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ORIGINAL ARTICLE

Clinical characteristics of hospitalised children with acute post-streptococcal glomerulonephritis in the Top End of Australia

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Aims: Despite the declining incidence of acute post-streptococcal glomerulonephritis (APSGN) in Australia, there is still a significant burden of disease amongst Aboriginal and Torres Strait Islander people in the Northern Territory. Childhood APSGN has been highlighted as a predictor of chronic kidney disease in this population. We aimed to describe clinical characteristics and outcomes of hospitalised children with APSGN in the Northern Territory.

Methods: Single-centre, retrospective cohort study of children (<18 years) with APSGN admitted to a tertiary hospital in the Top End of the Northern Territory between January 2012 and December 2017. Cases were confirmed using the Centre for Disease Control case definition guidelines. Data were extracted from the case notes and electronic medical records.

Results: There were 96 cases of APSGN with median age of 7.1 years (interquartile range (IQR) 6.7–11.4). Majority were Aboriginal and Torres Strait Islander (90.6%) and from rural and remote areas (82.3%). Preceding skin infections were identified in 65.5% and sore throat in 27.1%. Severe complications included hypertensive emergencies (37.4%), acute kidney injury (43.8%) and nephrotic-range proteinuria (57.7%). All children improved from their acute illness with supportive medical therapy; however, only 55 out of 96 (57.3%) children were followed up within 12 months of their acute illness.

Conclusions: APSGN disproportionately affects Aboriginal and Torres Strait Islander children and highlights the need for continued and improved public health response. There is room for significant improvement in the medium- and long-term follow-up of affected children.

Key words: acute kidney injury; chronic kidney disease; glomerulonephritis; Northern Territory; public health; streptococcus.

What is already known on this topic

1 Acute post-streptococcal glomerulonephritis (APSGN) is a preventable illness which disproportionately affects Aboriginal and Torres Strait Islander children.
2 The long-term sequelae of acute kidney injury (AKI) are increasingly appreciated, such as the progression to chronic kidney disease (CKD).
3 Repeated serious kidney injuries, such as childhood APSGN, are likely to contribute to the high burden of CKD amongst Aboriginal and Torres Strait Islander people in the Northern Territory (NT).

What this paper adds

1 Hospitalised children with APSGN in the NT have severe disease presentations, including severe AKI and extra-renal complications.
2 Low follow-up rates of this high-risk group are potentially causing under-recognition of persistent kidney impairment post APSGN episode.
3 There is an urgent need for increased resources in remote settings to prevent and mitigate the risks of CKD.

Acute post-streptococcal glomerulonephritis (APSGN) is an inflammatory kidney disease which is caused by a skin or throat infection with nephritogenic strains of Group A beta-haemolytic streptococcus (GAS).[1]

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The typical patient is a child who presents with sudden onset oedema, macroscopic or microscopic haematuria, oliguria or anuria, and hypertension following a skin or throat infection 2–4 weeks prior. Urine output usually improves after 4–7 days, leading to a rapid resolution of oedema and hypertension.[1] Subsequently, serum creatinine returns to baseline by 3–4 weeks,[2] proteinuria resolves within 3–6 months, and microscopic haematuria can persist for up to 2 years.[3]

Over the last few decades, there has been a sharp decline in the incidence of APSGN in middle-to-high-income countries; however, the incidence has remained disproportionately high amongst low-income countries – the difference is a median

incidence of 6.2 versus 24.3 cases per 100 000 person-years, respectively.[4] The World Health Organization estimates that of the 470 000 new cases of APSGN world-wide *per annum*, 97% are occurring in less affluent areas.[1,5] Furthermore, the incidence of APSGN can vary widely even within a country. This is most evident in countries like Australia, where Aboriginal and Torres Strait Islander children have one of the highest incidences in the world, 124.0 cases per 100 000 per-years, compared to 7.33 among non-Aboriginal children.[6]

The classical disease model of APSGN is that of an acute and transient condition which results in full kidney recovery.[7] However, emerging epidemiological and experimental evidence supports an alternative developmental model of disease,[8–10] whereby kidneys are programmed from fetal life in response to adverse conditions such as maternal malnutrition and gestational diabetes.[11] When superimposed by aquired kidney injuries during childhood, this sets ths stage for developing chronic kidney disease (CKD) in adulthood.[12,13]

There are published data on the epidemiology of childhood APSGN in the Top End of Australia[6]; however, the clinical spectrum, treatment and outcomes of hospitalised children have not been studied in detail. Therefore, we analysed a hospital cohort of children admitted with APSGN over a 5-year period.

