Infect Dis Ther (2022) 11:1649–1660
https://doi.org/10.1007/s40121-022-00663-3

ORIGINAL RESEARCH

Linezolid vs Vancomycin in Induced Thrombocytopenia

Dimah Al-Harbi · Abdulrahman Alturaiki · Ayshah Alshngeetee · Haya Aldabas · Layla AlBreacan · Renad Aljohani · Eid Hussein Alshahrani · Abdullah Althemery · Laila Carolina Abu Esba

Received: April 24, 2022 / Accepted: May 24, 2022 / Published online: June 21, 2022

ABSTRACT

Introduction: Linezolid and vancomycin have an important place among therapeutic antimicrobial options for multidrug-resistant gram-positive infections. Thrombocytopenia is an adverse effect reported with both and can lead to treatment interruption. Our objective was to compare the incidence of thrombocytopenia in patients receiving linezolid or vancomycin and to identify risk factors associated with thrombocytopenia.

Methods: This was a retrospective observational cohort study that involved patients who received linezolid (intravenously or orally) or vancomycin (intravenously) at a tertiary care hospital, between January 2016 and October 2019, for a minimum of 5 days and in whom platelet values were measured during treatment. Data on platelet count were collected during therapy in each group to identify the incidence of thrombocytopenia.

Results: A total of 453 patients fulfilled the study criteria; 241 patients received linezolid and 212 patients vancomycin. The main logistic regression analysis revealed that patients in the linezolid group had approximately a four times higher incidence of thrombocytopenia (OR 4.39; 95% CI 2.38–8.08) compared to vancomycin. An increased incidence of thrombocytopenia was associated with advanced age, baseline platelet count and vasopressor use.

D. Al-Harbi · A. Alturaiki · L. C. A. Esba (✉)
King Abdulaziz Medical City, Pharmaceutical Care Services, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia
e-mail: abuesbala@ngha.med.sa

A. Alturaiki · L. C. A. Esba
College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

A. Alturaiki · L. C. A. Esba
King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

A. Alshngeetee
College of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

H. Aldabas · R. Aljohani
College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

L. AlBreacan
College of Medicine, King Saud University, Riyadh, Saudi Arabia

E. H. Alshahrani
College of Medicine, University of Bisha, Bisha, Saudi Arabia

A. Althemery
Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia

Conclusion: Clinicians considering vancomycin or linezolid for a susceptible infection should weigh the higher risk of thrombocytopenia that may be observed with linezolid vs. vancomycin in their decision.

Keywords: Antimicrobial agents; Linezolid; Platelets; Risk factors; Thrombocytopenia; Vancomycin

Key Summary Points
Thrombocytopenia has been reported with both linezolid and vancomycin and can lead to treatment interruption
In this retrospective study, linezolid was associated with an approximately four times higher incidence of thrombocytopenia compared to vancomycin
Risk factors for development of thrombocytopenia included advanced age, low baseline platelet count and concomitant use of vasopressors
There is a variation in frequency of linezolid-associated thrombocytopenia in our study compared to the studies from other regions such as the USA and Canada; future studies focusing on establishing pharmacogenomic links are suggested

INTRODUCTION

Linezolid is the first antibacterial drug in the class of oxazolidinones. It inhibits the activity of a broad range of gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), glycopeptide-intermediate *S. aureus* (GISA) and penicillin-resistant *Streptococcus pneumoniae* [1]. Because it is available in an oral dosage form, linezolid is typically preferred for patients healthy enough to be treated on an outpatient basis. However, its adverse effects include peripheral neuropathy, increased liver enzymes, serotonin syndrome and myelosuppression [2]. Considering the global threat of antimicrobial resistance, linezolid has an important place among therapeutic antimicrobial options so that gaining further insights into its toxicities and identifying at-risk patients are crucial for optimizing therapy [2]. Vancomycin's spectrum closely resembles that of linezolid. This tricyclic glycopeptide antibiotic, which is used to treat and prevent many bacterial infections caused by gram-positive bacteria, including MRSA, is also used to treat streptococci, enterococci and methicillin-susceptible *Staphylococcus aureus* (MSSA) infections [3]. Linezolid and vancomycin are important treatments of multidrug-resistant infections in hospitalized patients, and thrombocytopenia has been reported with both [1, 3].

