Original article

A retrospective cohort study to screen linezolid-induced thrombocytopenia in adult patients hospitalized in the Midwestern Region of Brazil

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ABSTRACT

Background: Thrombocytopenia (TP) is the major event associated with linezolid (LZD) therapy. We investigated the incidence and risk factors for thrombocytopenia in hospitalized adults who received LZD (1200 mg/day) between 2015 and 2017. HIV-positive, death during follow-up and those with a baseline platelet count $\leq 100 \times 10^3/mm^3$ were excluded.

Method: TP was defined as a decrease in platelet count of $\geq 20\%$ from the baseline level at the initiation of linezolid therapy and a final count of $< 100 \times 10^3/mm^3$. The odds ratios (OR) for thrombocytopenia were obtained using multivariate stepwise logistic regression analysis.

Main results: A total of 66 patients were included (mean age [SD] 62 [18], male gender [%], 37 [56]). LZD-associated TP was identified in 12 patients (18.2%). For TP, the adjusted OR [95% CI] of the platelet count $\leq 200 \times 10^3/mm^3$, serum creatinine and renal impairment at baseline were 5.66 [1.15–27.9], 4.57 [1.26–16.5] and 9.41 [1.09–80.54], respectively. Male gender and dosage per weight per day (DPWD) >20 mg/kg/day were not risk factors.

Conclusion: The results showed that the incidence of linezolid-induced thrombocytopenia was lower in patients with normal renal function and higher in those with platelet counts $\leq 200 \times 10^3/mm^3$ or serum creatinine >1.5 mg/dL at the start of the treatment.

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Introduction

Linezolid (LZD) is an antibiotic of the oxazolidinone class that is used for the treatment of infections caused by Gram-positive bacteria, including those due to methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE). It inhibits protein synthesis by binding to a site on the bacterial 23 s ribosomal RNA of the 50 s subunit, which is essential to the replication process.[1] LZD use should be restricted as an alternative treatment for infections caused by multi-resistant microorganisms and should not be used when there are other effective drugs. The inadequate use of LZD could increase the selection of resistant strains, resulting in the loss of effectiveness of this antibiotic.[2]

The recommended dose in adults is 600 mg, administered orally or intravenously twice daily. The elimination half-life is approximately 5.5 h, the maximum serum concentration (Cmax) ranges from 15 to 21 μg/mL, and the time to reach the Cmax via oral intake, is approximately 1.5 h. It is not recommended to adjust the dose for patients with renal dysfunction.[3,4] However, the antimicrobial concentration is higher in patients with renal impairment, and current studies have indicated that renal impairment is a risk factor for the development of linezolid-induced thrombocytopenia.[5–7]

Although linezolid use has advantages, it has been associated with adverse effects such as gastrointestinal disorders, hematological toxicity and cutaneous reactions.[8,9] The hematological reactions include anemia, eosinophilia, myelosuppression, neutropenia, cell aplasia and thrombocytopenia.[10] The normal peripheral platelet count is between 150 and $450 \times 10^3/mm^3$. Thrombocytopenia has been defined as a platelet count $<150 \times 10^3/mm^3$, with or without spontaneous bleeding, ecchymosis or petechiae.[11] Thrombocytopenia can result from decreased platelet production, increased platelet consumption, or sequestration. In this sense, linezolid-induced thrombocytopenia may be the most common cause of platelet destruction, whether by immune-mediated reaction or by myelosuppression.[12] Some clinical studies have reported events linking linezolid therapy to thrombocytopenia development. For example, Tajima et al. suggested that LDZ use for more than 14 days, renal dysfunction and chronic liver disease were risk factors linked to linezolid-induced thrombocytopenia.[9] In addition, a low baseline platelet count and body weight were associated with a decrease in the peripheral platelet count.[13,14] However, the main mechanism that regulates the pathogenesis of this adverse effect is still obscure.

In response to the reports on this topic and the occurrence of such adverse effects associated with the use of linezolid, which may cause life-threatening risks to the patients, we performed this retrospective cohort study. Despite several case reports in Brazil, this is the first cohort study using this approach. Here, we aimed to identify the incidence and the risk factors, with focus on renal function, for linezolid-induced thrombocytopenia in adult patients hospitalized in the Mid-western Region of Brazil.

