Introduction
PWID are at risk for the development of pyogenic infections, including but not limited to skin soft tissue infections (SSTI), endocarditis, osteomyelitis, septic arthritis, and infections of the spine. There has been an unprecedented increase in ISUD over the past two decades in the United States (US). As a consequence, SSTI and endocarditis, the two most commonly associated pyogenic complications of ISUD, have been well described in numerous publications. There are fewer studies describing the impact of ISUD on
the risk of pyogenic infections of the spine or its complications.10–19 Spine infections, including spondylitis, spondylodiscitis, and epidural or paraspinous, or both, abscess, are associated with diagnostic challenges, extended courses of antibiotics, not infrequent need for surgical intervention, prolonged hospitalization, and post-discharge care as well as significant morbidity and mortality.20,21 Successful management of patients with spine infections requires a high level of inpatient care, a multidisciplinary approach by the healthcare team, and the cooperation and adherence by infected patients. Associated healthcare costs are high.11,13,22

Risk factors for the development of PSI include advanced age, immunosuppression, diabetes, malignancy, renal failure, malnutrition, alcoholism, and ISUD. With respect to the latter, the case reports and case series from several geographic regions have described increasing rates of PSI. Most of these studies reported findings exclusively on their population of ISUD without a comparative analysis of a non-ISUD cohort. Other studies have utilized an administrative database or populations, or both, having spinal epidural abscesses exclusively.18,19

The aim of this study was to identify trends, and describe the characteristics and complications of PSI among people who do and do not inject drugs admitted to this region’s academic tertiary care referral hospital in northeast NYS. This encompasses a large, predominantly rural geographic area of NYS that also includes bordering counties of western Massachusetts and southern Vermont. It is a region that has not previously been studied in this context. The study utilized a primary clinical database encompassing a twelve-year time span that coincides with the rising trend in ISUD-related infections, overdoses, and deaths in the United States.1–3,23,24

Methods

We conducted a retrospective chart review of adults (≥18 years old) admitted to Albany Medical Center Hospital (AMCH) with a diagnosis of primary infection of the spine during three time periods: 2007 and 2008 (Period 1), 2014 (Period 2), and 2017 and 2018 (Period 3). These periods coincided with the growing nationwide opioid epidemic and were representative of a time span during which we were aware of an increasing trend in the incidence of patients being admitted to our hospital with spine infections. Furthermore, during this time span, a single multidisciplinary team of clinicians was involved in the care of all of these patients. This afforded an opportunity to cross-reference our infectious diseases and surgical consultation database with that of the hospital’s discharge database in an effort to maximize the sensitivity and specificity of the captured hospital charts.

Hospital charts were identified using International Classification of Diseases, Ninth Revision (ICD-9) codes for Periods 1 and 2, and International Classification of Diseases, Tenth Revision (ICD-10) codes for Period 3. Primary codes were used to identify patients with infections of the spine (Supplementary Table 1). Given the low numbers of cases identified during 2007 and 2008 (Period 1), we included the year 2014 (Period 2) data in the analysis. Moreover, since ICD-9 codes had transitioned to ICD-10 codes in 2015, the addition of Period 2 patients would minimize the impact that the transition might have on our ability to capture the relevant charts during the earlier time period. We performed an initial review of the patients’ discharge summaries in order to determine whether patients met the study inclusion criteria. Case validation was then performed by reviewing our internal office infectious diseases and surgical specialist consultation records. All of the included charts were then reviewed in their entirety, and information was entered into a standardized data collection form.

Patients were included if they were diagnosed with primary spondylitis, spondylodiscitis, and epidural or paraspinous, or both, abscess. Diagnosis was made based on a combination of medical history, physical examination, radiologic studies, and cultures of blood or tissue. In cases where culture data were lacking, the diagnosis was made when clinical and radiological features were suggestive of spine infection, and elevated inflammatory markers were present. Patients were excluded if they presented with a postoperative wound infection, since this is considered to be a secondary infection, or if they were readmitted for the same condition, or complications of the condition.

