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Trends in Hospitalizations for Serious Infections Among People With Opioid Use Disorder in Ontario, Canada

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Objectives: Opioid use among people who inject drugs can lead to serious complications, including infections. We sought to study trends in rates of these complications among people with an opioid use disorder (OUD) and the sequelae of those hospitalizations.

Methods: We analyzed all inpatient hospitalizations for serious infections (infective endocarditis [IE], spinal infections, nonvertebral bone infections, and skin or soft tissue infections) among people with OUD in Ontario between 2013 and 2019. We reported the population-adjusted rate of hospitalizations for serious infections annually, stratified by type of infection and prevalence of prior opioid agonist therapy and hydromorphone prescribing. We reported characteristics of hospitalizations and 30-day mortality in the most recent 2 years.

Results: Among people with OUD there was a 167% increase in rates of IE (7.7–20.6 per million residents; $P < 0.01$), a 394% increase in rates of spinal infections (3.4–16.8 per million residents; $P < 0.01$), a 191% increase in rates of nonvertebral bone infections (8.9 to 25.9 per million residents; $P < 0.01$), and a 147% increase in infections of the skin or soft tissue (32.1–79.4 per million residents; $P < 0.01$) over 7 years in Ontario. Death in-hospital and within 30 days of discharge was highest among those with IE (11.5% and 15.9%, respectively), and lower among those with other infections (<5%).

Conclusions: Rates of serious infections among people with OUD are rising, placing a significant burden on patients. These findings suggest that early intervention and treatment of infections in this population are needed to prevent downstream harm.

Key Words: health services utilization, infections, opioid use disorder

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Despite increased public awareness, the Canadian overdose crisis continues to grow, due largely to opioid use from the unregulated (often called "illicit") drug supply.[1–3] In Ontario, Canada's largest province, the rate of emergency department (ED) visits for opioid toxicity more than doubled from 2015 to 2019 (26.3–71.6 ED visits per 100,000 Ontario residents)[4] and the rate of opioid-related mortality increased by 94% over this time.[4] These recent trends have been driven by the increased prevalence of fentanyl and other synthetic opioids in the unregulated drug supply, with fentanyl and fentanyl analogs contributing to 76% of opioid-related deaths in Ontario from July 2017 to June 2018 in Ontario.[4]

In addition to the risks of overdose, opioid use among people who inject drugs (PWID) can lead to serious complications, including infective endocarditis (IE) and other invasive infections (eg, osteomyelitis, cellulitis, discitis, epidural abscess, necrotizing fasciitis, sepsis) due to bacterial

bloodstream contamination.[5–16] IE and other invasive infections pose significant risks to the patient and place a burden on the healthcare system, as they are associated with significant morbidity, mortality, and increased hospital readmission after an overdose.[17–19] Data from 2011 to 2017 has demonstrated a significant increase in rates of IE and invasive infections among PWID in Canada and the United States.[4,9,11–14,20] In 2015, the annual incidence of deep tissue infections among Ontarians treated with opioid agonist therapy (OAT) was estimated to be 11.6 per 1000 population for IE, 3.1 per 1000 population for osteomyelitis, and 2.7 per 1000 population for septic arthritis, with the highest prevalence among patients living in southern urban locations in the lowest income group.[11]

People at risk of overdose or infections may access treatment for an opioid use disorder (OUD) (eg, OAT) or, increasingly, may be prescribed a pharmaceutical opioid as a safer alternative to the unregulated street supply. Safer supply prescribing is typically provided as daily-dispensed immediate release hydromorphone[21,22] because data has demonstrated a significant association between IE and controlled-release (CR) hydromorphone use (3.9% vs 1.1% for non-hydromorphone opioids, $P < 0.01$).[14] One hypothesis is that this is a consequence of enhanced *Staphylococcus aureus* survival due to the expedients in the CR hydromorphone formulation when dissolved for injection.[5,10,14]