Methods

Study design

This retrospective cohort study was conducted between March 2015 and March 2017 at the Hospital Universitário Maria Aparecida Pedrossian of the Universidade Federal de Mato Grosso do Sul (HUMAP-UFMS, 242 beds). This study was reviewed and approved by the ethics committee of the HUMAP hospital (CAAE 79967117.0.0000.0021).

Studied population

We examined hospitalized patients >18 years old treated with a daily dose of 1200 mg by IV (600 mg every 12 h) of linezolid for 10 days. HIV-positive patients, patients who died during treatment or the follow-up period and those that presented with a baseline platelet count $\leq 100 \times 10^3/mm^3$ were excluded from the study. Laboratory and clinical data were extracted from electronic medical records and stored in a Microsoft Excel file, without identifying patient names and/or numbers.

Thrombocytopenia, data analysis and risk factors

Thrombocytopenia was defined as a decrease in the platelet count of $\geq 20\%$ from the baseline level at the initiation of linezolid therapy and a final count of $<100 \times 10^3/mm^3$, based on the previous report.[6] Baseline platelets count was defined as the platelet count prior to the initiation of linezolid therapy. In addition, by using the criteria proposed by George et al.,[15] we were able to establish the clinical evidence for a causal relation between LZD and thrombocytopenia. The definition of levels (I, II, III and IV) of evidence were described previously by the authors.[15]

The thrombocytopenia severity grade was evaluated using the platelet count range at baseline, according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0), developed by the National Cancer Institute (NCI) and adapted by Hirano et al.[6]: grade 1 $(100 - 75 \times 10^3/mm^3)$, grade 2 $(74 - 50 \times 10^3/mm^3)$, grade 3 $(49 - 25 \times 10^3/mm^3)$, grade 4 $(<25 \times 10^3/mm^3)$.

All patients received a standard total daily dose of 1200 mg of linezolid, however, no adjustments of dose per body weight were considered.

The creatinine clearance (Cr CL) was estimated using the Cockcroft-Gault equation [Cr CL (mL/min) = (140 − age) × (weight/72)/serum creatinine (mg/mL)], and for females this was multiplied by 0.85.[16] To compare the relationship between renal function and the incidence of linezolid-induced thrombocytopenia, we grouped the patients according to their creatinine clearance. Patients with Cr CL rates of less than 30, 30–60, or greater than 60 mL/min, were classified as insufficient renal function,[6] mildly insufficient renal function or normal renal function, respectively.

The five variables: male, baseline platelet count $\leq 200 \times 10^3/mm^3$, baseline serum creatinine >1.5 mg/dL, baseline renal impairment (Cr CL < 60 mL/min) and dosage per weight per day (DPWD) >20 mg/kg/day were analyzed by logistic regression analysis as risk factors associated with

thrombocytopenia in patients who received linezolid during the follow-up.

Statistical analysis

Fisher's exact test was used for comparisons; the Mann–Whitney test was the nonparametric alternative, and; the Student's t-test was used for variables with non-normal distributions. The multivariate stepwise logistic regression analysis was performed to determine the odds ratios (OR) for thrombocytopenia. Resulting *p*-values <0.05 were considered significant. All analyses were performed according to BioEstat version 5.0 tutorials (https://www.mamiraua.org.br/pt-br/downloads/programas/bioest

Ethics approval and consent to participate

The study was in accordance with the ethical standards of the declaration of Helsinki and approved by the local ethics committee of the HUMAP hospital (CAAE 79967117.0.0000.0021). Given the retrospective data analysis nature, informed consent was not required.

Results

A total of 66 patients, being 37 males and 29 females of mean age (SD) 62 (18) years were included in this study (Figure 1). The patientśmean (SD) body weight at admission was 68 (18.4) kg and the DPWD of linezolid was 17.39 (4.26) mg/kg/day. The patient characteristics at baseline are listed in Table 1.

The linezolid was mainly administered for pneumonia (30/66) and sepsis (10/66), and among the treatment courses, 36 (54.5%) were administered to patients in the intensive care unit. At the start of the linezolid treatment, 36 patients (54.5%) had impaired renal function (Cr CL < 60 mL/min). The median (range) of baseline S Cr and Cr CL was 2.34 mg/dL (0.35–9.73) and 60 mL/min (7.08–252.6), respectively.