Thrombocytopenia, or a platelet count < 150,000/μl, can be triggered by many factors, including cancer, aplastic anemia, alcohol, toxic chemicals, medications, viruses and genetic conditions [4]. It can lead to life-threatening bleeding, petechiae, purpura or mucosal bleeding (e.g., epistaxis) [4]. In the intensive care unit (ICU), it can restrict patient management and may call for withholding or delaying necessary invasive interventions, decreasing anticoagulation dose, preparing platelet transfusion and/or changing anticoagulants [5]. The most commonly implicated drugs used in the ICU are heparin and antibiotics [5].

In the phase III approval trial for linezolid, the frequency of thrombocytopenia was reported to be 2.4% with a treatment duration of 28 days [2]. Soon after approval, reports surfaced of a higher incidence in clinical practice, reaching 48% [6–10]. A significant number of studies reporting such a higher incidence involved Japanese patients, but whether this phenomenon reflects a higher rate of observation in this population or simply reflects research interest remains unclear [7–9, 11–13]. Despite the wide use of vancomycin, the incidence of vancomycin-induced thrombocytopenia remains unknown. However, based on case reports and two retrospective studies, a prevalence of 5.9–7.1% was reported, which was

higher than expected. Nevertheless, the variation in thrombocytopenia definitions among these studies and their retrospective design might have influenced results [14–16].

Nasraway et al. attempted to compare the incidence of thrombocytopenia between vancomycin and linezolid by analyzing data from two separate clinical trials based on similarities in their population and design; they reported that linezolid was not associated with thrombocytopenia more frequently than with vancomycin. Considering the low incidence of such adverse effects in a clinical trial setting, the pooled analysis interpretation has its limitations [17].

Besides the reported incidences of thrombocytopenia from controlled trials, no studies have compared the incidence of linezolid and vancomycin-induced thrombocytopenia in a real-world setting. The primary objective of this study was to compare the incidence of thrombocytopenia in the linezolid and vancomycin groups. The secondary objective was to evaluate the risk factors associated with development of thrombocytopenia.

METHODS

This retrospective observational cohort study involved patients who received linezolid (intravenously or orally) or vancomycin (intravenously) at the Ministry of National Guard Hospital in Riyadh, Saudi Arabia, between January 2016 and October 2019 for a minimum of 5 days and whose platelet values were measured during treatment.

Patients were identified from the hospital's electronic health care database, and data collected included demographics, comorbidities, comorbidity index (using Charlson comorbidity index), concomitant drugs, indication for either vancomycin or linezolid, microbiological data, laboratory data and disease severity.

The laboratory values collected included baseline values (closest to initiation of linezolid or vancomycin) and the most divergent values seen during treatment.

Thrombocytopenia was defined as a platelet count $< 150{,}000/\mu l$ and further subdivided based on severity into platelet counts $< 150{,}000/\mu l$, $< 100{,}000/\mu l$ and $< 50{,}000/\mu l$.

Patients known to have hematological malignancy such as leukemia or myelodysplastic syndrome, with confirmed heparin-induced thrombocytopenia, who received chemotherapy and with a baseline abnormal platelet count $< 150{,}000/\mu l$ prior to therapy were excluded.

The sample size was estimated using the previous literature [16–18]. The incidence rate of thrombocytopeina in the linezolid and vancomycin treatment groups was 37.7% and 22.3%, respectively, with a 0.05 alpha level and a power of 90%. A total of 450 patients were required, with a minimum of 200 patients in each group.

Statistical analysis was performed using commercially available software SPSS 21.0 and R: A language and environment for statistical computing. Baseline characteristics between patients receiving linezolid and patients receiving vancomycin were compared. The association between each continuous variable and thrombocytopenia was tested using Student's *t*-test. The association between each categorical variable and thrombocytopenia was tested using chi-square test or Fisher's exact test. $p < 0.05$ was considered to indicate a statistically significant difference. The significant independent variables were included in the final multivariate logistic regression model to compare the association between these significant variables and the development of thrombocytopenia. A sensitivity analysis was added by applying a bootstrapped population from the original sample with the different thrombocytopenia severity levels [19].

The study protocol was reviewed and approved by the Institutional Research Ethics Board (#RC19/254/R). Individual patient consent was not required for a study of this type.