Although it is evident that the rates of invasive infections among PWID in Ontario are rising, there is a lack of data describing trends of opioid-related IE and other infections from 2016 onwards, a period that has seen dramatic increases in opioid-related overdoses.[9,13,14,16] This is an important gap in the literature as the drivers of opioid overdoses have changed considerably since this time, notably due to increasing prevalence of illicitly manufactured fentanyl in the unregulated drug supply.[3–5,10,14,23–27] Therefore, we sought to study the recent trends in rates of hospitalizations for IE and other serious infections among people with an OUD, a population with high likelihood of injection drug use, and the sequelae of those hospitalizations in Ontario, Canada.

METHODS

Setting and Design

We conducted a population-based repeated cross-sectional analysis of all inpatient hospitalizations for serious infections including IE, spinal infections (vertebral osteomyelitis, discitis, epidural abscess), nonvertebral bone infections (nonvertebral osteomyelitis or septic arthritis), and skin or soft tissue infections (cellulitis, necrotizing fasciitis, cutaneous abscess) among people with OUD in Ontario between January 1, 2013 and December 31, 2019.

Data Sources

We used the Canadian Institute for Health Information's Discharge Abstract Database and the National Ambulatory Care Reporting System to identify diagnoses and procedures during inpatient hospital admissions and ED visits, respectively. We used the Narcotics Monitoring System to capture all outpatient opioid dispensing of hydromorphone and medications for OAT (methadone, buprenorphine/naloxone, or daily dispensed Kadian or M-Eslon), and the Ontario Drug Benefit database to capture dispensing of publicly-funded medications used to treat hepatitis C. Finally, we used the Ontario Health Insurance Plan database to capture all physician services, and the Ontario Health Insurance Plan Registered Persons Database to describe demographic characteristics of the cohort. These datasets were linked using unique encoded identifiers and analyzed at ICES. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

Cohort Definition

We adapted definitions from previously published studies[18,31–33] to define inpatient hospitalizations for serious infections using International Statistical Classification of Diseases and Related Health Problems, 10th Revision diagnosis codes, which have been used in Ontario since 2002.[28] (Supplementary Appendix; eTable 1, http://links.lww.com/JAM/A310)[15,29–31] We defined the index date as the date of hospital admission (inpatient) and restricted to incident events by excluding cases where the individual had a hospital visit for the same reason in the prior 183 days. We restricted our cohort to individuals whose infection was likely related to injection drug use (IDU) by limiting it to those with a history of OUD, defined as having either a hospital or physician visit with a diagnosis of OUD, or being prescribed OAT in the 365 days before and including the index date (Supplementary Appendix; eTable 2, http://links.lww.com/JAM/A310). In a sensitivity analysis, we used a broader definition that included hospital or physician visits for substance use disorders, combined drug use disorders, or OUDs in the past 365 days, OAT in the past 365 days, or a hepatitis C diagnosis or treatment in the prior 5 years to align with definitions used to identify infections among PWID in previous publications (Supplementary Appendix; eTable 2, http://links.lww.com/JAM/A310).[29] Finally, we excluded individuals with missing or invalid age or sex (less than 3% of records), or non-Ontario residents.

Clinical Characteristics

Among included cases, we described prior treatment for OUD or indication of access to either CR or immediate-release (IR) hydromorphone. Specifically, we captured dispensing of OAT (methadone, buprenorphine/naloxone or daily dispensed Kadian or M-Eslon) in the past 90 days as a measure of engagement with the healthcare system related to their OUD and because it is anticipated that frequency of IDU would reduce if on treatment.[32] We also captured recent evidence of receipt of any CR hydromorphone (past 30 days), or daily-dispensed IR hydromorphone (past 30 days), which may be an indication of safer supply prescribing.

