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Assessment of a Pharmacist-Led Antibiotic Time-out for Transition of IV Vancomycin to Oral Linezolid

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ABSTRACT

Introduction: Intravenous (IV) vancomycin requires therapeutic drug monitoring and line placement and may prolong hospital stay. Linezolid requires less monitoring, is orally bioavailable, and may expedite transitions of care. This study assessed the impact of a pharmacist-led antibiotic timeout for the transition from IV vancomycin to oral linezolid.

Methods: This single-center, quasi-experimental study included admitted adult patients receiving IV vancomycin for over 48 hours. Patients receiving vasopressors, of immunocompromised status, or with specific antibiotic indications were excluded. The primary outcome was the pharmacist intervention acceptance rate. Secondary outcomes included median hospital length of stay, median antibiotic treatment days, and incidence of adverse effects.

Results: Of the 317 screened patients, 94 were eligible for the antibiotic time-out assessment, of which 66 met the criteria for oral linezolid. Of those meeting the criteria, 27 interventions were made, of which 20 (74%) were accepted. The median length of antibiotic treatment days was six days between both groups ($p = .352$). No differences in safety outcomes were observed.

Discussion: A pharmacist-led antibiotic timeout for IV vancomycin to oral linezolid resulted in a high intervention acceptance rate and increased oral linezolid use without impacting safety outcomes. These results support the use of this strategy for antimicrobial stewardship.

Conclusion: This study illustrates the impact of a pharmacist-led antibiotic timeout for the transition from IV vancomycin to oral linezolid therapy as an antimicrobial stewardship tool.

Keywords: Linezolid, Vancomycin, Methicillin-Resistant *Staphylococcus aureus*, Pharmacist

INTRODUCTION

Antimicrobial stewardship has gained significant importance in recent years as a crucial strategy to combat the rising threat of antimicrobial resistance. Antimicrobial stewardship programs (ASPs) are vital in optimizing antimicrobial use and improving patient outcomes (Fishman,

2006). To achieve these goals, the Infectious Diseases Society of America (IDSA) recommends the implementation of prospective audits with intervention and feedback initiatives such as an antibiotic "time-out" (ATO). An ATO prompts a reassessment of antibiotics' continuing need and choice and focuses on de-escalation from empiric broad-spectrum

therapy once clinical and laboratory data becomes available. One study found that frequent modifications to therapy with the implementation of an ATO led to a 25% increase in the appropriateness of the antibiotic regimen on antibiotic days 3 through 5 (Thom et al., 2019). A similar study found that ATO interventions decrease inappropriate therapy by 12% (Senn et al., 2004).

Intravenous (IV) vancomycin is a broad-spectrum gram-positive active antimicrobial agent frequently targeted by ASPs due to the risk of nephrotoxicity and cost of monitoring. Intravenous vancomycin is often overused for empiric coverage targeted at potential methicillin-resistant *Staphylococcus aureus* (MRSA) infection. One study found that IV vancomycin prescribed empirically was continued inappropriately in 25% of cases (Kim et al., 2015). Another study found that only 8.4% of patients receiving empiric IV vancomycin therapy subsequently had a positive MRSA culture (Waters & Caraccio, 2018).

Once prohibitive due to concerns for drug costs and toxicities (e.g., thrombocytopenia, serotonin syndrome), linezolid has recently emerged as a reasonable alternative agent to IV vancomycin with greater safety data along with lower-cost generic products. Linezolid is a weak, reversible monoamine oxidase inhibitor (MAOI) with antibacterial properties. Using oral linezolid in place of IV vancomycin can avoid the risk of vancomycin-associated nephrotoxicity, therapeutic drug monitoring requirements, and the need for IV access, and may expedite hospital discharge. Linezolid has demonstrated promising clinical outcomes when compared to vancomycin for several MRSA infections, including pneumonia and skin and soft tissue infections (Stevens et al., 2002; Kalil et al., 2010; Chavanet, 2013; Yue et al., 2013). The use of oral linezolid to reduce healthcare costs has been described in several retrospective studies, and there are data to support that it can shorten hospital length

