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Epidemiologic features of invasive group A *Streptococcus* infection in a rural hospital: 6-year retrospective report and literature review

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Introduction: High rates of invasive group A *Streptococcus* disease were suspected by clinicians in northwestern Ontario. Patients with sepsis were being encountered with bacteremia positive for group A *Streptococcus*. This study was designed to assess the incidence of invasive group A *Streptococcus* infection in the region and provide best-practice treatment information.
Methods: We performed a retrospective chart review at the Sioux Lookout Meno Ya Win Health Centre (SLMHC) from 2009 to 2014 to examine rates of infection due to invasive group A *Streptococcus* and outcomes. All blood cultures from 2015 were also examined to calculate the relative rates of distinct pathogens responsible for cases of bacteremia. A literature review on this topic was performed, with attention to rural incidence where available and clinical practice guidelines.
Results: Invasive group A *Streptococcus* disease was diagnosed in 65 patients during the study period. Most (37 [57%]) had bacteremia without a clinical focus. Type 2 diabetes mellitus was a comorbid condition in 27 (42%) and skin conditions in 30 (46%). The case fatality rate was 4.6%. In 2015, group A *Streptococcus* accounted for 8% of all positive blood cultures from in- and outpatients in the catchment area. The calculated annual incidence rate of invasive group A *Streptococcus* infection was 37.2 cases per 100 000 population.
Conclusion: Rural physicians may encounter group A *Streptococcus* bacteremia in their practice. The death rate associated with these infections can be as high as 20%, and patients require urgent treatment, typically with intravenous penicillin and clindamycin therapy. The rate of invasive group A *Streptococcus* infection in the predominantly First Nations population served by the SLMHC exceeded the Canadian rate eightfold and is comparable to rates observed in low-income countries and among Indigenous populations in Australia. This disparity may result from inadequate housing, overcrowding or limited access to clean water.

Introduction : Des cliniciens soupçonnaient des taux élevés d'infections invasives à streptocoque du groupe A dans le Nord-Ouest de l'Ontario. Les patients infectés présentaient une bactériémie positive pour les streptocoques du groupe A. Notre étude visait à évaluer l'incidence des infections invasives à streptocoque du groupe A dans la région et à offrir des renseignements sur les meilleures pratiques de traitement.
Méthodes : Nous avons mené une étude rétrospective des dossiers de patients du Centre de santé Meno Ya Win de Sioux Lookout (SLMHC) entre 2009 et 2014 afin d'étudier les taux d'infections invasives à streptocoque du groupe A et les résultats. Nous avons également examiné toutes les hémocultures effectuées en 2015 afin de déterminer les taux relatifs de pathogènes distincts responsables des cas de bactériémie. Nous avons procédé à une analyse documentaire sur le sujet, en portant attention à l'incidence en milieu rural lorsque les données étaient disponibles ainsi qu'aux guides de pratique clinique.

Résultats : Soixante-cinq patients ont reçu un diagnostic d'infection invasive à streptocoque du groupe A pendant la période à l'étude. La plupart d'entre eux (37 [57 %]) présentait une bactériémie sans manifestation clinique. Vingt-sept (42 %) patients présentaient également un diabète de type 2 et 30 (46 %) patients présentaient des affections cutanées. Le taux de mortalité clinique était de 4,6 %. En 2015, les infections à streptocoque du groupe A comptaient pour 8 % de la totalité des hémocultures positives provenant des patients hospitalisés et des patients externes dans la région à l'étude. On a calculé un taux d'incidence annuel d'infections invasives à streptocoque du groupe A de 37,2 cas par 100 000 personnes.

Conclusion : Les médecins en milieu rural peuvent rencontrer des cas de bactériémie à streptocoque du groupe A dans le cadre de leur pratique. Le taux de mortalité associé à ces infections peut atteindre 20 %. Les patients ont besoin d'un traitement urgent, reposant généralement sur l'administration de pénicilline et de clindamycine par voie intraveineuse. Le taux d'infections invasives à streptocoque du groupe A dans la population majoritairement autochtone desservie par le SLMHC était 8 fois plus élevé que le taux observé dans la population canadienne et est comparable aux taux observés dans les pays à faible revenu et chez les populations aborigènes d'Australie. Cette disparité pourrait être attribuable au logement inadéquat, au surpeuplement ou à l'accès limité à de l'eau potable.