RESULTS

Descriptive Analysis

Of 1420 patients identified in the database, 453 met the inclusion criteria, 241 received

linezolid and 212 received vancomycin for ≥ 5 days. The baseline characteristics of patients in both groups are presented in Table 1. Patients in the linezolid group were slightly older and had a higher Charlson comorbidity index, but weight, baseline platelet count and renal function were similar between the two groups.

The overall incidence of thrombocytopenia was 20.1% in our study group. Of these, 30.3% were in the linezolid group and only 8.5% of patients in the vancomycin group ($p < 0.001$). Of the patients in the linezolid group that developed thrombocytopenia, 30.3% had a platelet count < 150,000/μl, 13.7% had a platelet count < 100,000/μl and 4.6% had a platelet count < 50,000/μl. In the vancomycin group the platelet count was < 150,000/μl in 8.5%, < 100,000/μl in 3.78% and < 50,000/μl in 1.89% of the patients. The significant independent variables associated with thrombocytopenia are presented in Tables 2 and 3.

The main logistic regression analysis revealed that patients in the linezolid group had an approximately four times higher risk of thrombocytopenia (OR 4.39; 95% CI 2.38–8.08) and had a 3.8 times higher risk of having a platelet count < 100,000/μl (OR 3.77; 95% CI 1.55–9.17) compared to the vancomycin group (Table 4). In a bootstrapped sample, linezolid therapy was associated with a statistically significant 75% (OR 1.75; 95% CI 1.68–1.83) elevated risk of severe thrombocytopenia (platelets < 50,000/μl) compared to vancomycin group. Table 5 shows original and bootstrapped samples for different stages of thrombocytopenia.

Risk Factors

Patients with thrombocytopenia had a statistically significant older age, higher Charlson comorbidity index score and lower baseline platelet count (see Table 2). After controlling for other factors, only age and baseline platelet count were associated significantly with thrombocytopenia (OR 1.02; 95% CI 1.02–1.03; $p < 0.03$) and (OR 0.99; 95% CI 0.93–0.98; $p < 0.0002$), respectively (Table 4).

Table 1 Baseline characteristics

Factor	Linezolid	Vancomycin
Age (years), median (SD)	63.27 (20.7300)	55.66 (21.3639)
Weight (kg), median (SD)	70.39 (22.0632)	70.18 (18.7919)
Height (cm), median (SD)	161.1 (10.3248)	162.0 (16.8402(
Body mass index, (kg/m^2), mean (SD)	27.14 (8.8296)	27.02 (12.9278)
Gender		
Female, *n* (%)	99 (41.08)	78 (36.79)
Male, *n* (%)	142 (58.92)	134)63.21)
Platelet baseline (× 10^3/μl), mean (SD)	347.6 (145.2)	343.6 (146.7)
Serum creatinine baseline, μmol/l, median (SD)	129.8 (110.8)	102.2 (107.6)
Charlson comorbidity index, median (SD)	2.4979 (1.9)	1.6604 (1.63(
On mechanical ventilation		
No, *n* (%)	150 (62.24)	155 (73.11)
Yes, *n* (%)	91 (37.76)	57 (26.89)
On vasopressor		
No, *n* (%)	164 (68.05)	160 (75.47)
Yes, *n* (%)	77 (31.95)	52 (24.53)
On continuous renal replacement		
No, *n* (%)	223 (92.53(	202 (95.28(
Yes, *n* (%)	18 (7.47)	10 (4.72)
Diabetes mellitus		
No, *n* (%)	104 (43.15)	117 (55.19)
Yes, *n* (%)	137 (56.85)	95 (44.81(
Hypertension		
No, *n* (%)	86 (35.68)	103 (48.58)
Yes, *n* (%)	155 (64.32)	109 (51.42)
Chronic obstructive pulmonary disease		
No, *n* (%)	229 (95.02)	207 (97.64)