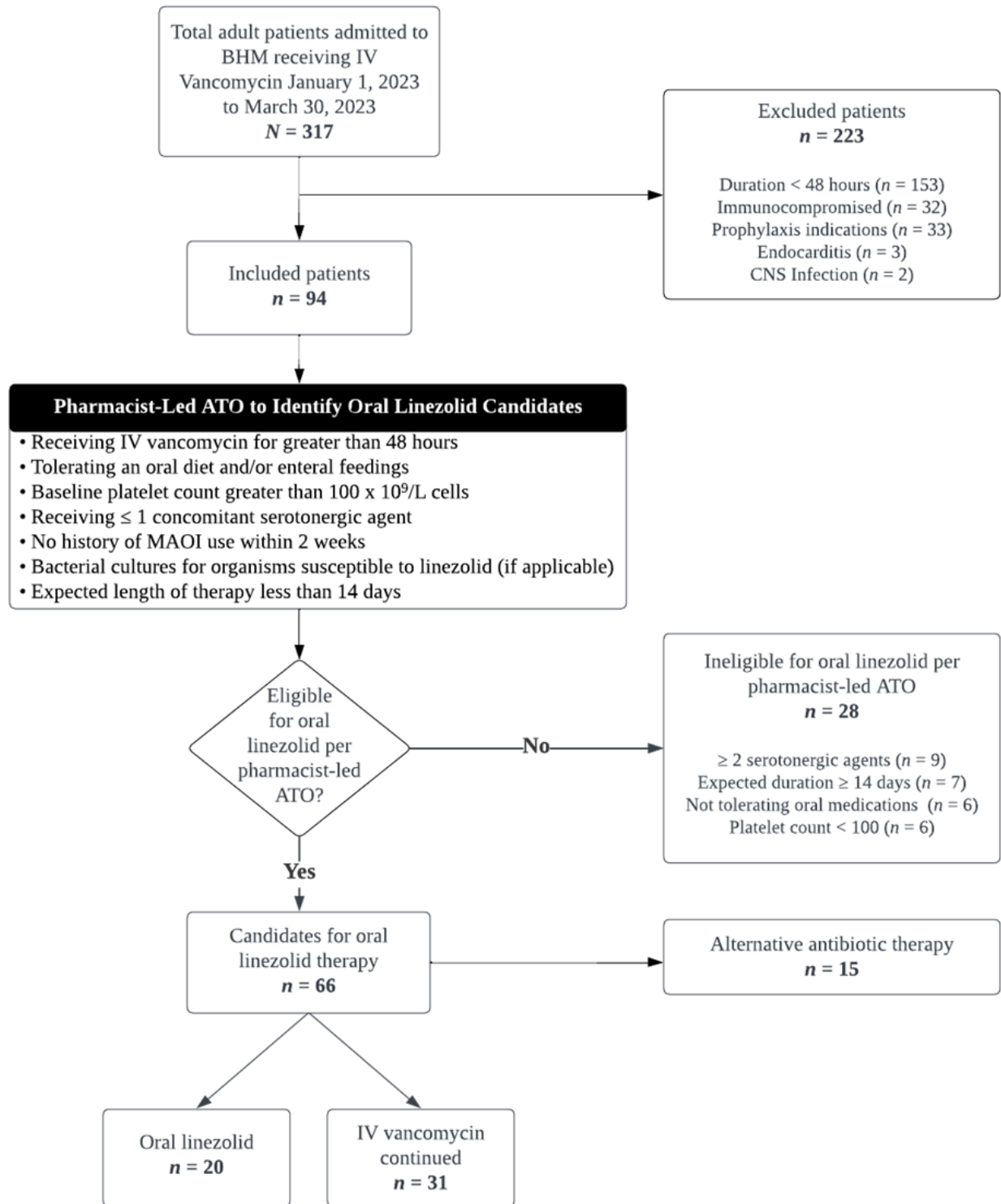
of stay (Parodi et al., 2003; McCollum et al., 2003; Plosker & Figgitt, 2005; Caffrey et al., 2014; Cua et al., 2022). The purpose of this study was to assess the impact of a pharmacist-led ATO for transitioning patients from IV vancomycin to oral linezolid.

