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ORIGINAL RESEARCH

# Characteristics and Clinical Outcomes of Hospitalized Patients with Community-Acquired Pneumonia who are Active Intravenous Drug Users

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## Abstract

**Background:** Intravenous drug users (IVDU) have a 10-fold increased risk of community-acquired pneumonia (CAP) compared to the general population. There is scarce data available evaluating the clinical outcomes of IVDU hospitalized patients with CAP and that data mostly focuses on mortality. The objective of this study was to evaluate the clinical characteristics, incidence and outcomes of hospitalized patients with CAP in active intravenous drug users in Louisville, Kentucky.
**Methods:** This was a secondary data analysis of the University of Louisville Pneumonia study. IVDU patients were propensity score matched to a non-IVDU group. Study outcomes were time to clinical stability (TCS), length of stay (LOS), mortality at discharge, and mortality at 1 year. Stratified Cox proportional hazard regression was performed to evaluate TCS and LOS. Conditional logistic regression was performed to evaluate mortality. Statistical significance was defined as $p \leq 0.05$.
**Results:** From a total of 8,284 hospitalized patients with CAP reviewed, 113 patients were matched per group. Median (IQR) age for the IVDU was 33 (28-43) versus 36 (28-48) for the matched non-IVDU group ($p<0.001$). Analysis showed no association with TCS (stratified hazard ratio (sHR): 0.81; 95% CI: 0.58-1.14; p=0.227), LOS (sHR: 0.71; 95% CI: 0.50-1.01; p=0.053), mortality at discharge (conditional odds ratio (cOR): 1.67; 95% CI: 0.40-6.97; p=0.484) and mortality at 1 year (cOR: 1.125; 95% CI: 0.43-2.92; p=0.808).
**Conclusions:** This study shows that active IVDU hospitalized patients with CAP do not have worse outcomes when compared with non-IVDU hospitalized patients with CAP. Patients in the IVDU group were significantly younger. Since severity scores commonly used are heavily influenced by age, these will not likely be useful tools to assist the physicians with the site for care and management.

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## Introduction

Opioid use has reached epidemic proportions in the US with the State of Kentucky ranking third in the country for age-adjusted rates of drug overdose deaths[1]. The highest overdose deaths in Kentucky were reported in the city of Louisville [2]. Infectious diseases are a major cause of morbidity and mortality among intravenous drug users (IVDU)[3-6]. Malnutrition, immunodeficiency, homelessness and needle sharing play a major role in this groups increased risk.

Community-acquired pneumonia (CAP) is one of the most serious infectious complications that has been described in IVDU [7-10]. IVDU has also been associated with greater severity of CAP which may be evident by the development of empyema, complicated parapneumonic effusion, or need of mechanical ventilation [11, 12].

Despite the knowledge of IVDU being at increased risk of acquiring pneumonia, there are no studies evaluating if intravenous drug use is associated with poor outcomes in hospitalized patients with CAP. The objectives of this study were to compare hospitalized patients with CAP who are active IVDU to patients with no history of active IVDU in regards to clinical characteristics and clinical outcomes.

## Methods

*Study Design & Study Population*
This was a case control study. The cases, hospitalized patients with IVDU, and controls, hospotalized patients without IVDU were obtained performing a secondary data analysis of the University of Louisville Pneumonia study, a prospective

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population-based cohort study of all hospitalized adults with CAP who were residents in the city of Louisville, Kentucky, from June 1st, 2014 to May 31st, 2016 [13].

*Inclusion Criteria*

Diagnosis of CAP required the presence of criterion A, B, and C:

A. New pulmonary infiltrate on imaging (CT scan or chest x-ray) at the time of admission to the hospital.
B. Signs and Symptoms of CAP (at least one of the following):
   - New or increased cough
   - Fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F)
   - Changes in WBC (leukocytosis >11,000 cells/mm$^3$, left shift > 10% band forms/microliter, or leukopenia < 4,000 cells/mm$^3$
C. Working diagnosis of CAP at the time of hospital admission with antimicrobial therapy given within 24 hours of admission.

*Study Groups*

Cases (group 1): Hospitalized patients with CAP with active IVDU documented in the medical record.

Controls (group 2): Hospitalized adults with CAP who did not have documentation of actively using intravenous drugs.

IVDU cases were matched 1:1 to control cases by age, race, and history of obesity (body mass index >30), current smoker, active alcohol use, chronic obstructive pulmonary disease, congestive heart failure, stroke, diabetes mellitus, HIV, renal disease, and liver disease.

*Study Variables*

- Patients' characteristics: demographics, medical and social history, physical, and laboratory findings were collected if documented in the medical records.
- Severity of disease: assessed by the following variables – acute altered mental status on admission, need of intensive care, ventilatory support, or vasopressor on the day of admission, pneumonia severity index risk class IV or V.
- Complications: defined as the presence of persistent bacteremia and/or endocarditis.

