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Socio-environmental and clinical features of invasive group A streptococcal disease in the Northern Territory of Australia

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Abstract

Objective

To describe the socio-environmental profile and clinical features of invasive group A streptococcal (iGAS) infections in the Northern Territory (NT) of Australia over 10 years.

Methods

Cases of iGAS disease diagnosed between 1 May 2011 and 30 April 2021 were retrospectively identified from the NT Notifiable Diseases System and electronic health records accessed. Remoteness of residence, socio-economic index, seasonality and clinical characteristics were recorded.

Results

There were 692 cases of iGAS disease identified in the NT during the period 1 May 2011 – 30 April 2021. The age-standardised incidence of iGAS disease was significantly higher in people living in very remote (57.1 cases per 100,000 population, 95% confidence interval [95% CI]: 48.6–65.5) and remote areas (40.9 cases per 100,000 population, 95% CI: 34.7–47.2) than in outer regional areas of the NT (15.7 cases per 100,000 population, 95% CI: 13.4–17.9). People with socio-economic disadvantage were also disproportionately affected, with an incidence of 52.6 cases per 100,000 population (95% CI: 46.2–58.9) in decile 1–3 populations, compared to 8.9 cases per 100,000 population (95% CI: 6.9–10.9) for decile 7–10.

For cases with recorded severity data, 135 of 378 (36%) met locally-defined criteria for severe iGAS disease. Recurrent iGAS disease was commonly observed in the dialysis cohort, affecting 17 of the 106 patients during the study period (16% recurrence rate) and causing two deaths. Five molecularly-confirmed clusters of iGAS disease were identified from the study period.

Conclusions

iGAS disease is unevenly affecting people in the NT. Those living in areas of socio-economic disadvantage, those in remote and very remote communities, and those receiving dialysis were most affected. It is important that primordial, primary and secondary prevention measures be directed towards supporting these disadvantaged population groups.

Keywords: streptococcus; epidemiology; public health; rural health; dialysis

Introduction

Group A streptococcal (GAS) infections are a major cause of morbidity and mortality in the Northern Territory (NT) of Australia, through both direct infection and post-streptococcal immunologic complications (acute rheumatic fever, rheumatic heart disease, glomerulonephritis). Invasive group A streptococcal (iGAS) disease can be associated with severe clinical syndromes including sepsis, necrotising fasciitis and toxic shock syndrome. GAS is the third most common organism causing bacteraemia in the Top End of the NT.¹

iGAS disease has been notifiable in the NT since 2011² and nationally in Australia since July 2021.³ The incidence of iGAS disease in Australia in 2017–2018 was estimated at 8.3 cases per 100,000 population.⁴ It has long been recognised that iGAS disease occurs at higher rates in the NT than elsewhere in Australia.^{5–7} From 1 May 2011 to 30 April 2021, the incidence of iGAS disease in the NT was 34.3 cases per 100,000 (95% confidence interval [95% CI]: 31.4–37.1) in the overall population, and 106 cases per 100,000 (95% CI: 95.0–117) in the Indigenous Australian population.⁸ There is known to be a very high burden of iGAS disease in NT patients receiving haemodialysis, with an incidence of 1,643 cases per 100,000 population in this category (95% CI: 1,374–1,950) between 2011 and 2021.⁸

The aims of this study were: (1) to review the socio-environmental profile of iGAS disease in the NT; (2) to examine the clinical features and impact of iGAS disease in people receiving haemodialysis over the past ten years; and (3) to report iGAS disease clusters, to inform public health action and policy.