Thrombocytopenia occurred in twelve adult patients treated with linezolid (18.2%), of whom five (42%) required platelet transfusions during follow-up. Our results supported probable (58%) and possible evidence (42%) for a causal relation of LZD with the occurrence of thrombocytopenia, using the proposed criteria.

The median platelet count at treatment initiation was significantly lower in patients who developed thrombocytopenia (Figure 2A). Regarding the thrombocytopenia severity grade, five patients (42%) were categorized as ≥grade 3, according to the criteria proposed in methods (Figure 2B). Subsequently, the characteristics of thrombocytopenic and non-thrombocytopenic patients were compared. As shown in Table 2, the patients with thrombocytopenia presented with lower platelet counts at baseline than those without thrombocytopenia (*p* = 0.012). Additionally, linezolid-induced thrombocytopenia in patients with an initial platelet count $\leq 200 \times 10^3/mm^3$ was seen in 58% (7/12) of the patients (*p* = 0.029).

The median of baseline creatinine clearance (Cr CL) was significantly lower in thrombocytopenic patients (*p* = 0.043) (Table 2). When patients were categorized intro three groups

Table 1 – Patient characteristics at baseline (2015–2017).

Variables	values
Number of patients	66
Age (years), mean (SD)	62 (18)
Weight (kg), mean (SD)	68 (18.4)
DPWD (mg/kg/day), mean (SD)	17.39 (4.26)
Male, n (%)	37 (56)
Baseline platelet count ($\times 10^3/mm^3$), median (range)	305 (170–943)
Baseline RBC ($\times 10^3/mm^3$), median (range)	3.1 (1.73–5.52)
Baseline hemoglobin (g/dL), median (range)	9.2 (5.3–13.9)
Baseline WBC ($\times 10^3/mm^3$), median (range)	14.9 (2.4–70.6)
Baseline PCR (mg/dL), median (range)	155.7 (1.9–491.5)
Baseline Na (mmol/L), median (range)	137.7 (122–160)
Baseline K (mmol/L), median (range)	4.3 (2.6–7.4)
Baseline urea (mg/dL), median (range)	82 (15.6–278.7)
Baseline S Cr (mg/dL), median (range)	2.34 (0.35–9.73)
Baseline Cr CL (mL/min), median (range)	60 (7.08–252.6)
Type of infection, n (%)	
Pneumonia	30 (45)
Sepsis	10 (15)
Cystitis	7 (11)
Skin and soft tissue infections	13 (20)
Meningitis	2 (3)
Peritonitis	4 (6)

The data are presented as n (%), median (range) or mean (SD); SD standard derivation, DPWD dosage per weight per day, RBC red blood cells, WBC white blood cells, PCR protein C reactive, S Cr serum creatinine, Cr CL clearance creatinine.

according to the sufficiency of their renal function at the start of linezolid treatment (Table 3), the renal insufficient group was significantly associated with thrombocytopenia (*p* = 0.046), while the non-thrombocytopenic patients presented with normal renal function (*p* = 0.016). In addition, Figure 3 presents the comparison of thrombocytopenia incidences in each renal function group, which were significantly higher in insufficient (25%, *p* = 0.041) and mildly insufficient (23%, *p* = 0.034) renal function than among patients with normal renal function (4%).

Finally, as shown in Table 4, a platelet count $\leq 200 \times 10^3/mm^3$ (OR = 5.66; 95% CI, 1.15–27.9; *p* = 0.045), serum creatinine >1.5 mg/dL (OR = 4.57; 95% CI, 1.26–16.5; *p* = 0.035) and renal impairment (OR = 9.41; 95% CI, 1.09–80.54; *p* = 0.043) at the treatment start were considered significant risk factors for linezolid-associated thrombocytopenia by statistical analysis.

