission, all of them had successful biopsies with no post procedure complications. Immune complex mediated crescentic glomerulonephritis accounted for more than 50 per cent of APSGN biopsies and 6.30 per cent of the total APSGN cases. This result confirms what has been described in SA in two separate studies. One study was a ten-year review of native kidney biopsy records at the RCWMCH from 2004 to 2015, and the other was a seven-year review from Natal province between 1981 to 1987, whereby crescentic glomerulonephritis accounted for 5.1 per cent and 5.8 per cent of native kidney biopsies respectively, with almost 60 per cent and 30 per cent of the crescentic glomerulonephritis being of an immune complex mediated subtype due to post-infectious nephritis [13, 14]. The outcome was noted to be poor in children with crescentic glomerulonephritis with more than 50 per cent progressing to ESKD. This is similar to earlier reports from both developing and developed countries [13, 15-17].

There is no specific therapy to cure APSGN, and management is mainly based on eradication of the streptococcal infection and on the supportive treatment of symptoms and complications as required [18]. A 10-day course of penicillin or, in allergic individuals, erythromycin is standard therapy for streptococcal eradication [19]. In this study's cohort almost all children were treated with 10 days' course of penicillin containing antibiotics. Antibiotic therapy was commenced on day one of admission and APSGN suspected. Preventive antibiotic treatment is indicated in the case of an epidemic situation, or for household members of index cases where APSGN is common, or when clusters of cases are reported [3]. This study did not prove an epidemic of APSGN and the researchers did not routinely check siblings for raised streptococcal titres.

The outcome of APSGN in children is usually favourable. Rodriguez *et al*. found that more than 90 per cent of APSGN had normal or only moderately reduced kidney function five to 18 years after an APSGN episode, and while 20 per cent had an abnormal urine analysis, but azotaemia was found in less than one per cent of the patients [3]. In this cohort some patients were admitted for one day only and were then referred to another healthcare facility for continuation of care and management. These patients usually did not come to follow-up at RCWMCH, hence the outcome of these patient was not known. Three patients had persistent proteinuria after six months post initial presentation, all of them had nephrotic range proteinuria and AKI on presentation. All of them were lost to follow up. Nevertheless, APSGN was significantly correlated with increased incidence of a decrease in the glomerular filtration rate and thus long-term follow-up of hypertension and proteinuria would be recommended.

Conclusion

APSGN during childhood continues to be a major health problem in SA with the majority of children from less privileged settings presenting with acute complications from circulatory congestion. Yet, despite the late presentation, the outcome is favourable in most subjects, except for the Crescentic Glomerulonephritis where most children progress to CKD. The follow-up of affected children was very short, with the majority of patients absconding from follow-ups after their first visit. Therefore, considerably further studies should be performed to study the outcome of this disease in SA children. The study has several limitations which resulted from the retrospective nature of the study, and the lack of knowledge of the recent local data on streptococcal serology titre, hence the authors strongly encourage researchers to identify the current upper limits of normal of ASO titre and anti-DNase-B antibodies is South Africa children and adults.

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Appendix E: Author Guidelines-Journal of the International Paediatric Nephrology Association

Title Page: Please make sure your title page contains the following information.

Title: The title should be concise and informative.

Author information

- The name(s) of the author(s)
- The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
- A clear indication and an active e-mail address of the corresponding author
- If available, the 16-digit ORCID of the author(s)
- If address information is provided with the affiliation(s) it will also be published.
- For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

Abstract: Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

Keywords: Please provide 4 to 6 keywords which can be used for indexing purposes.

Declarations: All manuscripts must contain the following sections under the heading 'Declarations'.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Funding (information that explains whether and by whom the research was supported)

Conflicts of interest/Competing interests (include appropriate disclosures)

Availability of data and material (data transparency)

Code availability (software application or custom code)

Authors' contributions (optional: please review the submission guidelines from the journal whether statements are mandatory)

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals

Ethics approval (include appropriate approvals or waivers)

Consent to participate (include appropriate statements)

Consent for publication (include appropriate statements)

Text

Text Formatting

- Manuscripts should be submitted in Word.
- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Headings: Please use no more than three levels of displayed headings.

Abbreviations: Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

References

Reference list**:** The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

The entries in the list should be numbered consecutively.

If available, please always include DOIs as full DOI links in your reference list (e.g. “https://doi.org/abc”).

Ideally, the names of all authors should be provided, but the usage of “et al” in long author lists will also be accepted:

Always use the standard abbreviation of a journal’s name according to the ISSN List of Title Word Abbreviations. If you are unsure, please use the full journal title.

Authors preparing their manuscript in LaTeX can use the bibtex file spbasic.bst which is included in Springer’s LaTeX macro package.

Tables

- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.

- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Electronic Figure Submission

Supply all figures electronically.

Indicate what graphics program was used to create the artwork.

For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MS Office files are also acceptable.

Vector graphics containing fonts must have the fonts embedded in the files.

Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Figure Lettering

To add lettering, it is best to use Helvetica or Arial (sans serif fonts).

Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).

Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.

Avoid effects such as shading, outline letters, etc.

Do not include titles or captions within your illustrations.

Figure Numbering

All figures are to be numbered using Arabic numerals.

Figures should always be cited in text in consecutive numerical order.

Figure parts should be denoted by lowercase letters (a, b, c, etc.).

If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures, "A1, A2, A3, etc." Figures in online appendices [21] should, however, be numbered separately.

Figure Captions

Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.

Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.

No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.

Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.

Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

When preparing your figures, size figures to fit in the column width.

For large-sized journals the figures should be 84 mm (for double-column text areas), or 174 mm (for single-column text areas) wide and not higher than 234 mm.

For small-sized journals, the figures should be 119 mm wide and not higher than 195 mm.

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Accessibility

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that

All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)

Patterns are used instead of or in addition to colors for conveying information (color-blind users would then be able to distinguish the visual elements)

Any figure lettering has a contrast ratio of at least 4.5:1