Methods

Setting

This research was conducted in the NT, which had an estimated population of 249,200 people in 2021 and a geographical area of 1,348,094

km².⁹ Approximately 30% of the population are Indigenous Australians.⁹ The NT has the highest dialysis rate of any state or territory in Australia, at 3,143 patients per million population in 2020, compared to 567 patients per million nationally.¹⁰

Central Australia was defined as the Statistical Area Level 3 (SA3) Census regions of Barkly and Alice Springs. The Top End included Greater Darwin (SA3 regions of Darwin City, Darwin Suburbs, Litchfield and Daly-Tiwi-West Arnhem), Katherine (Big Rivers) and East Arnhem (Figure 1).¹¹ The Australian Statistical Geography Standard (ASGS) Remoteness Structure classifies urban Darwin as ‘outer regional’, greater Darwin and Alice Springs regions as ‘remote’, and all other areas of the Territory as ‘very remote’.¹² The climate in Central Australia is predominantly arid, while the Top End is tropical. For this analysis, the wet season in the Top End was defined as November–April and the dry season as May–October.

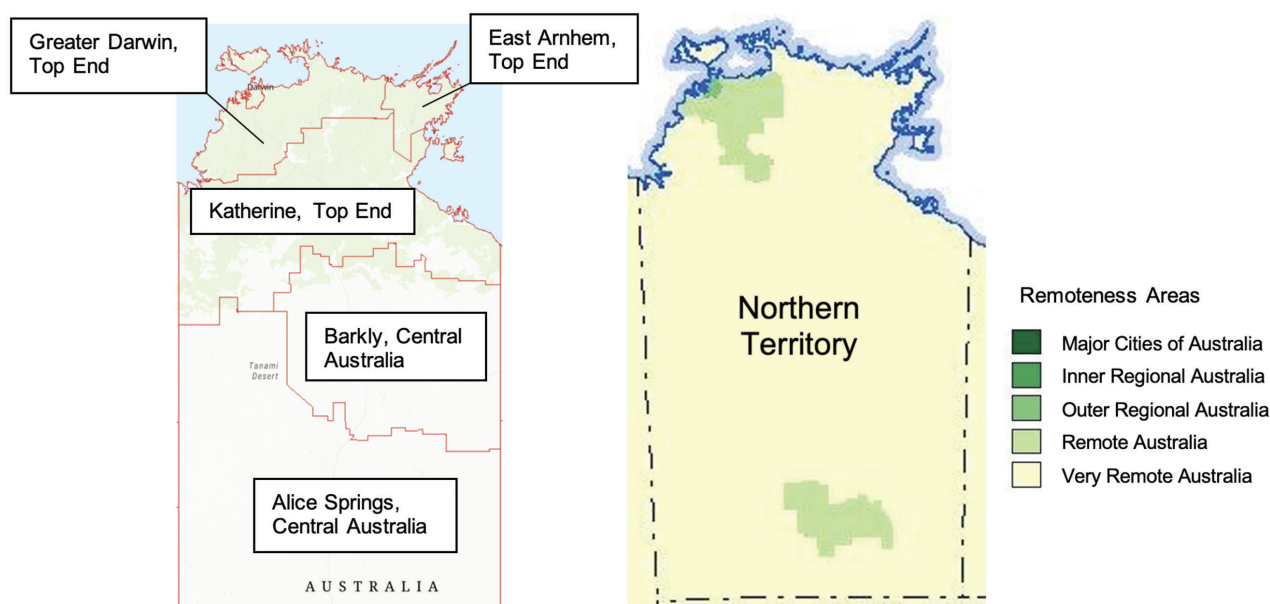
Selection of cases

Cases of iGAS disease diagnosed between 1 May 2011 and 30 April 2021 were identified from the NT Notifiable Diseases System (NTNDS). The confirmed case definition required isolation of GAS from a normally sterile site by culture or nucleic acid testing (NAT). The probable case definition (added October 2016) required isolation of GAS by culture or NAT from the site of necrotising fasciitis.¹³ All GAS isolates for an individual within a 30-day period were treated as a single case. The analysis allowed multiple infections in an individual if episodes were separated by more than 30 days.