Table 1 continued

Factor	Linezolid	Vancomycin
Yes, *n* (%)	12 (4.98)	5 (2.36)
Liver cirrhosis		
No, *n* (%)	232 (96.27)	207 (97.64)
Yes, *n* (%)	9 (3.73)	5 (2.36)
Heart failure		
No, *n* (%)	189 (78.42)	184 (86.79)
Yes, *n* (%)	52 (21.58)	28 (13.21)
Cancer		
No, *n* (%)	219 (90.87)	200 (94.34)
Yes, *n* (%)	22 (9.13)	12 (5.66)
Cerebrovascular accident		
No, *n* (%)	218 (90.46)	191 (90.09)
Yes, *n* (%)	23 (9.54)	21 (9.91)
Ischemic heart disease		
No, *n* (%)	227 (94.19)	191 (90.09)
Yes, *n* (%)	14 (5.81)	21 (9.91)
Chronic kidney disease		
No, *n* (%)	172 (71.37)	195 (91.98)
Yes, *n* (%)	69 (28.63(	17 (8.02)
eGFR at baseline (ml/min/1.73 m^2) a, median (SD)		
> 90	101 (41.91(	138 (65.09)
89–60	35 (14.52)	27 (12.74(
59–30	53 (21.99)	20 (9.43(
29–15	24 (9.96)	12 (5.66)
Hemodialysis	28 (11.62)	15 (7.08)
Duration of antibiotic (days), median (SD)	11.44 (6.84)	11.52 (10.68)

Table 2 Association between continues variables and thrombocytopenia

Factor	Thrombocytopenia		*P* value
	No	Yes	
Age (years)	57.54	68.37	< 0.001
Charlson comorbidity index	1.87	3.03	< 0.001
Baseline platelet level ($\times 10^3/\mu l$)	360.6	286.6	< 0.001

Table 3 Association between categorical variables and thrombocytopenia

Factor	Thrombocytopenia		*P* value
	No, *n* (%)	Yes, *n* (%)	
Antibiotic			< 0.001
Linezolid	168 (69.71)	73 (30.29)	
Vancomycin	194 (91.51)	18 (8.49)	
Mechanical ventilation			0.002
No	256 (83.93)	49 (16.01)	
Yes	106 (71.62)	42 (28.38)	
Continuous renal replacement			0.008
No	345 (81.18)	80 (18.82)	
Yes	17 (60.71)	11 (39.29)	
Vasopressor			< 0.001
No	278 (85.80)	46 (14.20)	
Yes	84 (65.12)	45 (34.88)	
Heparin			0.02
No	312 (81.89)	69 (18.11)	
Yes	50 (69.44)	22 (30.56)	
Amiodarone			0.01*
No	351 (81.06)	82 (18.94)	
Yes	11 (55)	9 (45)	

*Fisher exact test

Table 4 Logistic regression for the association between significant variables and the risk of thrombocytopenia

Factors	Point estimate	95% CI		*P* value
Main factor				
Antibiotic type				
Linezolid	4.39	2.38	8.08	< 0.001
Vancomycin	Reference level			
Other factors				
Age	1.02	1.00	1.03	0.03
Charlson Comorbidity Index	1.16	0.95	1.34	0.17
Baseline platelet level	0.99	0.93	0.98	< 0.001
Mechanical ventilation				
Yes	0.96	0.51	1.83	0.89
No	Reference level			
Continuous renal replacement				
Yes	1.09	0.43	2.76	0.85
No	Reference level			
Using amiodarone				
Yes	2.22	0.74	6.62	0.15
No	Reference level			
Using vasopressor				
Yes	2.39	1.23	4.66	0.01
No	Reference level			
Using IV heparin				
Yes	1.10	0.56	2.16	0.78
No	Reference level			

In the logistic regression, only vasopressor therapy showed an approximately 2.5 times higher incidence of thrombocytopenia (OR 2.39; 95% CI 1.23–4.66; p 0.01). No significant association was seen with piperacillin-tazobactam, penicillin, cephalosporin, trimethoprim sulfamethoxazole, ranitidine, GPIIb-IIIa Inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), carbamazepine and phenytoin ($p > 0.05$ for all variables). The non-significant variables are presented in Appendix 1.

Onset of Thrombocytopenia

The average duration of treatment to onset of severe thrombocytopenia in the linezolid group was 14 ± 9.3 days compared with 8.5 ± 6.9 days in the vancomycin group.

DISCUSSION

Multiple studies have used vancomycin as a reference to compare the incidence of linezolid-induced thrombocytopenia. The first by Nasraway et al. was a pooled analysis that compared the incidence of thrombocytopenia reported in two randomized clinical trials (RCTs) of linezolid and vancomycin in patients with nosocomial pneumonia; they described no significant difference in thrombocytopenia, but their study had multiple limitations, and the baseline platelet value for patients on linezolid for > 14 days was only available for 7% of patients [17].