Methods

Study design

We performed a retrospective cohort analysis of paediatric patients (<18 years) admitted to a tertiary hospital in the Top End of the Northern Territory (NT) with APSGN from 1 January 2012 to 31 December 2017.

Setting

The tertiary hospital for children and adults is in the Top End of Australia. The 'Top End' refers to the northern third of the NT which has a tropical climate consisting of the 'dry' season (April–September) and monsoonal 'wet' season (October–March). The hospital receives referrals from Darwin and surrounding areas, as well as 41 remote communities across the NT.

The NT covers 17% of the Australian land mass, but is sparsely populated with only 1% of the Australian population (232 601 in 2021).[14] Aboriginal and Torres Strait Islanders represent around 30% of this population (61 115) and children aged 0–19 years represent 27.1% (63 085).[14]

In the NT, 80% of the Aboriginal and Torres Strait Islander people live in remote or very remote communities of up to 2000 residents.[15] Many communities have a store, an airstrip, school and health clinic staffed by remote nurses, Aboriginal Health Workers and visiting general practitioners.[16]

Table 1 Case definition for notification of APSGN in the Northern Territory

Confirmed case	Probable case	Possible case
Laboratory definitive evidence† OR Laboratory suggestive evidence‡ and clinical evidence.§	A probable case requires clinical evidence§ only.	A possible case requires laboratory suggestive evidence‡ only.

† Laboratory definitive evidence is a kidney biopsy suggestive of APSGN. ‡ Laboratory suggestive evidence is haematuria on microscopy (RBC > 10/μL) AND evidence of recent streptococcal infection (positive Group A Streptococcal culture from skin or throat, or elevated ASO titre or Anti-DNase B) AND Reduced C3 level. § Clinical evidence is at least two of the following: facial oedema; ≥moderate haematuria on dipstick; hypertension; Peripheral oedema. APSGN, acute post-streptococcal glomerulonephritis.

Case ascertainment

APSGN is a notifiable disease in the NT with standardised case definitions (Table 1).[17] Data relating to 170 cases of APSGN were extracted from the NT notifiable diseases surveillance database (Fig. 1). We excluded children who were not hospitalised to the tertiary hospital and those who did not meet the definition of APSGN as per the APSGN guideline.[17] *Re*-presentation to the hospital within 1 month was considered a single illness episode.

Data collection

Data were obtained from case notes and electronic hospital records. Demographic details, including age at diagnosis, gender, Aboriginal and Torres Strait Islander status and residence, were included. Clinical data, including symptoms and signs during admission, co-morbidities, laboratory parameters and inpatient management, were collected. We obtained follow-up data up to 12 months from discharge through the hospital's electronic and hard copy records.

Definitions

Hypertension was defined as per the 2017 American Academy of Paediatrics (AAP) Guideline for Childhood Hypertension.[18] For children aged 1–13 years:

- Elevated: ≥90th percentile
- Stage 1: ≥95th to <95th percentile + 12 mmHg
- Stage 2: ≥95th percentile + 12 mmHg
- Acute severe: ≥95th percentile + 30 mmHg

For children aged ≥13 years:

- Elevated: 120/<80 to 129/<80 mmHg
- Stage 1: 130/80 to 139/89 mmHg
- Stage 2: ≥140/90 mmHg

Where the height was unknown, a cut-off of 130/80 to 139/89 mmHg was applied for stage 1 hypertension and ≥140/90 mmHg for stage 2 hypertension regardless of age.

Acute kidney injury (AKI) was defined as per the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline.[19] Changes from baseline serum creatinine (SCr) or urine output (UO) determined the severity of AKI.

