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BRIEF REPORT

Risk Factors Associated With Outpatient Parenteral Antibiotic Therapy Program Failure Among Intravenous Drug Users

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Sixty-one percent of intravenous drug users (IVDUs) who received outpatient parenteral antibiotic therapy (OPAT) failed treatment. Hospital readmission and adverse drug reactions occurred in 25%. By multivariate analysis, time since last IVDU was associated with failure (P = .04). Intravenous drug users requiring OPAT are at high risk for failure; additional studies are needed to explore alternatives.

Keywords. OPAT; IVDU; IVDA; outpatient antibiotics.

Outpatient parenteral antibiotic therapy (OPAT) has become the standard of care in many countries [1]. OPAT programs have been shown to be a safe, efficacious, and cost-effective alternative to hospitalization for the treatment of infections that require prolonged treatment [1]. In most circumstances, OPAT is reserved for patients who are clinically stable, who reside in a stable environment, and have a caregiver available to aide with the delivery of intravenous (IV) antibiotics [2]. As programs continue to grow, however, so too does the need to serve higher-risk patient populations. Intravenous drug users (IVDUs) are a rapidly growing population that often requires long-term IV antimicrobial therapy [3, 4]. Indeed, the number of people self-reporting heroin use within the past year doubled from 2002 to 2013 [5]. Moreover, the number of hospitalizations related to opioid abuse or dependence with associated serious infection sharply increased over the same period [4]. To date, only a single study evaluating the effectiveness of OPAT among IVDUs has been reported. In this study, the investigators describe favorable outcomes among IVDUs who received OPAT at an infusion center [6]. Such studies are particularly important given the logistic and financial barriers of prolonged inpatient treatment of infections among IVDUs. To this end, OPAT costs just 41% of what comparable inpatient antibiotic administration would cost [7], and it is estimated to save ~$4 million/year [8]. In light of the limited data and the growing need to provide OPAT to IVDUs, our goal was to report our initial experience providing OPAT to this population. Our objectives were to define the prevalence of OPAT among IVDUs eligible for hospital discharge and to identify factors associated with OPAT failures.

METHODS

To meet these objectives, we conducted a retrospective cohort study of all IVDUs on IV antimicrobial therapy who were eligible for hospital discharge at the University of Pittsburgh Medical Center between December 2013 and January 2015. Intravenous drug user was defined as self-reporting of IVDU or a positive urine drug screen plus suspicion of IVDU. We defined active IVDU as reported use within the 4 weeks preceding onset of infection. To measure the efficacy of OPAT, we defined OPAT failure as any of the following: worsening or ongoing infection requiring hospital readmission within 30 days, worsening or ongoing infection resulting in prolonged antibiotic therapy, antibiotic noncompliance, noncompliance with follow-up clinic appointments, or death during treatment course. Antibiotic noncompliance was further defined as any missed antibiotic doses identified through patient interviews, nursing notes, and visit encounters. To define adverse drug reactions (ADRs), we used the standard definition of an appreciably harmful or unpleasant reaction related to the use of a medication [9]. Neutropenia was defined as an absolute neutrophil count of less than 1500 cells/mm^3, and leukopenia was defined as a white blood cell count less than 4000 cells/mm^3. Acute kidney injury was classified as a 1.5-fold increase in serum creatinine levels from the baseline. Elevated liver function tests were defined as aspartate aminotransferase or alanine aminotransferase levels higher than 3 times the upper limit of normal (>123 IU/liter and >162 IU/liter, respectively), total bilirubin greater than 1.8 mg/dL, or a direct bilirubin greater than 0.4 mg/dL. Hypokalemia was defined as a serum potassium level of ≤3.3 mmol/liter.

Comparisons of dichotomous and continuous variables were made using Fisher's exact χ^2 and Mann-Whitney U test, respectively. Variables associated with OPAT failure at P values <.20 in univariate analysis were included in the multivariate logistic regression model using backward selection procedures. P values ≤.05 (2-tailed) were considered statistically significant. The study was approved by the University of Pittsburgh Institutional Review Board.

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RESULTS

During the study period, 118 patients receiving IV antibiotics with a history of IVDU were eligible for hospital discharge. Fifty-seven percent (67 of 118) were enrolled into our OPAT program. Patients not enrolled were either discharged on oral antibiotics (n = 33), remained hospitalized until the course of IV antibiotics was complete (n = 16), or died before hospital discharge (n = 2). Thirty percent (10 of 33) of patients discharged on oral antibiotics left the hospital against medical advice.