Discussion

In general, the drug linezolid is well tolerated, but its use could be limited by the potential risk of thrombocytopenia, attributable to reversible bone marrow suppression.[12] Linezolid-induced thrombocytopenia has been previously reported in 2.4–66% of patients who receive LZD therapy.[6,8,17–22] In the present study, we found an incidence of 18.2% in adult patients hospitalized in the Brazilian Midwest.
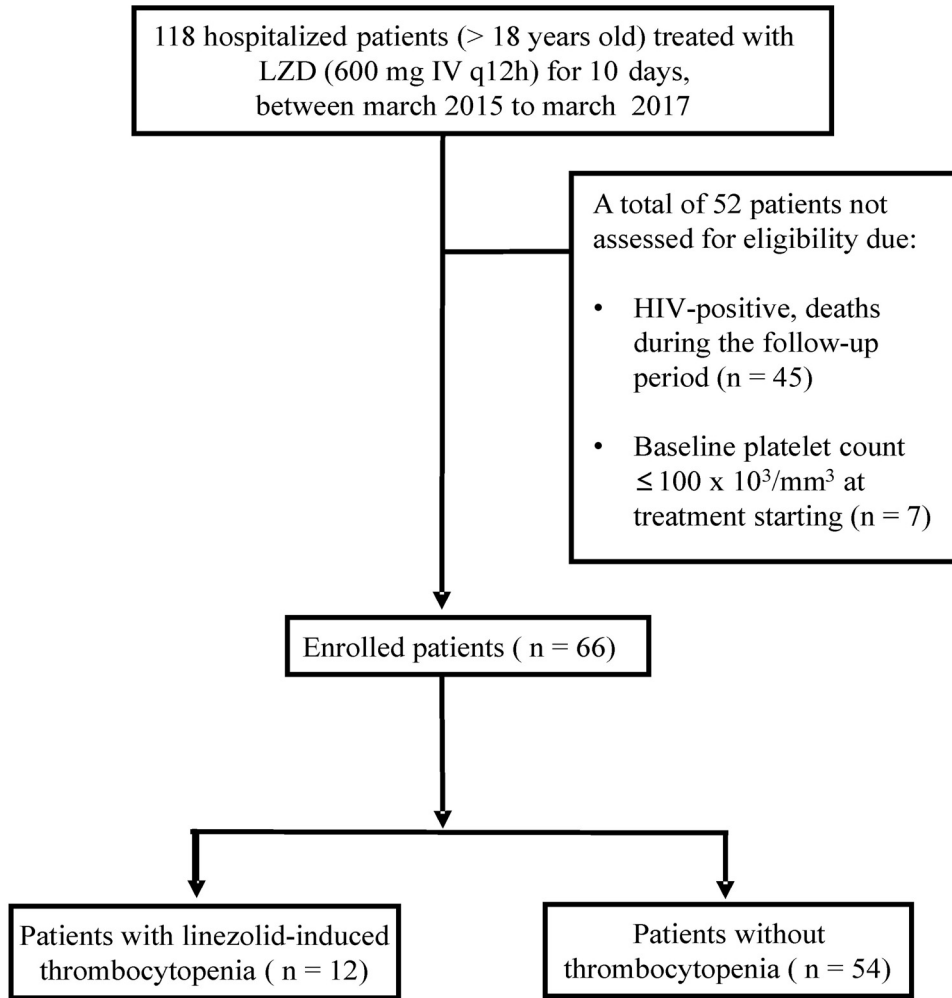
Figure 1 – The retrospective cohort study design and study flow chart.
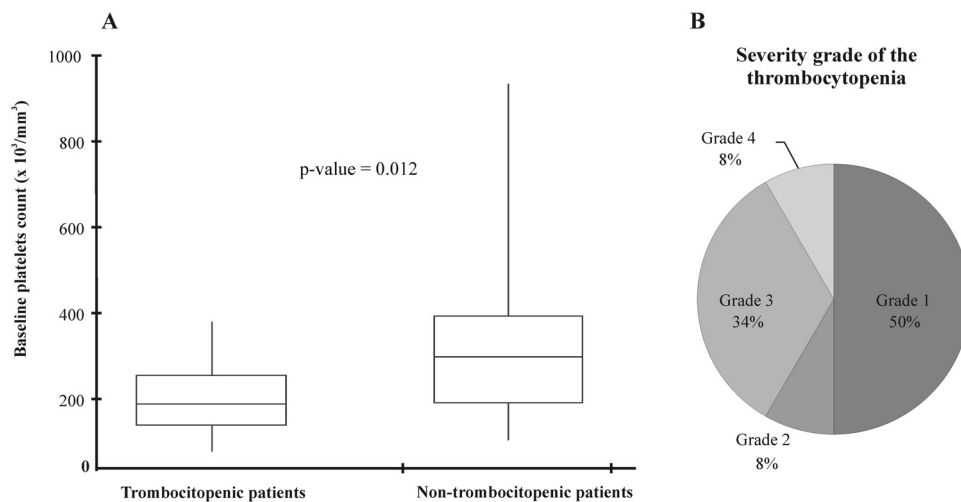

Figure 2 – Evaluation of thrombocytopenia induced by linezolid therapy in adult patients. (A) Platelet counts at baseline in adults who did or did not develop thrombocytopenia. (B) Pie chart showing the thrombocytopenia severity grade in thrombocytopenic patients.

