

Original Article

The Epidemiology of Endocarditis in Manitoba: A Retrospective Study

Duncan J. Maguire, MD,^a Rakesh C. Arora, MD, FRCSC,^b Brett M. Hiebert, MSc,^c
Brenden Dufault, MSc,^d and Mullein D. Thorleifson, MD, FRCPC^a

^aDepartment of Anesthesia, Perioperative and Pain Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

^bDepartment of Surgery, Section of Cardiac Surgery, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

^cDepartment of Surgery, Max Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

^dGeorge and Fay Yee Centre for Healthcare Innovation, College of Medicine, Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

ABSTRACT

Background: Recently, anecdotal evidence suggested an increase in infective endocarditis (IE) in Manitoba driven by an increasing proportion of patients with intravenous drug use (IVDU)-associated endocarditis. This study aimed to characterize the observed changing incidence and epidemiology of IE.

Methods: This retrospective study evaluated consecutive patients >18 years old with an International Classification of Disease–10 diagnosis of IE who presented to a tertiary referral center in Winnipeg, Manitoba between January 1, 2004 and December 31, 2018. Data were obtained by individual review of paper and electronic medical records and entered into the Research Electronic Data Capture database. Mortality and hospital readmission data were acquired by linking Research Electronic Data Capture data to the Manitoba Centre for Health Policy, which prospectively maintains a comprehensive population-based health database.

Results: A total of 612 cases of IE were identified. The incidence of IE increased from 2.03 per 100,000 in 2004 to 5.16 per 100,000 in 2018, with IVDU-associated cases increasing from 0.11 to 2.87 per

RÉSUMÉ

Introduction : Des données anecdotiques récentes montraient une augmentation de l'endocardite infectieuse (EI) au Manitoba attribuable à la proportion accrue de patients atteints d'une endocardite associée à l'usage de drogues par voie intraveineuse (UDVI). La présente étude avait pour but de caractériser les changements observés dans l'incidence et l'épidémiologie de l'EI.

Méthodes : Cette étude rétrospective a permis d'évaluer les patients consécutifs > 18 ans qui avaient un diagnostic d'EI conformément à la Classification internationale des maladies, 10^e révision, et qui s'étaient présentés dans un centre d'aiguillage en soins tertiaires de Winnipeg, au Manitoba, entre le 1^{er} janvier 2004 et le 31 décembre 2018. Nous avons obtenu les données par l'examen du dossier individuel et des dossiers médicaux électroniques de la base de données *Research Electronic Data Capture*. Nous avons obtenu les données sur la mortalité et les réadmissions à l'hôpital par la liaison des données de la *Research Electronic Data Capture* au *Manitoba Centre for Health Policy*, qui maintient de manière prospective une base de données exhaustive sur la santé de la population.

Infective endocarditis (IE) is an important worldwide problem with an incidence of 3–10 per 100,000 people per year.¹ Despite aggressive therapy,¹ the associated mortality rate remains high at approximately 20% at 30 days and 40% at 1

year.^{2,3} Risk factors for IE differ between high- and low-income countries. Rheumatic heart disease is the primary risk factor in low- and middle-income countries, where patients are often young; *Streptococcal* infection is the most common cause. In higher-income countries, degenerative and congenital valve disease, implantable cardiac devices, prosthetic valves, cancer, diabetes, and intravenous drug use (IVDU) have supplanted rheumatic heart disease as the major risk factors for IE.⁴

Most information regarding IE epidemiology comes from surveys in the United States, Europe, and Australia.^{5–7} Modern-day increases in the incidence of IE and changes in the causative organisms have been described in Denmark and Norway.^{8,9} Investigators in Ontario, Canada examined rates of IE hospitalizations after changes to the American Heart Association IE prophylaxis guidelines.^{10,11} Previous studies

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Ethics Statement: This retrospective study was approved by the University of Manitoba Health Research Ethics Board (REB #HS19078(H2015:411), approved November 19, 2018) and the Manitoba Health Information Privacy Committee, and the need for specific patient consent was waived. The research reported has adhered to the relevant ethical guidelines.

Corresponding author: Dr Mullein Thorleifson, L2035-409 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada. Tel.: +1-204-296-7320; fax: +1-204-231-0425.

E-mail: mthorleifson@sbg.h.mb.ca

See page 1481 for disclosure information.

100,000. Left heart vegetations were most common in the non-IVDU group, whereas right-sided vegetations dominated in the IVDU group. All-cause mortality did not differ between IVDU and non-IVDU IE, despite a significantly younger age in patients with IVDU. The IVDU group showed a higher rate of endocarditis recurrence.

Conclusions: In this first study to examine the longitudinal incidence of IE in Manitoba, we showed that the incidence of IE has significantly increased over the last 15 years, with a contribution of IVDU-associated IE that has a high rate of mortality and disease recurrence.

from our group have reported on outcomes for IVDU with right-sided endocarditis¹² and short- and long-term outcomes for surgically and medically managed left-sided endocarditis.^{13,14} Although these analyses have clarified important disease patterns, no longitudinal epidemiologic study of IE as a whole has been performed in Manitoba.

In Manitoba, clinical experience suggests that the incidence of IE may be increasing, particularly cases associated with IVDU. The purpose of this study is to describe the longitudinal epidemiology of IE in Manitoba to determine the annual incidence of IE, with trends in culprit organisms, echocardiographic characteristics, and clinical outcomes for both IVDU and non-IVDU patients.

Methods

Data collection

This retrospective study was approved by the University of Manitoba Health Research Ethics Board (REB #HS19078(H2015:411; approved 19/11/2018) and the Manitoba Health Information Privacy Committee, and the need for specific patient consent was waived. The study evaluated consecutive patients >18 years old with a diagnosis of IE who were admitted to either of the 2 tertiary referral centers in Winnipeg, Manitoba between January 1, 2004 and December 31, 2018. Patients were identified using the International Classification of Disease (ICD)-10 diagnostic codes I33, Acute and subacute endocarditis; I38, Endocarditis valve unspecified; and I39, Endocarditis and heart valve disorders in diseases classified elsewhere. Data from January 1, 2004 until December 31, 2016 was entered into the Research Electronic Data Capture (REDCap) database by previous investigators,^{12,13} with cases from January 1, 2016 until December 31, 2018 added during this specific study. Patients with multiple presentations over the study period were included once, with subsequent presentations for the same condition documented as disease recurrence. Data from the index presentation were obtained by individual review of paper and electronic medical records and entered into the REDCap database. Because IVDU does not have a specific