Patient characteristics and outcome measures

Age, sex, Indigenous status, region-of-residence, remoteness-of-residence (using the Australian Statistical Geography Standard (ASGS) remoteness structure),¹² Socio-economic Indexes for Areas (SEIFA) index of relative social

Figure 1: Map of the Statistical Area 3 regions¹¹ (left) and 2016 Remoteness Areas¹² (right) for the Northern Territory



disadvantage (IRSD),¹⁴ severity, laboratory specimen type and date, hospital admission and discharge dates, and all-cause mortality data (at 7 and 30 days after diagnosis) were extracted from the NTNDS and electronic health records (EHR). Statistical Area 2 (SA2) data (defined by usual place of residence) were used for remoteness and IRSD calculations. Population data were retrieved from the Population and Digital Health Unit¹⁵ and Australian Bureau of Statistics.^{12,14} Age-standardisation was performed using 2001 Australian Census data as the reference population. Cases with a residential address outside the NT were excluded from analyses associated with geographical factors.

Dialysis status at the time of diagnosis was assessed using EHR. For dialysis recipients, data on site of infection, dialysis type (peritoneal or haemodialysis) and vascular access, co-morbidities (diabetes mellitus, heart disease, chronic liver disease, cigarette smoking, active malignancy; as recorded as free text in patient notes), length of hospital stay, number and type of surgeries (from operating theatre notes), intensive care unit (ICU) admission and iGAS disease severity were also collected from EHR.

Severe iGAS disease is defined in the NT guidelines as iGAS cases presenting with pneumonia, meningitis, post-partum sepsis, necrotising fasciitis, toxic shock syndrome or any other manifestation requiring ICU admission or causing death.¹⁶ A cluster was defined as two or more epidemiologically-linked cases of iGAS disease which were identical on molecular typing. Molecular typing was undertaken for cases with suspected epidemiological link during public health response to a case notification. All-cause mortality data were stratified by Indigenous status, dialysis status, socio-economic status, and remoteness-of-residence.

Data analysis

Statistical analyses were performed using Microsoft Excel and Stata (Version 14.2). The 95% confidence intervals (95% CI) for proportions were derived via the Wilson score method, using an analytical tool from the Association of Public Health Observatories.¹⁷ Categorical data were compared using the chi-squared test with a significance level of 5%. The chi-squared test was used to compare 30-day mortality by Indigenous status and dialysis status (binary variables), and by remoteness-of-residence (three-category variable), as determined *a priori*.

Table 1: Characteristics of invasive group A streptococcal disease cases in the Northern Territory, May 2011 to April 2021

Characteristic	Value	n (%)
Cases		692 (100)
Sex	Female	380 (55)
	Male	312 (45)
Age group (years)	0–4	72 (10)
	5–9	10 (1)
	10–19	22 (3)
	20–29	34 (5)
	30–39	64 (9)
	40–49	134 (19)
	50–59	127 (18)
	60–69	126 (18)
	70–79	66 (10)
Indigenous status	Indigenous Australians	511 (74)
	non-Indigenous Australians	181 (26)
Region of occurrence	Top End (tropical)	386 (56)
	Central Australia (non-tropical)	306 (44)
Remoteness of residence ^a	Major cities / inner regional	0 (0)
	Outer regional	211 (30)
	Remote	196 (28)
	Very remote	251 (36)
Socio-economic status ^b	Interstate / unknown	34 (5)
	Most disadvantaged	212 (31)
	More disadvantaged	179 (26)
	Moderately disadvantaged	179 (26)
	Less disadvantaged	32 (5)
	Least disadvantaged	56 (8)
	Interstate / unknown	34 (5)

a Australian Statistical Geography Standard (ASGS) remoteness structure.¹²

b Socio-economic Indexes for Areas (SEIFA) Index of Relative Social Disadvantage (IRSD) quintiles.¹⁴

Incidence rate ratios (IRRs) were derived using the Stata incidence-rate ratio calculator to compare incidence of iGAS disease by remoteness and socio-economic category. For remoteness, 'outer regional' incidence was individually compared to 'remote' and 'very remote' incidence. For socio-economic status, incidence of iGAS disease in the 'least disadvantaged' category (decile 7–10) was individually compared to the 'moderately disadvantaged' (decile 4–6) and 'most disadvantaged' (decile 1–3) categories. Seasonality was independently analysed for Central Australia and for the Top End using proportions and the Walter-Elwood test, incorporating monthly case numbers and population data.^{18,19}

Ethics approval

The study was approved by the NT Health and Menzies School of Health Research Human Research Ethics Committee (2021-4125).