Table 2 – Background data of the patient characteristics with and without thrombocytopenia (2015–2017).

Variables	Patients with thrombocytopenia	Patients without thrombocytopenia	p-Value
n (%)	12 (18.2)	54 (81.8)	
Age, years, median (range)	67 (34–101)	61 (18–90)	0.122
Weight (kg), median (range)	65.5 (51.1–81)	68 (34–160)	0.940
DPWD (mg/kg/day), median (range)	18.3 (14.8–23.48)	17.64 (7.5–35.29)	0.792
Gender, mean (SD)			
Male	9 (75)	28 (52)	0.126
Female	3 (25)	26 (48)	
Laboratory data at the start of treatment, mean (range)			
Baseline platelet counts ($\times 10^3$/mm^3), median (range)	198.5 (123–387)	307.5 (110–943)	0.012*
RBC ($\times 10^3$/mm^3), median (range)	2.9 (1.7–5.0)	3 (1.7–5.5)	0.474
Hemoglobin (g/dL), median (range)	10 (5.3–13.9)	9 (5.7–13.8)	0.288
WBC ($\times 10^3$/mm^3), median (range)	17.81 (2.44–53.45)	14.23 (3.5–70.66)	0.345
PCR (mg/dL), median (range)	224 (6.26–347.32)	146 (1.9–491.5)	0.884
Na (mmol/L), median (range)	140 (123–160)	138 (122–160)	0.416
K (mmol/L), median (range)	5 (3.3–6.2)	4 (2.6–7.4)	0.163
Urea (mg/dL), median (range)	96 (28–182.6)	81 (15.6–2787)	0.753
S Cr (mg/dL), median (range)	3 (1.06–4.29)	2 (0.35–12.6)	0.345
Cr CL (mL/min), median (range)	24.08 (12.97–63.65)	51.42 (7.08–252.6)	0.043*
Type of infection, mean (SD)			
Pneumonia	6 (50)	24 (44)	0.485
Sepsis	3 (25)	7 (13)	0.353
Cystitis	1 (8)	6 (11)	0.625
Skin and soft tissue infections	0	13 (24)	0.103
Meningitis	0	2 (4)	0.667
Peritonitis	2 (17)	2 (4)	0.148
Baseline platelet count ≤200 × 10^3/mm^3, mean (SD)	7 (58)	16 (29.2)	0.029*

The data are presented as n (%), median (range or confidence interval) and mean (SD). The statistical analyses were performed by Mann-Whitney or Student's t-test using the obtained coefficient of variation (CV) from the descriptive analysis. The Fisher's exact test was used for comparisons of type of infection. SD standard derivation, DPWD dosage per weight per day, RBC red blood cells, PCR protein C reactive, S Cr serum creatinine, Cr CL clearance creatinine. Differences were considered significant for p-values <0.05 (*).

Table 3 – Renal function evaluation in thrombocytopenic and non-thrombocytopenic patients.

	Patients with thrombocytopenia	Patients without thrombocytopenia	p-Value
Cr Cl <30 mL/min	6 (60)	16 (32)	0.047*
Cr Cl 30–60 mL/min	3 (30)	11 (22)	0.292
Cr Cl >60 mL/min	1 (10)	23 (46)	0.017*

The data are presented as number (%) and statistical analysis performed by two binomial proportions test. The significant difference p-value <0.05 (*). Cr CL clearance creatinine.
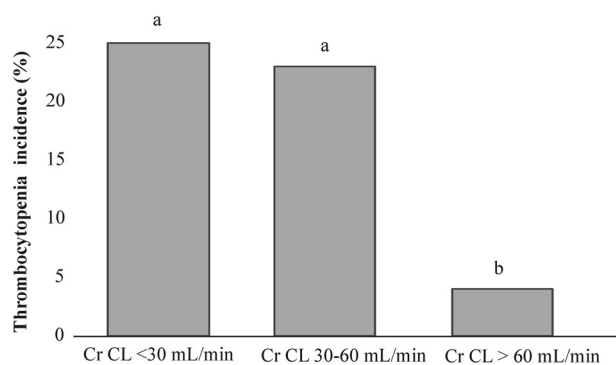
Table 4 – Risk factors for linezolid-induced thrombocytopenia in hospitalized adult patients.

