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ANISHINAABE
BIMAADIZIWIN
RESEARCH PROGRAM

A joint initiative of Sioux Lookout Meno Ya Win Health Centre and Sioux Lookout First Nations Health Authority

Research Compilation
2016-2017

Northern Ontario School of Medicine
École de médecine du Nord de l'Ontario

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ANISHNAABE BIMAADIZIWIN Research Compilation 2016-2017

Anishnaabe Bimaadiziwin Research Program continues to advance community-based research in Northwest Ontario. The program is a partnership of the Sioux Lookout Meno Ya Win Health Centre and the Sioux Lookout First Nations Health Authority.

This is the fourth Research Compilation of regional research based in Sioux Lookout. Each encompasses several years of peer reviewed literature, reproduced with permission of the authors. We thank the clinicians, fellow researchers, administrators, organizations and study participants for contributing to the knowledge of medical and social realities in our region. Over the past decade, research has become an integral part of the fabric of our healthcare provision.

Community-based research receives its mandate from the issues affecting the population we serve. Research can facilitate health program planning, evaluation, and advocacy as well as documenting system deficits and clinical areas needing attention.

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A 5 year retrospective study of Emergency Department use in Northwest Ontario: a measure of mental health and addictions needs. Matsumoto C, Madden S, O'Driscoll T, Lawrance J, Jakubow A, Loewen K, Kelly L. CJEM 2016. DOI 10.1017/cem.2016.387.

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Rural Medicine

A 5 year retrospective study of emergency department use in Northwest Ontario: a measure of mental health and addictions needs

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ABSTRACT

Objective: The main objective of this study was to understand the five-year trend in total emergency department (ED) visits, frequency of use, and diagnoses and disposition of patients. Since the region has experienced a profound increase in opioid use disorder since 2009, we were particularly interested in changes in the volume of mental health and addiction (MHA) ED presentations.

Methods: Retrospective aggregate data analysis of ED visits to the Sioux Lookout Meno Ya Win Health Centre 2010-2014.

Results: ED visit volume increased 29% over the five-year study period, while MHA ED visits increased 73%. The admission rate remained stable at 6.9% of ED visits. Five-year trends in clinically grouped diagnostic categories identified respiratory, MHA, and abdominal/pelvic complaints as the three most common ED presentations. In 2014, MHA presentations accounted for 10.3% of ED visits, 8.7% of admissions, and 20.0% of inter-hospital transfers.

Conclusion: The dramatic increase in MHA ED visits mirrors the opioid epidemic the region is experiencing. MHA may soon become the commonest ED presentation. If reasons for ED visits serve as a proxy for unmet outpatient needs, increased efforts at developing community MHA services and addressing the related social determinants of health are required.

RÉSUMÉ

Objectif: L'étude décrite ici visait principalement à comprendre les tendances dégagées de statistiques recueillies sur une période de cinq ans quant au nombre total de consultations au service des urgences (SU), à la fréquence d'utilisation du service et des diagnostics ainsi qu'aux suites à donner. Compte tenu du fait que la région a connu une forte augmentation des problèmes liés à la consommation d'opioïdes depuis 2009, les changements quant au nombre de consultations au SU pour des troubles de santé mentale et de toxicomanie (SMT) intéressaient tout particulièrement les auteurs.

Méthode: Il s'agit d'une analyse rétrospective de données agrégées sur les consultations médicales au SU du Sioux Lookout Meno Ya Win Health Centre, recueillies de 2010 à 2014.

Résultats: Le nombre de consultations au SU a augmenté de 29 % durant la période à l'étude, et le nombre de consultations au SU pour des troubles de SMT, lui, a augmenté de 73 %. Par contre, le taux d'hospitalisation est resté stable, à 6,9 % des consultations au SU. Les problèmes respiratoires, les troubles de SMT ainsi que les problèmes abdominaux ou pelviens se sont révélés les trois principaux groupes de diagnostics cliniques qui se sont dégagés des données recueillies sur la période de cinq ans. En 2014, les troubles de SMT représentaient 10,3 % des consultations au SU, 8,7 % des hospitalisations et 20,0 % des mutations interhospitalières.

Conclusions: L'augmentation considérable du nombre de consultations au SU pour des troubles de SMT reflète les proportions épidémiques que prend la consommation d'opioïdes dans la région. Les troubles de SMT pourraient bientôt devenir le principal motif de consultation au SU. Si les motifs de consultation au SU servent de déversoir de besoins non satisfaits parmi les patients externes, il faudra déployer davantage d'efforts pour mettre sur pied des services communautaires en santé mentale et en toxicomanie, et se pencher sur les déterminants sociaux connexes, liés à la santé.

Keywords: emergency, utilization, mental health, addiction

INTRODUCTION

Studies characterizing emergency department (ED) use have been largely confined to large urban centers. Rural ED use analysis is underrepresented in the literature, yet offers an interesting look at the fabric of medical services and the service needs in rural communities.

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In this study we examine the ED in a unique rural hospital setting in northwest Ontario which services a 385,000 km^2 region, where patients are often triaged from remote First Nations community nursing stations before transfer to the hospital ED by air ambulance.

The Sioux Lookout Meno Ya Win Health Centre (SLMHC) is a 60 bed hospital serving 29,000 primarily First Nations patients across 31 remote communities.[1]

In 2009, regional First Nations leaders identified an "epidemic" of opioid abuse in their communities.[2] In 2016, a state of emergency was declared concerning health status of the population, identifyinghealth inequities and wide gaps in services.[3] Social determinants of health, such as housing and access to clean water, are common deficiencies in the First Nations communities of NW Ontario.[4] Commentators describe underlying determinants of "colonialization, racism, social exclusion and lack of self-determination" as negatively affecting disparities in the health of Aboriginal peoples.[5]

In the context of these disparities, mental health and addiction (MHA) issues are significant concerns for the First Nations population in the SLMHC catchment area. First Nation youth experience significantly higher rates of mental health problems and have suicides rates six times the general population.[6,7]

The main objective of this study was to understand the five-year trend in total ED visits, and diagnoses and disposition of patients. Since the region has experienced a profound increase in opioid use disorder since 2009, we were particularly interested in the volume of MHA patients.[2,8]

METHODS

Sioux Lookout Meno Ya Win Health Centre obtained anonymized data for a five-year period (2010-2014) from the Northwest Health Alliance, a health care data collection organization which accessed hospital utilization information from National Ambulatory Care Registration System (NACRS). Ethics approval was granted by Sioux Lookout Meno Ya Win Health Centre Research and Review and Ethics Committee.

Data analysis was completed using SPSS (Version 21, IBM, Armank, NY). Descriptive statistics were completed for sex, age, ED volume, disposition, and primary diagnosis. Diagnosis was completed using ICD-10 codes and grouped into relevant clinical categories. Mental health ICD-10 coded visits were combined with codes for substance abuse, addictions and self-harm ED visits.

RESULTS

From 2010-2014 there were 80,212 ED visits to SLMHC resulting in an annual average of 55 (95% CI 50.2, 59.8) per 100 population. Fifty-four percent of visits were from Sioux Lookout while 41% were from Northern Communities and 5% were from areas outside of the catchment area. People aged 20-40 years made up the majority of visits with those aged 76 and older visiting the least. Women visited the ED more frequently than men: 55% versus 45% of visits.

The annual number of ED visits increased 29% from 2010-2014, for a total of 17,911 visits in 2014 (Figure 1). The annual visit rate per capita in 2014 was 62 per 100 population and averaged 55 per 100 over 5 years.

Admission rates were stable at 6.9% (95% CI 6.3, 7.5) (Figure 1) and less than 1% of ED patients were transferred on to tertiary care centers.

The three commonest diagnostic ED visit categories were respiratory, MHA, and abdominal/pelvic complaints. Our most dramatic finding was the increasing trend in ED visits for MHA, which increased 73% in the 5-year study period (Figure 2).

The ED workload of MHAs incurred significant inpatient service needs, constituting 8.2% of admissions (458/5,552) and 14.7% of transfers (111/755) from 2010-2014.

In 2014 alone, MHA presentations in the ED accounted for 10.3% of ED visits and 8.7% of hospital admissions, and accounted for 20.0% of patient transfers to tertiary care centers or psychiatric facility (Table 1). MHA ED patients were most commonly (59.2%) in the

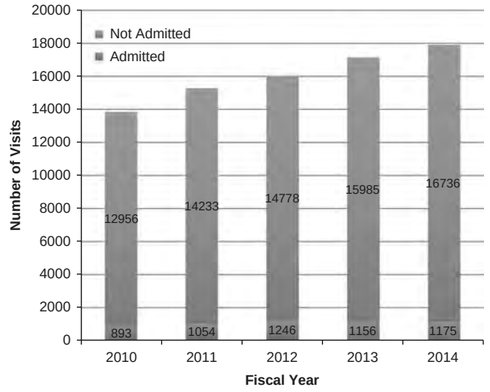

Figure 1. Yearly ED visits with disposition 2010-2014.

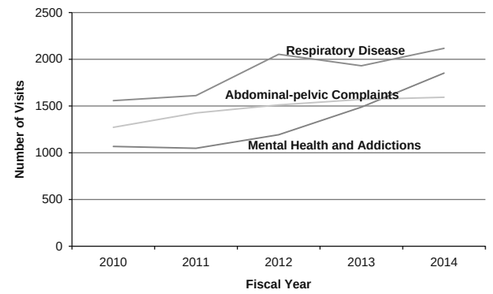

Figure 2. Three most frequent diagnoses at SLMHC ED 2010-2014.

Table 1. ED visits, admissions and transfers for SLMHC for 2014

Diagnostic category	ED Visits (%)	Admissions (%)	Transfers (%)
Respiratory	2117 (11.8)	182 (15.3)	3 (2.6)
Abdominal/pelvic complaints	1594 (8.9)	241 (20.3)	4 (3.5)
MHA	1852 (10.3)	103 (8.7)	23 (20)
TOTAL	17,911	1175	115

MHA, mental health and addiction

20-40 age group and demonstrated a slight preponderance of females (51.5%). This same age group also experienced the highest increase (90%) in MHA ED visits during the study period.

DISCUSSION

Ontario-wide ED visits per capita increased 27% between 1998-2008, when it was measured at 42 per 100 population.[9,10] This provincial utilization rate is slightly lower than the Canadian average ED utilization of 49 per 100 population.[11] The SLMHC ED visit volume increased a similar rate (29%) in just a 5-year period, without related population increases.

Rural utilization rates are typically higher than urban, given that rural EDs provide both emergency and urgent primary care service.[12,13]

Our 2014 visit rate of 62 per 100 population (five-year average of 55), was lower than expected for such a large and remote region, and was lower than other rural estimates found in the literature[14-17] (see Table 2). This likely reflects the geographic barrier of distance and access, as 80% of the catchment

Table 2. Estimated ED visits per capita in rural and general populations

Location, yearr	ED visits per 100 population
Ontario, 1977[9]	33
Ontario, 2008[10]	42
Canada, 2008[11]	49
Rural catchment areas	
Elliot Lake ON, 2001[14]	98
Huron Country ON, 1998[15]	89
Sussex NB, 2009[16]	84
Exeter ON, 2003[17]	51
Sioux Lookout ON, 2010-2014 average	*55*

Table 3. Mental health and addiction (MHA) ED visits per 100,000 population

Sioux Lookout Meno Ya Win Health Centre, 2014	6,386
Sioux Lookout Meno Ya Win Health Centre, 2012	4,114
Northwest Local Health Integration Network, 2012[34]	929
Ontario, 2012[34]	374

population reside in remote communities without road access to the hospital EDs. Patients in these communities visit their local nursing station for urgent and emergent care and our hospital data only captured this information when they were triaged and transported to the hospital ED.

Respiratory disease was the most common diagnosis responsible for our ED visits. Canada-wide data from 2014 places respiratory illness as the third most frequent ED diagnosis (behind abdominal/pelvic pain and chest pain).[18] Respiratory conditions are common in our catchment population.

We have previously documented high rates of admission for pneumonia for both infants and adults, likely a result of inadequate and crowded housing in northern communities.[19-24]

In general, respiratory and abdominal-pelvic complaints are common reasons for an ED visit, but MHAs are not in the national top ten common reasons for an ED visit.[18] Our hospital encountered a twelve-fold higher rate of MHA ED visits in 2012 when compared to Ontario-wide numbers and the gap is widening (Table 3).

The leading reason for transfer from our facility was for orthopedic care (21.0% of transfers). This was similar

to a southern Ontario rural emergency department study, where 23% of transfers were orthopedic.[15] However, our second leading reason for patient transfer (20.0%) in 2014 was MHAs, while it accounted for only 4.5% of transfers in the southern Ontario study.[15]

Our ED visits for MHA diagnoses increased 73% in the 5-year study period (Figure 2). This increase was consistent with the growing epidemic of opioid abuse described by regional First Nations leaders in 2009.[2] Opioid use disorder is additive to a preexisting burden of mental health challenges in the First Nations population.[25] In 2013, the regional maternity program documented 28% of pregnancies experiencing some narcotic exposure during gestation.[26,27] One regional First Nation community documented an adult age adjusted rate of treatment for opioid use disorder of 41%.[8] Many communities have begun to address addictions.

New community-based addiction treatment programs have been initiated in 22 of the 31 remote communities in the region and hospital-based services have developed to address with the burden of widespread opioid use disorder.[3,28-32] The community-based programs play an important role in decreasing drug-related "medivacs". One community with a robust First Nations Healing and opioid agonist treatment program recorded a 30% decrease in such medical transfers.[8] Positive community changes have resulted from one such community-based addiction treatment programming: school attendance has increased 33% and child protection cases have decreased by 58%.[8]

It may not be surprising that the regional visit rates to the ED for MHAs were orders of magnitude greater than the rest of the province (Table 3). ED visit rates for MHA include visits for intentional self-harm. Public Health Ontario statistics indicate our region has the highest rates of ED visits for self-harm in the province, particularly in youth (age 10-19).[33]

Increasing ED visits for mental health and addiction issues indicate that community-based and hospital MHA services need further development to address the scope of the problem. Substantial political, economic, and social changes are needed to address the social determinants of health which propagate an ongoing high burden of MHA issues in NW Ontario.

Limitations

Community nurses provide a substantial amount of primary and urgent care in the remote communities of our ED catchment area and this information is not captured in our study. The remote nursing stations and community MHA workers also locally manage a heavy workload related to MHAs, limiting transfers to the ED.

CONCLUSION

The Sioux Lookout ED provides rural hospital services in a unique hospital and community environment. The dramatic increase in MHA ED visits mirrors the opioid use disorder epidemic the region is presently experiencing. MHA may soon become the most common ED presentation. If reasons for ED visits serve as a proxy for unmet outpatient needs, increased efforts at developing community MHA services and addressing the underlying social determinants of health are required.

Competing Interests: None declared.

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Defining "high-frequency" emergency department use

Does one size fit all for urban and rural areas?

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Abstract

Objective To suggest a functional definition for identification of "high-frequency" emergency department (ED) users in rural areas.

Design Retrospective analysis of secondary data.

Setting Sioux Lookout Meno Ya Win Health Centre in northwestern Ontario.

Participants All ED visitors (N = 7121) in 2014 (N = 17911 visits) in one rural hospital.

Main outcome measures The number of patients and visits identified using different definitions of *high-frequency use*.

Results By using the most common definition of high-frequency use (≥4 annual visits) for our hospital data, we identified 16.7% of ED patients. Using 6 or more annual visits as the definition, we identified 7.9% of ED patients; these patients accounted for 31.3% of the ED visit workload. Using the definition of 6 or more identifies less than 10% of the patients, which is a similar result to using the lower visit standard (≥4) in urban centres.

Conclusion We suggest that the definition for high-frequency visitors to a rural ED should be 6 or more annual visits. Other useful subsets might include very high-frequency users (12 to 19 annual visits) and super users (≥20 annual visits).

EDITOR'S KEY POINTS

- Patients in rural areas tend to have a higher reliance on emergency departments (EDs) than patients in urban areas do. Definitions of *high-frequency use* commonly used in research in urban areas might not be appropriate in rural studies.
- This study aimed to identify a cutoff for high-frequency ED use that would identify a similar proportion of patients to that identified by the most common cutoff (≥4 annual ED visits) used in urban centres. A cutoff of 6 or more annual visits identified 7.9% of ED users in rural northwestern Ontario, similar to proportions identified in urban studies using the lower cutoff.
- The 7.9% of high-frequency users accounted for 31.3% of ED workload. Super users (≥20 annual visits) amounted to only 35 of the 7121 patients but accounted for 5.5% of ED workload. The 85 very high-frequency users (12 to 19 visits) accounted for a further 6.9% of workload. Graded interventions aimed at these groups could target a manageable number of patients with the potential for a relatively large reduction in workload.

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Analyses of emergency department (ED) use have always acknowledged patients who use the service more often than the norm.[1-3] Certainly, front-line ED physicians and nurses are very familiar with these patients. Despite the regularity of discussing high-frequency ED users, there is no consistent definition.[4] Agreeing on a broadly applicable definition of *high-frequency use* is important. In this study, we will examine common definitions in the literature, see how they might apply in one rural ED in northwestern Ontario, and suggest a rural standard.

Rural service environments are unique

In 1997 in Ontario, the number of ED visits per capita was 33 per 100 population.[5] Ten years later, it had increased to 42 per 100 population.[6] Rural figures differ: in an emergency-use analysis of 5 rural Huron County EDs in 2000, the rate of use was 89 per 100 population.[7] Although these figures do not account for the influx of summer-only populations to this area, it does highlight a heavier reliance on rural EDs.

Rural ED environments differ from urban centres in both context and complement. In a rural setting the same group of general practitioners who provide primary care during office hours also attend the ED after hours. They might, for convenience, have some patients "schedule" a visit when they are on shift in the ED. Similarly, patients know who is on shift and might choose an elective visit to the ED to see their family doctors.

The context also differs in a rural setting. There is typically no discrete set of emergency service providers, nor alternate treatment services available, and after-hours primary or urgent care is limited, by default, to the local ED. Patients with simple sprains and lacerations must seek ED treatment, where urban environments have alternative services for after-hours and weekend care for such concerns. The rural ED is an after-hours extension of primary care services. Such context and complement differences affect use and seem to increase it.

Defining high-frequency ED use

Published studies use a range of definitions and acknowledge that a standard has not been established.[1] The most common standard used to define high-frequency ED users is 4 or more annual individual patient visits, and definitions that have been used range from 3 or more to 12 or more annual visits.[1,8] These definitions generally identify 3% to 10% of the patients who have visited an urban hospital ED.[9]

No rural definition of high-frequency ED use has been developed.[10,11] The higher per capita visit rate indicates that rural patients have a lower threshold for visiting their EDs. Given these differences in overall use profile and service context, we sought to develop a functional definition of *high-frequency ED use* in rural EDs.

METHODS

We used anonymized annual ED visit information from 2014 for the Sioux Lookout Meno Ya Win Health Centre, a rural 60-bed facility in northwestern Ontario. Data were accessed from regional and national data sets (from the National Ambulatory Care Reporting System) through Northwest Health Alliance, regional health analysts. The data were analyzed to identify high-frequency use using SPSS, version 21. Descriptive statistics, frequencies, and means were obtained to define and characterize high-frequency, very high-frequency, and super users. Ethics approval was granted by the Meno Ya Win Health Centre Research Review and Ethics Committee.

RESULTS

In 2014, 7121 patients made a total of 17911 visits to the ED at the Sioux Lookout Meno Ya Win Health Centre. The total catchment population is 30000, for a visit per capita rate of 59.7 per 100 population. The region served encompasses 300000 km^2, and half of those in the 30000 catchment population require air transportation to access the ED for emergencies and further triaged care.[12]

Applying the common high-frequency definition of 4 or more annual visits to 2014 ED visitors, 1188 (16.7%) ED patients were identified as high-frequency users (**Figure 1**).

Using a standard of 6 or more ED visits a year identified a smaller number of patients (n = 566 [7.9%]) as the high-frequency subset and "normalized" ED use for the remaining 92.1% of patients (**Table 1**).

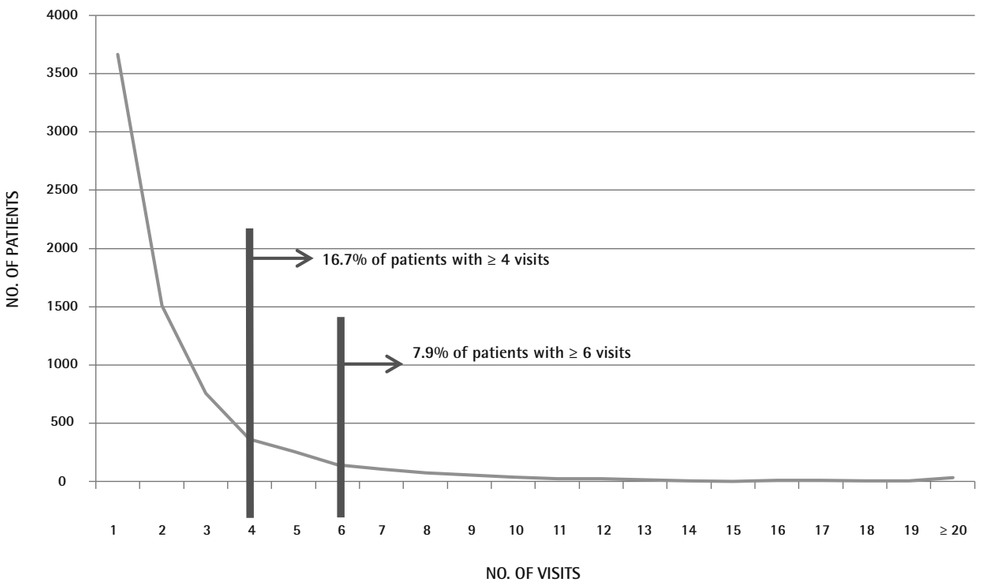
We analyzed further subsets of visit pattern categories of very high-frequency use (12 to 19 visits annually) and super users (≥20 visits annually). This identified sequentially smaller numbers of patients responsible for disproportionate ED workloads (**Table 2**).

DISCUSSION

The context of the ED in a rural setting is important. In an urban context, patients have access to after-hours primary care and urgent-care centres. Applying a high-frequency definition that works well in urban centres is a poor fit for a rural hospital ED when analyzing visit and service patterns.

A definition of high-frequency ED use (≥4 visits) that identifies 16.7% of the population as high-frequency users is intuitively overinclusive. A more manageable standard would identify the top 10% or less of ED patients who visit most frequently. Urban studies using the definition of 4 or more visits consistently characterize the high-frequency ED population as less than 10% (typically 3% to 6%) of their total ED visitor

Figure 1. Frequency of ED visits (≥ 4 and ≥ 6 annual visits) by patients to the Sioux Lookout Meno Ya Win Health Centre in northwestern Ontario in 2014



ED—emergency department.

Table 1. Number of visits and admissions for average and high-frequency ED users in 2014

NO. OF ANNUAL VISITS	PATIENTS, N (%)	VISITS, N (%)	ADMISSIONS, N (%)
0–5	6554 (92.1)	11 702 (65.3)	855 (72.8)
≥ 6	566 (7.9)	5607 (31.3)	284 (24.1)
Other	1 (0.01)*	602 (3.4)	36 (3.1)

ED—emergency department.
*Non-insured visits were removed from our analysis. In Ontario Health Insurance Plan data, they are all identified with the same patient identifier number and the number of visits by a specific patient is not available.

populations. It is important to identify such patients, as they account for up to 30% of the ED's visit workload.[3,4] Rather than reuse this definition, we propose a rural standard of 6 or more annual visits to capture a similar proportion of the rural ED visitor population. Applying that benchmark in our ED, we document that 7.9% of patients (with ≥ 6 annual ED visits) are high-frequency and account for 31.3% of visit workload and 24.1% of admissions. Using this high-frequency definition in our setting, we identify a proportion of the population similar to that described by applying the standard of 4 or more in larger urban settings.

Table 2. Subanalysis of ED user frequency by number of visits with admission data

NO. OF ANNUAL VISITS	PATIENTS, N (%)	VISITS, N (%)	ADMISSIONS, N (%)
Average user (0–5)	6554 (92.1)	11702 (65.3)	855 (72.8)
High-frequency user (6–11)	446 (6.3)	3381 (18.9)	205 (17.4)
Very high-frequency user (12–19)	85 (1.2)	1235 (6.9)	48 (4.1)
Super user (≥ 20)	35 (0.5)	991 (5.5)	31 (2.6)
Other	1 (0.01)*	602 (3.4)	36 (3.1)

ED—emergency department.
*Non-insured visits were removed from our analysis. In Ontario Health Insurance Plan data, they are all identified with the same patient identifier number and the number of visits by a specific patient is not available.

If the objective of identifying high-frequency ED users is to design programs and interventions that better meet the needs of these patients, we need a more manageably sized cohort.

Such interventions typically include a form of interdisciplinary case management for identified high-frequency patients and can decrease ED visits by up to 30%.[13-16]

Our initial high-frequency category (≥6) identified 566 patients. This is a rather large number of patients for a small rural hospital to attempt a case management style of intervention.

By further breaking down our visit volume to smaller categories of high-frequency users (≥6 to 11 visits), very high-frequency users (12 to 19 visits), and super users (≥20 visits), we identify increasingly smaller numbers of patients, with increasingly higher associated per patient visit workloads. This allows for a graded series of interventions, perhaps with greater attention to the 35 super users who are responsible for almost 5.5% of annual ED visits (**Table 2**). Less intensive interventions can be designed for the 85 patients who are very high-frequency users (12 to 19 visits) and account for almost 7% of the ED visits (**Table 2**).

Limitations

The setting in northwestern Ontario is unique. The catchment population of 30000 is spread across 31 remote communities in an area the size of France.[12] Most of the remote communities served have no road access to the hospital ED. In these communities, a system of care exists in which urgent care is provided by in-community nurses and emergent care is triaged by a physician in Sioux Lookout arranging a medical evacuation by air. This geographic access barrier likely explains the lower visit per capita ED visit rate of 59.7 per 100 compared with the Huron Country rural visit rate of 89 per 100, but the rate remains higher than the largely urban provincewide rate of 42 per 100 population.[5-7]

These unique regional characteristics make direct comparison of our high-frequency ED users with other rural centres uncertain. Nonetheless, understanding the demographic characteristics, clinical needs, disposition, and pattern of attendance of high-frequency users can clarify hospital service needs in our setting. The data and resultant high-frequency use definition might not be generalizable to other rural institutions. We encourage other rural EDs to see what visit cutoff level nets them the top 10% of frequent users of their ED.

Conclusion

We suggest the definition of high-frequency rural ED use should be 6 or more annual visits. It makes sense to differentiate the definition from that used in large urban ED centres, both because of the different service context and the size of the subset of ED patients subsequently identified. Further identifying intense users of ED services can be achieved with subset categories of very high-frequency users (12 to 19) and super users (≥20). These smaller categories of users allow a graded set of interventions to be considered in a manageable number of patients.

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Contributors
All authors contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests
None declared

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ORIGINAL ARTICLE
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Rates of diabetes-related lower-limb amputation in northwestern Ontario: an incidence study and introduction of a standardized diabetic foot ulcer management protocol

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Introduction: First Nations populations in Canada have higher incidence rates of type 2 diabetes mellitus than the general population and also incur more frequent complications, including lower-leg amputation. Patients with diabetes who present with a foot ulcer are at high risk for macrovascular events, with a 5-year mortality rate of up to 50%.
Methods: Using census and health administrative data, we reviewed the incidence of diabetes and rates of diabetes-related lower-limb amputation in 2010–2013 in the catchment area of the Sioux Lookout Meno Ya Win Health Centre in northwestern Ontario, which serves a largely First Nations population. We also describe a novel protocol for the management of diabetic foot ulcers.
Results: The rate of lower-limb amputation was 7 times the Ontario average and was 3 times higher than in other areas of the province. The Sioux Lookout Diabetic Foot Ulcer Protocol supports timely vascular assessment for concurrent peripheral vascular disease in patients with diabetic foot ulcers.
Conclusion: Patients with diabetes in the Sioux Lookout Meno Ya Win Health Centre catchment area appear to undergo below-knee amputation at a rate 3 times greater than in other Ontario regions. Patients with diabetic foot ulcers should be identified as being at high risk for other atherosclerotic events (e.g., myocardial infarction, cerebrovascular accident) and require aggressive risk-management strategies.

Introduction : Au Canada, les peuples des Premières Nations présentent des taux d'incidence de diabète de type 2 plus élevés que la population générale et ils en subissent également davantage les contrecoups, notamment les amputations des membres inférieurs. Les patients diabétiques qui souffrent d'ulcères pédieux sont exposés à un risque élevé de complications macrovasculaires, et à un taux de mortalité à 5 ans pouvant atteindre 50 %.
Méthodes : À partir des données du recensement et des données administratives sur la santé, nous avons établi l'incidence du diabète et les taux d'amputation des membres inférieurs liée au diabète de 2010 à 2013 dans la zone desservie par le Centre de santé Meno Ya Win de Sioux Lookout, dans le nord-ouest de l'Ontario, qui répond aux besoins d'une population en majeure partie autochtone. Nous décrivons aussi un nouveau protocole de prise en charge des ulcères pédieux diabétiques.
Résultats : Le taux d'amputation des membres inférieurs a été 7 fois plus élevé que la moyenne ontarienne et 3 fois plus élevée que dans d'autres régions de la province. Le protocole de Sioux Lookout pour l'ulcère pédieux diabétique permet une évaluation rapide de possibles maladies vasculaires périphériques concomitantes chez les patients présentant des ulcères pédieux diabétiques.

Conclusion : Les patients diabétiques de la région desservie par le Centre de santé Meno Ya Win de Sioux Lookout semblent nécessiter une amputation sous le genou 3 fois plus souvent que les patients d'autres régions de l'Ontario. Les patients qui présentent des ulcères pédieux diabétiques devraient être reconnus comme exposés à un risque élevé à l'égard d'autres complications athéroscléreuses (p. ex., infarctus du myocarde, accident vasculaire cérébral) et ont besoin de stratégies dynamiques de gestion des risques.

INTRODUCTION

A diabetic foot ulcer may at first glance appear to be a limited foot issue, but it may herald a more serious vascular problem and identify patients with diabetes at higher risk for mortality.

The lifetime risk for development of a foot ulcer in patients with diabetes is estimated at 15%–25%.[1] Patients with diabetic foot ulcers constitute a high-risk atherosclerotic population with significant overall death rates, generally acknowledged to be around 50% at 5 years. The risk of mortality generally increases as the patient progresses through the need for amputation and hemodialysis (Table 1).[2–11] These patients often have underlying peripheral vascular disease, with a prevalence of 50%–70%.[12,13] Neuropathic changes further expose their lower limbs to risk of amputation[14] (Fig. 1).

First Nations populations in Canada are acknowledged to have an incidence of type 2 diabetes mellitus up to 5 times that of the general population.[16] What is less well documented is that First Nations populations also incur more frequent complications, including rates of lower-leg amputation up to 18 times those among the general population.[17]

We examined the incidence of type 2 diabetes and rates of lower limb amputation in the catchment area of the Sioux Lookout Meno Ya Win Health Centre (SLMHC) in northwestern Ontario, which serves a largely First Nations population. We also describe a novel diabetic foot ulcer protocol to encourage aggressive management and risk stratification of patients at risk for amputation and increased mortality.

METHODS

Aggregate data for diabetes and lower limb amputations in patients with type 2 diabetes were retrospectively accessed for a 4-year period (2010–2013) for the catchment area of the SLMHC. Data were collected from the Decision Support Office at the Northwest Health Alliance, a shared health care data service organization. We used data from the

Table 1: Mortality rates for patients with diabetes with foot ulcers, amputation and hemodialysis

Investigator	Diabetes plus	No. of patients	Mortality rate, %
Moulik et al.,[2] 2003	Diabetic foot ulcer	30	44 (5 yr)
Iversen et al.,[3] 2009		155	37 (5 yr)
Søndergaard et al.,[4] 2015		43	36 (1 yr)
Wölfle et al.,[5] 2000	Diabetic foot ulcer, amputation	70	54 (3 yr)
Wölfle et al.,[6] 2001		312	27 (1 yr) 70 (5 yr)
Moulik et al.,[2] 2003		30	44 (5 yr)
Fortington et al.,[7] 2013		299	47 (1 yr) 77 (5 yr)
Wiessman et al.,[8] 2015		174*	33.1 (1 yr)
Wiessman et al.,[8] 2015		142†	45.1 (1 yr)
Hertzer et al.,[9] 2007		29	83 (4 yr)
Leers et al.,[10] 1998	Diabetic foot ulcer, amputation, hemodialysis	31	48 (2 yr)
Orimoto et al.,[11] 2013		234	44.8 (1 yr) 74.5 (3 yr) 76.6 (5 yr)

*Below-the-knee amputation.
†Above-the-knee amputation.

Statistics Canada population census, the Ontario Health Insurance Program diagnoses database and provincial hospital surgical codes to identify catchment population, numbers of adult patients with type 2 diabetes and incidence of below-knee amputation. Provincial statistics record all lower-limb amputations (both minor and major). Trauma- and cancer-related amputations were excluded.

We estimated the adult diabetic population from a 10-year analysis of province-wide physician billing for diabetes or related complications for the population of Sioux Lookout and the 31 northern First Nations communities served by the SLMHC.

Rates of diabetes and amputation were also calculated for 3 relevant provincial Local Health Integration Networks: Central Toronto, North West and North East.

We focused on patients with type 2 diabetes who had undergone below-knee amputation as they are the most common major amputation patient. It seemed more clinically relevant to focus on this major amputation than assessing the provincially tabulated rates of all lower-limb amputations, which include patients who might have repeated toe surgeries, eventually leading to a major amputation. We were able to access data for this single procedure for our catchment area and various Local Health Integration Networks in the province.

RESULTS

The population of the identified catchment area for the SLMHC from the 2013 census data was 22 776, 85% of which was First Nations.[18] The adult (age ≥ 18 yr) population with a diagnosis of diabetes was estimated to be 1585, 11% of the adult population.

The average rate of lower-limb amputation in the adult diabetic population in Ontario over the study period (2010–2013) was 146.5 per 100 000, compared to 1078.5 per 100 000 for the Sioux Lookout diabetic population.

The rate of diabetes-related below-knee amputation was 5.68 per 1000 adult patients, 3 times greater than the rates for other Local Health Integration Networks (Table 2).

The average age at below-knee amputation in the Sioux Lookout diabetic population was 50.2 (standard deviation [SD] 8.7) years, compared to 64.0 (SD 2.3) years in the Central Toronto, North West and North East Local Health Integration Networks.

The sex distribution was predominantly male (75.0%), as in other provincial regions.

DISCUSSION

The rate of lower-limb amputation in the adult diabetic population in the SLMHC catchment area in 2010–2013 was 7 times the provincial rate and was 3 times that in other areas of the province.

This high rate does not appear to be an anomaly. A 2012 Institute for Clinical Evaluative Sciences study also showed that northwestern Ontario had the highest regional rate of diabetes-related total lower-limb amputations (major and minor) in the province between 2006 and 2010.[19]

Lower-limb amputation occurred at an earlier average age in our studied population than in the general Canadian population[20] (50.2 [SD 8.7] yr v. 67 [SD 13] yr). Multiple factors may be at play: potentially more aggressive disease (peripheral vascular disease, type 2 diabetes), late presentation of diabetic foot ulcer, limited access to foot care services including inadequate monitoring, and variable investigation and treatment plans owing to limited resources and/or lack of clear clinical guidelines. Host susceptibility (e.g., cardiovascular risk factors, including smoking, and nutritional status) and broader social determinants of health are all relevant, potentially contributing factors.

Interestingly, geography may be protective. In a 2007 study of Manitoba First Nations, Martens and colleagues[17] identified a rate of type 2 diabetes 4 times that among the general population. They described population-based amputation rates 18 times those of the rest of the province. They also found that the more remote First Nations communities fared better, with lower amputation rates and more medical referrals. Those authors postulated that the system of integrated community-based and visiting health care providers (i.e., J.A. Hildes Northern Medical Unit) lowered barriers to accessing care and improved care for patients with diabetes.

Most of the Canadian literature on diabetic foot ulcers in Canadian Aboriginal populations comes from Manitoba.[21–23] Two retrospective reviews showed that Aboriginal Manitobans experienced higher rates of type 2 diabetes and a higher mean number of foot ulcers per patient and of diabetes-associated lower-extremity amputations than their non-Aboriginal counterparts.[21,23] A cross-sectional study of patients with diabetes from 1 First Nations community showed a disproportionately high rate of emergency department visits for complications of foot ulcers and relatively low availability of preventive foot and wound care services.[22]

Reid and colleagues'[22] 2006 study of 169 northern Manitoba Aboriginal patients showed an incidence of diabetic foot ulcers of 5% and the startling fact that 64% of the patients they studied were unable to perform their own foot surveillance. The patients received an average of 0.7 foot examinations annually over a 7-year period. In 2008, Rose and colleagues[21] concluded that the absence of home care services on reserve, inadequate footwear and limited access to foot care services contributed to foot ulcer development.

Similar trends are seen internationally. A 10-year retrospective study of diabetes-associated major amputations at a hospital in northern Queensland, Australia, showed disproportionately high amputation rates among Indigenous

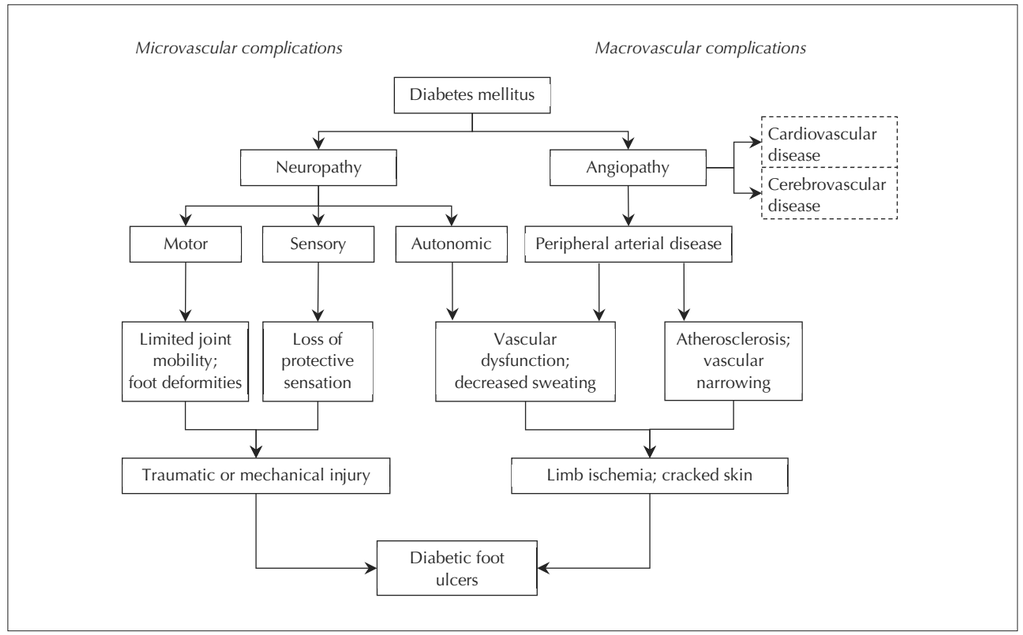


Fig. 1. Pathogenesis of diabetic foot ulcers (adapted from Alavi and colleagues[15]).

Table 2: Population data, rate of amputation and characteristics of patients with type 2 diabetes mellitus in the Sioux Lookout Meno Ya Win Health Centre catchment area and in 3 Ontario Local Health Integration Networks (LHINs), 2010–2013

Variable	Sioux Lookout Meno Ya Win Health Centre catchment area	3 Ontario LHINs[19]
Population*	22 776	–
Population aged ≥18 yr, no. (%)	14 384 (63)	–
Population aged ≥18 yr with type 2 diabetes mellitus, no. (%)	1585 (11)	Central Toronto (7) North East (10) North West† (9)
Rate of below-the-knee amputation per 1000 adult patients with diabetes	5.68	Central Toronto 1.81 North East 1.45 North West 3.13
Age at below-the-knee amputation, mean ± SD, yr	50.2 ± 8.7	64.0 ± 2.3 for all 3 LHINs
Male/female ratio of patients who underwent below-the-knee amputation	75/25	74/26 for all 3 LHINs

*2013 population census.
†The population of the Sioux Lookout Meno Ya Win Health Centre catchment area is a subpopulation of the North West LHIN and contributes to the latter's rate.

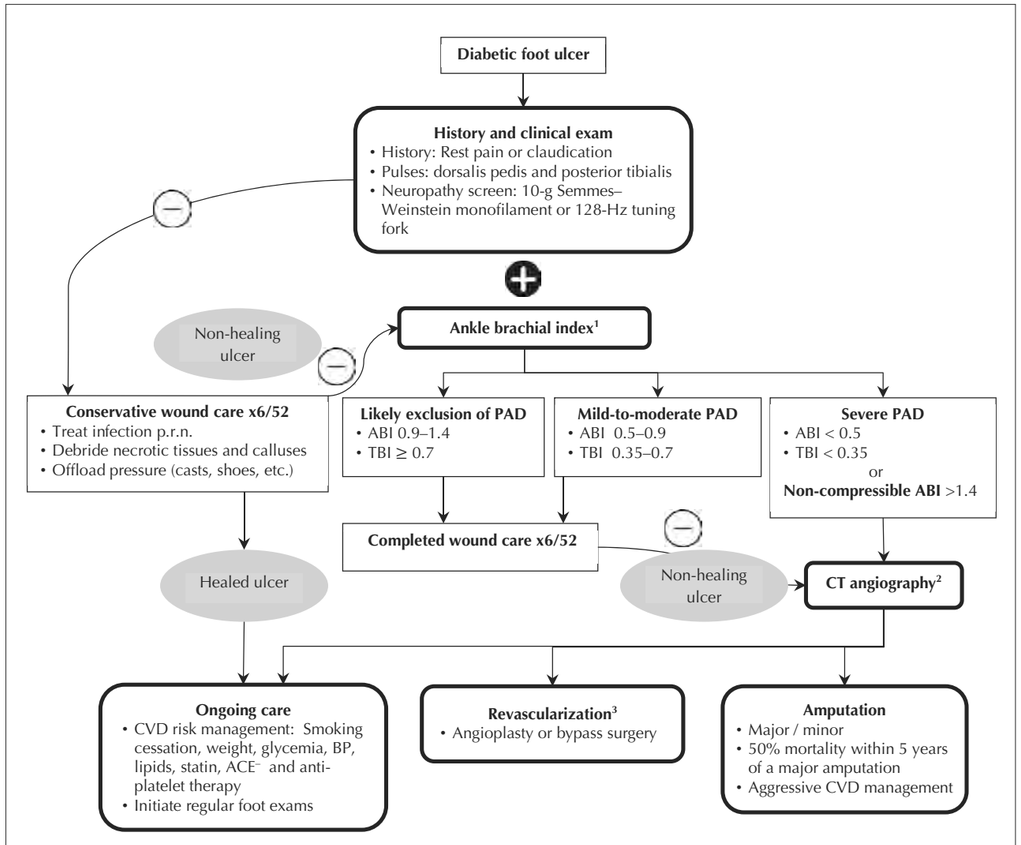
Australians.[24] Indigenous patients were, on average, 14 years younger than their non-Indigenous counterparts at the time of amputation. Our study reproduced this pattern, with below-knee amputation occurring 10–14 years earlier in our studied population. A US study of 1074 Aboriginal patients showed lower-limb amputation rates to be 3 times the national rate, with a hemoglobin A_{1c} level of 9.5% or higher.[25]

We found a male predominance (75%) in patients undergoing below-knee amputations. This is a common finding, for unknown reasons. A similar pattern exists in Canada-wide data, where males were more than twice as likely as females to undergo below-knee amputation.[20]

Sioux Lookout Diabetic Foot Ulcer Protocol

In response to such high amputation rates, we examined guidelines for management of diabetic foot ulcers, the common precursor to a diabetes-related lower-limb amputation. The International Working Group on the Diabetic Foot (http://iwgdf.org/guidelines/guidance-on-pad-2015/) guidelines were the most evidence-based and recommend early vascular assessment in patients with foot ulcers, especially patients whose ulcers fail to heal over 6 weeks.[13] Unfortunately, most of the working group's strong recommendations were supported by weak evidence.

We searched MEDLINE and Embase (January 2005–May 2016) for the MeSH search term "diabetic foot" combined with "arterial occlusive diseases" or "peripheral vascular disease"). We found 63 citations but none that described evidence that aggressive management of foot ulcers prevented amputation or conclusive evidence that any specific diabetic foot ulcer protocol improved outcomes. On discussion with clinicians, we were struck by the variety of approaches taken with patients with foot ulcers. Even in focused tertiary care centre "diabetic foot clinics," clinicians had different thresholds for ordering imaging investigations for concomitant peripheral arterial disease. We felt that describing a reasonable approach that organized investigations for concomitant peripheral vascular disease and coronary artery disease would at least standardize management of diabetic foot ulcers.



ABI = ankle brachial index, ACE = angiotensin-converting enzyme, BP = blood pressure, CTA = computed tomographic angiography, CVD = cardiovascular disease, MR = magnetic resonance, PAD = peripheral artery disease.

1. Toe-brachial index (TBI), if ABI > 1.4 (incompressible, unreliable ABI result). If ABI results remain unclear, proceed to CTA. Many authors suggest ABIs for all diabetic foot ulcer patients; additional testing may include transcutaneous oxygen pressure (TcP02).
2. Vascular surgery consideration requires angiography: CTA (other tests include MR angiography, intra-arterial digital subtraction angiography, and duplex ultrasound.
3. Contraindications to revascularization: unsuitable lesions, unsalvageable limb, patient frailty/short life expectancy.

Fig. 2. Sioux Lookout Diabetic Foot Ulcer Protocol.

The purpose of the Sioux Lookout Diabetic Foot Ulcer Protocol (Fig. 2) is 2-fold. The first is to identify a time frame for conservative wound management (6 wk), after which vascular assessment is suggested. The second is to identify the patient with a foot ulcer as being at high risk for other, extensive arterial disease. Patients who have comorbid peripheral, coronary or cerebral arterial disease would likely benefit from a risk-management approach. The protocol includes clinical history-taking, physical examination and risk-management components as well as vascular imaging, treatment of peripheral vascular disease and referral suggestions.

A history of claudication or pain at rest may indicate vascular compromise, whereas an easily palpable pedal pulse likely excludes serious arterial disease.[15] Many authors, however, recommend that all patients with diabetic foot ulcers receive an ankle–brachial index test at presentation.[26] This easy bedside Doppler examination uses the ratio of arm and leg pressures measured with a blood pressure cuff (Fig. 3); a small cuff can also be attached to a toe to perform a toe–brachial index test, which can correct for a false-negative result of an ankle–brachial index text (e.g., an ankle–brachial index > 1.4 suggests incompressible ankle arteries).[27] Any ankle–brachial index outside the normal range (0.9–1.4) necessitates further assessment (toe–brachial index test and/or computed tomography angiography). A low ankle–brachial index identifies vascular compromise, and a value above the normal range denotes a calcified and incompressible vessel; both necessitate further vascular assessment.

Patients with abnormal clinical findings or ankle–brachial index, or delayed foot ulcer healing require anatomic imaging. Computed tomography angiography may be the most readily available in some rural Canadian locations. Other angiographic imaging includes digital subtraction angiography or magnetic resonance angiography, both of which require contrast medium and may be nephrotoxic.[12] The sooner poor vascularization is identified, the better, as nutrient-deprived ulcers heal poorly (Fig. 4).

Macrovascular risk management is also suggested for all patients with diabetic foot ulcers. In a recent Ontario study, 791 patients with peripheral

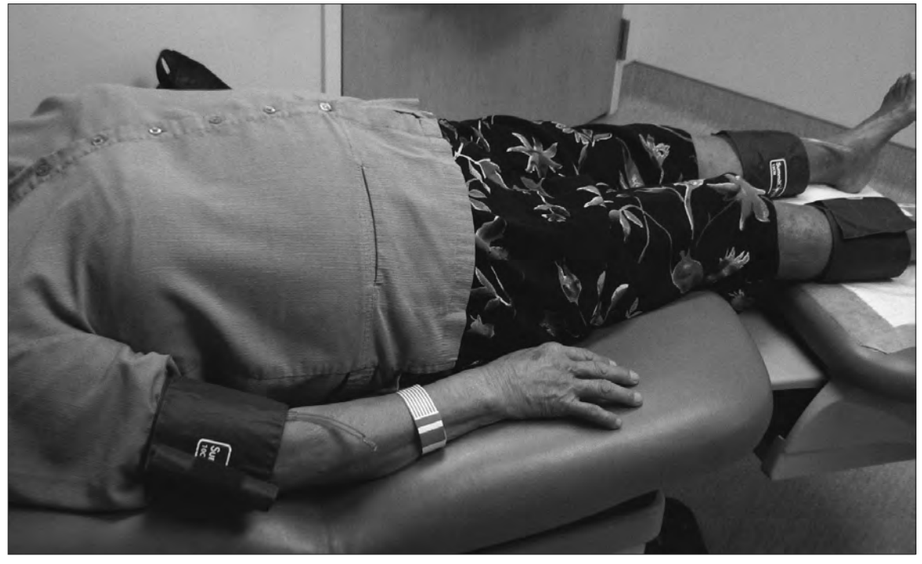


Fig. 3. Bedside Doppler examination uses ratio of arm and leg pressures measured with blood pressure cuff.

vascular disease (25% of whom were diabetic) were followed for 7 years.[28] The authors focused on 8 management categories: use of statins, angiotensin-converting-enzyme inhibitors and antiplatelet medications, and attention to smoking, weight, blood pressure, and lipid and glycemic control. They showed a 40% relative reduction in death, myocardial infarction and cerebrovascular accidents (adjusted hazard ratio 0.63, 95% confidence interval 0.13–0.54) and a 53% relative reduction for major amputations (adjusted hazard ratio 0.47, 95% confidence interval 0.29–0.77).

Wound management at our facility consists of measurement of the ulcer and débridement of both callus and devitalized tissue. Since there is such an array of wound care products, we have standardized ulcer management to the use of medical honey (Medihoney, Derma Sciences) under a dressing.[29] The Society for Vascular Surgery recommends expected healing as a 50% reduction in ulcer size after 4 weeks of conservative management.[30] Offloading with full-contact casts or boot/inserts may further benefit healing of plantar foot ulcers.[30]

This protocol may help standardize vascular assessment in patients with diabetic foot ulcers and, it is hoped, serve as a reminder that acetylsalicylic acid, statins and blood pressure control would benefit these patients even if they are not applied directly to the foot!

Limitations

Census data are not always accurate, particularly when enumerating numerous remote communities. Although other estimates of the population exist, we used census data in this study as it allowed us to make reliable comparisons to other regions of Ontario. We believe the population estimate may be underreported, owing to occasional community nonparticipation in census activity and remoteness. This would overestimate amputation rates to some degree but would not alter the underlying message that the rate of major amputation is very high in adult patients with diabetes in our catchment area.

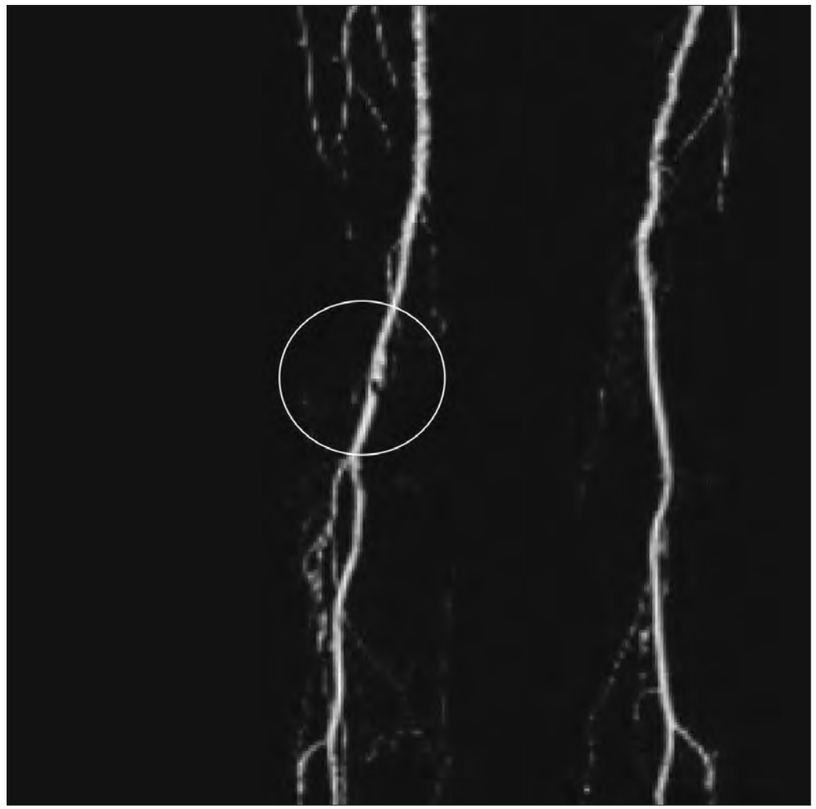


Fig. 4. Computed tomography scan showing 90% narrowing of right superficial femoral artery proximal to knee.

CONCLUSION

Patients with diabetes in the SLMHC catchment area appear to undergo major below-knee amputation at a rate 3 times greater than in other Ontario regions. Patients with diabetic foot ulcers are at high risk for arterial disease in the affected limb as well as for cardiac and cerebral events and death.

Poorly healing diabetic foot ulcers may be the first indication that a patient needs vascular assessment and aggressive management of cardiovascular disease risk.

We have developed a protocol that we hope will increase early detection of vascular compromise and assist in healing of diabetic foot ulcers and limit amputation. A prospective study to evaluate the application and outcomes of the protocol is planned.

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Competing interests: None declared.

Honey of a Wound:

The Use of Medical Honey to Heal Diabetic Foot Ulcers in a Low-resource Environment

By Katherine Kivi, BScN RN, CDE, CFCN; Cynthia Dwyer, BN RN, CFCN and Bradley Lance, RN

The following is a case report of two First Nations clients from remote, fly-in communities in northwest Ontario that illustrates the efficiency of medical honey and simple dressing methods in healing diabetic foot ulcers. Remote communities face significant health challenges, including limited access to specialty wound care and dressing supplies. In this case, the dressing choice, which can be administered at home or at a remote nursing station, resulted in complete closure of two serious foot ulcers.

Diabetes care can be accessed at Sioux Lookout Meno Ya Win Health Centre (SLMHC) in Sioux Lookout, Ontario. The hospital provides primary and preventative health care for a region that extends from Hudson Bay to Lake Superior. This vast area encompasses approximately 360,000 square kilometres of land and has the lowest population density in Ontario. More than two-thirds of the residents (77.8%) identify as First Nations people.[1] Most of the communities are accessible only by airplane or winter road. Type 2 diabetes has reached epidemic levels in First Nation populations, in which adults are three times more likely to have type 2 diabetes than non-indigenous Canadians.[2,3] Two registered nurses at SLMHC provide wound care for the population of 29,000. Many of our clients arrive by plane from more than 300 kilometres north of SLMHC.

Clinical methods need to be practical and easily managed in our environment, where, due to transportation limitations, we can only follow up with most patients every two weeks. Nursing station nurses and/or family members perform dressing changes and treatment in the interim. We have achieved success using medical honey as a diabetic foot ulcer (DFU) healing agent. Natural honey is a viscous, supersaturated sugar solution derived from nectar gathered and modified by the honeybee.[4] Medical honey is natural honey gamma-irradiated to eliminate any *Clostridium botulinum* contamination. Honey is acidic (pH of 3.2 – 4.5), and its antimicrobial properties have resolved MRSA and *Staphylococcus aureus* infection in wounds.[5,6] The anti-inflammatory effect of honey results in reduced wound exudate, edema and scarring.[7] Our methods promote ease of dressing changes, wound closure and client stated satisfaction.

Adding Honey to the Mix

The key features of our wound care method are the use of medical honey, conservative sharp wound debridement (CSWD) and simple wound coverings. The dressing components are inexpensive, and the nurses in the diabetes programs are qualified to perform CSWD. The use of medical honey at SLMHC was initially promoted in 2008 and implemented hospital-wide in 2010.

Two Cases

Two First Nations clients were asked to participate, and signed consents were obtained. Ethical approval was received by SLMHC Research Review and Ethics Committee. Names have been altered for confidentiality.

Lydia

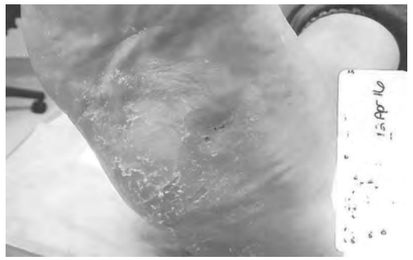
"Lydia" is a 55-year-old First Nations woman with a right plantar DFU complicated by Charcot foot. She lives in a fly-in-only community north of SLMHC. Lydia has type 2 diabetes, hypertension and hyperlipidemia. She was experiencing pain and edema in her right foot with increased symptoms on ambulation. The doctor's examination at the remote nursing station found a large mid-plantar callus, mild diffuse erythema of the forefoot and back pain. Oral clindamycin was prescribed.

Wound management began at SLMHC in November 2015. The callus was reduced with CSWD, revealing a diabetic foot ulcer 1.9 cm (length) x 0.9 cm (width) x 0.3 cm (depth). Local wound care included cleansing with normal saline, applying a small amount of honey and covering with an absorbent pad dressing (9 cm x 10 cm) secured with tape. A high, post-op, closed-toe offloading shoe was provided. Lydia returned home with orders for dressing changes every two days at the nursing station. With each return trip to SLMHC, CSWD was performed if required. Dressing supplies were sent home with Lydia each time. The wound on Lydia's right Charcot foot was healed in March 2016.

Successful resolution of her DFU was achieved through early detection of a serious wound, timely retrieval of the client from a remote community, specialized wound care in a rural hospital and consistent follow-up. Lydia's attendance at regular dressing changes and diligent offloading of the foot were significant contributions (see Figures 1 and 2).

