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MAJOR ARTICLE

Long-Acting Lipoglycopeptides: "Lineless Antibiotics" for Serious Infections in Persons Who Use Drugs

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Background. Injection drug use is associated with serious infections. Due to challenges with medical management of addiction, relapses and additional infections are common. Persons who use drugs (PWUD) are more likely to leave against medical advice before completing treatment, which could result in treatment failure. Prolonged intravenous (IV) antimicrobial therapy in PWUD may be complicated by concern for IV catheter misuse, sometimes requiring prolonged hospitalization. Ideal alternatives would provide the following: (1) high success rate; (2) reduced rate of medical complications; (3) improved safety profiles; and (4) improved cost-effectiveness. Long-acting lipoglycopeptides present such opportunity for treatment of serious Gram-positive infections.

Methods. We performed a system-wide, retrospective analysis of adults admitted to University of Colorado Health from September 2015 to June 2018 and treated with dalbavancin or oritavancin based on clinical judgment of their treating physicians.

Results. Fifty-six patients met inclusion criteria (17 PWUD vs 39 non-PWUD). The PWUD group were younger, healthier by Charlson comorbidity index, more likely insured by Medicaid, and admitted for conditions requiring longer treatment. Ten patients were lost to follow-up. Of the patients with follow-up, clinical failure was met in 1 PWUD patient (6%) and 6 non-PWUD patients (15%) (P = .413). The median hospital length-of-stay reduction was 20 days (interquartile range [IQR], 10–30 days) in PWUD vs 11 days (IQR, 9–14 days) in non-PWUD; P = .133. Estimated median savings were $40 455.08 (IQR, $20 900.00–$62 700.00) in PWUD vs $19 555.08 (IQR, $15 375.08–$23 735.08) in non-PWUD; P = .065.

Conclusions. Long-acting lipoglycopeptides may be equally effective as standard-of-care, present a safety advantage, and secure earlier discharge and significant cost-savings.

Keywords. dalbavancin; injection drug use; intravenous drug use; oritavancin; *Staphylococcus*.

Injection drug use is associated with serious infectious complications that can require prolonged antibiotic therapy [1–4]. Treatment of infections in the context of a substance use disorder (SUD) are challenging, presenting unique complications and a high risk of recurrent infections in the context of substance use relapse [5–7]. Individuals with SUD are also at higher risk for infections with multidrug-resistant (MDR) pathogens due to histories of incomplete treatment courses that are common after leaving against medical advice [8, 9]. Furthermore, frequent contact with the healthcare system also increases these patients' risk for colonization and infections with MDR pathogens [5, 10]. Even in instances when outpatient parenteral antimicrobial therapy (OPAT) is attempted, persons with SUD may experience readmissions and catheter-related complications [11–13].

After discharge from the hospital, relapse to substance use is common, and few hospitals currently have inpatient addiction medicine consultation services to address these issues [14]. Inpatient addiction treatment with linkage to outpatient care could improve treatment completion rates in these patients [15]; however, it would not adequately address the potential concerns that remain regarding safety issues with long-term maintenance of advanced intravenous (IV) access (eg, peripherally inserted central catheter [PICC] or tunneled central venous catheter/port) during the period of acute care hospitalization or after discharge.

The concern regarding safe management of PICCs or ports in patients with SUD result in patients requiring prolonged inpatient stays for IV antibiotics and/or increased cost of outpatient therapy through intensive monitoring and/or daily antibiotic treatments via outpatient infusion centers. Alternative treatments with high success rates, reduced rate of medical complications, improved safety profiles from the perspective of substance misuse, and improved cost-effectiveness are needed to address these unique problems.

Although oral antibiotics with high bioavailability are a possible solution, many clinicians are reluctant to use this route of administration. Typically, currently available agents lack desirable safety and effectiveness profiles as reliable replacements

