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MAJOR ARTICLE

Safety Profile of Linezolid in Older Adults With Renal Impairment: A Population-Based Retrospective Cohort Study

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Background. The objective of this study was to characterize the safety profile of linezolid in patients with renal impairment compared with patients without renal impairment.

Methods. A population-based retrospective cohort study using linked administrative databases included patients aged 66 years or older in Ontario, Canada

who were prescribed linezolid from 2014 to 2021. Renal impairment was defined using baseline estimated glomerular filtration rate <30 mL/min/1.73 m^2 or receipt of dialysis. The primary outcomes were change in platelet count and severe thrombocytopenia (platelet count $<50 \times 10^9$/L) within 90 days. Secondary outcomes included bleeding, neutropenia, peripheral neuropathy, optic neuropathy, acidosis, serotonin syndrome, and mortality. Inverse probability of treatment weighting on propensity score was used to balance comparison groups on baseline health.

Results. Of 625 patients, 98 (15.7%) patients had renal impairment. The mean (SD) platelet change was −88.3 (108.4) 10^9/L in the renal impairment group and −76.5 (109.8) 10^9/L in the no renal impairment group, with an adjusted mean difference of −29.4 (95% CI, −53.4 to −5.3; $P = .0165$). Severe thrombocytopenia occurred in 9.2% for the renal impairment group and 5.9% for the no renal impairment group, with an adjusted risk difference of 2.7% (95% CI, −3.1% to 8.6%; $P = .3655$). There were no significant differences in secondary outcomes between the 2 groups.

Conclusions. Patients with renal impairment on linezolid therapy had a larger decrease in platelet count, but their risks for severe thrombocytopenia and bleeding were not significantly different than patients without renal impairment. Linezolid is likely safe in renal impairment without dose adjustment or drug level monitoring.

Keywords. linezolid; safety; adverse events; renal impairment.

Linezolid is a synthetic oxazolidinone antibiotic with activity against gram-positive bacteria that can be used to treat bacteremia, pneumonia, or skin and soft tissue infections [1, 2]. In terms of adverse effects, linezolid therapy for >2 weeks may lead to myelosuppression, especially thrombocytopenia [3].

Linezolid is mainly cleared by nonrenal mechanisms [4]. In a pharmacokinetics study of 24 subjects that included patients with renal dysfunction on and off dialysis, linezolid clearance did not change significantly with renal function [4]. It was concluded that renal adjustment for linezolid was unnecessary [2, 4].

Yet, 35% of linezolid is renally cleared, and metabolites do accumulate in renal impairment [4]. In observational studies, linezolid use in renal impairment was consistently associated with a higher risk of thrombocytopenia [5]. However, the absolute decrease in platelet count is not well characterized because most studies defined thrombocytopenia based on a cutoff of 100×10^9/L or 150×10^9/L [5]. Furthermore, it remains unclear if the decrease in platelets translates to increased bleeding risk.

There are safety considerations other than thrombocytopenia for linezolid. Evaluation of linezolid safety in renal impairment should also address other uncommon but serious adverse effects including neutropenia [3], peripheral neuropathy [6], optic neuropathy [6], lactic acidosis [7], and drug interactions resulting in serotonin syndrome [8]. Of these adverse effects, peripheral neuropathy, optic neuropathy, and lactic acidosis were associated with longer duration of linezolid therapy [6, 7].

We conducted a retrospective cohort study to characterize the safety profile of linezolid in patients with renal impairment when compared with patients with no renal impairment in terms of thrombocytopenia, bleeding risk, and other rare adverse effects.

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METHODS

This retrospective population-based cohort study used databases housed at ICES (formerly the Institute for Clinical Evaluative Sciences). The ICES data repository consists of linked publicly funded administrative health service records for the Ontario population eligible for universal health coverage that are routinely collected by the Ontario government [9]. The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board approved this study.

This study was reported as per the REporting of studies Conducted using Observational Routinely collected Data (RECORD) guidelines (Supplementary Table 1) [10].

Patient Population

The Ontario Drug Benefit (ODB) database within ICES captured outpatient prescription medications dispensed to people over the age of 65 in Ontario, Canada. Oral linezolid was added to ODB starting in October 2014 [11]. The study population included adults aged 66 or older in Ontario who were dispensed oral linezolid for any duration from October 2014 to January 2021. This was a convenient sample size based on the study date cutoff.

