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The efficacy and safety of a shortened duration of antimicrobial therapy for Group A Streptococcus bacteraemia

Andrew D K Nguyen [1,2], Simon Smith[1], Tania J Davis [1], Trent Yarwood [1,2], Josh Hanson [1,3 *]

[1] Department of Medicine, Cairns Hospital, Cairns Queensland Australia

[2] Faculty of Medicine, University of Queensland, Brisbane, Queensland Australia

[3] The Kirby Institute, University of New South Wales, Sydney, News South Wales, Australia

* Corresponding author: jhanson@kirby.unsw.edu.au

Abstract

Objective: To determine if shorter courses of antibiotic therapy for Group A *Streptococcus* (GAS) bacteraemia are associated with excess mortality.

Methods: In this retrospective study of consecutive cases of GAS bacteraemia in tropical Australia, the duration of antibiotic therapy was correlated with 90-day all-cause mortality.

Results: There were 286 episodes of GAS bacteraemia; the patients' median (interquartile range) age was 60 (48-71) years and 169/286 (59.1%) identified as an Indigenous Australian. There were 227/286 (79.4%) with a significant comorbidity. All-cause 90-day mortality was 16/286 (5.6%), however, 12/16 (81.3%) died while still receiving their initial course of antibiotics and only 7/16 deaths (43.8%) were directly attributable to the GAS infection.

After excluding patients that died while taking their initial course of antibiotics - and those in whom the duration of therapy was uncertain - there was no difference in 90-day mortality

between patients receiving ≤5 days of IV antibiotics and those receiving longer courses (1/137 (0.7%) versus 3/107 (2.8%), p=0.32) nor in patients receiving ≤10 days of total therapy and those receiving longer courses (1/67 (1.5%) versus 3/178 (1.7%), p=1.0).

Conclusions: Even among patients with significant comorbidity, shorter antibiotic courses for GAS bacteraemia are not associated with excess mortality.

Keywords: Streptococcus pyogenes; Group A Streptococcus; Bacteraemia; Clinical Management; Antibiotic therapy; Indigenous Health.

Introduction

Streptococcus pyogenes, otherwise known as Lancefield Group A *Streptococcus* (GAS), is a common cause of uncomplicated skin and soft tissue infection. However, it can also cause life-threatening invasive disease which historically has a case-fatality rate of up to 48% (O'Loughlin et al., 2007). In Australia, the burden of GAS infection is disproportionately borne by its Aboriginal and Torres Strait Islander Australian population (hereafter referred to, respectfully, as Indigenous Australians), particularly those living in rural and remote settings. The higher incidence of GAS infections among Indigenous Australians is closely linked to the social determinants of health. Household crowding increases the incidence of chronic skin disease and its complications, and the disproportionate burden of comorbidity seen in Indigenous Australians increases the risk of invasive GAS (Coffey et al., 2018, Gear et al., 2015, Hempenstall et al., 2021). In Far North Queensland (FNQ), tropical Australia, the incidence of GAS bacteraemia is 10.3 per 100000 person-years, rising to 82.5 per 100,000 person-years among Indigenous Australians living in the region (Norton et al., 2004). These rates are far higher than the reported incidence of invasive GAS infections of 1.0 per 100000 person-years in Spain, 3.5 per 100000 person-years in Finland, and 3.8 cases per 100000

person-years in the United States (Nelson et al., 2016, Vallalta Morales et al., 2006, Vilhonen et al., 2020).

However, despite the significant global burden of invasive GAS infection, no randomised controlled studies have been performed to inform the optimal duration of antibiotic treatment. The recommended total duration of therapy for GAS bacteraemia varies significantly in different jurisdictions, ranging from 7-10 days in Australia, to 10 days in Ireland to at least 14 days in the United States (Australian Therapeutic Guidelines 2021, Invasive Group A streptococcus Sub-Committee of Ireland 2006, Llovet et al., 2021, Stevens, 2022). The optimal duration of intravenous (IV) therapy is even more uncertain; while some have suggested a higher rate of recurrent infections with early step-down to oral therapy (Al-Hasan and Rac, 2020, Arensman et al., 2020, Kang et al.), others have demonstrated that there is no mortality difference with shorter IV treatment (Ramirez and Bordon, 2001).

There is a global trend towards shorter duration of antimicrobial therapy; this has the potential to reduce healthcare costs, hospital length of stay, and the rates of antimicrobial resistance (Magalhaes et al., 2021). Anecdotally, clinicians in FNQ prescribe shorter courses of therapy for patients with GAS bacteraemia, with an early transition to oral therapy; this study aimed to determine the efficacy and safety of this practice.