Several preceding RCTs [20, 21] and meta-analyses of RCTs [22, 23] that randomized patients to linezolid or vancomycin reported a higher incidence of thrombocytopenia. The most recent meta-analysis [23] reported a significant difference in the incidence of thrombocytopenia (RR = 20.4, 95% CI 3.12–133.57), while data from observational studies reported conflicting results, reporting no significant difference [24–26] in a USA population and those that reported a significantly higher incidence with linezolid vs. vancomycin mainly in an Asian population [16, 27].

In a recent study from Canada, a modest incidence of 17.6% was reported in a retrospective review of 102 inpatients at a tertiary

Table 5 Sensitivity analysis with different values for thrombocytopenia with different population

Factor	Thrombocytopenia severity					
	Platelet < 150		Platelet < 100		Platelet < 50	
	OR	CI	OR	CI	OR	CI
Original sample						
Linezolid	4.39	2.38–8.08	3.77	1.55–9.17	1.76	0.44–6.99
Vancomycin	Reference		Reference		Reference	
Bootstrapped sample						
Linezolid	4.41	4.33–4.49	3.74	3.64–3.84	1.75	1.68–1.83
Vancomycin	Reference		Reference		Reference	

*Controlling for age, comorbid conditions, use of mechanical ventilation, continuous renal, amiodarone use, antihypotensive use and heparin

care hospital [28], and in another from France on patients admitted in the ICU only 13.8% developed thrombocytopenia; these lower rates could be due to the stricter definition of thrombocytopenia used in their study [29]. However, as in some inherited genetic disorders that can cause immune thrombocytopenia, a genetic predisposition to this drug-induced adverse effect can be expected; in fact, the conflicting results may allude to a genetic predisposition to this adverse effect [30]. Notably, a recent study reported a significant effect of abcb1 c.3435C>T polymorphism on linezolid clearance [31, 32].

Our results are consistent with most of the studies, showing a significantly higher incidence of thrombocytopenia in association with linezolid compared to vancomycin. In addition, the overall frequency was relatively similar to that reported in the Asian population. Conservatively, when only considering moderate to severe levels of linezolid-associated thrombocytopenia, our results may be closer to a recent study in France by Cazavet et al. [29].

The exact mechanism of linezolid-induced thrombocytopenia has not yet been elucidated. Proposed mechanisms include suppression of release of platelets from mature megakaryocytes [33], oxidative damage to circulating platelets [34] and immune-mediated platelet destruction [35, 36].

Risk factors reported are renal insufficiency, hemodialysis, prolonged treatment duration, elevated or low baseline leukocyte concentration, chronic liver disease and low baseline serum protein concentration [1, 5, 9].

There is also a notion that the adverse effect is dose dependent, as a higher trough concentration of linezolid in the plasma and higher values for area under the concentration-time curve (AUC) have been suggested as possible risk factors [11, 12].

Nevertheless, the pharmacokinetics of linezolid have been reported to be more influenced by a patient's renal function than their weight [37], with some studies recommending higher doses of linezolid in obese patients. In our study, the mean BMI was 27 in patients that developed thrombocytopenia, and we only included patients that were on the same dose [37, 38].

Concerning renal impairment, only 20% of the patients that developed linezolid-associated thrombocytopenia had an eGFR < 90, and renal impairment was not a significant risk factor. Therefore, the idea of a higher drug exposure might not fully explain the higher frequency seen in our study, but further studies on this subgroup of patients are needed.

An immune-mediated platelet destruction by linezolid has been reported; in these cases, linezolid-related antibodies were detected, and

response to immune globulin therapy was observed [35, 39]. The reports also describe a rapid and severe drop in platelets, which was not directly observed in our study where the average duration of treatment to onset of severe thrombocytopenia was 14 ± 9.3 days.

The only factors in our study that significantly increased the risk of thrombocytopenia were the presence of comorbidities and concomitant intake of drugs commonly used in critical patients (e.g., vasopressors). Although vasopressor use might have served as a confounder to the higher rates of thrombocytopenia in the linezolid group, the difference was small at 31% vs. 24% for linezolid and vancomycin, respectively, and cannot be fully attributed to the higher rate of thrombocytopenia in the linezolid group. Therefore, we recommend more frequent monitoring in patients with comorbid conditions that increase their risk of thrombocytopenia.

The weak association of risk factors to predict this adverse reaction and the wide use of linezolid are hurdles in implementing therapeutic drug monitoring (TDM). Considering a variation in frequency of linezolid-associated thrombocytopenia in our study compared to results from the USA and Canada, we suggest that future studies focus on establishing pharmacogenomics links, and healthcare systems should implement good pharmacovigilance practices for monitoring such adverse events [40].