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for parenteral agents. Moreover, the effectiveness of these oral therapies is also dependent on patient adherence to unobserved daily self-administration of antibiotic(s). An added consideration with oral therapy is that a majority of studied regimens include concurrent rifampin administration, which poses significant risks for drug interactions with both illicit substances abused and the medications used to manage SUD. Novel long-acting IV lipoglycopeptides (laLGP), such as dalbavancin [16, 17] and oritavancin [18, 19], appear to present a unique opportunity for the treatment of complicated bacteremia and other deep-seated infections due to susceptible Gram-positive organisms, which appear more prevalent in persons who use drugs (PWUD) [20]. These agents (1) have potent in vitro activity against a broad array of Gram-positive pathogens, (2) are well tolerated with few significant side effects or medication interactions, and (3) offer built-in treatment adherence owed to their extremely long half-life. Although clinical trials for these indications are currently lacking, retrospective reports accumulating in the literature seem to suggest that the effectiveness of these agents are almost equivalent to current standard-of-care in the general population [21–25] and may be even improved when compared with the standard-of-care in PWUD [26]. The utilization of laLGPs would also allow for appropriate full-spectrum addiction care in specialized facilities that are otherwise rarely equipped to manage patients with advanced IV access (ASAM [American Society of Addiction Medicine] Criteria facilities levels 2 and 3) [27]. Furthermore, laLGPs have also been shown to be significantly more cost-effective than current standard-of-care [22, 28, 29]. Given the potential advantages of laLGPs in patients with SUD, we performed a focused secondary analysis of data collected for a retrospective review regarding clinical use of these antibiotics.

MATERIALS AND METHODS

Patient Selection and Evaluation

We conducted a system-wide, retrospective subanalysis from a previously published study describing adult patients admitted to University of Colorado Health from September 2015 to June 2018 [30]. Inclusion criteria included patients ≥18 years old and who received at least 1 dose of a laLGP. Patients were excluded if they had incomplete medical records. Dalbavancin and/or oritavancin ordering through the electronic medical record identified patients for evaluation and inclusion. After the data collection was completed, the database was deidentified for further analysis. Our healthcare system follows the Clinical and Laboratory Standards Institute's (CLSI) antimicrobial susceptibility guidelines, and we do not routinely test for laLGP susceptibilities; however, vancomycin has been shown to be a reliable surrogate for in vitro susceptibility of both laLGPs [31, 32]. The use of laLGPs was only approved for vancomycin-susceptible isolates (with the exception of laLGPs used for culture-negative infections or empirically for acute bacterial skin and skin-structure infections [ABSSSIs]).

Definitions

Persons who use drugs were identified by chart review for personal history of persons with injection drug or polysubstance use history based on their chief complaint/history of present illness, positive toxicology screen (when clinically indicated), or upon review of past medical history and social history (aided by findings on physical examination, ie, track-marks). Based on observed and documented clinician attitudes, we broadly included all patients who are typically not offered traditional OPAT due to fear of IV access misuse [33]. Clinical success was defined as no further clinical or microbiological evidence of active infection (resolution of signs and symptoms related to bacterial infection and clearance of cultures, if applicable) without the need for further Gram-positive targeted therapy due to clinical worsening within 60 days of the last dose of laLGP. Clinical failure was defined as lack of clinical response, relapse with the primary infection within 60 days of last dose of laLGP, the need for alternative Gram-positive therapy due to clinical worsening during laLGP therapy, or death. Two infectious diseases (ID) physicians and 3 ID pharmacists analyzed all clinical success and failure cases for confirmation of the findings. Adverse effects were any potential adverse drug reaction that occurred during laLGP infusion or within 7 days of infusion (if results were available).

Pharmacoeconomic Analysis

We carried out a cost minimization analysis in the PWUD group and compared the findings to the patients in the non-PWUD group who were non-OPAT candidates: both groups were otherwise facing the prospect of inpatient stay for the duration of their treatment with standard-of-care therapy. Projected reduction in hospital length of stay (LOS) was extrapolated from a typical treatment duration for a given condition. Projected treatment duration was found in the electronic medical record through ID physician documentation or determined by interpretation of the authors. Projected hospital days saved were determined by subtracting projected hospital LOS from actual hospital LOS, which was then multiplied by the average cost of an inpatient hospital day ($2090) [29]. From this number, we then subtracted the costs of inpatient administration of oritavancin (1200 mg: $3584.40) and/or dalbavancin (1500 mg: $5524.92) multiplied by the number of inpatient infusions of oritavancin and dalbavancin, respectively: (projected LOS – actual LOS) × ($2090) – (cost of dalbavancin/oritavancin × number of inpatient infusions).

Statistical Analysis

Nominal variables were evaluated using χ^2 and Fisher's exact tests. Continuous variables were analyzed using Student's *t* test

or Mann-Whitney *U* test for parametric and non-parametric data, respectively. All analyses were conducted using SPSS, version 23.0 (SPSS Inc., Armonk, NY). All tests with *P* values <.05 were considered statistically significant.