Cohorts were divided into those with a known history or signs (e.g. physical examination findings on skin of recent injection drug use) of recent ISUD, and those without a history or signs of
recent ISUD (non-ISUD). In the rare instance of uncertainty, a toxicology screen would be performed. Collected outcome data included demographics, insurance type, comorbidities, history or signs of recent ISUD, or both, microbiologic results, need for surgical intervention, mortality, patient disposition, and hospital costs. With respect to the latter, Period 3 was used to obtain the inpatient cost data since it most closely reflected current costs.

**Statistical analysis**

We used R 4.1.2 (R Foundation, Vienna, Austria) to assess for heterogeneity between periods (Periods 1, 2, and 3). Chi-square and Fisher’s exact tests were used for categorical variables. All p values were two-tailed, and a p value less than 0.05 was interpreted as statistically significant. The map was created with ArcMap 10.8.1 (Esri, Redlands, CA).

**Results**

A total of 392 patient discharge summaries were identified and reviewed from which 270 cases met the inclusion criteria. Those excluded consisted of the following: patients whose hospital admission fell outside of the designated time periods; patients having non-primary spine infections; patients with primary spine infections that were readmitted for complications; patients with a remote history of spine infection that were not actively infected at the time of the admission under study. The number of ISUD- and non-ISUD-infected patients per time period is seen in Table 1. During the 24 months of Period 1, there were 43 patients admitted with spine infections. Of these, four (9.3%) were ISUD-related. During the 12 months of Period 2, there were 43 patients with spine infections of which eight (18.6%) were ISUD related. During the 24 months of Period 3, there were 184 patients admitted with spine infections of which 47 (25.5%) were ISUD related.

Demographic characteristics are shown in Table 2. The median age of the ISUD cohort was 39 (range 21–67), and that of the non-ISUD cohort was 65 (range 25–85) (P < 0.01). The cohorts did not differ with respect to sex: males comprised 71.2% of the ISUD cohort and 67.8% of the non-ISUD cohort. Race ethnicity did not differ significantly among the cohorts: ISUD cohort was 86.4% White/non-Hispanic, while non-ISUD cases were 88.6% White/non-Hispanic. The non-ISUD cohort had a significantly higher prevalence of diabetes (45.6%; P < 0.01; data not shown). Medicaid was the primary payer in the ISUD cohort (67.8%), and Medicare was the primary payer in the non-ISUD cohort (57.8%). There were 40 (67.8%) ISUD patients and 139 (65.9%) non-ISUD patients that were admitted to AMCH via transfer from outside hospitals. Those not referred from outside hospitals were admitted directly through the Emergency Department. The counties from which the patients resided at the time of admission are seen in Figure 1. Both ISUD and non-ISUD cohorts resided in a large, predominantly rural region of northeast NYS, southern Vermont, and western Massachusetts.

| Period | ISUD n (%) | Non-ISUD n (%) | Patients |
|--------|------------|----------------|----------|
| 2007   | 2          | 16             | 18       |
| 2008   | 2          | 23             | 25       |
| Period 1 | 4 (9.3)   | 39 (90.7)     | 43       |
| 2014   | 8          | 35             | 43       |
| Period 2 | 8 (18.6)  | 35 (81.4)     | 43       |
| 2017   | 15         | 64             | 79       |
| 2018   | 32         | 73             | 105      |
| Period 3 | 47 (25.5) | 137 (74.5)    | 184      |
| Total  | 59 (21.9)  | 211 (78.1)    | 270      |

ISUD, injection substance use disorder.
### Table 2. Demographic data of patients.