Figure 1: "Lydia" – Before

Figure 2: "Lydia" – After



Joseph

"Joseph" is a 64-year-old First Nations man with a left first metatarsophalangeal joint ulcer. He lives in a community north of SLMHC. Joseph has type 2 diabetes, hypertension and peripheral neuropathy. Management of Joseph's DFU began in February 2016. The wound was covered by a substantial callus over a pad of exposed fat and granular dermis. After CSWD, the wound measured 5 cm (length) x 3 cm (width) x 0.3 cm (depth). A cut-to-size piece of povidone-iodine-impregnated dressing was applied to the open area for two weeks, after which a thin application of medical honey was substituted. The choice of using 7 mm compressed felt to offload the plantar surface or a high, post-op, closed-toe offloading shoe was client-driven. The dressing was changed every two days at the remote nursing station. Joseph attended our wound clinic every second week as per travel allotment policy. CSWD was performed if required. Healing was evident at each visit, with the wound closing in April 2016.

How Honey Works in Wounds

The knowledge that *Klebsiella* and *Enterobacter* bacteria have been shown to be resistant to silver-impregnated dressings may indicate a need to return to natural antibacterial products that promote wound healing.[8–10] Honey is a traditional medicine used since ancient times, and its place in the history of human healing practices is readily accepted by our clients.[6,8] The antimicrobial properties of honey include high sugar concentration, low pH, the presence of hydrogen peroxide, methylglyoxal, antimicrobial peptide bee defensin-1 along with oxidase, and other compounds such as polyphenols and flavonoids from plant nectar.[6,12,13]

The high sugar/low moisture content of honey causes osmotic stress to microbial cells. Low pH is unfavourable for the growth of many micro-organisms. No bacteria are known to be completely resistant to the effects of honey.[6,12,13] Research by Camplin and Maddocks did identify some honey resistance by *Pseudomonas aeruginosa* in biofilm.[13] This illustrates the importance of periodic wound culturing to appropriately identify any pathogens in a wound. The authors' advise, "where recalcitrant or chronic, infected wounds are present it remains vital to ensure that topical treatments such as manuka honey are appropriately applied for a suitable length of time in combination with other antimicrobials where necessary to ensure that infection is resolved and the likelihood for resistance is minimised."[13]

Bowling et al. state that "the risk of MRSA infection and bacteremia in patients with colonized ulcers is recognized."[14]

Topical honey use has no known systemic effects.

Conclusion

Our clients often welcome the possibility of returning home with a dressing routine using simple, effective supplies. Sood et al. observe that "there is an overwhelming amount of wound dressings available in the market [which] implies the lack of full understanding of wound care and management . . . honey can inhibit biofilms of various species, is non-cytotoxic [and] a non-irritant with very low risk of client sensitization."[10]

Complex and/or expensive dressings are not readily available in northern nursing stations.

A 10 g tube of medical honey costs about $4. The absorptive adherent dressing we use costs less than $3, and our most basic dressings are only 12 cents each. These items are of practical use in a low-resource environment.

The ability to effect wound closure in clients with a diabetic foot ulcer living in remote communities, relying on inexpensive supplies that are easy for the clients to use when away from professional care, is an important outcome in wound care provision.

Self-care at Home

Each client and/or escort/family member is shown how to apply the dressing during the initial visit. Then the client is asked to demonstrate to the nurse how to apply the material to the wound. The client is given the time to reapply the dressing until comfortable with the process. Due to the simplicity of the dressing, most clients only require a one-time demonstration.

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Food-dependent exercise-induced anaphylaxis

Bryanne Minty MD CCFP

Exercise-induced anaphylaxis (EIA) is a rare disorder in which individuals develop immunoglobulin E (IgE)–mediated hypersensitivity in conjunction with exercise, causing anaphylaxis. The lifetime prevalence of EIA is about 0.05%. About 30% to 50% of EIA is food dependent, only occurring with the combination of a specific food and exercise.[1-5] In these patients exercise or food on their own do not cause anaphylaxis; only in combination do they trigger the reaction. The case presented here describes a rare life-threatening diagnosis in a previously well 22-year-old female jogger. Results of standard allergy testing were noncontributory. This case is unique because there are likely multiple triggers that in combination with exercise contribute to the patient developing the anaphylactic reactions. Diagnosis is made by a careful history and an awareness of the combination of food triggers and EIA. Prevention includes avoidance of the combined potential triggers and carrying an epinephrine autoinjector.

Case

A female patient presented after anaphylactic reactions at the ages of 19 and 22 years with unidentified triggers while jogging. The first event occurred in the spring after eating a salad with scallops and shrimp. She reported abdominal cramping within 5 minutes of starting her jog, then within 30 minutes she developed nausea, facial swelling, diffuse pruritus, and difficulty breathing. A passer-by called an ambulance and the patient lost consciousness. On presentation at the emergency department she had profound hypotension and bradycardia. Emergency treatment included epinephrine, intravenous fluids, steroids, antihistamines, and H_2 antagonists. Epicutaneous testing several weeks later revealed a positive reaction to dust mites and mild reactions to spring tree pollen, banana, avocado, and tomato; she did not react to any shellfish, including shrimp and scallops.

The second event occurred while exercising, again in the spring season, after eating curry with vegetables, shrimp, and white fish. She had been jogging for 45 minutes when she developed facial swelling and hives. In the emergency department she also had an episode of emesis and again was profoundly hypotensive. Subsequent repeat allergy testing showed positive reactions to dust mites, cats, birch, maple, rats, oak, elm, and grass. The foods she was tested for that resulted in negative reactions included the most common food triggers: egg, wheat, fish, shrimp, and peanuts. Also, at this time she had a pet rat in her house.

Discussion

To assess the literature MEDLINE was searched from 2000 to 2015 using the MeSH terms *exercise* and *food hypersensitivity* and *anaphylaxis*, identifying 134 articles.

Many different types of foods have been shown to cause food-dependent exercise-induced anaphylaxis (FDEIA), including wheat, shellfish, nuts, tomatoes, peanuts, fish, pork, beef, mushrooms, hazelnuts, eggs, peaches, apples, milk, and alcohol.[1,2] There are also reports in which the ingestion of 2 foods together along with exercise are required to trigger a reaction.[1] Nonfood combination triggers reported include medication (nonsteroidal anti-inflammatory drugs), cold or warm temperatures, menstrual cycle, pollens, and ingestion of dust mites.[1,2] Interestingly, these nonfood triggers are usually cofactors that appear to enhance the anaphylactic reaction but that do not cause the reaction on their own.

EDITOR'S KEY POINTS

- Food-dependent exercise-induced anaphylaxis is rare, and findings of allergy testing might be negative. Particular food triggers are benign unless combined with exercise.
- Prevention involves avoiding the combination of the trigger food and exercise, allowing 4 to 6 hours for digestion of the known trigger food before exercise, and carrying an epinephrine autoinjector during exercise. Treatment includes immediate intramuscular epinephrine injection and emergency department assessment.

POINTS DE REPÈRE DU RÉDACTEUR

- L'anaphylaxie de source alimentaire déclenchée par l'exercice est rare, et les résultats des tests d'allergie pourraient être négatifs. Certains déclencheurs alimentaires sont bénins, à moins d'être combinés à des activités physiques.
- Pour la prévenir, il s'agit d'éviter la combinaison de l'aliment inducteur et de l'exercice, d'attendre 4 à 6 heures pour que soit digéré l'aliment déclencheur connu avant de faire de l'exercice et de se munir d'un auto-injecteur d'épinéphrine pendant l'activité physique. Le traitement comporte une injection intramusculaire immédiate d'épinéphrine, suivie d'une évaluation à l'urgence.

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Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2017;63:42-3

There is no definite evidence for what mechanisms trigger the allergic reaction, but several proposed mechanisms might help to explain FDEIA. One of the proposed theories is that IgE cross-links with a specific food allergen and, when combined with exercise, it lowers the threshold for mast cell degranulation, histamine and vasoactive mediators are released, and this in turn leads to anaphylaxis.[2,4] Two other proposed mechanisms include changes in pH that might be a trigger for FDEIA[1] and that exercise increases blood flow to muscle, while decreasing circulation to gut mucosa, thus exposing more muscle tissue mast cells to the allergen.[1,4] The reaction usually occurs within the first 30 minutes of starting physical activity.[1] Symptoms include pruritus, cough, chest tightness, angioedema, urticaria, wheezing, and gastrointestinal complaints.[1]

Treatment of EIA and FDEIA involves the same emergent care as for other causes of anaphylaxis (epinephrine, antihistamines, H_1 and H_2 blockers, inhaled bronchodilators, and steroids as needed). Any patient who has self-administered epinephrine should still seek immediate medical care for further monitoring and treatment, as the anaphylactic reaction might have ongoing life-threatening effects.[2] Further preventive treatment of FDEIA involves avoidance of exercise for 4 to 6 hours after ingesting the known food trigger, carrying an epinephrine autoinjector during exercise, lowering the intensity of exercise, and avoiding exercise in extreme weather conditions such as hot and humid or cold temperatures.[4] Taking medications such as antihistamines or H_2 blockers before exercise is still a controversial topic, as there is currently inadequate evidence to support prophylactic treatment.[2,5] A case study described a successful trial of prophylactic omalizumab in a 14-year-old boy with refractory FDEIA. This relatively new recombinant DNA monoclonal antibody, which binds to IgE and mutes its activity in type I allergic reactions, was taken before exercise and reduced this patient's anaphylactic reactions.[6] Another case study in a 47-year-old Japanese man showed administration of misoprostol (a prostaglandin E_1 analogue) before exercise decreased his wheat-dependent anaphylactic reactions, perhaps owing to upregulation of gastrointestinal breakdown of allergic particles.[7]

Conclusion

The patient in this case is a young woman with FDEIA with an unknown trigger. Treating physicians presumed a combination of spring pollen, seafood, and exercise to be the trigger. She has since avoided any exercise for a minimum of 4 to 6 hours after consuming any fish or seafood. As the reactions occurred with both finned fish and shellfish, she was advised to avoid both possible triggers before exercise. She has not had any further anaphylactic reactions and she carries an epinephrine autoinjector while exercising. If she develops recurrent reactions, it might be reasonable to consider prophylactic exercise treatments such as omalizumab or misoprostol for this rare condition.[6,7]

Dr Minty is a staff physician at the Sioux Lookout Meno Ya Win Health Centre and undertook this report while a resident in family medicine at the Northern Ontario School of Medicine in Sioux Lookout.

Competing interests
None declared

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Original Article
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Interlaminar epidural steroid injections for low back pain in rural Ontario

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Introduction: We sought to document the efficacy of interlaminar epidural steroid injections (ESIs) for the relief of low back pain in a rural population.
Methods: We conducted a prospective observational cohort study with brief follow-up telephone interviews at 1, 3 and 6 months after interlaminar ESI.
Results: A total of 47 ESIs were administered to the 24 participants. In an intention-to-treat analysis, pain relief was achieved in 78.7%, 55.3% and 27.7% of participants at 1, 3 and 6 months.
Conclusion: Interlaminar ESIs, without fluoroscopic guidance, were effective for up to 3 months of symptom relief.

Introduction : Nous avons cherché à déterminer l'efficacité des infiltrations épidurales interlaminaires de stéroïdes pour réduire la lombalgie chez une population rurale.
Méthodes : Pour ce faire, nous avons mené une étude de cohorte observationnelle prospective au moyen de brèves entrevues téléphoniques de suivi après 1, 3 et 6 mois.
Résultats : Au total, 47 infiltrations épidurales ont été administrées à 24 participants. Dans le cadre d'une analyse par intention de traiter, 78,7 %, 55,3 % et 27,7 % des participants ont rapporté un soulagement de la douleur à 1, 3 et 6 mois, respectivement.
Conclusion : Les infiltrations épidurales interlaminaires sans guidage fluoroscopique peuvent procurer un soulagement des symptômes pendant jusqu'à 3 mois.

INTRODUCTION

Radicular low back pain (lumbar pain with neurologic signs and symptoms) constitutes 4%–5% of cases of back pain seen by general practitioners.[1] Because this subgroup of patients with low back pain includes those who may need surgical referral or intervention, they merit a particular focus.

Clinical findings and radiographic imaging allow us to categorize these patients into those with lumbar disc herniation (LDH) and/or lumbar spinal stenosis (LSS). Degree of pain does not consistently correlate with severity of imaging-detected spinal pathologies, and most initial episodes resolve with conservative treatment.[2,3] The frequency of spontaneous resolution varies according to diagnosis, with symptoms improving without operative intervention in 80% of patients with LDH and up to 45% of patients with LSS.[4]

Lumbar disc herniation involves mechanical compression from herniated disc material, whereas LSS encompasses the degenerative narrowing of the central canal, lateral recess or neural foramen.[4] In both cases, inflammation is widely believed to play a causal role in instigating radiculopathy.[2,3,5–9] Epidural steroid injections (ESIs) may therefore have a role in the treatment of radicular low back pain, after the failure of conservative management.[3,4,6–8]

There are 3 primary methods for the injection of corticosteroids into the epidural space: caudal, transforaminal and interlaminar ESI.[7,10–12] Caudal ESI involves the injection of medication through the sacral hiatus, transforaminal

ESI uses the neural foramen to target a specific nerve root and interlaminar ESI enters the epidural space between the laminae.[6,7,10,11,13] Although transforaminal ESI is generally considered the most effective, its safety profile mandates the use of fluoroscopic guidance, which may not be feasible in a rural setting.[4,6,7,12,14,15] Interlaminar ESI, on the other hand, is also considered effective and can be administered without real-time imaging guidance.[6,11,12,16–22] The technique is similar to that used by rural generalists performing lumbar punctures and by rural general practitioners and anesthesiologists for epidural analgesia during labour.[11,15]

Although widely considered safe,[15,22,23] the value of ESI as a clinical practice remains a subject of debate. Some literature supports the efficacy of ESI for short-term pain reduction,[23,24] other publications point out important flaws, such as a lack of cost-effectiveness, the absence of substantial improvement and — in 1 case — the worsening of outcomes.[9,25–27] Most research findings fall in between these 2 conclusions.[28–31]

This prospective study investigates the efficacy of interlaminar ESIs in treating low back pain in a rural population. It is a follow-up to a previous 5-year retrospective study that demonstrated substantial improvement of symptoms following interlaminar ESIs.[15]

METHODS

Setting

The Sioux Lookout Meno Ya Win Heath Centre serves a population of 30 000 in northwestern Ontario.

Data collection and analysis

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

Patients who presented for ESI at an outpatient clinic at the Sioux Lookout Meno Ya Win Heath Centre between October 2011 and December 2014 were invited to participate in this study. Exclusion criteria were local infection or full anticoagulation therapy with warfarin. After informed consent, key demographic characteristics for each participant, as well as the number of previous injections, analgesic usage, history of back surgery and current level of pain using numeric pain scale measures were recorded. Patients were contacted by telephone 1, 3 and 6 months postinjection and asked to rate their current level of pain as less, greater or the same as it had been preinjection. Patients were able to receive subsequent injections if medically indicated.

Data were collected in Microsoft Excel, and analysis was completed with Excel and IBM SPSS (version 20.0 for Windows). Means and frequencies were calculated as appropriate.

Method of injection

Epidural steroid injections were performed by 2 experienced general practitioners/anesthesiologists. Before injection, patients were briefed on the potential risks and benefits associated with the procedure. The interlaminar approach was used without real-time imaging guidance. The patient was seated in lumbar flexion, and the correct level was identified using the iliac crest as indicative of the L3–L4 level. In the case of patients with a history of back surgery, the location of injection was raised or lowered a level accordingly. The subcutaneous injection of 4 mL of 1% lidocaine was followed by the interlaminar advancement of a 17-gauge Tuohy needle and the identification of the epidural space using the loss-of-resistance technique. Then, 1 mL of 80 mg/mL methylprednisolone acetate with 4 mL of normal saline was injected. Instructions for postinjection care were provided.

RESULTS

Study population

Twenty-four patients gave informed consent and were enrolled in the study. Patient characteristics are provided in Table 1. Thirteen (54.2%) were women, and the mean age was 50.4 (standard deviation [SD] 13.3) years. Lumbar disc herniation was the most common diagnosis, occurring in 17 (70.8%) participants, followed by LSS, which affected 16 (66.7%). Eleven (45.8%) patients were diagnosed with both LDH and LSS. On average, each participant had received about 1 ESI before the commencement of the study (mean 0.9, range 0–6 injections). All patients were taking oral analgesics for low back pain at the beginning of the study. Fourteen (58.3%) used narcotics, 10 (41.7%) used acetaminophen and 9 (37.5%) used NSAIDs, with 8 (33.3%) using a combination therapy. Hypertension and diabetes were the most common comorbidities, with each affecting 9 (37.5%) participants. Other observed comorbidities included psychosocial factors (16.7%), coronary artery disease (8.3%) and peripheral vascular disease (4.2%) (Table 1).

Pain relief

A total of 47 ESIs were administered to the 24 participants, with 17 (70.8%) receiving a single injection and 3 (12.5%) receiving 4 or more injections (Fig. 1). The mean score on the numeric pain rating scale before interlaminar ESI was 6.48 (SD 1.94) out of 10. Adverse reactions to treatment were reported after 3 injections; 2 were headaches and 1 was new bilateral radicular pain.

Of those who received a single injection, 3 were lost to follow-up within a month and were excluded from further analysis. Two patients receiving multiple injections were lost to follow-up within a month of receiving a subsequent injection. Of the 42 injections with follow-up data, 37 (88.1%) were associated with reduced pain from baseline after 1 month, and the remainder were associated with no change in level of pain. The number of injections associated with pain relief fell to 26 (68.4%) of the 38 injections with follow-up data after 3 months; again, all remaining injections were associated with no change in pain level. After 6 months, of the 28 injections with follow-up data, 13 (46.4%) were associated with continued pain relief and 2 (7.1%) with increased pain relative to baseline.

In an intention-to-treat analysis (including those lost to follow-up), pain relief occurred in 78.7%, 55.3% and 27.7% at 1, 3, and 6 months (Fig. 2).

Table 1: Characteristics of participants receiving interlaminar epidural steroid injections, *n* = 24

Characteristic	No. (%)*
Age, yr, mean ± SD	50.4 ± 13.3
Sex	
Male	11 (45.8)
Female	13 (54.2)
Radiographic diagnosis	
LDH	17 (70.8)
LSS	16 (66.7)
LDH and LSS	11 (45.8)
Spondylolisthesis	3 (12.5)
Osteoarthritis	3 (12.5)
Back surgery	6 (25.0)
Analgesic use	
Narcotics	14 (58.3)
NSAIDs	9 (37.5)
Acetaminophen	10 (41.7)
Other analgesics	3 (12.5)
Combination therapy	8 (33.3)
No. of previous injections, mean ± SD	0.9 ± 1.5
Comorbidities	
Hypertension	9 (37.5)
Type II diabetes	9 (37.5)
Psychosocial factors (anxiety, depression, drug use)	4 (16.7)
Coronary artery disease	2 (8.3)
Peripheral vascular disease	1 (4.2)

LDH = lumbar disc herniation; LSS = lumbar spinal stenosis; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation.
*Unless stated otherwise.

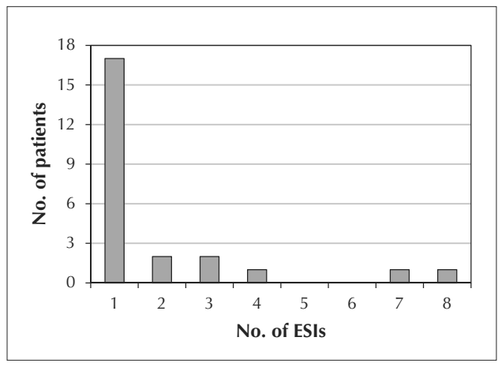

Fig. 1. Number of epidural steroid injections (ESIs) administered per patient during the course of the study (47 ESIs in 24 patients).

DISCUSSION

Our results show that interlaminar ESI, without fluoroscopic guidance, can effectively decrease low back pain for up to 3 months.

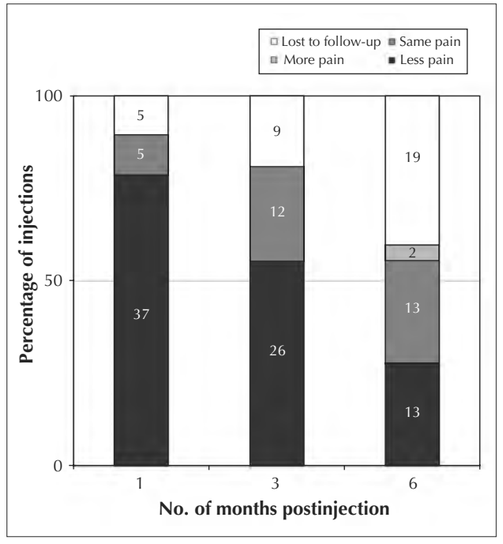

Fig. 2. Outcomes at 1, 3 and 6 months after epidural steroid injection as a proportion of the number of injections (*n* = 47).

Although the analgesic effects of interlaminar ESIs are only short term, there is a lack of consensus in the literature on exactly how short this term is. At one end of the spectrum, Brown[52] found that only 35.3% of patients who received a standard interlaminar ESI experienced effective pain relief after 6 weeks, and Ghai and colleagues[14] reported this percentage to be 16.7% after 6 months.[14,32] Other researchers have found that the effects of interlaminar ESI last at least 6 months,[5,21,22] 3 months,[19] 35 days[16] or 10 days.[20] In a previous retrospective study at our hospital, Mashari and colleagues[15] found that 80% of the 88 patients with follow-up data experienced improvement after receiving an interlaminar ESI. The present study reports a reduction of symptoms for up to 3 months after injection in 55% of patients.

Of the prospective studies found in our literature search, only Rivest and colleagues[17] explicitly described administering interlaminar ESIs in the absence of real-time imaging guidance, making this study of particular interest to the present study.[16–22] The rates of pain relief reported by Rivest and colleagues[17] — with 61% of patients with LDH reporting improvement after 2 weeks compared with only 38% of patients with LSS — are lower than the rates found in both of the studies carried out at our institution.[15,17] This difference could be due to the exclusion of patients who had experienced low back pain for less than 6 months in the study by Rivest and colleagues,[17] given that the effectiveness of ESI diminishes with increasing duration of symptoms.[6,7,17]

Two patients in this study experienced headaches after receiving an interlaminar ESI. This is noteworthy because needle misplacement, which is associated with post–dural puncture headache, is estimated to occur in 8%–40% of interlaminar ESIs administered without real-time imaging guidance.[4,7,23,31,33]

Limitations

This study has a number of limitations, including a small sample and the absence of a control group. Spontaneous improvement of symptoms often happens with LDH and LSS, and this can be erroneously attributed to interlaminar ESI.[4] Also, initial pain assessment was done using numeric pain scale measures, but subsequent telephone follow-up used categorical measures (i.e., pain better, worse or the same). This was done to simplify the nature of the often long-distance follow-up telephone interviews but limited the statistical analysis that could be performed on the data.

CONCLUSION

Interlaminar ESI was associated with pain reduction for up to 3 months for most patients. Interlaminar ESI can be administered in a context where fluoroscopic guidance is not available, such as in remote and rural communities.

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Competing interests: None declared.

DECISIONS

Clicking hip in a postmenopausal woman

Len Kelly MD MClSc, Rajiv Gandhi MD, Anukul Panu MD

A 55-year-old postmenopausal woman experiences intermittent anterior clicking and locking of her hip while walking. The clicking is painful and comes on without warning, causing her to stop walking for several minutes. The patient has no history of trauma and no night pain. She enjoys golf, but now has to ride in a golf cart to complete the round. Initial examination shows a normal range of motion without pain. There is no evidence of femoral or inguinal hernia or localized tenderness consistent with a trochanteric bursitis. Radiographs of her hip appear normal.

What causes of pain should be considered?

The patient's history of intermittent symptoms indicates a mechanical origin of pain. That the patient had normal range of motion without pain on examination is a pertinent negative finding for osteoarthritis. Because there was no evidence of osteoarthritis or metastatic disease on the plain radiographs, nor evidence of hernia (femoral or inguinal), trochanteric bursitis or local inflammation or infection on examination, a labral tear of the cartilage of the acetabulum should be considered.

A labral tear occurs at the relatively avascular proximal portion of the cartilaginous labrum where it attaches to the articular cartilage of the hip joint. It typically presents as anterior mechanical hip pain.

The labrum acts as a seal of the synovial fluid and extends the depth of the joint by as much as 25%. Pivoting in activities such as golf, hockey, soccer and ballet may cause tears.[1,2] Two common types of tears are described: traumatic tears (young athletes) and degenerative tears (early osteoarthritis in older patients).[1,3]

Labral tears may be asymptomatic. In a study involving 70 asymptomatic individuals (mean age 26 yr), a surprising 27 (39%) cases of labral tear seen on high-resolution magnetic resonance (MR) imaging were reported.[4]

Does this patient require any additional assessment on examination?

The clinical assessment for a labral tear involves evocative rotational end-point testing of a flexed hip. This test comprises stressing a 90° flexed hip both in abduction and adduction, and adding internal and external rotation to pinch the torn labrum between the femoral head and acetabular rim (a useful video of how to do a hip examination for a labral tear is available at www.youtube.com/watch?v=Rtp4oz0_3YY). Although painful or palpable clicking may indicate the presence of a labral tear, the physical exam shows low specificity.[3]

What investigations are required if a labral tear is suspected?

An MR arthrogram involving injection of contrast medium into the joint is typically used to identify labral tears[5] (Figure 1). Because a labral tear dis-

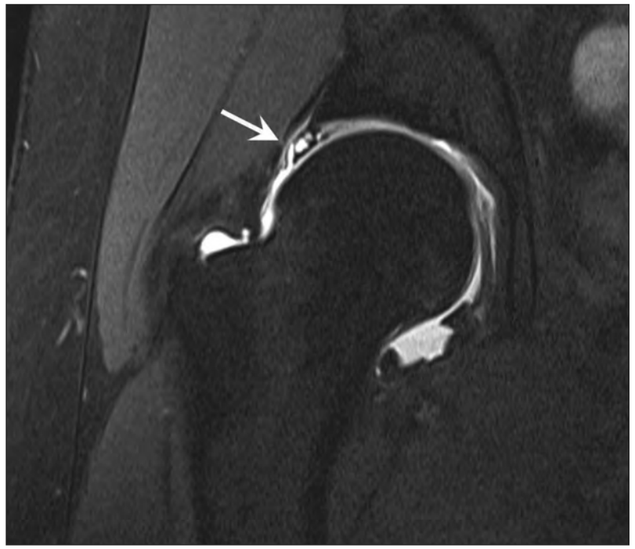

Figure 1: Magnetic resonance arthrogram of the right hip showing a tear of the superior labrum (arrow) with gadolinium contrast dissecting into the tear.

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The clinical scenario is fictional.

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rupts the seal of the synovial fluid within the joint, extravasation of the contrast medium shows the location and extent of the tear. For patients averse to intra-articular injection, high-resolution MR imaging may be a good substitute.[6]

If imaging shows a labral tear, what are the treatment options for this patient?

In this older patient, damage of the adjacent articular cartilage in her hip joint is likely, and labral débridement may not give definitive symptom relief.

Uncontrolled studies have shown that discrete sports-related labral tears may respond to arthroscopic hip surgery in younger athletic patients.[7] However, a Canadian study involving 41 older patients (> 45 yr; mean age 53.7 yr) showed poor results of surgery, with relatively high reoperation rates and minimal improvement in joint-specific and overall quality-of-life measures.[8] The authors of a similar American study involving 30 patients (mean age 63.9 yr) also recommended caution in advising surgery in older patients because of poor two-year overall survival (70%) and a reoperation rate of 37%, most often requiring total hip arthroplasty.[9]

In this patient's age group, a labral tear may be a sign of a deteriorating joint rather than an isolated repairable lesion. Watchful waiting and non–load-bearing exercise may be a good option. Physiotherapy techniques currently include active and deep-tissue release in addition to progressive resisted stretching and strengthening activities.[1] Poor response to conservative treatment and increasing disability may require revisiting surgery as a treatment option.

Case revisited

On further examination, rotational testing of the patient's flexed hip reproduced a painful click. The patient decided to proceed with an MR arthrogram, which showed a labral tear. Given the poor results of surgery in her age group, the patient decided not to consider surgery at this point and will seek conservative treatment with physiotherapy to maximize her overall flexibility and strength.

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Decisions is a series that focuses on practical evidence-based approaches to common presentations in primary care. The articles address key decisions that a clinician may encounter during initial assessment. The information presented can usually be covered in a typical primary care appointment. Articles should be no longer than 650 words, may include one box, figure or table and should begin with a very brief description (75 words or less) of the clinical situation. The decisions addressed should be presented in the form of questions. A box providing helpful resources for the patient or physician is encouraged.

The occasional digital nerve block

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This article has been peer reviewed.

In performing regional anesthesia of the fingers and hand, there are several general principles that need to be identified. The first is to relax. Successful blocks get easier with repetition. Most rural physicians do not perform them weekly or monthly, so it may take a while to get comfortable with them, and repeat blocks may be required for any given procedure.

PRELIMINARY PRECAUTIONS

1. Ensure that you have performed and documented any neurologic and vascular assessment before injection. Most injections will be performed with a 25-gauge needle. Because the needle will often be adjacent to an artery, aspiration before injection is needed. Paresthesia on initial needle placement indicates that the needle is in the nerve, and withdrawing slightly until it is absent identifies a safe injection site. Paresthesia does occur (older texts routinely used them as "landmarks"), so be slow and cautious with the pace of the needle insertion and injection.
2. Epinephrine containing anesthetic agents should not be used. There has recently been some debate about this in the fields of orthopedic and plastic hand surgery; a changing practice is developing in which epinephrine is being used along with a local anesthetic.[1–3] This change in practice does not necessarily extend medicolegally to the rural practitioner, when most textbooks still clearly admonish the use of epinephrine, particularly in finger anesthesia.[4,5]
3. The traditional ring block for digital nerve anesthesia is no longer a preferred technique owing to its lower safety profile from the tourniquet effect of anesthetic volume used.[6]
4. Use of lidocaine is common. If multiple injections are used, the toxicity range of 4 mg/kg needs to be considered (e.g., 20 mL total of 1% lidocaine may be toxic for a 50-kg patient if it rapidly becomes intravascular; 10 mL for a 2% solution). Toxicity is less of a concern when instilled into soft tissue, where it will be slowly absorbed and metabolized. Toxicity is more likely to be an issue with a hematoma block, which typically involves use of larger volumes and may function as a rapidly absorbed intraosseous infusion. This toxicity presents with a metallic taste in the mouth and may be followed by a seizure. Bupivacaine is a common, longer-acting equivalent choice for finger and hand anesthesia.

Digital nerve block is not synonymous with ring block.[7,8] Remember that there is a volar and a dorsal digital nerve on each digit. They bifurcate just proximal to the metacarpophalangeal joint, the visible knuckle. Finger anesthesia can be performed in 3 ways: web-space block, metacarpophalangeal block and ring block.

EQUIPMENT

- 25-gauge 3/4-inch needle
- lidocaine

WEB-SPACE BLOCK

This block is the easiest to perform and has been found to be the most effective digital block.[9] Simply insert a 25-gauge,

3/4-inch needle completely into the web space. Insert to a depth of about 1 inch and inject 3 mL of lidocaine (Fig. 1). This will likely reach both aspects of the digital nerve at or near their bifurcation.

Fig. 1. Web-space block: insert to a depth of about 1 inch.

METACARPOPHALANGEAL BLOCK

Metacarpophalangeal block is performed on the dorsum of the hand just proximal to the visible knuckle joint.[10] The needle is entered perpendicular to the skin, behind the visible knuckle, and advanced until the palmar aponeurosis is felt or the palmar skin is tenting. Then instill 3 mL of lidocaine (Fig. 2). Some clinicians enter the skin at an angle and advance the needle toward the web space until the needle is seen tenting there and then inject a similar volume.[7] Some lidocaine can be kept and used when the needle is almost out of the skin to tunnel subcutaneously across the metacarpophalangeal area and deposit a subcutaneous wheal, so that the entry point of the second injection is anesthetized in advance. The other side of the metacarpophalangeal area is entered in the same fashion with another 3 mL of lidocaine instilled.

Fig. 2. Metacarpophalangeal block: enter behind the visible knuckle and aim for the web space at the palm.

RING BLOCK

Because there is no place for fluid to expand as in the previous approaches, this commonly employed method may leave the patient exposed to a potential compartment syndrome.[7,8] Use it cautiously and not at all in patients with poor vascular health. The classic approach is 1–1.5 mL of lidocaine on each side of the digit.[11] The needle enters the dorsal finger skin just distal to the web space and the 1-mL volume is injected, partly at the dorsal branch and then further advanced to the volar branch of the digital nerve. The needle basically slides along the side of the finger as each nerve receives an injection. The total volume in the finger should total 3 mL or less (Fig. 3).

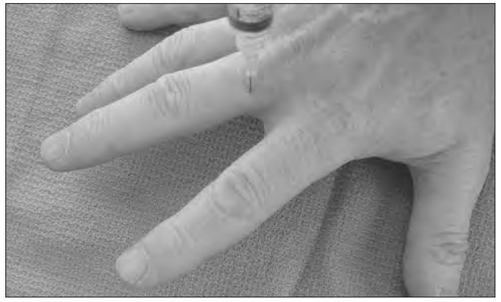

Fig. 3. Ring block: move the needle to reach both the dorsal and volar branches of the digital nerve.

Competing interests: None declared.

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The occasional regional nerve block of the hand

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This is the second of 2 articles on regional hand anesthesia. The general concepts are described in "The Occasional Digital Nerve Block."[1]

This article describes nerve blocks at the wrist for the median, ulnar and radial nerves. As with all procedures, our performance can improve over time, if we take our time. Also, an inadequate regional nerve block at the wrist may be supplemented with a related digital nerve block or local infiltration when required.

EQUIPMENT LIST

- 25-gauge 1.5-inch needle
- 1% or 2% lidocaine or bupivacaine
- 5 mL syringe

MEDIAN NERVE BLOCK

The median nerve block is useful for working on the middle and ring fingers and uses a similar technique to carpal tunnel injection. Inject 3–5 mL lidocaine at the wrist flexor crease between the palmaris longus and flexor carpi radialis muscles (Fig. 1). Withdraw the needle and deposit a 2 mL subcutaneous bleb above the palmaris longus muscle to anesthetize the superficial branch as well.[2] One of the simplest explanations I encountered in researching this article was to proceed slowly to the bone just to the thumb side of the palmaris longus, back up 1–2 mm and inject if there are no paresthesias.[3] If paresthesias are encountered, back up a bit more and redirect the needle. Do not inject in the presence of an ongoing paresthesia (Fig. 2).

ULNAR NERVE BLOCK

The ulnar nerve block, used for repair of the little and ring fingers, can be done in 3 ways. The first 2 methods — traditional and medial approaches — require aspiration before injection owing to the proximity of the adjacent artery. Both approaches also require blocking of the dorsal branch of the ulnar nerve. This is accomplished by establishing a subcutaneous wheal from the initial point of injection and "walking" under the skin around to the dorsal aspect of the wrist to the midpoint.[4]

To use the traditional method, enter the wrist crease at 90° lateral to the tendon of the flexor carpi ulnaris muscle[5,6] (Fig. 3). Abduct the little finger against resistance, as it attaches to the pisiform

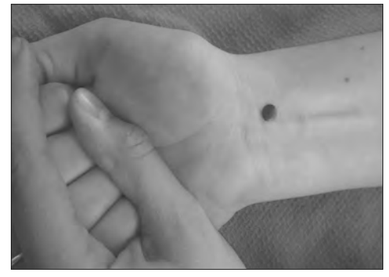

Fig. 1. Location of the median nerve.

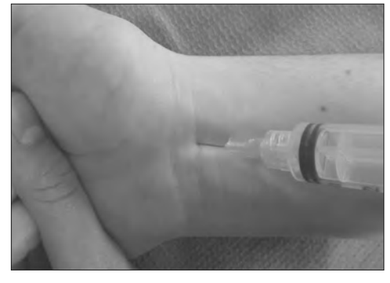

Fig. 2. Needle passing through the tough retinaculum to reach the median nerve.

bone, to string the tendon out. The ulnar nerve can be reached by injecting just on the thumb side of this tendon to reach the ulnar nerve by this volar approach (Fig. 4). The injection for the nerve essentially lies between the tendon and the nearby ulnar artery. A 2004 cadaveric study found damage to this artery almost 40% of the time.[7]

A medial approach to the nerve has demonstrated less risk of arterial damage.[3,7] Place the needle parallel to the wrist crease and slip it under the tendon, which is usually very easy to palpate (Fig. 5.) Advance the needle beneath the tendon to its far side where the nerve lies, and then inject 3–5 mL (Fig. 6).

Consider an alternative, less commonly described approach that is done more proximally, before the palmar and dorsal branch of the ulnar nerve bifurcate.[2,8] Find the spot 3 fingerbreadths (5–7 cm) proximal to the wrist crease, slide the needle under the flexor carpi ulnaris tendon and inject 3–5 mL of lidocaine. The artery is not so closely applied to the nerve, and this approach is safer and simpler (Figs. 7 and 8).

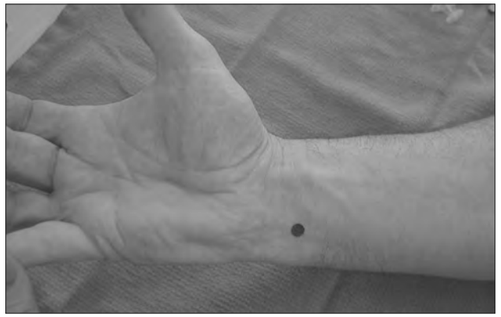

Fig. 3. Traditional distal approach to the ulnar nerve.

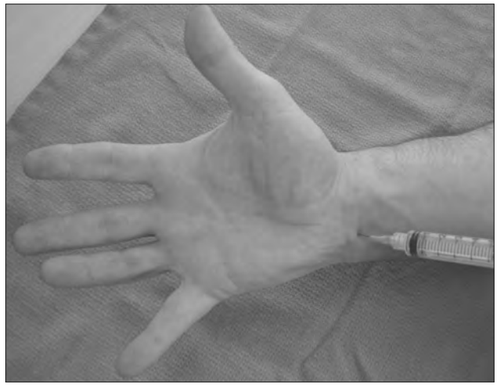

Fig. 4. Entering just lateral (thumb side) to the flexor carpi ulnaris muscle, located by flexing the wrist and abducting the little finger.

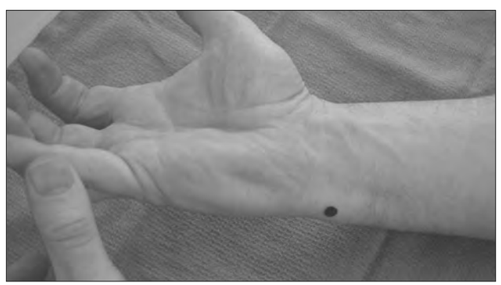

Fig. 5. The medial approach to the ulnar nerve.

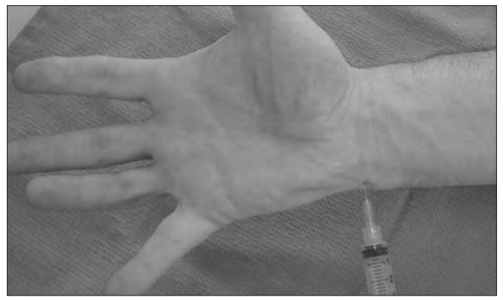

Fig. 6. Slipping the needle under the flexor carpi ulnaris tendon from the medial aspect is more protective of the ulnar artery.

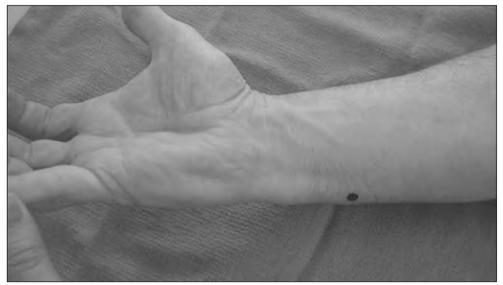

Fig. 7. Both branches of the ulnar nerve can be blocked 3 fingerbreadths (5–7 cm) proximal to the wrist crease.

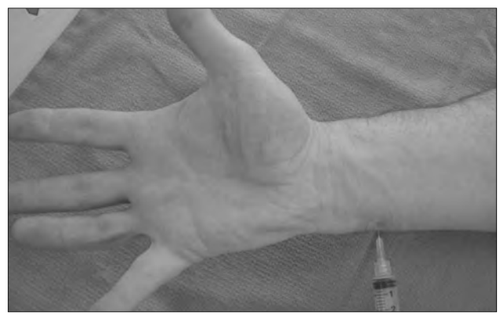

Fig. 8. Needle enters just under the flexor carpi ulnaris tendon and travels to the other side of it.

RADIAL NERVE BLOCK

The radial nerve innervates the dorsum of the hand and the first 3 fingers — but only up to the proximal interphalangeal joint, then the median nerve takes over. Remember this distinction for fingertip work.[9]

This nerve block is considered a field block because anesthesia is obtained by diffusion of a generous amount of solution rather than accurate placement of the needle beside a nerve, given that the nerve has multiple and varying bifurcations.[3] The first step is to place 3–5 mL of lidocaine subcutaneously in the anatomical snuff-box. Identify it by extending the thumb in typical hitchhiker style (Figs. 9 and 10). Other authors describe forming a subcutaneous wheal extending along one-half of the back of the wrist using another 3–5 mL of lidocaine[10] (Figs. 11 and 12). Some also extend a shorter subcutaneous wheal around the volar aspect of the wrist to cover the radial styloid[3,11] (Fig. 13). These additional subcutaneous wheals can be accomplished via a single needle puncture by withdrawing and reangling the needle under the skin.[12]

The regions of sensation to the hand are shown in Figure 14. The ultrasound-guided method allows direct visualization of the needle, artery and the

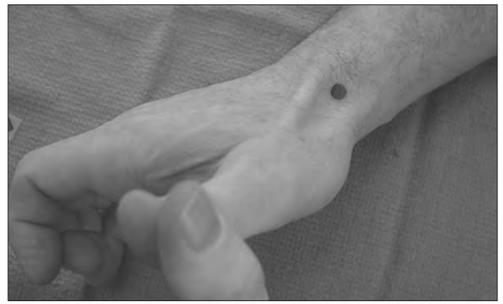

Fig. 9. Anatomical snuff-box formed by the extensor pollicis brevis and longus muscles.

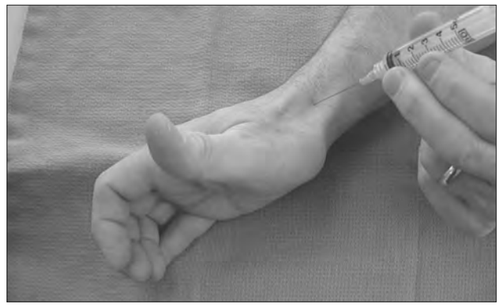

Fig. 10. Place 5 mL of lidocaine subcutaneously in the anatomical snuff-box.

Fig. 11. Follow that with 2 subcutaneous wheals as shown.

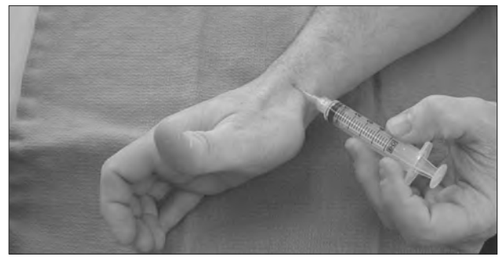

Fig. 12. The dorsal subcutaneous wheal should travel several inches around the back of the hand above the tendons.

Fig. 13. A volar subcutaneous wheal is shorter and also stays above the tendon.

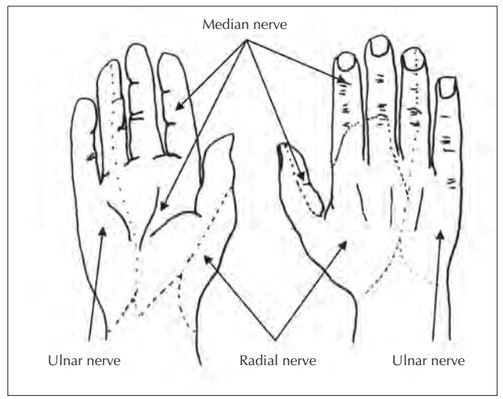

Fig. 14. Nerve regions of the hand.

nerve. With this approach, a smaller volume of anesthetic may be used, and there is less potential for trauma to the nerve.[13] Although such training is rapidly percolating throughout rural emergency departments, knowledge of the relevant anatomical landmarks and the ability to deliver regional hand anesthesia without technical aids will always be an asset. Epinephrine is sometimes used for prolonged surgeries by hand surgeons: the use of 5 mL of 2% lidocaine with 1:100 000 epinephrine can provide up to 9 hours of anesthesia.[14]

Competing interests: None declared.

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Addiction Medicine

Evaluation of 6 remote First Nations community-based buprenorphine programs in northwestern Ontario

Retrospective study

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Abstract

Objective To evaluate established opioid addiction treatment programs that use traditional healing in combination with buprenorphine-naloxone maintenance treatment in 6 First Nations communities in the Sioux Lookout region of northwestern Ontario.

Design Retrospective cohort study.

Setting Six First Nations communities in northwestern Ontario.

Participants A total of 526 First Nations participants in opioid-dependence treatment programs.

Intervention Buprenorphine-naloxone substitution therapy and First Nations healing programming.

Main outcome measures Retention rates and urine drug screening (UDS) results.

Results Treatment retention rates at 6, 12, and 18 months were 84%, 78%, and 72%, respectively. We estimate that the rate at 24 months will also be more than 70%. The UDS programming varied and was implemented in only 1 community. Initially urine testing was voluntary and it then became mandatory. Screening with either method found the proportion of urine samples with negative results for illicit opioids ranged between 84% and 95%.

Conclusion The program's treatment retention rates and negative UDS results were higher than those reported for most methadone and buprenorphine-naloxone programs, despite a patient population where severe posttraumatic stress disorder is endemic, and despite the programs' lack of resources and addiction expertise. Community-based programs like these overcome the initial challenge of cultural competence. First Nations communities in other provinces should establish their own buprenorphine-naloxone programs, using local primary care physicians as prescribers. Sustainable core funding is needed for programming, long-term aftercare, and trauma recovery for such initiatives.

EDITOR'S KEY POINTS

- Remote First Nations communities in northwestern Ontario have a high prevalence of opioid addiction and its consequences, such as crime, violence, and overdose. Communities in the Sioux Lookout region have established treatment programs using traditional healing in combination with buprenorphine-naloxone maintenance treatment. The authors were invited by 6 communities to evaluate their programs.
- The 6-month treatment retention rate of 84% for these programs is higher than that reported for most methadone and buprenorphine-naloxone programs in the United States and Canada, despite these programs lacking the expertise and resources other such programs typically have. In 1 community, the high rates of negative urine drug screening results when screening was voluntary were also demonstrated when screening became mandatory after the study data collection period.
- Despite many obstacles, these community-driven initiatives have creatively begun to address crippling levels of addiction. Although a causal relationship could not be determined, the 6 communities studied experienced a dramatic decline in suicides ($P = .035$) after the initiation of these programs. Culturally embedded, community-based programs can provide an important starting point for long-term healing.

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Since the opioid crisis began in the late 1990s, remote northwestern Ontario First Nations communities have experienced a massive surge in the prevalence of opioid addiction.[1,2] The Nishnawbe Aski Nation, in a news release in 2012, estimated that 9000 community members of a population of 25 000 in the Sioux Lookout region of northwestern Ontario were opioid dependent.[3] A recent study of one community north of Sioux Lookout estimated that 41% of the adults aged 20 to 50 were opioid dependent.[1] First Nations band councils and addiction workers report that opioid-related overdoses, crime, social dysfunction, and addiction are common in their communities.[4]

Until recently, treatment options have been limited. Abstinence-based programs have high relapse rates and have involved traveling out of the community to an urban treatment centre.[5] Methadone treatment is not feasible in many isolated First Nations communities, as they lack a methadone prescriber, a pharmacy open 7 days per week, and emergency services.

In 2012, the Ontario provincial drug plan added buprenorphine-naloxone to its formulary, and the Non-Insured Health Benefits program (which provides drug coverage for First Nations communities) followed suit. The College of Physicians and Surgeons of Ontario permits all physicians to prescribe buprenorphine-naloxone, even if they do not have a methadone licence. This has allowed community leaders and physicians in Ontario First Nations communities to design and implement their own buprenorphine-naloxone maintenance treatment programs. Buprenorphine-naloxone is a partial opioid agonist with a long duration of action. It has a much lower risk of overdose than methadone does, but also has lower treatment retention rates.[6-8] Buprenorphine-naloxone is a combination medication that includes buprenorphine, a long-acting opioid with strong opioid-receptor affinity, and naloxone, an opioid antagonist. When used sublingually, very little naloxone is absorbed, but if the drug is diverted to intravenous use, withdrawal symptoms ensue—hence it has a built-in diversion deterrent.

The Sioux Lookout catchment area consists of 32 remote First Nations communities with a land mass of 385 000 km^2 and a total population of 25 000.[9] Twenty-two of the northern communities have started their own buprenorphine-naloxone programs, with a total of 1399 participants. Buprenorphine-naloxone treatment is initiated either by the community physician, who visits each community 1 week a month, or by urban addiction physicians who act as fly-in locums. Follow-up is in person or by telemedicine. The community physician continues treatment, including dose changes, weaning, and other addiction and general medical needs.

A recent study documented remarkable results from a buprenorphine-naloxone program in one regional community, with dramatically reduced rates of crime and increased rates of school attendance.[1] The study measured only community outcomes. This current study is the first to report on treatment retention rates and urine drug screening (UDS) results for buprenorphine-naloxone maintenance programs in the Sioux Lookout region.

METHODS

Treatment setting

We conducted a retrospective cohort study. Six First Nations communities who requested program evaluation (with a total population of 4388) participated in the study. All are located north of the town of Sioux Lookout, where the Sioux Lookout Meno Ya Win Health Centre serves as their regional medical hub for primary and hospital care.[9] The population, medication use, and laboratory values were calculated from the physician-based electronic medical records (EMRs), which recorded buprenorphine-naloxone prescriptions. Population estimates were based on all patients covered by Ontario health insurance within each community, as listed in the EMR.

Program description

Administration and staffing. All 6 communities began providing buprenorphine-naloxone substitution in the summer or fall of 2012 and into 2013. Each community designed its own program and complement of staff and consultants. Communities provide a facility for the program, often in an unused or refurbished building. The programs are overseen by the band chief and council, the Health Director, and community leaders. The service delivery team consists of the local program coordinator, medication dispensers, consultant counselors, nurses, and physicians. Community nurses initiate bloodwork on admission to the program. Participants are self-referred. The local capacity to provide direct, observed therapy was often a limiting factor for inductions. Patients were admitted to the program on a first-come, first-served basis if they met the diagnostic criteria for opioid use disorder.[10]

Buprenorphine-naloxone prescriptions. Patients were often started on buprenorphine-naloxone in group inductions of 10 to 25 patients at a time, depending on funding and the availability of clinical personnel. Often inductions were initiated by visiting community physicians; if available, addiction physicians from urban centres assisted during group inductions. The physician completes a comprehensive assessment of all patients, and those who meet the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, criteria for opioid use disorder[10] begin taking buprenorphine-naloxone when

they have provided informed consent. Community physicians, who visit each community for 1-week periods each month, prescribe follow-up buprenorphine-naloxone doses. The buprenorphine-naloxone is dispensed daily under the supervision of a community nurse or community addiction worker. Take-home doses are prescribed by the addiction physician or the community physician in consultation with other members of the treatment team. A locally developed physician prescribing guideline was developed to assist induction prescribing and maintenance dosing.

Counseling. After induction, the group attends 4 weeks of intensive day treatment and aftercare. All programs provide daily, supervised dispensing of buprenorphine-naloxone. A "Land" aftercare program has been developed in some of the communities, with organized days of fishing, hunting, traditional walks for memorial events, and community gardening programs. Elders and experienced First Nations counselors provide individual and group healing sessions where possible. Some communities hire counselors from outside of the community if resources permit. In many programs, the community physician provides the core clinical support.

Data collection

The 6 programs started buprenorphine-naloxone substitution in the summer or fall of 2012 and into 2013. Data were collected from the start of each program until July 2015. Because UDS was only randomly available for that time period, we also included initial UDS results from early 2016, when it became mandatory in 1 community.

Information on buprenorphine-naloxone prescribing was accessed through the regional EMR system. Patients were considered retained in treatment from the date of their first buprenorphine-naloxone prescription until their last prescription ended. Twelve-month retention rates were calculated for patients who started buprenorphine-naloxone 12 months before July 2015. Buprenorphine-naloxone dosing data were available from 1 of the 6 communities and were analyzed for induction dose and the dose at every 6-month follow-up.

Urine drug screening was performed systematically in only 1 of the 6 communities. In 2014 and 2015, random and voluntary monthly testing was performed in the summer months. Urine testing was performed on 4 randomly chosen days during the summer (May to August). In 2016, monthly UDS became mandatory in that community. Point-of-care urine dipsticks were used to test for cocaine, oxycodone, morphine, benzodiazepines, and buprenorphine.

Diabetes prevalence was estimated by review of EMRs for all hemoglobin A_{1c} results above 6.5% in the study period, measured against total community populations. We chose to compare the prevalence of diabetes with that of opioid use disorder, as diabetes is a disease that attracts core funding and programming in federal funding schemes, while opioid use disorder and aftercare programming goes wanting. We chose to compare prevalences in the 20- to 50-year-old age group, as nearly all those receiving opioid agonist therapy with buprenorphine-naloxone were in that age group.

Suicide events were enumerated from internal documents from the Sioux Lookout First Nations Health Authority, as specifically requested by the 6 community Health Directors. Examination of drug involvement in these events was outside the scope of this study. Data were entered using Excel 2013, and analyses were completed using SPSS, version 21.0. Descriptive statistics were obtained in addition to χ^2 tests for independence.

Ethics approval

The study was launched in response to a request from 6 communities to evaluate their treatment programs. Ethics approval was granted by the Sioux Lookout Meno Ya Win Health Centre Research Review and Ethics Committee. The evaluation received partial funding from the Northern Ontario Academic Medicine Association. Most of the investigators on this study are also clinicians working in Sioux Lookout or community leaders.

RESULTS

Patient characteristics

In the 6 communities, 526 individuals were treated with buprenorphine-naloxone. The mean (SD) age was 32.3 (8.4) years; 55% were women. Most (96%) program participants were in the 20- to 50-year-old age range (**Table 1**). The rate of opioid-dependence treatment for adults in this population group was 28% (504 of 1800). We also surveyed the prevalence of type 2 diabetes mellitus in the same age group and found a prevalence of 14%.

Buprenorphine-naloxone dose

Doses were analyzed in only 1 community. The mean (SD) dose of buprenorphine-naloxone was 15.6 (5.8) mg at the end of the 1-week induction (n = 163), falling to 11.3 (6.8) mg at 6 months, 6.0 (3.6) mg at 18 months, and 6.1 (4.1) mg at 24 months.

Table 1. Age distribution of community members prescribed buprenorphine-naloxone in 2013 to 2015

AGE, Y	PARTICIPANTS, N (%)
< 20	6 (1)
20-29	247 (47)
30-39	184 (35)
40-49	73 (14)
50-59	13 (2)
≥ 60	3 (1)
Total	526 (100)

Treatment retention

Retention rates were measured at 6, 12, 18, and 24 months (**Table 2** and **Figures 1** to **3**). Of the 526 patients in the total sample, 474 had started buprenorphine-naloxone treatment at least 6 months before the end of the data collection period. Of these 474 patients, 396 were taking buprenorphine-naloxone for at least 6 months, for a retention rate of 84%. Of these 396 patients, 43 had started taking buprenorphine-naloxone less than 12 months before the end of data collection; of the remaining 353 patients, 17 dropped out, for a 12-month retention rate of 78%. Using similar calculations, the 18-month treatment retention rate was 72%, and the 24-month retention rate is estimated to be more than 70%.

Urine drug screening

Random, voluntary UDS in the 1 community that initiated it in May to August of 2014 and 2015 captured between 50% and 90% of program participants each month. The results demonstrated that between 84% and 95% of UDS results were positive for buprenorphine and negative for oxycodone, morphine, cocaine, or benzodiazepines.

Mandatory monthly UDS was initiated in January of 2016, after the end of the data collection period, and documented similarly high rates of negative results (**Table 3**). In January, 16 patients had a combination of urine findings positive for oxycodone (n = 10), morphine (n = 9), and cocaine (n = 4). February included 12 patients with positive urine findings: morphine (n = 10), oxycodone (n = 5), and benzodiazepines (n = 1).

Suicides

Suicides in these 6 communities declined significantly ($P = .035$) from 9 cases in the 3-year period of 2009 to 2011 to 2 cases in the subsequent 3-year period during which buprenorphine-naloxone programming began (2012 to 2014).

DISCUSSION

This study confirms the extraordinarily high prevalence of opioid addiction in First Nations communities. Among adults aged 20 to 50 years, 28% were taking buprenorphine-naloxone, double the prevalence of adults in these communities with type 2 diabetes (14%).