Ethical Approval

The initial study was submitted and subsequently determined to be exempt from a full review by the Colorado Multiple Institutional Review Board before initiation. This subanalysis was also submitted to the Colorado Multiple Institutional Review Board before initiation and was also determined to be exempt from a full review.

RESULTS

Of 59 patients screened, 56 patients met inclusion criteria (PWUD = 17 patients [30%]; non-PWUD = 39 patients [70%]). Two patients were excluded due to an incomplete medical record, and 1 patient was excluded for having a laLGP ordered but never administered. The mean age of the total population was 47 ± 15 years, mean weight 82 ± 20 kg, with the majority male (59%) and white (82%). Other baseline and pertinent characteristics are listed in Table 1. Median hospital LOS was 6.0 days (interquartile range [IQR], 3.5–12.0 days) in the PWUD group and 6.0 days (IQR, 3.0–14.0) in the non-PWUD group. Overall, the median follow-up was 6.1 months (IQR, 3.7–11.8 months); however, all patients had at least 1 month of follow-up from their last dose of laLGP. Outpatient ID follow-up was obtained with 9 patients (53%) in PWUD group and 21 patients (54%) in the non-PWUD group.

The most common indications for laLGP use in the PWUD and non-PWUD groups, respectively (all non-significant), were ABSSSIs (~35% in both groups), osteomyelitis (35% vs 23%), and endocarditis (18% vs 5%). Other indications included catheter-related bacteremia (0% vs 5%) and pneumonia (0% vs 5%), with concomitant bacteremia present in 8 patients (47%) in the PWUD group and 14 patients (36%) in the non-PWUD group (*P* = .432) (Table 2). The indications listed as "other" in Table 2 (1 patient each) included a vancomycin-resistant *Enterococcus faecium* (VRE) hardware infection and methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia with septic emboli from unknown source in the PWUD group. In the non-PWUD group, these conditions included VRE peritonitis/bacteremia, VRE intra-abdominal abscess, VRE bacteremia in the setting of previous dual umbilical cord hematopoietic stem cell transplant, disseminated VRE with multifocal abscess, MSSA bacteremia status-post cervical myomectomy, MSSA/methicillin-resistant *Staphylococcus epidermidis* left ventricular assist device infection, methicillin-susceptible *S epidermidis* bacteremia from unknown source, *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*)/*Corynebacterium* spp prosthetic joint infection, *Streptococcus gordonii* bacteremia from unknown source, and fever of unknown origin (also 1 patient each). Overall, the majority of patients in our analysis received the laLGP as targeted therapy (85%); however, 6 (11%) and 2 (4%) patients received these drugs as empiric therapy and suppression, respectively.

Before initiation of the laLGP, previous antibiotics were prescribed throughout hospitalization in 15 patients (88%) in

Table 1. Baseline and Pertinent Characteristics[a]

Characteristic	PWUD (n = 17)	Non-PWUD (n = 39)	*P* Value
Age (years), mean ± SD	34.5 ± 10.9	52.0 ± 14.1	<.001
Weight (kilograms), mean ± SD	83.0 ± 23.3	82.0 ± 19.4	.876
Height (centimeters), mean ± SD	175.1 ± 13.6	172.3 ± 9.9	.393
Male	12 (71)	21 (54)	.242
White	15 (88)	31 (80)	.706
Charlson Comorbidity Index, median (IQR)	1.0 (0.0–2.5)	3.0 (1.0–4.0)	.010
Intensive care unit admission	1 (6)	12 (31)	.082
Infectious diseases consult	15 (88)	34 (87)	>.999
Insurance Status[b]	—	—	—
Medicare	1 (6)	12 (31)	.082
Medicaid	14 (82)	20 (51)	.029
Commercial	2 (12)	10 (26)	.309
Self-pay	0	2 (5)	>.999
VA	0	1 (3)	>.999
Previous hospitalization within 30 days	9 (53)	21 (54)	.950
30-day readmission	3 (18)	7 (18)	>.999
30-day readmission due to initial infection	1 (6)	3 (8)	>.999
Reinfection within 60 days	1 (6)	3 (8)	>.999
Outpatient infectious diseases follow-up	9 (53)	21 (54)	.950

Abbreviations: IQR, interquartile range; PWUD, persons who use drugs; SD, standard deviation; VA, Veteran's Administration.

[a]Data reported as n (%) unless otherwise noted.

[b]n not equal to patient number (n = 56) due to some patients having both primary and secondary insurances.