Methods

This retrospective study was performed in FNQ, a region of 380,000 km^2 in tropical Australia. The FNQ population is approximately 290,000, 17% of whom identify as Indigenous Australians. All patients with ≥1 positive blood culture for GAS between January 1, 2014, and December 31, 2020, in the statewide health laboratory results database were eligible for inclusion. This study period was chosen as it coincided with the introduction of a

statewide electronic medical record. Patients with polymicrobial blood cultures were excluded unless the other isolates were of low virulence and considered contaminants. If a patient had a recurrent episode of GAS bacteremia within 30 days, only the initial presentation was included.

Episodes of bacteraemia were identified by searching the statewide electronic laboratory database. European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria were used to define antimicrobial resistance (EUCAST 2022). Emm types were recorded using standard definitions (Sanderson-Smith et al., 2014).

Patients' medical records were reviewed: demographic data, comorbidities, clinical presentation, management, and disease course were recorded. A child was defined as an individual ≤15 years. If individuals lived in the region's main city – Cairns – or were visitors from another city outside FNQ, they were said to have an urban address, otherwise they were deemed to live in a rural or remote area.

Comorbidities were categorised according to previously identified risk factors for invasive GAS in the region (S1 Table, Gear et al., 2015, Norton et al., 2004). A comorbidity was said to be present if it was documented in the medical record; comorbidities were quantified using the Charlson Comorbidity Index with severe comorbidity defined as a Charlson Comorbidity Index ≥5 (Charlson et al., 1987).

Streptococcal toxic shock syndrome (STSS) was defined using the consensus criteria from The Working Group on Severe Streptococcal Infections (1993). Patients were said to have complicated disease if they had one or more of the following conditions: empyema, myositis, septic arthritis, osteomyelitis, necrotising fasciitis, infective endocarditis, or required surgical

intervention or intensive care unit (ICU) admission. In the absence of these criteria, patients were said to have uncomplicated disease.

The route and duration of antimicrobial therapy prescribed was recorded and correlated with the patients' clinical course. Short-course IV therapy was defined as ≤5 days of IV therapy; short-course total therapy was defined as ≤10 days of total antibiotic therapy (combined IV and oral). Long course IV and long course total therapy were defined as >5 days and >10 days, respectively. Administration of adjunctive therapies was also recorded.

All-cause mortality within 30 and 90 days of admission and rehospitalisation within 30 and 90 days of discharge was recorded. Rehospitalisation or death were defined as attributable to GAS if this was documented in the medical record or on the death certificate. Complications of antimicrobial therapy were defined using published definitions (Devchand and Trubiano, 2019).

De-identified data were entered into an electronic spreadsheet (Microsoft Excel) and analysed using statistical software (Stata version 14.2). Groups were analysed using the Kruskal-Wallis, chi-squared, Fisher's exact test as appropriate. Multivariate analysis of selected groups was performed using backwards stepwise logistic regression; variables with a $p<0.20$ in univariate analysis were selected for the model, although only those with a p value of <0.05 were retained.

Results

There were 297 cases of GAS bacteraemia identified during the study. Two polymicrobial blood cultures with low virulent micro-organisms (*Staphylococcus epidermidis* and *Corynebacterium striatum*) were included. In 11 (3.7%) *Staphylococcus aureus* was also isolated; these cases were excluded. The remaining 286 episodes of GAS bacteraemia - all

included in the analysis – occurred in 274 individuals. Only one of these recurrent episodes occurred within 12 months of the initial episode.

The patients' median (IQR) age at presentation was 60 (48-71) years; 154 (53.9%) were male. There were 169/286 (59.1%) who identified as an Indigenous Australian, compared with 49977/289771 (17.2%) members of the total FNQ population at the end of the study period ($p<0.001$). The mean annual incidence in the total population was 14.5/100000 population during the study period; it was 49.2/100000 in the Indigenous population. There were 22 (7.7%) children in the cohort compared to 58843/289771 (20.3%) of the total FNQ population ($p<0.0001$). There was no statistically significant association between presentation and month (S1 figure).

Most of the patients (227/286 (79.4%)) had a chronic health condition; 140/286 (49.0%) had diabetes mellitus and 23/286 (8.0%) had a chronic skin disease (Table 1). Only 6/286 (2%) had scabies while 6/286 (2%) had pre-existing diabetic ulcers. The median (IQR) Charlson Comorbidity Index score was 4 (1-5); 126/286 (44.1%) had severe comorbidity (figure 1). Indigenous Australians were more likely to have a chronic health condition than non-Indigenous Australians (149/169 (88.2%) versus 78/117 (66.7%), $p<0.0001$) and were more likely to have severe comorbidity (85/169 (50.3%) versus 41/117 (35.0%), $p=0.01$). Diabetes mellitus was more common in Indigenous Australians (108/169 (63.9%) versus 32/117 (27.4%), $p<0.001$), although chronic skin disease was not (13/168 (7.7%) versus 10/117 (8.6%), $p=0.81$).