Résultats : Nous avons trouvé un total de 612 cas d'EI. L'incidence de l'EI est passée de 2,03 par 100 000 en 2004 à 5,16 par 100 000 en 2018, et l'incidence des cas d'EI associée à l'UDVI, de 0,11 à 2,87 par 100 000. Les végétations du cœur gauche étaient plus fréquentes dans le groupe de patients atteints d'une EI non associée à l'UDVI, alors que les végétations du cœur droit dominaient dans le groupe de patients atteints d'une EI associée à l'UDVI. La mortalité toutes causes confondues ne différait pas entre les patients atteints d'une EI associée à l'UDVI ou non associée à l'UDVI, en dépit de l'âge significativement plus jeune des patients atteints d'une EI associée à l'UDVI. Le groupe de patients atteints d'une EI associée à l'UDVI montrait un taux plus élevé de récurrence de l'endocardite.

Conclusions : Dans cette première étude, qui portait sur l'incidence longitudinale de l'EI au Manitoba, nous avons montré que l'incidence de l'EI avait considérablement augmenté au cours des 15 dernières années, puisque l'EI associée à l'UDVI a contribué à l'augmentation du taux de mortalité et de récurrence de la maladie.

ICD code, cases were identified through manual review of the patient charts that documented active or past IVDU, and both current and previous use resulted in inclusion in the IVDU cohort. Microbiologic data were obtained through the provincial microbiology laboratory service. The culprit organism was determined by review of relevant blood cultures. Transthoracic echocardiography was performed as part of the diagnostic process in 93.4% of patients; 29.4% of patients underwent diagnostic transesophageal echocardiography. All transthoracic and transesophageal echocardiography reports were reviewed. Left ventricular function, valve involvement, vegetation size, presence of an abscess, and any new valvular lesions were recorded.

Outcome data

Long-term mortality and hospital readmission data over 5 years were acquired by merging the REDCap data with the Manitoba Centre for Health Policy (MCHP) database. The MCHP is a not-for-profit research collaborator that prospectively maintains a comprehensive, population-based health-related database at the University of Manitoba. Annual age and gender-adjusted Manitoba population estimates for each period were obtained from the Manitoba Bureau of Statistics. The 2 tertiary care hospitals studied are the only centres that provided dedicated cardiac care during the study period; thus, the annual population of Manitoba was used as the denominator for the population incidence. Non-Manitoba residents were excluded from analysis.

Statistical analysis

Both descriptive and inferential statistical analyses were performed. Baseline characteristics of the study cohort were summarized using medians and interquartile ranges for continuous variables and percentages for categorical variables. The incidence of IE is reported as new cases per 100,000 people per year. Using R version 3.6.2 (Vienna, Austria), a Poisson regression model was used to test for linear trends in incidence over time. Differences in the distribution of culprit organisms between IVDU and non-IVDU were assessed using a Pearson χ^2 test. Individual microorganisms were compared using Bonferroni-adjusted *P* values. An analysis of variance

Table 1. Demographics of patients presenting to tertiary care centres in Manitoba with infective endocarditis from 2004-2018

Characteristic	Total n = 612 (%)	Non-IVDU n = 505 (%)	IVDU n = 107 (%)	P value
Female	221 (34)	158 (31)	43 (41)	< 0.0001
Congestive heart failure	159 (25.9)	126 (24)	33 (30)	< 0.0001
Type 2 diabetes mellitus	157 (25.6)	148 (37)	9 (10)	< 0.0001
Hypertension	276 (45)	270 (65)	6 (7)	< 0.0001
Smoker	146 (23.8)	75 (22)	73 (82)	< 0.0001
Intravenous drug use	107 (17.5)	0	107	< 0.0001
COPD	43 (7)	40 (12)	3 (4)	—
Asthma	31 (5.1)	22 (9)	9 (11)	0.025
Peripheral vascular disease	51 (8.3)	48 (14)	3 (4)	0.663
Dialysis	53 (8.6)	48 (14)	5 (6)	0.005
Immunosuppressive therapy	42 (6.9)	41 (12)	1 (1)	0.063
Indwelling catheter	29 (4.7)	28 (10)	1 (1)	0.001
Recent invasive procedure	94 (15.3)	88 (28)	6 (7)	< 0.0001

COPD, chronic obstructive pulmonary disease; IVDU, intravenous drug use.

test was used to compare the mean age between patients with IVDU-associated endocarditis and those without.

Kaplan Meier survival curves were generated to visualize unadjusted survival rates for both IVDU- and non-IVDU-associated IE. These cohorts were also stratified by those who were surgically treated vs medically managed. Corresponding Log-Rank tests were performed to compare respective study cohorts. Cumulative incidence curves were also generated to visualize hospital readmission rates stratified by similar cohorts for (1) recurrent or incessant endocarditis, (2) major bleeding, and (3) major adverse events (heart failure, stroke, or endocarditis) considering mortality as a competing risk. These cumulative incidence curves were compared using a Gray's test. Univariable and multivariable Cox proportional hazards regression models were generated to identify patient factors independently associated with time to survival and recurrent endocarditis. Multivariable regression models were generated using a stepwise selection process for survival time ($P < 0.05$ for entry; $P > 0.05$ for removal), and for recurrent endocarditis, all factors with a $P < 0.05$ were included in the final model. Statistical analyses of clinical outcome data were performed using SAS version 9.4.

Results

Endocarditis incidence

A total of 612 consecutive cases of IE were identified during the period of study. Population characteristics are reported in Table 1. The mean (\pm standard deviation) patient age was 56 ± 18 years, 221 (36%) were women, and 292 (48%) of cases were managed surgically. Important IE risk factors captured were hemodialysis, immunosuppression, indwelling catheter, recent invasive procedure, and IVDU. The incidence of IE increased from 2.03 per 100,000 in 2004 to 5.16 per 100,000 in 2018, with IVDU-associated cases making up a greater proportion of total cases in recent years (Fig. 1). The annual incidence of IVDU-associated IE increased from 0.11 per 100,000 to 2.87 per 100,000 over the study period. Incidence in the non-IVDU group was 1.91 per 100,000 in 2004 and increased to 2.29 per 100,000 in 2018. Over time, there is a significant increase in IE, with the increase driven entirely by IVDU-

associated IE. Overall, there is a no change in the incidence of non-IVDU-associated IE over the entire study period ($P = 0.1$), but the increase in IVDU-associated IE is significant ($P < 0.0001$). In the IVDU-associated IE group, the average age at presentation is significantly younger (Fig. 2).