We constructed a cohort of all individuals who were hospitalized for serious infections in the final 2 years of the

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study (January 1, 2018 to December 31, 2019) to allow us to capture clinical and demographic characteristics of patients experiencing these outcomes in more recent years. If an individual experienced more than 1 hospitalization meeting inclusion criteria in this period, we selected the first such occurrence of each type of infection. Within this cohort, we described demographic characteristics (age, sex, neighborhood income quintile), prior IE or other serious infections (5 years), prior OAT (90 days), prior hydromorphone exposure (30 days), prior HIV diagnosis, or prior Hepatitis C diagnosis (5 years). Finally, we captured characteristics of the index hospitalization, including whether the patient required major surgery during index hospitalization (defined as surgeries lasting for 2 hours or longer) length of stay, readmission to hospital for any cause (within 30 days of discharge), ED visit (within 30 days of discharge), and death (both in-hospital and within 30 days of discharge).

Analysis

In each year of the study period, we reported the number and population-adjusted rate (per million Ontario residents) of hospitalizations for serious infections, stratified by type (IE, spinal infections, nonvertebral bone infections, and skin or soft tissue infections) and the prevalence of prior OAT and hydromorphone prescribing. We used the Cochrane Armitage Trend Test to test for trends in each of the outcomes across each year of the study, with the exception of prior hydromorphone use where trends were evaluated between 2014 and 2019 due to low exposure rates in 2013. All clinical characteristics and hospital sequelae were summarized using percentages (binary variables) and medians with interquartile ranges (continuous variables). Analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC) and trend tests were performed using R, version 3.6.3.

RESULTS

We identified 143,359 hospitalizations for serious infections over our study period. After applying exclusion criteria restricting to patients with a history of OUD, 1427 incident IE hospitalizations, 899 incident hospitalization for spinal infections, 1596 incident hospitalizations for nonvertebral bone infections, and 5039 incident hospitalizations for skin or soft tissue infections were included. Over the 7-year study period, the rate of serious infections grew significantly among people with a history of OUD ($P < 0.01$), with the largest increases occurring between 2015 and 2019. Specifically, there was a 167% increase in the rate of IE (7.7 per million residents in 2013 vs 20.6 per million residents in 2019; $P < 0.01$), a 394% increase in the rate of spinal infections (3.4–16.8 per million residents; $P < 0.01$), a 191% increase in the rate of nonvertebral bone infections (8.9–25.9 per million residents; $P < 0.01$), and a 147% increase in the rate of infections of the skin or soft tissue (32.1–79.4 per million residents; $P < 0.01$; Fig. 1). From 2014 onwards, the prevalence of prior