Clinical presentation

The median (IQR) duration of symptoms prior to hospitalisation was 1 (1-3) days. The skin was considered the source of GAS bacteraemia in 204/286 (71.3%) (figure 2). Complicated

disease was present in 79/286 (27.6%); 43 (15.0%) required ICU admission and 19 (6.6%) had STSS.

Microbiology

Antimicrobial susceptibility testing was performed on all isolates. Antimicrobial resistance was present in 55/286 (19.2%), most commonly to tetracycline (48/286, 16.8%) (S2 Table). Multiple emm types were identified with 1, 11, 49, 53, 75, 89 and 113 the most common (S2 figure). Exotoxin B was present in all 280 isolates that were tested (S3 Table).

Antimicrobial therapy

There were 266 patients in whom the class of prescribed antibiotic therapy could be determined. Patients commonly received multiple classes antibiotics during their hospitalisation as empirical therapy was de-escalated to targeted therapy (S4 Table).

There were 231 (86.8%) who received a penicillin and 117 (44.3%) who received a cephalosporin. Lincosamide therapy was prescribed as adjunctive therapy in 42 patients - including 21/78 (26.9%) with complicated disease and 10/19 (52.6%) with STSS - for a median duration of 4 (range 1-13) days.

Despite the wide variety of antibiotic therapies prescribed at the patients' initial presentation, of the 256 (89.5%) in whom the initial therapy could be determined, 254 (98.8%) received antibiotic therapy with activity against GAS in the first 24 hours of their hospitalisation. It was possible to accurately define the total duration of antibiotic therapy in 256/286 (89.5%) and the total duration of IV antibiotics in 255/286 (89.2%). The median (IQR) duration of IV antimicrobial therapy in the patients who completed their antibiotic course was 5 (3-8) days. The median (IQR) duration of oral antimicrobial therapy in the patients who completed their antibiotic course was 7 (5-10) days. The median (IQR) total duration of antimicrobials

(combined IV and oral) in the patients who completed their antibiotic course was 14 (10-17) days.

Patients receiving short-course IV therapy were younger and less likely to have complicated disease (Table 2). However, in multivariate analysis only age (OR (95% CI): 0.98 (0.97-0.99), p=0.003) and ICU admission (OR (95% CI): 0.18 (0.08-0.38), p<0.001) independently predicted whether short-course IV therapy was - or was not - prescribed. Patients receiving short-course total therapy were more likely to be younger, less likely to have chronic comorbidity and less likely to have complicated disease (Table 3). However, in multivariate analysis, only the presence of a comorbidity independently predicted whether short-course total therapy was - or was not - prescribed (OR (95%CI): 0.42 (0.23-0.79), p=0.006).

Adverse effects of antimicrobial therapy

There were 13/286 (4.6%) who had an adverse reaction to antimicrobial therapy; this was non-immunological (predominantly liver function derangement) in 10 and immunological in 1 (S5 Table). An adverse reaction occurred in 1/76 (1.3%) of patients with a total duration of antibiotics of ≤10 days, compared with 10/180 (5.6%) of those with a longer course (p=0.18).

Specialist consultation and other adjunctive therapy

A surgical opinion was sought in 91/286 (31.8%), resulting in a procedure in 50 (17.5%). This was most commonly debridement (23/50 (46%)), although 4 (8%) had a laparotomy and 4 (8%) had a thoracotomy. Specialist infectious diseases advice was provided in 143/286 (50.0%), with bedside consultation in 37 (12.9%). Intravenous immunoglobulin was prescribed in 2/286 (0.7%); no patients received hyperbaric oxygen therapy.

Outcomes

There were 14/286 (4.9%) deaths at 30 days and 16/286 (5.6%) at 90 days. Death occurred at a median (IQR) of 13 (4-23) days after admission to hospital. Of the 16 deaths in the cohort, 12 (75.0%) occurred while the patient was still taking their primary course of antibiotics. Only 7 (43.8%) of these 16 deaths were directly attributable to GAS infection (S6 Table). Indigenous status was not associated with increased mortality or ICU admission (p=0.29) (Table 4).

Rehospitalisation after discharge

There were 40/286 (14.0%) patients who were rehospitalised within 30 days of discharge; 65/286 (22.7%) were rehospitalised within 90 days of discharge. Rehospitalisation was more common in patients with comorbidities (odds ratio (OR), 95% confidence interval (CI): 3.1 (1.3 - 7.6) (S3 figure). Only 19/65 (29.2%) were related to the original GAS infection (S7 Table). Rehospitalisation was not more common in Indigenous patients (OR (95%CI): 1.14 (0.65-2.01).