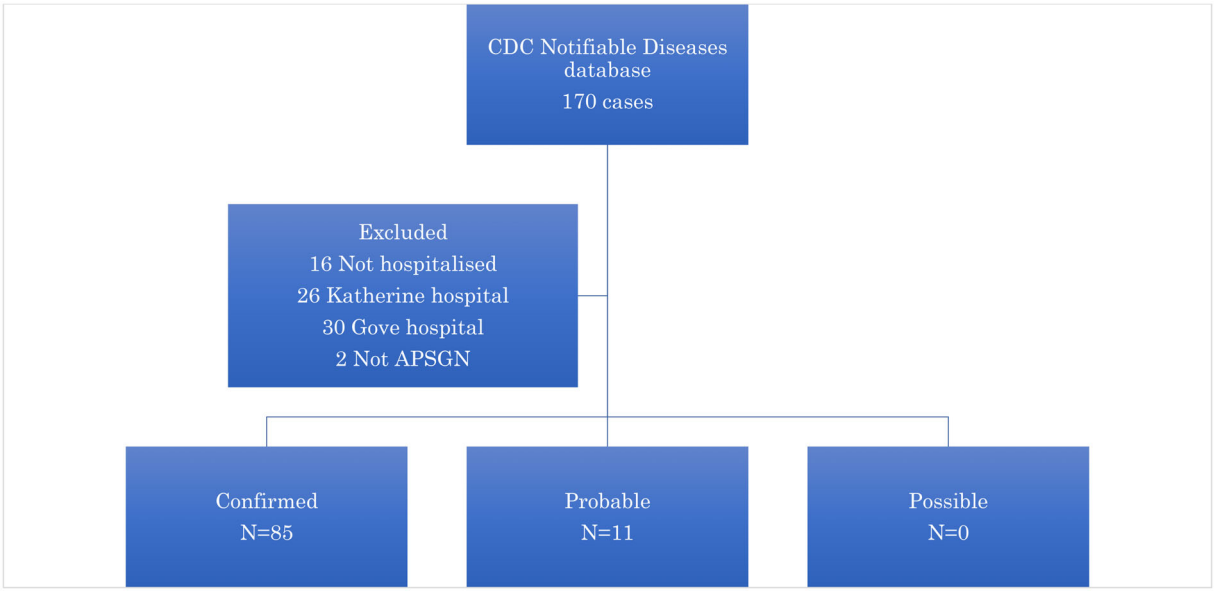


Fig. 1 Case ascertainment. A total of 170 cases of APSGN was identified through the Northern Territory notifiable diseases surveillance database for the study period. Children who were managed in the community, or admitted to a hospital other than the Royal Darwin Hospital, or assessed not to have APSGN were excluded from the study. CDC, Centre for Disease Control.

- Stage 1: SCr 1.5–1.9 times baseline or UO <0.5 mL/kg/h for 6–12 h.
- Stage 2: SCr 2.0–2.9 times baseline or UO <0.5 mL/kg/h for ≥12 h.
- Stage 3: SCr 3.0 times baseline or UO <0.3 ml/kg/h for ≥24 h or anuria for ≥12 h.

Where the baseline SCr was unknown, the normal SCr range for age and sex was used as the baseline. Other markers of kidney damage were defined as per the KDIGO guidelines[20]:

- Nephrotic-range proteinuria in the *acute* phase of APSGN: protein-creatinine ratio (PCR) > 200 mg/mmol.
- Albuminuria during the *convalescent* phase of APSGN: albumin-creatinine ratio (ACR) ≥ 3 mg/mmol.

Statistics

Descriptive analysis was performed using Microsoft Excel software. Continuous variables were reported as mean and standard deviation for normally distributed data or median and interquartile ranges (IQRs) for skewed data. Categorical data were represented as percentages.

Results

Baseline characteristics

Ninety-six children with APSGN met the study's inclusion criteria (see Table 2). Amongst these, 85 (88.5%) were *definite* APSGN and 11 (11.5%) were *probable* APSGN. The median age was 7.1 years (IQR 6.7–11.4) and 49 (51.0%) were male. Eighty-seven (90.6%) children were Aboriginal and Torres Strait Islander and 79 (82.3%) came from rural or remote areas. Majority (65.6%) had a history of preceding skin infection. One in 10 (11.5%) children had pre-existing co-morbidities, including congenital kidney disease, history of premature birth, previous episode of APSGN and type 2 diabetes with microalbuminuria.