Table 2. Antimicrobial, Infection, and Microorganism Characteristics[a]

Characteristic	PWUD (n = 17)	Non-PWUD (n = 39)	*P* Value
Dalbavancin	12 (71)	28 (72)	>.999
Oritavancin	4 (24)	10 (26)	>.999
Dalbavancin and oritavancin	1 (6)	1 (3)	.519
Lipoglycopeptide doses (number), median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	.769
Previous antibiotic received	15 (88)	36 (92)	.634
Concomitant antibiotics	5 (29)	12 (31)	.919
Empiric	2 (12)	4 (10)	>.999
Targeted therapy	15 (88)	32 (82)	.707
Suppression	0	2 (5)	>.999
Hospital length of stay, median (IQR)	6.0 (3.5–12.0)	6.0 (3.0–14.0)	>.999
Lipoglycopeptide Indication	—	—	—
ABSSSIs	6 (35)	14 (36)	.965
Osteomyelitis	6 (35)	9 (23)	.349
Endocarditis	3 (18)	2 (5)	.158
Catheter-related bacteremia	0	2 (5)	>.999
Pneumonia	0	2 (5)	>.999
Other	2 (12)	10 (26)	.309
Source control, if applicable	11 (65)	26 (67)	>.999
Concomitant bacteremia	8 (47)	14 (36)	.432
Isolated Microorganisms[b]	—	—	—
MSSA	8 (47)	8 (21)	.058
MRSA	5 (29)	7 (18)	.480
Enterococcus faecalis	1 (6)	6 (15)	.421
Coagulase-negative *Staphylococcus* spp	0	7 (18)	.088
VRE	1 (6)	4 (10)	>.999
Other organism	0	8 (21)	.090
Clinical success	13 (77)	27 (69)	.409
Clinical failure	1 (6)	6 (15)	.413
In-hospital mortality	0	2 (5)	>.999
Adverse effects	0	6 (15)	.163

Abbreviations: ABSSSIs, acute bacterial skin and skin-structure infections; IQR, interquartile range; PWUD, persons who use drugs; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*; VRE, vancomycin-resistant *Enterococcus faecium*.

[a]Data reported as n (%) unless otherwise noted.

[b]n not equal to patient number (n = 56) because some patients were culture free, whereas other patients had polymicrobial infections.

the PWUD group and 36 patients (92%) in the non-PWUD group; overall, most commonly vancomycin or daptomycin (vancomycin, 41%; daptomycin, 12%; vancomycin and daptomycin [not concomitantly], 27%; neither vancomycin or daptomycin, 20%).

Staphylococcus aureus was the predominant organism in both groups. Methicillin-susceptible *S aureus* was isolated in 47% of PWUD and 21% of non-PWUD, whereas methicillin-resistant *S aureus* represented 29% and 18% in PWUD and non-PWUD groups, respectively. The second most common were *Enterococcus* spp, with *Enterococcus faecalis* in 6% of PWUD and 15% of non-PWUD patients, and VRE isolated in 6% and 10% of these groups, respectively. Coagulase-negative *Staphylococcus* spp were cultured in 18% of non-PWUD but none of the PWUD patients (Table 2). Source control was obtained in approximately 65% in both groups.

Dalbavancin was administered in 40 patients (71%), oritavancin in 14 patients (25%), and both laLGPs in 2 (4%) patients. The laLGPs were given for a median of 1 dose (IQR, 1–2 doses) in each group. Concomitant antibiotics during or after laLGP therapy were prescribed in 5 patients (29%) in the PWUD group and 12 patients (31%) in the non-PWUD group, most commonly metronidazole (6 cases), sulfamethoxazole/trimethoprim (2 cases), or tedizolid (2 cases).

Forty-six patients and 47 cases (because 1 patient was counted as a failure and success) were deemed fit to be included in our success/failure analysis, because appropriate follow-up documentation was not available in 10 of the 57 eligible cases who were thus excluded from the success/failure analysis. Two patients remained on suppression after successful primary treatment with appropriate follow-up. Of the included 46 patients (47 cases) with sufficient follow-up information, clinical failure was met in 1 patient (6%) in the PWUD group and 6 patients (15%) in the non-PWUD group ($P = .413$). One patient was classified as both a failure and success, because they failed oritavancin but succeeded with subsequent dalbavancin therapy. Further information regarding antimicrobial use, infection, and microorganism characteristics are listed in Table 2.