Our study is limited by its retrospective and observational design; in addition, the doses of linezolid and vancomycin were not utilized to identify the role of a dose response and its effect on the incidence of thrombocytopenia in each group. We hypothesized that this adverse reaction is a type B reaction, likely immune mediated and host dependent, based on previous reports. Further studies should stratify patients by onset of thrombocytopenia and expected mechanism of this adverse effect.

CONCLUSION

Clinicians considering vancomycin or linezolid for a susceptible infection should weigh the higher risk of thrombocytopenia that may be observed with linezolid vs. vancomycin in their decision.

APPENDIX 1

List of independent variables that were non-significantly associated with the risk of thrombocytopenia

Factor	Thrombocytopenia		*P* value
	No	Yes	
Body mass index	29.46	27.32	0.34
Length of hospital stay	65.00	76.41	0.43
Duration of antibiotic	11.1326	12.8571	0.07
Gender			0.56
Female	139	38	
Male	223	53	
Piperacillin tazobactam			0.63
No	213	51	
Yes	149	40	
Penicillin			0.75*
No	348	89	
Yes	14	2	
Cephalosporin			0.37
No	290	69	
Yes	72	22	
Trimethoprim sulfamethoxazole			0.9*
No	356	90	
Yes	6	1	
Ranitidine			0.43
No	338	87	
Yes	24	4	
GPllb–llla inhibitors			0.66*
No	356	89	
Yes	6	2	
NSAID			0.27
No	245	67	

Table b continued

Factor	Thrombocytopenia		*P* value
	No	Yes	
Yes	117	24	
Carbamazepine			0.9*
No	358	90	
Yes	4	1	
Phenytoin			0.79*
No	344	86	
Yes	18	5	
Pneumonia			0.25
No	242	55	
Yes	120	36	
UTI			0.10
No	294	67	
Yes	68	24	
Osteomyelitis			0.59
No	329	81	
Yes	33	10	
Intra-abdominal infections			0.15*
No	358	88	
Yes	4	3	
Cellulitis			0.39*
No	329	86	
Yes	33	5	
Bacteremia			0.29
No	313	83	
Yes	49	8	
Line-related sepsis			0.75*
No	348	89	
Yes	14	2	
Endocarditis			0.27*
No	354	87	
Yes	8	4	
Streptococcus sp.			0.9*
No	351	89	
Yes	11	2	
Staphylococcus sp.			0.89
No	216	55	
Yes	146	36	
Enterococcus sp.			0.68
No	320	79	
Yes	42	12	

*Fisher exact test

ACKNOWLEDGEMENTS

Funding. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. The journal's Rapid Service Fee was funded by the authors.

Author Contributions. Dimah Al-Harbi: Conception or design of the work. Data collection. Drafting the article. Critical revision of the article. Abdulrahman Alturaiki: Conception and design of the study. Analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version to be submitted. Laila Abu Esba: Conception and design of the study. Analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version to be submitted. Ayshah Alshngeetee; Haya Aldabas; Layla AlBreacan; Renad Aljohani; Eid Hussein Alshahrani: Data collection. Data analysis and interpretation. Final approval of the version to be published. Abdullah Althemery: conception or design of the work. Final approval of the version to be published.

Disclosures. Dimah Al-Harbi, Abdulrahman Alturaiki, Ayshah Alshngeetee, Haya Aldabas, Layla AlBreacan, Renad Aljohani, Eid Hussein Alshahrani, Abdullah Althemery and Laila Abu Esba all confirm that they have no conflicts of interest to declare.

Compliance with Ethics Guidelines. The study protocol was reviewed and approved by the Institutional Research Ethics Board (#RC19/254/R). Individual patient consent was not required for a study of this type.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Caroline PM, Linezolid JB. A review of its use in the management of serious gram-positive infections. Drugs. 2003;61:525.

2. Pfizer (2018) ZYVOXAM®. 40.

3. Patel S, Preuss CV, Bernice F. Vancomycin. 2022 Mar 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. PMID: 29083794.