Culprit organisms

Blood culture, tissue culture from surgical specimens, or 16sRNA sequencing was positive in 502 (82%) of cases, with the remaining 110 (18%) cases representing culture-negative endocarditis. Among the culture positive cases, *Staphylococcus aureus* was the most commonly isolated organism (190 cases; 37.8%), of which 37 of 190 (19.5%) represented methicillin-resistant *S aureus* (MRSA). Other commonly isolated organisms included *Streptococci* in 128 (25.5%), *Enterococci* in 65 (12.9%), and coagulase-negative *Staphylococcus* (CoNS) in 34 (6.8%) cases. Table 2 reports the frequency of the culprit organisms for both non-IVDU and IVDU patients. The distribution between culprit organisms was different for IVDU compared with non-IVDU ($P < 0.0001$). There was a higher rate of MRSA in the IVDU-associated IE group—21 (20.6%) vs 37 (7.4%) ($P < 0.0001$). Figure 3 shows the change in culprit organism over time and indicates *S aureus* (including MRSA) has become more prevalent in recent years.

Echocardiographic findings

Endocarditis was shown by presence of vegetations in 574 (93.8%) patients (473 native-valve and 101 prosthetic-valve). Distribution of the affected valves is shown in Table 3. Left-sided vegetations were most common in the non-IVDU group ($n = 395$; 84.4%), whereas right-sided vegetations predominated in the IVDU group ($n = 57$; 53.8%). Vegetation size was documented as > 1 cm in 67 (63.2%) of 106 IVDU cases compared with 189 (40.4%) of 468 non-IVDU cases. Moderate-to-severe or severe valvular regurgitation was present in 224 (47.9%) of the non-IVDU group and 60 (56.6%) of the IVDU group. Transesophageal echocardiography (TEE) was uncommonly performed (180 patients; 29.4% of the entire cohort) and even more seldom in IVDU-associated IE (20 patients; 18.7%). Forty percent of the patients who

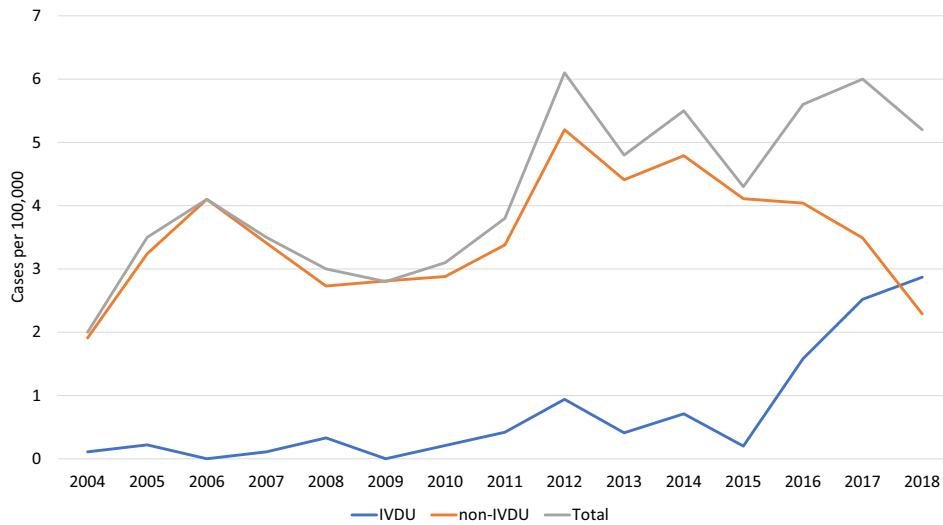


Figure 1. Province-wide annual incidence of infective endocarditis in Manitoba. The overall annual incidence of infective endocarditis in Manitoba has trended upward over the study period, with an increase in intravenous drug use (IVDU)-associated endocarditis. By 2018, IVDU-associated cases exceeded non-IVDU associated cases.

went on to have a surgical intervention had a TEE performed as opposed to only 23% of the patients who were medically treated ($P = 0.000027$).

Clinical outcomes

Clinical outcome data were assessed using the MCHP database was exported to the MCHP system resulting in a match for 526 of 612 patients (86%). The remaining 86 patients had a hospital identification number that could not be paired. Survival rate in the IVDU group was 83.3% (95% confidence interval [CI], 74.2 to 89.4) at 30 days, decreasing to 62.5% (95% CI, 49.8 to 72.8) by 5 years, and in the

non-IVDU group survival at 30 days was 82.6% (95% CI, 78.6 to 85.8) decreasing to 52.8% (95% CI, 47.6 to 57.6) by 5 years (Fig. 4). There was no significant difference in survival between the 2 groups ($P = 0.37$). We also compared all-cause mortality in the IVDU vs non-IVDU cohort based on whether they received medical or surgical treatment during the course of their care (Fig. 5). In the IVDU group, survival rate at 30 days was 92.9% (95% CI, 74.3 to 98.2) in surgically treated patients compared with 79.4% (95% CI, 67.7 to 87.3) in medically treated patients. However, despite an initial separation, there was no difference in overall long-term survival between surgically and medically treated patients ($P =$