INTRODUCTION

Streptococcal disease caused by the Lancefield group A *Streptococcus* (*S. pyogenes*) is a common occurrence in clinical practice, often presenting as common "strep throat" or impetigo. Group A *Streptococcus* is also associated with 2 autoimmune-mediated diseases that can follow simple infections: poststreptococcal glomerulonephritis and acute rheumatic fever.[1,2] More serious disease may occur when the streptococcal infection becomes invasive (Fig. 1).

Housing and access to clean water are among ongoing inequities in social determinants of health in many First Nations communities and are of particular relevance in the context of infectious diseases. In Australia, inadequate sanitation and overcrowding in Indigenous communities are associated with increased risk of infection, with group A *Streptococcus* being a predominant pathogen.[3,4]

We suspected that northwestern Ontario has a substantial burden of illness related to group A *Streptococcus*, as we have previously documented high rates of acute rheumatic fever[5] and poststreptococcal glomerulonephritis[6] in the region.

In this study, we report on the scope of invasive group A *Streptococcus* infections seen in a rural northwestern Ontario hospital and provide a summary of the relevant literature.

METHODS

Retrospective chart review

The Sioux Lookout Meno Ya Win Health Centre (SLMHC) in northwestern Ontario serves a primarily First Nations population. Its catchment area

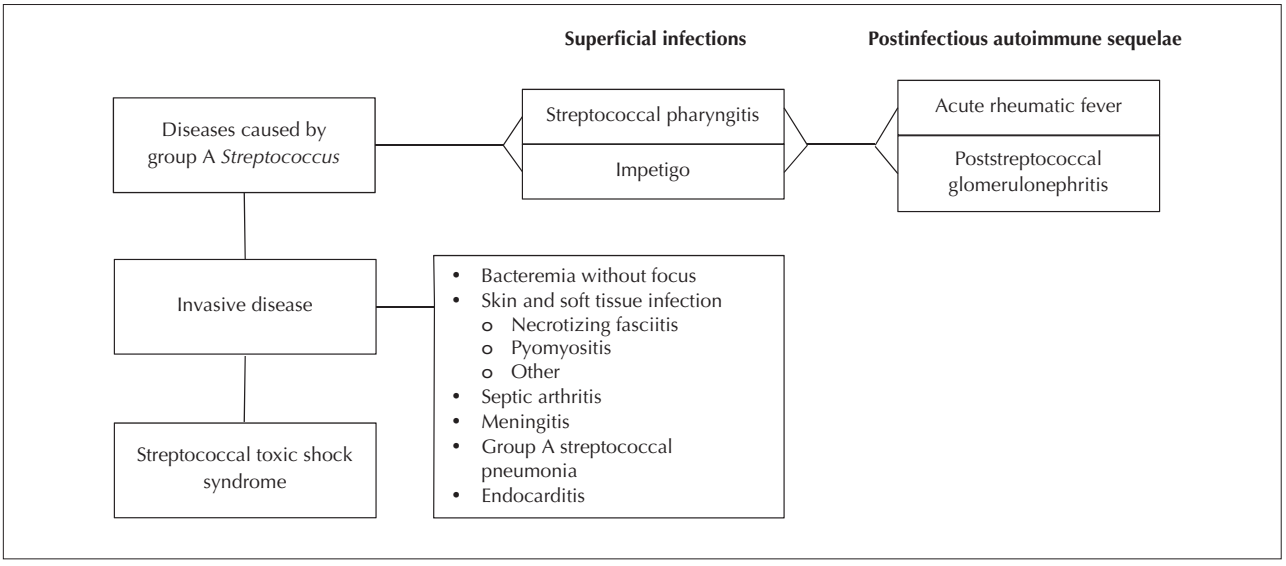

Fig. 1. Group A streptococcal diseases.

includes 31 remote fly-in communities across an area of 385 000 km^2. We used microbiology data from the SLMHC laboratory from Jan. 1, 2009, to Dec. 31, 2014, to identify potential cases of invasive group A *Streptococcus* infection. Case definition followed the Ontario guidelines[7] (Table 1). For each confirmed case, we recorded the patient demographic characteristics and disposition, and information relating to comorbidities and other risk factors.