METHODS

This single-center, quasi-experimental study was conducted at a hospital in Miami, a 900-bed tertiary non-profit community hospital. Adult patients admitted between January 10, 2023, through March 31, 2023, receiving IV vancomycin for greater than 48 hours were eligible for ATO assessment in this study. Patients were excluded if they had an active vasopressor order during the ATO, if the patient was immunocompromised (defined as receiving active chemotherapy, use of steroids greater than or equal to 10 mg of prednisone or equivalent for 14 days, presence of neutropenia with an absolute neutrophil count below 1,000 cells/mm³, or leukopenia with white blood cell count below 4,000 cells/mm³), or receiving IV vancomycin for central nervous system (CNS) infections, endocarditis, febrile neutropenia, or surgical prophylaxis.

A clinical pharmacist assessed IV vancomycin orders for ATO eligibility after 48 hours of IV vancomycin treatment. All patients eligible for assessment underwent screening (criteria included in Figure 1) utilizing a pharmacist-driven ATO. Patients were considered ATO candidates for transition to oral linezolid after 48 hours of IV vancomycin therapy if they were tolerating an oral diet and/or oral medications, had a platelet count greater than $100 \times 10^9/L$, were receiving less than two concomitant serotonergic agents, had no history of MAOI use within two weeks of intervention, had microbial cultures for organisms susceptible to linezolid (if available), and had an expected length of therapy less than 14 days. Following the screening, the pharmacist contacted the prescriber and recommended the transition of antibiotic thera-

Figure 1
Patient Screening, Antibiotic Time Out Criteria, and Ultimate Patient Disposition



Note. Adult, immunocompetent patients receiving IV vancomycin for greater than 48 hours, excluding specific antibiotic indications for CNS infections, endocarditis, febrile neutropenia, or surgical prophylaxis, were assessed by a clinical pharmacist for transition to oral linezolid. A clinical pharmacist reached out to the provider to recommend antibiotic therapy transition.

py for identified candidates. All data was collected retrospectively through chart review following the conclusion of the patient's hospital stay.

The primary outcome of this study was the pharmacist intervention acceptance rate. Secondary outcomes were explored in patients who were eligible for the intervention and continued vancomycin or received oral linezolid to ascertain if there were any benefits of intervention to oral therapy compared to the standard of care (IV vancomycin) during hospitalization. These endpoints included hospital length of stay in days, antibiotic treatment days, vancomycin doses avoided, vancomycin levels avoided, thrombocytopenia, and acute kidney injury. Vancomycin doses avoided were calculated with the assumption that IV vancomycin was to be continued at the same dose and frequency at the time of transition for the entire duration of antibiotic therapy. Calculation of vancomycin levels avoided assumed levels would have been obtained every 48 hours. Thrombocytopenia was defined as a platelet count of less than $100 \times 10^9/L$ cells or a 50% drop from baseline after therapy initiation. Acute kidney injury was defined by Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria as a serum creatinine

either three times that of baseline, greater than 4.0 mg/dL, or an acute rise greater than 0.5 mg/dL within 48 hours (Bellomo et al., 2004).

Mann-Whitney U test and Fisher's Exact test were used to evaluate continuous and categorical variables, respectively, as assessed in the primary and secondary endpoint metrics. A *p* value of less than .05 was considered significant. The local institutional review board approved the study.

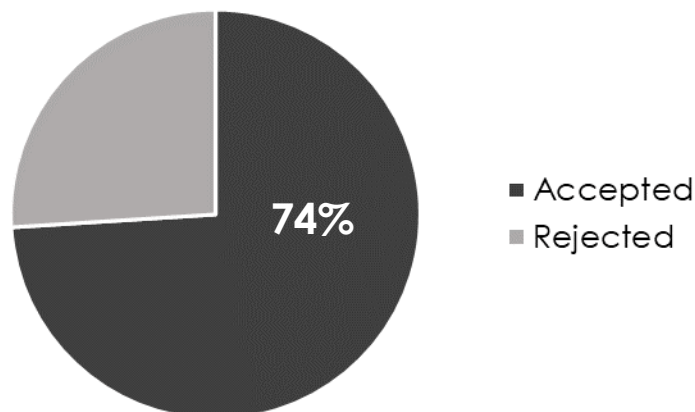
RESULTS

In screening 317 patients (Figure 1), 94 were eligible for the pharmacist-led ATO assessment. Of those eligible for the assessment, 66 met the criteria for transition to oral linezolid. For those meeting the criteria, 27 interventions were made, of which 20 were accepted (74%) (Figure 2). Of the accepted interventions, 15 led to conversion to oral linezolid, and five led to de-escalation to other oral therapies. For the five patients who transitioned to other oral therapy that was not linezolid, two patients received doxycycline, and three patients received amoxicillin-clavulanate.