|                      | ISUD, n (%) | Non-ISUD, n (%) | *p* value |
|----------------------|-------------|-----------------|-----------|
| **Sex**              |             |                 | 0.73      |
| Male                 | 42 (71.2)   | 143 (67.8)      |           |
| Female               | 17 (28.8)   | 68 (32.2)       |           |
| **Race**             |             |                 | 0.41      |
| White                | 51 (86.4)   | 187 (88.6)      |           |
| Asian                | 0 (0)       | 1 (<0.1)        |           |
| Black                | 4 (6.8)     | 18 (8.5)        |           |
| Unknown              | 2 (3.4)     | 3 (1.4)         |           |
| Other                | 2 (3.4)     | 2 (0.1)         |           |
| **Ethnicity**        |             |                 | 0.29      |
| Hispanic             | 3 (5.1)     | 4 (1.9)         |           |
| Not Hispanic         | 55 (93.2)   | 204 (96.7)      |           |
| Unknown              | 1 (1.7)     | 3 (5.1)         |           |
| **Insurance**a       |             |                 | <0.001    |
| Incarcerated         | 2 (3.4)     | 0 (0)           |           |
| Medicaid             | 40 (67.8)   | 25 (11.8)       |           |
| Medicare             | 6 (10.2)    | 122 (57.8)      |           |
| Military             | 0 (0)       | 11 (5.2)        |           |
| Other                | 1 (1.7)     | 1 (<0.1)        |           |
| Private              | 2 (3.4)     | 50 (23.7)       |           |
| Uninsured/self-pay   | 6 (10.2)    | 0 (0)           |           |
| Unknown              | 5 (8.5)     | 13 (6.2)        |           |
| **Transfer from outside hospital** | 0.14 | | |
| Yes                  | 40 (67.8)   | 139 (65.9)      |           |
| No                   | 17 (28.8)   | 71 (33.6)       |           |
| Unknown              | 2 (3.4)     | 1 (<0.1)        |           |
| **Age**              |             |                 | <0.001    |
| 18–29                | 8 (13.6)    | 2 (0.1)         |           |
| 30–39                | 24 (40.7)   | 7 (3.3)         |           |
| 40–49                | 15 (25.4)   | 20 (9.5)        |           |
| 50–59                | 7 (11.9)    | 42 (19.9)       |           |
| 60–69                | 5 (8.5)     | 67 (31.8)       |           |
| >70                  | 0 (0)       | 73 (34.6)       |           |

|                      | ISUD median (range) | non-ISUD median (range) | *p* value |
|----------------------|----------------------|--------------------------|-----------|
| **Age**              | 39 (21–67)           | 65 (25–85)               | 0.01      |

ISUD, injection substance use disorder.

*14 patients had more than one type of insurance.
Table 3 lists the microbiology data of the cohorts. Methicillin-sensitive and Methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA, respectively) were the most common causative organisms. MSSA accounted for infection in 22 (37.3%) ISUD and 86 (40.8%) non-ISUD patients. MRSA accounted for infection in 15 (25.4%) ISUD and 28 (13.7%) non-ISUD patients. Polymicrobial infections occurred in a total of 10 patients. No organisms were identified in five (8.5%) ISUD and in 28 (13.3%) non-ISUD patients. Bacteremia due to the causative organism occurred in 29 (49.2%) ISUD and 94 (44.5%) non-ISUD patients. *Streptococcus agalactiae* was the causative organism in 10 non-ISUD patients all of whom had diabetes or chronic renal failure, or both, as comorbid conditions.

Table 4 summarizes the anatomic levels of spine involvement, surgical intervention, LOS, inpatient cost, and disposition of the cohorts. Infection involving the lumbar spine predominated in both cohorts, and there was no significant difference in the incidence of infection involving multiple spinal levels: 15.3% in ISUD and 17.5% in non-ISUD patients, respectively. The indications for surgical intervention included need for open diagnostic biopsy, spinal cord compression with progressive neurologic deficit or mechanical instability, or both. Surgery was performed in 28 (47.5%) of the ISUD and 90 (42.7%) of non-ISUD patients. There was no difference in the rates of diagnostic versus therapeutic surgical interventions between cohorts. In many instances, the patients underwent both a diagnostic and a therapeutic surgical intervention. Death during the course of hospitalization occurred in one ISUD patient and eight non-ISUD patients.

LOS data were comparable between cohorts. The median LOS in the ISUD cohort was 12 days (range 1–64 days), and in the non-ISUD cohort was 12 days (range 1 – 101 days). However, a larger percentage of the non-ISUD patients were either discharged home or transferred to an inpatient physical therapy rehabilitation facility while completing their course of intravenous (IV) antibiotics. In contrast, none of the ISUD cohort was discharged home while receiving IV antibiotics, and a larger percentage were transferred back to

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**Figure 1.** Maps showing the counties from which the patients with pyogenic infections of the spine resided at the time of hospital admission (county boundary as solid lines). Inset shows map of NYS and surrounding regions, including Vermont and Massachusetts. ISUD, injection substance use disorder.
the hospitals from which they came once their acute care was completed. In addition, 11 (18.6%) ISUD and two (0.9%) non-ISUD patients were discharged against medical advice (DAMA). Follow-up data beyond discharge from AMCH were not included in this study.