We also collected laboratory data for all positive bacteremia results in 2015 in order to compare the epidemiologic features of invasive group A *Streptococcus* infection to those of other invasive infections treated at the same institution.

Data were input and analyzed with the use of Microsoft Excel.

Literature review

We conducted a search of the English-language literature from January 2005 to February 2016 using MEDLINE and Embase. Combinations of the following search terms were used: "*Streptococcus pyogenes*," "bacteremia," "arthritis, infectious," "cerebrospinal fluid," "peritoneal," "shock, septic," "fasciitis, necrotizing," "pyomyositis," "gangrene," "meningitis, bacterial," "death," "Canada," "Indians, North American," "Oceanic ancestry group," "rural health services," "rural population" and "rural health."

Ethics approval

This research was approved by the Sioux Lookout Meno Ya Win Research Review and Ethics Committee.

Table 1: Key definitions

Term	Definition
Confirmed case of invasive group A *Streptococcus* infection	Isolation of group A *Streptococcus* from a normally sterile site; *or* isolation of group A *Streptococcus* from a nonsterile site *and* evidence of clinical severity
Evidence of clinical severity	Any of the following: streptococcal toxic shock syndrome, necrotizing fasciitis, myositis, pyomyositis, gangrene, meningitis, group A streptococcal pneumonia (cannot be used as sole marker), presence of another life-threatening condition, death directly attributable to invasive group A *Streptococcus* infection
Streptococcal toxic shock syndrome	Hypotension plus 2 of the following: renal function impairment, coagulopathy, liver function abnormality, acute respiratory distress syndrome, generalized erythematous macular rash

RESULTS

Epidemiologic features in northwestern Ontario

In 2015, the SLMHC collected 106 positive blood culture isolates from 100 in- and outpatients. Duplicate and repeat cultures for the same patient were not included. Group A *Streptococcus* bacteremia accounted for 8% of the positive blood cultures (Fig. 2).

In the analysis of cultures positive for group A *Streptococcus* from 2009 to 2014, we identified 65 cases that met the case definition for invasive disease. Of the 65 patients, 48 were from remote First Nations communities north of Sioux Lookout, and 17 were from Sioux Lookout and Pickle Lake. The annual number of cases over the study period ranged from 6 to 14. No temporal or geographic clustering of cases was identified. The average annual incidence for the study period was 37.2 cases per 100 000 population.

Of the 65 cases, 34 (52%) were in females, and the mean age of all patients was 42.2 years (Table 2). The age distribution was bimodal, peaking among those aged less than 1 year and again among those aged 40–59 years (Fig. 3). Fifteen cases (23%) met the criteria for clinically severe infection. The most common comorbidities were skin conditions (30 patients [46%]) and diabetes mellitus (27 [42%]). Use of nonsteroidal anti-inflammatory drugs (NSAIDs) was the most common risk factor (17 patients [26%]) (Table 2).

Sixty-three cases (97%) were diagnosed based on the isolation of group A *Streptococcus* from a sterile site, typically blood (53 cases [82%]) (Table 3).

Bacteremia without focus was the most common clinical presentation (37 cases [57%]), followed by skin and soft-tissue infections (18 [28%]). Other presentations are listed in Table 4. Streptococcal toxic shock syndrome (STSS) developed in 3 of the 6 patients with necrotizing fasciitis and 4 of the 37 with nonfocal bacteremia.

Twenty-nine patients (45%) were transferred to a tertiary care centre for treatment. Three deaths directly attributable to invasive group A *Streptococcus* infection occurred during the study period, giving a case fatality rate of 4.6% (Table 5).