4. The National Heart & Lung and Blood Institute Thrombocytopenia. 2020. https://www.nhlbi.nih.gov/health-topics/thrombocytopenia. Accessed 10 Dec 2021

5. Greinacher A, Selleng K. Thrombocytopenia in the intensive care unit patient. Hematol 2010 Am Soc Hematol Educ Progr B. 2010;2010:135–43.

6. Attassi K, Hershberger E, Alam R, Zervos MJ. Thrombocytopenia associated with linezolid therapy. Clin Infect Dis. 2002;34:695–8.

7. Niwa T, Suzuki A, Sakakibara S, Kasahara S, Yasuda M, Fukao A, Matsuura K, Goto C, Murakami N, Itoh Y. Retrospective cohort chart review study of factors associated with the development of thrombocytopenia in adult Japanese patients who received intravenous linezolid therapy. Clin Ther. 2009;31:2126–33.

8. Takahashi Y, Takesue Y, Nakajima K, Ichiki K, Tsuchida T, Tatsumi S, Ishihara M, Ikeuchi H, Uchino M. Risk factors associated with the development of thrombocytopenia in patients who received linezolid therapy. J Infect Chemother. 2011;17:382–7.

9. Ikuta S, Yasui C, Aihara T, Yoshie H, Iida H, Beppu N, Kurimoto A, Yanagi H, Mitsunobu M, Yamanaka N. Chronic liver disease increases the risk of linezolid-related thrombocytopenia in methicillin-resistant *Staphylococcus aureus*-infected patients after digestive surgery. J Infect Chemother. 2011;17:388–91.

10. Chen C, Guo D-H, Cao X, Cai Y, Xu Y, Zhu M, Ma L. Risk factors for thrombocytopenia in adult Chinese patients receiving linezolid therapy. Curr Ther Res. 2012;73:195–206.

11. Natsumoto B, Yokota K, Omata F, Furukawa K. Risk factors for linezolid-associated thrombocytopenia in adult patients. Infection. 2014;42:1007–12.

12. Hirano R, Sakamoto Y, Tachibana N, Ohnishi M. Retrospective analysis of the risk factors for linezolid-induced thrombocytopenia in adult Japanese patients. Int J Clin Pharm. 2014;36:795–9.

13. Hanai Y, Matsuo K, Ogawa M, Higashi A, Kimura I, Hirayama S, Kosugi T, Nishizawa K, Yoshio T. A retrospective study of the risk factors for linezolid-induced thrombocytopenia and anemia. J Infect Chemother. 2016;22:536–42.

14. Mohammadi M, Jahangard-Rafsanjani Z, Sarayani A, et al. Vancomycin-induced thrombocytopenia: a

narrative review. Drug Saf. 2017;40:49–59. https://doi.org/10.1007/s40264-016-0469-y.

15. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson Comorbidity Index with administrative data bases. J Clin Epidemiol. 1996;49:1429–33.

16. Zhang Z, Liang Z, Li H, Chen L, She D. Comparative evaluation of thrombocytopenia in adult patients receiving linezolid or glycopeptides in a respiratory intensive care unit. Exp Ther Med. 2013;7(2):501–7.

17. Nasraway S, Shorr A, Kuter D, O'Grady N, Le V, Cammarata S. Linezolid does not increase the risk of thrombocytopenia in patients with nosocomial pneumonia: comparative analysis of linezolid and vancomycin use. Clin Infect Dis. 2003;37(12):1609–16.

18. Attassi K, Hershberger E, Alam R, Zervos M. Thrombocytopenia associated with linezolid therapy. Clin Infect Dis. 2002;34(5):695–8.

19. Brydon H, Blignaut R, Jacobs J. A weighted bootstrap approach to logistic regression modelling in identifying risk behaviours associated with sexual activity. SAHARA J J Soc Asp HIV/AIDS. 2019;16:62–9.

20. Weigelt J, Itani K, Stevens D, Lau W, Dryden M, Knirsch C. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother. 2005;49(6):2260–6.

21. Kohno S, Yamaguchi K, Aikawa N, Sumiyama Y, Odagiri S, Aoki N, et al. Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* in Japan. J Antimicrob Chemother. 2007;60(6):1361–9.

22. Kalil A, Klompas M, Haynatzki G, Rupp M. Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis. BMJ Open. 2013;3(10): e003912.

23. Li Y, Wei X. Efficacy and safety of linezolid compared with other treatments for skin and soft tissue infections: a meta-analysis. Biosci Rep. 2018;38(1):BSR20171125. https://doi.org/10.1042/BSR20171125.