	Odds	95% CI	p-Value
Male	3.85	0.95–15.59	0.094
Baseline platelet count ≤200 × 10^3/mm^3	5.66	1.15–27.9	0.045*
Baseline S Cr >1.5 mg/dL	4.57	1.26–16.5	0.035*
Baseline renal impairment (Cr CL <60 mL/min)	9.41	1.09–80.54	0.043*
DPWD >20 mg/kg/day	0.30	0.035–2.67	0.475

OR odds ratio, CI confidence interval, S Cr serum creatinine, Cr CL creatinine clearance calculated by Cockcroft–Gault equation, DPWD dosage per weight per day. Differences were considered significant for p-values <0.05(*).

Several studies describe risk factors associated with the development of thrombocytopenia in patients who received linezolid therapy. For example, Takahashi et al. reported that the oral administration of linezolid decreased the risk of thrombocytopenia, while the duration of treatment (≥14 days), creatinine clearance (<50 mL/min) and chronic liver disorders were associated with higher risk.[18] In addition, Hirano et al. described individuals with creatinine clear-

Figure 3 – The thrombocytopenia incidence (%) in each renal function group. The patients were stratified according to their creatinine clearance rates into three groups: insufficient renal function (Cr CL < 30 mL/min), mildly insufficient renal function (Cr CL 30–60 mL/min) and normal renal function (Cr CL > 60 mL/min). The lower-case letters (a) between bars indicate no significant differences, while statistically significant differences are presented by different lower-case letters (a and b) above the bars (binomial test, $p < 0.05$).

ance rates <30 mL/min having a significantly higher incidence of thrombocytopenia than those with Cr CL greater than 60 mL/min.[6] Other risk factors also have been reported, such as age, gender, body weight, daily dose per kg, serum creatinine, hemodialysis, platelet count at baseline, and anemia.[5,7,19,23]

Our data showed that the incidence of linezolid-induced thrombocytopenia was lower in patients with normal renal function. Although the renal function had little effect on the overall clearance of linezolid, the accumulation of metabolites produced by linezolid oxidation (2-aminoethoxy-acetate and hydroxyethyl-glycine analogue) has been reported in patients with renal dysfunction as possibly associated with this toxicity, but this remains unclear.[24] Tsuji et al. speculated that both metabolites induce injury to the liver, causing an increase in the linezolid serum concentration due the inhibition of its transfer to hepatocytes.[25] Rabon et al. associated severe renal dysfunction and hepatic dysfunction to thrombocytopenia development during LZD treatment.[23] Taken together, these events correlate with the adverse hematological events, such as peripheral platelet count reduction, with reduced peripheral platelet counts. In the literature, several reports have investigated the relationship between Cr CL rates and linezolid clearance in patients with kidney failure, reinforcing the association with linezolid accumulation and toxicity.[26,27]

Rayner et al., through pharmacokinetic and pharmacodynamic relationships, suggested that twice-daily 600 mg linezolid dosing might be considered an overdose in the treatment of elderly or adult patients with renal impairment.[28] The authors explained that this could be due to a decrease in linezolid clearance rates, as shown by the AUC (area under curve) analysis, which represents the duration and the degree of exposure to linezolid; an increase in the AUC was found in

these patients, culminating in the development of hematological alterations.

Matsumoto et al. (2010) quantified the plasma concentrations of linezolid by chromatography and demonstrated a correlation between impaired linezolid clearance and lower renal filtration rates. In this sense, platelet count monitoring had been recommended in patients treated with linezolid for longer than 7 days, especially for those with renal impairment, because of clearance reduction leading to linezolid accumulation.[29] Our results corroborate this recommendation, but we believe that further studies should be encouraged to determine the role of linezolid metabolites in linezolid-induced thrombocytopenia in patients with renal dysfunction, as well as to determine whether linezolid could be reduced by a dose adjustment according to renal function, for which there is currently no specific recommendation.