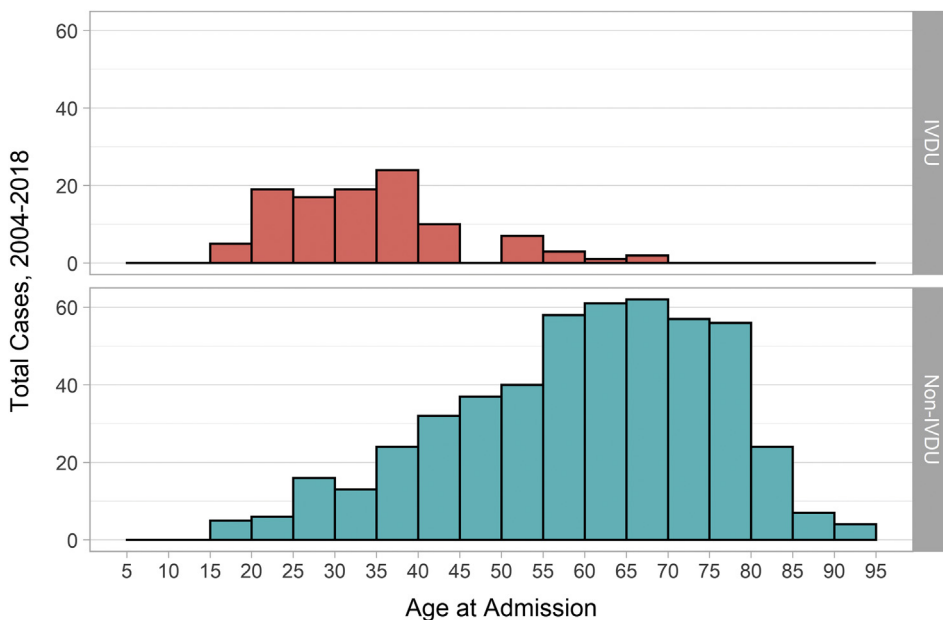


Figure 2. Patient age at presentation to a tertiary care centre in Manitoba with a diagnosis of infective endocarditis. Those patients with a comorbid history of intravenous drug use (IVDU) were significantly younger than those without.

Table 2. Culprit organisms identified in patients with infective endocarditis

Organism	Total n = 502 (%)	Non-IVDU n = 400 (%)	IVDU n = 102 (%)	P value
MSSA	153 (30.5)	103 (25.8)	50 (49.0)	< 0.00001
MRSA	37 (7.4)	16 (4.0)	21 (20.6)	< 0.00001
CoNS	34 (6.8)	33 (8.3)	1 (1.0)	0.00168
Enterococcus	65 (12.9)	61 (15.3)	4 (3.9)	0.00235
Streptococcus species	128 (25.5)	121 (30.2)	7 (6.9)	< 0.00001
Polymicrobial*	46 (9.2)	32 (8.0)	14 (13.7)	0.0736
Candida species	6 (1.2)	3 (0.8)	3 (2.9)	0.069097
HACEK	8 (1.6)	8 (2.0)	0 (0.0)	0.369
Other	25 (5.0)	23 (5.8)	2 (2.0)	0.116329

CoNS, coagulase-negative *Staphylococcus*; HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* species; IVDU, intravenous drug use; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

*Two or more microorganisms.

0.93). In the non-IVDU cohort medical management was associated with much poorer survival than surgical management, primarily manifested by significant early mortality in this group. The cumulative incidence of major adverse events was significantly higher in the IVDU group (Gray’s test; $P < 0.001$; Fig. 6). Recurrent or incessant endocarditis requiring hospitalization was investigated using cumulative incidence curves comparing the IVDU and non-IVDU groups (Fig. 7). The IVDU group showed a significantly higher rate of disease recidivism (Gray’s test; $P < 0.001$).

The older, non-IVDU-associated endocarditis group had increased comorbid illness, of which peripheral vascular disease and renal failure were risk factors for mortality. Increasing age, medical management, and prosthetic valve endocarditis also conferred an increased risk of mortality in multivariate analysis (Table 4). Those treated medically were more likely to have recurrent hospital admissions for endocarditis. In the IVDU-associated group, with fewer comorbid illnesses, both smoking and renal failure were associated with increased mortality (Table 5) as well as infection with CoNS. The risk of recurrent endocarditis was increased in those patients in

whom CoNS were isolated in blood or tissue cultures. Although only 2 patients had CoNS identified as a culprit organism (one as a sole organism and one as part of a polymicrobial infection), it was ultimately found to be statistically significant with a very high effect size (but a wide CI) in the multivariable model. Recurrent admission for endocarditis was more common in those patients with a history of IVDU who had a nonintraoperative TEE (Table 5). Multivariate analysis of all patients presenting with endocarditis finds that a history of IVDU is an independent predictor of both mortality and recurrent or incessant endocarditis (Table 6).

Discussion

This is the first longitudinal study to characterize the incidence and epidemiology of IE in the province of Manitoba spanning a 15-year period. A review of 612 consecutive IE patients showed an annual increase in the incidence of IE in Manitoba. In particular, cases related to IVDU have increased dramatically in the more recent years. Despite a younger age at presentation, the patients with IVDU-associated IE have

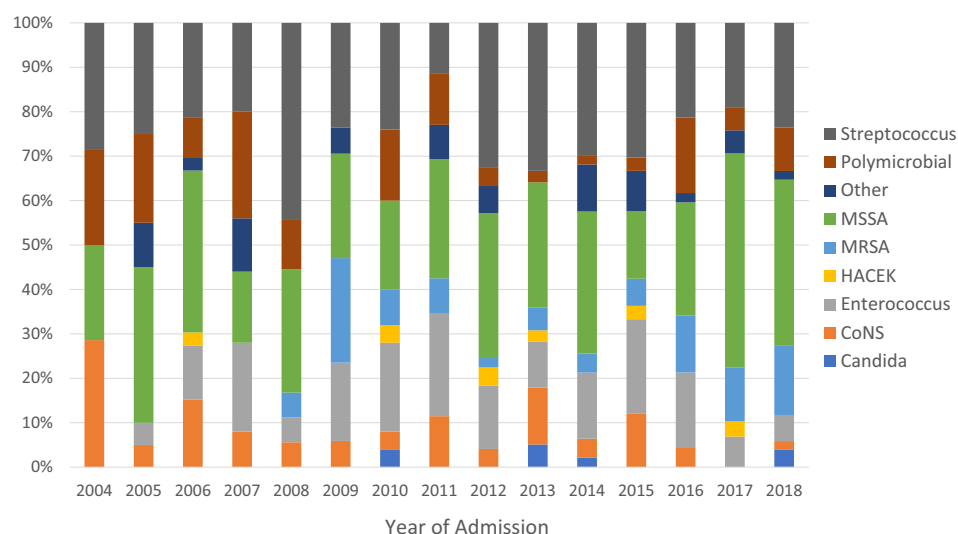


Figure 3. Culprit organisms, as a percentage of total cases with a culprit organism identified, over time. Trends in culprit organisms over time show an increasing number of presentations with *Staphylococcus aureus*. Although methicillin-sensitive *S. aureus* (MSSA) accounts for a larger number of cases, those cases in which methicillin-resistant *S. aureus* (MRSA) was identified as the culprit organism are also increasing. CoNS, coagulase negative *Staphylococcus*; HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* species; IVDU, intravenous drug use. Polymicrobial refers to 2 or more microorganisms.