Results

There were 692 cases of iGAS disease identified in the NT from May 2011 to April 2021 (Table 1), in 614 patients. This included 686 confirmed and 6 probable cases. GAS was isolated from blood culture in 652 cases (94%). Other normally sterile specimen types included synovial fluid ($n = 24$), peritoneal fluid ($n = 3$), pleural fluid ($n = 2$), cerebrospinal fluid ($n = 1$), and placental tissue ($n = 1$). Of the probable cases, GAS was isolated from subcutaneous tissue ($n = 4$) and wound swab ($n = 2$).

Socio-environmental risk factors

Over half of patients ($n = 380$; 55%) were female and 511 cases (74%) occurred in Indigenous Australian people. Median age at diagnosis was 50 years (interquartile range (IQR): 37–63 years), and 41 cases (6%) were in children under one year of age. 386 cases (56%) were diagnosed in the Top End and 306 (44%) in Central Australia.

A total of 658 cases (95%) had an NT residential address and 407 of these patients (62%) were living in remote or very remote areas. As illustrated in Figure 2, the age-standardised incidence of iGAS disease was significantly higher among people living in very remote and remote areas than in those living in outer regional areas of the NT (IRR 3.7 for very remote vs outer regional location [95% CI: 2.0–6.6; $p < 0.001$]; IRR 2.6 for remote vs outer regional location [95% CI: 1.4–4.9; $p < 0.001$]).

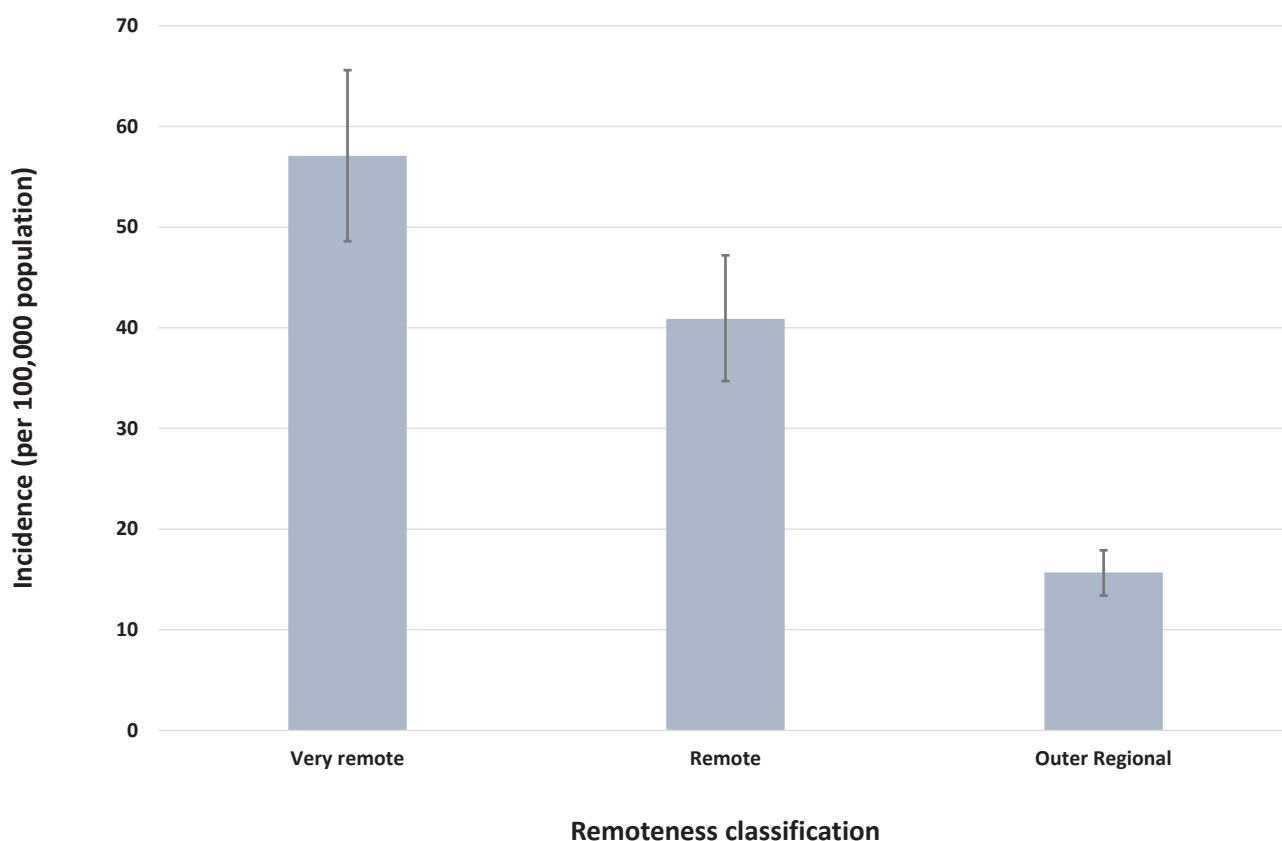
Of the 658 resident cases, 570 (87%) were living in areas of at least moderate social disadvantage (decile 1–6). As shown in Figure 3, the incidence of iGAS disease was significantly higher in the groups with greater socio-economic disadvantage (IRR 5.9 for 'most disadvantaged' vs 'least disadvantaged' [95% CI: 2.9–13.6; $p < 0.001$]; IRR 4.2 for 'moderately disadvantaged' vs 'least disadvantaged' [95% CI: 2.0–9.9; $p < 0.001$]). The proportion of cases in the lowest IRSD quintile was 33% in Central Australia (100 of 306 cases) and 29% in the Top End (112 of 386).