This paper is the first, to our knowledge, to report on the effectiveness of buprenorphine-naloxone maintenance programs in rural, aboriginal communities, in Canada or elsewhere. A recent study of an inpatient detoxification program in Sioux Lookout, using a rapid taper of buprenorphine-naloxone, reported relapse rates of 52% after 2 weeks and 70% after 6 months, confirming that tapering and detoxification are of limited usefulness in the treatment of opioid addiction.[11]

The 6-month treatment retention rate of 84% is higher than rates reported for most methadone and buprenorphine-naloxone programs in the United States and Canada. In a review of 9555 new methadone treatment episodes in Ontario between 1996 and 2001, 2-year treatment retention rates were only 50%.[12] Six-month retention rates for buprenorphine-naloxone programs in the United States range from 36% to 78%.[13-16] The few studies of buprenorphine-naloxone programs that have reported 12-month outcomes record rates of 25% to 75%.[17,18]

In these community-based programs, the high retention rates and low rates of illicit opioid use are consistent with the positive community-wide results of an earlier study in 1 of the 6 communities.[1] In that report, changes were measured for crime rates, addiction-related medical evacuations, and other outcomes after the introduction of buprenorphine-naloxone programming. One year after the buprenorphine-naloxone program started, criminal charges had fallen by 61.1%, child protection cases had fallen by 58.3%, and school attendance rates had increased by 33.3%.[1] Drug-related medical evacuations to hospital fell by 30.0%.[1]

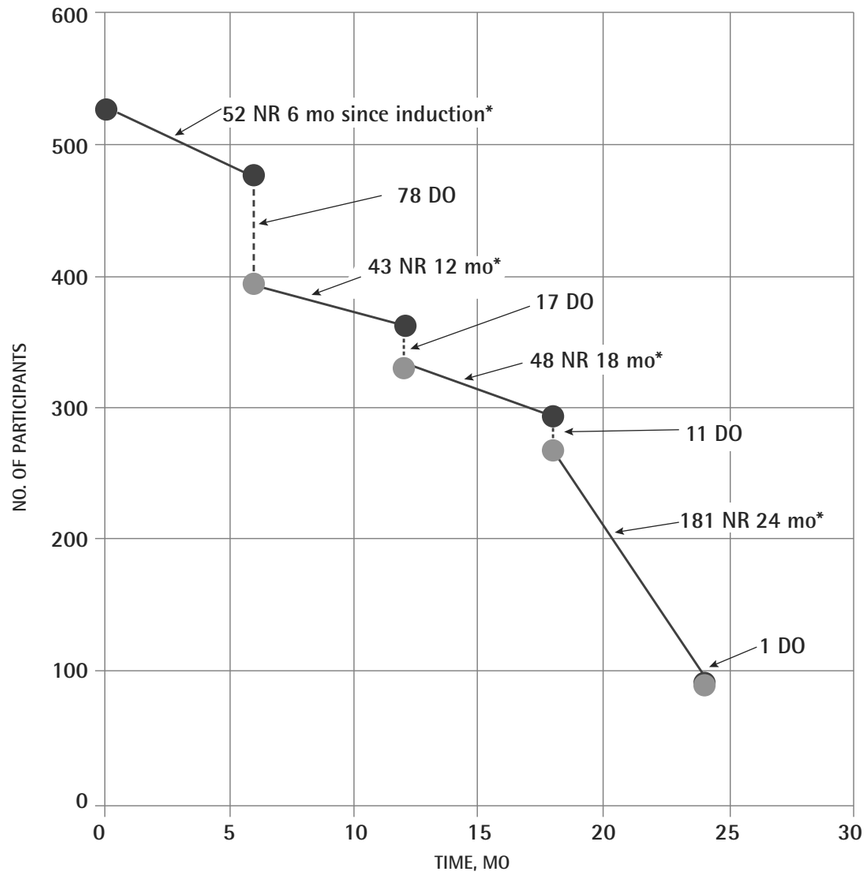
The 6 communities studied here have experienced a dramatic decline in suicides ($P = .035$) during the 3-year time period of the initiation of the buprenorphine-naloxone programs compared with the preceding 3-year period. Community Health Directors had requested this

Table 2. Dropouts and retention rates at 6-month intervals since induction

TIME SINCE INDUCTION, MO	NO. OF PARTICIPANTS (RETAINED AND DROPOUTS)*	RETAINED, N (%)	DROPOUTS, N	CUMULATIVE DROPOUTS
≥ 6	474	396 (84)	78	78
≥ 12	431	336 (78)	17	95
≥ 18	383	277 (72)	11	106
≥ 24	202	95 (estimated > 70)†	1	107

*Six months had not yet elapsed since induction for 52 of the 526 total participants at the time of data collection; 43 participants had not yet completed 12 months of treatment, 48 had not yet completed 18 months, and 181 had not yet completed 24 months.
†We expect that most of the 181 participants who had not yet completed 24 months of treatment will be retained.

Figure 1. Distribution of participants over time and at each 6-month retention evaluation point



DO—dropped out, NR—not yet reached 6-mo evaluation point.
*Because participants entered the program at different times, they reached the 6-mo follow-up intervals at different times. A total of 474 participants had been started on buprenorphine-naloxone at least 6 mo before the end of the data collection period.

statistic be included in the program evaluation, but our mandate did not extend to examining associated individual factors, such as concurrent opioid use or demographic information. We cannot therefore attribute a causal relationship between the reduction in suicides and addiction treatment programming.

The success of the programs runs counter to current knowledge about medication, patient, and treatment factors that affect treatment retention. Systematic reviews have demonstrated that buprenorphine has lower treatment retention rates than methadone does.[8] Yet Sioux Lookout patients required rather low buprenorphine-naloxone doses of 6.0 mg at 18 months (the usual therapeutic range is 8 to 16 mg) and have retention rates of 78% at the 1-year mark. In some communities, this could be because participants were not daily users and therefore had a lower degree of physical dependence. Despite this, we know anecdotally that in several of the

communities included in this study, there were histories of daily intravenous opioid use for greater than 5 years.

Further, many Sioux Lookout region patients have characteristics that have been associated with poor outcomes. Our clinical impression is that community members use illicit opioids often purchased from drug dealers, rather than oral opioids acquired from physicians' prescriptions; illicit opioid users have higher rates of treatment dropout than oral prescription opioid users do.[19,20]

Figure 2. Retained participants and dropouts in the buprenorphine–naloxone program at 6-month intervals: *Because participants entered the program at different times, not all retained participants had completed more than 6 months of treatment at the time of data collection. Most dropouts occurred in the first 6 months.*

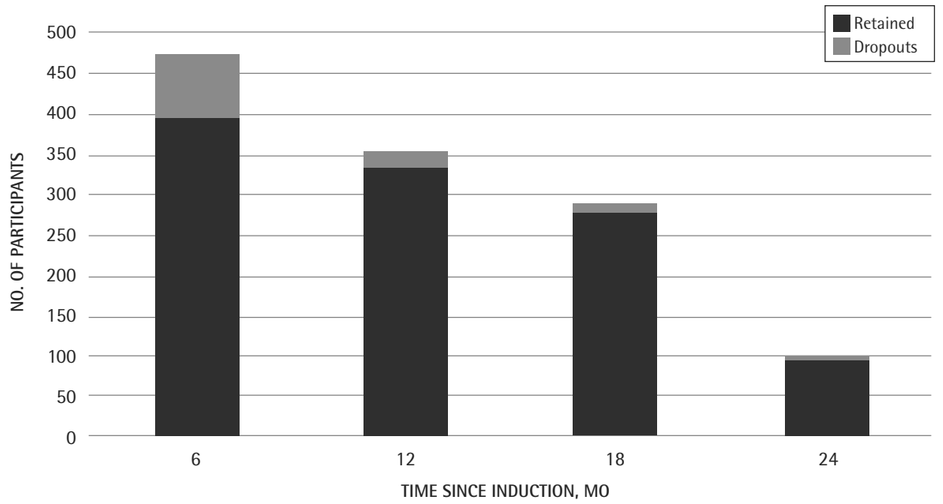


Figure 3. Timing of dropouts from the buprenorphine–naloxone programs

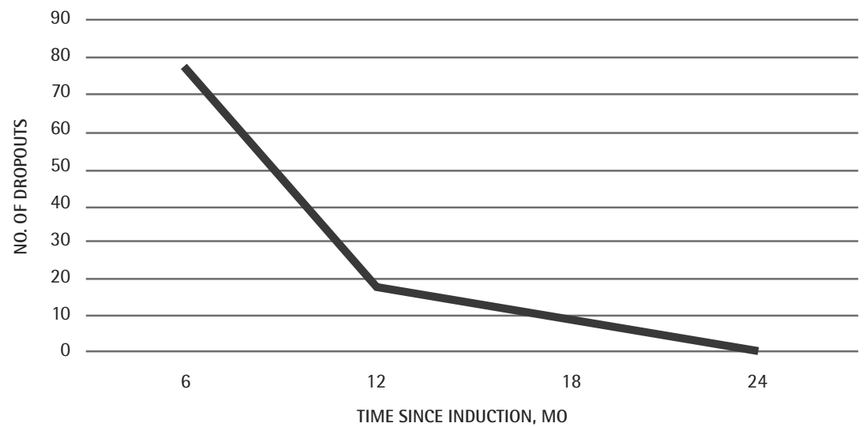


Table 3. Mandatory UDS results in 1 participating community

MONTH (2016)	PATIENTS IN THE PROGRAM, N	PATIENTS OUT OF THE COMMUNITY, N	PATIENTS TESTED, N (%)	PATIENTS WITH UDS RESULTS NEGATIVE* FOR ILLICIT DRUGS, N (%)	PATIENTS WITH UDS RESULTS POSITIVE FOR ILLICIT DRUGS, N (%)
January	148	20	128 (100)	112 (88)	16 (12)
February	148	27	121 (100)	109 (90)	12 (10)

UDS—urine drug screening.
*A negative UDS result refers to test results positive for buprenorphine alone.

Also, compared with the general population, First Nations individuals have substantially higher rates of depression, posttraumatic stress disorder, and binge drinking.[21] These factors are associated with an increased severity of addiction (eg, earlier onset of injection drug use).[22]

Another factor that would normally have predicted a poor outcome is that the 6 treatment programs lacked the expertise and resources that other methadone or buprenorphine-naloxone programs in Ontario have. Primary care physicians, community nurses, and addiction workers have little or no training in opioid substitution therapy; none of the family physicians has an exemption to prescribe methadone. All health care workers managed buprenorphine-naloxone patients on top of their regular duties, which were already very demanding. The few on-site mental health and addiction workers have little training in opioid substitution therapy.

Given these negative prognostic factors, the high treatment retention rates deserve further study. One possible explanation is that the 6 programs were funded, designed, and implemented by each individual community, and their approach differs radically from that of other opioid substitution programs in North America. In a typical program, the primary relationship is between the individual patient and the physician or counselor. The Sioux Lookout programs, in contrast, are primarily a community-wide "welcoming back" of addicted patients to their families and their previous roles. Groups of 10 to 20 patients start taking buprenorphine-naloxone on the same day. The induction is a community event, where local leaders, friends, and relatives congratulate the inductees. Psychosocial treatment programs lack formal activities such as group therapy; instead they are meeting places where patients can gather and hold healing circles and other traditional events. Families expect patients to resume parenting, work, school, or family obligations. The primary care physician who prescribes buprenorphine-naloxone also provides medical care for the patient's family and community.

Limitations

The study has important limitations. Much of the clinical information for participants was inaccessible, as it was contained in paper charts in 6 remote locations at considerable distance from one another. Results of the baseline patient assessment were not recorded in the EMR, so we do not know the patients' type, route, or dose of opioids used. Urine toxicology results were not systematically available. Treatment retention rates were calculated over 6-month intervals, so some information will have been lost (for example, data from participants who started taking buprenorphine-naloxone within 6 months of July 2015 were not included). The 24-month evaluation time had not yet occurred for a large cohort of participants (n=181). Information on the disposition of dropouts is unknown; they might have remained opioid free or returned to illicit drug use. The relationship between the reduction in suicides and program development cannot be determined, because an examination of causality was beyond the scope and mandate of this study.

Other considerations

Despite these limitations, the results are most likely valid because they are consistent with our clinical observations and the observations of other clinicians, as well as the study of community measures described above.[1] One community member described the effect of the buprenorphine-naloxone program:

> Five years ago, our community was in a mess. No one bought food. No one looked after their children; parents would bring them to grandparents and not come back for many days. Now [3 years after the introduction of the buprenorphine-naloxone program] bills are paid, people buy gas, play bingo, and go to fishing derbies. Children play, go to school, play hockey. We have many celebrations; everyone comes to Traditional Days.

In the Sioux Lookout region, short-term competitions for federal funding have pitted the needs of one community against those of another. Many communities have not been able to initiate programs owing to inadequate resources, and established programs have often suspended accepting new patients. Recently, federal funding competitions support up to 3 years of programming, but what is needed is a regional, and ultimately national, well resourced strategy and sustainable funding that flows to local communities, primary care, and First Nations health authorities for treatment planning, implementation, and evaluation.

Aftercare programming, including mental health and trauma recovery treatment, is particularly vulnerable to inadequate resourcing. Core program funding similar to that for other chronic diseases (eg, diabetes programs) is vital to the development and maintenance of community-based treatment programs.

Unfortunately, the Sioux Lookout success is an anomaly; the situation in other Canadian First Nations communities remains grim. In several provinces, medical regulators do not allow primary care physicians without a methadone exemption to prescribe buprenorphine-naloxone. As very few First Nations communities have methadone prescribers, these communities have no access to either buprenorphine-naloxone or methadone, 2 medications that are on the World Health Organization list of essential medications. This is very disturbing given that the opioid crisis is entering its 20th year, First Nations communities have been devastated by the crisis, and buprenorphine-naloxone is an inexpensive and highly effective intervention.

Now that the federal Non-Insured Health Benefits program has agreed to fund buprenorphine-naloxone, regardless of its provincial funding status, the next step is for medical regulators to remove barriers to primary care prescribing of buprenorphine-naloxone. This would allow other First Nations communities to establish their own programs, perhaps with long-distance training, support, and mentorship from Sioux Lookout community physicians and community leaders.

Conclusion

We have presented the successful outcomes of community-based opioid dependence treatment programs in 6 remote First Nations communities. Despite many obstacles, these community-driven initiatives have creatively begun to address crippling levels of addiction. The addiction rates seen in northwestern Ontario First Nations communities affect the fabric of those communities. Culturally embedded, community-based programs can provide an important starting point for long-term healing. Robust treatment programming and creative, culturally appropriate long-term aftercare are warranted. Medical regulators and provincial and federal governments need to empower such community-based treatment initiatives. Sustainable core resources are needed at the community and primary care levels.

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Contributors
All authors contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests
None declared

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Systematic Literature Review on Buprenorphine/naloxone Use in Outpatient Opioid Dependence Treatment

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ABSTRACT

Objective: Summarize the literature on buprenorphine/naloxone for outpatient treatment of opioid dependence disorder. **Methods:** a literature of EMBASE and Medline 2000-2014 using the terms "naloxone + buprenorphine" and "opioid-related disorders". **Results:** Over two hundred articles were retrieved. Seventeen studies were ultimately selected and reviewed for study quality, using Downs and Black's 1998 checklist, the Canadian Task Force on Preventive Health Care levels of evidence and study outcome analysis. **Conclusion:** Buprenorphine/naloxone appears to be a safe, effective treatment modality for treatment of opioid dependence. As a recently introduced medication in North America, clinicians are slow to fully embrace it use. It provides an opportunity to more widely provide opioid substitution therapy in primary care settings. Key words: addiction, opioid substitution therapy, buprenorphine/naloxone, outpatient.

Objectif: Résumer la littérature sur l'utilisation de buprenorphine/naloxone pour le traitement ambulatoire des troubles de dépendance aux opioïdes. **Méthodes:** Recherche des publications disponibles sur EMBASE et Medline entre les années 2000 et 2014 utilisant les mots clés "naloxone + buprenorphine" et "opioid-related disorders". **Résultats:** Plus de deux cents articles ont été extraits. Dix-sept études ont finalement été sélectionnées et examinées pour leur qualité en utilisant la grille d'évaluation développée par Downs and Black (1998), l'échelle de classement de la qualité des données probantes du Groupe d'étude canadien sur les soins de santé préventifs et l'analyse des résultats de l'étude. **Conclusion:** La buprenorphine/naloxone semble être une modalité de traitement sécuritaire et efficace pour le traitement de la dépendance aux opioïdes. Puisque cette médication est nouvellement disponible en Amérique du nord, les cliniciens sont lents à l'adopter dans leur pratique. Elle permet d'offrir à plus grande échelle une thérapie de substitution aux opioïdes dans les milieux de soins primaires. Mots clés: dépendance, thérapie de substitution aux opioïdes, buprénorphine/naloxone, consultation en externe

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INTRODUCTION

The introduction in the last decade of buprenorphine/naloxone to the choice of treatment for opioid dependence is reflected in new types of treatment options and research opportunities. With a recognized safety profile, less monitoring and even 'home starts,' it allows for outpatient management of substitution therapy where indicated. A relevant research base is developing. In this literature review, we explore the outpatient use of the combination medication buprenorphine/naloxone.

METHOD

A search of the literature from Jan 2000- July 2014 was conducted on EMBASE and Medline databases using the terms "naloxone + buprenorphine" and "opioid-related disorders". This yielded a total of 234 studies. Reference lists of review papers were also reviewed for relevant articles. The abstracts of all studies were reviewed and studies selected for original research dealing with outpatient buprenorphine-naloxone maintenance treatment for addiction. Studies looking at pregnant or HIV-positive populations, and those dealing with buprenorphine-naloxone induction or inpatient treatment were excluded. Seventeen studies were ultimately selected and reviewed for study quality, using Downs and Black's 1998[1] checklist, the Canadian Task Force on Preventive Health Care[2] levels of evidence and study outcomes analysis.

RESULTS

STUDY CHARACTERISTICS

The characteristics in the studies included are summarized in Table 1. The vast majority of studies had a predominance of male participants. Eleven/17 data sets specified type of opioid used (heroin vs. prescription opioids). Of these, three studies included only heroin users, four included a majority of heroin users, and four included a majority of prescription opioid users. Eleven/17 studies specified the race of their participants. In these 11 studies, 25-94% of participants were white, with the most common other races being African American and Hispanic. No studies identified Aboriginal participants. Fifteen/17 studies were conducted in the United States, and none in Canada. All studies were primarily conducted in urban settings.

Many studies had exclusion criteria for those suffering from serious medical and psychiatric illness, including comorbid addiction with alcohol.

Treatment in these studies was administered by a variety of medical specialties including family medicine. A combination of buprenorphine-naloxone, as opposed to buprenorphine alone, was used in all 17 of the studies.

RETENTION RATES

Major outcomes are summarized in Table 2. The most common length of time reported for retention was six months. At six months, from 36-78% of patients were retained in treatment with buprenorphine/naloxone.[3-8] One study reported sobriety rather than retention as primary outcome, and 54% were sober at six months.[9] At 12 months, between 25-77% of patients were retained in treatment.[10-12]

ABSTINENCE FROM OPIOIDS

In general, studies did not require abstinence from patients in order to continue treatment. The percentage of opioid negative urines was reported either as an average of the entire study period, or at the end point of the study. Between 40-85% of urine samples were free of opioids at six month end points.[3-6] There appeared to be positive correlation between observer rated abstinence and urine results.[13]

QUALITY OF LIFE MEASUREMENTS

Several studies showed significant improvement in quality of life and addiction related behavior during and after buprenorphine/naloxone treatment.[5,10,14,15,16,17] No studies which examined these outcomes found negative results.

EFFECTS DURING FOLLOW-UP

Relatively few follow up results suggesting long term efficacy of treatment are available. Several studies examined different durations of treatment followed by tapering, meaning that patient were all off buprenorphine/naloxone when followed up. One study found that patients treated with buprenorphine/naloxone and tapered off during the study were more likely to be in addiction treatment when followed up, compared to those treated and tapered off methadone.[13] This may be secondary to a shorter retention duration compared to methadone and/or a high satisfaction with buprenorphine/naloxone treatment. One high quality RCT comparing a two-week maintenance and taper to a 12-week maintenance and taper found that overall only 8.6% of tapered individuals maintained abstinence at follow-up.[18]

Two studies of longer maintenance treatments have shown varied retention rates demonstrated that of individuals who successfully completed six months of treatment with buprenorphine/naloxone, 38% were retained in treatment two years later.[3,4] An observational study found that of individuals who successfully completed 12 months of treatment, 77% were still in treatment a minimum of 18 months later.[15]

FACTORS PREDICTING SUCCESS

Several pre-existing patient factors were found to predict successful retention and abstinence during the studies. These factors are summarized in Table 3. The most common variable found to positively predict success was older age, both at time of treatment and at time of opioid dependence onset.[9,10,18,] Drug of choice was also a significant variable, with four studies finding that prescription drug users, rather than heroin users, had more successful outcomes.[3,7,13,15] Prescription drug users on average may be younger, have fewer years of opioid dependence, and less addiction treatment in their past.[3,8] Specifically, use of illicit buprenorphine and methadone may be a positive variable predicting success.[19] One study found that comorbid alcohol abuse may predict failure with buprenorphine/naloxone treatment.[19]

Race may be a variable affecting outcome, as two studies found that African American or Hispanic race negatively affected treatment success, while controlling for other variables.[7,12]

Route of drug abuse was also a significant variable in three studies, with two finding that non-intravenous (IV) drug users had more positive outcomes, and a third finding that recent IV drug user predicted success.[7,20-22] The latter study was conducted with youth aged 15-21, and intravenous drug use was thought to correlate with more self-perceived severity of illness and willingness to comply with treatment.[20]

Although sufferers of severe mental or physical illness were often excluded from these studies, several times patients with chronic mental or physical conditions were noted to have superior outcomes.[6,21,23] It may be that these patients benefit more from analgesic properties of buprenorphine/naloxone and mental stabilization secondary to treatment.

As expected, variables suggesting stability such as employment, marriage or long term relationship, and not being homeless are also predictors of treatment success.[9,10] In one study, history of incarceration was found to not significantly influence outcomes.[24]

In-treatment variables, which have been thoroughly studied, involve degree and type of psychosocial support provided. A Cochrane Review of 27 studies showed that there was no benefit of additional psychosocial intervention over standard maintenance treatment, in any outcome measured.[25] The control maintenance treatment in the studies in this Cochrane review all included some degree of counseling services. There does not seem to be any additional benefit offered by more intensive therapy, when retention, abstinence and success at follow-up are measured.[25]

Warden (2012) also found that youth who successfully abstained from illicit drugs during the first two weeks of treatment were much more likely to be retained for the study duration.[26] Particularly given the safety of buprenorphine/naloxone during induction, these findings recommend higher doses during the induction period.[14]

ADVERSE EFFECTS/MORTALITY

Adverse effects secondary to treatment were reported in the majority of studies reviewed, although not compared statistically. No significant or fatal increase in adverse events with buprenorphine/naloxone compared to other treatments was reported.

Although community-level harms such as crime related to opioid dependence are well documented, no studies were found which examined the impact of maintenance treatment on these outcomes.[27]

DISCUSSION

The documentation of the safety of the combination of buprenorphine/naloxone is developing. It can also be assumed from the literature on single agent buprenorphine. A review of buprenorphine from France revealed over a four year period, the risk of overdose attributable to buprenorphine was 10 times less than that attributable to methadone.[28] Overall, opioid dependence studies have found much lower risk of death for those in maintenance treatment with buprenorphine or methadone, compared to those not in treatment.[14] One buprenorphine study revealed that a shocking 4 of 20 patients in placebo control group died over the one year study period, compared to no deaths in the treatment group.[29]

Buprenorphine/naloxone seems well suited to substitution therapy with prescription drug use,[3,13,15,30] particularly with patients who have not progressed to intravenous drug use.[7,20-22]

CONCLUSION

Since approval in the USA in 2002 and Canada in 2007, buprenorphine/naloxone is safely meeting a need for outpatient management of opioid dependence. Research in its first decade of use has rendered a useful picture of its use in community-based programs. While inpatient programs will always be needed for complex case management and treatment. Primary care and outpatient treatment of opioid dependence is facilitated by the safety and efficacy of buprenorphine/naloxone. Primary care settings allow for easy access for co-morbid conditions and even other accompanying family members.

Research capacity, prescribing and treatment continuing medical education pose the next challenges in primary care leadership in treatment of opioid dependence in the community.

The literature demonstrates the safety and efficacy of buprenorphine/naloxone. This evidence supports the increased use of this treatment modality for treatment of opioid dependence in the outpatient setting.

TABLE 1: STUDY CHARACTERISTICS

STUDY	DOWNS & BLACK QUALITY SCORE (MAX 27)	NUMBER/ TRIAL TYPE	LEVEL OF EVIDENCE	PARTICIPANTS	TYPE OF USERS
Amato 2010	17	78, prospective, non-interventional	II	no race, Italy, urban	heroin
Apelt 2013	19	384, prospective, non-interventional	II	no race specified, Germany, likely urban	all were in maintenance tx already, type of opioid use not distinguished
Bell 2007	20	119, RCT	I	no race specified, Australia, likely urban	heroin only
Cunningham 2008	14	41, retrospective	II	90% non-white, urban, US	70% heroin
Curcio 2011	15	707 BP and 3105 MT, cohort	II	no race, urban, Italy	
Dreifuss 2013/Weiss 2011	19/21	360, RCT	I	90% white, urban, US	less than 1% were heroin users

TABLE 1: STUDY CHARACTERISTICS

STUDY	DOWNS & BLACK QUALITY SCORE (MAX 27)	NUMBER/ TRIAL TYPE	LEVEL OF EVIDENCE	PARTICIPANTS	TYPE OF USERS
Fiellin 2006 and 2008/Moore 2007/ Wang 2010	20/17/16/21	166, RCT, 54 in follow up	I	75% white race, urban, US	55% hx of IVDU
Fudala 2003	22	326 RCT, 461 open label observation	I	60% white, 2% Native American, urban, US	30% hx of IVDU
Kakko 2007	25	96, RCT		no race, Sweden, urban	all heroin
Mintzer 2007	17	99, prospective, non interventional	II	94% white, urban, US, primary care clinics	about 75% heroin addicts
Miotto 2012	15	94, RCT	II	58% white, urban, US	30% heroin
Neumann 2013	18	356, retrospective case control	II	80% white, urban, US, primary care	74% prescription drugs
Nielsen 2013/Ling 2009	21/20	516, RCT	I	no race, US, urban	stratified by type of use
Parran 2010	14	110, cross sectional (follow up)	II	73% white, urban, US	88% heroin
Woody 2008/Polsky 2010/Subramaniam 2011/Warden 2012	20/19/21/19	152, RCT	I	74% white, urban, US	41% heroin, youth 15-21
Potter 2013	20	1269 RCT, secondary analysis	I	74% white, 1% Indian, urban, US	stratified by type of use
Stancliff 2012	14	100, prospective, non interventional	II	25% white, 50% hispanic, lower SES, urban, US	86% heroin, half IVDU, "marginalized" population

TABLE 2: STUDY OUTCOMES

	RETENTION AT END OF STUDY	ABSTINENCE	RESULTS AT FOLLOW UP	OTHER OUTCOMES
Apelt 2013	57.1% at 12 mos	98% negative urine for opioid at final assmt		
Bell 2007	59% at 3 mos	self reported- 52% reported no use in past mos at 3 mos		
Cunningham 2008	71% at 3 mos	76% negative urines overall		Those on BP had significantly lower risk of death during induction; but treatment risk and post-treatment risk was similar.
Curcio 2011		BP users urine was 53% neg, MT users 30% neg		
Dreifuss 2013/ Weiss 2011	49% at 3 mos	61% negative urines overall	8 weeks after taper, 8% continued abstinence	
Fiellin 2006 and 2008/ Moore 2007/ Wang 2010	45% at 6 mos	40% negative urines overall	38% of those retained at 6 mos were retained at 2 years, with 91% opioid free urines	
Fudala 2003	55% at 6 mos	54% neg urine at six mos		Serum transaminases were followed with no significant adverse effects

TABLE 2: STUDY OUTCOMES

	RETENTION AT END OF STUDY	ABSTINENCE	RESULTS AT FOLLOW UP	OTHER OUTCOMES
Kakko 2003	75% at 12 mos	75% neg urine at 12 mos		self reported/observer reported health outcomes improved significantly
Kakko 2007	78% at 6 mos	80% neg urine at six mos		4/20 died in control group. Tx group showed sig improvement in addiction severity index
Mintzer 2007	54% "sober" at 6 mos- urine free of opioids			Presence of psychiatric illness not a significant predictor of tx outcome.
Miotto 2012	35% at 5 mos, 25% at 12 mos	opioid use "decreased" but no numbers given		
Neumann 2013	35.7% at 6 mos	85% of completers had all opioid neg urines		
Nielsen 2013/ Ling 2009		40% were urine opioid neg after taper, with no benefit to longer taper (28d vs 7d)	12% negative urines after 3 mos post taper	
Parran 2010			77% of those retained at 12 mos remained on tx 18-42 mos later	
Woody 2008/ Polsky 2010/ Subramaniam 2011/Warden 2012	70% at 12 weeks	57% negative urine at 12 weeks, reported less injecting, less opioid use, less cocaine use than control group	all tapered, 60% negative urines at 12 mos f/u, more likely to be in addiction tx than control group	Those who remained on bup had less substance use, fewer psychosocial complications of addiction, more AA affiliation activities, and increased employment at follow-up
Potter 2013	46% at 6 mos			
Stancliff 2012	42% at 12 mos			

TABLE 3: PREDICTORS OF OUTCOMES

	Predictors of Success	Predictors of Failure
Apelt 2013	older, married or living with a partner, working in a full-time job and living in their own flat	
Alford 2011	older, employed, and who self-maintained with illicit buprenorphine had significantly higher odds of success	African American or Hispanic race had significantly lower odds of treatment success
Cunningham 2008	users of street methadone	users of alcohol and opioid analgesics
Dreifuss 2013/Weiss 2011	age, lifetime major depressive disorder, having only used opioids by swallowing or sublingual administration, and receiving no prior opioid dependence treatment	previous use of heroin, having used Oxycontin as most frequent drug
Fiellin 2006 and 2008/ Moore 2007/Wang 2010	Prescription opioid use only.	Incarceration history was not significantly associated with tx outcomes
Mintzer 2007	private insurance coverage (possible surrogate for employment?), older age, and longer duration of treatment	
Neumann 2013	Counseling attendance and history of past injury/trauma. Chronic pain not measured.	
Nielsen 2013/Ling 2009	PO users had significantly more opioid free urine at end of study, significance disappeared when controlling for physical conditions.	
Parran 2010	being employed at entry into the study and the use of prescription opioids rather than heroin	Lower SES slightly more likely to be retained, but more likely to report continued opioid abuse.

TABLE 3: PREDICTORS OF OUTCOMES

	Predictors of Success	Predictors of Failure
Woody 2008/Polsky 2010/Subramaniam 2011/ Warden 2012	Recent IVDU, active medical or psychiatric condition, use of medications, early abstinence during study, non-heroin drug use	
Potter 2013	Opioid analgesic users as opposed to heroin or combined users. Non-injectors compared to injectors.	older age, African American
Stancliff 2012	African American race, not influenced by pre tx drug of choice	Latino

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Research

Web exclusive

Buprenorphine-naloxone use in pregnancy for treatment of opioid dependence

Retrospective cohort study of 30 patients

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Abstract

Objective To examine the maternal course and neonatal outcomes for women using buprenorphine-naloxone for opioid dependence in pregnancy.

Design Retrospective cohort study comparing outcomes for the group of pregnant patients exposed to buprenorphine-naloxone with outcomes for those exposed to other narcotics and those not exposed to narcotics.

Setting Northwestern Ontario obstetric program.

Participants A total of 640 births in an 18-month period from July 1, 2013, to January 1, 2015.

Main outcome measures Maternal outcomes included route and time of delivery, medical and surgical complications, out-of hospital deliveries, change in illicit drug use, and length of stay. Neonatal outcomes included stillbirths, incidence and severity of neonatal abstinence syndrome, birth weight, gestational age, Apgar scores, and incidence of congenital abnormalities.

Results Thirty pregnant women used buprenorphine-naloxone for a mean (SD) of 18.8 (11.2) weeks; an additional 134 patients were exposed to other opioids; 476 pregnant women were not exposed to opioids. Maternal and neonatal outcomes were similar among the 3 groups, other than the expected clinically insignificant lower birth weights among those exposed to opioids other than buprenorphine-naloxone.

Conclusion Buprenorphine-naloxone appears to be safe for use in pregnancy for opioid-dependence substitution therapy. Transferring a pregnant patient to another opioid agonist that has greater abuse potential might not be necessary.

EDITOR'S KEY POINTS

- Opioid dependence is common in northwestern Ontario, and buprenorphine-naloxone is widely used in community-based opioid-replacement programs. Although efforts are made to ensure patients use contraception, some women become pregnant while taking buprenorphine-naloxone. Switching to another maintenance agent can present challenges. This study aimed to examine the outcomes of pregnancies exposed to buprenorphine-naloxone.

- The authors found that, within the context of an established prenatal program that values opioid tapering to decrease neonatal abstinence syndrome, buprenorphine-naloxone could be safely used in pregnancy. Maternal and neonatal outcomes were generally similar to those of pregnancies exposed to other opioids and those not exposed to opioids.

- Pregnancies exposed to buprenorphine-naloxone had significantly larger (normal) birth weights than pregnancies exposed to other narcotics did ($P=.004$), and more patients taking buprenorphine-naloxone were able to cease illicit opioid use in pregnancy ($P<.001$).

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Buprenorphine-naloxone is a commonly used maintenance medication for nonpregnant patients with opioid dependence.[1-5] It has been demonstrated to be a safe and effective opioid agonist in outpatient and primary care settings.[1-5] Recent evidence shows buprenorphine to be equivalent or superior to methadone in managing opioid dependence in pregnancy.[6,7] Use of the combination of buprenorphine and naloxone in pregnancy is limited by concern about fetal exposure and possible withdrawal from the naloxone component of this medication.[6,7]

In northwestern Ontario, where opioid dependence is an epidemic, buprenorphine-naloxone is widely used in community-based programs as opioid-replacement medication.[8] In one community in our region, 41% of adults aged 20 to 50 years had taken this maintenance therapy in the preceding 2 years.[9] This sublingual preparation is favoured in community-based addiction programs owing to its safety profile and efficacy.[1-5] The naloxone component is intended to deter diversion to an intravenous route and the buprenorphine component is effective for managing narcotic cravings.[1-5]

Although efforts are made to ensure patients use contraception while taking buprenorphine-naloxone, some women with opioid dependence in our region become pregnant while participating in this maintenance program.[9,10] The combination medication buprenorphine-naloxone is rated category C by the US Food and Drug Administration (potential benefits should outweigh the potential risk).[11] Once the pregnancy is known and brought to the attention of health care providers, a decision is made to continue with the buprenorphine-naloxone or switch the patient to another long-acting narcotic. Long-acting morphine and single-agent buprenorphine are common choices.[12]

As the MOTHER study in 2010 and a 2014 meta-analysis informed us of the efficacy and safety of buprenorphine in pregnancy, our study is in large part an observational study of naloxone exposure in early pregnancy in the context of community-based treatment of opioid dependence.[7,13,14] Systemic absorption of low-dose sublingual naloxone is considered minimal owing to first-pass effect.[15,16] Outside of research centres, there is no easily applied measure of fetal well-being beyond late pregnancy ultrasound, nonstress testing, and actual birth outcomes.[17,18]

Our hypothesis is that buprenorphine-naloxone constitutes a safe harm-reduction strategy in pregnant women using opioids.

Our catchment area of 30 000 patients in northwestern Ontario includes 25 000 mostly First Nations patients in remote communities who receive their initial pregnancy care at the nursing stations in their communities.[19] Methadone is not available in such remote areas, as there is no local prescribing or dispensing capacity.[10] Changing a pregnant woman's opioid to single-agent buprenorphine requires sending written requests to Health Canada and the manufacturer, and it is usually weeks or months before the request is approved and the medication arrives. Because buprenorphine is not approved by Health Canada, the physician must receive and store the medication, rather than use commercial pharmacies. The alternative is a long-acting morphine preparation, which has been commonly used in our Integrated Pregnancy Program (IPP).[12] If the patient and physician decide to change from the prepregnancy maintenance use of buprenorphine-naloxone to another agent, there might be a prolonged delay for administrative reasons, or the patient might decide to continue taking buprenorphine-naloxone. The IPP is a multidisciplinary program supporting pregnant women, their partners, and their family members, with or without addictions.[12] It is a hospital outpatient clinic with nurses, counselors, physicians, and lactation consultants. The program has women from remote communities come to Sioux Lookout, Ont, for consultations during pregnancy and confinement for delivery. The program strives to provide comprehensive care to the family as a unit, including opioid-dependence treatment if needed. Opioid exposure during pregnancy occurs in up to 28% of pregnancies in our region.[12] Harm-reduction strategies include narcotic weaning in pregnancy to reduce the incidence of neonatal abstinence syndrome (NAS), as well as opioid-substitution therapy. The IPP program coordinates opioid-substitution therapy and aftercare with remote community-based addiction programs, which often involves use of buprenorphine-naloxone.[9] This study documents a cohort of women using buprenorphine-naloxone during pregnancy and describes the course and outcomes of their pregnancies.

METHODS

In this retrospective cohort study, maternal and neonatal data were collected from the Sioux Lookout Meno Ya Win Health Centre IPP program and from obstetric program and hospital records between July 1, 2013, and January 1, 2015, on all births beyond 20 weeks. Primary neonatal outcomes were incidence of congenital anomalies, stillbirths, birth weight, gestational age, Apgar scores, and incidence of NAS. Primary maternal outcomes included out-of-hospital deliveries, medical and surgical complications, route and time of delivery, change in illicit drug use, and length of stay.

Data were analyzed using Excel and SPSS, and analyses included independent-samples *t* tests for continuous data and Pearson χ^2 or Fisher exact tests, as appropriate, for categorical data. The study group was women exposed to buprenorphine-naloxone during pregnancy. Two comparison groups included pregnant women exposed to other narcotics during the same period and pregnant women not exposed to opioids. We used the nonexposed group as a normal control group and the group exposed to other narcotics to observe any outcomes in narcotic-exposed pregnancies that might vary as a result of exposure to buprenorphine-naloxone in particular. Ethics approval was granted by the Sioux Lookout Meno Ya Win Health Centre Research Review and Ethics Committee.

RESULTS

We collected data from all 640 deliveries from July 1, 2013, to January 1, 2015. There was a total of 164 narcotic-exposed pregnancies (25.6%), including 30 patients taking buprenorphine-naloxone at the commencement of their pregnancy (**Table 1**). The 164 patients in the narcotic-exposed group includes 34 patients who were taking opioid-replacement therapy at the time of conception (30 taking buprenorphine-naloxone and 4 taking other opioid agents) and 130 patients who were solely using illicit narcotics. Of the total group of narcotic-exposed (prescribed and illicit) pregnancies, all were offered opioid maintenance therapy and tapering during their pregnancy. Of the combined 164 narcotic-exposed pregnancies, 56 (34.1%) decreased their dose of illicit narcotics and 73 (44.5%) had quit by the time of delivery. For those women who reported quitting, results were confirmed by point-of-care testing and confirmatory chromatography urine drug screening. The group-specific rates of illicit narcotic use at delivery are listed in **Table 2**.

Five women took buprenorphine-naloxone throughout their pregnancies and they had results similar to the nonexposed pregnancies, but also included 1 mild case of NAS and 1 postpartum hemorrhage. Three of these 5 had quit using any additional illicit drugs at the time of delivery, and opioid maintenance for all 5 was managed with an average of 4 mg (range 1 to 6 mg) of buprenorphine-naloxone at delivery. There were no cases of congenital anomalies or stillbirths among these 5 patients.

The larger group of women exposed to buprenorphine-naloxone (n = 30, including the 5 described above) used the medication for a mean (SD) of 18.8 (11.2) weeks (**Table 1**). The mean (SD) exposure time was lower (15.9 [8.58] weeks) if the 5 women who remained on the medication throughout their pregnancies were excluded.

The comparison group exposed to other opioids (n = 134) was composed primarily of 130 patients not taking prepregnancy substitution therapy, including 40 patients who managed their dependence through

Table 1. Maternal characteristics and outcomes

CHARACTERISTICS	A: EXPOSED TO BUPRENORPHINE-NALOXONE (N = 30)	B: EXPOSED TO OTHER OPIOIDS (N = 134)	*P* VALUE (A–B)	C: NOT EXPOSED TO OPIOIDS (N = 476)	*P* VALUE (A–C)
Mean (SD) age, y	26.1 (4.03)	25.4 (4.56)	.442	24.9 (6.17)	.296
Mean (SD) gravidity	4.4 (2.50)	3.9 (2.03)	.240	3.2 (2.22)	.004
Mean (SD) time taking buprenorphine-naloxone, wk	18.8 (11.20)	NA	NA	NA	NA
Initial mean (SD) dose of buprenorphine-naloxone, mg	9.2 (6.20)	NA	NA	NA	NA
Smoker, n (%)	25 (83.3)	113 (84.3)	.893	229 (48.1)	< .001
Alcohol use, n (%)	6 (20.0)	32 (23.9)	.649	98 (20.6)	.938
Type 2 diabetes, n (%)	2 (6.7)	3 (2.2)	.227	14 (2.9)	.244
Hypertension, n (%)	3 (10.0)	8 (6.0)	.424	29 (6.1)	.426
Hepatitis C, n (%)	1 (3.3)	7 (5.2)		1 (0.2)	.115
History of marijuana use, n (%)	4 (13.3)	49 (36.6)	.014	46 (9.7)	.514
Urine positive for THC, n (%)	4 (13.3)	35 (26.1)	.137	28 (5.9)	.104
Gestational diabetes, n (%)	3 (10.0)	13 (9.7)	.960	42 (8.8)	.742
Mean (SD) gestational age, wk	38.9 (1.48)	38.6 (1.60)	.348	38.9 (1.52)	> .999
Cesarean section, n (%)	5 (16.7)	35 (26.1)	.276	120 (25.2)	.293
Postpartum hemorrhage, n (%)	3 (10.0)	10 (7.5)	.708	44 (9.2)	.752
Mean (SD) LOS, d	3.0 (1.63)	2.7 (1.71)	.382	1.9 (1.13)	< .001
Out-of-hospital delivery, n (%)	1 (3.3)	3 (2.2)	.558	10 (2.1)	.493

LOS—length of stay, NA—not applicable, THC—tetrahydrocannabinol.

Table 2. Illicit opioid drug use at delivery

OPIOID USE	WOMEN EXPOSED TO BUPRENORPHINE-NALOXONE (N = 30), N (%)	WOMEN EXPOSED TO OTHER OPIOIDS (N = 134), N (%)
Quit*	24 (80.0)	49 (36.6)
Decreased	3 (10.0)	53 (39.6)
Increased	0 (0.0)	1 (0.7)
No change	1 (3.3)	23 (17.2)
Unknown	2 (6.7)	8 (6.0)

*Significantly more women in the group exposed to buprenorphine-naloxone had quit using illicit opioids at delivery ($P < .001$).

illicit sources and declined ongoing offers of prescribed maintenance medication.

Neonatal outcomes were similar between the 3 groups with the exception of the expected clinically insignificant lower birth weights among the pregnancies exposed to other opioids (**Table 3**).

DISCUSSION

Our study found that, within the context of an established prenatal program that values opioid tapering to decrease NAS, buprenorphine-naloxone can be safely used in pregnancy. We also found that pregnancies exposed to buprenorphine-naloxone had significantly larger (normal) birth weights than pregnancies exposed to other narcotics did ($P = .004$), and more patients taking buprenorphine-naloxone were able to cease illicit opioid use in pregnancy ($P < .001$). Maternal outcomes were similar in all 3 groups in terms of route and time of delivery and medical and surgical complications (**Table 1**). Neonatal outcomes were also similar between the 3 groups, except for the expected clinically insignificant lower birth weights among the pregnancies exposed to other opioids (**Table 3**).

Few other studies report outcomes from buprenorphine-naloxone exposure in pregnancy.

A 2013 American retrospective study reported on 10 exposed women.[20] Eight of these women were already taking maintenance therapy at the time of conception, as was the case with the 30 participants in our study. A 2013 publication used data from the same 10 participants and compared them with data from other opioid-maintenance medication programs; the authors found outcomes similar to those for patients taking methadone or single-agent buprenorphine.[21]

Another 2015 study compared 31 mother-neonate dyads treated with buprenorphine-naloxone with a similar number of pregnancies treated with methadone maintenance. They demonstrated a 50% reduction in the incidence of NAS and an equal reduction in the length of stay for the buprenorphine-naloxone treated group.[22] The average dose of buprenorphine-naloxone in this study was 14.4 mg, higher than our 9.2 mg average dose, but our dose was a maintenance dose for women already stable on the medication, not an induction dose. This study did not undertake narcotic weaning during the pregnancies and excluded any births with congenital anomalies. It also did not record the length of time or initiation point for maintenance in the pregnancy. The positive comparison to a similar methadone-maintained group gives a clear signal that buprenorphine-naloxone therapy is about to find its place in opioid-dependence treatment in pregnancy.

Our comparison groups were not chosen to systematically show the effect on outcomes of buprenorphine-naloxone exposure in pregnancy, but to demonstrate its place in an obstetric program dealing with a heavy load of opioid-dependent women. The buprenorphine-naloxone cohort in our study was heterogeneous, as its members underwent medication switching and tapering as clinically indicated or preferred by the patient throughout pregnancy. Despite this limitation, we did believe it was useful to describe this reasonably sized prospective cohort who took buprenorphine-naloxone during the first trimester of their pregnancies, even without an ideal comparison group.

Table 3. Neonatal characteristics and outcomes

NEONATAL CHARACTERISTICS	A: EXPOSED TO BUPRENORPHINE-NALOXONE (N = 30)	B: EXPOSED TO OTHER OPIOIDS (N = 134)	*P* VALUE (A–B)	C: NOT EXPOSED TO OPIOIDS (N = 476)	*P* VALUE (A–C)
Preterm (< 37 wk), n (%)	1 (3.3)	6 (4.5)	.799	19 (4.0)	.857
Mean (SD) birth weight, g	3569.0 (491.91)	3243.7 (557.2)	.004	3531.0 (590.2)	.730
Mean (SD) 1-min Apgar score	8.8 (0.47)	8.7 (1.05)	.611	8.6 (1.1)	.323
Mean (SD) 5-min Apgar score	9.0 (0.18)	8.9 (0.83)	.513	8.9 (0.71)	.442
Any NAS score, n (%)	6 (20.0)	22 (16.4)	.637	0 (0.0)	< .001
NAS score > 7, n (%)	0 (0.0)	12 (9.0)	.126	0 (0.0)	> .999
Stillbirths, n (%)	0 (0.0)	1 (0.7)	> .999	3 (0.6)	> .999
Congenital anomalies, n (%)	1 (3.3)	0 (0.0)	.180	1 (0.2)	.115
Male sex, n (%)	15 (50.0)	74 (55.2)	.657	243 (51.1)	.911
Transfer to tertiary care, n (%)	1 (3.3)	5 (3.7)	> .999	9 (1.9)	.460

NAS—neonatal abstinence syndrome.

We demonstrated very few differences among our comparison groups in this study. Because the group exposed to other narcotics included patients who refused any prescribed maintenance therapy and often continued their illicit narcotic use, this group had the lowest birth weights (3243.7 g, $P = .004$), below the Canadian average of 3300 g.[23] As expected, both exposed groups had longer lengths of stay ($P < .001$) and more of their neonates experienced some NAS symptoms ($P < .001$) than the neonates in the nonexposed group did. Neonatal abstinence syndrome in narcotic-exposed pregnancies seems to generally affect approximately 20% of our deliveries, with few affected neonates historically requiring pharmacologic treatment for Finnegan scores of 8 or greater, likely owing to narcotic tapering, which has become routine in our practice.[8,12] A recent study of 94 methadone-maintained pregnant women demonstrated a rate of higher Finnegan scores requiring pharmacologic treatment at 26.6%, while only 7.3% of our opioid-exposed participants had Finnegan scores above 7.[24] This might be owing to our narcotic-dose tapering during pregnancy or lower doses of total opioid use at delivery.[12]

Rates of smoking were very high in both narcotic-exposed groups (more than 80%) and remained substantial in the nonexposed group as well (more than 50%), as has been seen in other studies in our region.[25,26]

The finding that more of the women taking buprenorphine-naloxone quit illicit narcotic use ($P < .001$) likely reflects that the comparison group included a large number of patients who declined opioid substitution and tapering rather than any inherent attributes of the medication itself. Many in the comparison group chose to maintain their own approach to opioid dependence rather than accept prescribed opioid-substitution therapy, although more than 35% of them did quit illicit narcotics (**Table 2**).

The mean length of stay in both groups of opioid-exposed pregnancies is quite short, at 3 days or less. This contrasts with a recent study of methadone-maintained pregnancies with a mean stay of 15 days.[23] Many of our patients live in remote communities and stay in a hostel located next to the hospital. They are able to be seen daily as outpatients and some have maternal and neonatal outpatient dispensing of opioid-withdrawal medications in that setting.

This study demonstrates in a limited way the safety of buprenorphine-naloxone in pregnancy. Because the drug is useful for its resistance to diversion to intravenous abuse and its opioid agonist component has a superior NAS profile than methadone, this combination medication might be a very useful medication in pregnancies complicated by opioid use disorder.[12]

Limitations

The opioid-exposed control and comparison groups were not homogeneous. This intention-to-treat prospective design followed the variable clinical course and patient preferences as negotiated throughout the pregnancy. In particular, most of those exposed to opioids other than buprenorphine-naloxone were not taking maintenance therapy before pregnancy, and many declined any substitution therapy during the pregnancy. It would stand to reason that they would have the greatest opioid-related effects and the lowest birth weights, which they did.

Small sample sizes such as those in our study are inadequate to comment on rare outcomes such as congenital anomalies, which would be the outcome of interest when examining medication exposure during the organogenesis period of the first trimester.

In a vast geographically dispersed region such as northwestern Ontario (which is the size of France), access to all commodities, including drugs of abuse, is intermittent. Both opioid-exposed groups had participants with ongoing illicit opioid use (20.0% of the buprenorphine-naloxone group and 63.4% of the group exposed to other opioids). We do not know the extent or effects of this withdrawal cycle experienced by ongoing illicit users resulting from variable availability of illicit opioids in these remote communities, many of which do not have road access.

Our outcomes are within the context of an established prenatal care program that values opioid tapering to decrease incidence of NAS. This treatment goal would affect the outcomes of both opioid comparison groups, although perhaps not equally, owing to patient preference.

Conclusion

Buprenorphine-naloxone appears to be safe in pregnancy. Larger prospective studies are warranted to understand the role it can play in the complex behavioural and chemical aspects of managing opioid use disorder in pregnancy. Transferring a pregnant patient to a different opioid agonist that has greater abuse potential might not be necessary.

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Contributors
Dr Kelly prepared all drafts of the article and the study design. **Dr Jumah** participated in study design. **Ms Balfour-Boehm** and **Ms Blakelock** were research assistants who gathered the data and helped design the data collection tool. **Drs Guilfoyle, Dooley, Antone,** and **Gerber-Finn** and **Ms Hopman** participated in the original study design and data collection. All authors contributed to revising the article and approved the final draft.

Competing interests
None declared

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Observational study of the safety of buprenorphine+naloxone in pregnancy in a rural and remote population

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ABSTRACT

Objectives: To describe the effect of in utero exposure to the buprenorphine+naloxone combination product in a rural and remote population.

Setting: A district hospital that services rural and remote, fly-in communities in Northwestern Ontario, Canada.

Participants: A retrospective cohort study was conducted of 855 mother infant dyads between 1 July 2013 and 30 June 2015. Cases included all women who had exposure to buprenorphine+naloxone during pregnancy (n=62). 2 control groups were identified; the first included women with no opioid exposure in pregnancy (n=618) and the second included women with opioid exposure other than buprenorphine +naloxone (n=159). Women were excluded if they had multiple pregnancy or if they were part of a methadone programme (n=16). The majority of women came from Indigenous communities.

Outcomes: The primary outcomes were birth weight, preterm delivery, congenital anomalies and stillbirth. Secondary neonatal outcomes included gestational age at delivery, Apgar scores at 1 and 5 min, NAS Score >7 and treatment for neonatal abstinence syndrome (NAS). Secondary maternal outcomes included the number of caesarean sections, postpartum haemorrhages, out of hospital deliveries and transfer of care to tertiary centres.

Results: No difference was found in the primary outcomes or in the Apgar score and caesarean section rate between in utero buprenorphine+naloxone exposure versus no opioid exposure in pregnancy. Compared to women taking other opioids, women taking buprenorphine+naloxone had higher birthweight babies (p=0.001) and less exposure to marijuana (p<0.001) during pregnancy.

Conclusions: Retrospective data suggest that there likely is no harm from taking buprenorphine+naloxone opioid agonist treatment in pregnancy. Larger, prospective studies are needed to further assess safety.

Strengths and limitations of this study

- Opioid misuse is epidemic in rural and remote areas of Northwestern Ontario, Canada, with up to 30% of women exposed during pregnancy. Community-based buprenorphine+naloxone programmes have engaged many rural women in treatment programmes who otherwise would not receive care.
- This is the largest cohort of women exposed to buprenorphine+naloxone in pregnancy and contains detailed information about the daily dose, cumulative dose and exposure time with respect to each trimester of pregnancy.
- While 62 women had exposure to buprenorphine +naloxone in pregnancy, only 3 women had exposure throughout all three trimesters, a further 48 had exposure in the first trimester only and the remainder had variable lengths of exposure.
- Data on illicit substances, smoking and alcohol use during pregnancy were determined by self-report and confirmed with urine drug screens. Data were not collected on other exposures or on the use of other medications such as antidepressants, anxiolytics and folic acid.
- Data were collected retrospectively and were limited to antenatal, maternal and neonatal outcomes. Prospective data and long-term outcomes would provide more robust safety data.

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INTRODUCTION

Opioid dependence in pregnancy is an increasingly common occurrence in rural and remote areas such as Northwestern Ontario, Canada, where up to 28% of pregnancies are exposed to opioid use.[1] Our catchment area of 30 000 patients includes 25 000 patients in remote communities who are mostly Indigenous and receive their initial pregnancy care at the nursing station in their community.[2] Methadone treatment has the most evidence regarding safety and efficacy in pregnancy;[3 4] however, due to logistical and regulatory limitations, methadone is often not available in rural and remote areas.[5] Community-based, sublingual buprenorphine+naloxone treatment programmes have been established in rural and remote, predominantly Indigenous

communities in order to provide access to treatment in areas with high rates of opioid dependence and no access to methadone.[5]

The WHO and several national Obstetrics and Gynaecology associations recommend that, when pregnancy is diagnosed, women participating in a buprenorphine+naloxone treatment programme switch to the buprenorphine mono-product because the safety of buprenorphine+naloxone has not been demonstrated in pregnancy.[6–8] A multicentred randomised controlled trial demonstrated that the buprenorphine mono-product has similar pregnancy outcomes and decreased severity of neonatal abstinence syndrome compared to methadone.[9] Naloxone was added to buprenorphine as a deterrent to illicit use as it precipitates withdrawal from opioids when administered intravenously or intranasally but not via the buccal or sublingual routes.[10 11] Precipitated withdrawal has been shown to result in adverse pregnancy outcomes.[12 13]

The caution against using buprenorphine+naloxone in pregnancy is not limited to concerns for withdrawal but also possible teratogenicity. However, to date, there have been no reports of teratogenicity in humans or animals.[14] Congenital anomalies are only one marker of drug safety in pregnancy. The live birth rate, spontaneous abortion rate and stillbirth rates are also markers of safety, and among live births, preterm delivery, low birth weight and functional deficits are factors that may be affected by a medication.[15] Further, the severity of pregnancy outcomes may be modified by the duration and intensity of the exposure to the medication.

In Canada, the buprenorphine mono-product is available only through a special access programme. In our setting, women are counselled to transition from buprenorphine+naloxone to either buprenorphine or long-acting morphine when they present for antenatal care. As a result of delays in obtaining buprenorphine through the special access programme, many women are exposed to buprenorphine+naloxone during early pregnancy and into the second trimester. In addition, for personal reasons, some women opt to remain on buprenorphine+naloxone throughout their pregnancy. This study documents the pregnancy outcomes of a cohort of women from rural and remote communities in Northwestern Ontario who continued to take buprenorphine+naloxone treatment during pregnancy as part of a community-based treatment programme.

METHODS

Participants

Maternal and neonatal data were collected from outpatient antenatal clinic records and inpatient medical records for all pregnancies between 1 July 2010 and 31 July 2015. Cases included all women who had exposure to buprenorphine+naloxone during pregnancy. Two control groups were identified; the first included women with no opioid exposure in pregnancy and the second included women with opioid exposure other than buprenorphine+naloxone. All women who were receiving opioid agonist treatment with buprenorphine+naloxone were advised to switch to the buprenorphine mono-product when available, once pregnancy was diagnosed as per national guidelines.[7] Cases represent those women who elected to stay on buprenorphine+naloxone during their pregnancy. Women were excluded if they had a multiple pregnancy or were taking methadone as part of a treatment programme. All infants room-in with their mother following delivery unless there is a medical or safety reason that precludes rooming-in. The majority of women came from Indigenous communities.

Data collection

A standard case report form was used to collect maternal and neonatal data. The maternal case report form contained information on the health and pregnancy history; smoking, drug and alcohol exposure; and intrapartum data. Smoking was defined by self-reported daily use of cigarettes and was further characterised by the number of cigarettes smoked per day. Alcohol and drug exposure were determined by self-report. Drug exposure was characterised further by urine drug screen results. The neonatal case report form contained information on birth weight, gestational age, Apgars, congenital anomalies and stillbirths.

The primary outcomes for the study was an assessment of the safety of buprenorphine+naloxone, including birth weight, preterm delivery (delivery prior to 37 +0 weeks gestational age), congenital anomalies and stillbirth. Secondary neonatal outcomes included gestational age at delivery, Apgar scores at 1 and 5 min, NAS Score >7 and treatment for NAS (two or more NAS Scores that are >7). NAS Scores were calculated using a modified Finnegan Scale at the bedside by nurses who have been trained to use this measure. Secondary maternal outcomes included the number of caesarean sections, postpartum haemorrhages, out of hospital deliveries and transfer of care to tertiary centres.

Statistical analysis

Categorical variables are presented as percentages while continuous variables are presented as a mean with SD. We compared cases to controls using a t-test for continuous variables and a Pearson χ^2 test of independence or a Fisher's Exact test, as appropriate, for categorical data. ORs are presented with the 95% CI. Data analysis was performed with SPSS statistical software V.20 (SPSS, Chicago, Illinois, USA) and Microsoft Excel V.14.1.0 (Microsoft Corp, Redmond, Washington, USA). A p value<0.05 indicated statistical significance.

Ethics

Ethics approval was granted by the Sioux Lookout Meno Ya Win Health Centre Research Review and Ethics Committee.