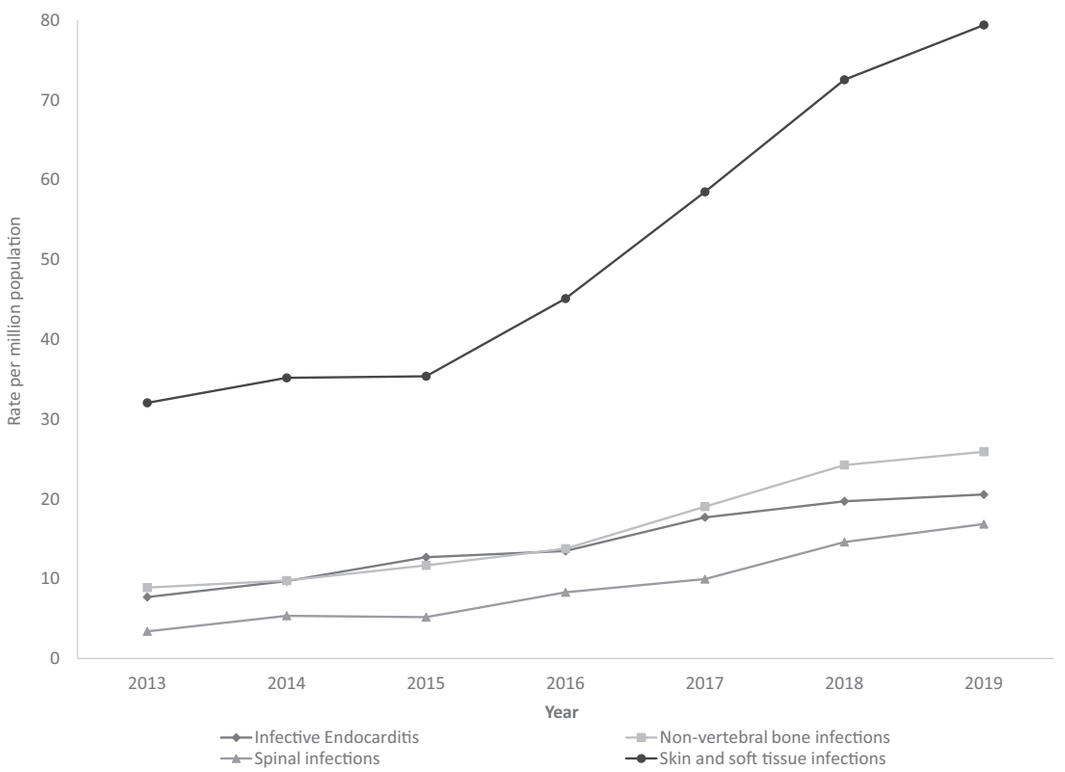

FIGURE 1. Rate of hospitalizations for serious infections among people with an opioid use disorder in Ontario, from 2013 to 2019. Annual population-adjusted rates (per million) of hospitalizations for serious infections in Ontario, Canada, stratified by infection type.

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CR hydromorphone decreased slightly among all infection types, but only demonstrated a significant trend among people with IE (8.3%–4.0%; $P = 0.02$) and among skin and soft tissue infections (9.0%–5.3%; $P < 0.01$) (Table 1). In contrast, there was a small, but significant rise in having recently received daily dispensed IR hydromorphone ($P < 0.01$) among people with IE and skin and soft tissue infections. However, despite the increasing trend, only 4.3% of people hospitalized with incident IE (13 of 299 hospitalizations) and 3.4% of people hospitalized for skin and soft tissue infections (39 of 1155 hospitalizations) had received daily dispensed IR hydromorphone in the past 30 days in 2019. Overall, there was a relatively high prevalence of recent OAT that was trending upwards among all hospitalizations for serious infections.

In the most recent 2 years of the study, there were 546 people hospitalized with an incident IE, 436 hospitalized for spinal infections, 686 hospitalized for nonvertebral bone infections, and 2,033 hospitalized with infections of the skin or soft tissue meeting our inclusion criteria. In general, people hospitalized for IE had a median age of 35 years, and 44.1% were male. In contrast, among those with other serious infections, the median age was slightly higher (range 40 to 44 years), and over half were male (Table 2). In all 4 groups, approximately half of the cohort resided in neighborhoods in the lowest income quintile, one-quarter had a prior Hepatitis C diagnosis, and nearly 5% had a HIV diagnosis at baseline. Among all incident serious infections, 5.6% were previously hospitalized for IE, 4.2% had been hospitalized for a spinal infection, 7.7% for nonvertebral bone infections, and 20.1% for an infection of the skin or soft tissue.

Major surgery was required among 5.6% of patients hospitalized for a serious infection, but varied considerably by infection type (range 2.1% [skin or soft tissue infection] to 15.6% [spinal infections]; Table 3). This was paralleled by longer hospital lengths of stay for individuals with spinal infections (median 19 days) and shorter stays for those with skin or soft tissue infections (median 5 days). Nearly half (42.9%) of individuals hospitalized with serious infections visited an ED within 30 days of hospital discharge, and readmission rates were high across all infection types (range 18.1% [skin and soft tissue infections] to 34.4% [IE]). Further, mortality both in-hospital and within the 30 days postdischarge were much higher among those with IE (11.5% in-hospital and 15.9% in the 30 days after discharge) compared with those with other serious infections, with lowest mortality rates among those hospitalized with skin or soft tissue infections (0.8% in-hospital; 2.0% within 30 days postdischarge).