*Study Outcomes*

- Time to clinical stability (TCS): A patient was defined as clinically stable the day that the following four criteria were met:
  1. Improvement in cough and shortness of breath
  2. Lack of fever for at least 8 hours
  3. Improving leukocytosis (decreased at least 10% from the previous day)
  4. Tolerating oral intake with adequate gastrointestinal absorption

  Patients were evaluated daily within the first 7 days of hospitalization to determine the day when clinical stability was reached.

- Length of hospital stay (LOS): defined in days and calculated for each patient as the day of discharge minus the day of admission. Patients hospitalized for >14 days and patients who died prior to 14 days were censored at 14 days.

- Mortality: defined as death by any cause 1) during hospitalization and 2) at one year after discharge.

**Table 1** Patients' characteristics for both study groups

| Variable | IV Drug Users | Non IV Drug Users | P-value |
|---|---|---|---|
| Total Population | n=113 | n=113 | |
| **Demographics** | | | |
| Age, median (IQR[a]) | 33 [28, 43] | 36 [28, 48] | 0.364 |
| Male sex, n (%) | 66 (58) | 70 (62) | 0.684 |
| Black or African American Race, n (%) | 9 (8) | 6 (5) | 0.593 |
| **Medical and Social History, n (%)** | | | |
| BMI ≥ 30 | 20 (18) | 22 (20) | 0.864 |
| HIV infection | 3 (3) | 1 (1) | 0.614 |
| Renal disease | 17 (15) | 10 (9) | 0.218 |
| Liver disease | 47 (42) | 37 (33) | 0.215 |
| Congestive heart failure | 3 (3) | 3 (3) | >0.999 |
| Chronic obstructive pulmonary disease | 23 (21) | 30 (27) | 0.346 |
| Stroke | 5 (4) | 4 (4) | >0.999 |
| Current Smoker | 100 (89) | 103 (91) | 0.660 |
| Diabetes mellitus | 9 (8) | 5 (4) | 0.408 |
| Cirrhosis | 6 (5) | 7 (6) | >0.999 |
| Alcohol use | 21 (19) | 27 (24) | 0.416 |
| Nursing home resident | 3 (3) | 2 (2) | >0.999 |
| Hospitalized within 90 days | 24 (21) | 14 (12) | 0.109 |
| IV antibiotics within 90 days | 15 (13) | 7 (6) | 0.116 |
| Home infusion | 0 (0) | 3 (3) | 0.245 |
| Chronic dialysis | 3 (3) | 0 (0) | 0.245 |
| Home wound care | 1 (1) | 1 (1) | >0.999 |
| Oral antibiotics within 30 days | 13 (12) | 20 (18) | 0.258 |
| Neoplastic disease within past year | 0 (0) | 7 (6) | 0.021 |
| Pneumonia vaccination | 16 (14) | 20 (18) | 0.586 |
| Flu vaccination | 16 (14) | 23 (20) | 0.305 |
| **Physical Exam Findings, median (IQR)** | | | |
| Temperature (Degrees Celsius) | 37 [37, 38] | 37 [37, 38] | 0.231 |
| Respiratory rate (Breaths/Minute) | 24 [20, 30] | 20 [20, 26] | 0.008 |
| Systolic blood pressure (mmHg) | 106 [92, 121] | 112 [97, 127] | 0.094 |
| Diastolic blood pressure (mmHg) | 58 [49, 68] | 61 [54, 73] | 0.055 |
| Heart rate (Beats/Minute) | 116 [106, 131] | 113 [97, 125] | 0.047 |
| **Laboratory Findings, median (IQR)** | | | |
| Serum bicarbonate (mEq/L) | 25 [22, 27] | 25 [22, 28] | 0.611 |
| Blood Urea Nitrogen (mg/dL) | 14 [9, 20] | 12 [9, 15] | 0.077 |
| Serum glucose (mg/dl) | 132 [116, 165] | 122 [104, 146] | 0.012 |
| Hematocrit (%) | 36 [33, 40] | 38 [34, 42] | 0.061 |
| Serum sodium (mEq/L) | 136 [133, 139] | 137 [134, 140] | 0.190 |
| **Severity of Disease, n (%)** | | | |
| Acute altered mental status on admission | 33 (29) | 18 (16) | 0.026 |
| Need of intensive care on admission | 37 (33) | 20 (18) | 0.014 |
| Need of ventilatory support on admission | 21 (19) | 15 (13) | 0.363 |
| Need of vasopressors on admission | 6 (5) | 3 (3) | 0.496 |
| Pleural effusion | 19 (17) | 21 (19) | 0.862 |
| PSI Risk Class IV or V[b] | 35 (31) | 26 (23) | 0.231 |

[a]IQR: Interquartile range
[b]PSI: pneumonia severity index

*Statistical Analysis*

Descriptive statistics were performed, with comparisons between groups analyzed by using a Chi-squared test or Fisher's exact test for categorical data and the Wilcoxon-Mann-Whitney U test for continuous data. Kaplan Meier curves were created for TCS and LOS. Differences in outcomes adjusting for propensity score matching were analyzed using stratified Cox proportional hazards regression for TCS and LOS and conditional logistic regression for mortality during hospitalization and at one year. Differences are reported as stratified hazard ratios (sHR) or conditional odds ratios (cOR), respectively.