Evaluating the 66 patients meeting transition criteria to oral linezolid, 20 received oral linezolid (15 due to the ATO and five outside of the ATO intervention),

Figure 2

Primary Outcome: Pharmacist-Led Antibiotic Time Out Acceptance Rate



31 were continued on vancomycin, and 15 received an alternate antibiotic. To characterize the 51 patients specific to the intervention who completed therapy with linezolid or vancomycin, Table 1 details their baseline characteristics, and Table 2 provides secondary outcomes for this group.

The one patient listed in Table 2 who received linezolid concomitantly with two serotonergic agents was placed on therapy outside the ATO, and no adverse effects were identified. One patient experienced thrombocytopenia during treatment with oral linezolid. This patient was transitioned back to IV vancomycin with no adverse clinical outcomes detected due to the thrombocytopenia. A total of 26 IV vancomycin doses were avoided during the hospital course, along with eight vancomycin levels in the

20 patients who received oral linezolid (Table 3).

DISCUSSION

This study demonstrated the impact of a pharmacist-led ATO for transitioning from IV vancomycin to oral linezolid, as indicated by the 74% acceptance rate when an intervention was made on a patient who met the established ATO criteria. Implementing systems that promote IV vancomycin-sparing regimens can support antimicrobial stewardship programs by helping mitigate the impact of IV vancomycin, as it is one of the most common antibiotics in hospitals.

The results of this analysis are most applicable to patient populations likely to receive at least three days of treatment, as the most common exclusion criterion during the screening process

Table 1

Baseline Characteristics of Patients Eligible for Pharmacy-Led Antibiotic Time Out

	Oral Linezolid <i>n</i> = 20	IV Vancomycin Continuation <i>n</i> = 31
Median age, <i>n</i> (IQR)	74 (25)	66 (30)
Male sex, <i>n</i> (%)	11 (55)	22 (71)
Critical Care Admission, <i>n</i> (%)	4 (20)	7 (23)
Indication, <i>n</i> (%)		
Abscess	0 (0)	1 (3)
Bloodstream infection	0 (0)	3 (10)
Cellulitis	6 (30)	14 (45)
Osteomyelitis	1 (5)	1 (3)
Pneumonia	6 (30)	0 (0)
Sepsis – Empiric	0 (0)	1 (3)
Skin and soft tissue infection	6 (30)	7 (23)
Other	1 (5)	4 (13)
Cultures, <i>n</i> (%)		
Culture positive	10 (50)	20 (65)
Culture not available	1 (5)	0 (0)
Concomitant Serotonergic Agents, <i>n</i> (%)		
One serotonergic agent	4 (20)	4 (13)
Two serotonergic agents	1 (5)	0 (0)

Table 2*Secondary Outcomes for Patients Eligible for Pharmacy-Led Antibiotic Time Out*

Secondary Outcomes	Oral Linezolid <i>n</i> = 20	IV Vancomycin Continuation <i>n</i> = 31	<i>p</i> value
Median Length of Stay (LOS), days (IQR)	9 (11.5)	7 (6)	.358
Median Antibiotic Length of Treatment, days (IQR)	6 (5)	6 (4.9)	.352
Adverse Effects			
Acute Kidney Injury, <i>n</i> (%)	1 (5)	1 (3)	.635
Platelet Count Drop > 50% from Baseline, <i>n</i> (%)	1 (5)	0 (0)	.392

Table 3*Secondary Outcomes for IV Vancomycin Dosing with Pharmacist-Led Antibiotic Time Out*