Total hospital costs were similar between cohorts. The median total cost in the ISUD cohort was $26,615 (range $1,725–$162,775), and in the non-ISUD cohort was $23,646 (range $2,543–$247,966). These represent AMCH inpatient costs and do not reflect additional hospital costs accrued for patients when they were transferred back to the referring hospital.

Discussion

Diagnosis and management of PSI are always complex. They invariably cause acute back or neck pain, or both, that can become chronic and debilitating even after treatment. If treatment is delayed, they can progress to paralysis, spinal instability, and death. Spine infections require prolonged courses of antibiotics, frequent surgical intervention, and prolonged acute and post-hospitalization care, all resulting in high healthcare costs. Prior to the beginning of the 21st century, PSI were considered relatively uncommon. Since then, the incidence of PSI has been on the rise. This increased incidence has been attributed to a combination of factors, most notably an increasing aging population with associated comorbidities, and an increase in ISUD.

To our knowledge, this report represents the largest study from a single, tertiary care hospital that utilized a primary clinical database to evaluate trends and characteristics of primary PSI among people who do and do not inject drugs. We retrospectively examined the incidence of spine infections occurring over a 12-year period from a relatively large geographic region in and around northeast NYS, an area not previously studied with respect to this infection. We found significant increasing trends in patients admitted with spine infections to this region’s tertiary care referral hospital between 2007 and 2018. Moreover, both the frequency of spine infections and the proportion of spine infections associated with recent ISUD substantially increased over this time period. Many of our findings are concordant with reports from other geographic areas, as well as from a large, nationwide study that utilized an administrative database.\textsuperscript{10–19}

The Census Bureau and the US Department of Agriculture have classified all of the counties

| Organisms                  | ISUD | Non-ISUD |
|----------------------------|------|----------|
| MSSA\textsuperscript{a}    | 22   | 86       |
| MRSA\textsuperscript{a}    | 15   | 28       |
| Coagulase-negative Staphylococci | 1 | 9       |
| Streptococcus agalactiae   | 0    | 10       |
| Groups A/C/G Streptococci  | 0    | 4        |
| Viridans group Streptococci | 1 | 8       |
| Streptococcus bovis        | 0    | 2        |
| Abiotrophia defectiva      | 0    | 1        |
| Enterococcus fecalis       | 0    | 6        |
| Cutibacterium species      | 1    | 1        |
| Corynebacterium species    | 0    | 1        |
| Escherichia coli           | 0    | 9        |
| Enterobacter cloacae       | 2    | 3        |
| Hemophilus parainfluenza   | 1    | 1        |
| Proteus mirabilis          | 1    | 1        |
| Klebsiella pneumoniae      | 0    | 2        |
| Pseudomonas aeruginosa     | 2    | 1        |
| Serratia marcescens        | 3    | 0        |
| Acinetobacter baumannii    | 1    | 0        |
| Aggregatibacter actinomycetemcomitans | 0 | 1       |
| Mycobacterium abscessus    | 0    | 1        |
| Candida species            | 3    | 2        |
| Blastomyces dermatitidis   | 0    | 1        |
| Polymicrobial              | 1    | 9        |
| Unknown                    | 5    | 28       |

\textsuperscript{a}Includes 2 cases of polymicrobial infection in non-ISUD.
encompassed by our study as being predominantly rural. It has been established that rural communities throughout the United States have been disproportionately impacted by the opioid epidemic. Substance use treatment infrastructure, and treatment resources are often lacking in these communities. Notably, Felsen et al. and Hartnett et al. reported on the increasing incidence of injection drug use associated bacterial and fungal infections between 2014 and 2017 occurring in a rural county in western NYS. Although not limited to spine infections, their study along with ours suggest that a large, predominantly rural geographic region of NYS has experienced a significant rise in ISUD. As a result, large, regional, tertiary care, medical centers such as ours are likely to experience significant impact.