Table 3. Echocardiographic findings in patients with infective endocarditis

Echocardiographic features	Total (n = 574)	Non-IVDU (n = 468)	IVDU (n = 106)	P value
Ejection fraction, mean (%)	55	55	59	0.01
Aortic (bicuspid)	45 (7.8)	42 (9.0)	3 (2.8)	0.033586
Aortic (tricuspid)	185 (32.2)	167 (35.7)	18 (17.0)	0.000199
Mitral	175 (30.5)	160 (34.2)	15 (14.2)	0.000052
Tricuspid	88 (15.3)	32 (6.8)	56 (52.8)	< 0.00001
Pulmonic	3 (0.5)	2 (0.4)	1 (0.9)	0.505835
Multiple	41 (7.1)	32 (6.8)	9 (8.5)	0.550724
		(26 exclusively left sided)	(2 exclusively left sided)	
ICD/permanent pacemaker*	7 (1.2)	6 (1.3)	1 (0.9)	0.77423
Transesophageal echocardiography performed	180 (29.4)	160 (31.9)	20 (18.7)	0.007381
Vegetation >1cm	256 (44.6)	189 (40.4)	67 (63.2)	0.00002
Moderate-to-severe valvular regurgitation	284 (49.5)	224 (47.9)	60 (56.6)	0.104116
Prosthetic valve endocarditis	101 (17.6)	96 (20.5)	5 (4.7)	0.000115
Abscess	53 (9.2)	48 (10.3)	5 (4.7)	0.075264

ICD, Implantable cardioverter defibrillator; IVDU, intravenous drug use.

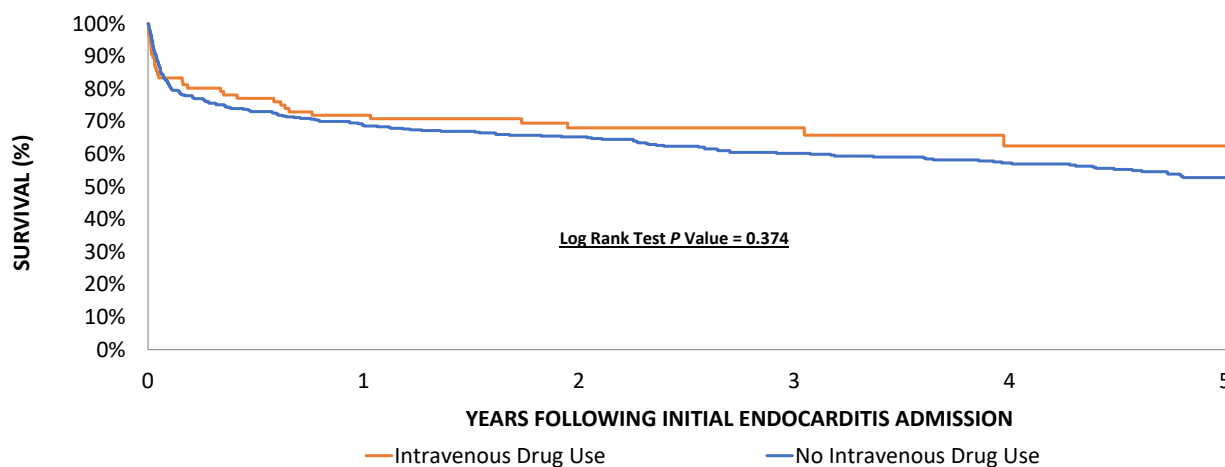
* Represents those patients with concomitant echocardiographically visible device infections and valvular endocarditis.

similar mortality to the non-IVDU cohort and higher rates of disease recurrence. The apparent decrease in non-IVDU-associated IE in the period from 2015 to 2018 was an unanticipated finding and is a clear area for future study.

Infective endocarditis is a complex disease process with evolving regional and temporal trends. Accurate diagnosis and effective therapy require contemporary understanding of the local epidemiology of IE. This study provides current data on patient population, culprit organisms, echocardiographic findings, and clinical outcomes in Manitoba. The incidence of *S aureus* (methicillin-sensitive *S aureus* and MRSA) IE increased over the study period, especially in those with

IVDU. Left-sided valve lesions were more common for the cohort as a whole, although right-sided vegetations predominated in the IVDU group.

Overall, the use of preoperative TEE (Table 3) was substantially lower than has been reported in other investigations¹⁵; given the well-established benefits of TEE over TTE, the existing local practice should be evaluated.^{16,17} The local practice in Winnipeg is limited by scarce physical space, funding, and nursing resources; thus, a system in which only patients for whom clinical utility is deemed high are referred and with a reliance on intraoperative TEE performed in surgical patients by the cardiac anesthesia group. The

Kaplan Meier Curve: All Cause Mortality

Cohort	30 Day		1 Year		3 Years		5 Years	
	At Risk	Rate (95% CI)	At Risk	Rate (95% CI)	At Risk	Rate (95% CI)	At Risk	Rate (95% CI)
Intravenous Drug Use (N=96)	80	83.3% (74.2% - 89.4%)	68	71.9% (61.7% - 79.8%)	31	68.0% (57.5% - 76.5%)	17	62.5% (49.8% - 72.8%)
No Intravenous Drug Use (N=431)	356	82.6% (78.6% - 85.8%)	295	68.8% (64.2% - 73.0%)	216	60.2% (55.3% - 64.7%)	144	52.8% (47.6% - 57.6%)

Figure 4. Kaplan Meier curve for all-cause mortality. Despite a younger age at presentation, the intravenous drug-use associated endocarditis cohort has a similar long-term mortality. CI, confidence interval.