Literature summary

Definition

In Ontario, invasive group A *Streptococcus* infection is a provincially reportable disease. The case

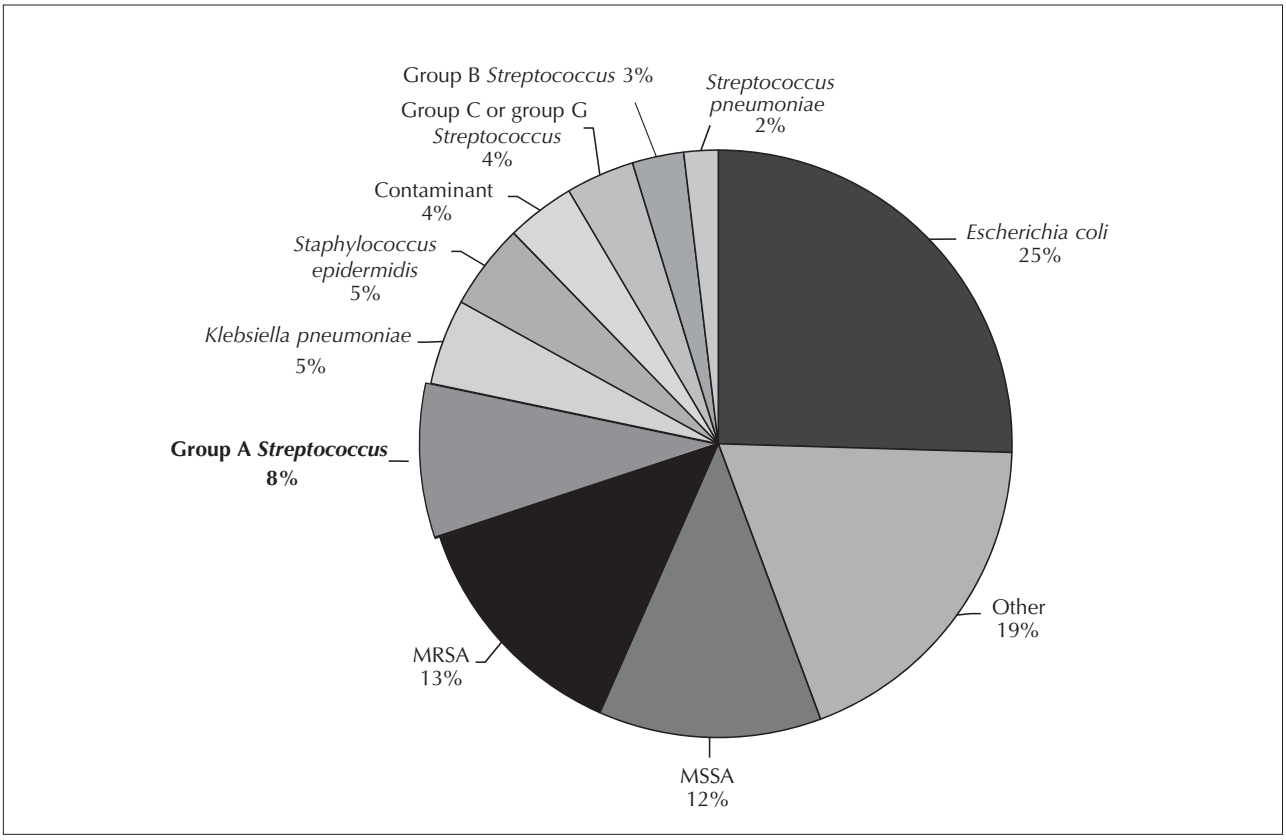

Fig. 2. Isolates from positive blood cultures from in- and outpatients at the Sioux Lookout Meno Ya Win Health Centre in 2015. Note: MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *S. aureus*.

Table 2: Characteristics of patients presenting with invasive group A *Streptococcus* infection to SLMHC between 2009 and 2014

Characteristic	No. (%) of patients* *n* = 65
Age, mean ± SD, yr	42.2 ± 24.9
Female	34 (52)
Clinically severe infection	15 (23)
Comorbid condition(s)	
Skin condition	30 (46)
Diabetes mellitus	27 (42)
Alcohol dependence	13 (20)
Coronary artery disease	8 (12)
Chronic renal failure	7 (11)
Risk factor(s)	
Use of nonsteroidal anti-inflammatory drug	17 (26)
Staphylococcus aureus cogrowth on current wound swab	14 (22)
Previous wound swab positive for group A *Streptococcus*	13 (20)
Previous diagnosis of invasive group A *Streptococcus* infection	5 (8)
Immunosuppressive drug use	4 (6)
Injection drug use	4 (6)

SD = standard deviation, SLMHC = Sioux Lookout Meno Ya Win Health Centre.
*Unless indicated otherwise.