Among patients who received OPAT (n = 67), the median age was 34.5 years (range: 19–63 years), 53% were men, and 92% were white. At the time of discharge, the median Charlson Comorbidity Index was 1.5 (0–8). Fifty-one percent (34 of 67) of patients were active IVDUs; the median time since last reported IV drug use was 4 weeks. Sixty-nine percent (46 of 67) were discharged to a nursing facility, 30% (20 of 67) were discharged to home, and 1% (1 of 67) were discharged to a rehabilitation facility.

Endocarditis was the most common indication for OPAT (n = 35), followed by epidural abscess (n = 5), bacteremia without endocarditis (n = 3), skin or soft tissue infection (n = 3), and other infection types (Table 1); 19% (13 of 67) of patients had more than 1 infection type. *Staphylococcus aureus* was the causative pathogen in 69% (46 of 67) of cases; 67% (31 of 46) of *S aureus* isolates were methicillin-susceptible. Other pathogens were identified less frequently (Table 1). Nine percent (6 of 67) of cases involved polymicrobial infections, whereas 7% (5 of 67) were culture-negative.

Thirty-three percent (22 of 67) of patients received vancomycin and 27% (18 of 67) received nafcillin. Other antibiotic regimens are listed in Table 2. Twenty-one percent (14 of 67) of patients required a change in antibiotic therapy due to ADRs

Table 1. Risk Factors for OPAT Failure

Factor	Overall (n = 67)	Success (n = 26)	Failure (n = 41)	Univariate *P* Value	Multivariate *P* Value	OR (95% CI)
Median age in years (range)	34.5 (19–63)	34 (25–62)	35 (19–63)	.82		
Median weeks since last IV drug use (range)	4 (0–999)	8 (0–999)	3 (0–520)	.02	.041	1.003 (1.001–1.006)
Median Charlson Comorbidity Index (range)	1.5 (0–8)	2 (0–7)	1 (0–8)	.54		
Adverse drug event to antibiotic, n (%)	17 (25)	6 (22)	11 (27)	.78		
Outpatient ID appointment kept, n (%)	42 (63)	19 (70)	23 (56)	.31		
Hospital Disposition						
Home, n (%)	20 (30)	6 (22)	14 (34)	.42		
Nursing facility, n (%)	46 (69)	20 (74)	26 (63)	.59		
Drug rehabilitation facility, n (%)	1 (1)	1 (4)	0 (0)	NA		
Infection Type[a]						
Endocarditis[b], n (%)	35 (52)	14 (54)	21 (51)	>.99		
Epidural abscess, n (%)	5 (7)	3 (12)	2 (5)	.13		
Bacteremia, n (%)	3 (4)	1 (4)	2 (5)	>.99		
Skin or soft tissue, n (%)	3 (4)	1 (4)	2 (5)	>.99		
Other[a], n (%)	8 (12)	3 (12)	5 (12)	>.99		
More than on type, n (%)	13 (19)	4 (15)	9 (22)	.75		
Pathogen						
Staphylococcus aureus	46 (69)	20 (74)	26 (63)	.29		
Streptococci, alpha hemolytic, or viridans group	5 (7)	1 (4)	4 (10)	.64		
Enterococcus faecalis	3 (4)	1 (4)	2 (5)	>.99		
Polymicrobial	6 (9)	2 (8)	4 (10)	>.99		
Culture negative	5 (7)	2 (8)	3 (7)	>.99		
Other	2 (3)	0 (0)	2 (5)	.52		
Antibiotic Regimen						
Vancomycin, n (%)	22 (33)	9 (35)	13 (32)	>.99		
Nafcillin	18 (27)	8 (31)	10 (24)	.58		
Cefazolin	7 (10)	2 (8)	5 (12)	.70		
Oxacillin	5 (7)	3 (12)	2 (5)	.37		
Ceftriaxone	4 (6)	2 (8)	2 (5)	.64		
Other	11 (17)	2 (8)	9 (22)	.18		

Abbreviations: CI, confidence interval; ID, infectious diseases; IV, intravenous; OPAT, outpatient parenteral antibiotic therapy; NA, not applicable; OR, odds ratio.

[a]Other infection types (n): osteomyelitis (2), myositis (1), diskitis (2), prosthetic joint infection (1), tenosynovitis (1), psoas abscess (1).

[b]All patients with endocarditis had concomitant bacteremia except one case, which was culture negative.

Table 2. Antibiotics Resulting in Adverse Drug Reactions

Drug	Number Treated, n (%)	Number with ADR, n (%)	Description of ADRs
Vancomycin	22 (33)	6 (27)	5 patients had neutropenia or leukopenia and 1 patient had AKI
Nafcillin	18 (27)	5 (28)	1 patient each had AKI, drug fever, thrombotic thrombocytopenic purpura, hypokalemia, and rash
Cefazolin	7 (10)	1 (14)	1 patient had pancytopenia
Oxacillin	5 (7)	3 (60)	2 patients had elevated LFTs and 1 patient had leukopenia
Ceftriaxone	4 (6)	0 (0)	
Other	11 (17)	2 (18)	1 patient had AKI on piperacillin-tazobactam plus vancomycin and 1 patient had neutropenia on ampicillin

Abbreviations: ADR, adverse drug reactions; AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test.