Association between duration of antibiotic therapy and outcome

Of the 255 patients with a known duration of IV antibiotic therapy, 11 (4.3%) died while still receiving antibiotic therapy. Among the 244 remaining patients, 90-day all-cause mortality was not higher in patients receiving ≤5 days of IV antibiotics than those who had a longer IV antibiotic course (1/137 (0.7%) versus 3/107 (2.8%), p=0.32) (figure 3). There was a single death (a patient with metastatic breast cancer transferred to a local private hospital to receive palliative care who died 7 days later) but no rehospitalisations at 90 days among the 31 patients in whom the duration of IV antibiotic therapy was uncertain.

Of the 256 patients with a known duration of total antibiotic therapy, 11 (4.3%) died while still receiving antibiotic therapy (IV or oral). Among the remaining 245 patients, 90-day all-cause mortality was no higher in patients receiving ≤10 days of antibiotics than those who

had a longer course of antibiotic therapy (1/67 (1.5%) versus 3/178 (1.7%), p=1.0) (figure 4). There was a single death (the previously highlighted patient) but no rehospitalisations at 90 days among the 30 patients in whom the duration of total antibiotic therapy was uncertain. In patients with a complicated course, the findings were similar (S4 figure and S5 figure).

Furthermore, there was no difference in 90-day hospital readmission rates among patients receiving short-course IV therapy and those receiving longer courses (25/130 (19.2%) versus 24/103 (23.3%), p=0.45) (S6 figure) after excluding those 22 patients - with a known duration of therapy - who died or were readmitted while still receiving antibiotics. Similarly, there was no difference in 90-day hospital readmission rates among patients receiving short-course total therapy and those receiving longer courses (17/65 (26.2%) versus 32/169 (18.9%), p=0.22) (S7 figure) after excluding those 22 patients - with a known duration of therapy - who died or were readmitted while still receiving antibiotics. In patients with a complicated course, the findings were similar (S8 figure and S9 figure).

Discussion

The 90-day all-cause mortality of 5.6% among patients with GAS bacteraemia in this study was far lower than in the reported literature, where, historically, rates of up to 48% have been described (Francis and Warren, 1988, Muller et al., 2003, Nelson et al., 2016, O'Loughlin et al., 2007). This is despite the fact that patients in this cohort had a higher median age than other GAS bacteraemia cohorts, 44% had severe comorbidity, 48% were living remotely and almost 60% identified as Indigenous Australians, a population that has poorer outcomes on almost every health metric (2020, Gear et al., 2015, Vallalta Morales et al., 2006). Importantly, the low case-fatality rate was achieved with many patients receiving durations of beta-lactam antibiotic therapy that are shorter than those recommended in international guidelines (2006, Llovet et al., 2021, Stevens, 2022). Most patients had ≤5 days of IV

antimicrobial therapy and almost 30% had ≤10 days of total antimicrobial therapy. Not only do shorter courses of antimicrobial therapy appear to achieve similar clinical outcomes for patients with GAS bacteraemia, but they have the potential to reduce antimicrobial-related complications, hospital costs and the development of antimicrobial resistance, while allowing earlier hospital discharge, improving patient satisfaction (Magalhaes et al., 2021, Olaison et al., 1999, Shepperd et al., 2009, Spurling et al., 2017).

The encouraging outcomes are likely to be largely the result of patients receiving comprehensive, multidisciplinary care in the well-resourced Australian health system. Almost all patients received prompt antibiotic therapy and early surgical consultation when indicated. Half the patients in the cohort were able to receive infectious diseases specialist advice and sophisticated ICU support was available when required. The case-fatality rate in patients requiring ICU admission was 16.3%, all of whom had STSS, emphasising the lethality of this condition. Deaths occurring outside ICU were strongly influenced by the patients' pre-existing comorbidities with less than half of the deaths in the cohort directly attributable to GAS infection.

There is a worldwide trend towards prescribing shorter antimicrobial durations. In one randomised trial, 5 days of therapy for GAS tonsillopharyngitis was non-inferior to 10 days (Skoog Stahlgren et al., 2019). Antibiotic courses can be shortened safely in uncomplicated methicillin-sensitive *Staphylococcus aureus* bacteraemia, in uncomplicated Gram-negative bacteraemia and in intra-abdominal infections once source control has been achieved (Sawyer et al., 2015, Thorlacius-Ussing et al., 2021, Yahav et al., 2019). Meanwhile early de-escalation to oral antibiotic therapy is safe and effective in joint infections, infective endocarditis, and in Gram-negative bacteraemia (Iversen et al., 2019, Li et al., 2021, Yahav et al., 2019). Shorter durations of antibiotics reduce the risk of antibiotic-related adverse events:

in patients with GAS-related tonsillopharyngitis, skin rash, vaginal candidiasis and gastrointestinal side effects were more common in those receiving 10 days of therapy than in those receiving five days (Skoog Stahlgren et al., 2019). The incidence of adverse drug reactions correlates with the duration of therapy in cases of infective endocarditis, while prolonged antimicrobial courses increase the risk of *Clostridioides difficile* infection (Olaison et al., 1999, Stevens et al., 2011). Indeed, in large observational studies, greater antibiotic use is associated with increased all-cause mortality, although the precise mechanism for any observed association remains incompletely understood (Heianza et al., 2020).