Seasonality of iGAS disease was not evident in Central Australia: 155 of 306 cases (51%; 95% CI: 0.45–0.56) were diagnosed in summer months (November–April), and 151 of 306 (49%; 95% CI: 0.44–0.55) in winter (May–October). In the Top End region there was a statistically significant dry season predominance: 225 of 386 cases (58%; 95% CI: 0.53–0.63) were diagnosed in the dry season (May–October), and 161 of 386 (42%; 95% CI: 0.37–0.47) in the wet season (November–April) ($p < 0.001$).

Disease clusters

Five molecularly-confirmed clusters of iGAS disease were identified from the May 2011 – April 2021 study period: (1) two cases within a household between twin infants (*emm* type 207.1); (2) two in elderly patients in a residential hostel, one of whom died (multi-locus sequence type 392); (3) two in peri-partum women admitted to the same maternity ward (*emm* type 28.5); (4) three in children attending a childcare

Figure 2: Age-standardised incidence of invasive group A streptococcal disease by remoteness of residential location in the Northern Territory, May 2011 to April 2021



a Australian Statistical Geography Standard (ASGS) remoteness structure.

facility (*emm* type 4.0); and (5) two in patients attending the same haemodialysis unit (*emm* type 114.6).

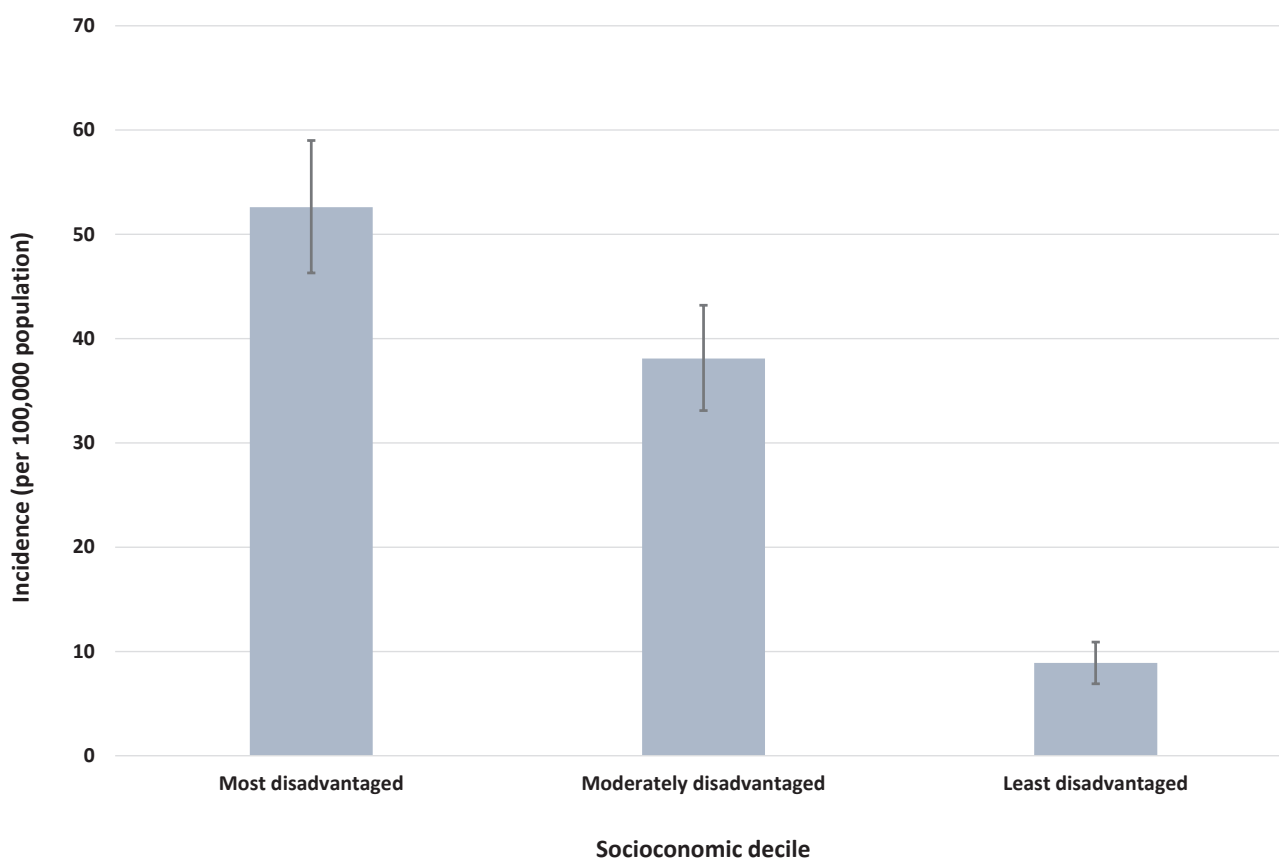
Severity and all-cause mortality