24. Rao N, Ziran B, Wagener M, Santa E, Yu V. Similar hematologic effects of long-term linezolid and vancomycin therapy in a prospective observational study of patients with orthopedic infections. Clin Infect Dis. 2004;38(8):1058–64.

25. Patel N, VanDeWall H, Tristani L, Rivera A, Woo B, Dihmess A, et al. A comparative evaluation of adverse platelet outcomes among Veterans' affairs patients receiving linezolid or vancomycin. J Antimicrob Chemother. 2011;67(3):727–35.

26. Peyrani P, Wiemken T, Kelley R, Zervos M, Kett D, File T Jr, et al. Higher clinical success in patients with ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus* treated with linezolid compared with vancomycin: results from the IMPACT-HAP study. Crit Care. 2014;18(3):R118.

27. Fujii S, Takahashi S, Makino S, Kunimoto Y, Nakata H, Noda N, et al. Impact of vancomycin or linezolid therapy on development of renal dysfunction and thrombocytopenia in Japanese patients. Chemotherapy. 2013;59(5):319–24.

28. Giunio-Zorkin N, Brown G. Real-life frequency of new-onset thrombocytopenia during linezolid treatment. Can J Hosp Pharm. 2019;72(2):133–8.

29. Cazavet J, Bounes F, Ruiz S, Seguin T, Crognier L, Rouget A, et al. Risk factor analysis for linezolid-associated thrombocytopenia in critically ill patients. Eur J Clin Microbiol Infect Dis. 2019;39(3):527–38.

30. Giordano P, Lassandro G, Sangerardi M, Faienza MF, Valente F, Martire B. Autoimmune haematological disorders in two Italian children with Kabuki syndrome. Ital J Pediatr. 2014;25(40):10. https://doi.org/10.1186/1824-7288-40-10 (**PMID: 24460868; PMCID: PMC3917534**).

31. Allegra S, Di Paolo A, Cusato J, Fatiguso G, Arrigoni E, Danesi R, et al. A Common mdr1 gene polymorphism is associated with changes in linezolid clearance. Ther Drug Monit. 2018;40(5):602–9.

32. Bolhuis M, Akkerman O, Sturkenboom M, de Lange W, van der Werf T, Touw D, et al. Different underlying mechanism might explain the absence of a significant difference in area under the concentration-time curve of linezolid for different ABCB1 genotypes. Ther Drug Monit. 2019;41(2):253–4.

33. Tajima M, Kato Y, Matsumoto J, Hirosawa I, Suzuki M, Takashio Y, et al. Linezolid-induced thrombocytopenia is caused by suppression of platelet production via phosphorylation of myosin light chain 2. Biol Pharm Bull. 2016;39(11):1846–51.

34. Wang T, Guo D, Bai Y, Wen K, Han W, Wang R. Thrombocytopenia in patients receiving prolonged linezolid may be caused by oxidative stress. Clin Drug Investig. 2015;36(1):67–75.

35. Pascoalinho D, Vilas M, Coelho L, Moreira P. Linezolid-related immune-mediated severe thrombocytopenia. Int J Antimicrob Agents. 2011;37(1):88–9.

36. Vayne C, Guéry E, Rollin J, Baglo T, Petermann R, Gruel Y. Pathophysiology and diagnosis of drug-induced immune thrombocytopenia. J Clin Med. 2020;9(7):2212.

37. Cojutti P, Pai M, Pea F. Population pharmacokinetics and dosing considerations for the use of linezolid in overweight and obese adult patients. Clin Pharmacokinet. 2017;57(8):989–1000.

38. Bhalodi A, Papasavas P, Tishler D, Nicolau D, Kuti J. Pharmacokinetics of intravenous linezolid in moderately to morbidly obese adults. Antimicrob Agents Chemother. 2012;57(3):1144–9.

39. Bernstein WB, Trotta RF, Rector JT, Tjaden JA, Barile AJ. Mechanisms for linezolid-induced anemia and thrombocytopenia. Ann Pharmacother. 2003;37:517–20.

40. Abu Esba LC, Al Mardawi G, AlJasser MI, Aljohani B, Abu Alburak A. Adverse drug reactions spontaneously reported at a tertiary care hospital and preventable measures implemented. J Clin Pharm Ther. 2021;46:460–9. https://doi.org/10.1111/jcpt.13306.

Publisher's Note