Prolonged antibiotic use has been associated with increased antimicrobial resistance at both an individual and community level (Costelloe et al., 2010, Dowson et al., 1993, Lodise et al., 2007, Modi et al., 2013, Seppala et al., 1997). Longer courses of IV antimicrobial therapy necessarily result in longer hospitalisation, increasing costs for the health system (Hecker et al., 2003, Shorr et al., 2011, van den Bosch et al., 2017). Shorter courses of treatment which allow earlier discharge and return to normal life may also increase patient satisfaction (Datta et al., 2020). This is important for Indigenous Australians who sometimes experience isolation and loneliness in hospital, which significantly impacts on their care (Askew et al., 2021).

Indeed, Indigenous Australians were overrepresented in this cohort and over half had severe comorbidity. Both findings are likely to be explained by the socioeconomic disadvantage that many Indigenous Australians continue to experience; socioeconomic disadvantage increases the risk of GAS infection, while also increasing the burden of the comorbidities that predispose to invasive GAS infection and its complications (2018, Coffey et al., 2018, Hempenstall et al., 2021, Kang et al., 2021). However, it was notable that there was no difference in the rates of death or readmission between Indigenous and non-Indigenous

Australians in this cohort. This was despite almost two-thirds of the Indigenous patients in the cohort residing in a remote location, several hundred kilometres from tertiary-level care. This is likely to result from the effectiveness of the hub and spoke model, effective electronic promulgation of clinical guidelines and an effective aeromedical retrieval network in the region (Franklin et al., 2021, Lee et al., 2018). This concords with other studies which show that remoteness is not necessarily associated with poor clinical outcomes if there is appropriate health network resourcing (Smith et al., 2019, Stewart et al., 2017).

The encouraging outcomes in the cohort were achieved with beta-lactam based therapy, which are highly effective against GAS (Nielsen et al., 2007). There was minimal use of IVIG, while adjunctive lincosamide was used intermittently - and for variable durations - even amongst those with complicated disease or STSS. Data from observational studies suggest that lincosamide and IVIG can inhibit toxin production and exert an immunomodulatory effect in severe GAS infection (Babiker et al., 2021, Laho et al., 2021). However, the optimal dosing and duration of these therapies remains uncertain and should be explored in prospective randomised trials.

This study had several limitations. Its retrospective design precluded comprehensive data collection. In about 10% of the patients, it was not possible to determine antimicrobial duration, although there was only one death (in a patient with widely metastatic cancer) and no rehospitalisations among the patients missing these data. The retrospective design also limits conclusions about the utility of adjunctive therapies. There were relatively few cases of STSS and necrotising fasciitis limiting detailed analyses of these important clinical syndromes. Indeed, although this was one of the largest series to present detailed clinical data on individual patients with GAS bacteraemia, type 2 errors are likely to be present. The study focused only on patients with GAS bacteraemia - excluding non-bacteraemic invasive GAS

infections - although the data are likely to be relevant for the latter patients as well. Finally, the study was performed at a single hospital in the well-resourced Australian health system. The cohort was older than comparable series and almost 60% identified as Indigenous Australians, potentially limiting the generalisability of our findings to other locations. However, the favourable outcomes seen in this cohort suggests that shorter antimicrobial courses may be feasible in younger populations with less comorbidity.

Conclusions:

Acknowledging these limitations, the study shows that that in most patients ≤5 days of intravenous and ≤10 days of total antimicrobial therapy is safe and effective for patients with GAS bacteraemia, even in those with significant comorbidity. Short-course therapy will also tend to reduce antimicrobial-related complications, hospital costs and the development of antimicrobial resistance, while allowing earlier hospital discharge, improving patient satisfaction. Future prospective studies should confirm these findings and determine the optimal duration of antimicrobial therapy for GAS bacteraemia, which is likely to be shorter than is currently recommended in many international guidelines.