Severity was recorded for 378 cases, of which 135 (36%) met the NT criteria for severe iGAS disease. For the total study cohort, the all-cause mortality rate at 7 days after diagnosis was 4% ($n = 30$) and at 30 days was 6% ($n = 40$). The 30-day mortality rate was equivalent in Indigenous Australians (6%, $n = 30$) and non-Indigenous Australians (6%, $n = 10$; $p = 0.86$), and was similar between dialysis (8%, $n = 10$) and non-dialysis patients (5%, $n = 30$; $p = 0.34$). When stratified by remoteness-of-residence, the 30-day mortality rate was similar across all areas: 8% ($n = 16$) in patients from outer-regional areas, 6% ($n = 12$) for remote areas, and 5% ($n = 12$) for very remote areas ($p = 0.45$).

Invasive group A streptococcal disease in people receiving dialysis

The number of dialysis recipients in the NT increased from 468 in 2011 to 795 in 2021.¹⁰ There were 133 cases of iGAS disease recorded in people receiving dialysis between May 2011 and April 2021. Median age at diagnosis in the dialysis cohort was 53 years (IQR: 45–60 years) and more than three-quarters of cases were female ($n = 101/133$, 76%). Table 2 outlines other patient characteristics and outcomes. The 133 cases comprised 106 patients, of whom 19/106 had multiple iGAS disease episodes separated by 30 or more days (an 18% recurrence rate) notified during the study period. Two of these 19 experienced chronic GAS osteomyelitis that accounted for multiple notifications, while true recurrence at different sites occurred in 17 patients (16%). Two of the 19 cases with multiple iGAS disease episodes died. No GAS typing was available for these recurrent cases.