Clinical and laboratory features

Clinical features are summarised in Table 3. Most common presentations were haematuria (93.8%), hypertension (90.6%) and

Table 2 Baseline characteristics of children hospitalised with APSGN

Baseline characteristics	All children ($N = 96$)
Median age – year (interquartile range)	7.1 (6.7–11.4)
Male sex – no. (%)	49 (51.0)
Ethnicity – no. (%)	
Aboriginal and Torres Strait Islander	87 (90.6)
Non-ATSI	9 (9.4)
Remoteness – no. (%)	
Rural/remote	79 (82.3)
Urban	17 (17.7)
Preceding infection – no. (%)	
Skin sores	63 (65.6)
Sore throat	26 (27.1)
Co-morbidities† – no. (%)	11 (11.5)

† Co-morbidities included history of APSGN, vesico-ureteric reflux grade 4, renal angiomyolipoma, right renal agenesis, type 2 diabetes with microalbuminuria, polycystic kidney disease, history of premature birth (including ex-24 weeker). APSGN, acute post-streptococcal glomerulonephritis.

Table 3 Clinical characteristics at presentation

Clinical characteristics	All children ($N = 96$)
Haematuria – no. (%)	90 (93.8)
Hypertension† – no. (%)	87 (90.6)
Elevated (≥90th percentile to <95th percentile)	5 (5.2)
Stage 1 (≥95th to <95th percentile + 12 mmHg)	15 (15.6)
Stage 2 (≥95th percentile + 12 mmHg)	67 (69.8)
Acute severe (≥95th percentile + 30 mmHg)	33 (33.4)
Facial oedema – no. (%)	66 (68.8)
Peripheral oedema – no. (%)	27 (28.1)
Dyspnoea – no. (%)	17 (17.7)
Headache and vomiting – no. (%)	15 (15.6)
Hypertensive seizure – no. (%)	1 (1.0)

† Hypertension definition based on the 2017 American Academy of Paediatrics Guidelines for Childhood Hypertension.[17]

oedema (68.8%). One third (33.4%) had acute severe hypertension with end-organ signs, including 16 cases of encephalopathy (headache, vomiting and/or seizure) and 17 cases of dyspnoea. Height measurements were missing in 33.3% of the cases.

Table 4 Laboratory characteristics at presentation

Laboratory characteristics	All children ($N = 96$)
Kidney function	
Acute kidney injury at presentation† – no. (%)	42 (43.8)
Stage 1	19 (19.8)
Stage 2	11 (11.5)
Stage 3	12 (12.5)
Nephrotic-range proteinuria (PCR > 200 mg/mmol) – no./total no. (%)	30/52 (57.7)
Any proteinuria on dipstick urinalysis – no. (%)	83 (86.5)
Haematuria on microscopy (RBC > 10/μL) – no. (%)	93 (96.9)
Microbiology	
Children with microbiological samples sent – no. (%)	84 (87.5)
GAS-positive skin swab – no./total no. (%)	20/84 (23.8)
GAS-positive throat swab – no./total no. (%)	3/84 (3.6)
Immunology	
Reduced C3 level (<0.83 g/L) – no. (%)	90 (93.8)
Elevated ASOT (>240 IU) or anti-DNase B (>187 IU) – no. (%)	85 (88.5)
Kidney ultrasound – no. (%)	36 (37.5)
Kidney biopsy – no. (%)	2 (2.1)

† AKI definitions based on 2012 KDIGO guidelines.[18] ASOT, anti-streptolysin O titre; GAS, group A streptococcus; IU, international units; PCR, protein-creatinine ratio; RBC, red blood cell.

Table 4 summarises the laboratory findings at presentation. Acute decline in kidney functions was observed in 43.8% with the following breakdown in AKI severity – stage 1: 19.8%, stage 2: 11.5% and stage 3: 12.5%. Biochemical examination of the urine showed nephrotic-range proteinuria in 30 children.

Out of 84 children who had microbiological samples collected, 23 (27.4%) had evidence of current GAS infection. Skin was the dominant source of GAS infection (23.8%), followed by the throat (3.6%). Majority had immunological markers of recent GAS infection indicated by low C3 complement levels (93.8%) and elevated streptococcal serology (88.5%).

Kidney ultrasounds were performed in 36 (37.5%) children, even though this is not a routine investigation for APSGN. Increased parenchymal echogenicity was reported in 50% of the studies, which is consistent with a diagnosis of 'medical renal disease'.[21,22]

Inpatient management

Table 5 summarises the inpatient management of APSGN. The majority (61.5%) required at least two anti-hypertensive agents to control their blood pressure. Frusemide and nifedipine were most frequently used in the acute setting, whereas angiotensin-converting enzyme inhibitors and beta-blockers were more common in long-term management. Twelve (12.5%) children were continued on anti-hypertensive treatment on discharge. Notably, none of the children required kidney replacement therapy including dialysis. Regarding anti-microbial therapy, 19.8% did not receive any antibiotics for streptococcal eradication despite recommendation in the guidelines.