We observed no association of DPWD with the risk of thrombocytopenia, possibly because the mean body weight of the patients studied was equivalent to the recommended total daily dose of 1200 mg linezolid and was below a defined cutoff (>20 mg/kg/day). On the other hand, Niwa et al. observed a higher incidence of thrombocytopenia in patients receiving daily doses $\geq$22 mg/kg.[19] Natsumoto et al. also reported in their study that patients with DPWD $\geq$27 mg/kg/day with body weight $\leq$45 kg developed thrombocytopenia, suggesting the need for dose adjustment by body weight of adult patients, as already indicated for pediatric patients.[7] Thus, in our opinion, the dose adjustment by body weight also in adults would be a good option in order to contribute to their safety, since this is a priority worldwide in hospitals.

With regard to other identified risk factors, we found that a low baseline platelet count ($<200 \times 10^3/mm^3$) was also considered a significant risk for thrombocytopenia in adults hospitalized in the Brazilian Midwest. In a retrospective cohort, evaluating factors associated with the development of linezolid-induced thrombocytopenia in adult Japanese patients, Niwa et al. reported an incidence of 44% (8/18) in patients with a low pre-treatment platelet count.[19] Minson et al.[30] identified that one variable independently associated with the development of thrombocytopenia (grade 3 and 4) was the presence of an initial blood platelet count between 50 and $99.9 \times 10^3/mm$, similar to the findings of Hanai et al.[5]

In conclusion, the incidence of linezolid-induced thrombocytopenia in adults hospitalized in the Brazilian Midwest was 18.2%. In addition, this study suggested that a platelet count $\leq$200 $\times 10^3/mm^3$, a level of serum creatinine >1.5 mg/dL and renal impairment at the start of treatment can be considered risk factors for thrombocytopenia in adults. However, future prospective studies based on pharmacokinetics and pharmacodynamics are required to guarantee better strategies in the use of this antimicrobial. Nevertheless, we suggest the need for blood count monitoring during prolonged therapy (>7 days) to assess the occurrence of thrombocytopenia. These data may help multidisciplinary teams predict who is likely to develop thrombocytopenia during linezolid therapy and thereby reduce or avoid the risk of unnecessary damage in health care.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

Study conception and design: LSL and SSW. Acquisition of data: LSL, ECAB and KM. Analysis and interpretation of data: SSW, EBP and RTP. Drafting of manuscript: LSL, ECAB, KM and SSW. Critical revision: EBP and RTP.