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RESULTS

A total of 855 consecutive singleton births were included in the study, of these, 62 had exposure to buprenorphine+naloxone, 618 had no opioid exposure and 159 used illicit opioids during the pregnancy (figure 1). Sixteen women were excluded due to participation in a methadone treatment programme. Twenty-five women were excluded due to a multiple pregnancy. Maternal characteristics are described in table 1. The overall rate of opioid exposure in pregnancy is 27.8%. Data on the racial and ethnic make-up of our study participants as well as data on educational attainment were not collected. Previous studies of this population show that the majority (85%) of women are Indigenous.[2] Educational attainment among Indigenous women living on reserve is low where 57% do not complete high school, 16% receive a high school diploma, 19% participate in postsecondary education and only 4% have a university degree.[16]

A total of 62 women had exposure to buprenorphine +naloxone in pregnancy (see figure 1). Of these women, three women continued prepregnancy buprenorphine +naloxone throughout pregnancy and after delivery. A further 48 women who were taking buprenorphine +naloxone prior to pregnancy switched to buprenorphine alone after the first trimester as per national and international guidelines.[6–8] Eleven women were induced onto buprenorphine+naloxone during pregnancy, and this occurred in the first trimester for 6 women. The average daily dose of buprenorphine+naloxone was 8.2 ±5.8 mg. Ongoing illicit opioid use was identified in 12 women (19.4%) through routine urine drug screening. Six cases had positive urine drug screens for marijuana. No other illicit substances were identified on urine drug screening. Data were not collected for other psychotropic medications or antidepressant medications.

Cases and controls were of similar age at the time of delivery. However, women who had no opioid exposure in pregnancy had fewer pregnancies and fewer births compared to cases. The OR of Hepatitis C infection for women taking buprenorphine+naloxone compared to no opioid use was OR 15.7, 95% CI 2.6 to 95.6. Women

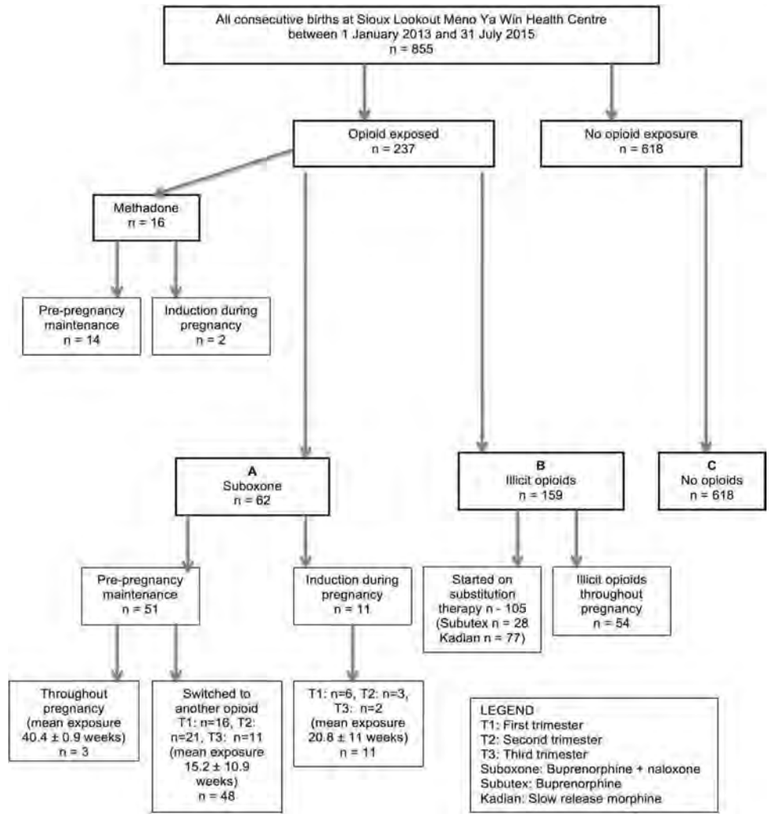

Figure 1 Patient flow chart.

Table 1 Maternal characteristics

Variable	A Bup/Nalox (n=62)	B No opioids (n=618)	A–B p Value	C Illicit opioids (n=159)	A–C p Value
Age (years)	25.9±4.4	25.2±6.3	0.21	25.5±4.6	0.63
Gravida	4.1±2.4	3.3±2.3	0.009	3.9±2.1	0.54
Parity	2.4±1.8	1.8±2.0	0.03	2.2±1.7	0.50
Comorbidities					
Type II diabetes	5 (8.1%)	26 (4.2%)	0.19†	3 (1.9%)	0.04†
Gestational diabetes	7 (11.3%)	63 (10.2%)	0.79*	14 (8.8%)	0.57*
Hypertension	6 (9.7%)	39 (6.3%)	0.29†	11 (6.9%)	0.58†
HIV	0	0		0	
Hepatitis B	0	0		1 (0.6%)	>0.99†
Hepatitis C	3 (4.8%)	2 (0.3%)	0.006†	12 (7.5%)	0.566
Prenatal smoking and alcohol exposure					
Smoking, cig/day					
None	7 (11.3%)	327 (52.9%)	<0.001*	20 (12.6%)	0.79*
1–5	33 (53.2%)	208 (33.7%)	0.002*	61 (38.4%)	0.045*
6–10	15 (24.2%)	51 (8.3%)	<0.001*	34 (21.4%)	0.65*
>10	7 (11.3%)	32 (5.2%)	0.08†	44 (27.7%)	0.009†
Alcohol	11 (17.7%)	134 (21.7%)	0.47*	41 (25.8%)	0.21*

Data are n (%) or mean±SD unless otherwise specified.
*χ^2 test was used.
†When assumptions for the χ^2 test were not met, the Fisher's Exact test was used.

taking buprenorphine+naloxone were more likely to smoke 1–5 cigarettes per day compared to women in the control groups while women continuing to use illicit opioids were more likely to be heavy smokers (>10 cigarettes per day). There was no difference in alcohol consumption between the three groups.

Prenatal patterns of substance use revealed a high number of women with polysubstance use defined as the use of at least one other illicit substance among women taking buprenorphine+naloxone (12.9%) and those continuing to use illicit opioids (53.5%) (table 2). Treatment with buprenorphine+naloxone decreased the odds of polysubstance use in pregnancy to 0.13 (0.06 to 0.29) compared to women with ongoing illicit opioid use. The most frequent non-opioid drug of abuse was marijuana followed by cocaine (see table 2). Among women continuing to use illicit opioids during pregnancy, the majority (59.7%) used morphine followed by oxycodone derivatives (30.8%). The route of administration for women continuing to use illicit opioids during pregnancy was predominantly intravenous (67.9%) and intranasal (30.8%). Data on the primary opioid of abuse and route of administration were largely missing for women taking buprenorphine+naloxone and as a result a valid comparison cannot be made.

The primary outcome of this study is the safety of in utero exposure to buprenorphine+naloxone (table 3). For the 62 women exposed to buprenorphine+naloxone during pregnancy, the duration of exposure (mean±SD) was 121.4±75.5 days with a daily dose of 8.2±5.8 mg. Among parameters used to define safety of the drug, there was no difference in the birth weight, number of preterm deliveries, number of congenital malformations or number of stillbirths in women taking buprenorphine +naloxone compared to women taking no opioids during pregnancy. Women who continued to use illicit opioids had a statistically significant reduction in birth weight of 262.7 g compared to women treated with buprenorphine+naloxone. There were no stillbirths among the cohort taking buprenorphine+naloxone, five among the women with no opioid exposure and one among the women taking illicit opioids.

There were a total of five congenital malformations in the control group with no opioid exposure and none in the group with illicit opioid exposure. Two infants exposed to buprenorphine+naloxone had congenital malformations: one case of bilateral cleft palate and another case of atrial septal defect. The infant with the bilateral cleft palate had exposure to buprenorphine +naloxone from conception until the third trimester at which point the mother was switched to buprenorphine mono-product. The daily dose ranged from 2 to 4 mg, and the cumulative dose was 525 mg. There was alcohol exposure and smoking (>10 cigarettes per day) during the pregnancy but no other illicit opioids. The infant with the atrial septal defect had exposure to buprenorphine+naloxone from the first trimester until delivery. The daily dose ranged from 2 to 4 mg, and the cumulative dose was 564 mg. There was no other smoking, drug or alcohol exposure during this pregnancy, and there is no family history of congenital heart disease. Data on prepregnancy folic acid supplementation and prepregnancy body mass index were not available for either woman. Both women were diagnosed with gestational diabetes.

Secondary neonatal outcomes (table 4) revealed no difference between cases and controls with respect to

Table 2 Prenatal exposure to drugs of abuse

	A Bup/Nalox (n=62)	B No opioids (n=618)	A–B p Value	C Illicit opioids (n=159)	A–C p Value
Primary opioid of abuse, n (%)					
Morphine	14 (22.6%)	0		95 (59.7%)	<0.001*
Oxycodone, Percocet and OxyNeo	5 (8.1%)	0		50 (31.4%)	<0.001†
Hydromorphone	4 (6.5%)	0		7 (4.4%)	0.507†
Tylenol+Codeine	0	0		4 (2.5%)	0.578†
Methadone	0	0		1 (0.6%)	>0.999†
Suboxone	1 (1.6%)	0		9 (5.7%)	0.289†
Unknown	39 (62.9%)	0		7 (4.4%)	<0.001*
Route of opioid administration, n (%)					
Intravenous	16 (25.8%)	0		108 (67.9%)	<0.001*
Snort/intranasal	5 (8.1%)	0		49 (30.8%)	<0.001†
By mouth/per os	0	0		9 (5.7%)	0.064†
Smoke/inhale	1 (1.6%)	0		7 (4.4%)	0.447†
Not available	42 (67.7%)	0		8 (5.0%)	<0.001*
Frequency of opioid use, n (%)					
Occasional (two times per week or less)	1 (1.6%)	0		25 (15.7%)	0.003†
Regular (three times per week or more)	5 (8.1%)	0		26 (16.4%)	0.111†
Daily	11 (17.7%)	0		97 (61.0%)	<0.001*
Unknown	45 (72.6%)	0		11 (6.9%)	<0.001*
Other drugs of abuse, n (%)					
Polysubstance use	8 (12.9%)	0	<0.001†	85 (53.5%)	<0.001*
Marijuana, reported	8 (12.9%)	60 (9.7%)	0.424*	58 (36.5%)	0.001*
Marijuana, positive urine screen	6 (9.7%)	36 (5.8%)	0.261†	44 (27.7)	0.004†
Benzodiazepines	0	0		3 (1.9%)	0.561†
Cocaine	1 (1.6%)	0	0.091†	10 (6.3%)	0.299†
Ecstasy	0	0		1 (0.6%)	>0.999†

*χ^2 test was used.
†When assumptions for the χ^2 test were not met, the Fisher's Exact test was used.

Table 3 Primary outcomes

	A Bup/Nalox (n=62)	B No opioids (n=618)	A–B p Value	C Illicit opioids (n=159)	A–C p Value
Primary outcomes					
Preterm delivery, n (%)‡	2 (3.2%)	26 (4.21%)	>0.999†	7 (4.4%)	>0.999†
Birth weight (g), mean±SD‡	3541±540	3553±569	0.924*	3274±551	<0.001*
Congenital anomalies, n (%)	2 (3.2%)	5 (0.8%)	0.127†	0	0.078†
Stillbirths	0	5 (0.8%)	>0.999†	1 (0.6%)	>0.999†

*χ^2 test was used.
†When assumptions for the χ^2 test were not met, the Fisher's Exact test was used.
‡Birth weight and gestational age were limited to live births that were >500 g and >20 weeks.

gestational age at the time of delivery, Apgar scores, NAS Scores and NAS treatment. Secondary maternal outcomes (table 4) showed that mothers exposed to buprenorphine+naloxone stayed in hospital an extra 1.1 days compared to mothers with no opioid exposure in pregnancy. There was no statistically significant difference in length of stay between cases and illicit opioid using controls. There was no difference in the number of caesarean sections, postpartum haemorrhages, out of hospital deliveries or transfers to tertiary care hospitals for cases compared to controls.

DISCUSSION

Almost one-third of the study population were exposed to opioids during pregnancy, but only 5.6% were on opioid agonist treatment prior to pregnancy. There was no evidence of teratogenicity or adverse pregnancy outcomes in a cohort of 62 women exposed to buprenorphine+naloxone during pregnancy compared to women who had no opioid exposure during pregnancy. Two cases of congenital malformations were identified in women exposed to buprenorphine+naloxone. One case of bilateral cleft lip and palate included a significant

Table 4 Secondary outcomes

	A Bup/Nalox (n=62)	B No opioids (n=618)	A–B p Value	C Illicit opioids (n=159)	A–C p Value
Neonatal outcomes					
Gestational age at birth, mean±SD	38.7±1.5	38.9±1.5	0.405	38.6±1.5	0.686
Apgar 1 min, mean±SD	8.7±0.8	8.6±1.3	0.780	8.6±1.2	0.407
Apgar 5 min, mean±SD	9.0±0.4	8.9±0.8	0.761	8.9±0.8	0.421
# NAS Score >7	1 (1.6%)	0		11 (6.9%)	0.186†
Treated for NAS	1 (1.6%)	0		9 (5.7%)	0.289†
Males	38 (61.3%)	325 (52.6%)	0.229*	81 (50.9%)	0.166*
Maternal outcomes					
Caesarean section	14 (22.6%)	151 (24.4%)	0.746*	42 (26.4%)	0.556†
Postpartum haemorrhage	10 (16.1%)	61 (9.9%)	0.124*	14 (8.8%)	0.116†
Length of maternal stay in hospital	3.1±1.5	2.0±1.1	**<0.001**	2.8±1.9	0.235
Out of hospital deliveries	1 (1.6%)	11 (1.8%)	>0.999†	3 (1.9%)	>0.999†
Transfer to tertiary care centre	2 (3.2%)	13 (2.1%)	0.639†	5 (3.1%)	>0.999†

*χ^2 test was used.
†When assumptions for the χ^2 test were not met, the Fisher's Exact test was used.

confounder in the form of in utero alcohol exposure. The second was a case of an atrial septal defect—one of the most common congenital malformations occurring in 1 in 1500 live births.[17] Data regarding other confounders such as folic acid supplementation, exposure to other medications and obesity were not available. In spite of these limitations, the rate of congenital malformations was not significantly different compared to the control group.

Women who continued to use illicit opioids during pregnancy did have babies with a statistically significant lower birth weight compared to those women taking buprenorphine+naloxone. The rate of congenital malformations was not above the rate in the general population although the cohort exposed to buprenorphine +naloxone is small and therefore may give a biased estimation of this risk. Exposure to buprenorphine+naloxone also had no observable impact on Apgar scores or treatment for NAS. The low rates of NAS observed in this study may be accounted for by several factors. First, the majority of community-based opioid agonist programmes included in the study use a low dose treatment protocol where the average maintenance dose of buprenorphine+naloxone is less than 8 mg daily. Second, for those women who continue to use illicit opioids, non-daily, binge use is the predominant pattern of opioid use and short acting opioids (morphine and oxycodone) are the most common opioids of abuse.[17] Furthermore, opioid tapering during pregnancy, with long-acting morphine, is a common practice in this setting and results in lower doses of opioids at the time of delivery.[18] Finally, all infants room-in with their mother after delivery and breastfeeding and supportive care are encouraged, all of which are beneficial in the management of NAS.

This study represents the largest cohort of women exposed to buprenorphine+naloxone in pregnancy and contains detailed information about the daily dose, cumulative dose and exposure time with respect to each trimester of pregnancy. We present an assessment of key safety parameters for mother and infant. A harm reduction strategy is applied in our catchment area as it has been shown that there are better pregnancy outcomes when a woman is part of a treatment programme compared to ongoing use of illicit opioids. Many of the women in this study were inducted on to buprenorphine+naloxone during pregnancy rather than the buprenorphine mono-product. In our jurisdiction, the buprenorphine mono-product is available through a special access programme with lengthy delays between applying for an exemption and receipt of the drug, whereas buprenorphine+naloxone is readily available in communities as part of community-based harm reduction programmes. As a result, women are induced onto buprenorphine+naloxone and maintained on this drug until such time that the buprenorphine mono-product becomes available.

Two small retrospective cohort studies are reported in the literature that look at the effect of buprenorphine +naloxone on pregnancy outcomes.[19–21] The first compared 10 women who took buprenorphine+naloxone in pregnancy to women who took buprenorphine or methadone in six other studies with similar outcome measures. No differences in maternal outcomes or neonatal outcomes were observed with the exception of head circumference which was larger among infants exposed to buprenorphine+naloxone compared to infants who were exposed to methadone withdrawal in utero.[19 20] The second retrospective cohort study compared 31 women who took buprenorphine+naloxone in pregnancy to a control group of 31 women who took methadone in pregnancy. The study excluded stillbirth and congenital malformations as well as women who received treatment for <30 days prior to delivery. Again, no significant differences in maternal or neonatal outcomes were observed. Infants exposed to methadone were born at an earlier gestational age than buprenorphine+naloxone, but the average gestational age for both was >38 weeks.[21]

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Buprenorphine+naloxone is an efficacious treatment for opioid dependence with the advantage of a lower overdose risk and ease of prescribing when compared to methadone.[22] Owing to these factors, it is being used widely in opioid treatment programmes in rural and remote settings where methadone treatment is not available.[23] Currently women participating in buprenorphine+naloxone treatment programmes who become pregnant are advised to switch to the buprenorphine mono-product out of theoretical concerns of the risk of naloxone to the developing fetus. This study demonstrates no increase rate of congenital malformations, stillbirth or low birth weight for women exposed to buprenorphine+naloxone. Anecdotally women who are stable on buprenorphine+naloxone prior to pregnancy express concern about changing medications and often reluctantly switch to the buprenorphine mono-product on the recommendation of their care provider.

Results from this study support the safety of buprenorphine+naloxone in pregnancy and provide evidence for inclusion of pregnancy as an indication for buprenorphine+naloxone therapy. A policy change of this nature would increase access to care for many women residing in rural and remote settings or where methadone is not an option. Ongoing research and postmarket surveillance would be required to assess rare outcomes. Furthermore, longitudinal studies of the infants exposed to buprenorphine in utero should be performed to assess developmental outcomes. This would add valuable information on the safety of this medication in pregnancy.

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Maternal-Fetal Monitoring of Opioid-Exposed Pregnancies: Analysis of a Pilot Community-Based Protocol and Review of the Literature

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Abstract

Objectives: To describe/analyse a novel, community-based prenatal monitoring protocol for opioid-exposed pregnancies developed by our centre in 2014 to optimize prenatal care for this population. A literature review of published monitoring protocols for this population is also presented.

Methods: Retrospective comparison of pre-protocol (n = 215) and post-protocol (n = 251) cohorts. Medline and Embase were searched between 2000–2016 using MeSH terms: [fetal monitoring OR prenatal care] AND [opioid-related disorders OR substance-related disorders] in Medline and [fetal monitoring OR prenatal care] AND [opiate addiction OR substance abuse] in Embase, producing 518 results. Thirteen studies included protocols for monitoring opioid-exposed pregnancies. No comprehensive monitoring protocols with high-quality supporting evidence were found.

Results: We evaluated 466 opioid-exposed pregnancies, 215 before and 251 after introduction of the protocol. Since implementation, there was a significant increase in the number of opioid-exposed patients who have underwent urine drug screening (72.6% to 89.2%, $P < 0.0001$); a significant reduction in the number of urine drug screenings positive for illicit opioids (50.2% to 29.1%, $P < 0.0001$); and a significant increase in the number of patients who discontinued illicit opioid use by the time of delivery (24.7% to 39.4%, $P < 0.01$). There was no difference in the CS rate (27.4% vs. 26.3%, $P > 0.05$). There were no observed differences in the rate of preterm birth, birth weight <2500 g, or Apgar score <7 ($P > 0.05$).

Conclusions: Care of women with increased opioid use during pregnancy is an important but under-studied health issue. A novel protocol for focused antenatal care provision for women with opioid-exposed pregnancies improves standard of care and maternal/fetal outcomes.

Key Words: Opioid-related disorders, fetal monitoring, ultrasonography, non-stress testing, pregnancy

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Résumé

Objectifs : Décrire et analyser un nouveau protocole communautaire de monitorage prénatal visant les femmes enceintes exposées aux opioïdes, élaboré par notre centre en 2014 dans le but de maximiser les soins prénataux administrés à cette population. Nous présentons également une revue de la littérature sur les protocoles déjà publiés portant sur le monitorage prénatal chez ces femmes.

Méthodologie : Nous avons fait une comparaison rétrospective de cohortes préprotocole (n = 215) et postprotocole (n = 251). Nos recherches dans les bases de données Medline et Embase ont été effectuées pour la période de 2000 à 2016 à l'aide de termes des MeSH : [fetal monitoring OR prenatal care] AND [opioid-related disorders OR substance-related disorders] dans Medline, et [fetal monitoring OR prenatal care] AND [opiate addiction OR substance abuse] dans Embase. Nous avons obtenu 518 résultats. Treize études présentaient des protocoles de monitorage visant les femmes enceintes exposées aux opioïdes. Nous n'avons cependant trouvé aucun protocole exhaustif appuyé par des données probantes.

Résultats : Au total, nous avons suivi 466 femmes enceintes exposées aux opioïdes, soit 215 avant et 251 après l'introduction du protocole. Depuis la mise en application de ce dernier, nous avons observé une hausse significative du nombre de femmes enceintes exposées aux opioïdes qui ont subi un dépistage urinaire de drogues (de 72,6 % à 89,2 %; $P < 0,0001$), une baisse significative du nombre de résultats positifs au dépistage urinaire des opioïdes consommés illégalement (de 50,2 % à 29,1 %; $P < 0,0001$) et une hausse significative du nombre de patientes ayant cessé la consommation illégale d'opioïdes au moment de l'accouchement (de 24,7 % à 39,4 %; $P < 0,01$). L'introduction du protocole n'a eu aucun effet significatif sur le nombre de césariennes (27,4 % c. 26,3 %; $P > 0,05$), ni sur le nombre de naissances prématurées, le nombre de bébés naissant avec un poids inférieur à 2 500 g et le nombre de bébés présentant un indice d'Apgar inférieur à 7 ($P > 0,05$).

Conclusions : Les soins administrés aux femmes enceintes dont la consommation d'opioïdes est accrue constituent un sujet d'étude important, mais on manque de données à ce sujet. L'introduction d'un nouveau protocole axé sur les soins prénataux destinés aux femmes enceintes exposées aux opioïdes a permis d'améliorer les normes de soins, ainsi que les issues cliniques pour la mère et le bébé.

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INTRODUCTION

The abuse of illicit and prescription opioids is a rapidly developing problem in North America. In 2015, the Canadian Centre on Substance Abuse reported that 15.7% of females aged 15 or older had used prescription opioids in the preceding year.[1] In northwest Ontario, opioid use has reached "epidemic" proportions.[2] Remote First Nation communities are especially affected by opioid abuse, where up to 41% of adults between 20 and 50 years old are receiving opioid agonist therapy in their community.[3]

Pregnant women pose a particular challenge in treating opioid use disorder. The 2010 U.S. National Survey on Drug Use and Health reported that 4.4% of pregnant women used illicit drugs in the past month.[4] Although heroin use is relatively uncommon during pregnancy, abuse of prescription opioids is more prevalent and was reported by 1% of American pregnant women.[4] The Canadian Maternity Experiences Survey, conducted by the Public Health Agency of Canada in 2009, reported that 6.7% of mothers had used illicit drugs in the 3 months preceding their pregnancy, and 1% admitted to use during pregnancy.[5] In contrast, up to 30% of pregnancies in northwest Ontario are exposed to opioids.[6] Obstetric health care providers in the region have responded to this social and clinical crisis by developing effective strategies to mitigate the maternal and fetal effects of opioid addiction.[7,8]

ABBREVIATIONS

BPP	biophysical profile
IPP	Integrated Pregnancy Program
IUGR	intrauterine growth restriction
NST	non-stress test
OAT	opioid agonist therapy
SLMHC	Sioux Lookout Meno Ya Win Health Centre
UDS	urine drug screening

Table 1. Fetal, neonatal, maternal, and obstetric complications of opioid use in pregnancy

	OR (95% CI)
Congenital malformations[9]	
Conoventricular septal defect	2.7 (1.1 to 6.3)
Glaucoma	2.6 (1.0 to 6.6)
Atrioventricular septal defect	2.4 (1.2 to 4.8)
Hypoplastic left heart syndrome	2.4 (1.4 to 4.1)
Atrial septal defect	2.0 (1.2 to 3.6)
Ventriculomegaly/hydrocephalus	2.0 (1.0 to 3.7)
Spina bifida	2.0 (1.3 to 3.2)
Gastroschisis	1.8 (1.1 to 2.9)
Pulmonary valve stenosis	1.7 (1.2 to 2.6)
Tetralogy of Fallot	1.7 (1.1 to 2.8)
Right ventricular outflow tract obstruction	1.6 (1.1 to 2.3)
Conotruncal defect	1.5 (1.0 to 2.1)
Neonatal complications[10–12]	
Admission to NICU	6.2 (5.1 to 7.4)
Low birth weight	3.8 (2.6 to 5.7)
SGA	2.2 (1.9 to 2.6)
Obstetric complications[10,12]	
Intrauterine growth restriction (IUGR)	2.7 (2.4 to 2.9)
Preterm labour	
<37 weeks	2.5 (2.0 to 3.1)
<32 weeks	3.0 (1.7 to 5.3)
Placental abruption	2.4 (2.1 to 2.6)

Note: IUGR, growth <10th percentile or growth velocity decreasing across centiles for gestational age; low birth weight, <2500 g; SGA, <10th percentile birth weight for gestational age.

Because some of the more common fetal complications associated with opioid use during pregnancy include intrauterine growth restriction, low birth weight, and some cardiac malformations (Table 1),[9–12] one of the primary goals of prenatal monitoring is to evaluate fetal growth and well-being. Despite the well-documented adverse effects of opioid exposure in pregnancy and the relatively high rate of occurrence in some communities, little research has been done regarding the optimal schedule of prenatal monitoring for these cases. This article describes the protocol that has been developed and implemented in our Integrated Pregnancy Program at Sioux Lookout Meno Ya Win Health Centre and reviews the literature on prenatal monitoring of opioid-exposed pregnancies.

METHODS

Descriptive patient population and prenatal data for SLMHC were gathered retrospectively. Pre-protocol and post-protocol fetal and obstetric variables were recorded from maternal and infant hospital charts including urine drug screening frequency and results, illicit drug use, birth

weight, prematurity, Apgar score, and CS rate. A total of 466 pregnancies were analysed. Data from July 2011 to June 2013 were used as a pre-protocol baseline (n = 215). Data from July 2013 to June 2014 were removed to account for a transition period, and post-protocol data were examined from July 2014 to June 2016 (n = 251). *P* values were calculated using risk ratios for pre- protocol versus post-protocol cohorts. Ethics approval for this study was granted by the Sioux Lookout Research Review and Ethics Committee.

A literature search was also conducted using the Medline and Embase databases from January 2000 to August 2016. In Medline, ["Fetal Monitoring" OR "Prenatal Care"] was combined with ["Opioid-Related Disorders" OR "Substance-Related Disorders"] to produce 231 results. In Embase, ["Fetus Monitoring" OR "Prenatal Care"] was combined with ["Opiate Addiction" OR "Substance Abuse"] to produce 287 results.

Abstracts of these 518 articles were read to determine relevancy. Levels of evidence were rated based on the recommendations of the Canadian Task Force on Preventive Health Care.[13]

Sioux Lookout Meno Ya Win Health Centre Protocol

SLMHC is a 60-bed hospital in northwest Ontario with a catchment population of 28 000, primarily Indigenous, people. It provides care to 31 remote First Nation communities and has over 400 deliveries annually, approximately one third of which are opioid exposed.[6] Maternal comorbidities in our catchment population are summarized in Table 2. Our general population has higher rates of smoking, heavy drinking, diabetes, and hypertension compared with the North West Local Health Integration Network and the rest of the province of Ontario.[8,14]

The high prevalence of opioid use during pregnancy in our region has led to the refinement of our management approach. The resulting IPP provides obstetric and addiction/lifestyle counseling under a generalist model of prenatal and postnatal care provided by family physicians, nurses, interpreters (for Oji-Cree–speaking patients), lactation consultants, and social workers. The program integrates addiction medicine and prenatal care into one setting and takes a family-centred approach. Addiction treatment services are simultaneously offered to male partners. Prenatal addiction treatment includes OAT and opioid tapering in the third trimester.[8] The average maintenance dose of buprenorphine used in these OAT-treated pregnancies was 9.2 mg (standard deviation ± 6.2), excluding higher doses used during induction. The most commonly reported drugs of abuse were intravenous morphine and oxycodone.[7]

Table 2. Maternal characteristics of opioid-exposed pregnancies from July 2014 to June 2016

Characteristic	Number of cases (%), n = 251
Hypertension	25 (10.0)
Type II diabetes mellitus	12 (4.8)
Gestational diabetes	26 (10.4)
HIV	0 (0.0)
Hepatitis B	1 (0.4)
Hepatitis C	20 (8.0)
Prenatal nicotine use	217 (86.5)
Prenatal alcohol use	62 (24.7)
Prenatal cannabis use	44 (17.5)

Prenatal care is often initiated at remote nursing stations and transferred to the IPP in Sioux Lookout for an initial consultation around 12 to 14 weeks. IPP consultations are available at any point in the pregnancy, and telephone support is offered on a continual basis with physicians and nurses at the remote nursing stations. Depending on the community, ultrasounds may be available in nursing stations, but most often patients are required to travel by air to SLMHC, providing an opportunity for attendance at the IPP. Pregnant women with addiction issues are often temporarily housed in a federally funded hostel in Sioux Lookout until their treatment course has been stabilized. In 2014, the IPP initiated a standardized prenatal monitoring protocol for pregnant patients with opioid use disorder (Figure 1).

The SLMHC protocol was developed on the basis of guidelines for monitoring pregnancies with hypertension, which have some similar feto-placental effects to opioid exposure, including IUGR, abnormal fetal heart rate, oligohydramnios, and absent or reversed end-diastolic umbilical artery Doppler velocimetry.[15] The protocol is mainly focused on detecting placental insufficiency and IUGR. Fetal well-being and placental function are assessed using standard biophysical profile consisting of fetal tone, movement, breathing movements, amniotic fluid volume,[16] and umbilical artery Doppler analysis of the systolic/diastolic ratio. Growth ultrasounds consist of measurements of head circumference, biparietal diameter, femur length, and abdominal circumference. Non-stress tests are not integrated into routine BPP scores and are performed as clinically indicated. Patients monitor fetal movement (kick counts) informally without a set schedule. Due to high rates of intravenous drug use in our region, hepatitis C serology is performed in addition to the standard provincially mandated prenatal screening.

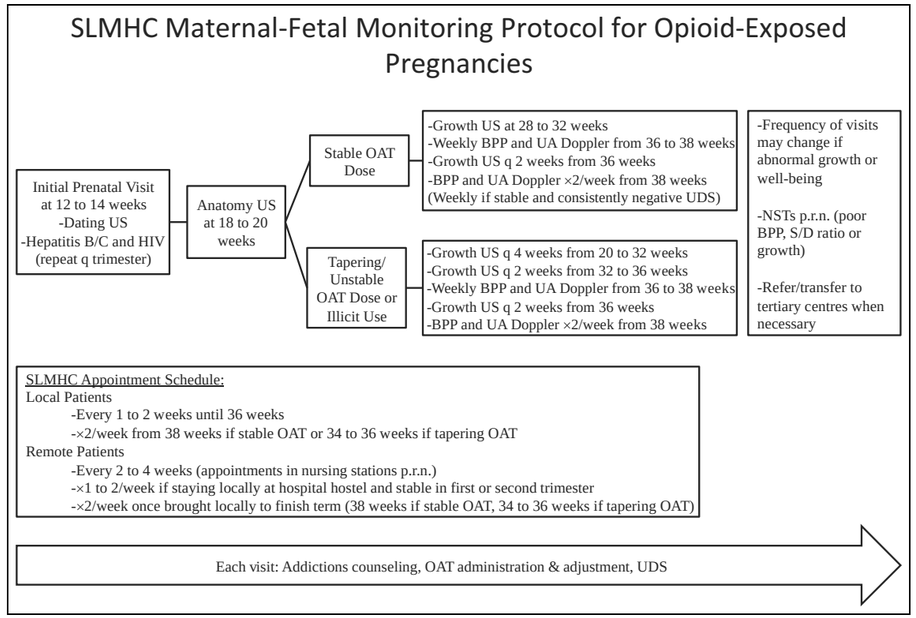
Even though aspects of the protocol are specific to residents from remote communities, most are universally applicable. Travel, geography, and multiplicity of care providers add extra challenges to providing safe and effective regional obstetric care. As a result, the frequency of appointments may vary for patients living in remote communities. Patients with any complications are flown from their community to stay locally at a federally funded hostel adjacent to the hospital where they remain for the last portion of their pregnancy to allow for increased monitoring of fetal well-being and hospital care as needed. This confinement occurs at around 34 to 36 weeks for patients tapering OAT or with illicit drug use and at 38 weeks for stable OAT patients. Although induction of labour is not standard practice for opioid-exposed pregnancies, some pregnancies may be induced around 37 to 38 weeks if there is a perceived risk of maternal relapse to illicit drug use or indication of IUGR.

Delivering away from home without community support adds additional stressors for patients and their families, which we attempt to address by ensuring that all patients have an escort who travels with them to their appointments in Sioux Lookout.[17] Although SLMHC is equipped to manage a variety of obstetric complications, 4% of patients are referred to distant (>350 km) urban obstetric centres when specialty support is anticipated. Although nuchal translucency, ductus venosus Doppler, and more advanced monitoring methods are available in larger centres, they are currently unavailable at most rural centres. Given the documented benefits of nuchal translucency in early detection of cardiac anomalies,[18–21] it will be included in future protocols once available. Postpartum, babies all room-in with mother. Upon discharge, coordination with remote community-based opioid use treatment programs is the norm. Follow-up with family physicians and community nurses is undertaken as needed, either in the patient's home community or in Sioux Lookout.

RESULTS

Limited analysis of our protocol's efficacy revealed a significant increase in the number of opioid-exposed patients who underwent UDS following implementation, from

Figure 1. The Sioux Lookout Meno Ya Win Health Centre prenatal monitoring protocol for opioid-exposed pregnancies. US: ultrasound; OAT: opioid agonist therapy; BPP: biophysical profile; UA: umbilical artery; UDS: urine drug screen; S/D: systolic/diastolic.



72.6% to 89.2% ($P < 0.0001$). There was also a significant reduction in the number of UDSs positive for illicit opioids from 50.2% to 29.1% ($P < 0.0001$). We observed a significant increase in the number of patients who had quit using illicit opioids at the time of delivery, from 24.7% to 39.4% ($P < 0.01$). There were no observed significant differences in the number of infants born <37 weeks, <2500 g, or with an Apgar score <7 at 1 and 5 minutes ($P > 0.05$); however, our sample size was insufficient to provide a robust analysis of these variables. The small sample size also prevented an analysis of rates of stillbirth, IUGR, oligohydramnios, placental abruption, and congenital anomalies. Despite following a more rigorous schedule of prenatal monitoring, there was not a significant change in the rate of CS, 27.4% pre-protocol versus 26.3% post-protocol ($P > 0.05$). We did not have access to important determinants of health, such as maternal nutritional data, but we noticed that the availability of OAT provided some relief from the extreme poverty associated with opioid use disorder in our setting, allowing resources for improved nutrition.

Literature Review

Of 518 total search results, only 13 contained some form of prenatal monitoring protocol specific to substance-exposed pregnancies (Table 3).[22-34] None of the protocols are supported by high-quality studies, and all are based on level III evidence (expert opinion). Some of the literature concerning specific components of monitoring protocols, such as frequency of prenatal visits or ultrasonography, includes level I and II studies.

We reviewed the fetal monitoring protocols used in two retrospective cohort studies examining the effects of prenatal illicit opioid use, OAT, or detoxification on the fetus. The other 11 were described in review articles or clinical commentaries. Protocols varied in complexity and specificity. Some briefly mentioned one or two tests and their frequency, whereas others described a basic set of guidelines. Although some studies examined individual components of a prenatal monitoring protocol, no study subjected its entire protocol to statistical outcomes evaluation.

Prenatal Visits

Prenatal appointments are the cornerstone of providing care to all mother-infant dyads, regardless of drug exposure. There is no clear consensus in the literature regarding the optimal baseline frequency of visits for opioid-exposed pregnancies. Most authors suggest "routine" or "frequent" appointments without stating the exact frequency or rationale.[24–26,28,29] Two authors provided specific intervals for prenatal visits. Bolnick and Rayburn[30] suggest biweekly visits until 32 weeks followed by weekly visits until delivery, whereas Curet and Hsi[31] suggest weekly visits throughout the entire pregnancy.

Three authors[35–37] reported that an increased frequency of prenatal visits decreased the risks of prematurity, low birth weight, SGA, and perinatal mortality in infants exposed to illicit drugs in utero (level II evidence). The 1992 study by Broekhuizen et al. of 23 926 pregnancies found that the association between prenatal care and infant outcomes was so marked that the authors claimed it was a stronger predictor of infant outcome than was substance abuse (level II evidence).[35] Chang et al.[38] were the only authors to specify an exact frequency of visits, reporting that weekly prenatal care from approximately 10 weeks' gestation was associated with a reduction in the number of positive urine toxicology results and an increase in birth weight (level II evidence).

Opioid dependence is often accompanied by other challenging determinants of health such as poverty, homelessness, job instability, mental and physical health issues, and other addictions.[39–42] These factors can make engagement in prenatal care difficult. Many women may fear losing custody of their child or legal proceedings against them and may be hesitant to disclose their drug abuse or may avoid prenatal care altogether.[43,44] Comprehensive care programs that provide addiction counselling, social support, and prenatal care in one setting, such as the Toronto Centre for Substance Use in Pregnancy and the Early Starts program at Kaiser Permanente Northern California, have been shown to improve maternal-fetal outcomes and attendance of regular prenatal care (level III evidence).[45,46]

Serology and Toxicology

Given the association with intravenous drug use, standard serology for illicit drug-exposed pregnancies includes hepatitis B and C, HIV, and sexually transmitted infection screening.[23,25–28,30–33] Tests are generally performed at the initial visit and repeated in the second and third trimesters.[25,28,30,31,33] General population and low risk screening for HIV and hepatitis C virus are antibody tests and cover a 3- to 6-month timeframe. High-risk patients (e.g., those who inject drugs) need the more recent test parameters offered by polymerase chain reaction testing, which reduces the diagnostic window to 2 to 3 weeks.

Maternal history may be unreliable and UDS can be a useful adjunct.[46] UDS can provide an accurate profile of usage patterns and detection of other unknown substances

Table 3. Summary of previously published protocols

Author, year	Prenatal visits	Serology and toxicology	Ultrasound	Biophysical profile	Fetal heart rate analysis
Krans, 2015[22]	N/A	N/A	Growth monthly from 24 weeks	N/A	Weekly from 32 weeks
Gopman, 2014[23]	Serial SFH	Hep C, STDs	Growth at 28 and 34 weeks	N/A	Weekly from 32 weeks
Izquierdo, 2014[24]	Frequent visits and SFH	UDS each visit	Dating and anatomy at 20 weeks Growth every 4 to 6 weeks if normal Growth every 3 weeks if abnormal	Weekly if abnormal growth	Twice weekly NST if abnormal growth
Stanhope, 2013[25]	Routine	Hepatitis C, HIV, STDs at initial visit Repeat HIV and STDs at 36 weeks UDS each visit	Growth monthly from 24 weeks	N/A	Weekly from 32 weeks
Shainker, 2012[26]	Routine	Hepatitis B/C, HIV Weekly until stable on buprenorphine then every 2 to 3 weeks Every 2 to 3 weeks on methadone	Growth monthly	Partial BPP: Weekly amniotic fluid index from 36 weeks	Weekly NSTs from 36 weeks
Young, 2012[27]	Same as general population	Hepatitis B/C, STDs, HIV UDS each visit	Dating and anatomy at initial visit Anatomy at 19 to 21 weeks Growth monthly from initial visit	As indicated	As indicated
Alto, 2011[28]	Frequent	Hepatitis B/C, HIV at initial visit and third trimester UDS each visit	Anatomy at 15–20 weeks Growth at 24 to 32 weeks	N/A	N/A
Pinto, 2010[29]	Routine	N/A	Anatomy at 18 to 20 weeks Growth at 28 and 34 weeks	N/A	N/A
Bolnick, 2003[30]	Biweekly until 32 weeks then weekly	Hepatitis B/C, HIV at initial visit Repeat at 33 to 34 weeks UDS at initial visit, 15 to 19 weeks, 25 to 28 weeks, 33 to 34 weeks, and 37 weeks	Dating and anatomy at initial visit Anatomy at 15 to 19 weeks Growth at 35 to 36 weeks	N/A	N/A
Curet, 2002[31]	Weekly	Hepatitis B/C, HIV, STDs, TB at initial visit Repeat at 34 weeks Frequent random UDS	Monthly growth and development analysis	As indicated	NSTs as indicated
Dashe, 1998[32]	N/A	Hepatitis B/C and HIV UDS as indicated and at delivery	Dating and anatomy at initial visit, rule out IUGR	N/A	Twice weekly from 24 weeks
Kaltenbach, 1998[33]	N/A	Hepatitis B/C, HIV, STDs at initial visit and 24 to 28 weeks Routine UDS	Dating and anatomy at initial visit Anatomy at 18 to 22 weeks Growth during third trimester	N/A	If on OAT with negative UDS, NST only if IUGR Weekly NST from 32 weeks if abusing
Woods, 1995[34]	N/A	Weekly UDS throughout pregnancy	Growth at 8 to 12 weeks, 18 weeks, and 33 weeks	As indicated	Weekly NSTs from 33 weeks

SFH: symphysis-fundal height; STD: sexually transmitted disease; UDS: urine drug screen; BPP: biophysical profile; NST: non-stress test; TB: tuberculosis; OAT: opioid agonist therapy; IUGR: intrauterine growth restriction.

that may have been cut into a drug. Most authors suggest performing UDS either routinely[31,33] or at each prenatal visit.[24,25,27,28] Shainker et al.[26] differentiate between mothers on buprenorphine and methadone OAT, suggesting weekly UDS until stable on buprenorphine, then every 2 to 3 weeks until delivery versus every 2 to 3 weeks if on methadone. Bolnick and Rayburn[30] suggest performing UDS at the initial visit and again at 15 to 19 weeks and monthly thereafter. In addition to diagnostic value, some centres use UDS as an incentive for patients, rewarding clean urines with tokens or awards.

Fetal Movement

Fetal movement counting is one of the simplest forms of prenatal monitoring. Several authors have found that maternal opioid use results in acute reductions in fetal movement.[47–52] Decreased fetal movement is a non-specific observation, which may signal placental insufficiency, fetal hypoxia, or acidemia. An extensive meta-analysis by Froen in 2004[53] revealed that in high-risk pregnancies, reduced fetal movement was associated with an increased risk of mortality (OR 44, 95% CI 22.3 to 86.8); 5-minute Apgar score <7 (OR 10.2, 95% CI 5.99 to 17.3); need for emergency delivery (OR 9.40, 95% CI 5.04 to 17.5); and IUGR (OR 6.34, 95% CI 4.19 to 9.58) (level I evidence). Despite the link between decreased fetal movement and mortality, fetal movement counting may not be the most accurate screening method. A 2015 Cochrane review[54] reported that there is currently insufficient evidence to support the use of fetal movement counting, with no documented reductions in stillbirths, low Apgar scores, or low birth weight (level I evidence). The SOGC currently recommends daily fetal movement counting starting at 26 to 32 weeks' gestation for pregnancies at risk of IUGR.[16]

Despite the documented effects of opioids on fetal movement, only two of the 13 prenatal monitoring protocols for opioid-exposed pregnancies suggest fetal movement counting. Bolnick and Rayburn[30] suggest daily movement charting starting at 31 to 32 weeks, and Dashe et al.[32] advocate daily charting from 24 weeks onwards.

Ultrasonography

IUGR is one of the most commonly reported adverse outcomes in opioid-exposed pregnancies[30,33,55] (OR 2.7, 95% CI 2.4 to 2.9),[12] (RR 3.5, 95% CI 1.7 to 7.1),[56] occurring in up to 27% of opioid-exposed pregnancies.[56] As a result, monthly growth ultrasounds are suggested by the majority of authors starting at 20 to 24 weeks.[22,24–27,31] Risk of congenital anomalies is similar to that of the general population (Table 1), and an anomaly scan between 18 to 22 weeks is recommended.[24,27–30,32,33] There is consensus in the literature regarding the importance of ultrasonography in opioid-exposed pregnancies; however, all 13 protocols suggest different frequencies of examination (Table 3). The most common structural congenital anomalies encountered in this population (ventriculomegaly, neural tube defects, and gastroschisis) are detectable using the standard views of an anatomic ultrasound at 18 to 20 weeks.[57] Common cardiac anomalies (conoventricular septal defect, atrioventricular defect, hypoplastic left heart, atrial septal defect, Tetralogy of Fallot, pulmonary stenosis, and right ventricular outflow tract obstruction) are also observable on this routine anatomic ultrasound.[57] The SOGC recommends that this examination include standard cardiac views (four chambers, outflow tracts, cardiac axis, and situs).[57] The International Society of Ultrasound in Obstetrics and Gynecology advocates adding more detailed cardiac views, which may extend the optimal timing for cardiac views up to 22 weeks.[58]

Frequent ultrasounds in such long-term antenatal patients dealing with opioid use disorder has the additional unmeasured benefit of providing an opportunity for bonding between parents and baby.

Biophysical Profile

Given the risk of placental insufficiency, as evidenced by an increased risk of oligohydramnios (OR 1.7, 95% CI 1.6 to 1.9)[12] and decreased fetal movement[47–49,52] associated with in-utero opioid exposure, BPPs may be an important tool in monitoring these pregnancies; however, the literature is equivocal. A 2008 systematic review of five RCTs (level I evidence) found inadequate evidence to support the use of routine BPPs in high-risk pregnancies.[59] Other studies have, however, reported correlations between low BPP scores and fetal acidosis[60,61] and perinatal morbidity/mortality,[62,63] both of which are associated with fetal opioid exposure. In a study examining the effects of methadone on BPP testing, Cejtin et al.[64] found that although methadone did not have a significant effect on the mean modified BPP score, the mean test length increased from 3.8 to 19.8 minutes when performed following methadone dosing.

Five protocols mentioned the use of BPPs, three of which suggest performing BPPs "as indicated."[27,31,33] Izquierdo and Yonke[24] suggest performing weekly BPPs if fetal growth is abnormal, whereas Shainker et al.[26] suggest performing weekly ultrasound assessment of amniotic fluid volume from 36 weeks onwards, with no mention of the other BPP components.

Fetal Heart Rate Analysis

Fetal heart rate analysis and NST are frequently referenced in the literature. Fetal exposure to opioids may result in bradycardia, decreased heart rate accelerations, decreased coupling of heart rate to fetal movement, and decreased long-term variability (level II evidence).[47–51,65] Most authors suggest starting weekly NSTs at 32 to 36 weeks,[22,23,25,26,34] whereas others suggest twice weekly from 24 weeks onwards[32] or twice weekly if IUGR is detected.[24] Kaltenbach et al.[33] suggest that mothers currently on OAT with consistently negative urine toxicology only require NSTs if IUGR is detected on ultrasound. If mothers are still using illicit opioids while on OAT, they suggest weekly NSTs beginning at 32 weeks.[33] Although not specified in any of the protocols, performing NST prior to OAT dosing may provide a more accurate measure of cardiac activity, given the acute effects of opioids on the fetus.[47–51,65]

Doppler Flow Velocimetry

It is generally recommended that umbilical artery Doppler velocimetry be used to assess the feto-placental circulation in women with suspected severe placental insufficiency and IUGR.[16,66–68] The SOGC suggests that reduced, absent, or reversed umbilical artery end-diastolic flow is an indicator for early delivery or enhanced fetal monitoring if delivery is not an option.[16] One protocol for monitoring opioid-exposed fetuses mentioned the use of Doppler velocimetry but did not advocate it as routine screening, suggesting its use "as indicated by NST or ultrasound."[34] In an article on non-drug–specific IUGR, Thompson et al.[69] suggest weekly umbilical artery Doppler, increasing to twice weekly if absent or reversed end-diastolic flow velocity was noted.

Limitations

We found no high-quality studies examining prenatal monitoring protocols for opioid-exposed pregnancies. Although only 13 protocols were found in the literature, it is likely that other institutions have a "working" protocol in place, which we were unable to review. All 13 monitoring protocols reviewed were supported by level III evidence, or expert opinion. The lack of RCTs is one of the major limitations in this area. It stands to reason that the previously published protocols are considered "standard of care" in their respective settings and that deviating from them for research purposes might compromise perinatal care. This is also the case with our own protocol, which outlines a comprehensive set of guidelines based on clinical experience caring for the population with the highest rate of prenatal opioid exposure in Ontario. Although we performed basic outcome analysis before and after implementation of our protocol, our sample size (at around 100 opioid-exposed pregnancies per year) was underpowered for more rigorous study. Data collection is ongoing. Because the approach to obstetric care of the opioid-dependent patient is multifaceted, it is not possible to ascribe outcomes to any one aspect of the screening and treatment program.

CONCLUSION

The large number of pregnant women with opioid use disorder in northwest Ontario and the limited research on prenatal monitoring in this population prompted the development of a prenatal monitoring protocol at our centre. Our protocol is clinically based, standardizing care in a region with diverse geography and travel requirements, and based on early analysis, appears to be effective in caring for this patient population and mitigating risks for the mother and infant. We will continue to monitor the effectiveness of our rural, primary care–focused protocol over the coming years.

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Opioid use disorder and type 2 diabetes mellitus

Effect of participation in buprenorphine-naloxone substitution programs on glycemic control

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Abstract

Objective To measure the effect of buprenorphine-naloxone as opioid substitution therapy on glycemic control in patients with type 2 diabetes mellitus and opioid use disorder.

Design Retrospective cohort study and secondary data analysis.

Setting Northwestern Ontario.

Participants Patients with diabetes receiving opioid substitution therapy, as well as patients with diabetes only, who live in 6 remote First Nations communities.

Main outcome measures Glycated hemoglobin A_{1c} values during a 2-year time period in the 2 groups.

Results Over a 2-year period, there was an absolute decrease of 1.20% in mean glycated hemoglobin A_{1c} values in patients with diabetes who also received opioid substitution therapy, compared with patients with diabetes who were not being treated for opioid dependence, whose values rose by 0.02%.

Conclusion Patients with diabetes who also suffer from opioid use disorder achieve significant ($P = .011$) improvement in glycemic control when treated with buprenorphine-naloxone substitution therapy compared with other patients with diabetes. Treating opioid use disorder with buprenorphine-naloxone substitution therapy has an unintended positive effect on diabetes management.

EDITOR'S KEY POINTS

- The glycated hemoglobin A_{1c} levels in patients with diabetes were examined along a 2-year continuum. Patients with diabetes participating in a buprenorphine-naloxone substitution program were compared with those not participating in such a program.
- Participation in a buprenorphine-naloxone program was associated with a decrease in glycated hemoglobin A_{1c} level compared with the control group. The mean absolute decrease of 1.20% is clinically significant and statistically different compared with the control group ($P = .011$).
- While it is possible that some of the effect might be related to medications, such a large effect is likely owing to improved self-care and improved adherence to treatment of all health issues.

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Opioid use disorders and type 2 diabetes mellitus (T2DM) might coexist in many patients. This overlap occurs in many First Nations communities in northern Ontario, where both diseases have high prevalence.[1]

Diabetes rates in Indigenous Canadian populations have ranged from 2.7% to 19%, with some estimates of age-standardized prevalence as high as 30%.[1] First Nations persons living on-reserve are at the highest risk of diabetes, with a prevalence of 15.3% for people aged 18 years and older, compared with 6.0% for non-Aboriginal populations.

The 2008 to 2010 First Nations Regional Health Survey reported that 6.8% of Ontario on-reserve respondents used opioids without a prescription.[2] Prescription opioid abuse prevalence has been estimated to be between 35% and 50% in several Nishnawbe Aski Nation communities.[3] The number of Indigenous people seeking treatment for prescription opioid use disorders in Ontario tripled between 2009 and 2014.[4] In response to this public health and social crisis, a number of communities in northwestern Ontario have initiated opioid use disorder treatment programs combining psychosocial interventions with buprenorphine-naloxone substitution.[5] There is a paucity of data available on whether participating in the buprenorphine-naloxone programs has an effect on glycemic control in patients with diabetes.

Both opioid use disorders and T2DM are chronic medical illnesses in which noncompliance with treatment is a common problem influenced by psychosocial factors.[6] Opioid exposure is consistently associated with poorer glycemic control, as indicated by significantly elevated glycated hemoglobin A_{1c} (HbA_{1c}) levels relative to control groups ($P < .05$).[7] Duration of addiction is a mediating factor, with substantially higher HbA_{1c} levels among patients who had been using opioids for 2 or 5 years versus those who had been addicted for 5 months or 1 year.[7]

Different treatment methods for opioid use disorders have varying effects on diabetes control. Methadone maintenance therapy (MMT) in patients without T2DM is associated with increased sugar intake, elevated body mass index, and changes in glucose metabolism akin to those observed in T2DM patients.[8] Conversely, acute administration of buprenorphine to laboratory animals is associated with reduced sugar consumption; this effect is reduced with chronic buprenorphine administration, with test animals consuming less sugar but a normal overall amount of calories.[8] This effect is also seen with opioid antagonists such as naltrexone.[8] A retrospective observational study comparing MMT and buprenorphine maintenance therapy with regard to incidence of T2DM diagnosis found that patients receiving MMT were significantly more likely to be diagnosed with T2DM, even after controlling for confounding variables in regression analysis ($P = .0458$). However, among patients who were diagnosed with T2DM, HbA_{1c} results were not significantly different between the MMT and buprenorphine maintenance therapy groups, nor were they considered to be elevated.[9]

METHODS

One of the authors (D.T.) noticed a trend of improved HbA_{1c} values in patients with diabetes treated with buprenorphine-naloxone in her First Nations community practice. This prompted a literature search and subsequent retrospective study.

The literature search was carried out using MEDLINE and EMBASE from 1982 to 2015 for the following terms and combinations: *buprenorphine and/or naloxone, naloxone, narcan, opioid antagonist,* and *naltrexone;* and *diabetes mellitus, type 2, diabetes control, t2dm control, diabetes mellitus control, hyperglycemia, non-insulin dependent diabetes,* and *glucose metabolism*. Naloxone was marginally associated with an increased risk of hyperglycemia. No articles focused on the effect of buprenorphine on glycemic control or treatment of patients with addiction.

Written permission was obtained from 6 First Nations communities in northern Ontario to participate in the study. The 6 communities being studied had buprenorphine-naloxone substitution programs ranging in size from 33 to 160 patients. The total population of the 6 communities was 4388 and included 526 patients receiving buprenorphine-naloxone and 573 patients with diabetes. A total of 62 patients had both opioid substitution therapy and diabetes, and these patients were the study group. The remaining 511 patients with diabetes functioned as the control group.

Using anonymized data from electronic medical records, we examined the HbA_{1c} levels in patients with diabetes along a 2-year continuum in patients participating in a buprenorphine-naloxone substitution program compared with those not participating in such a program. The initiation of the buprenorphine-naloxone programs roughly coincided with the adoption of electronic medical records in the communities. The 62 study patients who had diabetes and were participating in buprenorphine-naloxone substitution therapy were identified. A total of 511 control participants consisting of patients with diabetes who were not prescribed buprenorphine-naloxone were also identified. Hemoglobin A_{1c} levels from the beginning of the study period (July to December 2013), which were the earliest data in the electronic medical record and roughly correlated with the start of most of the community programs, were compared with HbA_{1c} levels from January to July 2015. Independent 2-sample *t* tests were performed for equal variances. The study was approved by the Sioux Lookout Meno Ya Win Health Centre Research Review and Ethics Committee.

RESULTS

The average change in HbA_{1c} level of the study group was an absolute decrease of 1.20%. It varied by community from an increase of 0.34% to a decrease of 2.30%, with 5 of 6 communities showing an improvement in this measure of glycemic control (**Table 1**).

In comparison, the control group of patients with diabetes and without buprenorphine-naloxone treatment experienced an average absolute rise in their HbA_{1c} results of 0.02%. This average control group change in HbA_{1c} level varied by community from an increase of 0.52% to a decrease of 0.50%, with half of the communities having a small increase and the other half a small decrease.

The absolute difference between the HbA_{1c} levels in the 2 groups was 1.22% (P=.011), which is both clinically and statistically significant.

DISCUSSION

In this study, participation in a buprenorphine-naloxone program was associated with a decrease in HbA_{1c} level compared with not participating in such a program. The decrease of 1.20% is clinically significant and favourably compares to the decrease associated with oral diabetes medications such as α-glucosidase inhibitors (1%), biguanides such as metformin (1%), dipeptidyl peptidase 4 inhibitors (0.75%), sulfonylureas (1.25%), and thiazolidinediones (1.25%).[10] It is interesting that the study group had a higher baseline HbA_{1c} level than the control group did (9.76% vs 8.90%) despite having a younger average age. This appears to reflect the burden of opioid use disorder on diabetes control shown by previous research.[7] By the end of the study this relationship was reversed and the study group's HbA_{1c} level was lower than that of the control group (8.57% vs 8.91%). Perhaps participation in buprenorphine programs will reduce disease burden and diabetes complications in the long term. This might have an even bigger effect considering the relatively young age of the patients with both comorbidities.

While it is possible that some of the effect might be medication-related, such a large effect is likely owing to improved self-care and improved adherence to treatment of all health issues, as previous research on the pharmacobiology of buprenorphine administration did not find such a large effect. It is conceivable that patients participating in these programs also have more contact with health care professionals in regard to substance use disorders and might therefore receive improved follow-up of other health issues such as diabetes.

Limitation

One limitation of this study was the difference in age between the study group and the control group. Those in the diabetes-only control group were older than those in the buprenorphine-naloxone–treated group by an average of 13 years. However, as all eligible study participants with diabetes were included, this age difference likely reflects the difference in prevalence of opioid use disorder among different age strata in the communities, with people aged 20 to 50 most predominantly affected. Our study also had a greater proportion of female participants than male, which reflects the different sex distribution of diabetes diagnoses in these communities.