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Ethical Approval statement: The Far North Queensland Human Research Ethics Committee provided ethical approval for the study (EX/2021/QCH/77095–1560 QA). As the data were retrospective and de-identified, the Committee waived the requirement for informed consent.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. The prevalence of different comorbidities at presentation, stratified by Indigenous status

Comorbidity at presentation	Entire cohort n=286	Indigenous Australian n=169	Non-Indigenous Australian n=117	p
Any Chronic Disease	227 (79.4%)	149 (88.2%)	78 (66.7%)	<0.0001
Cardiac disease	105 (36.7%)	69 (40.8%)	36 (30.8%)	0.08
Respiratory disease	54 (18.9%)	33 (19.5%)	21 (18.0%)	0.74
Diabetes mellitus	140 (49.0%)	108 (63.9%)	32 (27.4%)	<0.0001
Chronic skin disease	24 (8.4%)	13 (7.7%)	10 (8.6%)	0.81
Hazardous alcohol use	29 (10.1%)	20 (11.8%)	9 (7.7%)	0.25
Immunosuppression [a]	23 (8.0%)	10 (5.9%)	13 (11.1%)	0.11
Chronic kidney disease	87 (30.4%)	73 (43.2%)	14 (12.0%)	<0.0001
Receiving dialysis	20 (7.0%)	19 (11.2%)	1 (0.9%)	0.001
Perinatal	3 (1.0%)	2 (1.2%)	1 (0.9%)	1.0

[a] immunosuppression defined as long term >7.5mg daily prednisone or equivalent for >30 days

Table 2. Characteristics of the patients who received short and long IV courses for GAS bacteraemia

	Short IV course n=136 [a]	Long IV course n=107 [a]	p [b]
Age (years)	58 (35-71)	63 (51-72)	0.01
Child	16 (11.8%)	4 (3.7%)	0.03
Male gender	78 (57.4%)	54 (50.5%)	0.29
Indigenous Australian	85 (62.5%)	55 (51.4%)	0.08
Remote residence	57 (41.9%)	47 (43.9%)	0.75
Any comorbidity	102 (75.0%)	88 (82.2%)	0.18
CCI ≥ 5	60 (44.1%)	52 (48.6%)	0.49
ICU admission	7 (5.2%)	28 (26.2%)	<0.001
Complicated disease	20 (14.7%)	45 (42.1%)	<0.001
STSS	0	10 (9.4%)	<0.001

All numbers are median (IQR); absolute number (%).

[a] Of the 255 patients in whom the duration of IV therapy was available. Excludes the 12 patients who died while receiving antibiotics. Short course therapy: ≤5 days. Long course >5 days.
[b] Variables with a p<0.20 were selected for multivariate analysis
CCI: Charlson Comorbidity Index. ICU: Intensive Care Unit. STSS: Streptococcal Toxic Shock Syndrome

Table 3. Characteristics of the patients who received short and long total antibiotic courses for their GAS bacteraemia

	Short total course n=67	Long total course n=177	p [b]
Age (years)	56 (34-69)	62 (50-72)	0.01
Child	11 (16.7%)	10 (5.7%)	0.007
Male gender	37 (55.2%)	95 (53.7%)	0.83
Indigenous Australian	40 (59.7%)	101 (57.1%)	0.71
Remote residence	30 (44.8%)	74 (41.8%)	0.68
Any comorbidity	44 (65.6%)	146 (82.5%)	0.005
Severe comorbidity	28 (41.8%)	84 (47.5%)	0.43
ICU admission	4 (6.0%)	32 (18.1%)	0.02
Complicated disease	10 (14.9%)	56 (31.6%)	0.009
STSS	0	11 (6.2%)	0.04

All numbers are median (IQR); absolute number (%).

[a] Of the 256 patients in whom the total duration of antibiotic therapy was available. Excludes the 12 patients who died while receiving antibiotics. Short course therapy: ≤10 days. Long course >10 days.
[b] Variables with a p<0.20 were selected for multivariate analysis
CCI: Charlson Comorbidity Index. ICU: Intensive Care Unit. STSS: Streptococcal Toxic Shock Syndrome

Table 4. Factors associated with ICU admission or death in GAS bacteraemia patients

	Alive without ICU admission at 30 days n=236	Death or ICU admission within 30 days n=50	p
Age	60 (46-71)	59 (49-71)	1.0
Child < 15 years of age	19 (8%)	3 (6%)	0.80
Indigenous Australian	150 (63.6%)	27 (54%)	0.29
Remote residence	121 (51.3%)	15 (30%)	0.006
Duration of symptoms prior to hospitalisation (days)	1 (0-3)	2 (1-3)	0.38
Any chronic disease	196 (83%)	39 (78%)	0.61
Underlying cardiac disease	87 (36.9%)	19 (38%)	0.80
Diabetes mellitus	122 (51.7%)	18 (36%)	0.04
Underlying respiratory disease	49 (20.8%)	8 (16%)	0.56