In the sensitivity analysis, applying a broader definition for prior substance use disorders, we identified 1878 incident cases of IE, 1196 incident cases of spinal infections, 2187 incident cases of nonvertebral bone infections, and 7553 incident cases of serious infections of the skin or soft tissue from 2013 to 2019. In general, the trends over time and prior exposure to OAT and hydromorphone were similar to our primary analysis (Supplementary Appendix; eTable 3 and eFigure 1, http://links.lww.com/JAM/A310).

DISCUSSION

In this population-based study spanning 7 years of hospitalization data, we found that the rates of serious

TABLE 1. Trends in Rates of Serious Infections, and Prior Opioid Use Among People With Opioid Use Disorder. 2013 to 2019

	2013	2014	2015	2016	2017	2018	2019	Cochrane-Armitage Trend Test
Infective endocarditis								
Hospital visits (N, rate per million)	104 (7.70)	132 (9.69)	174 (12.69)	187 (13.48)	249 (17.70)	282 (19.71)	299 (20.56)	<0.01
Controlled Release hydromorphone (prior 30 days)	≤5	11 (8.3%)	13 (7.5%)	14 (7.5%)	12 (4.8%)	15 (5.3%)	12 (4.0%)	0.02*
Daily Dispensed IR hydromorphone (prior 30 days)	≤5	≤5	≤5	≤5	≤5	7 (2.5%)	13 (4.3%)	<0.01*
Opioid agonist therapy in prior 90 days	49 (47.1%)	76 (57.6%)	93 (53.4%)	102 (54.5%)	137 (55.0%)	147 (52.1%)	184 (61.5%)	0.09
Spinal infections								
Hospital visits (N, Rate per million)	46 (3.40)	73 (5.36)	71 (5.18)	115 (8.29)	140 (9.95)	209 (14.61)	245 (16.84)	<0.01
Controlled Release hydromorphone (prior 30 days)	≤5	7 (9.6%)	7 (9.9%)	14 (12.2%)	12 (8.6%)	19 (9.1%)	19 (7.8%)	0.36*
Daily Dispensed IR hydromorphone (prior 30 days)	0	≤5	0	≤5	≤5	8 (3.8%)	8 (3.3%)	0.26*
Opioid agonist therapy in prior 90 days	20 (43.5%)	41 (56.2%)	45 (63.4%)	69 (60.0%)	89 (63.6%)	118 (56.5%)	162 (66.1%)	0.03
Nonvertebral bone infections								
Hospital Visits (N, rate per million)	120 (8.88)	133 (9.77)	160 (11.67)	191 (13.77)	268 (19.05)	347 (24.25)	377 (25.92)	<0.01
Controlled Release hydromorphone (prior 30 days)	9 (7.5%)	16 (12.0%)	22 (13.8%)	21 (11.0%)	22 (8.2%)	44 (12.7%)	30 (8.0%)	0.13*
Daily Dispensed IR hydromorphone (prior 30 days)	≤5	≤5	≤5	≤5	≤5	9 (2.6%)	8 (2.1%)	0.99*
Opioid agonist therapy in prior 90 days	73 (60.8%)	71 (53.4%)	86 (53.8%)	110 (57.6%)	169 (63.1%)	197 (56.8%)	239 (63.4%)	0.11
Skin or soft tissue infections								
Hospital visits (N, rate per million)	433 (32.05)	479 (35.18)	485 (35.38)	626 (45.12)	823 (58.49)	1038 (72.54)	1155 (79.41)	<0.01
Controlled Release hydromorphone (prior 30 days)	28 (6.5%)	43 (9.0%)	39 (8.0%)	44 (7.0%)	56 (6.8%)	60 (5.8%)	61 (5.3%)	<0.01*
Daily Dispensed IR hydromorphone (prior 30 days)	≤5	6 (1.3%)	6 (1.2%)	11 (1.8%)	12 (1.5%)	19 (1.8%)	39 (3.4%)	<0.01*
Opioid agonist therapy in prior 90 days	238 (55.0%)	274 (57.2%)	284 (58.6%)	368 (58.8%)	523 (63.5%)	639 (61.6%)	730 (63.2%)	<0.01