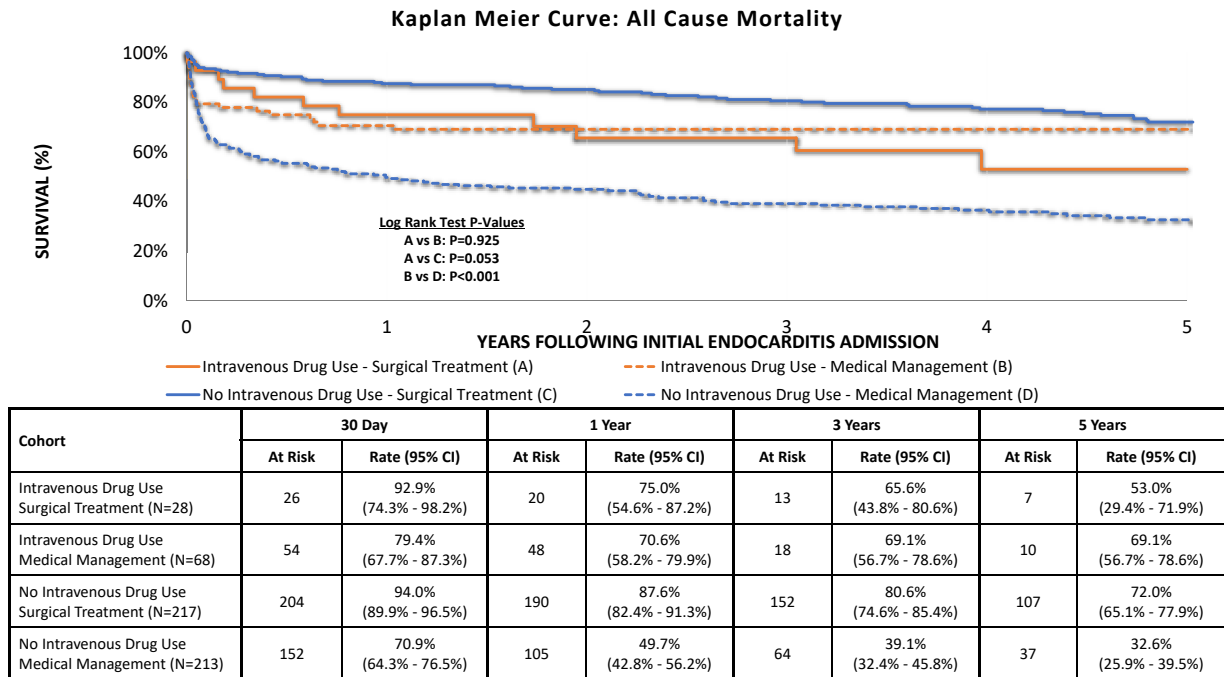


Figure 5. Kaplan Meier curve for all-cause mortality in cases managed medically vs surgically. In the non-intravenous drug use-associated endocarditis cohort, the mortality rate is significantly higher in the medically managed group than those surgically managed. This may reflect selection of patients expected to benefit from surgical intervention. CI, confidence interval.

association of TEE with disease recurrence is likely related to selection bias (patients with more severe disease are more likely to receive the test), as a causal relationship is not mechanistically plausible. There was a greater proportion of patients surgically treated who had a TEE, which may relate

to discovery of surgical disease. Alternatively, this observation could be explained by a selective practice of performing TEE only when there is a high index of suspicion of unrecognized or unconfirmed surgical disease in appropriate surgical candidates.

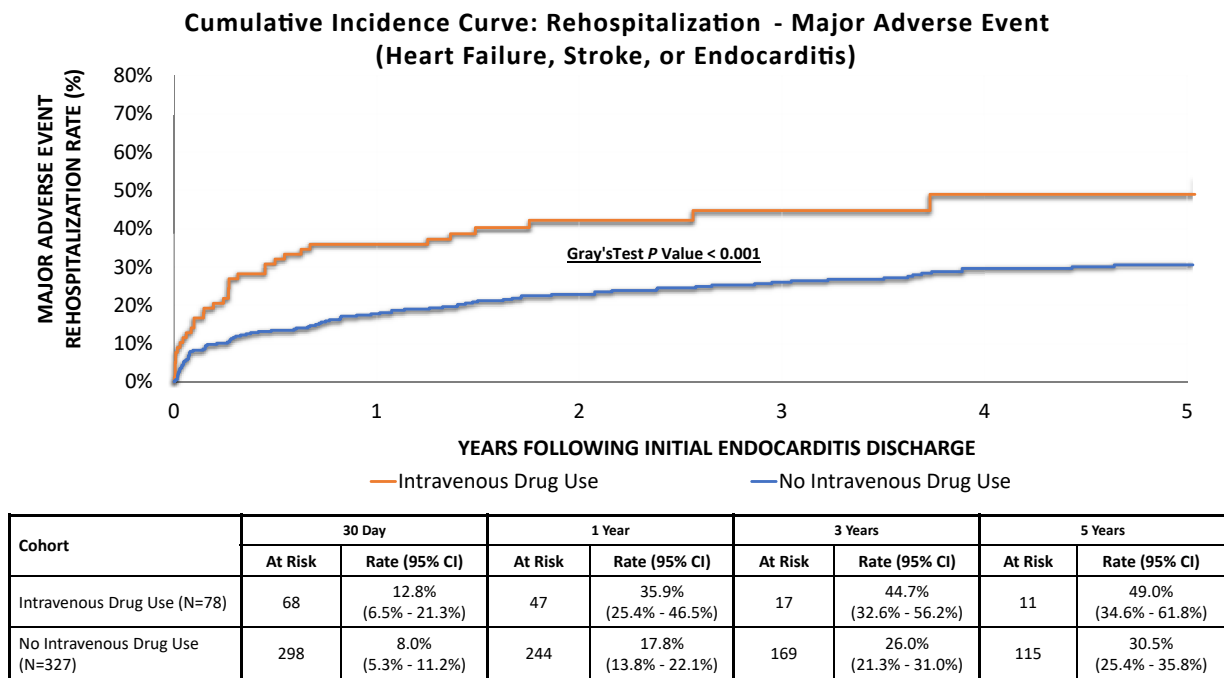
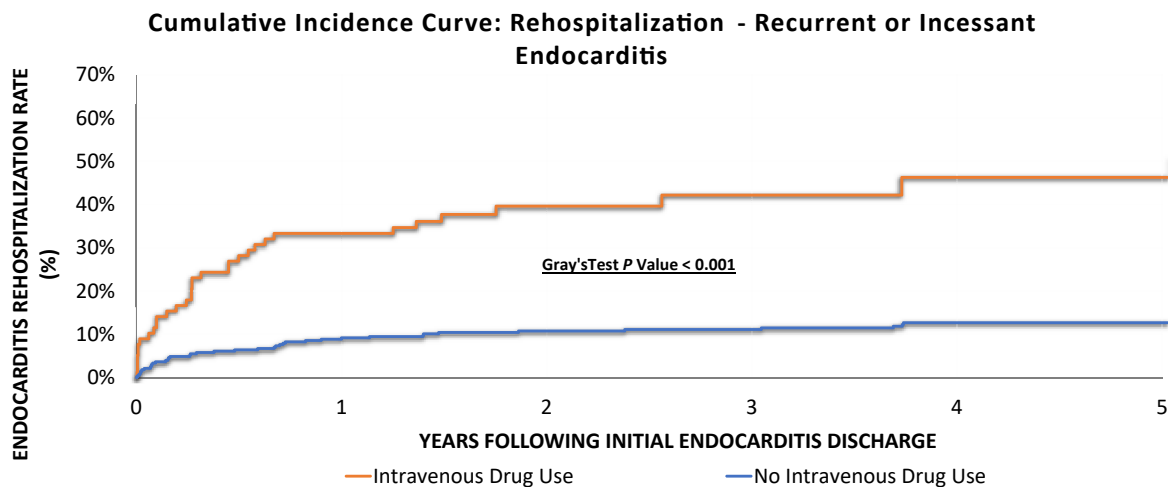