(n = 11) or new/ongoing infections (n = 3). Overall, 25% (17 of 67) of patients had an ADR to their prescribed therapy (Table 2).

DISCUSSION

We identified OPAT failure in 61% (41 of 67) of patients. Reasons for failure included 30-day readmission (41%), worsening infection requiring prolonged antibiotics (24%), missed clinic follow-up visit (17%), noncompliance with antibiotic therapy (10%), death (5%), and documented line manipulation (2%). Risk factors for OPAT failure included more recent IVDU (3 weeks vs 8 weeks; $P = .02$), but not the presence of ADRs (22% vs 27%; $P = .78$) (Table 1). By multivariate analysis, time since last IVDU was independently associated with OPAT failure (odds ratio = 1.003 per week; 95% confidence interval, 1.0001–1.006; $P = .041$).

To our knowledge, this is the first study to assess the efficacy of OPAT among IVDUs. Our most notable finding is that only 39% of IVDUs were able to complete their prescribed OPAT, which was due to a combination of clinical and social factors. The most common reason for failure was 30-day readmission to the hospital (25% of all IVDUs on OPAT), which is significantly higher than the 14% (267 of 1901) readmission rate among non-IVDU patients at our center ($P = .02$; data provided by K. Sheridan, written personal communication on 15 February 2017). The higher failure rates reported here attest to the complex nature of treating IVDUs receiving OPAT, who tend to have severe, life-threatening infections such as endocarditis. In contrast, OPAT clinical failures are rare among general, non-IVDU populations [10], who have various infections but tend to be older with more comorbid conditions. The disproportionately high rate of clinical failure among IVDUs is compounded by a high rate of ADRs. It is clear from this investigation that additional steps are needed to best care for IVDUs requiring OPAT. Our definition of OPAT failure is supported by previous studies [11] and identified time since last IVDU as an independent predictor of failure. Most notably, we identified both clinical and social factors that contributed to failures. Not surprisingly, active (or recent) IVDU may lead to poorer patient outcomes. Accordingly, the use of OPAT among such patients should be carefully scrutinized and potentially avoided. On balance, however, we found that patients with remote histories of IVDU (>5 years) had much lower rates of failure (21%). These data suggest that a detailed patient history may identify IVDU patients who are suitable for OPAT; however, further studies are needed to confirm these findings.

The present study is also noteworthy for the new insight it provides into the microbiology of IVDU infections that require OPAT. Although we have corroborated previous reports describing the predominance of *S aureus* as the causative pathogen in infective endocarditis among IVDUs, we have extended the literature for other common infection types such as epidural abscesses and osteomyelitis [12]. Not surprisingly, we found that methicillin-susceptible *S aureus* was the most common pathogen recovered across all infections among IVDUs. However, it is notable that a significant percentage of IVDUs develop infections due to more than 1 organism or are treated empirically.

Next, our investigation supports recent findings regarding the poor tolerability of vancomycin and nafcillin used in the OPAT setting [13, 14]. Among our IVDU population, approximately one third of patients receiving these agents experienced an ADR. In comparison, fewer patients experienced ADRs with cephalosporins, cefazolin, or ceftriaxone. Where clinically appropriate, the cephalosporins may be more amenable to OPAT given their excellent tolerability [13]. This is particularly important for IVDUs because our overall rate of ADRs appears to be higher than ADR rates reported among other patient populations [10]. It is not immediately apparent why ADR rates are higher among IVDUs; however, future investigations are warranted to identify socioeconomic and clinical factors that may contribute to this disparity.

CONCLUSIONS

Taken together, we hope that this study opens the door to future investigations that may provide a deeper understanding of the complex factors that contribute to the high rates of OPAT failure among IVDUs. Specific research objectives should include the effectiveness of long-term oral antibiotics as an alternative to OPAT and the utility of residential addiction treatment

at the time of OPAT [15]. Like all retrospective studies, ours has limitations, including its single-center design and limited sample size. Accordingly, the high rates of ADRs observed in our IVDU population may be due to random chance alone, and this merits investigation in future studies. It is also important to acknowledge that defining current and past IVDU is arbitrary, and we were limited to information collected from patients or documented in the electronic medical record. Nevertheless, our study helps to fill a widening knowledge gap of OPAT efficacy among IVDUs. Identification of recent or ongoing IVDU may be considered as a contraindication to OPAT based on our analysis to date.

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