Our control group was made up of patients with diabetes who were not prescribed buprenorphine-naloxone. This group would include participants without opioid use disorder but might also include participants with untreated or undiagnosed opioid use disorder. However, this inclusion does not change the positive effect that the treatment of opioid use disorder had on diabetes control, as all patients had the percentage of change in their HbA_{1c} level compared against their own baseline HbA_{1c} level. As this was a retrospective observational study, we did not control for the initiation of various diabetes medications. As the control group was substantially larger than the study group, we believe such an analysis would not change the results. Furthermore, we postulate that the change in glycemic control is related to positive lifestyle changes, including improved adherence to diabetes medications. Therefore, changes in diabetes medications prescribed would not obfuscate the results.

All of the patients in this study were First Nations Canadians living in remote communities, who are known to experience high rates of T2DM.[1] It is unknown if the results would be similar for other Indigenous populations, other ethnic groups, or urban populations.

Table 1. Patient demographic characteristics and change in HbA_{1c} levels in the 2-year study period

GROUP	N	MALE, N (%)	MEAN AGE, Y	INITIAL HBA_{1c}, %	FINAL HBA_{1c}, %	MEAN CHANGE IN HBA_{1c}, %
T2DM only	511	218 (43)	51.8	8.90	8.91	+0.02
T2DM and buprenorphine-naloxone	62	20 (32)	38.5	9.76	8.57	-1.20*

HbA_{1c}—glycated hemoglobin A_{1c}, T2DM—type 2 diabetes mellitus.
*P=.011 for the difference between groups.

Conclusion

This study demonstrates that patients with diabetes and opioid use disorder achieve improved glycemic control when enrolled in a community-based opioid substitution program. Both diseases have multiple long-term sequelae. Early investment in such community-based opioid use treatment programs might have many subsequent health and cost benefits.

Dr Tilbrook is a physician practising in Sioux Lookout, Ont. **Mr Jacob** is Health Director of Webequie First Nation in Ontario. **Mr Parsons** was Electronic Medical Records Technologist for Sioux Lookout First Nations Health Authority. **Mr Edwards** is a researcher, **Ms Loewen** is a research intern, and **Dr Kelly** is a research consultant for the Anishinaabe Bimaadiziwin Research Program.

Contributors
All authors contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests
None declared

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REVIEW ARTICLE

Prescription opioid prescribing, use/misuse, harms and treatment among Aboriginal people in Canada: a narrative review of available data and indicators

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ABSTRACT

Introduction: Prescription opioid (PO) misuse and related harms are high in Canada, and a major public health challenge. In Canada, 1.4 million individuals (4.3% of the total population) self-identify as Aboriginal, among whom substance use and related harms are elevated. While there are reports of PO use and associated problems among Aboriginal groups, no comprehensive data review currently exists.

Methods: A review of available data sources (ie journal publications, public reports and 'grey' literature) was conducted following principles of a scoping review. Information and data were identified, extracted, and organized into major indicator categories: *PO prescribing/dispensing*, *use/abuse*, *morbidity/mortality harms and treatment*, and narratively reported.

Results: Data suggest that PO dispensing, use and misuse levels among Aboriginal populations are high and/or rising in select settings when compared to the general Canadian population. High levels of PO-related dependence and pregnancy harms exist (mainly in Northern Ontario); there is some indication of elevated opioid mortality among Aboriginals. Vast discrepancies in availability and access to interventions exist; some recent pilot studies suggest improved care.

Conclusions: Data regarding PO use and harms among Aboriginal people are limited, even though elevated problem levels are indicated; improved monitoring, and more effective yet culturally and contextually appropriate interventions for this acute problem are needed.

Key words: Aboriginal, Canada, harms, misuse, prescription opioids, review.

Introduction

Prescription opioid (PO) misuse and related harms have been an acute and prominent public health challenge in Canada for some time. Canada has one of the highest levels of PO misuse, morbidity and mortality globally, set in the context of the second highest (after the USA) PO dispensing rates on a per capita basis[1-3]. Despite a variety of recent interventions on different (eg provincial) levels, some of the main PO-related problem indicators have continued to rise in Canada[4].

Canada is home to a substantial Aboriginal population of approximately 1.4 million people (4.3% of the total population), comprising diverse groups of self-identified First Nations (ie registered (status) and non-registered Indians), Métis and Inuit peoples. Canadian Aboriginal peoples have unique histories, traditions and languages as well as sociocultural and environmental diversity, encompassing more than 600 distinct communities with more than 60 languages[5,6]. Aboriginal people in Canada are mostly concentrated in Ontario and the Western provinces; their population, with children and youth comprising 46%, is growing rapidly[5,6].

Substance abuse and related harms are a major health and social problem in the Canadian Aboriginal population, at mostly elevated levels when compared to the general Canadian population[7-9]. For instance, 43.2% of First Nations adults living on-reserve (vs 19% in the general Canadian population) are daily smokers; similarly, rates of binge drinking are substantially higher[10]. Alcohol-related death rates are almost double (43.7 vs 23.6 per 100 000 in the general Canadian population)[11,12], and drug-related overdose rates are estimated to be two to five times higher[13]. Four in five First Nations adults on-reserve identified alcohol and drugs as the biggest challenges currently facing their communities[14]. Aboriginal youth cohorts are at between two and six times greater risk for every alcohol-related problem than their general population counterparts, and are more likely to use all types of illicit drugs[15]. However, of note, there can be substantial variability among Aboriginal communities, and homogeneity should not be assumed. Further, Aboriginal populations have faced generational abuse, trauma and both systemic and individual racism by way of colonial structures and experiences (such as the residential school system), which have been directly linked to adverse mental and physical health outcomes and directly or indirectly contributed to the elevated substance use/abuse rates among these populations[16-18].

Consistent with these patterns, sporadic indicators of PO misuse and harms have recently arisen as a distinct problem among Aboriginal populations[19,20], particularly in rural and remote locations in conjunction with acute challenges of limited access to related interventions or care[21-23]. However, comprehensive or systematic data on PO-related use, misuse or harms among the Aboriginal population are limited, inconsistent, or simply absent in Canada, partially due to the fact that Aboriginal populations are often excluded from national health surveys or health data information systems (which are regularly governed by jurisdictions or institutions different to those for general populations). Aboriginal populations are commonly not included in relevant survey sampling frames, and their heterogeneity and dispersed geographical placement further undermine their inclusion. Moreover, misclassification errors, non-response bias and a

lack of Aboriginal-specific identifiers can contribute to inconsistencies in existent survey data[24-26].

In this context, the main objective of this article was to compile and review available data indicators on PO prescribing and dispensing, use and misuse and related morbidity and mortality among Aboriginal populations in Canada, and hence to both assemble existent data as well as identify major data and information gaps in this important arena.

Methods

After identifying our topic of interest (ie PO prescribing/use/misuse and related harm indicators among Aboriginal populations in Canada), we searched relevant scientific literature databases (ie Google Scholar, ProQuest, PubMed, MEDLINE, JSTOR, EBSCO), conducted web-based searches to identify information from relevant websites, reports and other non-journal publications ('grey literature', eg from Statistics Canada, Health Canada, First Nations and Inuit Health Branch websites, publications, government/survey/technical reports, organizational and Aboriginal-specific publications) between August and November 2015, using variations on applicable search terms (ie *Aboriginal/Indigenous/First Nation/Métis/Inuit*, *prescription opioid/opiate*, *drug*, *substance*, *prescribing*, *disorder*, *prevalence*, *use/misuse/abuse*, *harms*, *overdose*, *mortality*, *morbidity*, *prevention*, *treatment*, *interventions*); in addition, we manually cross-referenced sources and references, and consulted with select topic experts who provided additional references and source leads. In line with a scoping/narrative review, we sought to find all relevant information on all possible key indicators and we did not place strict limitations on search terms or study designs to be included. All databases were searched one at a time using all variations on applicable search terms until all relevant data was extracted and the database had been exhausted.

Data inclusion criteria included all sources from 2000 to 2015 that contained any information on Canadian Aboriginal peoples and PO use and indicators of interest (including where information on POs may have been amalgamated with other psychoactive medication). Conversely, the scope of our review does not explicitly include information on non-POs (eg heroin); such information was excluded. Information was excluded also when more recent data/information was available (eg from a series of reports) or where information was non-quantitative. Once the literature was assembled, relevant data and information were identified, screened and extracted, organized and narratively presented in the major content categories: *PO prescribing and dispensing*; *PO use and misuse*; *PO-related morbidity and mortality harms and treatment and interventions* among Aboriginal populations in Canada. For the purposes of this review, the term 'Aboriginal' was inclusively used to refer to all status and non-status First Nations, Métis and Inuit peoples in Canada living both on- and off-reserve, and data were reported as such unless it was explicitly specified otherwise (eg only First Nations; on-reserve) in the respective information source. POs were defined as opioid analgesics available for prescription in Canada, unless the terms deviated or data were aggregated, in which case the specific term(s) were indicated (prescription pills, prescription and illicit drugs, etc.). Direct comparisons with non-Aboriginal populations were included where available.

Results

Prescribing and dispensing

Available data suggest elevated amounts of PO dispensing to Aboriginal recipients compared to the general Canadian population, with mostly rising trends; the data also suggest high rates of prescribing of strong PO formulations and multi-prescriptions. Specifically, the federal Non-Insured Health Benefits (NIHB) program provides essential health goods and services to approximately 800 000 eligible Aboriginal (ie status First Nations and Inuit but not non-status First Nations or Métis) people across Canada living on- and off-reserve; the NIHB client population (in 2013/2014) is considerably younger than the overall Canadian population with 34.7% (vs 22.1%) aged less than 20 years, fewer seniors

(≥65 years; 7.0% vs 15.7%), and an average age of 32 (vs 40) years[27]. In 2006/2007, the NIHB recorded 740 000 claims for PO prescriptions. Overall, annual PO claims increased to 933 000 by 2012/2013, constituting a 26% increase[19,28].

In 2012/2013, 'weak' POs (ie meperidine and codeine) accounted for 64.1% of NIHB opioid claims, while 'strong' POs (ie oxycodone and hydromorphone) accounted for 22.3%. Overall, 5.8% of all NIHB drug plan claims were made for POs (vs 2.4–4.3% in general population public drug plans)[28]. Approximately 2500 (0.3% of total eligible population) NIHB clients made concurrent claims for POs, benzodiazepines and methadone in 2013/2014. Claimants with more than 10 claims for POs accounted for 19.9% of all NIHB opioid claimants (vs 9.9–17.7% in general population plans) in 2012/2013. These high-use claimants accounted for the majority of PO claims costs and morphine equivalents dispensed; they were also more likely to receive higher-potency PO formulations[27,28]. There were 935 548 claims for PO agonists (eg Tylenol 3) in 2012/2013, which also accounted for the largest NIHB pharmacy expenditure (C$20,359,000)[27].

In addition to national patterns, there is evidence of regional variations in NIHB-based PO dispensing. Nearly 16 000 NIHB clients made a claim for an oxycodone formulation in 2006/2007; the majority (8200 or 51%) of these claimants were based in the province of Ontario, home to the largest percentage of NIHB clients in 2014 (197 092 or 24.4%)[27]. In addition, 56% of all Percocet and 49% of all OxyContin claimants were Ontario-based[19]. In 2007, 898 PO prescriptions were dispensed per 1000 eligible NIHB clients aged ≥15 years in Ontario; 119 per 1000 were for oxycodone formulations. The rate of NIHB clients in Ontario receiving PO prescriptions has remained relatively stable at around 20% (as of 2000–2009), yet the quantity of POs dispensed has increased[29].

Outside NIHB data, regional variations in PO prescribing exists. In Manitoba, levels of PO prescriptions and the prevalence of repeat PO prescriptions in 2006/2007 were found to be higher among Métis compared to all other Aboriginal and non-Aboriginal general population comparison groups. This difference was consistent by age and sex; however, no significant differences in the amount of POs dispensed (measured in daily defined doses) emerged[30]. Specifically, 20.8% of Métis had a prescription for one or more POs (vs 15.3%) and 7.7% of Métis had repeat (ie three or more in the past year) prescriptions (vs 4.4%)[30]. In the city of Winnipeg, 22.7% of Métis aged ≥16 years had one or more PO prescriptions (vs 15.8%) and 8.4% had repeat prescriptions.

NIHB-eligible First Nations populations in Alberta feature among the highest PO utilization across Canada, with codeine combinations identified as the most frequently dispensed PO formulation[31-33]. Conversely, all Atlantic provinces (New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador) reported a decrease in PO claims between 2009 and 2013; 10% of NIHB-eligible Atlantic region First Nation residents aged ≥15 years made a PO claim in 2013[34].

Use and misuse

Some indicators of PO use and misuse are available for select Aboriginal subpopulations, indicating somewhat higher rates for Aboriginals compared to general populations, although markedly higher rates have been reported for select (local) communities. Nationally, 4.7% of on-reserve First Nations adults aged ≥18 years and 1.3% of youth aged 12–17 years reported past-year non-prescription use of POs in 2010; correspondingly, 5% of on-reserve First Nations adults with at least one chronic health condition (vs 3.6% without) reported non-prescription use of POs[14].

Based on Health Canada's 2008/2009 National Youth Smoking Survey, PO use among a total of 2620 off-reserve Aboriginal youth was found to be more common than among the general Canadian youth population and 'abuse of prescription painkillers was five times greater among Inuit youth compared to non-Aboriginal youth'[35]. Rates were also higher among female and older youth[36]. The prevalence of prescription drug (including POs as well as sedatives and

stimulants) use 'to get high' among off-reserve Aboriginal youth was 10.6% (vs 5.9% non-Aboriginal); specific rates for Aboriginal subgroups were 18.4% among Inuit, 11% among First Nations and 8.8% among Métis[36].

The use and misuse of POs has been found to vary by province and region, with some (eg remote or Northern) communities reporting increases and higher levels compared to general populations. In Ontario's North East Local Health Integration Network (including 41 First Nations and 19 urban and rural Aboriginal communities) higher rates of prescription and illicit drug use among Aboriginal people have been found[37]. In 2009, the Nishnawbe Aski Nation (comprising 49 smaller Northern Ontario reserve communities with a population of approximately 45 000) declared a 'state of emergency' due to widespread PO misuse[38]. In some of this Nation's communities, 50–80% of the adult population, and up to 50% of youth, misuse POs and require treatment[39,40]. In 2012, the Matawa First Nation (comprising nine Nishnawbe Aski Nation communities) estimated that approximately 2000 people (of a total on-reserve population of 4912) were addicted to POs[41]. Constance Lake First Nation reported that 46% of community members admitted to abusing POs[42]. Other individual reserve communities (mostly 'fly-in' only, ie reachable only by air transportation) have also witnessed increases in PO misuse[43]. For example, both Eabametoong and Cat Lake First Nation declared a 'state of emergency' due to an estimated 70% of community members, ranging in age from 11 to ≥60 years, abusing POs and consequent major social disruption (including crime, child neglect, loss of employment or economic functioning at a community level)[35,41,42].

Elevated levels of PO use and misuse among Aboriginal populations are also prevalent in non-reserve contexts. In the city of Hamilton, Ontario, 19% of a total of 554 self-identified First Nations adults reported PO use (including codeine, morphine, oxycodone and fentanyl formulations) within the previous year[44]. In Calgary, Alberta, 48% (n=144) of Aboriginal patients accessing addiction treatment through Native Addiction Services in 2000 reported inappropriate (mainly sedatives, relaxants and POs) medication use. Of those, 47% did so more than 10 times in the previous year; 41% obtained their medication from a physician[45]. A secondary analysis compared rates of prescription drug abuse in Alberta, specifically among a sample (n=103) of illicit opioid users in inner-city Edmonton comprising and assessed as Edmonton-based subsamples from two other multi-site street drug-user studies. Nine in ten (>90%) of off-reserve First Nations respondents in both samples reported prescription drug abuse – most commonly POs (eg OxyContin, Dilaudid and Tylenol 3,4) – in the previous 30 days[46]. In a sample (n=381) of urban Aboriginal adults in Edmonton, 24.8% reported past-year prescription drug abuse, with more than half (13.8%) involving POs; 69.5% of PO abusers acquired their POs through prescriptions[47]. Prescription drug abuse was lower among First Nations and Métis students in Edmonton compared to First Nations and Métis student respondents from other areas of the province in the previous 12 months (6.9% vs 8.2%) as well as by lifetime (2.1% vs 6.8%)[46]. Furthermore, the 2008 Alberta Youth Experience Survey, measuring psychoactive drug use among grade 7–12 students (n=3469), found that 24.1% of off-reserve Aboriginal students (vs 16.8% non-Aboriginal students) reported ever using illicit prescription drugs. Specifically, 21.5% of Aboriginal students (vs 15.1%) reported past-year use of codeine formulations; of these, the largest proportion (39.7%) reported using one or two times, while 27.7% reported using more than 10 times[48].

Combined data from provincial youth health surveys conducted in British Columbia (BC) in 1992, 1998 and 2003 involving more than 4800 Aboriginal youth found that 11% of urban respondents had lifetime non-prescription use of prescription pills. A repeat survey (2008) involving more than 3000 Aboriginal youth found that 22% reported non-prescription pill use. Rates for on-reserve Aboriginal youth were even more elevated, with 13% reporting lifetime non-medical prescription pill use in 2003; this number had increased to 28% by 2008, including higher rates among females (24%) compared to males (19%)[49,50]. Another province-wide health survey of Aboriginal youth living on and off-reserve in BC (n=410) found that 11% reported any

prescription drug use (past month), while 4% reported use the day prior to the survey[51]. The 2008 BC Adolescent Health Survey showed 23% of self-identified Métis youth aged 12–19 years who were enrolled in the public-school system reported ever trying non-prescribed prescription pills[52].

Morbidity and mortality

Pregnancy-related opioid misuse and harms: Various studies, mainly from Northern Ontario, have reported disproportionately high, and rising, levels of PO-exposed pregnancies, and related complications, primarily among First Nations women. In Northern Ontario's Sioux Lookout Meno Ya Win Health Centre (SLMHC) – which provides health care to approximately 28 000 First Nations patients in the region including women flown in from remote reserves for delivery – overall PO (mostly oxycodone) exposure in pregnancy increased from 13% in 2009 to greater than 26% in 2014[53,54]. Among narcotic-exposed pregnancies during 2010–2013, about half (48%) of the pregnant women who had used illicit narcotics reported binge use several times a month, while 46.5% of patients reported daily use of narcotics, which was a shift from predominantly occasional use in 2009–2010; route of administration shifted to intravenous use among some (30%), and became similarly common to snorting (32%)[21,55].

In 2009–2010, 61 neonates out of a total (primarily First Nation) 482 live births in the SLMHC were exposed in utero to oxycodone. The incidence of oxycodone exposure during pregnancy tripled from 8.6% (2009) to 28.6% (2013), with more than four out of five cases related to oxycodone formulations[39,55,56]. Rates of births involving neonatal abstinence syndrome in the SLMHC have simultaneously increased. Neonatal abstinence syndrome incidence rose from 4.4% of all births in 2010 to 5.3% in 2014, but was much higher in PO-exposed pregnancies[53]. Among infants exposed to opioids in utero, the rate of neonatal abstinence syndrome was 66% among daily opioid-using mothers in 2010[56]. About 20% of births among First Nations women (vs 5.6% of in the general population) in Canada were born to teenage mothers in 2000; rates of neonatal abstinence syndrome have been found to be five times greater (9.2 vs 1.6 per 1000 hospital births) among infants born to teenage mothers compared to mothers older at first delivery[23,57,58].

Emergency room hospitalizations, accidents, overdoses: As for other key indicators of morbidity, there were 12.1 emergency room visits per 10 000 First Nations people related to narcotic-specific withdrawal, overdose, intoxication, psychosis and harmful use in 2008/2009 in a sample of Ontario-based community hospitals; by 2010/2011, this rate increased four times to 55 per 10 000[59]. On-reserve (vs off-reserve) motor vehicle collisions in Saskatchewan between 2003 and 2005 were more likely to include multiple collisions and result in severe injuries. Individuals involved in on-reserve motor vehicle collisions were more likely to feature substance use, with rates for prescription or illicit drug use 3.75 times greater than for those involved in off-reserve motor vehicle collisions[60,61]. Among a total of 87 Aboriginal motor vehicle collision-related fatalities in BC between 2003 and 2005, drug use was considered a primary contributing risk factor in 16.9%[62].

In BC, 11.4% of the total 909 overdose deaths in the period 2001–2005 were among First Nations individuals. Opioids (including but not limited to POs) were detected in 48.1% of the deaths[13].

Treatment and other interventions

Aboriginal communities, especially on-reserve, have traditionally experienced extreme shortages and access problems for substance abuse treatment (including, but not limited to, PO disorders)[19,63,64]. Treatment initiatives and availability – with specific tailoring for distinct populations and settings – for programs targeting PO abuse among Aboriginal peoples in Canada have been expanding, although many communities (particularly Northern and remote ones) still face barriers to availability and access. These communities often have limited access to healthcare services; where these services exist, long wait lists are common and many individuals have to travel outside of their home communities to access treatment[19,65,66]. Thousands of First

Nations individuals among a base population of 25 000 were estimated to be in need of treatment for PO-related addiction in Northern Ontario[39,41,67]. A study among urban Aboriginal youth aged 14–30 years (n=397) in BC using opioids showed that only 23.4% had ever accessed methadone maintenance treatment, a standard opioid maintenance treatment; the majority (54.3%) of daily opioid-injecting participants had never received methadone maintenance treatment[68].

The National Native Alcohol and Drug Abuse Program – which provides on-reserve culturally based addiction services to 58 centers and administers more than 550 community-based prevention programs across Canada – reported an increase in cases citing prescription drugs as the primary substance of abuse, from 24.8% of all program clients in 2008/2009 to 45% in 2013/2014 in the Atlantic region[34,69,70]. Approximately 300 First Nations individuals living on- and off-reserve received addiction treatment services for prescription opioid-related problems in the two Northern Ontario Local Health Integration Networks in 2004/2005; this number had increased to 901 by 2008/2009[22,71]. NIHB claims for opioid dependence treatment medications (eg methadone) had the highest claims incidence among the major NIHB therapeutic classes, totaling C$1,222,720 in 2013/2014[27]. The number of NIHB claimants for methadone increased from 598 in 2000 to 6,038 in 2011 (23% annualized growth rate). The number of NIHB clients making claims for Suboxone, a newer opioid treatment medication, has increased from 41 in 2011 to approximately 750 in 2012[23].

Recently, various pilot programs for PO dependence have been implemented principally in remote and Northern communities to address the lack of available treatment options. In a pilot study in a Nishnawbe Aski Nation community examining the feasibility of a community-based Suboxone taper-to-low-dose maintenance program in a sample of PO-dependent First Nations adults (n=22), 95% completed the program's taper phase and 88% had no evidence of PO use 30 days post-treatment initiation[39]. In the SLMHC, a year-long program evaluation of the Medical Withdrawal Support Service, involving inpatient opioid-detoxification with Suboxone, reported that 81% of clients (primarily First Nations individuals) successfully completed the program; 30% remained abstinent at 6-month follow-up[71].

The Dennis Franklin Cromarty High School in Thunder Bay, Ontario (offering residential schooling for grades 9–12 students from 24 remote First Nations communities) initiated a unique opioid-detoxification pilot initiative with integrated clinical, cultural and psycho-educational support for students with PO misuse. Of the 33 students enrolled, 22 (63%) were opioid-free at the end of the tapering period. Further, most students experiencing relapses continued to successfully finish their treatment cycle; 14 students engaged in Suboxone-maintenance for up to 6 months[72].

Other pilot programs and treatment interventions have shown success beyond rates of abstinence. In 2014, 140 self-referred First Nations patients (20–50 years) were enrolled in an outpatient Suboxone substitution program in North-Western Ontario's North Caribou Lake First Nation community. There, criminal or drug charges, including those involving youth, decreased by more than 60%; the needle distribution program dispensed less than half its previous volume, and school attendance increased in the year following program implementation[43].

While neonatal abstinence syndrome rates increased within Northern Ontario's SLMHC overall between 2010 and 2013, a pilot opioid-tapering program featuring maternal long-acting morphine provision resulted in a decrease (from 30% in 2010 to 18% in 2013) in neonatal abstinence syndrome prevalence in opioid-exposed pregnancies among mothers who enrolled in the program. Of the 166 narcotic-using First Nations women at the SLMHC, half (52%) agreed to participate; by the time of delivery, 9% had quit and 83% had decreased their dose, although half still used oxycodone at least occasionally[73]. As of 2014, the rate of NAS appears to have stabilized at approximately 20% of narcotic-exposed pregnancies in the SLMHC[53]. These community-based opioid-substitution programs have now been implemented in 16 of the 30 First Nations communities in the SLMHC catchment area[53]. In addition to these opioid-substitution therapy programs, many First Nations communities have developed and implemented culture-based and/or land-based interventions specifically designed for their community members[74]. To further address PO-related concerns in Northern Ontario's SLMHC, 20 physicians participated in a pilot educational intervention, resulting in a substantial reduction in physicians' concerns about getting patients addicted to POs; in-depth interviews confirmed that safer PO prescribing practices had occurred following the intervention[75].

Discussion

In the context of recently high levels of PO misuse and related harms across general and special risk (eg street-involved) populations throughout Canada, we examined available data and indicators for Aboriginal populations[1,3,4].

A first observation is that data on PO misuse and related harms among Aboriginal populations are extremely limited, largely fragmented and inconsistent; available data are mostly ad hoc or cross-sectional snapshots that allow for little examination of over-time trends or comparisons within Aboriginal or with non-Aboriginal populations. In this respect, the data situation on PO-related indicators among Aboriginals may be considered worse than that for the general Canadian population, where grave deficiencies in systematic documentation and monitoring exist[3]. Given the acuteness of the phenomenon under study, indicators on PO-related misuse and harms urgently need to be added to the essential health data. For these health indicators to be improved, better, more rigorous and consistent data and monitoring among Aboriginal populations are urgently required[24,25,76].

From the limited body of data available, the evidence suggests that PO misuse and harms among Aboriginal people in Canada are high (commonly higher than general populations) and have been rising in the select contexts where such assessments are possible. This includes the extreme examples of PO misuse or PO-related morbidity (eg regarding dependence or pregnancy-related problems) in Northern Ontario, where large proportions of entire communities or subpopulations have been severely afflicted by the harms of PO-related problems, but also extends to other settings[19,20,38,66]. This picture resembles the overall situation of substance use and acute or chronic harms among Aboriginal people, where predominantly higher levels (eg than general populations) have been observed across different substance categories[8,10,11,77]. Notably, most available problem indicators (regarding PO misuse or harms) are from (mostly Northern) Ontario and, to some extent, from Alberta, BC or Manitoba, whereas there is little information from other regions. While these reflect the regions with higher concentrations of Aboriginal peoples in Canada, it is not clear whether problems elsewhere are truly lower in occurrence or simply less documented.

Our data review can be considered positivist in nature and is largely limited to quantitative measures that do not consider the quality of data, methods or contexts in which these data were collected; in addition, our particular scoping/narrative approach to the research may have missed relevant information. Beyond these possible methodological constraints, the specific socioeconomic and cultural contexts of substance use among Aboriginal people need to be taken into consideration, although the extent of these complex interactions is beyond the scope of this article. It is well documented that substance use and its harm outcomes among Aboriginal people are crucially linked with the larger determinants of health, specifically the rampant health inequities, colonization, generational abuse and trauma, cultural suppression, poverty, unemployment, individual and systemic racism, and overall marginalization that uniquely characterize Aboriginal populations in Canada[7,16-18,77-80]. While the interplay of these historical or ecological determinants and harms for substances like alcohol (but also other substances) have been fairly well examined[8,12,81], this is less the case for psychotropic prescription drugs. In this wider context, POs may constitute a special case study that warrants attention; also in that a large proportion of the extensive amounts of POs consumed – and implicated in the

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problems documented – among Aboriginal peoples has been actively prescribed to them by their (governmental) healthcare providers (ie the institutions mandated to care for their health)[27,74,78,82].

In addition, yet directly related, are extensive needs and deficiencies in interventions (eg specialized treatment for substance use disorders as well as many other health problems). These shortcomings have been uniquely severe in some contexts (eg in Northern Ontario communities, where large numbers of people require care for PO-related problems but interventions are categorically unavailable or inaccessible)[63,66,83]. This, again, reflects aspects of the general situation of highly limited and inadequate healthcare services among Aboriginal populations. While addressing these deficiencies first and foremost requires resources, these also need to be based on culturally appropriate approaches for which illustrative examples exist[70,74,84-86]. On this basis, there are some positive examples of effective implementation or expansions of (innovative or tailored) interventions for PO-related misuse and harms among Aboriginal people, specifically in Northern Ontario settings, including community-based opioid substitution treatment programs or medication-supported opioid tapering for pregnant women[39,43,71-73]. Yet, there are also concerns regarding the long-term and intrusive nature of opioid substitution therapy among Aboriginal patients, especially young patients[87]. Clearly, much more is necessary in terms of implementation and interventions that are sensitively framed and undertaken within the above principles crucial for and unique to Aboriginal populations. While there are numerous social and health intervention priorities (eg housing, education, chronic diseases) for Aboriginal peoples in Canada that urgently need to be addressed by effective policy programs, the problem of PO misuse and harms is an acute and major issue that should be included in a comprehensive action program.

Conclusions

This review found limited indicators of high levels of PO misuse and problems among Aboriginal populations in Canada. Much-improved data and monitoring (eg through system inclusion of Aboriginal populations in relevant large-scale survey samples), and culturally and contextually appropriate as well as evaluated interventions, are urgently needed for this acute problem in one of the main high-risk populations for substance use and harms characterized by pronounced health inequities.

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The occasional treatment of opioid use disorder

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INTRODUCTION

Opioid use disorder (OUD) has become common in many regions of Canada, particularly in rural northwest Ontario.[1,2] In the past, addicted patients had to access methadone-dispensing physicians if opioid agonist therapy was indicated. This generally took patients out of a primary care setting and away from their community, where robust addiction services were absent.[3,4] Rural physicians who decide that opioid agonist therapy is a good option for their patient may now consider initiating sublingual buprenorphine/naloxone combination therapy in the office setting or even offer home induction.[5–12] Rural physicians may encounter patients who mismanage their opioid prescriptions and are subsequently found to have OUD. Treating the addiction locally can help patients eliminate much of their dysfunctional behaviour and allow them to identify underlying life issues.

Buprenorphine/naloxone combination therapy was approved for the treatment of opioid dependence in 2003 in the United States and in 2007 in Canada. Numerous cases of safe office-based and home induction of buprenorphine/naloxone therapy have been documented. [5–12] This combination agonist–antagonist medication has a demonstrated safety profile (see "Pharmacologic characteristics") and can be used for managing opioid withdrawal or for opioid substitution maintenance therapy.[13]

In northwest Ontario, where an epidemic of OUD has been observed since 2009,[14] rural clinicians are becoming familiar with inducing buprenorphine/naloxone therapy and maintaining patients on this treatment.[14,15] This article reviews the medication and describes induction and maintenance therapy.

OPIOID USE DISORDER

The terminology now used by the American Psychiatric Association is "opioid use disorder," and clear criteria have been established for diagnosis. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5),[16] OUD "includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition." Specific criteria can be found in DSM-5.[17]

TREAT THE WHOLE PERSON

In almost all cases, the underlying cause for OUD is pain — physical, emotional, spiritual and/or mental. Suffering in any of these realms may be the root cause for a person's initial use of opioids and the subsequent development of OUD. A patient receiving opioid agonist (substitution) therapy will no longer experience the euphoric effects of illicit opioids, thereby losing a key coping mechanism. In addition to opioid agonist therapy, supports (typically called after-care) will be needed to assist the patient in dealing with his or her underlying issues. Although studies differ in their findings regarding the

benefits of psychosocial supportive programs in the treatment of addictions,[18,19] there is general consensus that opioid agonist therapy should be accompanied by psychosocial supportive therapy.[16] Furthermore, fear of withdrawal symptoms can be a powerful driver of ongoing addictive behaviours; buprenorphine/naloxone therapy works well to mitigate those symptoms.

PHARMACOLOGIC CHARACTERISTICS

At first glance it may seem an odd combination: an opioid agonist and an antagonist. The opioid component, buprenorphine, is a semisynthetic opioid derived from the opium poppy that is 40 times more potent than morphine.[13] It binds strongly to the body's opioid receptors (particularly the μ receptor) and acts very much like methadone, by competing with other opioids for access to these receptors. As with methadone, its long half-life provides relief from withdrawal symptoms. Compared to methadone, which is a full μ-opioid receptor agonist, buprenorphine is a partial μ-opioid receptor agonist and has a better safety profile, with minimal respiratory depression and associated morbidity and mortality.[13]

When used as a single component, buprenorphine has limited euphoric effect when administered sublingually, but if administered intravenously, it can become a drug of abuse. When combined with naloxone, the risk of such diversion is decreased, as intravenous use may lead to withdrawal. Naloxone has almost no bioavailability when taken sublingually or orally. Hence the naloxone component of buprenorphine/naloxone allows the buprenorphine component to be safely used as agonist replacement therapy, with a built-in deterrent against diversion to intravenous use.

Precipitated withdrawal at induction must be avoided by ensuring the patient is in some opioid withdrawal. Because of buprenorphine's higher affinity for the μ-opioid receptor, it displaces other opioids from the receptor. Given that most opioids are full agonists, this creates sudden withdrawal symptoms as the expression of full agonist activity is replaced by partial agonist activity.[13] Another disadvantage of this strong receptor binding is that, should the patient require emergency analgesia, much higher dosages of opioids must be used to overcome the buprenorphine that is bound to the receptors.

The safety profile of buprenorphine notwithstanding, concurrent administration of other respiratory depressants such as alcohol, illicit opioids and benzodiazepines should be avoided.

PATIENT ASSESSMENT

A clinical assessment is needed to confirm the diagnosis of OUD, identify concurrent disorders and clarify the patient's treatment goals. Screening blood tests are beneficial for diagnosing bloodborne infections and other health issues in a high-risk population. Investigations should include a pregnancy test, complete blood count, liver function tests, screening for hepatitis B, hepatitis C and HIV infection, a urine drug test and screening for sexually transmitted infections. Useful resources are available through the Centre for Addiction and Mental Health for this initial assessment.[20] Since opioid agonist therapy is a harm-reduction strategy, the patient with OUD must have adequate harmful effects to warrant therapy. It is also important to recognize that chronic pain is a common comorbidity in patients who have opioid addiction. Adjunctive therapies (e.g., anticonvulsives, antidepressants, nonsteroidal anti-inflammatory drugs) may be required to manage pain while the patient is receiving opioid agonist therapy.

STARTING BUPRENORPHINE/ NALOXONE THERAPY

Starting the treatment is typically referred to induction. Induction and maintenance therapy can be given in outpatient settings including the office,[5–10] unsupervised at home[11,12] or as direct observed therapy.[21] Induction instructions are similar in all 3 settings. Provinces have different prescribing requirements (Table 1).

Since buprenorphine/naloxone binds powerfully to opioid receptors, it displaces any illicit opioids present. The patient must therefore be in moderate withdrawal before therapy is started. Measuring withdrawal has been standardized by use of the Clinical Opioid Withdrawal Scale (COWS), available online (https://www.naabt.org/documents/COWS_induction_flow_sheet.pdf).[22] Moderate withdrawal is generally identified by a COWS score of 12 or greater.[22] Patients in moderate withdrawal can safely receive induction therapy with buprenorphine/naloxone without great risk of precipitating increased withdrawal symptoms.

Table 1: Provincial and territorial buprenorphine/naloxone prescribing requirements

Methadone exemption required	No methadone exemption required*
Saskatchewan	British Columbia
Manitoba	Alberta
Newfoundland and Labrador	Ontario
Northwest Territories	Quebec
	New Brunswick
	Nova Scotia
	Prince Edward Island
	Yukon Territory
	Nunavut

*Some jurisdictions require online continuing medical education.

USE IN PREGNANCY

There are 3 published articles regarding patients who were incidentally or purposefully exposed to buprenorphine/naloxone prenatally (including induction therapy during pregnancy).[23–25] No adverse outcomes were observed in the total of 71 patients exposed for months to buprenorphine/naloxone.

If buprenorphine/naloxone is diverted to intravenous or intranasal use, however, it can cause severe withdrawal and pose a risk for the fetus.[26] For this reason, current recommendations are that women who become pregnant while taking buprenorphine/naloxone should continue their present treatment but should transition to buprenorphine monotherapy when possible, owing to concerns about withdrawal if buprenorphine/naloxone is used improperly (i.e., injected).[27] Since the single component buprenorphine is available only by special access from the manufacturer, this process can take weeks to set up. The combination drug is available through pharmacies.

PRECIPITATED WITHDRAWAL

Precipitated withdrawal may occur when the first dose of buprenorphine/naloxone is provided to a patient who still has a significant amount of full-agonist opioid occupying the μ-opioid receptors. Precipitated withdrawal differs from the "typical" withdrawal to which patients are accustomed. Precipitated withdrawal has a sudden onset of full withdrawal symptoms within 30 to 60 minutes of the first dose of buprenorphine/naloxone. In addition, it is difficult to reverse because of the high affinity that buprenorphine has for opioid receptors. It is important to prevent precipitated withdrawal by ensuring the patient is in moderate withdrawal before starting buprenorphine/naloxone therapy (it is easier to avoid precipitated withdrawal than to treat it).

Recommended lengths of abstinence before the first dose of buprenorphine/naloxone are listed in Table 2.

Table 2: Recommended length of abstinence before first dose of buprenorphine/naloxone

Drug/route	Length of abstinence
Buprenorphine by any route	None
Methadone by any route	≥ 3–5 d (great individual variance), ideally from a dosage ≤ 30 mg
Other opioids	
Intravenously	≥ 12 hr
Intranasally (snorting), smoking, chewing, orally	≥ 24 hr

WITHDRAWAL SYMPTOMS

Be prepared to manage withdrawal symptoms and common side effects. Patients are typically still experiencing significant withdrawal symptoms for the first 2 days of induction therapy. Some physicians simply provide reassurance and remind patients that their withdrawal will be relieved within a couple of days (most patients have significant improvement by day 3).

Many patients experience at least some transient side effects from buprenorphine/naloxone (e.g., headache, nausea). Table 3 lists the most common side effects. Note that there is some overlap between the symptoms of withdrawal and the side

Table 3: Typical opiate withdrawal signs and symptoms, and common acute buprenorphine/naloxone side effects

Opiate withdrawal signs and symptoms	Buprenorphine/naloxone side effects
Nausea/vomiting	Headache
Diarrhea	Nausea/vomiting
Abdominal cramps	Hyperhidrosis
Diaphoresis	Constipation
"Bone pain" or arthralgia	Insomnia
Myalgia	Unmasking of chronic pain
Fever/chills	Somnolence
Yawning	Euphoria
Rhinorrhea	
Lacrimation	
Piloerection	
Tremors	
Anxiety	
Restlessness	
Irritability	
Insomnia	
Headache	
Fatigue, "feeling lazy"	
Mydriasis	

effects of buprenorphine/naloxone. Most of the side effects are transient and resolve within a few days, except for constipation, hyperhidrosis and any underlying chronic pain.

PROCEDURE

After OUD has been established as a diagnosis, a clinical assessment has been completed and the patient agrees to the treatment plan, induction therapy can be scheduled. The patient must be instructed to abstain from opioids according to the time frames suggested in Table 2; otherwise he or she may risk precipitated withdrawal. The goal of induction therapy is to determine the dosage of buprenorphine/naloxone that relieves symptoms of withdrawal for a full 24 hours, without overmedicating. In the case of office induction, during daily visits for the first 4 to 5 days, assess for signs of drowsiness. Excessive drowsiness may indicate that the dosage is too high and should be decreased by 2 mg (or more). Some mild drowsiness can be expected at first, and the patient should be cautioned against driving or using heavy equipment until this effect resolves, typically within a week.

Day 1

- Ask the patient about his or her last illicit opioid use (when, which opioid, how much and by what route). If the patient has used an opioid within the time frames listed in Table 2, it may be best to delay induction therapy by a few hours.
- Assess the patient's level of opioid withdrawal by using the COWS. A COWS score of 12 or greater is recommended, but lower scores may still be acceptable depending on how long it has been since the patient's last illicit opioid use.
- Buprenorphine/naloxone comes in 2 mg and 8 mg dosages of buprenorphine. The tablets can be divided and are applied under the tongue until dissolved (2–10 min). For most patients, 4 mg is an appropriate first dosage (a smaller dosage may be appropriate for some patients; a larger starting dosage is not recommended). This dosage is provided by direct observed therapy.
- The patient then returns for reassessment at least 3 hours later, at which time, if he or she is still experiencing withdrawal symptoms, another 4 mg dose (or less if appropriate) is given. **The maximum amount given on day 1 is typically 8 mg** (in 2 divided doses). However, a third dose of 4 mg (total 12 mg) can be given 2–3 hours later for certain patients (e.g., those who are pregnant or are at high risk for not completing induction therapy owing to severe withdrawal) to reduce withdrawal symptoms as quickly as possible.

Day 2

- Assess the patient's level of withdrawal. If he or she is still experiencing any withdrawal symptoms, more than the total dosage given on day 1 will be needed. A COWS score of 12 or greater was required only to avoid precipitated withdrawal on day 1; now the goal is to eliminate withdrawal. Typically, 4 mg is added to the previous day's total, but if the previous day's dose lasted almost the full 24 hours, 2 mg may be a more appropriate titration. Hence, the dosage given at the beginning of day 2 is [day 1 total dosage + 4 mg (or 2 mg)].
- If the patient is not experiencing any withdrawal symptoms on day 2, it may be that the total dosage given on day 1 is the appropriate dosage. In that case, the amount given on day 2 is the same as the total dosage that was given on day 1.
- If the patient seems excessively drowsy, the dosage from day 1 may have been too much, and less than the day 1 total dosage should be given.
- Patients can be given the option of returning later in the day for an additional dose if withdrawal symptoms return.
- **The recommended maximum total dosage for day 2 is 16 mg.**

Day 3

- Assessment and dosing continues as described for day 2.
- Typically only 1 dose is provided on day 3 (and beyond).
- **The recommended maximum total dosage for day 3 is 20 mg**.

Day 4

- **The recommended maximum total dosage for day 4 is 24 mg**.

To go above 24 mg of buprenorphine/naloxone is off-label use in Canada. However, some patients may require a higher dosage. In Europe and the US, the maximum dosage is set at 32 mg; beyond this amount, there is no further benefit owing to the ceiling effect of buprenorphine.

STABILIZATION PHASE

The first 2 to 3 months of buprenorphine/naloxone therapy are referred to as the stabilization phase. The concept of stability in the treatment of opioid addiction generally refers to achievement of many or all of the following goals:

- Discontinuation of injection drug use
- Consistent attendance for direct observed therapy, with very few missed doses
- Improved function in activities of daily living
- Improved quality of life.

It is important to recognize that it is common for patients to still use illicit drugs during the stabilization phase, and some patients will continue to use illicit drugs throughout buprenorphine/naloxone therapy. In these cases, one should remember the overall goals of harm reduction. Abstinence may not be achieved for every patient, so consideration should be given to the benefits of therapy, such as

- Decreased or discontinued injection drug use
- Improved finances
- Improved nutrition
- Ability to maintain employment or to care for children
- Decreased risk of violent altercations
- Improved attendance for routine health care.

The following criteria are helpful in determining a therapeutic dosage for the patient:[16]

- No withdrawal symptoms for the full 24 hours between doses
- Reduced cravings (but cravings may still be present)
- Cessation of opioid abuse
- A slip or relapse to opioid use does not result in euphoria
- No sedation and minimal other side effects.

MAINTENANCE THERAPY AND BEYOND

The overall goal is to reduce harm caused by OUD that affect the individual, the family and the community. These harms include, but are not limited to:

- Transmission of blood-borne infections (e.g., HIV, hepatitis C) and sexually transmitted infections (e.g., hepatitis B, chlamydia, gonorrhea)
- Complications of intravenous drug use (e.g., soft tissue infections, deep vein thrombosis, pulmonary embolus, endocarditis, osteomyelitis, sepsis)
- Financial difficulties (e.g., selling necessary belongings, not buying adequate groceries)
- Prostitution
- Criminal activities, especially break and enter, and theft
- Physical assaults and altercations
- Pregnancy complications (e.g., spontaneous abortion, preterm labour)
- Neonatal abstinence syndrome among infants born to women with OUD
- Children being neglected
- Children being apprehended and placed into care by child protective services
- Poor school attendance by children
- Poor vaccination rates (with resulting risks of outbreaks of vaccine-preventable diseases)
- Suicide and homicide.

One of the primary goals of therapy is to retain the patient in treatment, as dropping out or sudden discontinuation of buprenorphine/naloxone therapy leads to high rates of relapse to opioid abuse. With this in mind, we need to consider the various barriers and events that might increase the risk of attrition.

The maintenance phase is the time to address various issues related to OUD, such as

- Psychiatric comorbidities
- Other drug and alcohol abuse
- Unstable relationships
- Parenting skills, education, employment
- Financial issues
- Health issues.

It is a time for long-term goal setting. Moving beyond OUD and avoiding future relapse requires that the patient has constructed a different life, with healthy coping mechanisms and strong social supports. Often, there is deep emotional trauma from which the patient needs to heal.

Some patients will therefore be in the maintenance phase for life. Others may be able to taper off after several months to a year. The length of maintenance therapy is very individual.

Patients who wish to stop buprenorphine/naloxone therapy should be counseled carefully, as the risk of relapse is very high. They may wish to attend a detoxification program to get through the final withdrawal from buprenorphine/naloxone, or medications for symptom management can be provided by the family physician. Slow tapering over several weeks is recommended.[28] If relapse occurs, the patient should be welcomed back to opioid ago-

nist therapy without judgement. Recovering from relapse may provide lessons and insights that could allow a successful discontinuation later.

Alternative dosing regimens

Once a patient has been maintained on a stable dosage for a period of time, an alternative dosing schedule might be preferred if the patient's dosage is appropriate to allow it. The long half-life of buprenorphine allows the option of longer dosing intervals of up to 2 or even 3 days, as long as the maximum dosage given on any one day does not exceed 24 mg. One caveat of alternative dosing regimens is that managing missed doses can become complicated.[19,29,30]

URINE DRUG SCREENING

The clinical utility of urine drug testing is as follows:

- To assess stability of the patient's condition
- To provide a starting point for discussion of triggers and coping strategies
- To assess for illicit nonopioid drug use and allow for additional treatment planning
- To enable the patient to participate in an incentive program
- To corroborate the patient's self-report of drug use or abstinence
- To detect substances that may be unsafe in combination with buprenorphine/naloxone (e.g., benzodiazepines)
- To document the presence of buprenorphine as a replacement therapy agent.

It is important to note that there is no evidence to support the use of punishment, or the threat of punishment, in the treatment of addictions. This means that buprenorphine/naloxone therapy should not be withheld as a consequence (punishment) for a positive urine drug test result. The fear of being "kicked off" buprenorphine/naloxone creates an unnecessary stress for patients who may still be struggling with drug use. Many patients have intense fear and anxiety regarding opioid withdrawal. Stress and anxiety are common triggers for drug use, and therefore any addiction treatment program should aim to decrease stress in a patient's life and assist with general stress management.

CONCLUSION

Buprenorphine/naloxone combination therapy is a safe and effective outpatient treatment strategy for OUD. Rural physicians can benefit from knowing about it. Even if they decide not to become involved in prescribing it, some of their patients may be taking it, and it is important to understand its pharmacologic characteristics and be comfortable with its use.

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Infectious Diseases

First Nations hepatitis C virus infections

Six-year retrospective study of on-reserve rates of newly reported infections in northwestern Ontario

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Abstract

Objective To document rates of newly reported hepatitis C virus (HCV) cases from 2010 to 2015 in remote First Nations communities.

Design Retrospective analysis of aggregate data of newly reported HCV antibody-positive (Ab+) cases.

Setting Northwestern Ontario.

Participants A total of 31 First Nations communities (an on-reserve population of 20 901) supported in health care by the Sioux Lookout First Nations Health Authority.

Main outcome measures The aggregate characteristic data included year of notification, age range, and sex for a 6-year period (2010 to 2015).

Results There were 267 HCV Ab+ cases in the 6-year study period. The incidence in 2015 was 324.2 per 100 000 population. This is 11 times the rate for all of Ontario. The most common associated risk factor was sharing of intravenous drug use equipment. Women made up 52% of patients with newly reported HCV Ab+ cases. More than 45% of cases were in patients between 20 and 29 years of age.

Conclusion This high burden of newly reported HCV Ab+ cases in geographically remote First Nations communities is concerning, and prevention and treatment resources are needed. This burden of disease might pose more urgent health and social challenges than can be generalized from the experience of the rest of Canada.

EDITOR'S KEY POINTS

- Canada's Aboriginal population faces a disproportionate and increasing burden of newly reported hepatitis C virus (HCV) infections. This problem has been increasing in northwestern Ontario since the First Nations leaders declared an "epidemic" of opioid abuse in 2009. In 2015, the rate of newly reported HCV antibody–positive cases was 324.2 per 100 000 in the 31 rural and remote First Nations communities in northwestern Ontario.

- First Nations community members in their 20s comprised more than 45% of newly reported cases between 2010 and 2015. There was a high rate of intravenous drug use among those with newly reported HCV antibody-positive cases (86.5%).

- Much can be learned about the course of HCV infection in isolated communities. Some of these lessons might be applicable to urban-based subcultures with loosely defined geographic and social boundaries. Community awareness, education, and prevention strategies are critical aspects of such clinical and research initiatives and exploration of these questions must move forward within individual community contexts.

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National rates of newly reported hepatitis C virus (HCV) infection in Canada are declining.[1] Despite this reduction, Canada's Indigenous population faces a disproportionate and increasing burden of disease.[2-4] Modeled estimates of HCV prevalence in Canada have shown a 3-fold higher prevalence among the Aboriginal population compared with the non-Aboriginal population.[1]

There is a paucity of robust population-based data on HCV infection in Aboriginal Canadians. Available information largely focuses on urban-based populations. Studies in Winnipeg, Man, and in Vancouver and Prince George, BC, document high rates of HCV infection in "street-exposed" urban Aboriginal people.[5,6] These high rates of HCV infection are associated with intravenous drug use (IVDU), similar to Canada-wide data, which show that 80% of newly reported HCV infections in 2007 were IVDU-related.[7]

In 2009, First Nations leaders in northwestern Ontario declared a state of emergency concerning the widespread use of opioids in their communities.[8] Since then, regional hospital- and community-based programs have been developed to offer treatment for opioid use disorder.[9-12] An important aspect of these programs is increased screening for blood-borne infection. The rising levels of HCV infection encountered by local clinicians prompted clinical and research initiatives.

This study of an on-reserve First Nations population spread across 31 remote communities in northwestern Ontario documents rates of newly reported HCV antibody-positive (Ab+) test results in a rural Aboriginal population over a 6-year period, 2010 to 2015.

METHODS

In 2015, the Sioux Lookout First Nations Health Authority (SLFNHA) Chiefs in Assembly and the regional Chiefs Committee on Health approved research on HCV infection in their communities.[13] The SLFNHA supports community-based medical services and other health promotion programs in 31 remote First Nations communities in northwestern Ontario.

Aggregate data were received from the Health Canada First Nations and Inuit Health Branch (FNIHB)–Ontario Region on newly reported HCV Ab+ test result notifications from these 31 on-reserve communities. The data consisted of HCV antibody status notifications received by the FNIHB–Ontario Region through the provincial reportable disease system from 2010 to 2015. Case characteristics were collected by the FNIHB through routine case and contact management of reportable diseases. The aggregate characteristic data included year of notification, age range, and sex. Risk factor data were limited to a 5-year period (2011 to 2015). Testing was done both in local community nursing stations and in hospital settings. The total number of screening tests performed and RNA serology data were not available.

Cases were limited to individuals with HCV Ab+ test results who were reported to the provincial public health system and who lived on reserve in the SLFNHA catchment area. Individuals who lived off reserve were not included in this study. According to Indigenous and Northern Affairs Canada (INAC), the on-reserve population of the 31 communities was 20 901 in 2015. Population counts were estimated by INAC using the Indian Registration System. Age-standardized rates were calculated by the indirect method using the 2006 Canadian population. The population estimate does not account for patient migration and does not include nonregistered community members.

Ethics approval was received from the Sioux Lookout Meno Ya Win Health Centre Research Review and Ethics Committee.

RESULTS

In 2010, 15 notifications for HCV Ab+ status were recorded. This increased to 86 notifications in 2014 and 73 in 2015 (**Table 1**). The age-standardized annual rate of HCV Ab+ test result notifications increased dramatically between 2010 (56.6 per 100 000 population, 95% CI 41.9 to 71.3) and 2015 (324.2 per 100 000 population, 95% CI 288.9 to 359.5). **Figure 1** compares these rates with those of Ontario and Canada.[14,15]

Women accounted for 52% of patients with newly reported HCV Ab+ cases. More than half (54%) of the female patients were in the 20- to 29-year-old age group. Only 41% of HCV infection cases in men were in patients in the 20- to 29-year-old age group, with 52% in the 30- to 64-year-old age group. More than 45% of cases were in patients between 20 and 29 years of age (**Figure 2**).

The most commonly reported risk factor was sharing IVDU equipment, which occurred in 86.5% of cases (**Table 2**).

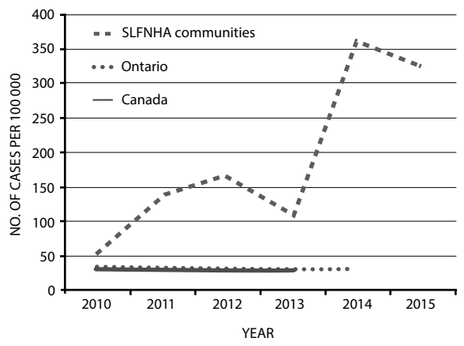
Fewer than 5 new notifications for HIV infection were reported during the 6-year study period.

Table 1. Newly reported HCV antibody-positive test results and rates per 100 000 in SLFNHA communities by year: The total no. of reported cases was 267.

YEAR	ON-RESERVE POPULATION	NO. OF CASES	RATE PER 100 000 (95% CI)
2010	18 536	15	56.6 (41.9 to 71.3)
2011	19 072	27	135.5 (112.7 to 158.3)
2012	19 505	38	169.9 (144.4 to 195.5)
2013	20 076	28	113.1 (92.3 to 133.9)
2014	20 463	86	364.7 (327.3 to 402.1)
2015	20 901	73	324.2 (288.9 to 359.5)

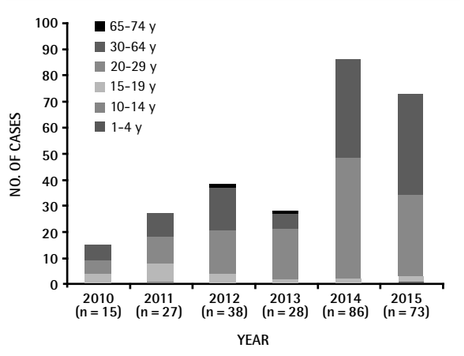
HCV—hepatitis C virus, SLFNHA—Sioux Lookout First Nations Health Authority.

Figure 1. Age-adjusted rates (per 100 000 population) of newly reported hepatitis C virus antibody-positive test results among First Nations patients living on reserve in SLFNHA communities by year (2010 to 2015) and corresponding rates in Canada and Ontario



SLFNHA—Sioux Lookout First Nations Health Authority.
Data from Public Health Ontario[4] and Public Health Agency of Canada[5].

Figure 2. No. of reported hepatitis C virus antibody-positive cases by age group in First Nations communities serviced by the SLFNHA from January 1, 2010, to December 31, 2015



SLFNHA—Sioux Lookout First Nations Health Authority.

DISCUSSION

In 2015, the rate of newly reported HCV Ab+ cases was 324.2 per 100 000 population in the 31 rural and remote First Nations communities in northwestern Ontario. This is 11 times the 2014 provincial rate of 30.1 per 100 000 and higher than previous estimates for the Canadian Aboriginal population (**Figure 1**).[5,14,15]

Table 2. Risk factors of individuals with HCV antibody-positive test results in SLFNHA communities: *Patients often identified >1 risk factor; there were 252 reported cases from 2011 to 2015.*

RISK FACTOR	N (%)
Epidemiologic link to confirmed case	30 (11.9)
Had unsafe sex	19 (7.5)
Shared IVDU equipment	218 (86.5)
Other	8 (3.2)
Unknown	17 (6.7)

HCV—hepatitis C virus, IVDU—intravenous drug use, SLFNHA—Sioux Lookout First Nations Health Authority.

Previous HCV infection incidence rates calculated for Canadian Aboriginal populations have focused on inner-city First Nations and Metis populations.[5,6] In 2013, Uhanova et al documented the newly diagnosed HCV infection rate at 91.1 per 100 000 population among First Nations living in Winnipeg, which was 2.5 times the provincial rate.[6] In their study, most (73%) Aboriginal participants with HCV infection resided in the inner city. The Cedar Project in British Columbia (2003 to 2009) studied 148 inner-city Aboriginal youth in Vancouver and Prince George who used illicit drugs.[5] They found that 26% of participants became infected with HCV within 2 years of initiating IVDU.

Our study documents a high proportion of IVDU among those with newly reported cases of HCV infection (86.5%) in remote First Nations communities, which is higher than the present estimated Canadian risk of 80% for newly acquired HCV infection,[16] but is similar to the 58% to 86% range found in many other studies.[7,17-20]

First Nations community members in their 20s comprised more than 45% of newly reported cases between 2010 and 2015 (**Figure 2**). This is ominous, as progression to hepatic complications is acknowledged to occur over a 20-year period.[21] This age distribution is similar to that in Ontario as a whole, where HCV infection incidence was highest among those aged 25 to 29 years.[1,18] Other population studies demonstrate a younger affected age group among Aboriginal participants.[5,6]

The proportion of newly reported HCV Ab+ cases reported among women 20 to 29 years of age in this review was slightly higher (52%) than that among men in this age group (41%), but the relative number of women tested is not known. This result is similar to other studies of Canadian Aboriginal populations, but differs from the Ontario balance, in which men accounted for 62.2% of newly reported HCV Ab+ cases in 2014.[14] Opioid use disorder is common in our region and community-based opioid agonist therapy (OAT) programs have been recently developed in many communities and include routine screening for blood-borne infections.