Types of serious infections are not mutually exclusive. Tests for trends for prior hydromorphone prescribing were calculated from 2014 to 2019 due to low prevalence of hydromorphone use among cases in 2013.
*Trend calculated from 2014 to 2019 due to low frequencies in 2013.
IR, immediate release.

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TABLE 2. Characteristics of Individuals With an Opioid Use Disorder Hospitalized for Incident Serious Infections Between 2018 and 2019

Characteristic	Overall N = 3026	Infective Endocarditis N = 546	Spinal Infections N = 436	Nonvertebral Bone Infections N = 686	Skin or Soft Tissue Infection N = 2033
Age at admission (Median, IQR)	40 (32–51)	35 (29–43)	44 (36–52)	43 (34–53)	40 (32–50)
<35	991 (32.7%)	272 (49.8%)	86 (19.7%)	180 (26.2%)	648 (31.9%)
35–64	1,895 (62.6%)	267 (48.9%)	331 (75.9%)	462 (67.3%)	1,289 (63.4%)
65+	140 (4.6%)	7 (1.3%)	19 (4.4%)	44 (6.4%)	96 (4.7%)
Male (N, %)	1,725 (57.0%)	241 (44.1%)	231 (53.0%)	384 (56.0%)	1,211 (59.6%)
Urban residence	2,619 (86.5%)	478 (87.5%)	368 (84.4%)	581 (84.7%)	1,777 (87.4%)
Income quintile					
1 (lowest)	1,523 (50.3%)	279 (51.1%)	229 (52.5%)	360 (52.5%)	995 (48.9%)
2	595 (19.7%)	112 (20.5%)	78 (17.9%)	130 (19.0%)	412 (20.3%)
3	413 (13.6%)	69 (12.6%)	66 (15.1%)	90 (13.1%)	280 (13.8%)
4	251 (8.3%)	47 (8.6%)	30 (6.9%)	56 (8.2%)	172 (8.5%)
5 (highest)	192 (6.3%)	34 (6.2%)	24 (5.5%)	41 (6.0%)	132 (6.5%)
Missing	52 (1.7%)	≤5	9 (2.1%)	9 (1.3%)	42 (2.1%)
Infections in prior 5 years					
Infective endocarditis	169 (5.6%)	86 (15.8%)	53 (12.2%)	68 (9.9%)	110 (5.4%)
Spinal infection	128 (4.2%)	38 (7.0%)	46 (10.6%)	88 (12.8%)	97 (4.8%)
Nonvertebral bone infections	232 (7.7%)	56 (10.3%)	58 (13.3%)	111 (16.2%)	167 (8.2%)
Skin or soft tissue infection	608 (20.1%)	133 (24.4%)	104 (23.9%)	234 (34.1%)	438 (21.5%)
Controlled Release hydromorphone (prior 30 days)	176 (5.8%)	26 (4.8%)	38 (8.7%)	70 (10.2%)	108 (5.3%)
Daily Dispensed Immediate Release Hydromorphone (prior 30 days)	68 (2.2%)	17 (3.1%)	16 (3.7%)	17 (2.5%)	48 (2.4%)
OAT prescription (prior 90 days)	1,863 (61.6%)	313 (57.3%)	265 (60.8%)	409 (59.6%)	1,261 (62.0%)
Hepatitis C diagnosis (prior 5 years)	727 (24.0%)	167 (30.6%)	124 (28.4%)	182 (26.5%)	506 (24.9%)
HIV diagnosis (before hospitalization)	127 (4.2%)	23 (4.2%)	17 (3.9%)	34 (5.0%)	83 (4.1%)

Types of serious infections are not mutually exclusive. The majority of the hospitalizations had only 1 type of infection (N = 3333, 91.9%), 267 (7.4%) had a combination of 2 types of infections, and 28 (0.8%) had 3 or 4 infection types.