Figure 3: Age-standardised incidence of invasive group A streptococcal disease by socio-economic status (of residential location) in the Northern Territory, May 2011 to April 2021



a Socio-economic Indexes for Areas (SEIFA) Index of Relative Social Disadvantage (IRSD): most disadvantaged = deciles 1–3, moderately disadvantaged = 4–6, least disadvantaged = 7–10.

Severity was recorded for 121 dialysis cases, with 60 (50%) experiencing severe iGAS disease. Admission to hospital was required for 127 of the 133 dialysis cases (95%), with median length of hospital stay of 10 days (IQR: 6–16 days). Admission to ICU occurred for 33 cases (25%), with median length of ICU stay of 5 days (IQR: 3–7 days).

Discussion

This NT review presents socio-environmental and clinical findings from the longest period of notifiable disease surveillance for iGAS disease in Australia, to inform public health efforts. While the NT has locally-developed guidelines for iGAS disease,¹⁶ Australia-wide public health management guidelines (in the Series of National Guidelines) are currently under development. Our findings are important for considering whether more intensive public health

responses are required for remote and socially-disadvantaged populations, particularly in areas with a high incidence of GAS-related disease.

In the NT, we found that iGAS disease disproportionately affects people who are living in remote and very remote areas and those at greatest socio-economic disadvantage. This inequity is consistent with previous studies demonstrating an association of GAS-related disease with social disadvantage and high-density living.²⁰ We recommend a public health response based on remote community engagement and long-term collaboration across multiple government sectors (including housing, education and health) to address the social determinants of skin health. It is also important that healthcare staff working in remote and disadvantaged communities receive education about the importance of early detection and treatment of skin infections and are on alert for clinical features

Table 2: Characteristics of invasive group A streptococcal disease cases in the dialysis population, Northern Territory, 2011 to 2021

Characteristic	Value or attribute	Number of cases	Proportion of cases (%)
Number of cases in dialysis patients		133	100
Number of dialysis patients		106	—
Sex	Female	101	76
	Male	32	24
Indigenous status	Indigenous Australians	130	98
	non-Indigenous Australians	3	2
Type of dialysis	Haemodialysis	131	98
	Peritoneal dialysis	2	2
Region of occurrence	Top End (tropical)	52	39
	Central Australia (non-tropical)	81	61
Comorbidities (as recorded in electronic medical records)	Diabetes mellitus (type 1 or 2)	99	74
	Heart disease	85	64
	Chronic liver disease	36	27
	Current cigarette smoking	16	12
	Active malignancy	7	5
Dialysis access	Arteriovenous fistula	92	69
	Central venous catheter or vascular graft	30	23
	Peritoneal dialysis catheter	2	2
	Unknown	9	7
Site of infection	Skin ^a	74	56
	Pneumonia	22	17
	Bacteraemia with no known focus	22	17
	Osteomyelitis or septic arthritis	21	16
	Other sites ^b	13	10
Specimen type	Blood culture	131	98
	Synovial fluid culture	1	1
	Peritoneal fluid culture	1	1
Severity status	Severe ^c	60	45
	Non-severe	61	46
	Unknown	12	9
Management	Admitted to hospital	127	95
	Admitted to intensive care unit	33	25
	Required surgery	38	26
Mortality	Within 7 days of diagnosis	6	5
	Within 30 days of diagnosis	10	8

a Including impetigo, ulcer, wound, abscess, burn, scabies, vascular access site, cellulitis, necrotising fasciitis.

b Infected vascular graft or fistula, endocarditis, urosepsis, dental abscess, tubo-ovarian abscess.

c Cases presenting with pneumonia, meningitis, necrotising fasciitis, streptococcal toxic shock syndrome or any other manifestation requiring admission to an intensive care unit or causing death.

of iGAS disease. Comprehensive prevention and treatment guidelines are available from the NT Healthy Skin Program.²¹

People receiving dialysis in the NT continue to be at significantly increased risk of iGAS disease.⁸ A combination of multiple host risk factors, relative immunocompromise, frequent vascular access and often-limited access to hygiene infrastructure may explain the high incidence in this group. As most patients (69%) were dialysing through an arteriovenous fistula at the time of diagnosis, intravenous line sepsis is unlikely to be a key mechanism of iGAS infection.