IV Vancomycin Dosing Secondary Outcomes	Oral Linezolid <i>n</i> = 20
Saved IV Vancomycin Doses	26
Saved IV Vancomycin Therapeutic Drug Monitoring Levels	8

was IV vancomycin treatment for less than 48 hours. Often, patients are given IV vancomycin empirically, only to be transitioned off in a day or two. Published evidence demonstrates that despite vancomycin targeting MRSA infections empirically, it is often not substantiated with cultures (Waters & Caraccio, 2018). Institutions considering IV vancomycin reduction strategies can consider designing local interventions to target patients who are likely to have an MRSA infection and be on IV vancomycin treatment beyond 48 hours. To help optimize the empiric use of vancomycin, a structured 48-hour ATO should be implemented to assess the opportunities for de-escalation.

This study had a low intervention rate, with 27 pharmacist interventions out of 66 eligible patients. The lack of intervention in eligible patients was due to limitations in pharmacist availability to perform reviews. A greater focus on this initiative would be expected to generate a great-

er volume of interventions. Notably, in this study cohort, five patients transitioned from IV vancomycin to oral linezolid but were not a result of a pharmacist intervention. It is likely that as the study was conducted, it brought further awareness and education for the use of linezolid as a therapeutic option. This potential collateral effect is perceived to be favorable and further supports physician acceptance of the ATO initiative beyond the high intervention acceptance rate.

Given the small sample size, a significant difference in clinical outcomes was not anticipated, which was ultimately consistent with the findings presented in the secondary endpoints. However, unlike results reported by Cua et al. (2022), patients who transitioned to oral linezolid in this study had a numerically higher length of stay while they had the same number of median antibiotic treatment days compared to patients who continued IV vancomycin. The likely rea-

son for these findings is that patients who transitioned to oral linezolid may have been in the hospital longer for incision and debridement or surgical procedures to obtain source control. Additionally, a prospective study of this nature may have internal bias, as patients with a longer stay in the hospital had a higher probability and likelihood for pharmacist ATO intervention throughout their stay.

There was an equal but very low incidence of acute kidney injury between both comparator groups. Clinical pharmacists monitor and dose all IV vancomycin regimens at the study site for admitted patients. This robust practice supports a low risk for inappropriate dosing or monitoring, which is reflected in the outcomes with a low rate of acute kidney injury. For linezolid, the one patient who experienced thrombocytopenia did not incur a negative clinical impact, but the importance of monitoring is appreciated. Per the U.S. Food and Drug Administration product labeling, the risk for thrombocytopenia with linezolid use is increased with extended durations of therapy of 14 days or greater (Pfizer, 2013).

This study's pharmacist-led ATO considered patients receiving less than two serotonergic agents as candidates for oral linezolid therapy. Despite product labeling that states to halt serotonergic antidepressants before initiating linezolid, serotonin toxicity associated with linezolid is rare and largely idiosyncratic (Pfizer, 2013). A review of the incidence of serotonin syndrome with the use of linezolid identified 32 cases of serotonin syndrome out of 2,357 patients taking linezolid in combination with a serotonergic agent (Woytowish & Maynor, 2013). Of these 32 cases, 50% involved two or more concomitant serotonergic agents. To align with these findings, this study prevented linezolid candidates from receiving more than two concomitant serotonergic agents in combination with linezolid therapy. Institutions seeking to increase oral linezolid use should be mindful of the risk

for serotonin syndrome based upon concomitant medication use both when linezolid is initially prescribed as well as during the treatment course.

This study was limited by the small sample size and relatively short timeline; however, it was intended to be an exploratory analysis to inform feasibility. It is likely that a study over a longer duration and including a greater number of patients may yield more informative feasibility outcomes. However, information from the experience described here may serve to inform the creation of parallel interventions that are more streamlined. An additional opportunity is to enhance the use of technology for patient identification and screening. For example, utilization of clinical decision support systems may simplify the intervention workflow by enhancing efficiencies in patient selection.

CONCLUSION

A pharmacist-led ATO for IV vancomycin to oral linezolid resulted in a high intervention acceptance rate and increased oral linezolid use without impacting safety outcomes. These results demonstrate the impact of a pharmacist prospective antibiotic timeout and intervention strategy for patients receiving empiric or targeted MRSA therapy.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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