OAT, opioid agonist therapy.

infections have increased considerably among people with OUD, with serious infections of skin or soft tissue being the most prevalent type of infection. Importantly, the increase in the rates of serious infections began largely in 2016, a trend that parallels rising rates of opioid overdoses, polysubstance overdoses, and the presence of fentanyl in the unregulated drug supply in Ontario.[4] The burden of these serious clinical events is high as approximately 1 in 5 people hospitalized with a serious infection were readmitted to hospital within 30 days of discharge, and more than one-quarter of those hospitalized for IE died in-hospital or within 30 days of discharge.

Our findings indicating rising trends of serious infections are consistent with the literature; however, most of the previously reported data focused more on populations of PWID, and was collected before 2016, a period before the increase in trend observed in our analysis.[8,11,14,15,33,34] For example, an Ontario-based retrospective cohort study found that rates of IE among PWID grew 162% from 2006 to 2015, which the authors attributed to a shift in prescription opioid patterns from CR oxycodone to hydromorphone.[15] In contrast, our study demonstrates that shifts in the unregulated market towards nonprescription fentanyl in 2016 align with an acceleration in the rising rates of IE and invasive infections across the province.[4,24] This is mirrored in a recent study from the US which showed rising cases of IE among people with substance use disorder beginning in 2017.[20] Although the

TABLE 3. Patient Outcomes Among People With an Opioid Use Disorder Hospitalized for Incident Serious Infections Between 2018 and 2019

Characteristic	Overall N = 3026	Infective Endocarditis N = 546	Spinal Infections N = 436	Nonvertebral Bone Infections N = 686	Skin or Soft Tissue Infection N = 2033
Required major surgery	168 (5.6%)	41 (7.5%)	68 (15.6%)	76 (11.1%)	43 (2.1%)
Length of stay in-hospital (days; median, IQR)	7 (3–16)	18 (9–41)	19 (11–40)	13 (6–26)	5 (3–10)
Readmission to hospital within 30 days	655 (21.6%)	188 (34.4%)	131 (30.0%)	157 (22.9%)	367 (18.1%)
ED visit within 30 days	1,298 (42.9%)	206 (37.7%)	203 (46.6%)	320 (46.6%)	881 (43.3%)
Death in-hospital	77 (2.5%)	63 (11.5%)	10 (2.3%)	12 (1.7%)	17 (0.8%)
30-day postdischarge mortality	121 (4.0%)	87 (15.9%)	18 (4.1%)	19 (2.8%)	40 (2.0%)

Types of serious infections are not mutually exclusive. The majority of the hospitalizations had only 1 type of infection (N = 3333, 91.9%), 267 (7.4%) had a combination of 2 types of infections, and 28 (0.8%) had 3 or 4 infection types.

ED, Emergency Department.

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reasons for this increase are not currently well understood, several studies have suggested more frequent injection among people who inject fentanyl, which may put them at increased risk of infective complications.[35–37] Although few studies have characterized patients with IE and other serious infections, an Ontario study among patients receiving OAT found that middle age (35–64), female sex, urban residence, and low income were all factors associated with IE and invasive infections.[11] This is consistent with our findings and suggests that action to address the burden of infections among people with OUD should prioritize reducing barriers to treatment in these populations and access to preventative healthcare.