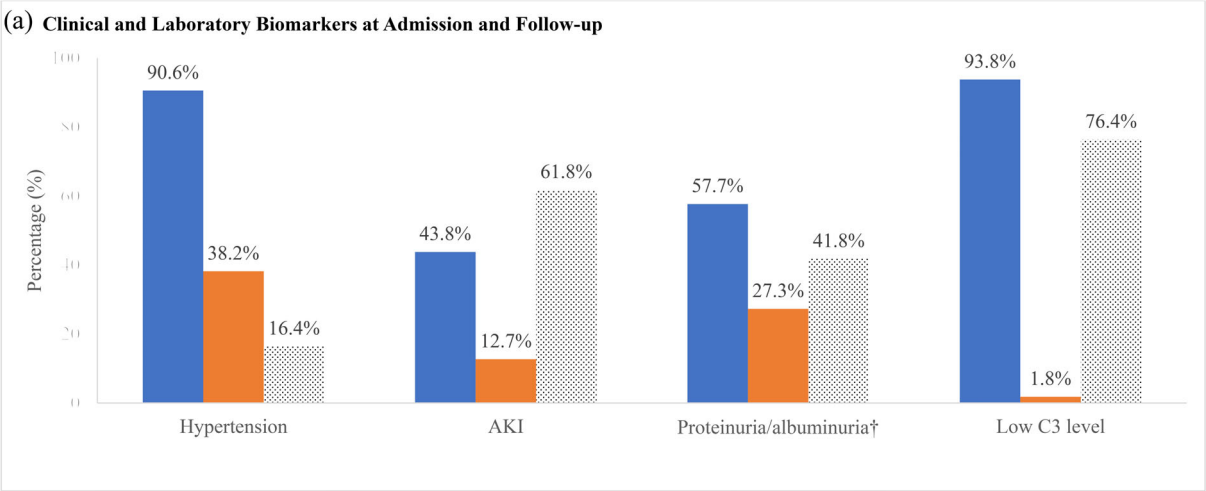
Severe cases

Two children underwent a kidney biopsy due to progressively worsening kidney function. One child had crescentic APSGN and received a short course of steroid with improvement. The second child had a biopsy confirming APSGN. A different third child was transferred interstate to a tertiary children's hospital; however,

Table 5 Medical management of APSGN

Management	All children ($N = 96$)
Anti-hypertensives	
Any anti-hypertensive – no. (%)	77 (80.2)
≥2 anti-hypertensive – no (%)	59 (61.5)
Frusemide – no. (%)	76 (79.2)
Nifedipine – no. (%)	60 (62.5)
Amlodipine – no. (%)	7 (7.3)
Other – ramipril, lisinopril, atenolol, hydralazine – no. (%)	4 (4.2)
Kidney replacement therapy – no. (%)	0 (0.0)
Anti-microbial therapy	
LAB or other anti-streptococcal agent – no. (%)	77 (80.2)
No antibiotics – no. (%)	19 (19.8)

APSGN, acute post-streptococcal glomerulonephritis; LAB, long-acting benzyl penicillin.



(b)	Hypertension (≥90th percentile)	AKI	Proteinuria/ Albuminuria†	Low C3 Level
Admission – no./total no. (%)	87/96 (90.6)	42/96 (43.8)	30/52 (57.7)	90/96 (93.8)
Follow-up – no./total no. (%)	21/55 (38.2)	7/55 (12.7)	15/55 (27.3)	1/55 (1.8)
Incomplete data at follow-up – no./total no. (%)	9/55 (16.4)	34/55 (61.8)	23/55 (41.8)	42/55 (76.4)
Median time to follow-up – days (IQR)	68 (27-137)	62 (23-139)	81 (50-139)	118 (69-187)

Fig. 2 Clinical features and biomarkers of kidney injury. Panel (a) shows the proportion of children with hypertension (≥90th percentile), AKI, proteinuria, albuminuria and low C3 levels at presentation versus follow-up. †Clinically significant proteinuria is represented by nephrotic-range proteinuria (PCR > 200 mg/mmol) at admission and microalbuminuria (ACR ≥ 3 mg/mmol) at follow-up. Panel (b) compares the data in detail, including incomplete data and median time to follow-up. ACR, albumin-creatinine ratio; AKI, acute kidney injury; IQR, interquartile range; PCR, protein-creatinine ratio; SBP, systolic blood pressure. (■) Presentation; (■) Follow-up; (⁙) Incomplete data at follow-up (%).

spontaneous improvement in kidney function precluded them from a biopsy.