Figure 6. Cumulative incidence of rehospitalization for major adverse events (heart failure, stroke, or endocarditis). The intravenous drug use-associated endocarditis cohort experienced a greater burden of major adverse events requiring rehospitalization. CI, confidence interval.



Cohort	30 Day		1 Year		3 Years		5 Years	
	At Risk	Rate (95% CI)	At Risk	Rate (95% CI)	At Risk	Rate (95% CI)	At Risk	Rate (95% CI)
Intravenous Drug Use (N=78)	70	10.3% (4.8% - 18.2%)	49	33.3% (23.1% - 43.9%)	18	42.2% (30.2% - 53.7%)	11	46.3% (32.3% - 59.1%)
No Intravenous Drug Use (N=327)	312	3.4% (1.8% - 5.7%)	267	9.2% (6.4% - 12.6%)	196	11.1% (8.0% - 14.8%)	132	12.7% (9.3% - 16.7%)

Figure 7. Cumulative incidence of hospital readmission for endocarditis. The intravenous drug use–associated endocarditis group experienced a significantly higher rate of recurrent or incessant endocarditis requiring admission to hospital. CI, confidence interval.

Table 4. Multivariable proportional hazard regression for mortality and recurrent hospital admission for endocarditis in patients with no history of intravenous drug use

Characteristic	Mortality*		Recurrent hospital admission for endocarditis†	
	HR (95% CI)	P value	HR (95% CI)	P value
Demographics				
Age	1.03 (1.02-1.04)	< 0.001		
Sex (male vs female)				
Comorbidities				
Hypertension				
Type II diabetes				
Hypercholesterolemia				
Current smoker				
Smoking history				
COPD				
Peripheral vascular disease	1.61 (1.09-2.38)	0.017		
Renal failure	2.58 (1.85-3.59)	< 0.001		
Dialysis				
Cerebrovascular accident				
Prior endocarditis				
Medical vs surgical treatment	3.36 (2.44-4.63)	< 0.001	2.27 (1.26 - 4.10)	0.007
Organisms				
<i>Streptococcus viridans</i> group				
<i>Streptococcus</i> spp.				
Group G and group C <i>streptococcus</i>				
Coagulase-negative <i>Staphylococci</i>				
MRSA				
MSSA				
Culture-negative endocarditis				
Enterococcus spp.				
Other				
Transesophageal echocardiogram				
Moderate-to-severe regurgitation				
Multiple organisms				
Prosthetic valve endocarditis	1.39 (1.01-1.92)	0.045		

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

* Model selected using stepwise selection ($P < 0.05$ entry; $P > 0.05$ removal); Listwise deletion was applied to final multivariable model.

† Model includes all variables with $P < 0.05$ in univariable analysis; Listwise deletion was applied to final multivariable model.

Table 5. Multivariable proportional hazard regression for mortality and recurrent hospital admission for endocarditis in patients with a history of intravenous drug use

Characteristic	Mortality*		Recurrent hospital admission for endocarditis†	
	HR (95% CI)	P value	HR (95% CI)	P value
Demographics				
Age				
Sex (Male vs female)				
Comorbidities				
Hypertension				
Type II diabetes				
Hypercholesterolemia				
Current smoker				
Smoking history	2.99 (1.27-7.06)	0.012		
COPD				
Peripheral vascular disease				
Renal failure	4.33 (1.74-10.77)	0.002		
Dialysis				
Cerebrovascular accident				
Prior endocarditis				
Medical vs surgical treatment				
Organisms				
<i>Streptococcus viridans</i> group				
<i>Streptococcus</i> spp.				
Group G and group C <i>Streptococcus</i>				
Coagulase-negative <i>Staphylococci</i>	5.04 (1.16-21.91)	0.031	3.85 (2.41-6.18)	< 0.001
MRSA				
MSSA				
Culture-negative endocarditis				
<i>Enterococcus</i> spp.				
Other				
Transesophageal echocardiogram			2.40 (1.06-5.46)	0.037
Moderate-to-severe regurgitation				
Multiple organisms				
Prosthetic valve endocarditis				

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

* Model selected using stepwise selection ($P < 0.05$ entry; $P > 0.05$ removal); Listwise deletion was applied to final multivariable model.

† Model includes all variables with $P < 0.05$ in univariable analysis; Listwise deletion was applied to final multivariable model.

An important observation was that survival was not different between IVDU and non-IVDU groups for the index procedure despite a younger patient population (average age, 35 years) in the IVDU- vs non-IVDU- (60 years) associated IE. This finding may reflect the unique comorbidities, psychosocial factors, and/or surgical technical factors associated with IVDU-associated IE.¹⁸ A recent multicentre study by Pericàs et al¹⁹ found a decreased mortality rate in persons who inject drugs than in those who did not, with a comparable distribution of affected valves. This finding speaks to the need for specialized care for these patients in our province. Furthermore, the Pericàs study does not describe the presence of rheumatic heart disease, which predominantly affects left-sided valves and remains a major predisposing factor for IE worldwide.¹⁹

Medical vs surgical management for IVDU-associated IE was not associated with a difference in overall survival, although this does not account for potential underlying differences in the groups. For example, patients with a surgical indication may have presented with more severe disease than those in the medical group. In the non-IVDU-associated cohort, medical management was associated with significantly higher mortality than surgical management particularly early in the clinical course, and this may reflect selection of patients expected to benefit from surgical

intervention. Nonetheless, the IVDU group was associated with a significantly higher incidence of major adverse events and recurrent IE, thus highlighting the need for interdisciplinary management regardless of treatment strategy, including the need for treatment of the addiction as a component of the disease.¹⁸ Few risk factors aside from intravenous use of drugs significantly affect survival or recurrent admissions for endocarditis in this group, and when all patient with endocarditis are examined, IVDU alone confers an increased risk of both mortality and recurrent admissions for endocarditis. This finding suggests the focus of prevention of disease might best target the treatment of substance misuse and the promotion of safe injection techniques.