Opioid use in pregnancy can occur in as many as 30% of pregnancies in the Sioux Lookout Meno Ya Win Health Centre catchment population. Hepatitis C virus infection screening is therefore regularly added to provincially recommended HIV and hepatitis B testing.[22] This increased testing in the pregnant population might account for some of the preponderance of female patients with newly reported HCV Ab+ cases. Studies in Winnipeg and Prince George also documented overrepresentation of Aboriginal women in the IVDU population.[23,24]

Low rates of HIV infection are reported in this study. Ontario HCV infection models estimate 5% to 10% of people who actively inject drugs are living with HIV, while HCV infection rates are 50% to 75%.[25] It is not clear why the incidence of HIV infection is particularly low in our study population. Establishing surveillance, education, prevention, treatment, and harm reduction strategies for HCV infection will provide capacity for management if increases in HIV infection occur.

Findings of this study are not generalizable to other on-reserve populations. The recent HIV outbreak in on-reserve First Nations communities in Saskatchewan speaks to the vulnerability of isolated communities to public health emergencies.[26] Centralized federal management of on-reserve public health and infectious disease surveillance might be too cumbersome to provide an appropriately efficient, focused response. Well-resourced regional health services might be more able to monitor and respond to serious changes in disease profiles.[27]

In response to changes in drug use patterns and increased rates of HCV infection, an interagency Sexually Transmitted and Blood-borne Infection Working Group was established in 2011. Participants included representatives from the SLFNHA, the Shibogama First Nations Health Authority, the FNIHB, the local provincial health unit, and the Sioux Lookout Meno Ya Win Health Centre, and local physicians.[13] With support from the regional chiefs, early activities included increasing public awareness about blood-borne infections, providing education to health care providers, and making harm-reduction education and needle distribution programming accessible to remote communities. Ongoing responsibility for these initiatives has been assumed by the SLFNHA under Approaches to Community Wellbeing, a developing First Nations–governed public health system for SLFNHA communities. In addition to health promotion activities, the SLFNHA, in collaboration with local primary care physicians, is establishing a program to treat and support individuals with HCV infection.

On-reserve community-based OAT programs were first developed in the Sioux Lookout region in 2011. Since then, opioid addiction treatment programs, often integrating OAT, traditional healing practices, and grief and addiction counseling, have become available in numerous communities. Programs have demonstrated high retention rates and meaningful community-wide social change including decreases in community criminal charges and child protection cases, and increased school attendance.[11] The obstetric program at the Sioux Lookout Meno Ya Win Health Centre has also responded to high rates of opioid exposure in pregnancy with targeted OAT programming. The program has since experienced a decrease in rates of neonatal abstinence syndrome in opioid-exposed pregnancies.[9,28]

Aboriginal populations have been documented to have an increased risk of HCV infection, but have no known relevant genetic susceptibility.[2-4] "Colonization, racism, social exclusion and a lack of self-determination"[29] affect the alarming disparities in the health of Aboriginal peoples. These ongoing determinants of health play a key role in the high burden of addiction and preventable illness in northwestern Ontario.

Robust, community-based education and case detection, and increased management and treatment capacity will be needed to meet this challenge. Such regional initiatives will need special attention in any national HCV strategy.[30,31] Limited funding for opioid use disorder treatment programs has already taxed many communities' resources and additional support is required for the prevention and management of HCV infection.[32]

Further collaborative research efforts are currently under way. With the support of local First Nations leadership, SLFNHA has recently partnered with researchers at the University Health Network in Toronto, Ont, to examine access to community-based testing for blood-borne infections and to better our understanding of the prevalence of HCV infection in the region. Spontaneous clearance rates, viral genotyping, disease progression, treatment outcomes, re-infection rates, and community attitudes are all potential areas to explore.

According to the 2010 Ontario Burden of Infectious Disease Study, HCV infection accounts for the largest number of years of life lost owing to premature mortality attributed to infectious diseases.[33] Newly available antiviral agents offer successful and well tolerated treatment of HCV infection, which can be delivered in remote communities.[30] These drugs are expensive, and encouraging early treatment should be considered in such isolated communities. This will require support by the federally funded health insurance program.

Much can be learned about the course of HCV infection in isolated communities. Some of these lessons might be applicable to urban-based subcultures with loosely defined geographic and social boundaries. Community awareness, education, and prevention strategies are critical aspects of such clinical and research initiatives and exploration of these questions must move forward within individual community contexts.

Limitations

This study has many limitations. Cases were defined as newly reported HCV Ab+ test results, but do not necessarily reflect new exposures to the virus. The increase in reported HCV Ab+ cases in northwestern Ontario might partly reflect increased testing associated with the initiation of opioid use disorder treatment programs, health provider education, and regional health promotion campaigns. Case detection was primarily through targeted screening of high-risk individuals and is likely an underestimate of the actual prevalence of the disease. This is similar to Canada-wide detection practices, in which population screening is primarily focused on high-risk individuals. As RNA results were not available for research purposes, we were unable to distinguish between cases that evolved into chronic HCV infection and those that resolved spontaneously. As such, the actual burden of chronic HCV infection is still unknown. Population-level data from INAC are sourced from the Indian Registration System and likely underestimate actual populations living on reserve. Given the small population sizes, rates should be interpreted with caution. Not all communities were similarly affected by HCV infection and some communities had no newly reported cases. Genotype results and comorbidity information were not available. As information on testing by sex and age group is absent, conclusions about incidence in these groups are limited.

Conclusion

We report high rates of newly reported HCV Ab+ cases in 31 remote First Nations communities in northwestern Ontario. This is likely associated with the recent opioid "epidemic" recognized by regional First Nations leaders in 2009 and the resulting increase in testing for blood-borne infections. These communities are geographically remote and the burden of HCV infection in such isolated communities might pose more urgent health and social challenges than can be generalized from the experience in the rest of Canada.

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Contributors
All authors contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests
None declared

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Management of infectious diseases in remote northwestern Ontario with telemedicine videoconference consultations

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Abstract
Northwestern Ontario in Canada provides a unique clinical challenge for providing optimal medical care. It is a large geographic area (385,000 km^2) and is home to 32 remote First Nations communities, most without road access. These communities suffer a heavy burden of infectious disease and specialist consultations are difficult to obtain. The Division of Infectious Diseases at the Ottawa Hospital and the Sioux Lookout Meno Ya Win Health Centre established a telemedicine-based infectious disease consultation service in July 2014. We describe the implementation of this service, types of cases seen and patient satisfaction, as well as some of the challenges encountered. Information on visits was prospectively collected through an administrative database, and patient satisfaction surveys were administered after each initial consultation. During our first year of operation, 191 teleconsultations occurred: 76 initial consultations, 82 follow-up appointments and 33 case conferences. The scope of cases has been broad, mostly involving musculoskeletal infections (26%), followed by skin and soft tissue infections (23%). HCV, acute rheumatic fever, and respiratory infections (including pulmonary tuberculosis) were other diagnoses. Patient satisfaction has been very high and 28 telemedicine patient visits have occurred in their remote home communities, minimizing travel. The infectious disease consulting service and local clinicians have succeeded in addressing needs for care in infectious diseases in northwestern Ontario, where important gaps in service to First Nations' communities continue to exist. Regular scheduled available access to an infectious disease specialist is a well-received advancement of care in this remote region of Canada.

Keywords
Telemedicine, infectious diseases, remote, indigenous

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Introduction

Infectious diseases are very common in the remote 32 First Nations communities in the Sioux Lookout region in northwestern Ontario. The area suffers from a high incidence of tuberculosis, and has documented higher rates of other infectious diseases such as hepatitis C, blastomycosis, acute rheumatic fever, and infections due to CA-MRSA, compared to the rest of Canada.[1–4] Reasons for this are thought to primarily reflect social determinants of health: lack of access to clean running water, and overcrowded and inadequate housing.[1] Some infections, such as blastomycosis, are highly endemic in the region. Illnesses are often advanced on presentation, due to a high prevalence of comorbidities such as diabetes, drug use and limited access to health resources.

While rural physicians are used to diagnosing and treating complex diseases, the high burden of infectious diseases in the region benefits from the integrated, systematic support of infectious disease specialists who are familiar with the geographic and cultural characteristics of the region and its population. Involvement of infectious diseases specialists in the care of patients with infections has been shown to improve patient and economic outcomes.[5–8]

Sioux Lookout Zone is primarily a First Nations population, 82% of the 28,000 population being Ojibway or Cree First Nations members.[9] The region covers an area of 385,000 km^2 with Sioux Lookout Meno Ya Win Health Centre (SLMHC) in Sioux Lookout serving as the regional hospital. Of its 32 remote northern communities, only seven can be reached by road. All others rely on scheduled flight connection to Sioux Lookout operated by small

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aircraft for non-emergent medical transfer by the provincial air ambulance for emergent cases, at a cost of approximately CDN$3000 and CDN$15,000 respectively. The closest tertiary care centers are located in Thunder Bay, Ontario (370 km from Sioux Lookout) and Winnipeg, Manitoba (440 km from Sioux Lookout and crossing provincial boundaries).

The need for infectious disease consultations and the introduction of high-speed Internet connectivity in many regional First Nations nursing stations over the last decade allowed for the development of a regional infectious disease telemedicine service. Prior to this program, infectious disease expertise was only available through informal telephone "curbside" consultations to specialists at either of the tertiary care centers, with no formal assessments or follow-up available save for a minority of complex patients. These patients were flown over 300 km to Thunder Bay or Winnipeg for an in-person consultation. Telemedicine has successfully been applied to provide infectious disease expertise in both acute and chronic infectious diseases across a variety of settings, including rural communities.[10] While telemedicine has also been used to connect to remote and isolated Aboriginal communities,[11,12] its use and acceptability in the infectious disease context has not been documented in this setting.

We describe the development and first year of operation of a telemedicine-based consultation service between SLMHC, Ontario, Canada, and the Division of Infectious Diseases at The Ottawa Hospital (TOH), Ontario, Canada.

Characteristics of the telemedicine application

Development

The first aspect of program development was two independent visits to the region by the infectious disease specialists (RS, YSS). They met with local healthcare providers, hospital and laboratory facility, telemedicine service providers, Sioux Lookout First Nations Health Authority (SLFNHA) leaders and visited nearby nursing stations and First Nations community leaders. Plans for regular consultations were created from this local needs assessment and discussion. While infectious diseases expertise was available as an ad-hoc, informal telephone consultation, telemedicine consultation or in-person visits, particularly follow-ups, were rare owing largely to limited human resources at the tertiary care center, jurisdictional barriers (specialists in Winnipeg, Manitoba, not being responsible to provide service to another province), high costs of transport, and absence of systematic referral and follow-up pathways.

Technical characteristics

Telemedicine videoconferencing facilities existed at both the SLMHC and the remote communities via the Ontario Telemedicine Network (OTN) and Keewaytinook Okimakinak eHealth Telemedicine Services (KOeTS). The latter is a community-based and owned network providing telehealth infrastructure to First Nations communities in the Sioux Lookout region, and partners with OTN to connect communities to other sites in Ontario. Telemedicine video-consultations had already been applied to other services in the region, and examples include mental health, critical care, nutrition, diabetes care, and various ad-hoc specialist consultations from tertiary care centers. The infectious diseases clinic was able to start without further infrastructure requirements in July 2014.

Current use

Patients attended the clinic by regional referral. Physicians at SLMHC or in the communities would refer patients to the infectious diseases clinic though a referral pathway that was integrated into the local electronic medical records system (OSCAR). The hospital-based telemedicine nurse scheduled appointments during clinic days with the infectious disease specialist in Ottawa (weekly July 2014–March 2015 and twice weekly thereafter) and on an ad-hoc basis if clinically required. A telemedicine nurse was in attendance to help with the appointment and assist the specialist at SLMHC, but the patient was seen alone at community stations (a nurse was available on request). Translators were present as necessary. Infectious disease specialists had obtained privileges at SLMHC and thus were able to access electronic health records (EHRs) remotely. Follow-up patient appointments were arranged as necessary. In addition to telemedicine visits, the local family physicians and the two infectious disease specialists conducted patient case conferences (without the patient attending) by videoconferencing to ensure that follow-ups had taken place. In order to create a legal, permanent record of the visit, patients were registered in TOH's EHR as telemedicine visits and clinic notes were distributed directly from this EHR to SLMHC. Orders, test requisitions, and other forms were faxed directly to the SLMHC telemedicine office and were then forwarded along with clinic notes to the referring physicians, health records for inclusion into the local EHR, and community nursing stations.

Evaluation

Patient satisfaction surveys were conducted following each patient's initial consultation. The questionnaire was administered at the end of the initial consultation by a non-clinical team member, and addressed experience related to technical components and physician-patient interaction through telemedicine. Patient demographics and general clinical data were collected through an administrative database for a one-year period, July 2014–July 2015.

Demographic data included: age, gender, home community, diagnoses, visit type (consultation or follow-up), and location of visit (Sioux Lookout or remote First Nations community). Ethical approval was received by SLMHC Research Review and Ethics Committee.

Demographics and summary of operations

Of the 76 patients seen over a one-year period in the infectious diseases telemedicine clinic, all but one were First Nations (see Table 1). Ages ranged from 2–84 years, with a mean age of 45.1 years. English was the mother tongue of only 24 of the 50 survey respondents and translators were available at all clinics. Most (61/76) patients lived in remote First Nations communities; 11 patients were from Sioux Lookout and four from neighboring rural communities.

In this first year of operation there were 76 initial consultations and 115 follow-up appointments or case conferences, for a total of 191 infectious diseases telemedicine appointments (see Table 2). Out of 191 appointments, 28 (14.7%) were seen in their home community thus eliminating travel to SLMHC. The number of follow-up appointments per patient ranged from 0–10, with an average of 1.1 (standard deviation (SD) ± 1.87) (see Table 2).

The scope of diagnoses was broad and included rare conditions such as pediatric cases of acute rheumatic fever and active adult tuberculosis. Skin and soft tissue infections (23%) such as infected diabetic foot ulcers were common, accounting for 32 of the 76 diagnoses. Respiratory infections accounted for nearly one-fifth of visits and included one case of pulmonary blastomycosis and three patients with active tuberculosis. Table 3 summarizes visits in relation to type of infection. During the time of implementation of the infectious diseases telemedicine clinic, a high incidence of acute rheumatic fever was observed.[1] Three patients with rheumatic fever were also seen in the clinic to assist public health with case management. About a quarter of visits occurred for musculoskeletal infection (including osteomyelitis and pyomyositis). Three visits were in relation to HCV.

Overall patient satisfaction was 98% in the nine questions asked of each patient (see Table 4). Patients who indicated an unsatisfactory experience did not provide any reasons in the free commentary section of the questionnaire. Interestingly, two people were satisfied but would not recommend telemedicine to a friend. Image and sound quality were acceptable from a patient perspective, but clinicians felt examination of wounds was limited by poor image resolution and lack of three-dimensionality. Inability to conduct a hands-on physical exam, especially in the assessment of pedal pulses and assessment of sensation in patient with diabetic foot ulcers, was identified as a particular limitation by the specialists, especially when no healthcare provider was present at the interview.

Smooth running of the program was largely driven by a core team of "telemedicine champions" at either end: the two infectious diseases specialists and their administrative assistant in Ottawa, and a family physician and the nurse telemedicine coordinator in Sioux Lookout. Absence of one or more of the members negatively impacted the scheduling of patients, visit and/or follow-up process

Table 1. Patient demographics ($n = 76$ patients).

Gender	
Male	49 (65%)
Female	27 (35%)
Age groups	
0–17 years	4 (5%)
18–44 years	30 (40%)
45–64 years	28 (37%)
65+ years	14 (18%)
Ethnicity	
First Nations	75 (98.6%)
Caucasian	1 (1.4 %)
Mother tongue (collected from surveys), $n = 50$	
English	24
Ojicree	14
Ojibway	12

Table 2. Visit types.

	Consultations	Follow-ups
Visits ($n = 191$)		
Sioux Lookout	67	96
Community	9	19
Patients ($n = 76$)		
Seen in Sioux Lookout alone	57	
Transferred care to community	10	
Only seen in community	9	

Table 3. Reason for visit ($n = 191$ visits).

Infection site	No. of visits (%)
Skin and soft tissue	43 (23%)
Respiratory	37 (19%)
Musculoskeletal	50 (26%)
Genitourinary	15 (9%)
Intra-abdominal	5 (3%)
Bloodstream	26 (14%)
Blood borne	3 (2%)
CNS	7 (4%)
Other	5 (3%)
Total	191

CNS: central nervous system.

Table 4. Results from patient satisfaction surveys.

Patient satisfaction survey question	Number of patients who either strongly agreed or agreed ($n = 50$)
Patient understood the nurse's explanation of how their session would run.	49 (98%)
Help was available if problems were to arise.	50 (100%)
Able to hear specialist comfortably.	49 (98%)
Satisfied with picture quality of specialist.	47 (94%)
Privacy was respected.	49 (100%)
Would use telemedicine again.	47 (94%)
Would recommend to family/friends.	46 (92%)
Overall satisfied with appointment.	49 (98%)
Number of team members was not overwhelming.	48 (96%)

(distribution of documentation). Transfer of patients out-of-province for tertiary care resulted in difficulty accessing important health records.

Discussion

Rural northwestern Ontario in Canada comprises a unique clinical challenge for providing optimal medical care. Infectious diseases are common in this First Nations population, and gaps in access to and support for healthcare and healthcare workers have been thoroughly documented in the 2015 Auditor General of Canada's spring report on the state of healthcare in the First Nations.[13] First Nations communities in northwestern Ontario are not only remote and isolated geographically, but have been the subject of systemic under-resourcing and neglect. In addition, patients and healthcare providers alike are often caught in jurisdictional red-tape when attempting to access care, in view of the common need for care across a provincial boundary. Most healthcare in Canada comes under provincial jurisdiction, with the exception being care of First Nations on reserves which is a federal responsibility. Amongst others, these factors have contributed to an ever-growing gap in the provision of healthcare to First Nations compared to the rest of Canada.[13]

Previously described telemedicine specialist care programs have been found to benefit patient and physicians and demonstrate high patient satisfaction.[11,12] There is limited information on the use of telemedicine in indigenous communities. While support for infectious diseases through telemedicine has been used in the management of different types of infections[10] in various settings, our program is the first (to our knowledge) to implement an infectious diseases telemedicine program in a region with primarily First Nations communities. Overall, most patients were pleased with the encounter and would recommend it to others.

A review of the types of consultations received indicates that complex infections are common in this population, and that our telemedicine program can provide clinical expertise and follow-up care. Although we did not assess patient outcomes, other studies have demonstrated infectious diseases consultants' involvement improves patient-related outcomes and shortens length of hospital stay.[5,7,8] The latter may be particularly important since patients are often required to stay in Sioux Lookout for their care. Earlier return home would allow patients to benefit from their personal support systems in their communities and follow-up care at their local nursing station. Allowing a visit to occur in the community minimizes disruption of work and family life.

Furthermore, we were able to assist local public health initiatives addressing a high number of incident acute rheumatic fever cases. Active case management was provided through our telemedicine clinic. This clinical link created the foundation for specialists' involvement in regional rheumatic fever control efforts through establishment of a multidisciplinary Acute Rheumatic Fever working group, and most, recently, an Emerging Infectious Diseases Response Team.

Avoiding expensive travel out of community (CDN$3000–15,000 per flight) for patients for visits in Sioux Lookout, Thunder Bay and Winnipeg has the potential for massive government cost savings. Currently, most communities lack the infra-structure and resources to support administration of intravenous antibiotics in the communities. For this reason, patients are often required to stay in Sioux Lookout to complete their intravenous treatment. Once there is adequate support for home intravenous programs in the communities, lengths of stay could be further reduced and more follow-ups could occur in the community. Previously published economic analyses question whether telemedicine is indeed cost-effective from the standpoint of the provider.[14] It is generally believed that true monetary gains rely on overall socioeconomic benefits that take patient and physician travel costs and hours of missed work for appointments into account.[15] Our study underlines the potential positive impact that specialist consultations through telemedicine can have on health and well-being, as well as on community and healthcare associated costs.

Limitations of our study include no formal assessment of clinical outcomes. Similarly, we can only hypothesize that the program helps save costs from transportation, but we did not perform an economic analysis. Savings on travel for a specialist appointment may be offset in part by requirements for travel from the community to Sioux Lookout, Thunder Bay or Winnipeg for imaging procedures. Overall, the telemedicine program was well-received among most patients. Unfortunately, we were unable to gain more insight on why telemedicine may not be satisfactory since no explanations were provided by the two

patients who did not enjoy the experience. Understanding why telemedicine may not be favorably received by some, while also aiming to update audiovisual components, will help improve the experience.

There are program limitations regarding the ability to perform physical examination. These limitations relate in part to the technology available. As the technology improves, the ability to auscultate and to observe the three-dimensionality of lesions and perhaps even palpate lesions may increase. In the interim, the presence of a healthcare provider who can perform a physical examination under the direction of the specialist would be useful in bridging this gap. Heavy reliance on "telemedicine champions" at either end jeopardizes the sustainability of the program in face of high staff turn-over in northern communities. Formalizing the relationship through contracts or a memorandum of understanding can assist in securing reliability and ensuring accountability.

Our program began by initiating community visits by the urban infectious disease specialist clinicians, who met local key stakeholders, patients and First Nations leadership, as well as local clinicians. Now well-informed on the regional and cultural character of our patients, the specialists provide a valuable integrated service to the region. Future work will involve assessment of the economic impact of the program, assessing the opinions of local family physicians who initiate the consultations, assessing patient outcomes, and ongoing monitoring of patient satisfaction.

Conclusion

With our program we demonstrate telemedicine to be a meaningful tool for clinical specialist support in rural practice, specifically in First Nations communities. Understanding local needs and infrastructure is key to filling important gaps. Regular scheduled available access to an infectious disease specialist from a region that suffers a large burden of infectious disease and geographic challenges is a well-received clinical advancement for care in our region, with potential for major socioeconomic benefits.

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Declaration of conflicting interests

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Research

Potential role for interferon-γ release assays in tuberculosis screening in a remote Canadian community: a case series

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Abstract

Background: Current Canadian guidelines suggest that neonatal Bacille Calmette–Guérin (BCG) vaccination does not result in false-positive tuberculosis (TB) skin tests, despite a growing body of evidence that interferon-γ release assays may be a more specific alternative in identifying latent tuberculosis infections in vaccinated populations. We set out to evaluate the relationship between TB skin tests and interferon-γ release assays in patients who previously received neonatal BCG vaccine.

Methods: All children with a positive skin test at age 14 years in a remote community north of Sioux Lookout, Ontario, were considered for interferon-γ release assay testing.

Results: Of the 11 children who underwent routine screening at 14 years of age for latent TB infection, 7 had a positive TB skin test (≥ 10 mm). All 7 of these children had received the BCG vaccine as newborns and all had a negative TB skin test during their routine screening at 4 years of age. No potential exposure to active TB could be identified. Chest radiographs were normal, and none of the children had symptoms suggestive of active TB. The 7 children underwent interferon-γ release assay testing using QuantiFERON Gold. All 7 tests were negative.

Interpretation: With the addition of interferon-γ release assays to routine skin test screening, we provide evidence that neonatal BCG vaccination may contribute to a false-positive skin test in youth at 14 years of age. Consideration should be given to the possibility that neonatal BCG may contribute to false-positive TB skin tests.

Evidence that the Bacille Calmette–Guérin (BCG) vaccine can contribute to a false-positive tuberculosis (TB) skin tests has led to interferon-γ release assays being a preferred option for identifying latent TB infection in vaccinated populations.[1] Because of the complexity and cost of implementing interferon-γ release assay testing, TB skin tests continue to be the predominant screening tool for latent TB infection in many Canadian jurisdictions.[2,3]

Although the BCG vaccine is not routinely used in most parts of North America, routine vaccination is still done in certain high-incidence communities. Specifically in Canada, infants from some First Nations and Inuit communities receive the BCG vaccine as newborns (within first 28 d after birth). Current recommendations from the Canadian Tuberculosis Standards (7th edition) state that the BCG vaccine, if given during infancy, should not be considered as a contributor to a false-positive TB skin test if the patient is older than 10 years of age.[2] A growing body of evidence suggests that a proportion of positive skin test results among those who have received the vaccine may not be true-positives.[4–8]

False-positive TB skin tests could potentially contribute to unnecessary TB control activities and treatment for latent TB infection. We set out to examine the proportion of positive interferon-γ release assays in a group of 14 year old children who did not have an identifiable TB risk factor.

Methods

Setting

A remote community north of Sioux Lookout, Ontario, was the site of our investigation.

Study population

Current policy supports BCG vaccine for newborns in this region, and children undergo routine TB skin testing for latent TB infection at 4 and 14 years of age. All children with a positive skin test at age 14 years in 1 community with no identified exposure were considered for interferon-γ release assay testing. Interferon-γ release assay testing was done within 6 months of the positive skin test result.

Study design

QuantiFERON Gold tubes were used and shipped to nurses in the community. Once the blood samples were collected, they were flown the same day to a hospital where they were incubated as per protocol,[9] then shipped to Ottawa for further processing. All testing was completed between March and August 2014.

Data sources

Vaccination history, previous TB skin test results, active TB exposure and TB disease history were provided by the Sioux Lookout First Nations Health Authority. All data are maintained on site at the health centres of local communities under the guidance of the health authority. The maintenance of these records follows standard clinical practice and is supervised by the TB control program of the health authority. Consent for the TB skin test and interferon-γ release assay was obtained from each child's guardian by a nurse in the community. This work was part of a program evaluation and was done by the Sioux Lookout First Nations Health Authority.

Results

Among the children with a positive skin test at age 14 years, 4 were excluded from participating in the study: 1 with prior BCG adenitis, 1 with a positive TB skin test at age 4, 1 with a TB skin test wheal of 5 mm, and 1 who was unavailable to participate. Seven children were eligible to participate in the study, all of whom had received the BCG vaccine as newborns and had a positive TB skin test at 14 years of age, with no identifiable risk factors for TB exposure. None of the 7 had positive test results with the QuantiFERON Gold assay (0.00 IU/mL, 0.01 IU/mL, 0.00 IU/mL, 0.00 IU/mL, 0.00 IU/mL, 0.03 IU/mL, 0.02 IU/mL), and there were no indeterminate results. No samples were lost or ruined in transit. In addition, chest radiographs were all normal, and none of the children showed symptoms of active TB. No treatment for latent TB infection was initiated for these 7 children.

Interpretation

With the addition of interferon-γ release assays to routine skin test screening, we provide evidence that neonatal BCG vaccination may contribute to a false-positive skin test in youth at 14 years of age. The growing body of evidence supports that a more targeted application of treatment of latent TB infection can be accomplished in response to adding interferon-γ release assays to the screening protocol.[1,4–8]

The findings of this study are in agreement with other studies that have anchored interferon-γ release assays as a more specific test than the skin test for people who have received the BCG vaccine. The work of Katsenos and colleagues suggested that BCG vaccination after infancy contributed substantively to a false-positive skin test.[5] Although evidence supports the idea that induration size is predictive of concordance with interferon-γ release assays, there remain a number of skin tests even at larger size that may we be false-positive results.[4,6] Although these studies all involved adults, Jacobs and colleagues performed a similar analysis among First Nation children in Alberta, and once again documented false-positive skin test results with previous BCG vaccination.[7]

Ensuring that samples were incubated in the appropriate setting and for the appropriate duration was logistically challenging in this small community. Careful organization of collection of samples and alignment with availability of the relatively limited shipping capabilities is necessary. A multidisciplinary approach involving numerous jurisdictions was required to coordinate interferon-γ release assay testing in our investigation. Most recently, Alvarez and colleagues conducted interferon-γ release assay testing in Iqaluit, Nunavut, and showed that such testing was feasible for 256 people.[8] Similar to previous studies, a high degree of discordance between skin test and interferon-γ release assay results was noted in people who had previously received the BCG vaccine. Outside of Canada, Soborg and colleagues also presented data suggesting the potential for false-positive skin test results when the interferon-γ release assay is not used in the Inuit population.[10]

Limitations

It should be noted that although the small community in question had a 10-year average incidence rate of smear positive TB of 13.4 per 100 000,[11] our efforts to uncover any sick contacts (including active TB contacts) among the children who underwent testing all proved to be negative. It appears unlikely that recent contact with an active TB patient would have influenced the current study results. However, the possibility of nontuberculous mycobacteria causing a positive skin test result cannot be ruled out with the current study's data. On the contrary, recent studies have documented some of the limitations of the interferon-γ release assay.[12] As with the TB skin test, the sensitivity of the interferon-γ release assay in immunocompromised patients has been questioned given that this population is most susceptible to latent TB infection.[13] In addition, the interferon-γ release assay has been shown to be less accurate in younger children.[14] Lastly, as mentioned in this current study, the costs and logistics of implementing interferon-γ release assay testing need to be considered when recommending its use in smaller communities.

Conclusion

There is a need for considering the role of interferon-γ release assay testing in adolescents with positive TB skin test results who have received the BCG vaccine as newborns. Implementing such practices into First Nation communities must take into account the unique and remote conditions inherent to these populations. The costs and logistics of implementing interferon-γ release assay testing need to be considered when recommending its use in smaller communities.

Competing interests: None declared.

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Open Forum Infectious Diseases

MAJOR ARTICLE

High Incidence of Invasive Group A Streptococcal Infections in Remote Indigenous Communities in Northwestern Ontario, Canada

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Background. Worldwide, indigenous populations appear to be at increased risk for invasive group A streptococcal (iGAS) infections. Although there is empirical evidence that the burden of iGAS disease is significant among remote First Nations communities in Northwestern Ontario, Canada, the epidemiology of iGAS infections in the area remains poorly characterized.

Methods. Individuals that met case definition for iGAS disease and whose laboratory specimens were processed by Meno Ya Win Health Centre in Sioux Lookout, Canada or who were reported to Thunder Bay District Health Unit, Canada were identified for the period 2009 to 2014. Case demographics, clinical severity, comorbidities, and risk factors were collected through chart review. Strain typing and antibiotic susceptibility were determined when possible. Basic descriptive statistics were calculated.

Results. Sixty-five cases of iGAS disease were identified, for an annualized incidence of 56.2 per 100 000. Primary bacteremia was present in 26.2% of cases, and cellulitis was identified in 55.4% of cases. The most common comorbidities identified were diabetes (38.5%) and skin conditions (38.5%). Prevalent risk factors included alcohol dependence (25%). Fourteen different *emm* types were identified among 42 isolates, with the most common being *emm114* (17.4%), *emm11* (15.2%), and *emm118* (13.0%). Resistance to erythromycin and clindamycin was found in 24.6% of isolates.

Conclusions. Rural and remote First Nations communities in Northwestern Ontario experience iGAS infections at a rate 10 times the provincial and national average. Compared with other North American series, a lower proportion of isolates causing infection were of *emm* types included in candidate GAS vaccines.

Keywords. health equity; indigenous health; invasive group A *Streptococcus*.

β-hemolytic group A *Streptococcus* (GAS) (also known as *Streptococcus pyogenes*) is a Gram-positive bacteria that causes a range of human illness and contributes to significant morbidity and mortality worldwide. Severe manifestations of invasive GAS include streptococcal toxic shock syndrome and necrotizing fasciitis [1].

High rates of invasive bacterial diseases, including invasive GAS (iGAS) disease, are frequently reported among indigenous populations in different countries, including Canada, the United States, Australia, and New Zealand [2–5]. A recent publication by the Public Health Agency of Canada from the International Circumpolar Surveillance system reported a rate of iGAS among indigenous peoples in Northern Canada approximately 2.5-fold higher than that of other Canadians [2]. No other peer-reviewed publications have characterized the incidence of iGAS among First Nations, Inuit or Metis (collectively referred to as the indigenous population of Canada).

Northwestern Ontario, Canada, is home to 26 remote on-reserve First Nations communities, comprising approximately 22 000 people (approximately 12% of registered First Nations in Ontario), who occupy a geographic area the size of France. Primary care, acute care, and public health services are fragmented and complicated by historical and political jurisdictional barriers. Sioux Lookout Meno Ya Win Health Centre (SLMHC) is the primary referral hospital for all 26 communities; however, critically ill patients may be transferred directly from their home community to tertiary centers in Thunder Bay, Ontario or Winnipeg, Manitoba. The First Nations and Inuit Health Branch of Health Canada is primarily responsible for surveillance and communicable disease control for on-reserve First Nations in Canada.

Recent publications have reported high rates of invasive bacterial diseases among remote on-reserve First Nations in Northwestern Ontario [6, 7]. We hypothesized that the burden of illness related to iGAS infections is particularly high in this region.

METHODS

All GAS-positive cultures processed by SLMHC between January 1, 2009 and December 31, 2014 were extracted from

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hospital electronic laboratory archives. Possible iGAS cases were identified if (1) the isolate was recovered from a normally sterile site (defined below), (2) the patient was admitted to hospital, or (3) the specimen was obtained in the operating room. Chart reviews were completed on all possible cases to determine whether patients met the Ontario Provincial Case Definition for iGAS [8]. The case definition included GAS isolated from normally sterile sites (blood, joint [excluding bursa], cerebrospinal, pleural, peritoneal, pericardial, and deep tissue/abscess specimens obtained during surgery) or GAS isolated from a nonsterile site with evidence of clinical severity (toxic shock syndrome, necrotizing fasciitis, pyomyositis, gangrene, meningitis, GAS pneumonia, or death directly attributed to iGAS).

In order to capture iGAS cases transferred directly from Sioux Lookout to Thunder Bay, cases reported to Thunder Bay District Health Unit (TBDHU) with a primary residence from one of the 26 communities were identified. As one of 36 public health units in Ontario, TBDHU has undertaken active surveillance for iGAS since an outbreak of *emm*59 iGAS in 2008 [9]. Duplicates of cases already identified through SLMHC were removed. Details on cases transferred directly to Winnipeg were unavailable.

Information collected by chart review included basic demographics, specimen details, clinical severity, comorbidities, risk factors, and antibiotic sensitivity profiles. Streptococcal toxic shock syndrome was defined as previously described [10]. History of skin condition included chronic dermatitis/wound causing breaks in skin integrity. Cases identified as nosocomial were excluded. In addition, the number of throat and wound swabs that yielded GAS and were submitted to SLMHC from the 26 communities was obtained for each year of the study. Crude incidence (removing duplicate isolates occurring within a 14-day period) and temporal trends of positive throat and wound swabs were assessed. The *emm* types of isolates from confirmed iGAS cases were determined through traditional Sanger sequencing using previously described primers and conditions [11].

Data were stored within Excel (Microsoft Office 2010; Microsoft, Redmond, WA) and analyzed using SPSS version 21 (IBM, Armank, NY). Basic descriptive statistics were completed with confidence intervals (CIs) where appropriate. Denominator data for the 26 communities were obtained from First Nations Inuit Health Branch, extracted from the Indian Registry System. Overall incidence was determined from an average of the crude rates each year and calculated per 100 000 population. Ethics approval was obtained through the SLMHC Research Review and Ethics Committee as well as the Research Ethics Board from the University of Toronto, Canada.

RESULTS

Overall, 6674 specimens processed between 2009 and 2014 yielded GAS, and 65 cases of iGAS disease were identified. The number of cases per year ranged from 9 to 18. The annualized incidence of iGAS was 56.2 per 100 000 (95% CI, 35.4–76.9). The mean age of cases was 40 years, with a range of <1 to 87 years. There was a bimodal distribution of age-specific incidence with peaks in the 0–19 and 40–59 age groups (Figure 1). Eleven cases (17%) occurred among infants less than 1 year of age.

The majority of iGAS cases occurred during the months of October to March; however, there was no statistically significant seasonal trend (Figure 2). The annual proportion of wound swabs positive for GAS ranged from 40% to 48%. The average annual rate of wound swabs positive for GAS was 61 episodes per 1000 population. Rates increased between 2009 and 2013 and decreased in 2014. The average annual rate of throat swabs positive for GAS was 46.6 episodes per 1000 population. Rates increased between 2010 and 2014. Wound swabs positive for GAS were more prevalent during the summer months, whereas GAS-positive throat swabs did not demonstrate a seasonal

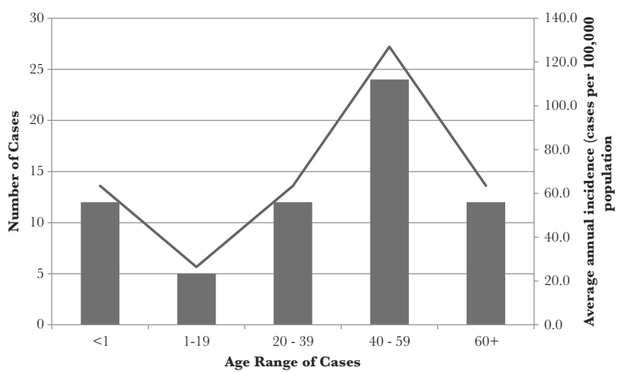

Figure 1. Incidence of invasive group A streptococcal cases in 26 rural and remote First Nations communities in Sioux Lookout area between 2009 and 2014 by age.

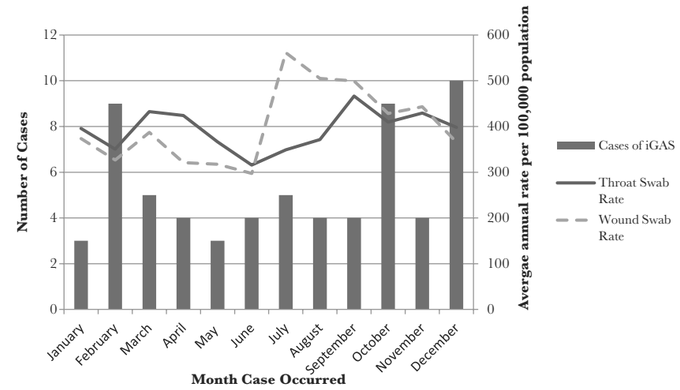

Figure 2. Temporal distribution of invasive group A streptococcal (iGAS) cases compared with group A streptococcal (GAS)-positive throat swabs and GAS-positive wound swabs submitted from 26 rural and remote First Nations communities in Northwestern Ontario between 2009 and 2014.

trend. There was no detectable association between trends of iGAS incidence and either positive wound swab or positive throat swab rates.

The 2 most common comorbidities identified were diabetes mellitus (38.5%) and skin conditions (38.5%) (Table 1). The most prominent other potential risk factor was alcohol dependence (25%). There was significant overlap in underlying conditions: among the 25 patients with underlying diabetes, 10 had skin conditions, 3 had alcohol dependence, and 2 had both skin conditions and alcohol dependence. Seven of 16 persons with alcohol dependence also had skin conditions, and 5 of 7 persons reporting intravenous drug use were also dependent on alcohol.

Table 1. Characteristics of 65 iGAS Cases Identified From 26 Rural and Remote First Nations Communities in Northwestern Ontario Between 2009 and 2014

Case Characteristics	Number (%)
Chronic underlying medical conditions	
Diabetes	25 (38.5)
Skin conditions	25 (38.5)
Coronary artery disease	6 (9.2)
Active cancer	3 (4.6)
Peritoneal dialysis*	3 (4.6)
Hepatitis C	3 (4.6)
Liver failure	3 (4.6)
Connective tissue disorder	3 (4.6)
Other potential risk factors	
Alcohol dependence	16 (24.6)
Previous positive wound swab for GAS	16 (24.6)
Regular use of nonsteroidal anti-inflammatory drug	11 (16.9)
Injection drug use	8 (12.3)
Other substance use	6 (9.2)
Underhoused/homeless/living in shelter system	5 (7.7)
Varicella within the previous month	1 (1.5)

Abbreviations: GAS, group A streptococcal; iGAS, invasive group A streptococcal.

*Patients must move from their rural or remote community to a larger center (primarily Thunder Bay) to receive hemodialysis. Only peritoneal dialysis is available at community level.

Overall, 49 (75.4%) cases had positive blood cultures; among the 13 with blood cultures that were negative or not done, 9 (13.8%) had positive deep tissue/abscess specimens (taken aseptically in the operating room), 5 (7.7%) had positive synovial fluid, and 1 (1.5%) had positive peritoneal fluid cultures. One case had a nonsterile specimen positive for GAS with evidence of clinical severity. Primary bacteremia was present in 17 (26.2%) cases (Table 2); 1 postpartum bacteremia was identified. Cellulitis was identified at the time of presentation in 36 (55.4%) cases, and septic arthritis was present in 6 (9.2%) cases. Streptococcal toxic shock syndrome and necrotizing fasciitis each occurred in 6 (9.2%) cases, and the crude 28-day case-fatality rate for all iGAS was 6.2%. No cases of nosocomial infection were identified.

Antibiotic susceptibility profiles were available for 59 isolates. All isolates were sensitive to penicillin. Sixteen isolates (24.6%) were resistant to both erythromycin and clindamycin. Of the 65 iGAS cases, 46 isolates were available for *emm* typing. Among these, 14 different *emm* types were identified (Table 3). The most common *emm* types were *emm114* (17.4%), *emm11* (15.2%), *emm118* (13.0%), *emm68* (10.9%), and *emm82* (10.9%). *emm* type variability over time was observed. Of the 16 isolates demonstrating resistance to erythromycin and clindamycin, 7 were identified as *emm11* and 5 were identified as *emm114*. The cases associated with these isolates were from different communities and temporally unrelated.

DISCUSSION

The incidence of iGAS in Canada increased significantly over the last decade (from 2.81 to 4.03 per 100 000 between 2000 and 2009) [12]. In 2013, the Canadian and Ontario rates for

Table 2. Clinical Features of 65 iGAS Cases Identified From 26 Rural and Remote First Nations Communities in Northwestern Ontario Between 2009 and 2014

Clinical Features	Number (%)
Culture source	
Blood	49 (75.4)
Other sterile source	15 (23.1)
Nonsterile source	1 (1.5)
Clinical presentation	
Cellulitis	36 (55.4)
Primary bacteremia	17 (26.2)
Septic arthritis	6 (9.2)
Pyomyositis	2 (3.1)
Peritonitis	2 (3.1)
Meningitis	1 (1.5)
Pneumonia	1 (1.5)
Disease severity	
Streptococcal toxic shock syndrome	6 (9.2)
Necrotizing fasciitis	6 (9.2)
Deceased	4 (6.2)

Abbreviations: iGAS, invasive group A streptococcal.

iGAS were 4.72 and 4.6 per 100 000 population, respectively [12, 13]. In contrast, the crude incidence rate of iGAS calculated in this study among 26 rural and remote First Nations communities in Northwestern Ontario between 2009 and 2014 was more than 10 times higher at a rate of 56.2 per 100 000 population. Although significantly higher than the incidence of iGAS among indigenous peoples in Northern Canada (2.25–20.44 per 100 000 population) [2], it is comparable to indigenous populations in Australia and New Zealand [3, 4, 14, 15].

High prevalence of substance use has been thought to be a contributing factor to overall higher rates of iGAS in Northwestern Ontario [9]. The high burden of substance use among indigenous peoples in Canada is recognized nationally as a legacy of historical assimilation policies, multigenerational trauma, and systemic racism [16]. The prevalence of alcohol dependence among iGAS cases in this study (25%) was consistent with iGAS epidemiology for both indigenous and non-indigenous populations in Northern Australia [17]. Prescription drug abuse, particularly injection drug use (IDU), is a significant issue facing many of the communities included in this study [18, 19]. However, only 12.3% of cases in this study were identified as having a history of IDU. Although it is likely underreported, this proportion is consistent with iGAS epidemiology reported in non-indigenous populations [20–22].

Table 3. *emm* types of 46 Cases of iGAS Identified From 26 Rural and Remote First Nations Communities in Northwestern Ontario Between 2009 and 2014

emm types (N = 46)	2009	2010	2011	2012	2013	2014	Total No.
1	0	0	0	0	2	1	3
3	0	1	0	0	0	0	1
11	0	0	0	1	3	3	7
53	0	0	0	0	1	0	1
59	0	0	0	0	1	1	2
68	0	0	0	1	1	3	5
80	0	0	0	1	0	0	1
82	0	0	2	3	0	0	5
83	0	0	0	1	0	0	1
87	0	0	0	0	0	1	1
101	0	1	1	0	1	0	3
114	1	3	2	1	1	0	8
115	0	0	0	0	2	0	2
118	0	0	0	1	4	1	6
Total	1	5	5	9	16	10	46

Abbreviations: iGAS, invasive group A *Streptococcus*.

Diabetes and skin conditions were found to be common comorbidities among iGAS cases in this review. The prevalence of diabetes among First Nations in Canada is disproportionately high compared with the non-indigenous population [23]. Given the increased risk of iGAS associated with underlying diabetes, this contributes to increased risk for First Nation communities [24].

In addition, high prevalence of skin conditions such as eczema and impetigo has been observed in many remote First Nations communities [25]. It has been hypothesized in Northern Australia that a major risk factor for GAS bacteremia in Aboriginal people is exposure to an overall high burden of GAS infections, primarily skin infections such as impetigo and pyoderma [3, 26]. These populations also experience high prevalence of nonsuppurative sequelae to GAS infection including acute rheumatic fever and poststreptococcal glomerulonephritis [27, 28]. Although largely eliminated from Canada, rheumatic fever in First Nations communities in Northwestern Ontario has been documented at rates consistent with Northern Australia (21.3 and 26 per 100 000, respectively) [29]. In Australia, the burden of GAS associated with skin and soft-tissue infections has been primarily related to inadequate and overcrowded housing [30, 31]. Disparities in the social determinants of health, including inadequate and overcrowded housing, are well documented public health issues facing First Nations communities in Northwestern Ontario [32–34].

The proportion of iGAS isolates that demonstrated resistance to erythromycin (24.6%) and clindamycin (24.6%) was higher than reported in other regions in Canada. A recent analysis of iGAS cases from Peel and Toronto regions in Ontario demonstrated an increase in erythromycin resistance from 2.2% in 1992–1995 to 19.5% in 2008–2010 and then to 7.5% in 2013 [35]. A 2011 publication from the Canadian province of British Columbia reported resistance in all GAS isolates in 2011 to be 14.5% and 11.9% for erythromycin and clindamycin, respectively [36].

LIMITATIONS

Data from Winnipeg could not be accessed; therefore, our data likely underestimates iGAS infection acquired in some communities. Given the small population size and reported case numbers, rates should be interpreted with caution. Risk factors were self-identified in patient charts and may therefore be underestimated. Community population statistics from the Indian Registry System relies on individuals to register for "Indian status" and may thus underrepresent the true population of communities, which would result in an overestimation of iGAS rates.

CONCLUSIONS

More than 200 different GAS *emm* types have been reported worldwide [37]. The most common *emm* types identified in the present investigation belong to the so-called skin (eg, *emm*83, *emm*101) and generalist (eg, *emm*68, *emm*82, *emm*87, *emm*114) *emm* types with only a few strains belonging to *emm* types with tropism for throat (eg, *emm*1) [38]. This is similar to the epidemiology of iGAS cases in nearby Thunder Bay region but differs from the remainder of Ontario [9, 13]. This variation in *emm* type distribution has important vaccine implications. A 30-valent M-protein vaccine for GAS began clinical trials in Canada and the United States in September 2015. Although this new vaccine is reported to account for greater than 90% and 78% of invasive disease serotypes in the United States and Europe, respectively, only 70% of the *emm* types identified in this population are covered. The diversity of strains and rapid serotype replacement observed in Northwestern Ontario may mean that the vaccine will offer reduced protection in a population that experiences a disproportionate burden of severe disease [39, 40].

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Original Article
Article original

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.

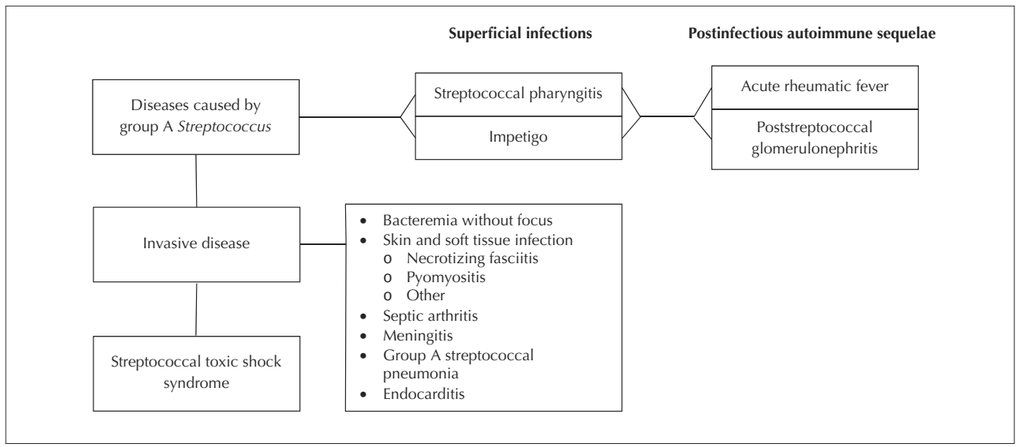

Fig. 1. Group A streptococcal diseases.

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 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

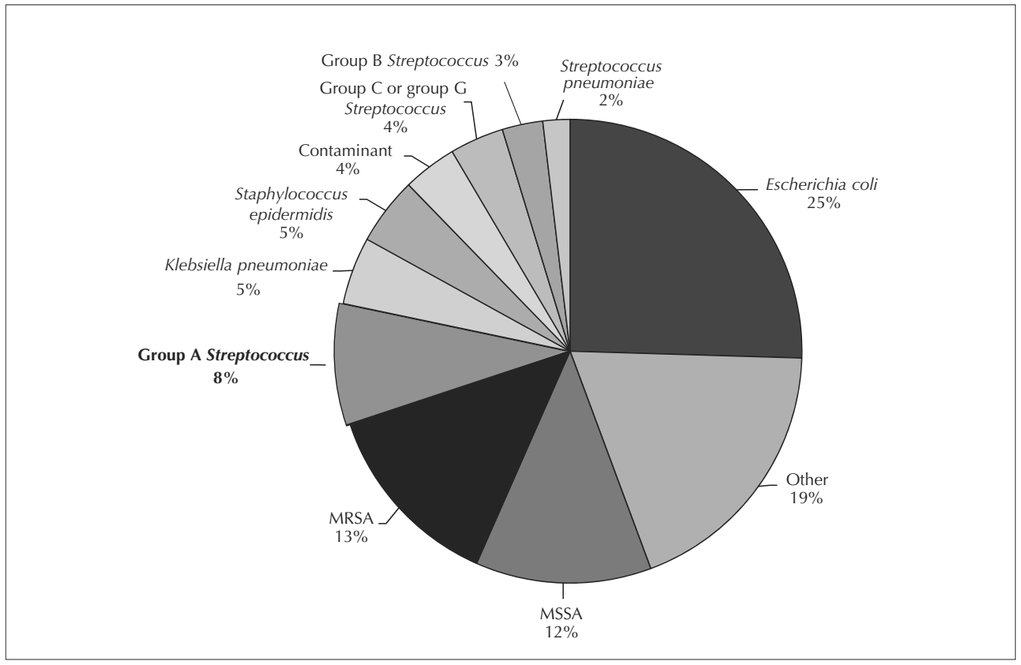

Fig. 2. Isolates from positive blood cultures from in- and outpatients at the Sioux Lookout Meno Ya Win Health Centre in 2015. Note: MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *S. aureus*.

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.

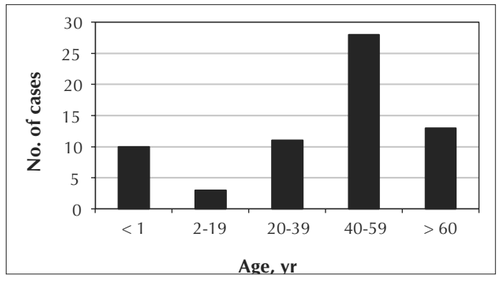

Fig. 3. Age at presentation of cases of invasive group A *Streptococcus* infection seen at the Sioux Lookout Meno Ya Win Health Centre between 2009 and 2014.

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 invasive 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]

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

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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ORIGINAL ARTICLE

Acute post-streptococcal glomerulonephritis in northwestern Ontario: A six-year retrospective study

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BACKGROUND: Recent reports have described a high incidence of acute rheumatic fever in northwestern Ontario. However, the full burden of Group A streptococcal infection and its complications, including acute post-streptococcal glomerulonephritis (APSGN), in the region is not well understood.
OBJECTIVE: To document the pediatric and adult incidence of APSGN in a predominantly First Nations population in northwestern Ontario
METHODS: The present study was a retrospective case series conducted over a six-year period in a population of 29,000 in northwestern Ontario. Adults and children meeting selection criteria for possible, probable or confirmed APSGN within the study period were included. Outcome measures included patient demographics, comorbidities, investigations, clinical course and status of renal function at last follow-up.
RESULTS: The authors identified 10 pediatric and five adult cases of APSGN. The incidence rate of APSGN for children <15 years of age was 20.8 cases per 100,000 person-years and, for adults, was 4.0 cases per 100,000 person-years. These rates are comparable with those observed in developing countries and more than triple the expected rate in the rest of Canada.
CONCLUSION: The incidence rate of APSGN in northwestern Ontario exceeds the norm for a developed country. Inadequate, overcrowded housing and limited access to clean water experienced by many remote First Nations communities may drive the high burden of Group A streptococcal infection and its sequelae in this region.

Key Words: *Aboriginal; Acute post-streptococcal glomerulonephritis; Renal disease*

Sioux Lookout serves a population of 29,000 primarily First Nations patients in a large region (385,000 km^2) of northwest Ontario. A large proportion of bacteremias at Sioux Lookout Meno Ya Win Health Centre (SLMHC), the regional acute care hospital, are due to community-acquired methicillin-resistant *Staphylococcus aureas* (CA-MRSA) (31%) and Group A streptococcal (GAS) (20%) infections (1-3). While the full burden of GAS infection in the region is not well understood, one post-streptococcal infection complication, acute rheumatic fever (RF) is found at rates 75 times higher than the rest of Canada (4-6). Little is known about the prevalence of the other nonsuppurative GAS-related complication acute post-streptococcal glomerulonephritis (APSGN).

Inadequate housing, limited access to clean water and inadequate sanitation have also been documented in the First Nations communities in our catchment area (1,4,7,8). Overcrowded housing is a recognized risk factor for the spread of all communicable diseases, including GAS infections and their autoimmune sequelae (4,9,10). A case-controlled study from northern Saskatchewan in 2010 involving a similar population of 115 subjects with skin and soft tissue infections identified overcrowded housing and household exposure as two of the risk factors for bacterial skin infections (3). A 2010 New Zealand meta-analysis of 34 studies (11) documented a statistical association between crowded and poor-quality housing and rates of RF. There is a paucity of research documenting a relationship between overcrowded housing and APSGN.

National and regional rates of APSGN are unknown. In the present article, we document the regional pediatric and adult rates in northwestern Ontario.

APSGN

APSGN is characterized by acute nephritic syndrome (hematuria, edema and hypertension) in the context of low serum C3 levels and elevated antistreptolysin O titre (ASOT) (12-14). APSGN causes up to 21% of acute renal failure among children in developing countries (15). APSGN most commonly occurs in children two to 12 years of age (14,16-18), with the clinical onset one to three weeks following GAS-positive pharyngitis; or three to six weeks after GAS impetigo (6,14,19). Because postinfectious nephritic syndrome is indistinguishable from different antecedent infectious etiologies, diagnosis of APSGN relies on documentation of preceding GAS infection.

Nephritogenic strains of GAS are distinct from those that are rheumatogenic (causing acute RF) (13,14), and concurrent cases of APSGN and acute RF are rare (20-22).

The short-term prognosis of APSGN is usually favourable, with only 2% of pediatric patients and 3% to 5% of adult patients progressing to end-stage renal disease (ESRD) (9,17,18,23). Risk factors for a more severe APSGN course in adults include older age and presence of comorbidities (12,15,24). Elderly patients with pre-existing renal risk factors have the highest APSGN mortality rate (up to 20% to 25% [15,24]).

METHODS

The SLMHC is a rural hospital in northwestern Ontario serving a population of 29,000 patients (including 8000 pediatric patients); 80% are First Nations, the majority of whom live in 31 remote communities (25). The SLMHC acts as the regional referral centre for emergency and inpatient services for these remote communities.

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TABLE 1
Acute post-streptococcal glomerulonephritis (APSGN) diagnostic criteria

Definitive evidence:
Renal biopsy suggestive of APSGN
Clinical evidence, at least two of:
Facial edema
Moderate hematuria on dipstick
Hypertension or
Peripheral edema
Laboratory evidence, all three of:
Hematuria on microscopy
Evidence of recent streptococcal infection (culture or ASOT) and
Reduced C3 level
Expert opinion:
Diagnosis of APSGN made by nephrologist
Confirmed case:
Definitive evidence or clinical and laboratory evidence
Probable case:
Clinical evidence only
Possible case:
Laboratory evidence only or expert opinion

Medical records for hospital admissions occurring between January 1, 2010 and December 31, 2015, were searched for the discharge diagnosis of 'unspecified nephritic syndrome' (*International Classification of Diseases, 10th Revision* [ICD10]) code N09.5). All ASOTs ordered through the SLMHC laboratory during the period of study were also reviewed. ASOT results were cross-referenced with serum creatinine levels and chart reviews were completed for 235 patients. Colleagues were invited to communicate clinical cases they had treated with the research team. This timeframe of the study was chosen to match investigation for cases of acute RF (4). Cases were identified as confirmed, probable or possible (Table 1) (10). Ethics approval was granted by the SLMHC Research Review and Ethics Committee and the Ottawa Health Science Network Research Ethics Board.

RESULTS

Fifteen cases of APSGN in nine geographically different communities within the six-year period were identified: six met the diagnostic criteria for confirmed, eight for probable and one for possible APSGN (Figure 1). The number of cases identified in each year of study ranged from one to five in the six-year study period. All patients were First Nations.

Pediatric cases

Of the 15 cases identified, 10 occurred in children (<15 years of age) with a mean age of 6.8 years (range three to 10 years), and a male to female ratio of 4:1 (Table 2). None of the children had a medical history of kidney disease, diabetes, hypertension or APSGN.