Discharge and follow-up

The median length of stay was 7 days (IQR 5–12). All patients were discharged home, except for one child who was referred to another hospital (see above). Two children were readmitted to hospital within a month for a prolonged course of APSGN.

Regarding follow-up, 55 (57.3%) children were reviewed by a paediatrician or nephrologist within the first 12 months of their APSGN episode. Figure 2 summarises their clinical and laboratory biomarkers. The time to follow-up was widely variable and persistent abnormalities were observed over a large spread of intervals: 38.2% had hypertension (median days to follow-up: 68 days, IQR 27–137), 12.7% had AKI (median 62 days, IQR 23–139), 27.3% albuminuria (median 81 days, IQR 50–139) and 1.8% had low complement levels (median 118, IQR 69–187).

Discussion

This study is the first to describe the clinical characteristics of children who have been hospitalised and followed up with APSGN in the Top End of Australia. Our findings provide detailed information on the profiles and patterns of paediatric APSGN and complements previous epidemiology studies which have canvassed the topic comprehensively.[6,23]

In our cohort, children who identified as Aboriginal and Torres Strait Islander outnumbered children of other ethnic backgrounds by 10-fold. Similarly, a 2010–2014 study from Central Australia found that all children hospitalised with APSGN were Aboriginal and Torres Strait Islander.[24] The disparities in kidney disease burden for Aboriginal and Torres Strait Islander children in Australia is akin to other First Nations' experience around the world. For example, a study from New Zealand reported that the incidence of APSGN was 7- to 17-fold higher amongst Pacific Islander and Māori children compared to those of European descent.[25]

Aboriginal and Torres Strait Islander, Māori and Pacific Islander people share common risk factors that perpetuate the high prevalence of GAS in their communities (e.g. crowded housing). Skin infection was the most common source of GAS in our group, consistent with the widespread awareness that impetigo is a more ubiquitous problem than pharyngitis amongst Aboriginal and Torres Strait Islander children.[26] In remote Australian settings, almost half of the children are said to have impetigo at any given time and a further third to have scabies.[27] Prospective trials are underway to understand the true burden of GAS impetigo