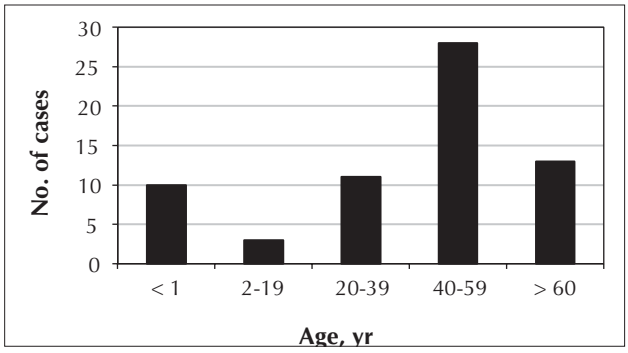

Fig. 3. Age at presentation of cases of invasive group A *Streptococcus* infection seen at the Sioux Lookout Meno Ya Win Health Centre between 2009 and 2014.

Table 3: Source of group A *Streptococcus* isolates from patients presenting to SLMHC between 2009 and 2014

Source	No. (%) of patients
Sterile site	63 (97)
Blood	53 (82)
Synovial fluid	4 (6)
Deep tissue (obtained during surgery)	3 (5)
Abscess (aseptic aspiration)	3 (5)
Peritoneal fluid	1 (2)
Cerebrospinal fluid	1 (2)

SLMHC = Sioux Lookout Meno Ya Win Health Centre.

definition includes cultures positive for group A *Streptococcus* obtained from a normally sterile site (e.g., blood, cerebral spinal fluid, deep tissue)[8,9] or the isolation of group A *Streptococcus* from a nonsterile site with evidence of clinical severity.[7] Clinical severity is determined based on evidence of STSS, necrotizing fasciitis, myositis, meningitis or group A streptococcal pneumonia.[7] However, pneumonia should not be used as a sole indicator of severity.[7]

Epidemiologic features

The highest incidence rates of invasive group A *Streptococcus* infection are typically reported among young (≤ 5 yr) and older (> 70 yr) patients.[10–12] Predisposing factors for this infection include diabetes, immunosuppression, malignant disease, varicella infection, intravenous drug use, alcohol abuse, skin trauma and NSAID use.[8,13–15]

The global incidence of invasive group A *Streptococcus* infection has been increasing since the mid-1980s.[10,16–19] In Canada, the incidence increased from 2.86 per 100 000 population in 2004 to 4.72 per 100 000 population in 2013.[20]

The highest reported incidence rates of invasive group A *Streptococcus* infection are associated with Indigenous communities in Australia, with rates of 23.8–82.5 per 100 000 population.[21,22] A recent 14-year study of the incidence of this infection in Australia showed that, although Indigenous patients constituted less than 10% of the study population, they accounted for 53% of cases of bacteremia due to group A *Streptococcus*.[23]

Table 4: Clinical presentation of invasive group A *Streptococcus* infections

Presentation	No. (%) of patients
Bacteremia without focus	37 (57)
Skin and soft-tissue infection	
Necrotizing fasciitis	6 (9)
Pyomyositis/myositis	2 (3)
Other	10 (15)
Septic arthritis	4 (6)
Deep-tissue infection	2 (3)
Meningitis	1 (2)
Group A streptococcal pneumonia	1 (2)
Endocarditis	1 (2)
Other	1 (2)

Table 5: Disposition and outcomes of patients with invasive group A *Streptococcus* infection

Disposition/outcome	No. (%) of patients
Transferred care	29 (45)
Treated locally	
Inpatient	32 (49)
Outpatient	4 (6)
Death due to invasive group A *Streptococcus* infection	3 (5)