All APSGN cases presented with microscopic hematuria, and all but one were hypertensive at diagnosis. All cases except 7 and 9 had evidence of recent streptococcal throat infection. These two patients had been prescribed amoxicillin for pharyngitis with negative reported cultures in the weeks preceding presentation (Table 2). Case 1 had both throat and skin cultures positive for GAS.

The most clinically severe case of APSGN occurred in case 9, who presented to her remote nursing station with difficulty breathing, and progressed to respiratory failure secondary to pulmonary edema requiring intubation and medical evacuation by air ambulance to a pediatric intensive care unit. A week previously she had been assessed for pharyngitis, had a negative throat culture and was, nevertheless, treated with amoxicillin. Her subsequent course included pulmonary

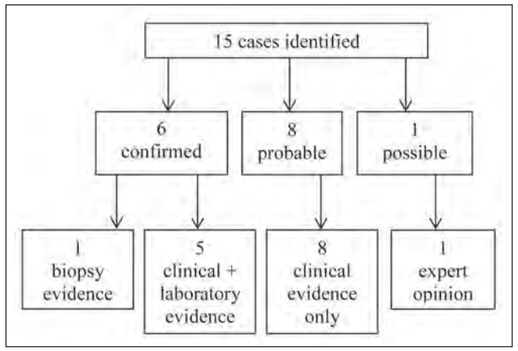

Figure 1) *Cases of acute post-streptococcal glomerulonephritis*

edema, a nine-day hospital admission and a week of outpatient observation before returning to her home community. Seven weeks after medical evacuation, at follow-up, she had persistent hypertension, microscopic hematuria, and proteinuria and was on two oral antihypertensives (amlodipine and hydrochlorothiazide). Because she was transferred out of province, her laboratory values are not presently available.

All confirmed APSGN cases were associated with low serum C3 levels, microscopic hematuria, proteinuria and admission to hospital (Table 2). Case 2 was treated concurrently for pneumonia and pulmonary edema. Case 3 presented with anuria lasting 24 h, which recovered (Table 2). No other complications of acute hypertension, such as encephalopathy, were observed

Six patients did not require admission. With the exception of case 9, treatment ranged from observation to inpatient treatment with diuretics, antihypertensive medication and a low-sodium diet, with antibiotics prescribed as indicated. No patients underwent a kidney biopsy or required hemodialysis. Six of the 10 pediatric cases resulted in complete remission (Table 2). Patients 7 and 10 had persistent hematuria, whereas patient 3 had ongoing hypertension at last follow-up. There was no geographical clustering of cases because nine communities were involved over a six-year period.

During this six-year period, the incidence rate of APSGN among 8026 children in northwestern Ontario was 20.8 cases per 100,000 pediatric person-years.

Adult cases

Five cases occurred in adults, with a mean age of 49.8 years (range 29 to 63 years) and a male to female ratio of 1:4 (Table 3). None had previous APSGN, but all had pre-existing renal risk factors. Four of the five adult patients had type 2 diabetes mellitus (T2DM). The three oldest patients (11, 12 and 14) had histories of pre-existing chronic kidney disease, hypertension and T2DM. The 44-year-old woman (patient 13) had T2DM alone. The 29-year-old woman (patient 15) had received a previous kidney transplant 11 years earlier due to immunoglobulin A nephropathy ESRD.

All adult APSGN cases presented with acute hypertension. Those with complete urinalysis showed proteinuria and microscopic hematuria, and all four tested for serum complement levels showed reduced serum C3 (Table 3). Four of five had evidence of recent streptococcal infection (positive throat cultures and/or increased ASOT); the fifth had the diagnosis confirmed on biopsy. No other biopsies were conducted.

Two cases required admission, with one of these transferred to a tertiary centre. Three cases (patients 11, 12 and 15) experienced acute renal failure and one required dialysis. Treatment in the other cases ranged from outpatient observation to diuretic and antihypertensive therapy coupled with fluid and salt restriction. No cases were complicated by pulmonary edema or acute encephalopathy.

TABLE 2
Characteristics of pediatric acute post-streptococcal glomerulonephritis cases

							C & S			Hematuria			Peak serum		
Case	Age, years	Sex	Case definition	Admitted	Low C3	ASOT, IU/mL	Throat	SSTI	Edema	Gross	Micro	Protein-uria	Peak BP, mmHg	creatinine, µmol/L	Outcome
1	6	Male	Confirmed	Yes	Yes	1933	Positive	Positive	Yes	Yes	Yes	Yes	160/108	67	Cure
2	7	Male	Confirmed	Yes	Yes	131	NT	NT	Yes	No	Yes	Yes	159/111	44	Cure
3	3	Male	Confirmed	Yes	Yes	885	Positive	NT	No	Yes	Yes	Yes	113/69	198	Improved
4	10	Female	Probable	No	NT	224	Negative	NT	No	No	Yes	No	118/80	70	Cure
5	3	Male	Probable	No	NT	669	NT	NT	No	No	Yes	No	110/70	38	Cure
6	4	Male	Probable	No	Yes	148	NT	NT	No	Yes	Yes	Yes	116/70	66	Cure
7	7	Male	Probable	No	NT	197	Negative; pharyngitis treated with amoxicillin	NT	No	Yes	Yes	Yes	140/84	56	Improved
8	8	Male	Probable	No	No	413	NT	NT	No	No	Yes	No	134/85	26	Cure
9	10	Female	Probable	Yes	NA	NA	Negative; pharyngitis treated with amoxicillin	NT	Yes	No	NA	Yes	140/110	NA	Improved
10	10	Male	Possible	No	No	134	Positive	–	No	Yes	Yes	Yes	No HTN	56	Improved

ASOT Antistreptolysin O titre; BP Blood pressure; C&S Culture and susceptibility; HTN Hypertension; NA Data not available; NT Not tested; SSTI Skin and soft tissue infection

TABLE 3
Characteristics of adult acute post-streptococcal glomerulonephritis cases

										Hematuria					Lowest	Peak serum	
Case	Age, years	Sex	Case definition	Admitted	Low C3	ASOT, IU/mL	Throat C&S	SSTI C&S	Edema	Gross	Micro	Proteinuria	Peak BP, mmHg	eGFR, mL/min	creatinine, µmol/L	Outcome
11	60	F	Confirmed	Yes	Yes	198	Neg	NT	Yes	No	Yes	Yes	189/77	<15	361	Improved
12	63	F	Confirmed	Yes	Yes	854	Pos	NT	Yes	Yes	Yes	Yes	180/106	<15	515	Dialysis
13	44	F	Confirmed	No	Yes	395	NT	NT	Yes	No	Yes	Yes	187/95	89	63	Cure
14	53	M	Probable	No	Yes	265	Pos	NT	Yes	No	NT	NT	>180/NR	28	212	Improved
15	29	F	Probable	No	NT	177	Pos	–	No	Yes	Yes	Yes	165/105	31	168	Improved

ASOT Antistreptolysin O titre; BP Blood pressure; C&S Culture & susceptibility; eGFR Estimated glomerular filtration rate; F Female; M Male; Neg Negative; NT Not tested; Pos Positive; SSTI Skin and soft tissue infection

One adult patient achieved complete remission. Three cases had persistently increased creatinine levels relative to pre-illness levels, and case 12 developed ESRD and remains on hemodialysis.

During this six-year period, the incidence of adult APSGN was 4.0 per 100,000 person-years (adult population 21,079) (Table 4).

DISCUSSION

The present study was part of a broader investigation examining the burden of GAS disease in northwestern Ontario. We have already reported rates of acute RF exceeding the Canadian norm (4). Epidemiological studies investigating nasopharyngeal colonization and invasive GAS infections are currently underway.

The pediatric and adult incidence rates of APSGN in northwestern Ontario are higher than expected in a developed country and are comparable with those in less-developed countries (Table 4). The literature suggests that subclinical APSGN cases outnumber clinically detected cases by as much as 19 to one, and the incidence rates we report, therefore, likely significantly underestimate the burden of APSGN in northwestern Ontario (12,17,26). Our male predominance of 4:1 is higher than the 2:1 ratio commonly cited (27).

Remote Indigenous communities in Australia report high rates of both APSGN and chronic kidney disease (28,29). The Maori and Pacific Islander populations of New Zealand document pediatric APSGN rates of 15.7 to 45.5 cases per 100,000 (30,31). In one remote Australian community, a history of APSGN occurring more than five years previously was significantly associated with increased risk for overt albuminuria. There is growing concern that APSGN may be associated with increased renal disease risk later in life, especially when superimposed on the high prevalence of other renal risk factors such as T2DM (6,24,28,29,32,33).

Similar to Australia, Canada's Indigenous populations are known to have high rates of T2DM and ESRD (34,35). In the CIRCLE study and Saskatchewan data, First Nations people were found to develop diabetes at a younger age, and have higher incidence of ESRD associated with longer exposure to diabetes (36,37). T2DM is associated with worse APSGN outcome in adults, with up to 65% of patients developing ESRD and only 12% achieving remission (12). Our report of disproportionately high rates of APSGN in a primarily First Nations population raises concerns about the role postinfectious glomerulonephritis may play in the development chronic kidney disease in this population.

The risk of developing APSGN following infection with a nephrogenic strain of GAS is estimated to be 15% (17,26,38). The causative infection may be GAS pharyngitis or impetigo (6,14,19). We documented only one case of GAS-related skin and soft tissue infection versus six patients with culture-positive pharyngitis in our 15 cases. Elevated ASOT and decreased C3 levels aided the diagnosis in the other cases. Molecular typing of clinical isolates of GAS circulating in the community would be helpful to ascertain whether there is overlap between strains causing APSGN and acute RF, as well as better delineate transmission networks and hot-spots, which in turn can inform prevention measures.

Unlike acute RF, APSGN does not appear to be averted by antibiotic treatment of the causative infection (13,17,39,40). Prophylactic

TABLE 4
Incidence of acute post-streptococcal glomerulonephritis in developed and less-developed countries compared with the rate in northwestern Ontario

	Children	Adults
Developed countries*	6.0	0.3
Less-developed countries*	24.3	2.0
Northwestern Ontario	20.8	4.0

*Incidence rates presented as cases per 100,000 person-years. *Data adapted from reference 5*

antibiotic therapy may reduce pathogen spread in an APSGN outbreak (14). This is of limited relevance to our cases given the sporadic pattern of cases we report. Primordial prevention of GAS infections remains the most effective strategy for mitigating the burden of APSGN (41).

The conceptual framework developed by the World Health Organization Commission on Social Determinants of Health illustrates the complex pathways in which social determinants of health impact health equity and well-being (42). Research highlights the role poverty, residential segregation, stigma and discrimination, incarceration and educational attainment on health outcomes (43). 'Aboriginal Social Determinants of Health' as described by Reading in 2007, compound these issues: effects of colonialism, dispossession of land, discrimination, education systems, access to health care, food insecurity and lack of adequate housing (44-46).

A direct causative pathway from particular determinants of health (such as inadequate housing and access to potable water) to a particular infectious disease cannot be proven without rigorous prospective methodology. Conditions that facilitate the transmission of infectious disease may make the primordial prevention of GAS infections a challenging objective (47). A Chilean study (38) observed a correlation between lower socioeconomic status, greater household crowding and increased number of APSGN cases, with 80% of cases over a 20-year period involving patients with a history of social disadvantage. In Australia, inadequate sanitation and overcrowding in Indigenous communities were associated with increased risk for infection, with GAS being a predominant pathogen (48,49). In this and previous studies, we have documented high regional rates of infections due to CA-MRSA (skin and soft tissue infections, bacteremias) and GAS (RF, APSGN) (1,4,7,51). The remote First Nations communities in our catchment area struggle with overcrowded housing and many communities have decades-long 'boil water' advisories (50).

We acknowledge the limitations of our study. The present study was a retrospective chart review with general limitations of and possible errors in data collection, missed cases and potential bias of cases recalled by clinicians. Subclinical APSGN cases may not have been identified by clinicians nor investigated. Longer-term follow-up data were not available for patients diagnosed in the latter years of our study (microscopic hematuria and proteinuria can take years to resolve following APSGN) (16,17,49). Our study period overlapped for one month with the establishment of a new set of normal ranges for ASOT values. We used the absolute patient titres in our table. Not all ASOT results would be considered elevated according to the new standards, although they were at the time of the study. Due to the retrospective nature of our study, we were also not able to perform strain typing of clinical isolates of GAS, which would be helpful in understanding the epidemiology of GAS infection in the region as a whole. We were also unable to collect environmental data from the chart that would help delineate the contributions of crowding and sanitation to transmission and infection.

CONCLUSION

The incidence rate of APSGN in northwestern Ontario matches the norm for a less-developed country and is more than triple that expected for the rest of Canada. Inadequate, overcrowded housing and limited access to clean water experienced by many remote First Nations communities may drive the high burden of GAS infection and its sequelae in this region.

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ORIGINAL ARTICLE

Northern tropics? Seven cases of pyomyositis in northwestern Ontario

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K Loewen, M Kirlew, PS Benvenuto, et al. Northern tropics? Seven cases of pyomyositis in northwestern Ontario. J Assoc Med Microbiol Infect Dis Can 2016;1(3):104-108.

OBJECTIVE: To document the incidence and clinical characteristics of (tropical) pyomyositis in a predominantly First Nations population in northwestern Ontario.
METHODS: The present study was a retrospective case series conducted over a 38-month period in a population of 29,105 in northwestern Ontario.
RESULTS: The authors identified seven cases of pyomyositis and describe demographics, comorbidity, clinical course, and the results of imaging and microbiology investigations. The incidence of pyomyositis in northwestern Ontario is 7.6 cases per 100,000 person-years, a rate that is approximately 15 times higher than the only published incidence rate for a developed country (Australia).
CONCLUSION: The rate of pyomyositis is high. It may be mediated by overcrowded housing, inadequate access to clean water, and high background rates of methicillin-resistant *Staphylococcus aureus* infection, injection drug use and type 2 diabetes mellitus.

Key Words: *Indigenous peoples; MRSA; Pyomyositis*

Pyomyositis is a rare primary infection of skeletal muscle characterized by intramuscular abscesses. It is believed to involve hematogenous spread and *Staphylococcus aureus* is the predominant causative organism (1-8). Primary pyomyositis is distinct from secondary pyomyositis, which arises from contiguous spread from nearby osteomyelitis, septic arthritis or extramuscular abscess (4,9-11).

More commonly encountered in the tropics, it has often been identified as 'tropical pyomyositis' (4,12). Since first being reported outside of tropical countries, in the United States in 1971, cases of pyomyositis are being encountered in temperate regions with increasing frequency (4,13-15). This trend has been correlated with increasing rates of community-acquired methicillin-resistant *S aureus* (CA-MRSA) infections and increased number of patients with compromised immune function (16,17), including those with type 2 diabetes mellitus (T2DM) (4,6,18), injection drug use (IDU) or HIV infection (7,19).

METHODS

Setting

The catchment area for the Sioux Lookout Meno Ya Win Health Centre (SLMHC) in northwestern Ontario comprises approximately 29,105 individuals, 80% of whom live in remote First Nations communities where access to adequate housing and clean water is often limited (20-22). Previous regional research has demonstrated rates of CA-MRSA infection that are among the highest in Canada (21,23). IDU also has a high prevalence in the authors' catchment area (24-26), with one community documenting >40% of adults participating in treatment for opioid use disorder (27). The regional population is disproportionately affected by T2DM, with age-standardized rates in some communities as high as 26.1% (28,29). Rates of end-stage renal disease (ESRD) are three times higher than the Canadian average (28-30). HIV rates, by contrast, are one of the lowest in the province (31,32).

Chart review

A retrospective chart review was conducted for patients with pyomyositis treated at the SLMHC between January 1, 2013 and February 29, 2016 (38 months). Suspected cases of pyomyositis were identified through communication from colleagues and discharge diagnoses with the *International Classification of Diseases, 10th Revision* (ICD-10) code for infective myositis (M60.0). Definitive evidence of primary intermuscular infection was the criterion for inclusion. Ultrasound (US)-guided needle aspiration, computed tomography (CT) or magnetic resonance imaging (MRI) results were considered to be diagnostic for pyomyositis (4). Intraoperative discovery of intramuscular abscess was also diagnostic. Patient demographics, comorbidity, clinical course, as well as microbiology and imaging results, were recorded for each confirmed case. Cases were confirmed radiographically by CT, MRI and/or surgical findings. The incidence was calculated by measuring the number of cases averaged over 38 months divided by the regional population of 29,105 and adjusted for 100,000 person-years.

The present study was approved by the Sioux Lookout Meno Ya Win Research Review and Ethics Committee. Written, informed individual (or parent) consent was obtained by one of the authors (LK, NB) for the use of anonymized images (Figures 1 and 2).

RESULTS

Seven confirmed cases of primary pyomyositis were identified. Two other patients were excluded: one with a muscle infection secondary to osteomyelitis; the other had inconclusive radiographic findings.

The average age at diagnosis was 33.1 years (range 11 to 48 years), with a male to female ratio of 2.5:1. Of seven cases, three had T2DM, two had a history of IDU, one had ESRD and three had no relevant comorbidities (Table 1). No HIV or malignancies were reported and one patient had recently been prescribed prednisone. There were no deaths; however, several patients experienced prolonged and complicated hospital admissions.

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TABLE 1
Characteristics of patients with pyomyositis

Patient	Age, years	Sex	Comorbidity	Working Dx	Time to correct Dx since symptom onset, days	Dx modality	Causative organism: Source of culture	Causative organism: Muscle	Causative organism: Culture result	Antibiotic therapy: IV	Antibiotic therapy: PO	Antibiotic therapy: Duration	Drainage	Disposition	Clinical outcome
1	36	Male	IDU, T2DM	Discogenic low back pain, pyelonephritis	21	US/CT	Blood; psoas and deltoid abscesses	Psoas, deltoid	No growth	Vancomycin + piperacillin-tazobactam	Cefprozil	IV – 3 weeks PO – 2 weeks	Yes	Tertiary care	Recovery
2	11	Male	None	Leg pain NYD	9	US/MRI	Rectus femoris abscess	Rectus femoris	GAS	Cefazolin + clindamycin	Keflex	IV – 10 days PO – 4.5 weeks	Yes	Tertiary care	Recovery
3	48	Male	ESRD, T2DM	Polymyalgia rheumatica	21	MRI	Blood	Paraspinal: C5-T6	MRSA	Vancomycin	–	IV – 6 weeks	No	Tertiary care	Probable osteomyelitis (*C7*)
4	44	Male	T2DM	Leg pain NYD	5	CT	Vastus medialis abscess	Vastus medialis	MRSA	Clindamycin	Clindamycin	IV – 4 weeks PO – 2 weeks	Yes	Tertiary care	Recovery
5	25	Female	IDU	Septic arthritis	8	MRI	Blood	Gluteus medius, iliopsoas	MRSA	Vancomycin	–	IV – 6 weeks	No	Tertiary care	Osteomyelitis (left acetabular and sub-pubic ramus)
6	21	Female	None	Hip fracture	28	US/CT	Blood	Psoas, iliopsoas	no growth	Ceftriaxone + clindamycin	Clindamycin + keflex	IV – 1 week PO – 1 week	No	Outpatient	Recovery
7	47	Male	None	Necrotizing fasciitis	4	Intra-operative evidence	Vastus intermedius, abscess	Vastus intermedius, vastus medius	MRSA	Vancomycin	Septra	IV – 4 week PO – 3 weeks	Yes	Tertiary care	Recovery

CT Computed tomography; Dx Diagnosis/diagnostic; ESRD End-stage renal disease; GAS Group A streptococci; IDU Injection drug use; IV Intravenous; MRI Magnetic resonance imaging; NYD Not yet diagnosed; PO Per os MRSA Methicillin-resistant Staphylococcus aureus; *T2DM Type 2 diabetes mellitus; US Ultrasound*

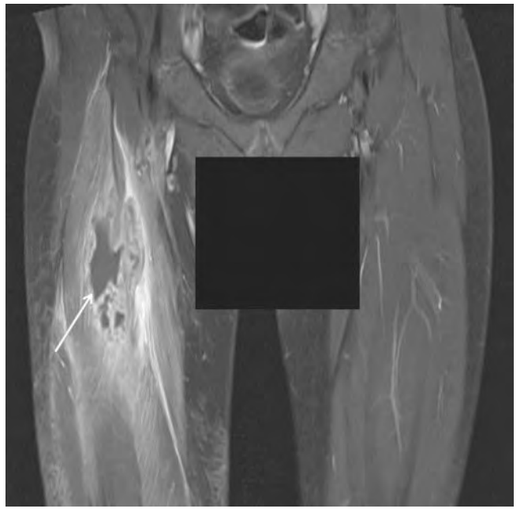

Figure 1) *Magnetic resonance image (T1 fat sat post-gadolinium) of the thighs in patient 2 revealing a complex collection centred in the right rectus femoris muscle (arrow) with surrounding myositis with inflammatory change, which partially extends into the remainder of the anterior compartment*

In no case was pyomyositis the initial working diagnosis. Initial diagnoses included polymyalgia rheumatica, discogenic low back pain and pyelonephritis, and necrotizing fasciitis. On average, the diagnosis of pyomyositis was made 13.7 days (range four to 28 days) after symptom onset. All cases were diagnosed based on CT or MRI results, with the exception of patient 7 who was diagnosed during an emergency fasciotomy. Three cases underwent initial US examinations before CT or MRI.

In some cases, predisposing conditions were present. Patient 5 had been diagnosed with a previous soft-tissue infection positive for *S aureus*, group A Streptococcus, and *Streptococcus agalactiae* 18 days before developing symptoms of pyomyositis and had not completed his course of antibiotics. Patient 6 had fallen a distance of 5 ft (1.52 m) and landed on her right gluteus two weeks before presenting. Hers was the only case with a known history of muscle trauma.

All cases but one involved muscle groups of the pelvis and thigh, the outlier being the paraspinal pyomyositis running from C5 to T6 in patient 3. Five patients had leukocytosis at presentation. MRSA was the most common causative organism and was cultured from blood (patients 3 and 5) or abscess (patients 4 and 7). All MRSA isolates were resistant to erythromycin and susceptible to tetracycline, clindmaycin and trimethoprim/sulfamethoxazole, with one exception, (patient 3) in whom the MSRA was resistant to the latter two antibiotics. Group A Streptococcus was the only other causative organism identified (patient 2). Cultures were negative in the remaining two cases.

All patients received parenteral antibiotics, with vancomycin or clindamycin being the most common. Length of parenteral therapy ranged from one to six weeks, and was followed by up to four weeks of oral antibiotics. All but one case required transfer to a tertiary care facility, although three cases (patients 3, 5 and 6) were successfully managed without percutaneous or operative drainage. Patient 6 was not admitted to hospital.

Seven confirmed cases in 38 months in a population of 29,105 corresponds to an incidence of 7.6 cases per 100,000 person-years. There was no obvious temporal or geographical clustering of cases.

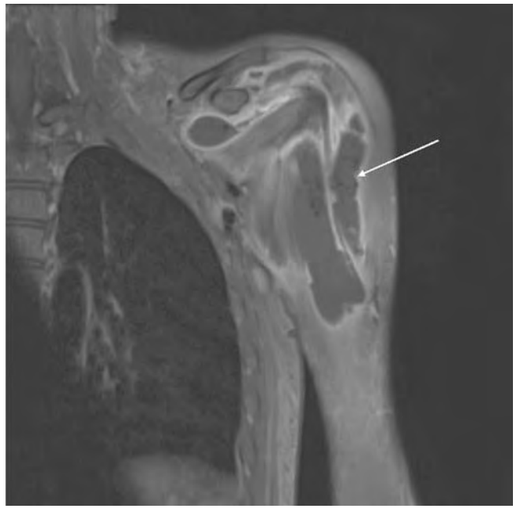

Figure 2) *Magnetic resonance image (T1-fat sat post-gadolinium) of the left arm confirming the presence of a complex intramuscular collection of the deltoid muscle (arrow) with no evidence for osteomyelitis in pyomyositis pateint 1*

DISCUSSION

Pyomyositis is a difficult diagnosis given its rarity, vagueness of initial signs and symptoms, and lengthy differential diagnosis (19,33,34). A high index of suspicion is required to prompt imaging investigations with hopes of clarifying the diagnosis.

The clinical course of pyomyositis is divided into three stages: invasive, suppurative and septic (1,4,7,12,35-39). The invasive stage (seven to 21 days) is characterized by local pain and the affected muscles feel 'woody' to palpation (1,4); accompanied by fever and leukocytosis (4). Erythema and warmth may or may not be present depending on the depth of infection (4). The suppurative stage – the formation of intramuscular abscesses – may not demonstrate fluctuance or swelling if the infection is deep (1,4,40), but high, spiky temperatures and exquisite local pain are common (2,4,41). Most patients present in this stage, as did six of our seven cases. The same number presented with infections of the large muscles of the leg and pelvis, such as the quadriceps, glutei and iliopsoas, considered to be a common clinical presentation (2-5,13,15,16,36,42). Progression to sepsis is less common. It occurred in one of our patients (patient 5), who survived.

The pathogenesis of pyomyositis is poorly understood (4,39,43). The dominant model explaining pyomyositis involves the seeding of injured or overused muscle tissue in the context of transient bacteremia (1,4,5,12,35). Only one of our cases had documented muscle injury from a previous fall. Skin lesions can be associated with the development of pyomyositis because they provide an entry point for bacteremia (14,15,39). Nonsterile injections, anabolic steroid(s) or IDU, also provide portals of entry for infection (44,45). Two cases in the present series were associated with IDU.

Regional patient factors include high rates of comorbid chronic underlying medical conditions such as T2DM and ESDR. Immunomodulating diseases (eg, T2DM, ESRD, HIV, malignancy) are recognized risk factors, and three of the seven cases we present included these: three T2DM, one of whom also had ESRD (46-48).

Nonresolving severe muscle pain, particularly in the presence of symptoms of infection, may be the starting point for many presentations. Leukocytosis (five of seven cases) and blood cultures (positive in two of seven) are often normal and the diagnosis is achieved by aspiration of pus from a muscle abscess (three of five positive isolates) (4).

Four of the five cases with an identified bacterial source were MRSA, the other was group A Streptococcus. In 2014, we documented increasingly high rates of invasive CA-MRSA with 23 cases of bacteremia in a two-year period in the same population (21). Genetic typing of those bacteremia cases identified eight isolates as CMRSA-10, the most common strain in Canada, and six CMRSA-7 isolates, the most common strains identified in the northern region of Manitoba, our neighbouring province. We concluded social determinants of health, housing and sanitation were likely contributing factors (21).

Regional environmental factors include overcrowded and inadequate housing, often with limited access to clean water (20,21,49). These deficiencies have been associated with regional rates of CA-MRSA infection (21,23), acute rheumatic fever (20) and post-streptococcal glomerulonephritis (50) that exceed the Canadian norm. A case-controlled 2010 study from northern Saskatchewan in a similar setting (51) identified overcrowded housing and as a risk factor for bacterial skin infections. Another study involving Alaskan Native communities (52) found that regions with low rates of water service had significantly higher rates of MRSA infection resulting in hospitalization (rate ratio 4.51 [95% CI 3.59 to 5.66]).

Imaging will assist technically and diagnostically. US is often readily available in emergency departments and can demonstrate fluid collections and assist in guiding aspiration (1,41,42). US preceded more definitive imaging (three MRI, three CT) in three cases in the present series. MRI provides the most reliable diagnostic image of a primary intramuscular abscess (53). CT may be the only modality available at the initial referring hospital but can be less accurate in differentiating swollen muscle from abscess (54); however, US can be directed to abnormal areas on CT if an abscess is not readily apparent.

There is a paucity of epidemiological research investigating pyomyositis and Canadian incidence rates are unknown (4). One study from urban Australia provided a population-based incidence rate for pyomyositis of 0.5 cases per 100,000 person-years (14). By comparison, in tropical regions, pyomyositis accounts for 1% to 5% of all hospital admissions (5,55). We report an incidence of 7.6 cases per 100,000 person-years, a rate of pyomyositis more than 15 times higher than the estimated Australian incidence (14).

Our results contribute to the sparse North American literature on the topic. There is a case series from Michigan (USA) involving 32 patients over a nine-year period ending in 2009 and a 20-year meta-analysis of 119 non-HIV cases published in 2004 (13,47). Our case series shows similarities to these studies: presence of underlying chronic medical conditions (high rates of T2DM and ESRD) and a preponderance of *S aureus* as the causative bacteria, often affecting the lower limb (13,47).

Limitations

The present study may not have captured all cases of pyomyositis during the period of study. It is an easy diagnosis to miss and severely ill patients may be transferred directly to tertiary care from remote nursing stations. These cases bypass our institution and would not be captured in our data. Also, diagnosis is often initially uncertain before transfer to a tertiary care centre and ICD-10 codes at the hospital of origin may not be accurate, nor are clinicians' recollection of cases.

CONCLUSION

The incidence of pyomyositis in northwestern Ontario exceeds the Australian rate by 15-fold. This elevated rate in a temperate climate may be mediated by social determinants of health and high background rates of MRSA infection, IDU, T2DM and ESRD.

Pyomyositis is a rare disease and defies easy clinical diagnosis without imaging. In populations with high rates of diabetes and renal disease or in immunocompromised patients, follow up, with expectant resolution, of presumed traumatic or inflammatory muscle injuries would be prudent. If symptoms worsen, CT/MRI imaging may be warranted, especially if there is evidence of infection.

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Clinical Review

Community-associated methicillin-resistant *Staphylococcus aureus* infection

Literature review and clinical update

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Abstract

Objective To provide information on the prevalence and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections and the distinction between community-associated MRSA and health care–associated MRSA.

Quality of evidence The MEDLINE and EMBASE databases were searched from 2005 to 2016. Epidemiologic studies were summarized and the relevant treatment literature was based on level I evidence.

Main message The incidence of community-associated MRSA infection is rising. Certain populations, including indigenous Canadians and homeless populations, are particularly affected. Community-associated MRSA can be distinguished from health care–associated MRSA based on genetic, epidemiologic, or microbiological profiles. It retains susceptibility to some oral agents including trimethoprim-sulfamethoxazole, clindamycin, and tetracyclines. Community-associated MRSA typically presents as purulent skin and soft tissue infection, but invasive infection occurs and can lead to severe, complicated disease. Treatment choices and the need for empiric MRSA coverage are influenced by the type and severity of infection.

Conclusion Community-associated MRSA is a common cause of skin and soft tissue infections and might be common in populations where overcrowding and limited access to clean water exist.

EDITOR'S KEY POINTS

- Isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) that were first identified as hospital acquired are called *health care–associated MRSA* and are highly antibiotic resistant. Isolates of MRSA that appear in young and otherwise healthy patients are identified as *community-associated* (previously *community-acquired*) *MRSA* (CA-MRSA). Neither of these bacteria exist solely in the community or in hospitals.
- Empiric treatment is the norm for these typically purulent skin and soft tissue infections and includes consideration of severity of illness, access to follow-up, and patient adherence. Clinical practice guidelines for CA-MRSA treatment recommend increasingly aggressive treatment with increased severity of infection.
- Predisposing factors for CA-MRSA infection are varied and include living in a group setting, participation in sports teams, and social determinants of health. Crowded living environments and lack of access to clean water are also associated with increased risk of CA-MRSA infection.

POINTS DE REPÈRE DU RÉDACTEUR

- Les isolats des *Staphylococcus aureus* résistants à la méticilline (SARM), initialement identifiés comme étant d'origine nosocomiale, sont appelés les *SARM associés aux soins de santé* et ont une forte résistance aux antibiotiques. Les isolats des SARM détectés chez des patients jeunes et autrement en santé sont connus sous le nom de *SARM d'origine communautaire* (auparavant *acquis dans la communauté* – SARM-AC). Ni l'une ni l'autre de ces bactéries n'existe que dans la communauté ou dans les hôpitaux.
- Un traitement empirique est la norme pour ces infections de la peau et des tissus mous, typiquement purulentes; il comporte la prise en compte de la gravité de la maladie, l'accès à un suivi et l'observance du traitement par le patient. Les guides de pratique clinique concernant le traitement des SARM d'origine communautaire recommandent une thérapie proportionnelle à la sévérité de l'infection.
- Parmi les divers facteurs qui prédisposent à une infection aux SARM d'origine communautaire figurent la vie en groupe, la participation à des sports d'équipe et les déterminants de la santé. La vie dans un environnement surpeuplé et le manque d'accès à de l'eau potable sont aussi associés à un risque accru d'infection aux SARM d'origine communautaire.

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Infection à *Staphylococcus aureus* résistants à la méticilline d'origine communautaire

Revue de la littérature médicale et mise à jour clinique

Résumé

Objectif Fournir des renseignements sur la prévalence et le traitement des infections aux *Staphylococcus aureus* résistants à la méticilline (SARM), de même que sur la distinction entre les SARM d'origine communautaire et les SARM associés aux soins de santé.

Qualité des données Une recension dans les bases de données MEDLINE et EMBASE a été effectuée, portant sur la période de 2005 à 2016. Les études épidémiologiques ont été résumées, et les ouvrages pertinents sur les traitements se fondaient sur des données probantes de niveau I.

Message principal L'incidence des infections aux SARM d'origine communautaire est à la hausse. Certaines populations, dont les Canadiens autochtones et les sans-abri, sont particulièrement touchées. Les SARM d'origine communautaire se distinguent des SARM associés aux soins de santé d'après leurs profils génétiques, épidémiologiques ou microbiologiques. Ils demeurent susceptibles à certains agents oraux, notamment la combinaison triméthoprime-sulfaméthoxazole, la clindamycine et les tétracyclines. Les SARM d'origine communautaire se présentent habituellement sous la forme d'une infection purulente de la peau et des tissus mous, mais une infection invasive peut se produire et entraîner une maladie plus sévère et compliquée. Les choix de traitement et la nécessité d'une approche empirique aux SARM sont influencés par le type et la gravité de l'infection.

Conclusion Les SARM d'origine communautaire sont une cause fréquente d'infection de la peau et des tissus mous et peuvent être courants dans les populations surpeuplées et où l'accès à l'eau potable est limité.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is recognized in the popular press as a "superbug." Medically, it is a common bacterium that can affect clinical care in important ways. Much of what we know about MRSA has been discovered in the past 30 years. The purpose of this literature review is to describe the evolving knowledge about MRSA and its associated risk factors and epidemiology, and to provide an update on best practices for family physicians.

Quality of evidence

In MEDLINE and EMBASE (2005 to 2016), the term *methicillin-resistant* Staphylococcus aureus was combined with the MeSH terms *abscess* or *synovial fluid* or *cerebrospinal fluid* or *shock, septic* or *bacteremia* or *skin diseases, bacterial* or *soft tissue infections* or *skin and soft tissue infections,* and *incidence*.

The abstracts or titles of generated papers were read for relevance to the review topic. Additional papers were extracted from reference lists. A total of 85 relevant articles were chosen for this review. Most of the recommendations of the Infectious Diseases Society of America were based on level II or level III evidence. We have identified any level I evidence support for treatment-related findings.

Main message

Staphylococcus aureus is a common component of skin flora, and 30% to 50% of healthy adults are colonized with it at any given time.[1] Preferred colonization sites include the axillae, anterior nares, pharynx, vagina, rectum, and perineum, and damaged skin.[1,2] Colonization with *S aureus* is a commensal, asymptomatic relationship.[1] Symptomatic *S aureus* infection is less common and might occur following breaks in skin or mucosal barriers. Its severity is influenced by isolate virulence and host factors.[1,3] Diseases caused by *S aureus* range from superficial skin and soft tissue infections (SSTIs) to life-threatening invasive disease, including bacteremia, endocarditis, and toxic shock syndrome.[1] Most *S aureus* infections are caused by methicillin-sensitive *S aureus* (MSSA), which responds to penicillin.[4] Methicillin-sensitive *S aureus* infections predominate (75%) in tertiary care centre staphylococcal infections, while some rural hospitals report MRSA accounts for slightly more than half (56%) of staphylococcal infections.[4,5] This review will concentrate on strains that are resistant to penicillin (MRSA), for which *methicillin* (or *oxacillin*) is the term used by laboratories to identify penicillin resistance.

Methicillin-resistant* S aureus: *2 distinct origins. Methicillin-resistant *S aureus* was first identified at a hospital in the United Kingdom in 1961, shortly after the introduction of methicillin.[6-9] In Canada, MRSA was first documented in 1964 and the first outbreak occurred in 1978 at the Royal Victoria Hospital in Montreal, Que.[9] From the time of its emergence until the 1980s, MRSA was essentially a hospital-acquired pathogen.[8] Today, these isolates of MRSA are called *health care–associated MRSA* (HA-MRSA) and are highly resistant to most oral antibiotics.

In the late 1980s and early 1990s cases of MRSA in young and otherwise healthy patients without any health care–related risk factors were reported.[2,7,8,10] Some of the earliest reports of such infections in Canada and Australia came from isolated indigenous communities.[11-14] Today, these isolates of MRSA have been identified as *community-associated* (previously *community-acquired*) *MRSA* (CA-MRSA).

Community-associated MRSA and HA-MRSA can be differentiated in several ways. These include presumed location of acquisition (ie, community or hospital),[15] antibiotic susceptibility pattern,[16] and genotyping,[17-19] the latter being the most definitive. Our review included many articles with genotyped definitions, but some smaller studies use antibiotic susceptibility patterns.

Some newer, highly resistant strains have arisen, but they are rare in Canada and are currently limited to tertiary care centres. They include vancomycin-intermediate *S aureus* (VISA), heterogeneous VISA, and vancomycin-resistant *S aureus*.[20,21]

Comparing CA-MRSA and HA-MRSA. Community-associated MRSA and HA-MRSA are genetically, epidemiologically, and phenotypically distinct (**Table 1**).[2,4,6-8,10-15,19,22-34]

Contemporary advances in laboratory technology have demonstrated that methicillin resistance was acquired through different genes in CA-MRSA and HA-MRSA isolates. Specifically, staphylococcal chromosomal cassette *mec* (SCC*mec*) types I, II, and III confer methicillin resistance in HA-MRSA whereas SCC*mec* types IV and V confer methicillin resistance in CA-MRSA.[2,23-27]

The SCC*mec* types carried by HA-MRSA are larger than those carried by CA-MRSA and confer resistance to additional non–β-lactam antibiotics. Community-associated MRSA is therefore susceptible to a broader range of antibiotics than HA-MRSA is.[4,27,30,33] A study of pathogens isolated at Canadian hospitals between 2007 and 2009 found the susceptibility of CA-MRSA to trimethoprim-sulfamethoxazole (100.0%), gentamicin (98.7%), and clindamycin (86.1%) to be greater than that of HA-MRSA (86.5%, 85.5%, and 27.8%, respectively).[4] Antibiotic sensitivity profiles can consequently be used as an inexpensive means of classifying MRSA as health care associated or community associated.[16,35] For example, clindamycin susceptibility is predictive of CA-MRSA with 95% sensitivity, 80% specificity, and a likelihood ratio of 4.86.[35] Methicillin-resistant *S aureus* isolates that are resistant to 3 or more non–β-lactam antibiotics can safely be categorized as HA-MRSA.[16]

Before advances were made in laboratory genetic technologies, epidemiologic risk factors were used to differentiate cases of HA-MRSA and CA-MRSA infection: the location of acquisition (ie, community or hospital) provided its designation.[26,27] In the contemporary context, this method of differentiating HA-MRSA and CA-MRSA no longer aligns with clinical reality, as CA-MRSA has found its way into hospitals and is becoming an increasingly prevalent hospital pathogen.[2,32] An American study found that community-associated strains of MRSA are increasing both in communities and in hospitals.[15] In Canada, more than 20% of nosocomial MRSA infections are caused by CA-MRSA.[17,30] A recent study from Alberta found 27.6% of such hospital-onset MRSA infections were caused by CA-MRSA and 27.5% of community-associated infections were caused by HA-MRSA.[36] Both communities and hospitals have become antibiotic-rich environments and are apparently exchanging bacterial isolates.

Table 1. Comparison of CA-MRSA and HA-MRSA

CHARACTERISTIC	CA-MRSA	HA-MRSA
Time and location of emergence[2,6-8,10-14,22,23]	1980s-1990s, in the community	1960s, in hospitals
Genotype[2,23-27]	SCC*mec* types IV and V	SCC*mec* types I, II, and III
Virulence factors[23,26-30]	Panton-Valentine leukocidin often present; other virulence factors believed to exist	Uncommon
Common subtypes[19,24,25,27,29]	CMRSA-10 (USA300), CMRSA-7 (USA400)	CMRSA-2 (USA100)
Predominant type of infection[2,7,27,28,31]	Skin and soft tissue infections	Respiratory tract, urinary tract, bloodstream, and postsurgical infections
Infection onset[2,8,15,30,32]	Typically in the community in young, healthy individuals	Typically in hospital, often associated with older age, intensive care unit stay, and central lines
Antibiotic susceptibility[4,27,30,33]	Susceptible to a range of antibiotics	Limited range of antibiotic susceptibility
Risk factors	Community risk factors[25,34] • Living or working in a group setting (such as military barracks, subsidized housing, or a shelter) • Use of illegal drugs within the past year • History of CA-MRSA infection or colonization • Regular contact with somebody who lives or works in a group setting, has used drugs in the past year, or has a history of CA-MRSA • Absence of in-home water service • Recent antibiotic use • Being HIV positive • Playing contact sports	Health care risk factors[26,27] • Surgery, hospitalization, residence in a long-term care facility, or dialysis within the past 12 months • The presence of an indwelling percutaneous catheter • Being hospitalized for more than 48 hours at time of first positive culture

CA-MRSA—community-associated methicillin-resistant *Staphylococcus aureus*, CMRSA—Canadian epidemic strain, HA-MRSA—health care–associated methicillin-resistant *Staphylococcus aureus*, SCC*mec*—staphylococcal chromosomal cassette *mec*.

There is consistent evidence that CA-MRSA is more likely than HA-MRSA to be associated with SSTIs.[2,7,9,10,12,17,19,22,23,25-28,30,31,37-44] Community-associated MRSA is more likely than HA-MRSA to carry Panton-Valentine leukocidin, a known virulence factor[23,26-30] often associated with tissue necrosis SSTIs.[16,23,28,31,45]

Methicillin-resistant *S aureus* SSTIs are associated with higher mortality rates, longer hospital admissions, and greater hospital costs than SSTIs caused by MSSA strains are.[31,46] The reason for this is unclear, but might involve greater virulence of MRSA relative to MSSA,[46,47] or increased effectiveness of β-lactam antibiotics against MSSA.[48]

In 2012, Golding reported a high rate of CA-MRSA infection in northern Saskatchewan (168.1 cases per 10 000 population in 2006). A compilation of 8 years of data from this region, including 2731 cases, shows that most cases (78.2%) are SSTIs, followed distantly by ear infections (6.7%), urogenital infections (2.4%), respiratory infections (1.1%), and joint or blood infections (0.4%) (**Figure 1**).[41]

A community and hospital study done in northern Ontario documented that 56% of the burden of staphylococcal illness was caused by CA-MRSA.[5]

The predominant strains of CA-MRSA identified are Canadian epidemic strain (CMRSA) 10 (also known as USA300) and CMRSA-7 (also known as USA400). The predominant strain of HA-MRSA is CMRSA-2 (also known as USA100).[19,24,25,27,29] Health care–associated MRSA is more likely to be associated with respiratory tract, urinary tract, bloodstream, and postsurgical infections.[2,7,27,28,31]

Risk factors. The original epidemiologic definition of HA-MRSA infection captures its principal risk factors: hospitalization, other prolonged exposure to a health care environment, or the presence of a percutaneous device such as a central line.[17,26,27]

Predisposing factors for CA-MRSA infection are more varied and are intimately associated with social determinants of health.[9,47] Frequent skin-to-skin contact, wound contact, and poor sanitation facilitate the transmission of CA-MRSA.[2] Crowded living environments, including military barracks, homeless shelters, subsidized housing, and prisons, are associated with increased risk of CA-MRSA infection.[10,12,23,25] A study of the relationship between in-home pressurized water service and infectious diseases among Alaska Natives found that regions with limited access to clean water had significantly higher rates of MRSA infections (rate ratio = 7.1; 95% CI 3.6 to 14.0) and hospitalization for skin infections (rate ratio = 2.7; 95% CI 1.8 to 4.1).[34] Socially disadvantaged minority populations are consistently associated with higher rates of CA-MRSA infection,[47] including African Americans,[40,49] Canadian First Nations communities,[5,9,19,22,37,50,51] and the indigenous populations of Australia and New Zealand.[16,52] Homelessness is another recognized risk factor for CA-MRSA infection,[9,10,23,26,30,32,47] as is intravenous drug use.[8,17,23,27,31,32,47]

Epidemiology. During the 2000s, increasing incidence rates of CA-MRSA infections were widely reported by researchers in the United States and Canada,[10,15,17,19,24,30,32,38-41,43,53,54] along with a corresponding increase in SSTIs caused by *S aureus*.[10,19,43,52,54-58] Rates of CA-MRSA infection are increasing, while HA-MRSA infection rates are generally reported to be in decline.[19,53,57]

Several studies documenting the epidemiology of MRSA in indigenous populations have been published. Studies from communities in the United States,[6,34] Canada,[5,19,39,41,50,51] Australia,[11,16] and New Zealand[52] demonstrate high and increasing rates of CA-MRSA infection in the indigenous populations, where HA-MRSA is rare.

In Canada, Muileboom et al found the proportion of *S aureus* isolates demonstrating methicillin resistance isolated from cultures obtained in one northern Ontario laboratory increased from 31% in 2008 to 56% in 2012.[5] Kirlew et al reported an incidence rate of MRSA bacteremia of 41.1 cases per 100 000 person-years in northwestern Ontario.[51] In northern Saskatchewan, Golding et al found that the rate of CA-MRSA infection increased from 8.2 cases per 10 000 person-years in 2001 to 168.1 cases per 10 000 person-years in 2006.[41] A previous study found that 99.5% of MRSA isolates from these remote communities were CA-MRSA.[50] A 1-year study at the Children's Hospital of Winnipeg in Manitoba found that 79% of patients from outside of Winnipeg who presented with community-onset *S aureus* infection lived in rural communities in northern Manitoba, southern Nunavut, or northwestern Ontario.[39] Among these patients, the rate of MRSA infection was relatively high (61%).[39] A large study assessing MRSA infection rates among children across Canada between 1995 and 2007 found that 25% of all cases occurred in First Nations children.[19]

Like their counterparts in Canada, indigenous populations in the United States, Australia, and New Zealand face disproportionately high rates of MRSA-associated infection and hospitalization.[6,11,16,52]

The confluence of environmental and host factors might explain the disproportionate MRSA burden in indigenous communities. Environmental conditions associated with social and material deprivation, such as overcrowding and inadequate access to in-home pressurized water service, are associated with the transmission of MRSA and the development of MRSA-associated SSTIs.[34] These same environmental conditions are pressing concerns in indigenous communities around the world.[11,16,34,51] Additionally, the prevalence of host factors increasing vulnerability to infection by modulating the immune response (such as diabetes mellitus) or providing a portal of entry (skin disease, injection drug use) might be elevated in some indigenous communities.[59-63]

Treatment. Empiric treatment is the norm for infections and must take into consideration information about likely infecting agents, severity of illness, access to follow-up, patient adherence, and other factors. Published guidelines, original research, and knowledge of local epidemiology might assist clinicians in making clinical judgments that adhere to principles of antimicrobial stewardship.[52,63-65]

The current clinical practice guidelines for CA-MRSA and HA-MRSA treatment from the Infectious Diseases Society of America recommend increasingly aggressive treatment with increased severity of infection.[65]

A distinction is made between purulent and nonpurulent SSTIs. Uncomplicated abscesses without evidence of systemic toxicity might be treated by incision and drainage without antibiotics (level I evidence).[2,22,28,65] Evidence from 3 randomized controlled trials and a systematic review indicates not providing antibiotics to patients who undergo incision and drainage for uncomplicated abscesses is associated with lower reinfection rates and comparable wound healing (level I evidence).[22,66-69] Empiric treatment of purulent cellulitis, when needed, might include oral clindamycin, trimethoprim-sulfamethoxazole, tetracyclines, or linezolid (level II evidence).[65] Nonpurulent cellulitis is generally caused by *Streptococcus* (group A, C, or G), while purulent cellulitis is substantially more likely to be caused by *S aureus*, most commonly CA-MRSA.[70-73] Treatment of nonpurulent cellulitis should therefore target streptococcal species with a β-lactam antibiotic, without routine addition of an agent active against MSSA or MRSA. Most, if not all, MRSA encountered by family physicians will be CA-MRSA, as it occurs primarily in the community context and is distinct from its highly drug-resistant relative, HA-MRSA (**Table 2**).[65,74]

Complicated SSTIs and invasive MRSA infections, including bacteremia, septic arthritis, endocarditis, meningitis, and pneumonia, are typically treated with parenteral vancomycin (level I and III evidence).[28,65] Susceptibility to clindamycin, trimethoprim-sulfamethoxazole, and tetracyclines is often retained in CA-MRSA isolates[4,75] and these agents can be considered in nonsevere infection or as step-down therapy. These agents have good oral bioavailability.

Figure 1. Rates of community-associated methicillin-resistant *Staphylococcus aureus* infections in northern Saskatchewan: *N = 2731.*

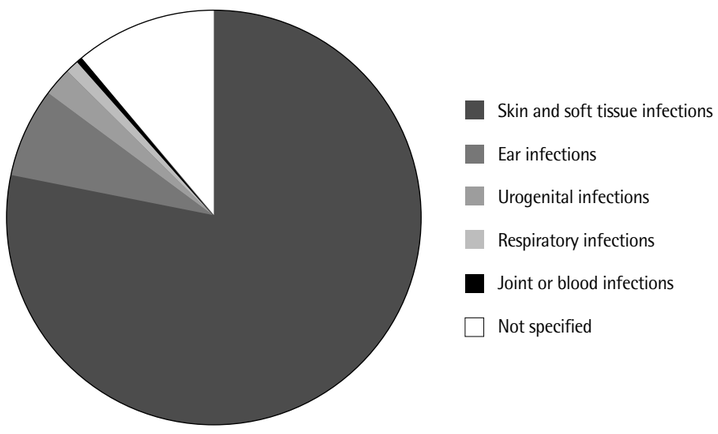

Table 2. Treatment of outpatient SSTI in the era of CA-MRSA

SSTI	TREATMENT*
Simple cutaneous abscess (in a low-risk patient not involving face, hands, or genitalia)	Incision and drainage alone; obtain culture
Purulent cellulitis (without abscess): treat for CA-MRSA if risk factors present	Tetracycline, trimethoprim-sulfamethoxazole, or clindamycin
Nonpurulent cellulitis (no exudate): treat for β-hemolytic streptococcus	β-Lactam antibiotic (cloxacillin or first-generation cephalosporin)

CA-MRSA—community-associated methicillin-resistant *Staphylococcus aureus*, SSTI—skin and soft tissue infection.
*A detailed management algorithm is available within the Infectious Diseases Society of America guidelines 2014 update on SSTIs.[74]
All recommendations are level II evidence, adapted from the Infectious Diseases Society of America 2011 guidelines.[65]

Alternatives to vancomycin for the treatment of severe or invasive MRSA infection include linezolid, daptomycin, and tigecycline.[4,28] Newer agents recently approved or developed that have shown promise are the cephalosporins ceftaroline and ceftobiprole; the lipoglycopeptides telavancin, dalbavancin, and oritavancin; and the oxazolidinone tedizolid.[75-81] Pharmacologic and clinical considerations for each antimicrobial agent are listed in **Table 3**. Telavancin, oritavancin, and dalbavancin might be of particular interest to community-based health care services because of their once-daily, one-time, and weekly dosing, respectively (only dalbavancin is currently available in Canada).[78-80] **Table 4** provides a list of additional agents active against MRSA that are not available in Canada.

Failure of vancomycin therapy has been documented in the context of resistant strains (heterogeneous VISA, vancomycin-resistant *S aureus*), but these are unlikely

Table 3. Antibiotics relevant in the treatment of MRSA

AGENT	ROUTE	ACTIVITY	DOSAGE FOR MRSA INFECTIONS	COMMENTS
Lincosamides				
• Clindamycin	Oral or IV	Bacteriostatic	300-450 mg orally 4 times daily or 600-900 mg IV every 8 h	Increasing resistance among community-associated MRSA and methicillin-sensitive *Staphylococcus aureus*; inducible resistance in MRSA
Sulfonamides				
• Trimethoprim-sulfamethoxazole	Oral	Bactericidal	1-2 double-strength tablets (160 mg and 800 mg) orally twice daily	Contraindicated in severe renal or hepatic dysfunction; multiple drug interactions (including ACEIs and ARBs)
Tetracyclines				
• Tetracycline	Oral	Bacteriostatic	250–500 mg orally 4 times daily	Caution about teratogenicity
• Doxycycline	Oral	Bacteriostatic	100 mg orally twice daily	Caution about teratogenicity
• Minocycline	Oral	Bacteriostatic	100 mg orally twice daily	Caution about teratogenicity
• Tigecycline	IV	Bacteriostatic	100-mg IV loading dose, then 50 mg IV every 12 h	Caution about teratogenicity; indicated for SSTI and intra-abdominal infections (unfavourable outcomes in community-associated pneumonia)
Oxazolidinones				
• Linezolid	Oral or IV	Bacteriostatic	600 mg orally twice daily or 600 mg IV every 12 h	Indicated for SSTI; multiple drug interactions, risk of myelosuppression if used 2 wk or longer; high cost
Lipopeptides				
• Daptomycin	IV	Bactericidal	4 mg/kg IV every 24 h for SSTI; 6 mg/kg IV every 24 h for bacteremia or right-sided endocarditis, up to 12 mg/kg IV every 24 h	Indicated for SSTI, endocarditis, and bloodstream infection; not indicated for pneumonia unless from hematogenous origin; might cause eosinophilic pneumonia, abnormal coagulation, myopathy, and rhabdomyolysis
Lipoglycopeptides				
• Vancomycin	IV	Bactericidal	15-20 mg/kg per dose every 8-12 h; consider loading dose of 25-30 mg/kg in seriously ill patients	Dose monitoring; target levels vary with site and severity of infection
•Telavancin	IV	Bactericidal	10 mg/kg IV every 24 h (if creatinine clearance > 50 mL/min)	Indicated for SSTI; increased mortality observed in chronic kidney disease

ACEI—angiotensin-converting enzyme inhibitor, ARB—angiotensin receptor blocker, IV—intravenous, MRSA—methicillin-resistant *Staphylococcus aureus*, SSTI—skin and soft tissue infection.

Table 4. Additional agents active against MRSA not available in Canada

AGENT	ROUTE	STATUS (AT TIME OF WRITING)
Tedizolid	Oral or IV	Received NOC; not yet marketed
Ceftobiprole medocaril	IV	Received NOC; never marketed
Ceftaroline	IV	Not available
Dalbavancin	IV (weekly)	Not available
Oritavancin	IV (1-time dose)	Not available

IV—intravenous, MRSA—methicillin-resistant *Staphylococcus aureus*, NOC—Health Canada Notice of Compliance.

to be commonly encountered.[20,22] Treatment of these infections is beyond the scope of this article.[52,82]

For patients colonized with MRSA, decolonization treatment can be considered under special circumstances, such as recurrent infections in an individual or household (level III evidence).[22,28,65] Decolonization regimens might involve nasal administration of mupirocin, daily 4% chlorhexidine soap baths, and a course of doxycycline and rifampin (level I).[22,83] Success rates are modest (<50%) at best and largely influenced by comorbidities, and thus decolonization is not routinely recommended.[3,47,84,85] It is recommended that household contacts and patients exercise good handwashing practices. Household members should avoid sharing razors and other personal hygiene equipment; however, family bedding, clothing, and dishes can be washed together as usual. Aside from covering open wounds, there is no need to isolate persons colonized with MRSA within a household or to wear personal protective equipment when engaging with the colonized individual. However, gloves should be used when handling wounds.[47]

Future research directions. This is an evolving science, and there is much to learn about community spread of CA-MRSA. As HA-MRSA primarily involves inpatients, it lends itself more easily to study. As CA-MRSA began entering the hospital setting it now lends itself to hospital-based research. While specific clinical questions around initial drug choice and duration remain, regional population studies are needed to inform empirical treatment for the community-based clinician.

Conclusion

The prevalence of CA-MRSA appears to be on the rise globally, and disadvantaged communities with overcrowded housing and homeless populations are disproportionally affected. Community-associated MRSA can be found in both hospitals and the community and is predominantly associated with purulent SSTIs. Treatment of endemic CA-MRSA infections needs to be balanced with the principles of antibiotic stewardship.

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Cross-Cultural Medicine

The cultural erosion of Indigenous people in health care

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Idealized versions of health care are common, and access to health care is often viewed as an unambiguous good. In the social determinants of health literature, for example, access to health care is treated as an intermediate determinant of health. This conceals a simplistic inference: the better your access to health care, the better your health. The reality is more complex: a modern industrial health care system can be a determinant of *ill* health, especially where it is culturally unsafe. At present, Canadian health care for Indigenous people is not culturally safe owing to the ways that health law, health policy and health practice continue to erode Indigenous cultural identities.

The origins lie at the colonial foundations of Canada. Colonialism is the primary distal determinant of Indigenous ill health.[1,2] As a process of enforced assimilation of Indigenous peoples, the drive to assimilate Indigenous communities into mainstream Canada continues to this day.[3] Contemporary health care contributes to assimilation through what one Anishnabe healer describes as "cultural erosion" (Tom Chisel, Sioux Lookout First Nations Health Authority: personal communication, 2015). As I use the phrase, it refers to the damage to individual and cultural Indigenous identities, with consequent ill health, that is inflicted by Canada's health care system. It is a problem of racism arising from the imposition of Canadian health law and health policies on Indigenous communities.