Patients were included in this study if they satisfied all the following:

1. creatinine at least once from 1 year before linezolid start date to 90 days after linezolid start date;
2. complete blood count within 1 year before linezolid start date as well as within 90 days after linezolid start date.

Data Collection

The ODB databases were linked at a person level and included the following: census data, the Canadian Institute for Health Information (CIHI) discharge abstract database (DAD), the National Ambulatory Care Reporting System (NACRS), the Ontario Health Insurance Plan (OHIP) and Ontario Laboratories Information Systems (OLIS). Census data contained demographics and vital statistics. The CIHI DAD, NACRS, and OHIP databases provided information on diagnoses, comorbidities, and health care utilization including ambulatory care visits, emergency room (ER) visits, and hospitalizations. OLIS data consisted of bloodwork results. All patients had complete linked data.

The following baseline characteristics were collected from these databases:

1. demographic: age, sex, rural or urban home address;
2. comorbidity: modified Charlson comorbidity index (mCCI), which was the Charlson comorbidity index [12] score without the chronic kidney disease category;
3. linezolid: dose, frequency, duration of use.

The investigators had access to the deidentified database that was prepared by the ICES team based on the eligibility criteria on an online secure server for analysis. Data cleaning was done by data checking and removal of data outside the relevant study time frame.

Definition for Renal Impairment

Renal impairment was based on the most recent creatinine on bloodwork within the time frame from 1 year before the linezolid start date to 90 days after the linezolid start date. The age category, sex, and creatinine were entered into the 2021 CKD-EPI equation to derive the estimated glomerular filtration rate (eGFR) [13]. Renal impairment was defined as eGFR <30 mL/min/1.73 m^2. This threshold was chosen to reflect the cutoff for stage 4 chronic kidney disease with severely decreased eGFR [14].

Dialysis status was determined based on OHIP physician billing codes. Patients on dialysis were assigned 0 mL/min/1.73 m^2 for eGFR.

Two sensitivity analyses were performed. First was a re-analysis using creatinine only within 1 year before starting linezolid to determine if the results remained consistent with a stricter time frame criterion. Classification based on creatinine before and not after linezolid therapy would exclude patients with acute kidney injury from the renal impairment group. Second was a comparison between eGFR of >60 mL/min/1.73 m^2 vs eGFR of 30 mL/min/1.73 m^2 to 60 mL/min/1.73 m^2 to determine if the no renal impairment group based on an eGFR of >30 mL/min/1.73 m^2 was a homogeneous group.

Safety Outcomes

The primary outcome was thrombocytopenia, defined using 2 approaches. In the first approach, pretreatment platelet count was defined as the most recent platelet count within the year before starting linezolid. Post-treatment platelet nadir was defined as the lowest platelet count within 90 days from starting linezolid. Platelet change was defined as the difference of post-treatment platelet nadir minus pretreatment platelet count. For the second approach, the proportion of patients whose platelets decreased to $<50 \times 10^9$/L (ie, severe thrombocytopenia) was collected. While prior studies used 100×10^9/L as the threshold to define thrombocytopenia, we used a lower threshold of 50×10^9/L because it seemed to be a more clinically significant threshold and was used in a randomized controlled trial [15]. In addition, there was general consensus that the risk of spontaneous bleeding significantly increased when the platelet count was $<50 \times 10^9$/L [16].

Secondary outcomes included the following:

1. critical bleeding, which was defined as bleeding into a critical anatomical site (eg, intracranial, intraocular, or pericardial) within 90 days of starting linezolid [17];

2. noncritical bleeding, which was defined as any bleeding that did not satisfy the definition of critical bleeding within 90 days of starting linezolid;
3. neutrophil change based on post-treatment neutrophil nadir within 90 days of starting linezolid minus pretreatment neutrophil count;
4. decrease in neutrophil to $<0.5 \times 10^9$/L (ie, severe neutropenia [18]);
5. peripheral neuropathy within 90 days of starting linezolid;
6. optic neuropathy within 90 days of starting linezolid;
7. acidosis within 90 days of starting linezolid;
8. serotonin syndrome based on physician diagnosis, Sternbach's criteria [19], or Hunter's criteria [20] within 30 days of starting linezolid;
9. all-cause mortality within 30 days of starting linezolid.