Chronic kidney disease	76 (32.2%)	13 (26%)	0.44
Receiving dialysis	18 (7.6%)	2 (4%)	0.54
Immunosuppression [a]	19 (8%)	4 (8%)	1.0
Hazardous alcohol use	20 (8.5%)	9 (18%)	0.04
Charlson Comorbidity Index	4 (1-6)	4 (2-6)	0.64
Exotoxin A	28 (11.9%)	9 (18%)	0.24
Exotoxin C	57 (24.1%)	16 (32%)	0.22
NSAID use prior to admission	83 (35.2%)	13 (26%)	0.25
Any antimicrobial resistance in GAS isolate	48 (20.3%)	10 (20%)	0.99
Streptococcal toxic shock syndrome	0	19 (38%)	<0.0001
Complicated infection	13 (5.5%)	46 (92%)	<0.0001
Any infectious diseases consultation	110 (46.6%)	40 (80%)	<0.0001
Infectious diseases bedside consultation	30 (12.7%)	10 (20%)	0.16
Antibiotic prescription concordant with guidelines [a]	175/218 (80.3%)	46/50 (92%)	0.049
Use of adjunctive lincosamide	23/217 (10.6%)	19 (38%)	<0.0001
Surgical consultation	65 (27.5%)	27 (54%)	<0.0001

[a] immunosuppression defined as long term >7.5mg daily prednisone or equivalent for >30 days

[b] Australian Therapeutic Guidelines (Llovet et al., 2021)

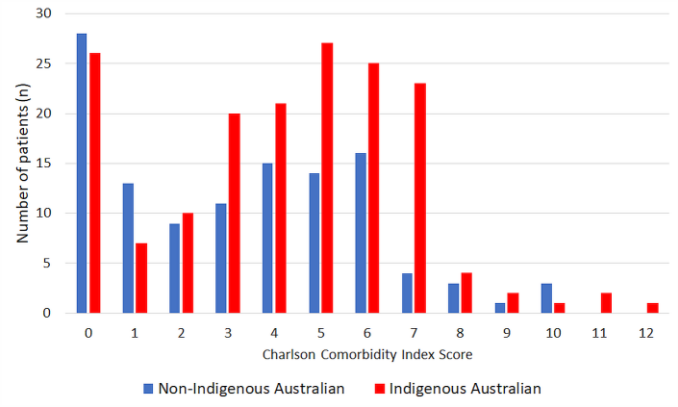

Figure 1. Charlson Comorbidity Index score of the patients in the study, stratified by Indigenous status

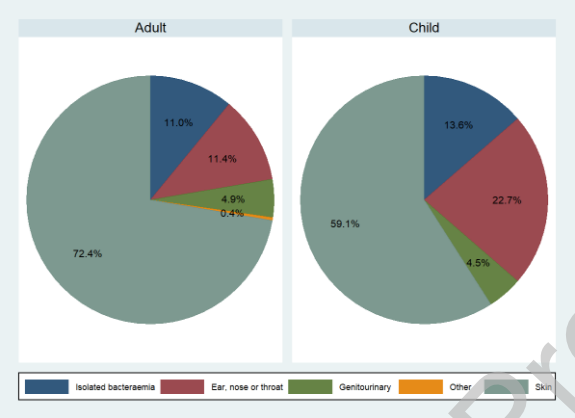

Figure 2. Source of GAS bacteraemia, stratified by age.

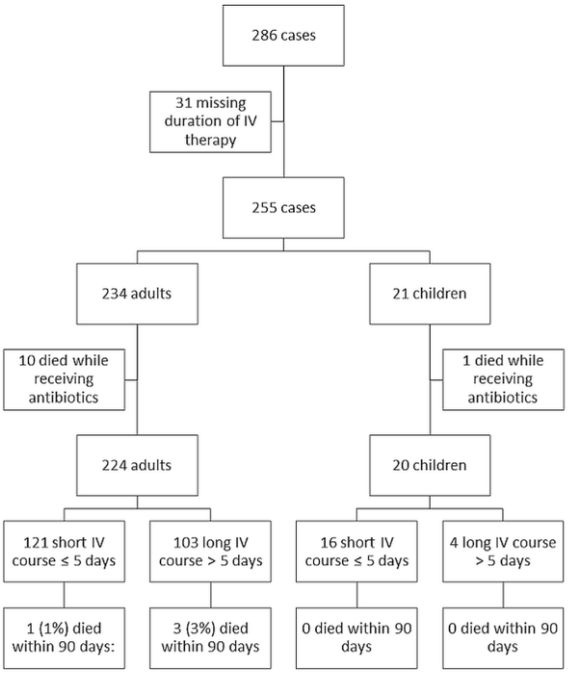

Figure 3. 90-day all-cause mortality of the patients with GAS bacteraemia, stratified by age and duration of intravenous antimicrobial therapy.