Our study identifies several additionally important demographic findings. Compared with the non-ISUD cohort, the ISUD cohort was younger, was more likely to have Medicaid as the primary insurance payer, and was more apt to be DAMA. Many of these same demographic features have been identified in studies of

| Table 4. Characteristics of patients with spine infections admitted during three time periods between 2007 and 2018 at Albany Medical Center Hospital. |

| ISUD, n (%) | non-ISUD, n (%) | p value |
|-------------|----------------|---------|
| Anatomic involvement | 0.85 |
| Cervical | 13 (22.0) | 48 (22.7) |
| Thoracic | 22 (37.3) | 68 (32.2) |
| Lumbar | 33 (55.9) | 132 (62.6) |
| Multiple levels | 9 (15.3) | 37 (17.5) |
| Surgical intervention | 28 (47.5) | 90 (42.7) | 0.61 |
| DAMA | 11 (18.6) | 2 (0.9) | <0.001 |
| Discharge location | <0.001 |
| Private residence | 16 (27.1)* | 89 (42.2) |
| Acute care facility | 13 (22.0) | 17 (8.1) |
| SNF | 2 (3.4) | 15 (7.1) |
| IRF | 10 (16.9) | 74 (35.1) |
| Temp housing | 0 (0) | 1 (<0.1) |
| Unknown | 6 (10.2) | 5 (2.4) |
| Death | 1 (1.7) | 8 (3.8) |

| ISUD median (range) | non-ISUD median (range) |
|---------------------|-------------------------|
| LOS (days)a | 12 (1–64) | 12 (1–101) |
| Inpatient costb | $26,615 ($1,725–$162,775) | $23,646 ($2,543–$247,966) |

DAMA, discharge against medical advice; IRF, Inpatient Rehabilitation Facility; ISUD, injection substance use disorder; SNF, Skilled Nursing Facility.

aThe LOS and inpatient cost data were calculated based on the number of days, and total hospital costs accrued during the inpatient stay at Albany Medical Center Hospital, and does not account for additional number of inpatient days once the patient was returned back to their referring hospital.

bAfter completing a full course of inpatient antibiotic therapy.
ISUD associated invasive infections, including endocarditis and SSTI. The most commonly identified causative organisms in both cohorts in our study were MSSA and MRSA. Given the likely pathogenesis of hematogenous dissemination to the spine from a skin source, these organisms have most commonly been identified in other published reports. Infection due to *Streptococcus agalactiae* was seen in 4.7% of our non-ISUD patients. This is likely due to their older age and higher rate of comorbid conditions when compared with the ISUD group. There were a large number and variety of pathogens (bacterial and fungal) that were identified as causing spine infections in our study, and in 12.2% of our study population, no organism was identified. In the latter case, it is quite possible that the administration of empiric antibiotics prior to obtaining blood or tissue cultures may have prevented growth and identification of the causative pathogen. Hadjipavlou et al., Ziu et al. (both groups from Texas), Wang et al. (from Canada), and Ananda et al. (from Australia) reported similar microbiologic findings. Given these results, and consistent with published guidelines, attempts should be made to identify the causative pathogens before initiating empiric antibiotics.

Regarding the anatomic level of spine involvement, the need for surgical intervention, and mortality due to infection, our series is consistent with several published reports. However, in their prospective study of ISUD and non-ISUD spine-infected patients, Wang et al. reported a higher rate (86%) of surgical intervention in both groups. The primary indications for surgery were progressive neurological deterioration or mechanical instability, or both. They point out that 60% of their patients presented with neurologic deficits: The cervical spine was most often involved in the ISUD group, whereas the thoracic spine was most often involved in the non-ISUD group. We, and others, observed a higher rate of lumbar spine involvement and a lower rate of patients requiring surgery.