Racism affects every aspect of health care delivery for Indigenous peoples in Canada.[4] To understand cultural erosion, systemic and epistemic racism merits particular attention. Systemic racism concerns the unjust distribution of power that is built into law, policy and economic practice. It is the imposition and perpetuation of inequities through governance, rather than through individual intention, decision or behaviour. Examples are commonly bureaucratic. Dr. Michael Kirlew, a community physician for Wapekeka First Nation, cites two (personal communications, 2015/16). First, federal Non-insured Health Benefits medical referral forms require physicians to provide a patient's personal health information irrespective of consent from the Indigenous patient. If the physician does not provide the information, the referral is denied. Second is the routine denial of requests for medical transportation — for example, Indigenous children from remote communities being denied travel for care despite their physicians' judgment. Another familiar example is the underfunding of the nursing stations of northwestern Ontario and Manitoba.[5]

Canadian health care is founded on systemic racism through the violent unilateral imposition of Canadian social, economic, cultural and political dominance over Indigenous land and lives under section 91(24) of the Constitution Act, 1867, Indians, and Land Reserved for the Indians, as well as under the Indian Act, 1985. The Truth and Reconciliation Commission (TRC) of Canada[6] describes it succinctly:

> Canada asserted control over Aboriginal land. In some locations, Canada negotiated Treaties with First Nations; in others, the land was simply occupied or seized. The negotiation of Treaties, while seemingly honourable and legal, was often marked by fraud and coercion, and Canada was, and remains, slow to implement their provisions and intent.

Indigenous peoples were tricked out of, robbed of or pushed off their traditional lands, with the consequent erosion of their own complex systems of spirituality, law, trade, governance and health. Health law and policy in Canada is part of this unilateral assertion of governance, and thus,

Dream/escape: Dundas Street Car, Toronto, Ont. (www.jeff-thomas.ca; the photographer has obtained consent from the boy in this image.)

despite the technical excellence or best intentions of individual practitioners, is a priori systemically racist.

Epistemic racism — the imposition of one world view over another — also contributes to cultural erosion. One example is the privileging of mainstream biomedical knowledge over Indigenous healing practices and traditions. Anishinabek health laws, customs and practices, for instance, are often not permitted to influence local health institution practices, regardless of their merits. Where they are permitted, they are subordinated to provincial and federal legal and health norms. Epistemic racism explains the diminution and alienation experienced by Indigenous healers owing to disrespect for their knowledge and cultural roles. Epistemic racism is also evident in resource allocation — for example, if a health care facility that serves a substantial Indigenous population upgrades technology instead of building a requested sweat lodge.

Systemic and epistemic racism work in tandem. They ensure that only biomedical knowledge is taken seriously; they shape how scarce economic resources are distributed and to whom; they allocate and deny respect and thereby determine who is paid and how much; and they influence medical training, determining what counts as a medicine, medical intervention or treatment. Such inequities affect which patients have access to which health care resources, as well as the quantity and quality of the care. Hence, contemporary Canadian health law, policy and practices continue the cultural erosion of Indigenous healing and cultural traditions begun at the foundation of Canada.

Nonetheless, much can be done. The Truth and Reconciliation Commission calls to action provide systemic suggestions:[6]

- recognize the Indigenous health care rights enshrined in international and national law
- dialogue with Indigenous peoples to identify and eliminate health care inequities
- acknowledge, respect and address the distinct health needs of Métis, Inuit and off-reserve First Nations people
- provide sustainable funding for existing and new Aboriginal healing centres to address the harms caused by residential schools
- in collaboration with Indigenous healers and elders, recognize as medically legitimate the value of traditional healing practices
- hire and retain Indigenous health care professionals, as well as ensure that all staff have cultural competency training.

The basic moral principles familiar to all health care professionals oblige us to end cultural erosion.

Two principles from the cultural safety literature are also invaluable: first, that Indigenous peoples should be empowered to determine what is culturally safe; and, second, that health care professionals need to recognize how their advantages and power may distort health care decision-making.[7,8] In particular, we must share power and compensate for or eliminate unjust advantages. Health worker expertise becomes considerably more valuable for marginalized communities once cultural safety is priortized. For example, a skilled emergency department doctor is no use if patients don't come to emergency departments because of systemic or interpersonal racism. Referrals for medical interventions are pointless if Health Canada won't allocate appropriate resources. A proper dialogical relationship with Indigenous groups allows Indigenous peoples to coshape a culturally safe health care environment and ensures that health institutions adequately serve Indigenous interests.

Practical options for action are many: engage with Indigenous healers and elders; pay them well and include them in policy-making; provide ongoing antiracism education; build, maintain and adequately staff sweat lodges, where appropriate; advocate for change to harmful policies like those of the Non-insured Health Benefits to make them consistent with superior provincial health care norms; advocate for transformation of health law; and perhaps most important, support Indigenous sovereignty and the treaty relationships — especially as they relate to health care.

The basic moral principles familiar to all health care professionals oblige us to end cultural erosion. Restitution for the extraordinary harms inflicted on Indigenous peoples is required by moral *justice*; recognition of human and cultural identity is mandated by *respect for persons*; and *beneficence* and *nonmaleficence*, interpreted through the lens of cultural safety, promote the best health outcomes. Ending the ongoing erosion of Indigenous cultures requires integration of these principles, as well as the TRC's calls to action, into personal behaviours, health policy-making and health law.

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PROJECT REPORT

Community-based first aid: a program report on the intersection of community-based participatory research and first aid education in a remote Canadian Aboriginal community

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Community-based first aid: a program report on the intersection of community-based participatory research and first aid education in a remote Canadian Aboriginal community
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ABSTRACT

Context: Community-based first aid training is the collaborative development of locally relevant emergency response training. The Sachigo Lake Wilderness Emergency Response Education Initiative was developed, delivered, and evaluated through two intensive 5-day first aid courses. Sachigo Lake First Nation is a remote Aboriginal community of 450 people in northern Ontario, Canada, with no local paramedical services. These courses were developed in collaboration with the community, with a goal of building community capacity to respond to medical emergencies.

Issue: Most first aid training programs rely on standardized curriculum developed for urban and rural contexts with established emergency response systems. Delivering effective community-based first aid training in a remote Aboriginal community required specific adaptations to conventional first aid educational content and pedagogy.

Lessons learned: Three key lessons emerged during this program that used collaborative principles to adapt conventional first aid concepts and curriculum: (1) standardized approaches may not be relevant nor appropriate; (2) relationships between course

participants and the people they help are relevant and important; (3) curriculum must be attentive to existing informal and formal emergency response systems. These lessons may be instructive for the development of other programs in similar settings.

Key words: Aboriginal health, community-based participatory research, emergency responders, first aid education, prehospital medicine.

Context

This article considers the intersection of conventional first aid education and the remote fly-in Aboriginal community of Sachigo Lake First Nation in sub-Arctic Canada. This intersection highlighted incompatibilities between standard first aid and local community needs. These were addressed through a community-based collaboration and the development of a unique, community-specific first aid program.

Over the past 4 years, through a process of community consultation and collaboration, the Sachigo Lake Wilderness Emergency Response Education Initiative (SLWEREI) was developed, delivered, and evaluated. This unique community-based first aid program involved two intensive 5-day first aid training courses for lay community members, held in 2010 and 2012. Through two courses, the program has trained 26 adults, approximately 5% of the community population.

Training centered on providing essential life-support in emergency situations, with a focus on patient transport and the provision of adaptive care in low-resource and wilderness settings. Course curriculum and pedagogy were based on community priorities, needs, and feedback received through community consultation.

Community consultation was both formal and informal involving an initial 3-day site visit and needs assessment, formal interviews with key stakeholders focused on curriculum and pedagogy, survey feedback from course participants, and conversations with community members over the telephone and during the weeks spent in Sachigo Lake First Nation over the past 4 years.

Curriculum covered topics ranging from basic trauma care and cardiopulmonary resuscitation to mental health first aid, diabetic emergencies, and safe patient transport. The courses involved little time in a classroom setting with the majority of learning focused on practical skills training and simulation with debrief. The SLWEREI was based on a simple premise, buttressed by World Health Organization and American Heart Association guidelines: in underserviced settings, first response education may enhance community resilience and capacity to manage emergencies and save lives[1,2].

This article reports on curricular and pedagogical lessons learned as the authors developed a unique first aid training program. Its purpose is not to present the research details or outcomes of this initiative; these have been described elsewhere[3,4]. The specific adaptations to first aid educational content and methodology required to deliver effective community-based training in remote Aboriginal communities have not been described elsewhere.

Sachigo Lake First Nation is a remote Aboriginal community of 450 people in northern Ontario, Canada with no local paramedical services. The community is accessible by plane throughout the year, and by seasonal ice road for several weeks during the winter. Full-time nursing staff provides services at a local nursing station. A family physician visits the community for 2–3 days per month. Hospital care is provided hundreds of kilometres away in Sioux Lookout, with transport times rarely less than 4 hours.

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Issue: Standard first aid and community based first aid

First aid is 'the assessment and interventions that can be performed by a bystander (or by the victim) with minimal or no medical equipment'[2]. First aid emerged from a paramilitary tradition, rooted in the International Red Cross[5]. In North America, organizations such as the American Heart Association, National Life Saving Society, and the Red Cross outline the scope and principles of conventional first aid education.

As a field of clinical practice, first aid arises from a tradition of algorithmic guidelines, universal practice standards, strictly delineated levels of certification and scopes of practice, and a normative and a fundamentally positivistic approach to health and physiology. The notion that health emergencies are adequately similar across cultures and geographies forms a central premise of 'standard first aid', permitting a universal and algorithmic bystander response and educational model. Clinical protocols and first aid practice have been rooted in the simplification of diagnostic, therapeutic, and transport decisions for sick patients, coupled with a drive to provide simple and universal approaches to emergencies through basic training for non-clinicians. This model for immediate and on-scene clinical care and transportation has proven tremendously successful across a variety of settings from the battlefield to shopping centers, and first aid training programs have been recognized internationally as an essential form of health protection and promotion[6]. Non-conventional first aid programs have been successful at improving outcomes in low-resource contexts with minimal paramedical services in places such Ghana, Northern Iraq, Cambodia, and Uganda[7-10].

Over a period of years, this team has worked with Sachigo Lake First Nation to analyze the pedagogy and curricula of conventional courses. Through this partnership, the team has customized a first aid training curriculum to Sachigo Lake First Nation. This collaborative approach revealed incompatibilities between standard first aid and the lived experience and needs of the Sachigo Lake community. The customized first aid program and experience captures several lessons learned that the authors now identify as central to first response capacity-building and first aid programs in remote settings. Together, these core concepts describe what the authors call 'community-based first aid', a community-oriented approach to first aid education.

Lessons learned

The authors distilled several concepts into three lessons:

1. Standard algorithmic approaches may not be relevant or appropriate.
2. Relationships between course participants and the people they help are relevant and important.
3. Curriculum must be attentive to existing informal and formal emergency response systems.

First aid education pedagogy in a unique context

In a remote community, standard first aid approaches may be neither relevant nor appropriate. Standard first aid curricula face limitations in a remote Aboriginal community such as Sachigo Lake. To build a first response curriculum for this program, the authors drew on basic life support and first aid resources from the Heart & Stroke Foundation, American Heart Association and the European Resuscitation Council; wilderness medicine programs from Wilderness Medical Associates International; and emerging mental health first aid materials from the Mental Health Commission of Canada. These conventional first aid resources face two serious limitations for effective capacity building in a remote setting like Sachigo Lake.

First, these sources often assume an advanced literacy and the cultural and cognitive dominance of the written word among learners. Participants had a wide range of literacy levels, but few participants learned primarily from text. It was identified that these first aid curricula place heavy emphasis on flow charts and acronyms, both of which led to significant

challenges for participants. For example, some conventional first aid curricula use the acronym AVPU when assessing a patient's level of consciousness to represent *Awake*, *responds to Voice*, *responds to Pain*, or *Unresponsive*. Early course simulations showed that prompting learners to use this acronym as a memory tool was leading to confusion and flustering students. This issue was not specific to one or two students, but a challenge expressed by all students. Assessment of the patient's level of consciousness was altered to an intuitive approach, requiring participants to identify if the patient was behaving normally, abnormally, or unresponsive, and to identify if the level of consciousness was improving or worsening. Through consultation, the authors focused on similar assessment principles but phased acronyms out of the curriculum as they were found to be a stumbling block, rather than a helpful cognitive aid.

Second, conventional curricula emphasize pathophysiology, requiring trainees to develop health and physiology literacy in order to understand and provide emergency care. For example, Heart & Stroke Foundation resources on stroke and myocardial infarction are laden with graphics about atherosclerosis and thrombosis. While these pathophysiological teachings serve some learners well, it was observed that this approach could distract participants from the essential steps involved in responding to a family member with signs of stroke or chest pain. The program described in the present article did not treat pathophysiological knowledge as a prerequisite for problem solving and decision-making. Pathophysiology was addressed in the curriculum when questions arose from participants. Participants were not taught to identify symptoms of a myocardial infarction in order to make first response decisions because this would require an unnecessary cognitive link between symptoms, pathophysiology, and first response decision-making. Instead, participants were taught a generalized approach to patients complaining of chest pain, requiring only a link between observed symptoms and behaviors, and first response actions. This approach focused on symptom recognition, critical decision-making, safety, and treatment.

Third, both conventional and wilderness first response algorithms were found to be contextually and geographically inappropriate. Seemingly universal instructions like 'call 911', 'wait for the ambulance' or 'go to your nearest emergency department' appear throughout commonly available first aid programs. This provides incomplete or inappropriate training to first responders who provide care over extended periods in settings without ambulances or formalized dispatch services.

In Sachigo Lake, where there are no paramedical or 911 services, using conventional urban first aid materials re-emphasized service inequities without providing meaningful training alternatives. The current program focused not on when to call for help, nor on protocols, but on relying on oneself and each other to identify a problem, think critically about the situation, and to initiate an appropriate treatment based on the situation. A significant amount of time was spent discussing which patients needed to be transported to the nursing station, how, how quickly, and by whom. While similar principles are taught in conventional first aid courses, the emphasis is on the fact that there is a professional coming to help in an emergency. This is not the case in remote communities such as Sachigo Lake.

Conversely, wilderness medicine curricula offer an emphasis on remote settings and delays in accessing professional care, but this approach implies a specific notion of 'wilderness' that may alienate an indigenous community from their traditional environment and way of life. Further, wilderness medicine curricula often are designed for the person who occasionally travels in a remote context. This program's participants articulated a sense of home, safety, and comfort in remote parts of the boreal forest, which was incongruous with discourses and imagery of intrepid adventurers and rescue helicopters that dominate wilderness medicine approaches. Helicopters do not have the range to reach Sachigo Lake First Nation. As such, to reach the nursing station or an aircraft, patients are transported by a combination of snow machine, all-terrain vehicle, boat or truck, depending on location and season.

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In Sachigo Lake, presenting wilderness medicine materials might inappropriately convey that the program participants' traditional way of life is inherently or unacceptably dangerous. For example, it is common for members of Sachigo Lake to travel alone or in small groups to hunt and fish in the region surrounding the community. While this might represent a health or safety risk to outsiders, locals in Sachigo Lake understand traveling in their local region and wilderness surroundings as a safe and normal activity. As part of the program curriculum, simulations were based on this context. During simulations, participants had only the materials and resources that they would have with them while traveling by snow machine or boat, such as a tarpaulin, a gun, an axe, a sleeping bag, rope, tape, food, water, and an extra set of clothes. To manage mock patients, they were instructed to use the materials and equipment they would carry routinely to stabilize, treat, and transport patients to the nursing station in their community. Significant periods of time were spent debriefing simulations, discussing ways to improvise splints, bandages, or transportation packages. This program's curriculum offered approaches to emergency management suited for extended patient care in remote settings.

Developing a community-based first aid program with a remote First Nations community highlights subtle conflicts between the culture of first aid and the context in which it was being taught. Neither conventional urban programs nor alternative wilderness first response curricula offer training that is particularly well suited to an isolated, Aboriginal community like Sachigo Lake First Nation. Delivering community-based first response curricula may reveal similar geographical or cultural themes in other unique settings.

First aid delivery in a small close-knit community

Community-based first aid programs must consider the relationships between course participants and the people they may help. Conventional structured approaches to teaching first response, whether designed for the general public or for professional rescuers, are developed under the assumption that the majority of responses involve patients who are strangers. 'You are walking along the street and you suddenly come across an elderly man who has collapsed …', and so the scenario plays out. This 'stranger assumption' in standard first aid education, where the victim is identified as an anonymous individual identifiable only by their pathology or clinical problem, is incongruous in a tightly-knit community such as Sachigo Lake, where everyone is a friend or a family member.

The stranger assumption in standard first aid creates barriers in a remote community by disregarding existing well-developed relationships. Course participants in Sachigo Lake approached first aid role-play scenarios not as an individual within a community of strangers, but within a network of existing interwoven relationships. This community-based first aid education program adapted to meet the needs in such a community. Patients had names, rescuers were related, first response necessarily involved close friends. These relationships were important community resources. For example, during training exercises, relationships and personal connections to the patient were mentioned frequently and were treated as an asset in the provision of personalized, appropriate, and holistic care. Conventional medical and professional models might identify these relationships as a liability, conflict, or problematic barrier to dispassionate decision-making. In Sachigo Lake, these relationships were used as an asset, to involve close family members from within the community as a health resource, and to build community resilience by strengthening the health capacity of families rather than addressing community needs exclusively through access to health professionals.

As part of the 2012 course, the authors added a module on mental health curriculum that focused on three key areas: thoughts of suicide or self-harm, substance misuse and intoxication, and disorganized behavior. These themes were identified by the community as priority topics based on their shared experience and previous incidents.

Mental health and substance abuse issues disproportionately impact Aboriginal population compared to the rest of Canadian population. Suicide is one of the largest

contributors to premature death on reserve in Canada, with Aboriginal populations suffering three times the potential life years lost due to intentional injury compared to the general population[11]. There were several suicide attempts in 2011 in Sachigo Lake, all among young people. All were non-fatal. Similarly, substance abuse is a major issue in the region, with some remote communities reporting a narcotic addiction rate of 70% among their adult population[12]. In a survey investigating the severity of substance misuse problems as reported by Aboriginal Canadians, 83% of locally elected leaders reported alcohol and illegal drugs as problems in their community[13].

When a layperson provides first aid to a stranger, one would rarely encounter someone who would disclose their suicidal thoughts. This program's needs assessment and evaluation identified that although mental health first aid is rarely considered part of a conventional life-saving first response program, mental health emergency skills were as important to local responders as trauma management or cardiopulmonary resuscitation. In this small, remote Aboriginal community, where everyone is a family member or close friend, the mental health curriculum was central to meeting community needs and building local capacity to manage emergencies in a holistic and realistic fashion.

Language and curricula need to embrace established relationships for a community-based course to connect with community priorities and to reflect the community in which they live. The authors believe that community-based first aid programs can enhance community capacity by adapting curriculum to recognize these existing and important relationships.

Formal and informal systems

In a remote community, first aid education must be attentive to existing informal and formal emergency response systems. Conventional first aid training is intrinsically reliant on the existence of an identifiable transition point between bystander first aid providers and a formal healthcare system. Red Cross or American Heart Association Guidelines, for example, assume that first aid providers will intersect with a formal system of professional providers outside the hospital. In many Canadian communities, informal emergency response involves a bystander performing a varying level of first aid, and using a telephone to dial 911 dispatch services. Once dispatch services are contacted, a formal system is activated, and a patient's care will flow from paramedical to hospital care. In settings where emergencies are not addressed in this manner, developing local capacity requires that planners understand how a community responds to an emergency to be able to enhance systems without supplanting, bypassing, or ignoring them.

Because Sachigo Lake has no formal dispatch or paramedical services, the activation of formal emergency services begins when the patient arrives at the nursing station. All pre-nursing station care is provided through an informal system. Trying to understand this informal system has been part of the collaboration. In Sachigo Lake, this informal system is complex, situational, seasonal, adaptive, and well understood by community leaders. The authors' observation is that, in many cases, it is also extremely effective. Patients requiring urgent care often receive treatment and transport to the nursing station within minutes. In many cases, nearly the entire community responds to an emergency. Hence, nearly all available resources are present.

During course development and delivery in Sachigo Lake, curriculum and simulations allowed participants to activate and enhance both formal and informal response systems. Just as course delivery was unique because everyone on course was a friend or family member, so too was it distinct because of a shared experience of an informal emergency response system.

In a final large simulation on course, community members responded to a mock plane crash where four patients had been critically injured. This simulation was based on a previous aircraft crash in the community, and other similar incidents in the region. Participants responded to the incident, stabilized, packaged, and transported the four patients to the nursing station where two nurses on duty

received the patients. This simulation integrated an informal pre-nursing station response system with professional nursing care, and it was seen as a success by course participants, local government, nursing staff, and course instructors. This simulation represented a unique intersection of community-based methods and first aid education where the conventional interface between layperson and professional emergency systems was modified to meet the needs in this remote community. Understanding how individuals in a community respond informally to an emergency is a latent strength in the community that can be reinforced through adaptive curricula. Other communities may have similar informal response systems that can be enhanced through a similar approach to community-based first aid. Community-based first response training initiatives must be mindful of these informal systems, and find ways to enhance, rather than supplant or undermine, them.

Conclusions

Conventional first aid education relies on the notion that protocols and approaches to managing emergencies are applicable across all settings. In a remote Aboriginal community in northern Canada, with no paramedical services, such algorithmic approaches to first response are inappropriate. This program's collaborative approach to community-based first aid revealed three lessons central to building capacity in a remote community through the development of an education program. They stand in contrast to principles of 'standard' and 'universal' first aid that have previously dominated this field. The reported observations may be instructive for the development of other programs in similar settings.

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Community-Based Emergency Care: A Model for Prehospital Care in Remote Canadian Communities

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INTRODUCTION

Over 95,000 First Nations people live in 85 remote communities in Canada where federal nursing stations or clinics are the only source of local healthcare.[1] Most of these communities are without ambulance services; citizens need to board a plane to access an emergency department. Health Canada reports identify first responders as "critical" requirements in remote communities, but untrained laypeople usually deliver on-scene care and transport patients to local health centres.[2] Despite a $2.4 billion annual expenditure on Ontario's prehospital care system, approximately 25,000 Ontarians in 29 remote First Nations communities have no formal paramedicine or 911 dispatch services.[3]

Standard ambulance systems, 911 dispatch, and uniformed paramedic professionals have been developed and refined for settings with road access and hospitals, but may not meet first response needs in isolated communities. Addressing unique geographical, cultural, and epidemiological circumstances in remote communities demands a new approach to local medical first response, and the development of systems founded on First Nations self-determination and self-governance of health services.[4] A community-based approach might answer the urgent call for effective, sustainable, and scalable local care.[5,6]

EMERGENCY CARE IN REMOTE CANADIAN COMMUNITIES

Remote and isolated First Nations populations in Canada face dramatically elevated morbidity and mortality from mental health and addiction problems, cardiovascular and respiratory diseases, diabetes and obesity, and infectious diseases.[1,7] These problems all manifest in health emergencies, ranging from mental health crises to myocardial infarction, stroke, diabetic emergencies, severe sepsis, and physical trauma. Remote communities in Northwestern Ontario also face injury rates five to eight times the Canadian average, accounting for 30% of deaths.[8]

Delivering quality care for these patients requires a strong "chain of survival," with integrated care systems from the place of initial injury or illness to definitive treatment at local clinics or regional hospitals.[1,9] For most Canadians, that chain of survival begins with bystander first aid and the relatively prompt activation of a formal Emergency Medical Services (EMS).

Health Canada's report on essential services in remote and isolated communities identifies that "Community-Based First Responders are critical to transport the patient from the community to the nursing stations."[2] Remote communities in the Nishnawbe Aski Nation (NAN) in Northern Ontario are without formal paramedic services, with the exception of a handful of reserves on the James Bay coast. In a few communities, Canadian Ranger programs and Crisis and Emergency Response Teams deliver fragmented and heterogeneous services. Volunteer teams struggle with burnout, turnover, and inconsistent service.[10]

Patients with urgent medical needs can overwhelm community clinics and nursing staff, who often deliver emergency care beyond their regulated scope of practice while communicating simultaneously with regional consulting physicians and air ambulance providers.[1] Air ambulance and private aviation services transport patients from nursing stations to regional hospitals.[10] These evacuations are not infrequent: roughly one in 12 people in the region were transported by air

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CAMBRIDGE UNIVERSITY PRESS CAEP | Canadian Association of Emergency Physicians ACMU | Association canadienne des médecins d'urgence

ambulance between January 2012 and September 2013.[11] In the 2013-2014 fiscal year, Health Canada spent $175 million on medical transportation for Ontario and Manitoba remote communities, mostly by air ambulance and scheduled flights. During this same period, $103 million was spent on direct clinical care delivery.[1]

Without formal paramedicine systems in many remote First Nations communities in Canada, bystanders, friends, and family members shoulder the responsibility to transport severely ill and injured patients to local nursing stations and clinics.[5,6,10,12] The result is a fragile and unpredictable chain of survival. In spite of the occasional heroic success story, these informal systems are an unsafe and unreliable patchwork of community goodwill and clinical near-misses.[6,12] All are characterized by inadequate training, tragic underfunding, and inexcusable inequity.[1,6,10,12] Remote communities and their citizens deserve better.

LIGHTS AND SIRENS MAY NOT WORK EVERYWHERE

The Canadian Association of Emergency Physicians' (CAEP) 1997 position paper on rural, remote, and isolated emergency health care in Canada tasks nursing stations with initial triage of outpatients, definitive care for minor conditions, and stabilization and transfer to hospital where required.[13] The report asserts that "adequate access to ambulance services should be available in all rural communities," and "regional 911 dispatch by qualified emergency medical dispatchers should be available throughout Canada."[14] This is the conventional approach to fixing a gap in prehospital care: expand the standard EMS system based on 911 dispatch, professional paramedics, and standardized clinical protocols. While these may be effective strategies in regions with easier access and more resources, conventional approaches are unlikely to meet the needs of remote First Nations communities.

Under previous initiatives and pilot programs, some communities in Ontario's remote north poured funding into ambulances and paramedicine equipment. These were costly, broke down quickly, and required specialized training.[10,12] Now, old ambulance carcasses litter some community truck dumps. Dust gathers on unused or broken first response equipment in nursing station storage closets. Some communities are without a working defibrillator or serviceable oxygen tank. While accessing and maintaining essential equipment is paramount, the right equipment does not itself guarantee excellent care.

Imposing unmodified standard emergency medicine protocols in settings with limited resources, austere environments, and minimally trained providers will not ensure quality care. In some cases, basic paramedical or first responder standards can be ineffective or dangerous in these settings. Immobilizing a patient on a backboard while waiting hours or days for air ambulance transport in –40°C temperatures may have adverse consequences. Fulfilling recommendations for imaging before reducing a dislocated shoulder is unattainable when there is no hospital available for imaging. Teaching standard first aid courses without modification also has limitations; often, the first step taught is to call 911, but in these settings there is no 911 service, no paramedics, and no local hospital.

Deploying paramedics to fill the emergency care gap in remote communities has the appearance of an appropriate strategy, but conventional paramedicine professionals might not be a good fit for two reasons. First, the Paramedic Association of Canada's professional scopes of practice and Ontario EMS patient care standards presuppose a direct link between paramedicine services, ambulances, emergency equipment, and hospitals, but in remote communities paramedics would provide patient care for longer periods and would interface mostly with nursing stations and air ambulance providers.[15] Second, mandating and funding paramedicine services in the remote north is unlikely to create sustainable access to service. Health Canada already struggles with significant vacancy rates among rewarding and lucrative nursing positions.[1] This overwhelming health human resources challenge would likely extend immediately to a paramedicine system reliant on imported professionals.

Through our work with health leaders from remote Northern Ontario communities, we have learned that one-size-fits-all paramedicine protocols and land ambulance service might not meet the needs of patients and providers in remote communities.[5] CAEP's 1997 position statement identifies that the "principles of emergency medicine do not differ between rural and urban settings… but the method. … differs significantly." The principle here is that remote communities should have excellent prehospital care. Importing standard ambulance services to remote communities is likely not the right method. Developing local capacity is perhaps a more appropriate strategy.

COMMUNITY-BASED EMERGENCY CARE

We propose a different solution based on community workers. Training locals as first responders and educators, instead of focusing on recruiting professionals trained elsewhere, would improve local capacity by giving locals the skills to recognize illness and injury, provide basic treatment, and focus on disease prevention and health promotion. In communities where untrained volunteers are already doing their best to deliver care, community-based programs would support the existing culture of caring and helping behaviour with reasonable remuneration, coordinated leadership, appropriate training, and basic equipment. Local programs could encourage nursing station staff to work with first responders and community health workers. Lay health workers have been shown to deliver transformative maternal-child health and infectious disease interventions in low resource settings—a similar approach might improve emergency care in remote Canadian communities.[16] In short, a community-based emergency care strategy could reduce unnecessary costs and unnecessary deaths.

Over the past five years, we worked with First Nations leaders to develop Community-Based Emergency Care (CBEC), a new approach to prehospital care in remote communities.[5] CBEC is a proposed model grounded in the development of a new group of emergency health providers called Community Emergency Health Workers (CEHWs). Supported by a handful of paramedics at the regional level, CEHWs from remote communities would be trained through a customized, comprehensive, and culturally appropriate curriculum, based on their own distinct set of emergency clinical protocols.[6] Hired in remote communities to deliver essential and timely care, transport patients, and collaborate with local nursing and medical staff, CEHWs would also lead local health promotion and disease prevention programs and train local volunteer first responders. This community-based approach to interdisciplinary healthcare delivery, and the integration of acute care, chronic disease management, and health promotion, extends emerging models for community paramedicine to address health care needs in some of Canada's most underserviced settings.[17] CEHWs and volunteer responders would form the backbone of a distributed model of community-based emergency care.[5] CBEC workers would provide a fully integrated model for first response emergency care in these unique geographical and cultural settings, delivering on-scene first response and connecting it with local community care, transport medicine services, and regional advanced care.

Rather than displacing informal systems with standard paramedicine services, CBEC aims to enhance and support existing systems with the training and infrastructure needed to deliver excellent and accessible services. Operated through First Nations governance institutions and delivered by local providers, CBEC contributes to a philosophy of self-determination that has been linked with positive health outcomes and is essential to the cultural vision of First Nations in Canada.[4] Like similar international initiatives, CBEC would build on a global evidence base demonstrating that local lay health providers can deliver essential culturally appropriate emergency care and transform community health for conditions ranging from physical trauma to mental health.[14,18,19,20] CBEC can create jobs, enhance community resilience, improve access to care, and save lives. CBEC offers a new approach to a problem that has been ignored for too long.

CONCLUSIONS

In remote communities, citizens face stark inequities in access to emergency services, and have identified CBEC as a homegrown approach to delivering care in settings where conventional ambulance services would be ineffective. Local workers can develop the skills to deliver essential features of quality emergency care. In remote communities, excellent evidence-based first response and transport to a local clinic may come in the form of a trained and skilled friend or family member. It is time to invent new approaches to first response and invest in community-based approaches to emergency care.

Keywords: First Response, prehospital care, rural and remote health, community-based health care, Aboriginal health

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RESEARCH ARTICLE

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An environmental scan of emergency response systems and services in remote First Nations communities in Northern Ontario

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ABSTRACT

Background: Approximately 24,000 Ontarians live in remote Indigenous communities with no road access. These communities are a subset of Nishnawbe Aski Nation (NAN), a political grouping of 49 First Nations communities in Northern Ontario, Canada. Limited information is available regarding the status of emergency care in these communities.

Objective: We aimed to understand emergency response systems, services, and training in remote NAN communities.

Design: We used an environmental scan approach to compile information from multiple sources including community-based participatory research. This included the analysis of data collected from key informant interviews (n=10) with First Nations community health leaders and a multi-stakeholder roundtable meeting (n=33) in October 2013.

Results: Qualitative analysis of the interview data revealed four issues related to emergency response systems and training: (1) inequity in response capacity and services, (2) lack of formalised dispatch systems, (3) turnover and burnout in volunteer emergency services, and (4) challenges related to first aid training. Roundtable stakeholders supported the development of a community-based emergency care system to address gaps.

Conclusions: Existing first response, paramedical, and ambulance service models do not meet the unique geographical, epidemiological and cultural needs in most NAN communities. Sustainable, context-appropriate, and culturally relevant emergency care systems are needed.

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Introduction

In 2015, Canada's Auditor General identified inequitable health services among remote First Nations communities, including severely under-equipped nursing stations and healthcare staff working beyond their scope of practice [1]. Emergency medical services are among the most deficient. The burden of emergency health conditions among remote First Nations is dramatically elevated compared with other Canadian communities. Elevated rates of chronic and infectious disease manifest as critical health emergencies including mental health and addictions crises, myocardial infarctions, diabetic emergencies, and acute sepsis [1,2]. These service deficiencies coupled with increased risk of emergency health conditions exacerbate the potential for severe illness or death.

Background

The February 2016 Health and Public Health Emergency declaration issued by Nishnawbe Aski Nation (NAN) and the Sioux Lookout Area Chiefs Committee on Health aimed to bring public attention to the healthcare inequities that exist in the province of Ontario within the remote reserves north of Sioux Lookout and NAN Territory [3]. NAN is a First Nations political organisation that represents 49 First Nations communities in northwestern Ontario, many of which are located in remote regions in the far north of the province. Figure 1 geographically depicts NAN communities connected by seasonal and permanent roads, and with their proximity to closest hospitals. The majority of communities are grouped into seven Tribal Councils according to region [4]. Of the estimated 49,000 people represented by NAN on and off reserve, roughly 24,000 live in communities

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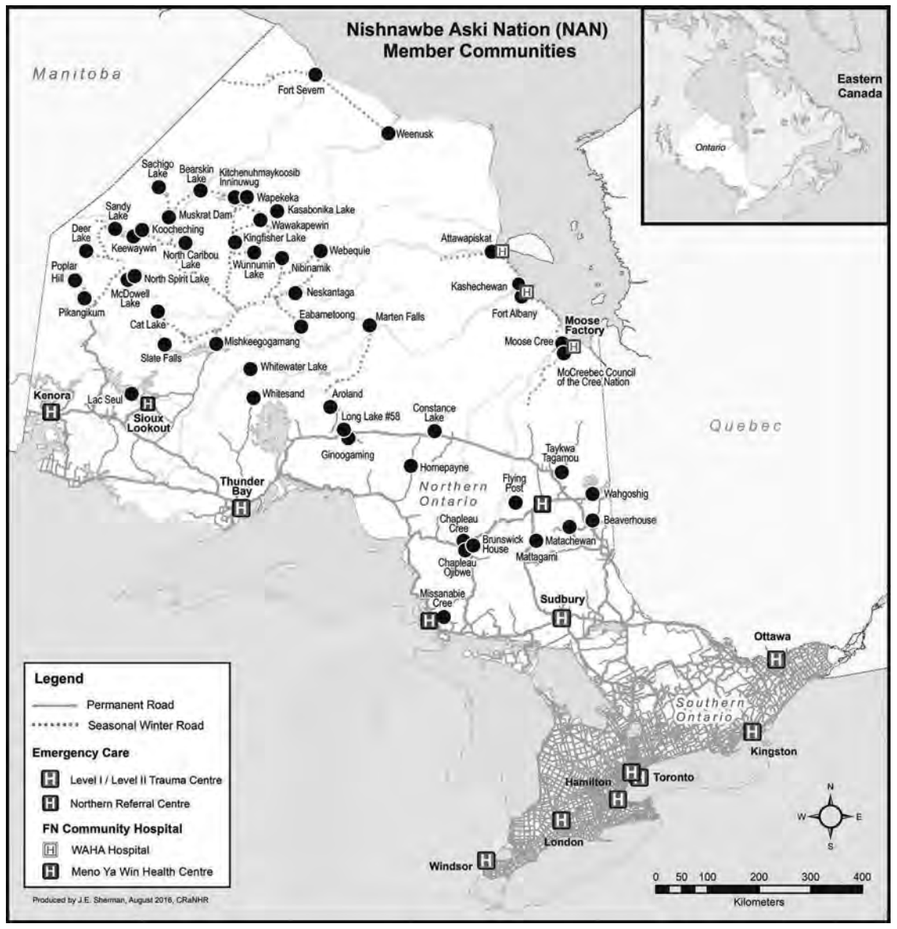

Figure 1. Map of Nishnawbe Aski Nation member communities, road access and nearest emergency care services. (Reproduced with permission from Jill E. Sherman).

without permanent road access and rely on federal nursing stations or clinics as their only source of local healthcare.

Emergency department care is accessible only by plane or helicopter [1,5]. Air transportation services are operated under air ambulance and private aviation services such as Ornge, the largest supplier, or SkyCare. Landing strips on First Nations reserves often lack navigational equipment available at other airports across Canada [6–9]. Because many of these remote airports are not serviced by instrument approach, pilots must fly "by sight", limiting the ability to land and take off in adverse weather [8]. Emergency medical evacuations can be delayed as a result of these equipment limitations. These evacuations are not infrequent. Citizens within the remote reserves north of Sioux Lookout face rates of injury five to eight times the national average, accounting for 30% of all deaths in the region [10]. Between January 2012 and September 2013, Ornge performed at least 2033 medical evacuations, equating to 1 medical evacuation for every 12 people over this 21-month period [11].

These communities often do not have formal ambulance services. Despite this disparity in emergency health services, our team was unable to locate scholarly work that systematically described the state of emergency care systems and services in remote NAN communities. The purpose of this study was to better understand the available first response

emergency care services and systems in remote NAN First Nations primarily from the beliefs and perspective of community health leaders. Rather than relying solely on government assertions of existing regional or national service provision, we were interested in local perceptions of available care. We defined emergency care as any service that evaluates and/or treats critical medical emergencies to those who are ill and injured, including mental health emergencies. We were guided in our approach by principles of community-based participatory research under a transformative-emancipatory paradigm [12], which posits that the purpose of this project is to improve societal equity for First Nations and addresses power and privilege during the entire research process [13]. We used an environmental scanning (ES) approach to consolidate information from community leaders, frontline practitioners, and publically available sources [14,15]. The first phase of our ES employed an *active approach* by gathering information from primary sources such as perspectives of First Nations health leaders and relevant stakeholders [15]. The second phase employed a *passive approach* by gathering information from secondary sources, such as publically available information, to supplement the results obtained from the active approach [15]. This paper provides the only systematic account of local beliefs and perceptions on the status of emergency response capacity, systems, and training in NAN communities.

Methods

Phase I: primary sources

The active approach of the ES consisted of two parts conducted sequentially (1): structured telephone interviews with a group of community health leaders from NAN; and (2) a roundtable with an interdisciplinary group of stakeholders relevant to emergency services in NAN communities. Both the interviews and roundtable process constituted an active approach because the research team interacted with the people and organisations involved in emergency care to both collect data and take action [15]. Both components received ethical approval from Lakehead (#128 12–13/ROMEO 1463141) and Laurentian (#2013–02-11) Universities.

Structured interview questionnaires were developed to assess the status of emergency care within the member communities of each tribal council (Table 1). Ten key informants from the NAN Health Advisory Group agreed to participate in telephone interviews. These informants were invited to participate because they had the collective knowledge of the emergency response systems across NAN communities. Only two of 49 NAN communities were not represented by these informants. Nine informants were community health leaders and one informant was a representative from a local emergency response organisation. Questionnaires were sent to informants prior to each interview. Three team members conducted semi-structured interviews and follow-up phone calls between August and November 2013 using telephone scripts and a data collection template based on the question guide in Table 1. We member-checked our findings by sharing the interview notes with participants and reviewing their responses during follow-up phone calls to confirm accuracy.

Table 1. Sample of informant interview questions from telephone scripts.

1. Who responds to health emergencies, like heart attacks, accidental injuries or mental health emergencies, and provides first aid services in the communities you represent?
2. Who trains people to provide emergency first aid in each of the communities you represent?
3. How satisfied are the people of this community/these communities with their emergency response system?
4. Have first response services or training changed in any of your communities in the past 10 years? If yes, can you describe how?
5. Considering the funding, travel, and human resource constraints, what do you believe are the essential elements of an effective emergency response system for a remote NAN community?
6. Do you have anything else you would like to share about pre-nursing station emergency care in the communities you represent?

Quantitative descriptive analyses were conducted using Microsoft Excel. Question-specific response rates (QSRR) differed substantially between questions, as key informants did not always have access to or know relevant information about a particular community they were responsible for. Qualitative content analyses were conducted using NVivo 9.0 to identify: (1) issues related to emergency response systems and training in NAN communities; and (2) essential elements of an effective emergency response system for a remote NAN community. Provisional themes were reviewed and revised by the research team for each analysis to increase reliability [16].

Our team held a two-day multi-jurisdictional meeting in October 2013 with a range of health stakeholders in Sioux Lookout, Ontario (Table 2). The meeting was convened to confirm and interpret the interview data, and to collaboratively develop solutions to improve emergency service limitations and gaps. This included the development of a vision, key recommendations, and guiding principles to improve emergency care services in NAN communities.

Table 2. List of representative organisations who attended the multi-jurisdictional roundtable.

- Dignitas International
- Health Canada
- Independent First Nations Alliance
- James Bay Ambulance Services (Weeneebayko Area Health Authority)
- Keewaytinook Okimakanak
- Matawa First Nations
- Mushkegowuk Council
- Nishnawbe Aski Nation
- Northern Ontario School of Medicine
- Ontario Ministry of Aboriginal Affairs
- Ontario Ministry of Health and Long-Term Care
- Ornge
- Sachigo Lake First Nation
- Sandy Lake First Nation
- Shibogama First Nations Council
- Sioux Lookout First Nations Health Authority
- Sioux Lookout Meno Ya Win Health Centre
- Sioux Lookout Regional Physician Services Incorporated
- Windigo First Nations Council

Phase II: secondary sources

The passive approach of the ES consisted of two parts conducted sequentially: (1) reviewing the literature related to emergency response services in NAN communities; and (2) targeted Internet searches of known services to provide information not previously identified. The purpose of this phase was simply to supplement the results of Phase I to identify any additional programmes or services that were previously not mentioned or identified in Phase I. Phase II did not require ethical approval.

We conducted a literature review in February 2016 to identify published and grey literature. The following electronic bibliographic databases were searched: ProQuest, Web of Science, MEDLINE, and Scopus. Inclusion criteria included: (1) NAN community context or authorship; and (2) content primarily related to the delivery and/or access to emergency response services. Citations involving environmental emergency preparedness initiatives were excluded. This search was further supplemented with two independent Google searches including: *"nishnawbe aski nation" emergency services* and *"first nations" emergency services remote ontario*. EM retrieved and reviewed all websites and citations sequentially until saturation. This review also included documents acquired from correspondence between the research team and stakeholders who attended the roundtable meeting.

From the key informant interviews, 12 programmes and services were identified that aimed to provide some degree of emergency care in NAN communities. Targeted website searches were completed in July 2016 to identify publicly available information regarding these 12 programmes.

Results

Phase I: primary sources

Quotations are directly from informant interviews.

NAN health leader interviews

The majority of NAN communities have limited emergency response resources and services. Although there were ambulance or medical transportation vehicles in 35 (78%) communities (92% QSRR), the condition of vehicles was often unknown and some were believed to be in poor or unusable mechanical condition. Many of these vehicles are regular passenger vehicles not designed for patient transport and medical services, and therefore may be inadequate for the intended role despite being in serviceable condition. It was also outside the scope of practice for Health Canada nurses to respond to emergencies outside of a nursing station, as stated by one informant: "Nurses are now stuck in the nursing station because of the memo." Although some nurses may not act according to this memo, the policy has nevertheless led to challenges, as another informant indicated that "a patient died on the road in front of the nursing station, and during this incident the nurse could not leave the nursing station". Despite a lack of permanent road access, the James Bay Ambulance Service operates five paramedic bases in five remote communities in northeastern Ontario: Attawapiskat, Fort Albany, Kashechewan, Moose Factory, and Moosonee. There are no paramedical services in 28 (61%) remote NAN communities (98% QSRR).

Informants identified 12 local programmes, training organisations, health service providers, and political organisations that are involved in emergency care training and response (Table 3). Even when formal emergency response services were available, informants identified a strong community response in attempts to fill service gaps: "there is a reliance on the community to respond to emergencies." Lay community members such as friends, family and chief and council were known to routinely transport patients to the nursing station in response to all types of emergencies. In communities without access to an ambulance, ill or injured community members are often left to "find their own transportation" to care at the nursing station.

The operation of formal programmes is fragmented and heterogeneous. Thirty (79%) communities reported having crisis response teams (78% QSRR) who respond to situations involving suicide attempts and family violence [17]. Only 18 (50%) of communities reported that Canadian Rangers in their community respond to emergencies (73% QSRR) and 18

Table 3. List of local programs, training organisations, health service providers, and political organisations involved in emergency care training and response.

- Canadian Ranger Program
- Crisis Care Coordinators/Crisis Care Teams operated jointly by NAN and Sioux Lookout First Nations Health Authority
- Ontario Provincial Ministry of Health & Long Term Care First Nations Emergency First Response Team Program
- James Bay Ambulance Service Paramedic Program
- Junior Ranger Program/Ontario Ranger Program
- Medical Driver Program
- Nishnawbe-Aski Police Service
- Ornge/SkyCare
- Red Cross
- Sachigo Lake Wilderness Emergency Response Educational Initiative
- St. John's Ambulance Service
- Volunteer Firefighters

(39%) of communities reported that paramedical services respond to emergencies (94% QSRR). Communities reported that the provincial Emergency First Response Team (EFRT) programme was active in six (13%) communities (94% QSRR). This programme recruits volunteers from the community to be trained in emergency first response, first aid, and cardiopulmonary resuscitation (CPR) based on provincial first responder standards.

There is limited first aid and CPR training in NAN communities. Three (7%) communities had no first aid or CPR training; the remaining 43 (93%) communities had at least one first aid and CPR training session (98% QSRR). St. John's Ambulance provided training in 31 (78%) communities (85% QSRR), Canadian Red Cross in 12 (39%) communities (66% QSRR), and the Ontario Ministry of Health and Long Term Care in seven (16%) communities (91% QSRR). Ornge did not provide training in any communities (79% QSRR). Eight (17%) communities had first aid and CPR training from at least two sources, of which six (75%) received services from St. John's Ambulance and the Red Cross. Other sources of training cited by informants included: the Aboriginal Health and Wellness Strategy, the Canadian Ranger Program, James Bay Emergency Medical Services, and the Sachigo Lake Wilderness Emergency Response Educational Initiative. First aid and CPR training frequency ranged from "twice per year" to every "three to four years". Estimated training frequency averaged once every 2 years (81% QSRR); although many comments indicated that training frequency varied significantly or was irregular with many years between training cycles. Average length of training was 2.7 days (87% QSRR) ranging from "two to three days" to "five days plus two-day training in Sioux Lookout". An estimated average number of 18 people per community were trained with each training session, ranging from two to 200 people. Forty-two (91%) communities identified that trainers were from outside the communities (98% QSRR).

Table 4. Themes extracted from key informant interviews identifying challenges within existing emergency response system in NAN communities and components of a perceived effective emergency response system for remote NAN communities.

Issues in existing emergency response systems	Components of an effective emergency response system
• Inconsistent and inadequate response capacity and services. • No formalised emergency service dispatch system. • Turnover and burnout in volunteer teams. • Challenges related to first aid training for community members.	• Reliable emergency service dispatch system. • Support for volunteer emergency response teams. • Reliable and responsive transportation. • Context-relevant system infrastructure. • Training that is reliable and context appropriate.

Four themes emerged related to the issues surrounding emergency response systems and training in NAN communities (Table 4):

(1) *Inconsistent and inadequate response capacity and services*. There is a wide variety of emergency response capacity and services across NAN communities, as "different communities have different emergency services available to them". Some communities have access to paramedic services, such as five communities serviced by James Bay Ambulance Service, or have road access and are serviced by the existing provincial system; however, many smaller remote communities have limited, if any, response capacity and services: "the community doesn't have a program to address emergency response [nor]…an ambulance response service, and that is required. They make use of what they have. They've been lucky so far."

(2) *No formalised emergency service dispatch system*. There is a lack of consistent, reliable and standardised communication. Many communities lack 911 services, cell services, reliable landlines, and street names or household identifiers. Often the communication system is unclear, requiring two or three different phone calls during times of emergency: "when there is an issue or emergency in a community, community members call at least two or three different numbers. At times, there is no

24 hours per day coverage, so the calls go unanswered, and it is then the responsibility of the community members to get the sick or injured person to the nursing station."

(3) *Turnover and burnout in volunteer teams*. Some communities have volunteer-run EFRTs that support pre-nursing station care; however, there is high volunteer turnover where the team is dispatched often: "being called repeatedly at 3 am, 4 am, or 5 am is draining for volunteers, and if there is too much demand, the team turns over frequently."

(4) *Challenges related to first aid training for community members*. There is a wide variety in first aid training, providers, and curriculum. Urban-developed first aid training courses are not appropriate in communities without paramedical services. For example, "patient transfer is not covered in normal CPR and first aid training, which is a problem … [because] training usually assumes that there are ambulance and 911 services nearby". Training in many remote communities is infrequent, inconsistent, or does not occur at all. Training is usually only 2–3 days long and is often only provided to staff, employees, or teams in a community: "there is no regular [first aid] training", "first aid training is way too short", and "trainers are from outside the communities [and] this is part of what makes it challenging".

Five themes emerged related to identifying the essential elements of an effective emergency response system for a remote NAN community (Table 4):

(1) *Emergency service dispatch system*. Community members need access to an effective system of communication to access first responders in an emergency: "A 911 for the North is needed." Since people frequently travel in, out, and between remote communities, one respondent indicated that "a standardised system is required that is consistent across communities". Another critical element of an effective emergency dispatch system is reliability: "When there is an issue or emergency in a community, the members call at least two or three different numbers (nursing station, on-call person, Nishnawbe-Aski Police Service). At times there is not 24 hour per day coverage, so the calls go unanswered, so it is then the responsibility of the community members to get the sick/injured person to the nursing station."

(2) *Support for volunteers*. Existing volunteer emergency response teams need to be trained, equipped, and supported to enhance continuity to prevent burnout and turnover: the life expectancy of a team member is directly proportional to the call volume", and "turn-over is problematic since the new people start at square one again." One respondent summarised the challenge facing the use of EFRT programme: Most people dedicate themselves to the training and find the long-term commitment far too extensive, or find this is something they pursue as a career and leave to acquire the education needed to become a member of the medical field. In our region, emergency response teams will have cycled out a complete membership after 2 years with the exception usually of one or two people who are truly committed and suited to emergency work."

In summary, "The proper support and coordination of a team is required to ensure any measure of longevity". Volunteer emergency care positions must be supported by paid professional or paraprofessional roles.

(3) *Reliable and responsive transportation*. There needs to be a safe, reliable and timely transportation system for patient preparation and transition to the nursing station or health centre. "Each community should have an emergency transport vehicle or ambulance." In addition, the transport system may need to include "boat, motor, skidoo and sled for winter". Considering the geographical context of large tracts of wilderness surrounding remote communities, one respondent summed this need succinctly: "safe transfer to a vehicle and safe transport to the nursing station."

(4) *Context-relevant system infrastructure*. The emergency response system needs to be adapted and standardised for small remote communities, and this requires infrastructure funding and support for resources, training, and equipment. One respondent stated: "Each community should be outfitted with the resources (equipment and people) necessary to be able to respond to emergencies in the community." Patient transition to the nursing station and health centres needs to reflect the reality of the community context with strong working relationships between nurses and first responders: "There should be a strong working relationship and system in place with the nursing station so the transition occurs smoothly and effectively."

(5) *Training that is reliable and context appropriate*. Training needs to be longer than 3 days, more frequent, and more consistent: "There needs to be consistency in trained people that are able to respond to emergencies" and "regular refresher courses in the communities as a preventative measure, perhaps once a year to keep people fresh and up-to-date". The curriculum needs to be adapted to deal with relevant critical health emergencies and adjusted to non-urban contexts without typical emergency response systems: "First aid & CPR deal with physical health, but communities need mental health first aid as well to deal with abusive situations, suicide and situations involving drugs and alcohol." Community members should be encouraged to participate in training because they are a valuable first response resource in each community as "training is key and this includes training for lay community members".

Multi-jurisdictional roundtable

Representatives of this roundtable included an interdisciplinary group of 33 partners including 16 (48%) representatives from First Nations governance and community organisations, seven (21%) representatives from Ontario Provincial and Canadian Federal governments, seven (21%) representatives from nursing and paramedical services, and three (9%) representatives from non-governmental organisations.

Representatives confirmed the accuracy of results from the informant interviews and interpreted these results to identify improvement opportunities for NAN communities. There were two main outcomes from this meeting: (1) a shared vision for the future of emergency medical services in NAN communities; (2) guiding principles central for implementation of the vision. The shared vision is: "people in remote and isolated First Nation communities should have access to excellent community-based first response emergency care" [5]. The six guiding principles for advancing solutions in pre-nursing station care in remote NAN communities are: community-based, sustainable, capacity-building, collaboration, integration, and excellence (Table 5). The roundtable meeting also led to the identification of two recommended actions including: (1) collaboration between NAN and Federal and Provincial governments; and (2) plan and test a community-based approach to emergency care in partnership with a selection of NAN communities. This approach has been described elsewhere [18]. The meeting report "Community-Based Emergency Care: An Open Report for Nishnawbe Aski Nation" is a public summary of this meeting and it is available at www.nosm/cbec [5].

Table 5. Summary of guiding principles developed by stakeholders at the multi-jurisdictional roundtable meeting to guide building an effective emergency response system in remote NAN communities.

Guiding Principle	Description
Community-based	Identify, respect, and learn from the diversity of remote and isolated First Nation communities. Address individual and population health needs by building on local priorities, relationships, skills, strengths and culture. Develop, deliver and evaluate programs with the community, and for the community.
Sustainable	Strive for lasting and scalable community-based emergency care programmes, rooted in sound health, human resources, economic, and community planning. Build on opportunities to develop community resilience and health services as a sustainable and renewable local resource.
Capacity building	Build capacity by providing emergency care training across a large cross-section of community members. Explore opportunities to develop employment opportunities for local emergency care and training.
Collaboration	Work with partners in healthcare delivery, such as community health workers, nurses, paramedics and physicians in the design, delivery, evaluation and funding of community-based emergency care programmes. Develop programmes as a collaboration between First Nations and local, provincial and federal governance organisations.
Integration	Ensure that community-based emergency care programmes integrate with emergency health services provided by nurses, paramedics and physicians, as well as other community emergency management strategies including Canadian Rangers and Crisis Response Teams.
Excellence	Evaluate and study programmes in collaboration with communities, to bring high-quality, equitable, innovative and evidence-based emergency care to ill and injured patients in remote communities.

Phase II: secondary sources

The literature search yielded 53 citations, four of which met inclusion criteria. Two news articles stated the need for improved emergency response from First Nations leaders [19,20]. The remaining two articles were research publications describing the Sachigo Lake Wilderness Emergency Response Educational Initiative [21,22]. Google searches yielded 31 relevant websites. Two sources were statements from First Nations leaders calling for improved pre-nursing station emergency response services [20,23]. The remaining websites did not provide novel information.

We could not locate significant amounts of publicly available information for the majority of programmes and services. Those that could be located provided no novel information. Documents from professional correspondence revealed that the Canadian Red Cross developed a partnership with Moose Cree First Nation in 2012 called the *Strength & Spirit Campaign* to develop and deliver existing and novel Red Cross programmes and services to better meet community needs [24].

Discussion

Existing emergency response systems, efforts, and programmes are inadequate in NAN communities. Given the small population sizes and a variety of other contextual, historical, and geographical factors, many communities do not have 911 services or other essential emergency prevention and response systems. There are several programmes and services that address pre-nursing station care; however, the operation of these programmes is heterogeneous and fragmented. Many existing programmes depend on volunteers for operation, leading to burnout, turnover, and unreliable care. These challenges often place the burden on community members to transport patients to the nursing station; however, there is also lack of equitable, frequent, and effective training opportunities to ensure that lay responders are adequately prepared to manage the medical emergencies that occur in rural and remote NAN communities.

Themes related to issues in emergency care that were identified from interviews with NAN health leaders included limited capacity, services, formalised dispatch systems, and contextually appropriate models of emergency medical service delivery. The expansion of conventional ambulance, first responder, and first aid programmes in these isolated and remote First Nations may not meet the unique geographical, epidemiological, and cultural needs of communities [18]. Standard first aid protocols and equipment in such settings with limited resources, isolated contexts, and minimally trained providers will not ensure quality care [18]. In some cases, basic first aid standards may even be ineffective [18].

Innovative, sustainable, and community-based innovations in emergency health services delivery are urgently needed. Local First Nations emergency response stakeholders agreed that "people in remote and isolated communities should have access to excellent community-based first response emergency care". Possible benefits for a community-based emergency care model include reduction in morbidity and mortality, the building of safer and more resilient communities, more local health knowledge and leadership, enhanced emergency response and crisis management capacity, enhanced community ownership and self-determination of health services, and economic development for remote communities [5]. In the absence of local paramedical services, the management of health emergencies depends on the capacity of lay community members. The addition of a comprehensive community-based pre-nursing station care model could reduce morbidity and mortality.

There are limitations to this study. Most of the data were based on interview responses and were not subject to verification from other community experts. Informants were responsible for up to eight First Nations communities, and this increased the challenge of accurately recalling or describing local contexts; however, many informants did take the time to research their answers. This increased the overall accuracy of the results reported, and therefore the results most likely provide a reliable assessment of local services and resources. Individual quotations may not be representative of overall trends or perceptions, but given that our respondents were legitimate representatives of a regional First Nations governance organisation, we feel that they represent credible perspectives. The passive phase of the project was conducted nearly 3 years after the active approach, so local circumstances may have changed in the intervening years; however, secondary sources did not identify any evidence that there has been improvement since the time of the interviews in 2013.

Emergency response systems, efforts, and programmes are grossly insufficient in NAN communities. As these communities operate in isolated and remote contexts, the expansion of conventional ambulance or first responder programmes may not be an appropriate nor realistic solution. Remote communities are the most vulnerable, and transformation in health care to improve equity is needed. It is therefore paramount that novel, sustainable and community-based innovations are developed, particularly those addressing pre-nursing station care. The results of this paper can empower NAN communities with the information to advocate for improved emergency services and systems, which will then result in healthier, stronger, and more resilient communities.

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Conflict of Interest

AO and DV declare a non-financial conflict of interest through their affiliation with Remote Health Initiative, a non-profit entity dedicated to enhancing care in remote settings. The remaining authors declare no conflicts of interest.

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Notes