Historically, CoNS was believed to be nonpathogenic which may lead to incomplete or delayed treatment in patients with blood cultures positive for CoNS; however, recent research supports CoNS as a causative agent, especially in the presence of prosthetic material, and has been reported to be the culprit organism in IE in up to 8% of native valve endocarditis presentations.²⁰ Our finding of CoNS as a significant predictor of recurrent admission is interesting; however, given the very small number of affected patients, more research would be warranted to determine whether a true association exists.

Table 6. Multivariable proportional hazard regression for mortality and recurrent hospital admission for endocarditis in all patients with infective endocarditis

Characteristic	Mortality*		Recurrent hospital admission for endocarditis†	
	HR (95% CI)	P value	HR (95% CI)	P value
Demographics				
Age	1.03 (1.02-1.04)	< 0.001	1.00 (0.98-1.02)	0.959
Sex (Male vs female)				
Intravenous drug use	1.89 (1.18-3.01)	0.008	2.86 (1.41-5.79)	0.004
Comorbidities				
Hypertension			0.93 (0.55-1.57)	0.792
Type II diabetes				
Hypercholesterolemia			1.05 (0.53-2.05)	0.896
Current smoker			1.10 (0.66-1.85)	0.707
Smoking history				
COPD				
Peripheral vascular disease	1.58 (1.08-2.30)	0.019		
Renal failure	2.70 (1.98-3.69)	< 0.001		
Dialysis				
Cerebrovascular accident				
Prior endocarditis				
Medical vs surgical treatment	2.95 (2.19-3.98)	< 0.001	1.69 (0.99-2.89)	0.055
Organisms				
<i>Streptococcus viridans</i> group				
<i>Streptococcus</i> spp.				
Group G and group C <i>Streptococcus</i>				
Coagulase-negative <i>Staphylococci</i>				
MRSA			0.94 (0.40-2.21)	0.895
MSSA			1.07 (0.61-1.88)	0.814
Culture-negative endocarditis				
<i>Enterococcus</i> spp.				
Other				
Transesophageal echocardiography				
Moderate-to-severe regurgitation				
Multiple organisms			1.72 (0.97-3.06)	0.063
Prosthetic valve endocarditis	1.45 (1.06-1.99)	0.019		

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

* Model selected using stepwise selection ($P < 0.05$ entry; $P > 0.05$ removal); listwise deletion was applied to final multivariable model.

† Model includes all variables with $P < 0.05$ in univariable analysis; listwise deletion was applied to final multivariable model.

The clinical outcome data reinforce our impression of IE as a disease with high morbidity and mortality despite modern therapy. Additionally, it shows the long-term impact of IE on patients and the health care system. The high rate of mortality and disease recurrence in the IVDU population emphasize the need for improved efforts in preventative and harm reduction strategies. Manitoba has existing strategies including provision of safe injection equipment but currently is not funded for other evidence-based approaches including supervised injection sites. The observed comparable survival for both medically and surgically managed IVDU-associated IE, along with the high rate of recurrence, may have treatment implications and requires further investigation. Controversy exists around the appropriate management of IVDU-associated endocarditis; however, no evidence exists to suggest we should manage patients who inject drugs with endocarditis differently than those who do not.²¹ Medical care for comorbid illnesses that contribute to the morbidity and mortality of endocarditis should be provided, and this includes management of substance use disorder. Important considerations for provision of patient care include avoidance of stigmatization of this patient population, harm reduction strategies to reduce recurrence of endocarditis, and employment of best clinical practices to all patients presenting with endocarditis.²¹

Limitations

This was a retrospective observational study and is subject to the usual limitations inherent with this design. In particular, the accuracy of our calculated incidence relies on appropriate referral and admission of all IE cases to tertiary care centres in Winnipeg. Cases managed exclusively in rural or community hospitals without referral to a tertiary care hospital are not captured and therefore would lead us to underestimate the true incidence; however, cardiac diagnostics and care have been centralized at the 2 studied tertiary care centres in Winnipeg from 2004-2012 and at one hospital since 2012. Similarly, this study relies on appropriate ICD coding of IE cases and could lead to an underestimation of the incidence. Further, although the clinical data set was designed to study IE patients, it was not created a priori with this particular study in mind. As such, this database did not capture certain information that would have been of interest, for example, the presence of coexisting blood-borne infection in IVDU patients. A limitation of our retrospective database includes the inability to capture treatment failure (ie, incessant IE) for either native or prosthetic valve endocarditis as separate from recurrent endocarditis. We plan to collect this information prospectively for a future analysis.

The use of the MCHP database for longer-term outcomes limits the patients examined to Manitoba residents, and inconsistencies in patient identification techniques resulted in incomplete data linkage. However, data linkage was relatively high for identified cases (86%). It is unclear why these patients could not be matched, and because our clinical outcome data are dependent on matching to the MCHP data outcome, differences can not be determined between those who are matched and those who are not.

Not all patients had a diagnostic echocardiogram documented. This finding reflects a combination of both clinical diagnoses only (ie, Duke criteria) and the nature of cardiac care in Manitoba prior to centralization at the current cardiac care centre. The process of care prior to centralization has meant that some patients may have had a TTE at a different site before transfer to a cardiac centre for definitive treatment, and these studies would not have been available for analysis for our database. Others may have been treated for clinical endocarditis at one of the tertiary care centres but not referred for TTE.

Increased rates of diagnostic testing (such as echocardiography) and completeness of ICD coding over time may result in increased diagnostic rate and reporting of IE without an increase in the true incidence.

Conclusions

We report an increasing provincial incidence of IE, recently driven by disease associated with IVDU. A high level of morbidity and mortality associated with IE in Manitoba was observed. It is anticipated that demonstrating a dramatic increase in the incidence of IE driven by cases associated with IVDU will facilitate interdisciplinary care strategies and public policy discussions directed at mitigating the harms of injection drug use.

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Disclosures

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