## Results

A total of 113 patients with active IVDU and 113 patients matched controls were enrolled in the study.

Patients' characteristics are shown in **Table 1**. Significant higher rates of acute altered mental status and need of intensive care were found in the IVDU group.

The IVDU group was found to have significantly more persistent bacteremia (20% vs. 1%, p < 0.001), significantly more endocarditis (14% vs 1%, p < 0.001), and significantly more pulmonary emboli (15% vs 1%, p < 0.001) than the non-IVDU group. Image characteristics compatible with septic emboli were seen in 10% of patients in the IVDU group compared to 0% in the non-IVDU group (p <0.001).

The top two organisms were *Staphylococcus aureus* (23% [35 patients] in the IVDU group versus 3% [275 patients] in the non-IVDU group, p= <0.001) and *Streptococcus pneumoniae* (3% in both groups, p= 0.438) as shown in **Table 2**. IVDU had higher rates of Methicillin-resistant *Staphylococcus aureus* (MRSA) and Methicillin-susceptible *Staphylococcus aureus* (MSSA) among positive cultures, (37% versus 11% and 25% versus 5%, respectively). In the IVDU group, MRSA was obtained from 11 blood cultures, 1 from both blood and sputum cultures and 1 from bronco alveolar lavage (BAL). Also from the IVDU group MSSA was obtained from 5 blood cultures, 6 from both blood and sputum cultures and 3 from sputum culture. Among the non IVDU group MRSA was obtained from 1 blood culture and 1 from BAL. From the control group MSSA was obtained from 1 sputum culture. Antiocrobial susceptibility patterns of these organisms were not collected.

Median (IQR) TCS was 2 (2, 5) days for IVDU group and 2 (1, 4) days for non-IVDU group (sHR: 0.81; 95% CI: 0.58-1.14; p=0.227). Kaplan-Meier curves for TCS are shown in **Figure 1**.

Median (IQR) LOS was 5 (2, 9) days for IVDU group and 4 (2, 6) days for non-IVDU group (sHR: 0.71; 95% CI: 0.50-1.01; p=0.053). Kaplan-Meier curves for LOS are shown in **Figure 2**.

Mortality rates during hospitalization were 4% for IVDU group and 3% for non-IVDU group (cOR: 1.67; 95% CI: 0.40-6.97; p=0.484). Mortality at one year was 12% for IVDU group and 14% for non-IVDU group (cOR: 1.125; 95% CI: 0.43-2.92; p=0.808).

**Table 2** Microorganisms isolated

| Organism | IV Drug Users, n (%) | Non IV Drug Users, n (%) |
|---|---|---|
| *Staphylococcus aureus* | 29 (72) | 3 (18) |
| *Streptococcus* other | 2 (5) | 3 (18) |
| *Streptococcus pneumoniae* | 2 (5) | 4 (24) |
| *Streptococcus pyogenes* | 2 (5) | 0 (0) |
| *Enterobacter* spp. | 1 (2) | 0 (0) |
| *Klebsiella pneumoniae* | 1 (2) | 0 (0) |
| *Pseudomonas aeruginosa* | 1 (2) | 0 (0) |
| *Respiratory Syncytial Virus A* | 1 (2) | 0 (0) |
| Rhinovirus/*Enterovirus* | 1 (2) | 2 (12) |
| *Aspergillus* spp. | 0 (0) | 1 (6) |
| Coronavirus HKU1 | 0 (0) | 1 (6) |
| Coronavirus OC43 | 0 (0) | 1 (6) |
| *Mycoplasma pneumoniae* | 0 (0) | 1 (6) |
| Parainfluenza Virus 4 | 0 (0) | 1 (6) |

## Discussion

This study shows that IVDU is not associated with poor outcomes in hospitalized patients with CAP. The more aggressive management that these patients may receive upon admission may be the reason for similar outcomes in both groups despite differences found in the severity of the disease. To our knowledge, this is the first study evaluating clinical outcomes in IVDU hospitalized with CAP.

Active IVDU presented with more severe CAP as evidenced by their higher rates of admission to the intensive care unit and altered mental status. The higher rates of altered mental status could be explained by drug overdose and consequent aspiration. Our findings are in concordance with published data indicating that active substance abuse is a predictor of more severe pneumonia and the need for more intensive management. Considering that IVDU patients tend to be younger, as shown in our study, scores are heavily influenced by age are those commonly used to assess severity at presentation to the hospital. These may not be useful tools to assist physicians in care and management of IVDU CAP patients.