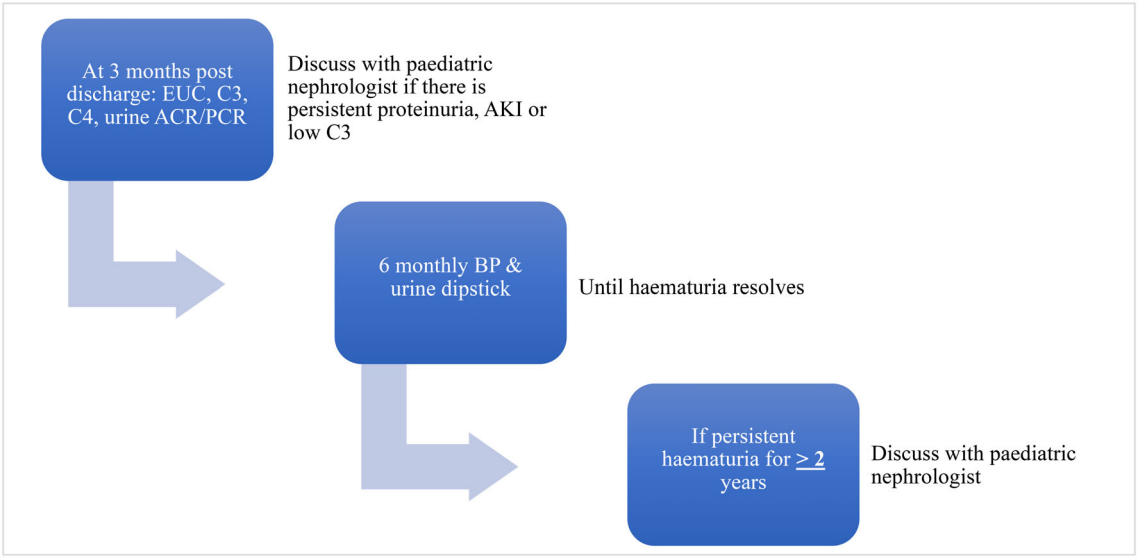


Fig. 3 Proposed follow-up process post APSGN in the Northern Territory. Screen for persistent kidney impairment at 3 months following an episode of APSGN. Consult a paediatric nephrologist if there is persistent proteinuria, AKI or low complement levels. It is normal for microscopic haematuria to persist for up to 2 years post APSGN; however, these children should have six-monthly monitoring with BP and urine dipstick. Persistent haematuria beyond 2 years should prompt a consultation with paediatric nephrologist. ACR, albumin creatinine ratio; AKI, acute kidney injury; APSGN; acute post-streptococcal glomerulonephritis; BP, blood pressure; EUC, electrolytes, urea and creatinine; PCR, protein creatinine ratio.

and pharyngitis in these endemic areas.[28,29] Group A streptococcal vaccine may be available in the future.[30]

Severe presentations (acute severe hypertension, encephalopathy and cardiac failure) and severe acute kidney failure (AKI stages 2–3) accounted for a high proportion of presentations in our group compared to other studies. One study from French Polynesia[31] showed that severe presentations occurred in 22% of their sample, compared to 33.4% in our group; a study of hospitalised children in Nanjing, China,[32] showed that 40.0% were hypertensive compared to 80.2% in our group; and a study from New Zealand[33] showed that encephalopathy occurred in 9.1%, compared to 16.6% in our group.

Despite the high acuity of presentations in our study, most children improved with supportive medical management (antihypertensives, fluid restriction and antibiotics), consistent with the view that the short-term prognosis of APSGN is favourable when appropriate health care is available. However, while our study reflected a rigorous approach to the acute management of APSGN, it exposed a shortcoming in the systems of follow-up post-discharge from the hospital. Overall, 42.7% were lost to follow-up; and even amongst those who attended their follow-up review, key clinical makers of kidney disease – such as blood pressure, SCr, urinalysis, complement levels – were incompletely recorded in up to 76.4% of encounters.

The lack of a robust system of follow-up is particularly concerning given the severity of APSGN and AKI in this group. These children require careful monitoring to ensure their kidney function and complement levels normalise after the acute phase of their illness. Failure to resolve may indicate recurrent APSGN, an alternative diagnosis or worsening of pre-existing kidney disease. The KDIGO guideline recommends that all patients after AKI be evaluated at 3 months due to their increased risk of developing CKD.[19] AKI has the potential to cause maladaptive repair, nephron loss and functional adaption before CKD is clinically evident.[34] Although it is difficult to quantify how singular insults like APSGN can contribute to the development of CKD, one study has shown that the risk of overt albuminuria is six times higher in adults with a history of APSGN than without.[35]

The logistics of follow-up in the NT are complicated by the geographical spread of its inhabitants, limited access to specialists and pathology services, short turnover of the health-care workforce and the tyranny of distance between hospital and community health services.[36] Opportunities exist to reduce these barriers and we propose that future work is targeted towards the following priority areas: standardising follow-up and referral practices (Fig. 3), stratifying AKI severity to target those at highest risk of developing CKD, providing effective knowledge translation from nephrologists to general paediatricians and general practitioners, and unifying electronic medical records across all health networks in the NT. The disproportionate burden of CKD affecting Aboriginal and Torres Strait Islander people warrants increased availability of needed clinical services, and the fact that these services are under-resourced in the settings that need them the most represents a form of systemic discrimination.

There are several limitations to this study. Due to the retrospective nature and the tertiary hospital setting, it is likely that case ascertainment was biased towards severe presentations. Subclinical or milder cases that either escaped detection or managed in the community, were not captured in our analysis. Additionally, researchers did not have access to all community health records; hence, children who may have been discharged to primary health-care follow-up were missed in our analysis. Similarly, the incomplete clinical data at follow-up may have been due to a lack of documentation (rather than omission) by the

clinician, or were requested by the clinician following their review, such as serology to measure complement levels.

Conclusions

This study contributes to the profile of kidney health in the NT, where there is a high burden of childhood APSGN. Children who are hospitalised for APSGN are likely to survive their acute illness; however, they represent a high-risk group for developing CKD later in life. Our study highlights the need for assertive monitoring following an episode of APSGN in the NT, as early recognition of persistent kidney impairment may mitigate the long-term progression to CKD.

Ethics Statement

The study was approved by the Top End Human Research Ethics Committee (HREC: 2018-3137).

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