Although not statistically significant, there were clinically and economically observed differences in median hospital LOS reduction (PWUD, 20 days [IQR, 10–30 days] vs non-PWUD, 11 days [IQR, 9–14 days]; P = .133) and estimated median healthcare savings (PWUD, $40 455.08 [IQR, $20 900.00–$62 700.00] vs non-PWUD, $19 555.08 [IQR, $15 375.08–$23 735.08]; P = .065) between the 2 groups.

During the follow-up period for our total population, 4 patients experienced reinfection within 60 days of hospital discharge (PWUD, 1 [6%]; non-PWUD, 3 [8%]). Six patients experienced mild adverse effects potentially attributable to the laLGP, and all of them were in the non-PWUD group. One patient each experienced infusion reactions (itching, rash), nausea, chest tightness, IV line infiltration with edema, acute kidney injury, and headache. The patient with chest tightness had resolution when the rate of infusion was decreased. More importantly, the patient with acute kidney injury also suffered from dehydration and was concurrently using an angiotensin-converting enzyme inhibitor. The patient experiencing headache underwent a recent decompressive craniectomy.

DISCUSSION

In this comparative analysis of laLGP utilization, effectiveness and safety was demonstrated with substantial reductions in hospital LOS and composite healthcare cost savings, particularly among the PWUD group. Despite the retrospective nature of this study, a few remarkable differences became apparent in baseline characteristics (Figure 1). The patients who were in the PWUD group were significantly younger and healthier by Charlson comorbidity index (Table 1), which certainly fits with what is known about the PWUD population from the available literature [34, 35]. Although the breakdown of clinical success/failure rate did not reach statistical significance, it appears that PWUD patients did not have worse outcomes. This finding may correlate with their younger age and lower Charlson comorbidity index, as well as the benefit of a reliable systemic presence of IV-administered antibiotic compared with individualized courses of orally administered alternatives. Our findings parallel a similar trend of improved outcomes as observed by Bryson-Cahn et al [26]. More importantly, the reliable systemic presence of laLGPs along with a relatively favorable safety profile of these agents may offer some advantages even when

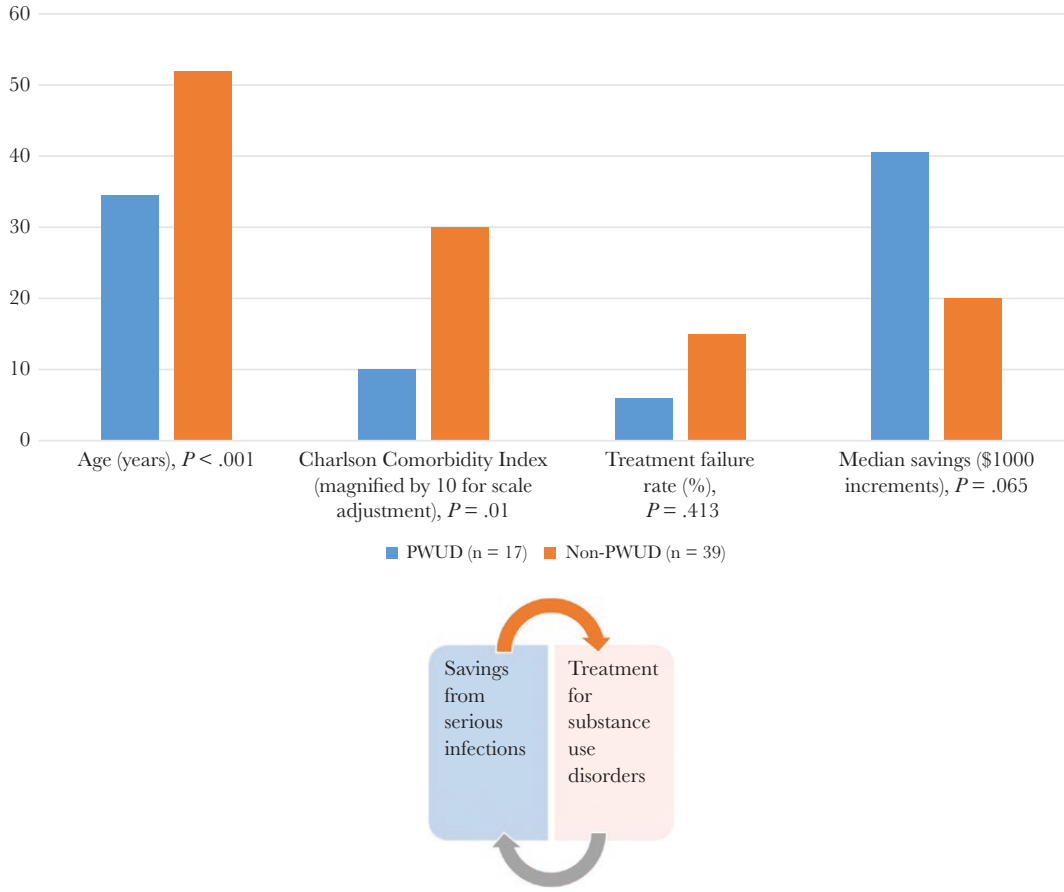

Figure 1. Notable differences observed and their potential for improved healthcare delivery. PWUD, persons who use drugs.