It has been reported that IVDU patients develop more complications. In a study evaluating risk factors for complicated parapneumonic effusion and empyema, IVDU was independently associated with the development of these complications [11]. However, in our study, a lower number of IVDU presented with pleural effusions/empyema. This could be related to a higher percentage of patients with congestive heart failure in the non-IVDU group who may have developed effusions secondary to this baseline comorbidity and not the pneumonia. IVDU commonly developed persistent bacteremia and endocarditis, particularly in the tricuspid valve with the subsequent septic emboli to the lungs [14-16]. Our study also showed higher rates of persistent bacteremia and pulmonary embolism, both independently associated with poor outcomes. There was a higher percentage of patients with chest images compatible with septic emboli. This could indicate that the pneumonia is actually a consequence of infective endocarditis bringing the relevance of obtaining blood cultures on admission to the hospitals and allowing an early identification of this population.

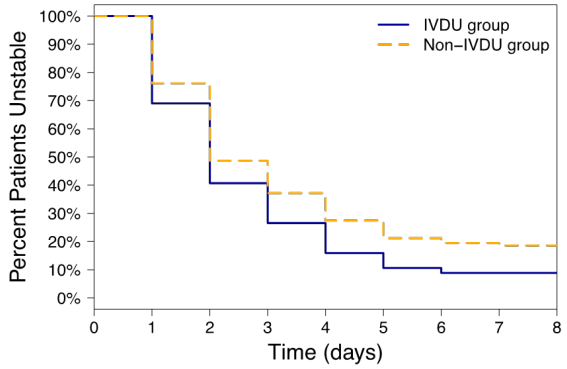


**Figure 1** Kaplan Meier Curves for Time to Clinical Stability

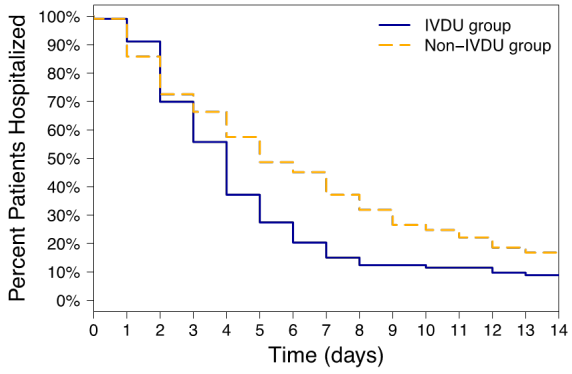


**Figure 2** Kaplan Meier Curves for Time to Hospital Discharge

*Staphylococcus aureus* has been reported as the most commonly isolated pathogen in IVDU hospitalized [3]. However, only 2% of these cases were due to MRSA. Our study shows high prevalence of MRSA among IVDU with over 50% of those with *Staphylococcus aureus* as the etiology being MRSA. Current guidelines for the management of CAP list injection drug use as a risk factor for *Staphylococcus aureus* without further recommendations regarding coverage for MRSA. [17] If our findings are confirmed, empiric therapy against MRSA might need to be considered in this population.

Our study has several strengths. The Louisville Pneumonia Study was a population-based study that included all consecutive hospitalized patients with CAP in the same city for a period of 2 years. Lack of exclusion criteria for enrollment into the study generates a database with a "real-life" approach to CAP management. For each individual case, more than 500 variables are collected resulting in a comprehensive database.

This study has also several limitations. First, limitations in care (do not resuscitate orders or decisions of not to escalate therapy), as well as standard preventive measures known to reduce complications (deep venous thrombosis/pulmonary embolism prophylaxis, early mobilization, etc.) were not captured in the study database. Second, the cause of death was not captured in the study database. Third, other variables like immunosuppressive conditions, immunosuppressive medications or long term steroid use was also not captured. Among IVDU group, duration of intravenous drug use was not captured which may influence outcomes. Finally, patients were defined as having a particular comorbidity if this comorbidity was documented in the medical record. Specific information related to comorbid diseases (e.g. pulmonary function tests, hemoglobin A1c, T cell count) was captured if available in the medical record. Antibiotics prior to enrollment were not analyzed.

In conclusion, our study shows that IVDU is not associated with poor outcomes among hospitalized CAP patients. IVDU patients were significantly younger and presented with more severe CAP as evidenced by higher rates of admission to the intensive care unit and altered mental status. These patients also developed significantly higher complications like persistent bacteremia, pulmonary emboli and endocarditis. A more aggressive management may be needed in this young population in order to achieve good outcomes and prevent further complications.

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**Conflict of Interest:** All authors declared no conflict of interest in relation to the main objective of this work.

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