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REFERENCES

1. Shinabarger D. Mechanism of action of the oxazolidinone antibacterial agents. Expert Opin Investig Drugs. 1999;8(8):1195–202.
2. Pea F, Viale P, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother. 2012;67(8):2034–42.
3. Gee T, Ellis R, Marshall G, Andrews J, Ashby J, Wise R. Pharmacokinetics and tissue penetration of linezolid following multiple oral doses. Antimicrob Agents Chemother. 2001;45:1843–5.
4. Stalker DJ, Jungbluth GL, Hopkins NK, Batts DH. Pharmacokinetics and tolerance of single- and multiple-dose oral or intravenous linezolid, an oxazolidinone antibiotic, in healthy volunteers. J Antimicrob Chemother. 2003;51:1239–46.
5. Hanai Y, Matsuo K, Ogawa M, Higashi A, Kimura I, Hirayama S, et al. A retrospective study of the risk factors for linezolid-induced thrombocytopenia and anemia. J Infect Chemother. 2016;22:536–42.
6. 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.
7. Natsumoto B, Yokota K, Omata F, Furukawa K. Risk factors for linezolid-associated thrombocytopenia in adult patients. Infection. 2014;42:1007–12.
8. Birmingham MC, Rayner CR, Meagher AK, Flavin SM, Batts DH, Schentag JJ. Linezolid for the treatment of multidrug-resistant, Gram-positive infections: experience from a compassionate-use program. Clin Infect Dis. 2003;36:159–68.
9. 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;39:1846–51.
10. Nie X, Zhang Y, Wu Z, Jia L, Wang X, Langan SM, et al. Evaluation of reporting quality for observational studies using routinely collected health data in pharmacovigilance. Expert Opin Drug Saf. 2018;17:661–8.
11. Marshall AL, Kenneth K, Josef TP, Marcel ML, Linda JB, James OA. Williams manual of hematology. 9th ed. New York: McGraw-Hill Education/Medical; 2016, 672 p.
12. Nishijo N, Tsuji Y, Matsunaga K, Kutsukake M, Okazaki F, Fukumori S, et al. Mechanism underlying linezolid-induced thrombocytopenia in a chronic kidney failure mouse model. J Pharmacol Pharmacother. 2017;8:8–13.
13. Chen C, Guo DH, Cao X, Cai Y, Xu Y, Zhu M, et al. Risk factors for thrombocytopenia in adult Chinese patients receiving linezolid therapy. Curr Ther Res Clin Exp. 2012;73:195–206.
14. Dong HY, Xie J, Chen LH, Wang TT, Zhao YR, Dong YL. Therapeutic drug monitoring and receiver operating characteristic curve prediction may reduce the development of linezolid-associated thrombocytopenia in critically ill patients. Eur J Clin Microbiol Infect Dis. 2014;33:1029–35, http://dx.doi.org/10.1007/s10096-013-2041-3.
15. George JN, Raskob GE, Shah SR, Mujahid AR, Stephen AH, Scott O, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med. 1998;129(11):886–90.
16. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;6:31–41.
17. French G. Safety and tolerability of linezolid. J Antimicrob Chemother. 2003;5:45–53.
18. Takahashi Y, Takesue Y, Nakajima K, Ichiki K, Tsuchida T, Tatsumi S, et al. Risk factors associated with the development of thrombocytopenia in patients who received linezolid therapy. J Infect Chemother. 2011;7:382–7.
19. Niwa T, Suzuki A, Sakakibara S, Kasahara S, Yasuda M, Fukao A, et al. 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.
20. Attassi K, Hershberger E, Alam R, Zervos MJ. Thrombocytopenia associated with linezolid therapy. Clin Infect Dis. 2002;34:695–8.
21. Lin YH, Wu VC, Tsai IJ, Ho YL, Hwang JJ, Tsau YK, et al. High frequency of linezolid-associated thrombocytopenia among patients with renal insufficiency. Int J Antimicrob Agents. 2006;28:345–51.
22. Rao N, Hamilton CW. Efficacy and safety of linezolid for Gram-positive orthopedic infections: a prospective case series. Diagn Microbiol Infect Dis. 2007;59:173–9.
23. Rabon AD, Fisher JP, MacVane SH. Incidence and risk factors for development of thrombocytopenia in patients treated with linezolid for 7 days or greater. Ann Pharmacother. 2018;52:1162–4.
24. Brier ME, Stalker DJ, Aronoff GR, Batts DH, Ryan KK, O'Grady M, et al. Pharmacokinetics of linezolid in subjects with renal dysfunction. Antimicrob Agents Chemother. 2003;47:2775–80.
25. Tsuji Y, Hiraki Y, Mizoguchi A, Hayashi W, Kamohara R, Kamimura H, et al. Pharmacokinetics of repeated dosing of linezolid in a hemodialysis patient with chronic renal failure. J Infect Chemother. 2008;14:156–60.
26. Nukui Y, Hatakeyama S, Okamoto K, Yamamoto T, Hisaka A, Suzuki H, et al. High plasma linezolid concentration and impaired renal function affect development of linezolid-induced thrombocytopenia. J Antimicrob Chemother. 2013;68:2128–33.
27. Tsuji Y, Hiraki Y, Matsumoto K, Mizoguchi A, Kobayashi T, Sadoh S, et al. Thrombocytopenia and anemia caused by a

persistent high linezolid concentration in patients with renal dysfunction. J Infect Chemother. 2011;17:70–5.

28. Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet. 2003;42:1411–23.

29. Matsumoto K, Takeshita A, Ikawa K, Shigemi A, Yaji K, Shimodozono Y, et al. Higher linezolid exposure and higher frequency of thrombocytopenia in patients with renal dysfunction. Int J Antimicrob Agents. 2010;36:179–81.

30. Minson Q, Gentry CA. Analysis of linezolid-associated hematologic toxicities in a large veterans affairs medical center. Pharmacotherapy. 2010;30(9):895–903.