Receipt of OAT in the 3 months before hospitalization for serious infections was common and increased over time. This mirrors local trends of increasing prescribing of OAT in Ontario.[38] Although our study was not designed to examine whether engagement in OAT reduced the risk of injection-related infections through reduced frequency of IDU or increased engagement with the healthcare system, the specifics of this relationship are an important area for future research. This is particularly important as previous research in Canada has demonstrated a high degree of ongoing IDU among people engaged in OAT, reinforcing this as an opportunity for clinicians to support access to harm reduction tools as a component of the treatment program. Our findings related to recent hydromorphone dispensing also require further discussion. Specifically, we found a declining prevalence of CR hydromorphone dispensing and slightly increased prevalence of daily dispensed IR hydromorphone over the study period. The declining trend in CR hydromorphone could be reflective of changes in clinical practice in response to the evolving evidence of an association between CR hydromorphone and incident IE,[10,11,13–15] or a result of shifts in clinical practice away from prescribing CR hydromorphone more generally.[38] This relatively small increase in prior exposure to IR hydromorphone may also be reflective of broad shifts in clinical practice towards IR opioid formulations (including IR hydromorphone)[38] or could be a result of the expansion of safer supply programs across the province that provide this medication to people with severe OUD who have previously found OAT to be ineffective.[39] Because our study was not designed to identify a causal link between injection of IR hydromorphone and infection risk, we cannot determine whether these findings are reflective of shifting opioid analgesic prescribing patterns at the population-level and changing treatment and harm reduction patterns among high risk individuals at the community level, or a risk of infections when injecting IR hydromorphone. More research is needed to further elucidate this relationship.

Strengths and Limitations

A core strength of this study is our ability to capture all hospitalizations for serious infections among people with OUD across the entire population of Ontario, Canada's most populous province, and to link this data to medication dispensing records to characterize recent access to OAT or hydromorphone. However, several limitations merit discussion. First, there is not a well-validated definition of OUD or IDU in Ontario.[40] Therefore, it is possible that there was some misclassification of our serious infection cases when restricting to those with an OUD. However, the trends observed were consistent when we broadened our cohort definition to include all incident serious infections among people with healthcare contacts related to substance use disorder and IDU, a definition validated in a study of IE among PWID,[29] suggesting that our findings are robust. Further, because we were unable to accurately estimate the population of people with OUD, our rates were calculated per million population of Ontario and we were unable to estimate the rate of these infections among people with OUD in the province. Second, it is impossible to confirm participation in a safer opioid supply program using administrative data, and we, therefore, relied on identifying people who were recently recipients of daily dispensed immediate release hydromorphone as this is how safer opioid supply programs are generally structured in Ontario.[39] Because IR hydromorphone prescribing has been increasing across Ontario over our study period[38] it is possible that the observed trends are reflective of rising hydromorphone prescribing more generally, and not increased access to safer supply programs. Third, the nature of the administrative data used precludes us from determining the types of drugs injected. Therefore, we are unable to specifically determine the changing role of polysubstance use and unregulated fentanyl on infection rates. Finally, administrative hospital data does not capture the underlying pathogen leading to the infection, meaning that we cannot further stratify the serious infections by pathogen type.

CONCLUSIONS

The rate of serious infections among people with OUD has more than doubled over the past 7 years, and people with these conditions commonly reside in low-income neighborhoods, have previously been treated for serious infections, and have recently received treatment for an OUD. This trend is concerning as it parallels rapid increases in opioid overdoses linked to increased fentanyl in the unregulated drug supply and represents another important opioid-related harm that leads to considerable loss of life and cost to the healthcare system. These findings reinforce the need for broad, low-barrier access to harm reduction programs, including needle and syringe exchange programs, and integration of treatment for OUD into primary care to promote early intervention among people experiencing infective complications from IDU. Future research is needed to elucidate the drivers of serious infections, and to evaluate the accessibility and effectiveness of early interventions and treatments to prevent downstream harm.

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