Clinical manifestations

Streptococcal toxic shock syndrome

A diagnosis of STSS requires hypotension as well as the presence of at least 2 of renal impairment, coagulopathy, liver function abnormality, adult respiratory distress syndrome or generalized erythematous macular rash.[11,24,25] The clinical course of STSS can be rapidly progressive, with death rates as high as 56%.[26–34]

Streptococcal toxic shock syndrome may develop in 5.0%–28.6% of patients with invasive group A *Streptococcus* infection.[10–12,16,22,29,31,35] Patients with necrotizing fasciitis appear to be at greatest risk (50%).[36–39] Treatment of STSS often includes combination therapy with penicillin/clindamycin, as the latter is a protein synthesis inhibitor and may therefore reduce toxin production.[8,12,16,40] Intravenous immunoglobulin treatment may also be of benefit in some patients.[27,39,41]

Necrotizing fasciitis

A total of 3.6%–21.8% of cases of invasive group A *Streptococcus* infection present as necrotizing fasciitis.[11,13,16,28,36,37,42–45] This disorder presents nonspecifically and is difficult to diagnose initially.[42,46,47] Severe pain, disproportionate to external appearance, is characteristic.[48] Necrotizing fasciitis due to group A *Streptococcus* is associated with young and otherwise healthy patients[47] and often affects the lower extremities.[41,42,49]

Timely and extensive débridement is associated with better outcomes.[40–42,48] Volume resuscitation, intravenous antibiotic therapy and intravenous immunoglobulin therapy may also be important components of treatment; clindamycin may inhibit toxin production.[39,41] Death rates range from 16% to 50%.[11,13,16,28,39,42,49–51]

Meningitis

Group A streptococcal meningitis is the presence of isolates positive for group A *Streptococcus* in cerebrospinal fluid, or clinical and biochemical signs of meningitis accompanying group A streptococcal bacteremia.[18] Up to 5% of cases of invasive group A *Streptococcus* infection are meningitis,[14,18,28,32] but the

pathogen is a rare cause of bacterial meningitis (1%).[52,53] Group A streptococcal meningitis has a high mortality rate (23%–50%).[14,18,54] Neurologic sequelae develop in almost half of survivors,[18] a higher proportion than with other forms of meningitis.[53]

Other manifestations

The most common manifestation of invasive group A *Streptococcus* infection is bacteremia without focus (up to 27% of cases).[11,12,14,28,32,33,36] Other infection profiles include septic arthritis (4%–15%)[11,14,28,32,55] and pneumonia (10%).[14,32,35,44] Nonnecrotizing skin and soft-tissue infections are also common, occurring in 20%–30% of cases.[16,33,36,56]

Treatment

Treatment for invasive group A *Streptococcus* bacteremia consists of high-dosage penicillin and clindamycin given intravenously for 14 days (Table 6). Surgical and intensive care support may also be needed. Canadian guidelines recommend chemoprophylaxis for close contacts of people with confirmed severe cases. Close contact is defined as more than 4 hours of household contact per day, sharing the same bed, having sexual relations, direct mucous membrane contact or sharing needles with an infected person.[57] First-generation cephalosporins and erythromycin are recommended as first-line chemoprophylaxis for contacts. In addition, all close contacts should be counselled about the signs and symptoms of group A *Streptococcus* infection and should be advised to seek medical attention if signs and symptoms develop within 30 days after exposure.[58]

DISCUSSION

The average annual incidence rate of invasive group A *Streptococcus* infection in our rural population was 37.2 cases per 100 000 population, with a case fatality rate of 4.6%. This incidence is 8 times higher than the 2013 Canadian rate, 4.7/100 000 person-years, and 7 times the 2014 Ontario rate.[20,59] It is comparable to rates observed in low-income countries[60–62] and among Indigenous populations in Australia.[21,22] Our findings are consistent with previous research at our institution showing disproportionately high rates of other infectious diseases, such as methicillin-resistant *Staphylococcus aureus* infection,[63,64] and autoimmune sequelae of group A *Streptococcus* infection including acute rheumatic fever,[5] poststreptococcal glomerulonephritis[6] and pyomyositis.[65]