We found high rates of concurrent diabetes (74%) and heart disease (64%) in people receiving dialysis who developed iGAS disease. In comparison, approximately 56% of all people receiving haemodialysis in Australia in 2020 were diabetic and 38% had known coronary artery disease.¹⁰ A recent data-linkage study of iGAS disease in Victoria, Australia found a much lower rate of diabetes (15%) and heart disease (30%) in their general iGAS cohort, which was not limited to dialysis recipients.²¹ However, despite the lower comorbidity burden, the rate of ICU admission (33%) was higher in the Victorian than NT dialysis cohort, and the case fatality rate (6%) was similar.²² These results may partly reflect differences in data collection methodology, with non-severe cases and comorbidities less likely to be identified through data-linkage than through mandatory notification and direct review of EHR. Future research using multivariable regression would be valuable in exploring the risk factor profile of iGAS infection, and further characterising which patients are at greatest risk of severe disease.

Skin infections (such as cellulitis and infected wounds) were the most common documented antecedent to iGAS disease, and scabies remains endemic in much of the NT.^{23–25} Our study highlights the considerable morbidity, mortality and healthcare burden arising from iGAS disease in people receiving dialysis, which may be preventable through primordial, primary and secondary prevention measures.

This includes action on the social determinants of skin health (such as improved housing and hygiene infrastructure for dialysis recipients), education of patients and health professionals, prompt identification and treatment of superficial skin infections, and targeted use of antibiotic prophylaxis for secondary prevention.¹⁶

No seasonal difference was noted in iGAS disease case numbers in Central Australia. However, in the Top End region, a significantly higher number of cases were diagnosed in the dry season (May–October) than in the wet season. Possible contributing factors include dry season population movements between communities and urban locations such as Darwin, with increased social interaction and GAS transmission, and the routine administration of wet season co-trimoxazole prophylaxis against melioidosis for Top End haemodialysis recipients since November 2014.⁸

There was evidence of GAS transmission in households, residential hostel, childcare and health care settings. These settings are particularly important for consideration of an appropriate public health response, as outlined in the NT public health guidelines.¹⁶ Further studies are required to identify the efficacy of chemoprophylaxis for close contacts in high-risk settings. This research is necessary to direct the public health response for prevention of further transmission of GAS-related disease and to support decision-making for efficient use of public health resources.

Limitations

This study will have missed some cases of iGAS disease in the NT, where appropriate cultures were not performed to obtain a sterile site isolate or because of laboratory limitations. In addition, the probable case definition was only added in 2016, relied upon clinician awareness and reporting, and only included necrotising fasciitis cases. The NT probable case definition has recently been revised to increase sensitivity, now incorporating other compatible clinical syndromes of iGAS disease¹³. Comorbidity data

were collected through review of dialysis patient electronic medical records during healthcare encounters for iGAS disease, and co-morbidity frequencies may be underestimated if incompletely documented. As GAS isolates from sterile sites do not routinely undergo molecular typing, we may have missed clusters of disease where an epidemiologic link was not recognised.

This study involved descriptive analysis, without correction for multiple comparisons. There is likely to be a high correlation between analysed variables, such as remoteness and socio-economic status. Future studies using multivariable regression modelling could provide further insights into the contributions of and relationships between different social determinants of iGAS disease.

Conclusions

iGAS disease is unevenly affecting people in the NT, with most affected being those living in areas of socio-economic disadvantage, in remote and very remote communities, and those receiving dialysis. iGAS disease causes substantial morbidity, mortality and healthcare cost within the NT community. It is important that primordial, primary and secondary prevention measures be directed towards supporting these disadvantaged population groups.

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