compared with reasonably bioavailable oral regimens, which have recently drawn attention as a replacement for prolonged IV courses [36–38]. These oral regimens still require daily, if not more frequent, dosing with some regimens posing a higher potential for toxicity and adverse events than the laLGPs. It is also important to note that there are minimal data for use of those nonstandard antibiotic approaches for serious infections in PWUD. Furthermore, individuals in the PWUD group were also significantly more likely to be insured by Medicaid compared with the non-PWUD patients.

Apart from the management of SUD, a primary concern among providers regarding the treatment of serious infections in the PWUD population revolves around complications from vascular access utilization for illicit drug use. This has been found to be significantly increased due to use of injection drugs (incidence rate ratio = 3.32, 95% CI = 1.16–7.46; $P = .01$) in a retrospective study that evaluated 1461 subjects among which 16 were PWUD [13]. However, the low number of accepted PWUD participants in this study reflects the level of skepticism among clinicians with respect to considering patients with history of use of injection drugs for OPAT [33]. The patients in the PWUD group may also have been selected based on provider perception that they would be reliable. As a result, the higher relative risk of complication may be an underestimate of the number of complications if conventional OPATs were readily offered to this population. Reports specifically evaluating OPAT in the PWUD population have shown mixed results [11, 12, 39, 40]. These studies have all been retrospective, and the numbers of participants with PWUD have been small. This uncertainty around safety suggests that well designed prospective evaluations of the treatment of serious infections with integrated treatment of SUDs are needed.

With the higher prevalence of Gram-positive pathogens responsible for serious infections in this population [15], laLGP use in lieu of OPAT would provide greater flexibility in this population, because it offers a full IV antibiotic course administration in 1 to 2 doses (in most instances) without the need for IV access after the infusion [16, 24]. Such flexibility would allow more time for scientifically based inpatient addiction treatment, as well as earlier discharge to specialized residential addiction treatment centers, and/or earlier linkage to outpatient SUD therapy, all of which are known to benefit this population [14, 15, 27]. However, a concern that remains unknown is the potential development of resistance given the long half-lives of (possible extended time below the MIC) and cross-resistance linked to the laLGPs. Werth et al [41] described a case in which the emergence of vancomycin and dalbavancin nonsusceptibility occurred after a patient was treated with these 2 antimicrobials.

Medicaid (comprising the majority of PWUD in our study) typically offers lower reimbursement rates than commercial insurers and Medicare; however, in many instances, Medicaid has fewer restrictions for coverage of conditions that are overrepresented in the population it serves and that are otherwise more restricted by commercial insurers or Medicare (eg, hepatitis C, addiction treatment). Based on the LOS and cost-minimization analysis differences between the groups, it appears that most patients from the PWUD group were admitted for conditions with longer treatment durations, thus requiring a greater cost expenditure. A limitation of our cost-minimization analysis is that it did not include mark-up fees, which are commonly added to physician-/nursing-administered drugs. Therefore, we are likely to be underestimating the potential cost savings. Moreover, there was a relatively low number of patients, especially in the PWUD group, and we did not observe a statistically significant difference in savings. Further research should expand these analyses to include larger patient cohorts with sensitivity analyses around cost-savings estimates.

CONCLUSIONS

Further studies regarding use of laLPGs for Gram-positive bloodstream and deep-seated infections are certainly needed, especially because the trends and implications shown in the currently available observational studies are encouraging. The projected potential for overall cost savings (by reducing hospital LOS) using laLGPs should be confirmed in prospective studies, which would ideally also demonstrate acceptable treatment efficacy. This may provide the opportunity for many patients to continue the treatment/recovery at their preferred home environment. The currently inadequate access to addiction services for PWUD can be improved in the inpatient as well as outpatient setting, including under Medicaid. Long-acting antibiotics may facilitate shorter time to hospital discharge, cost savings, and earlier SUD treatment engagement in outpatient or residential setting.

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