There were five patients who died within 90 days; four are described in Fig 4: one died from *Escherichia coli* bacteraemia during a subsequent admission 20 days after the GAS bacteraemia, one died from progressive uraemia following end-stage renal disease in a subsequent admission 61 days after the GAS bacteraemia, one died from a cardiac arrest on a background of hypertrophic obstructive cardiomyopathy and congestive cardiac failure in a subsequent admission 29 days after the GAS bacteraemia, and another died from a myocardial infarction with ventricular fibrillation 71 days after the GAS bacteraemia. The fifth patient who died receiving palliative care for her metastatic breast cancer is not presented in this figure as her duration of antibiotic therapy was unknown.

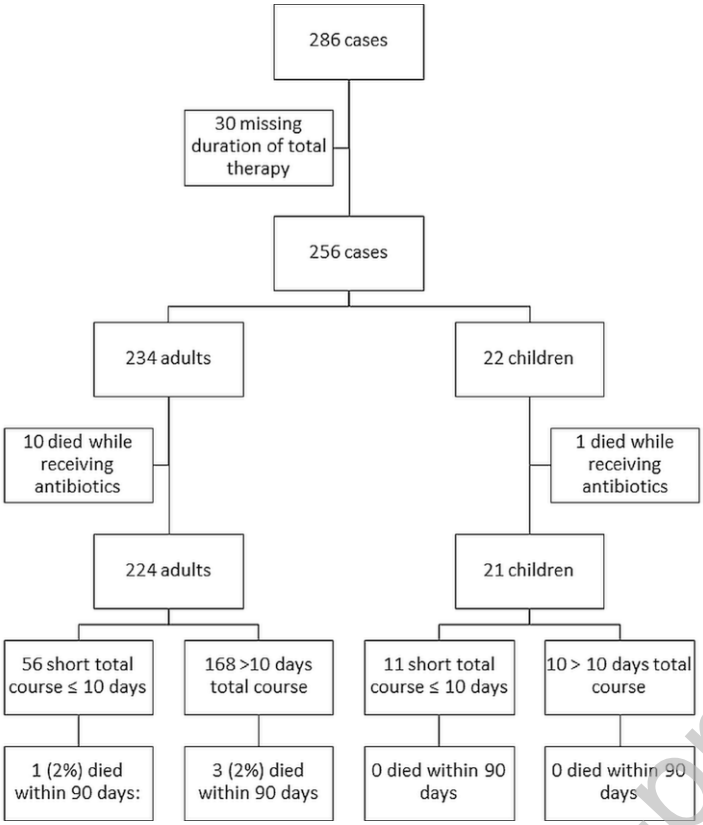

Fig 4. 90-day all-cause mortality of the patients with GAS bacteraemia, stratified by age and total duration of antimicrobial therapy.

There were five patients who died within 90 days; four are described in Fig 5: one died from *Escherichia coli* bacteraemia during a subsequent admission 20 days after the GAS bacteraemia, one died from progressive uraemia following end-stage renal disease in a subsequent admission 61 days after the GAS bacteraemia, one died from a cardiac arrest on a background of hypertrophic obstructive cardiomyopathy and congestive cardiac failure in a subsequent admission 29 days after the GAS bacteraemia, and another died from a myocardial infarction with ventricular fibrillation 71 days after the GAS bacteraemia. The fifth patient who died receiving palliative care for her metastatic breast cancer is not presented in this figure as her duration of antibiotic therapy was unknown.

Supporting information

S1 Table. Yarwood T. 2014. Clinical and laboratory epidemiology of invasive group A streptococcus infections in north Queensland (2006-2013). Unpublished data.

S2 Table. Frequency of GAS bacteraemia susceptible to antimicrobials

S3 Table. Exotoxins seen in the GAS isolates patients in the cohort among all emm types

S4 Table. Classes of antibiotics during hospitalisation

S5 Table. Antimicrobial related complications according to immunological and non-immunological adverse effect profile reported among GAS bacteraemia cases

S6 Table. Descriptions of the deaths not directly attributable to GAS bacteraemia

S7 Table. Rehospitalisation according to indication

S1 Figure. Frequency of GAS bacteraemia cases by month, represented 1-12 for each calendar month.

S2 Figure. Frequency of most common emm types isolated, Far North Queensland, Australia 2014-2020.

S3 Figure. Rehospitalisation frequency attributed to GAS bacteraemia

S4 Figure. Short IV antimicrobial therapy for complicated GAS bacteraemia in complicated cases stratified by death within 90 days

S5 Figure. Short total antimicrobial therapy for complicated GAS bacteraemia in complicated cases stratified by death within 90 days

S6 Figure. Short IV antimicrobial therapy for GAS bacteraemia stratified by rehospitalisation within 90 days

S7 Figure. Short total antimicrobial therapy for GAS bacteraemia stratified by rehospitalisation within 90 days

S8 Figure. Short IV antimicrobial therapy for GAS bacteraemia in complicated cases stratified by rehospitalisation within 90 days

S9 Figure. Short total antimicrobial therapy for GAS bacteraemia in complicated cases stratified by death within 90 days