The LOS and hospital costs were similar between our ISUD and non-ISUD cohorts. However, it is important to recognize that due to the home care agency policy’s that existed during the study our patients with ISUD were not permitted to go home with IV antibiotics. In addition, once their acute care phase of treatment was completed, they were often transferred back to their referring hospitals to complete their course of therapy. We did not obtain additional inpatient cost data after patients were discharged from our hospital. In addition, approximately 19% of our ISUD was DAMA. These transfers and early discharges artificially reduced both the LOS and cost figures. These data were likely offset to some degree by the ISUD patients that were admitted directly to AMCH and were required to complete at least six weeks of IV antibiotic therapy as inpatients. We note that during their inpatient stay at AMCH all of the ISUD cohort were evaluated by addiction medicine services and offered medications for opioid use disorder. It is possible that a larger proportion of our ISUD patient cohort may have been DAMA had they not received medications for their opioid use disorder. Our LOS and cost figures are similar to those described by Issa et al. in their 1998 to 2013 Nationwide Inpatient Sample (NIS) database report. In another NIS-based study, Ronan and Herzig found that between 2002 and 2012 the total inflation adjusted charges for hospitalizations due to opioid use/dependence with associated infection more than tripled. They also found that the population with hospitalizations related to opioid use/dependence with associated infection was more likely to be discharged to a second medical facility. They and others point out that the high proportion of Medicaid patients in the ISUD cohort results in a substantial cost burden placed on hospitals as well as on state and federal budgets.

There were several limitations to our study. First, ours was a retrospective study that used ICD codes to identify patients with spine infections. ICD codes are subject to coding errors that could result in overestimating or underestimating the true number of spine-infected patients. We sought to mitigate this potential for inaccuracy by using a broad range of primary codes that would reliably identify spine-infected patients. In addition, in an effort to maximize ICD code sensitivity and specificity, we cross-referenced the captured hospital charts with our infectious diseases and surgical office databases. Second, there were a small number of patients in time Period 1, and the ICD codes were revised between Period 1 and Period 3. This transition to revised ICD-10 codes may have resulted in a change in the sensitivity and specificity of the codes used. We believe that this was unlikely given the similarities between the ICD-9 and ICD-10 codes with...
respect to a diagnosis of spine infection. In addition, we included time period 2 (ICD-9) patients in our analysis to strengthen the comparative number of patients between ICD-9 and ICD-10 periods. We believe that the change in ICD codes had a negligible effect on our ability to track the trajectory of spine-infected patients admitted to our hospital over this period of time. Third, there may have been an increase in the overall referrals of spine-infected patients to AMCH from outlying communities during Period 3. This may have resulted from loss of spine surgeon workforce from outlying communities. To our knowledge, this did not significantly contribute to the increased incidence, nor would it have likely changed the proportion of ISUD and non-ISUD spine-infected patients that were admitted to AMCH. Fourth, we did not obtain long-term follow-up data and did not collect inpatient or outpatient cost data once patients were discharged from our hospital. Despite these limitations, this study provides additional important information to the current literature on the trends of PSI among people who do and do not inject drugs, and the associated substantial morbidity and healthcare costs.

In conclusion, the incidence of primary PSI and its associated costs have increased significantly over the past 20 years. Those at risk include an aging population with associated comorbidities, and those at highest risk are the growing population of PWID. The significant contribution by the latter group to the rising incidence of PSI has been identified in published reports from widely diverse regions of the world. We have identified this problem in a large geographic region in and around northeast NYS, an area composed of predominantly rural communities where substance abuse treatment resources may be lacking. The burden of the opioid epidemic in rural communities is not unique to this geographic area. The management of PSI consumes large amounts of healthcare resources. Spine infections constitute a complex infectious disease, and the impact of ISUD significantly adds to the complexity. Our findings can help inform hospitals, and state and federal agencies regarding the need for expanding community-based harm reduction programs and services. In addition, the staggering costs associated with inpatient care of the infected ISUD population should prompt a consideration for developing strategies to implement outpatient IV antibiotic therapy programs for this challenging population. Currently, at our large, regional, tertiary care medical center, policy and procedures governing the administration of outpatient IV antibiotics, extending outpatient infusion center availability, and the use of IV antibiotics that require significantly less frequent administration are being evaluated. It remains to be determined whether these, or similar strategies, can be successfully employed by the smaller, rural, community-based hospitals in our region.

**Ethics approval and consent to participate**
The study was approved by the Albany Medical Center Committee on Research Involving Human Subjects (CFR 45.46.116(d); 5415) and the New York State Department of Health Institutional Review Boards (ref 19-030), and informed consent was waived.

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