In February 2016, the Nishnawbe Aski Nation declared a health and public health emergency in response to the high burden of preventable diseases, including invasive bacterial infections, in remote First Nations communities in the Sioux Lookout region.[66] Overcrowded housing and inadequate access to clean water, factors known to facilitate the spread of communicable disease, exist in many of these communities and may help explain the high rates of infectious disease in the region.[5,6,63–65,67]

Pre-existing skin conditions were common in our study, occurring in 46% of patients with invasive group A *Streptococcus* infection. This raises the possibility that, in this population, skin may serve as an entry point for more invasive disease. Type 2 diabetes was also common (42%). Our age distribution was bimodal, with the second peak occurring in a younger age bracket (40–59 yr) than documented in the literature (> 70 yr).[10–12] The prevalence of type 2 diabetes may have contributed to the observed earlier onset of invasive group A *Streptococcus* infection.

Use of NSAIDs is associated with increased risk of STSS[68] and necrotizing fasciitis.[69,70] Use of these drugs may facilitate the seeding of damaged muscle tissue by *Strep. pyogenes*, exacerbate pre-existing group A *Streptococcus* infection and reduce the effectiveness of antibiotic therapy.[71] In our study, 26% of patients reported antecedent NSAID use, a proportion comparable to that in a New Zealand chart review on necrotizing fasciitis.[72]

Compared to previous studies, the case fatality rate of 4.6% reported here is low. Death rates for invasive group A *Streptococcus* infection typically range from 10%–20%.[14,19,21,28,35,36,61,62,73] There is a lack of consensus in the literature on how to define case fatality rate. The definition of death associated with invasive group A *Streptococcus* infection includes in-hospital death[16,36] and death within 7 days,[9,19,28,33,50,51] 28 days[23] or 30 days[32] of infection. The definition that we used was death known to be directly attributable to inva-

Table 6: Treatment for group A streptococcal bacteremia[25]

Population	Antibiotic and dosage	Duration, d
Adult	Penicillin G, 4 million units intravenously every 4–6 h, *and* clindamycin, 900 mg intravenously every 6–8 h	14
Child	Penicillin, 200 000–400 000 units/kg per day intravenously divided every 4–6 h (maximum 24 million units/d), *and* clindamycin, 20–40 mg/kg intravenously divided every 6–8 h (maximum 2.7 g/d)	14
Chemoprophylaxis	Cephalexin, 25–50 mg/kg per day in 2–4 divided doses (maximum 1 g/d)	10

sive group A *Streptococcus* infection. The use of this more stringent definition excluded several deaths and may explain our lower than expected mortality rate.

The scope of invasive group A *Streptococcus* infection in northwestern Ontario was similar to the disease profiles encountered in the literature. Most of our cases (57%) were bacteremia without focus, which is often the most common presentation of invasive group A *Streptococcus* infection.[11,12,14,28,32,33,36] The second most common presentation was skin and soft-tissue infection (28%), including necrotizing fasciitis (9%). Streptococcal toxic shock syndrome developed in 11% of cases, which is also in keeping with established estimates of 5%–28%.[10–12,16,22,29,31,35]

Limitations

Some cases may not have been captured owing to the retrospective nature of our review. Severely ill patients may have been transferred directly from their home community to a tertiary care centre; these patients would not have been seen at the SLMHC and were therefore not included in this study. The incidence rate of invasive group A *Streptococcus* infection reported here may therefore underestimate the true burden of the disease.

We identified only 65 cases in a 6-year period, which limited possible statistical analyses. Furthermore, only limited clinical data (outcome, diagnosis, comorbidities) were available for each case of invasive group A *Streptococcus* infection, and the data did not include treatment information for each patient, as our focus was on disease incidence during data collection.

CONCLUSION

Rural physicians may occasionally encounter group A *Streptococcus* bacteremia in their practice. The death rate associated with these invasive infections is high, and patients require urgent treatment, typically with intravenous penicillin and clindamycin therapy. The rate of invasive group A *Streptococcus* infection in the predominantly First Nations population served by the SLMHC in northwestern Ontario exceeds the Canadian norm eightfold and is comparable to that of low-income countries. This disparity may result from inadequate housing, overcrowding or limited access to clean water.

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