New diagnoses of critical bleeding, noncritical bleeding, peripheral neuropathy, optic neuropathy, acidosis, and serotonin syndrome were captured by OHIP physician billing diagnosis codes when applicable and International Classification of Diseases, 10th revision (ICD-10), codes from ambulatory care visits, emergency room (ER) visits, or hospitalization (Supplementary Table 2). Peripheral neuropathy, optic neuropathy, and acidosis were associated with longer-term use of linezolid [6, 7], so the time frame was defined to be 90 days. In contrast, serotonin syndrome was more likely to be an acute reaction [8]. Serotonin syndrome and death were defined within 30 days because events beyond 30 days were unlikely to be related to linezolid.

Other outcomes included hemoglobin change and decrease to hemoglobin <70 g/L (ie, transfusion threshold [21]). Renal impairment is associated with anemia by itself [22]. Therefore, anemia in renal impairment may not be entirely attributed to linezolid.

Table 1. Baseline Characteristics of Patients With and Without Renal Impairment

	Renal Impairment (n = 98)	No Renal Impairment (n = 527)	Std. Diff
Age, No. (%)			
66–69 y	21 (21.4)	107 (20.3)	0.0277
70–79 y	47 (48.0)	232 (44.0)	0.0790
≥80 y	30 (30.6)	188 (35.7)	0.1077
Female, No. (%)	34 (34.7)	246 (46.7)	0.2458
Rural home address, No. (%)	7 (7.1)	68 (12.9)	0.1927
mCCI, mean (SD)	2.3 (2.0)	1.9 (2.0)	0.2382
eGFR, mean (SD), mL/min/1.73 m^2	13.4 (11.6)[a]	74.7 (22.7)	3.4035
Days of linezolid therapy, mean (SD)	11.2 (6.4)	11.8 (7.2)	0.0777
Linezolid for ≥14 d, No. (%)	39 (39.8)	221 (41.9)	0.0435
Baseline hemoglobin, mean (SD), g/L	100.6 (15.4)	111.0 (19.5)	0.5961
Baseline neutrophils, mean (SD), 10^9/L	5.8 (2.8)	5.9 (4.0)	0.0385
Baseline platelets, mean (SD), 10^9/L	247.4 (106.6)	270.3 (124.5)	0.1974

There were no missing data.

Abbreviations: eGFR, estimated glomerular filtration rate; mCCI, modified Charlson comorbidity index; Std. Diff, standardized difference.

[a]Patients on dialysis were assumed to have an eGFR of 0 mL/min/1.73 m^2.

Statistical Analysis

A complete case analysis was done. The descriptive analysis included means with SDs for continuous variables and counts with percentages for categorical variables. ICES data policy states that research outputs and reports must not contain information that identifies an individual or could foreseeably be used, either alone or with other information, to re-identify an individual. Therefore, all cells containing or revealing ≤5 individuals were suppressed to comply with this policy.

Comparisons between the renal impairment group and no renal impairment group were done using the Fisher exact test for categorical variables and the unpaired Student *t* test for continuous variables. Comparison between the groups was also described in terms of mean differences for continuous outcomes and risk differences for categorical outcomes. The 95% CI for risk difference was estimated using the normal approximation method. There was no loss to follow-up, as all outcomes data were captured by the administrative databases.

Propensity score–based analysis was used to adjust for potential confounders and address potential bias. A logistic regression model was used to estimate the propensity score for renal impairment. The propensity score was estimated based on the following baseline characteristics: age, sex, rural home address, mCCI, days of linezolid therapy, pretreatment neutrophil count, and pretreatment platelet count. Age in years was categorized into 66–69, 70–79, and ≥80. Other continuous variables were analyzed as is. An inverse probability of treatment weighting (IPTW) using propensity scores was used to balance the selected variables and estimate the average treatment effect [23]. The adjusted mean or risk differences 95% CI after IPTW adjustment was then used to back-calculate the *P* value using methods described by Altman et al. [24].

A descriptive subgroup analysis was done within the renal impairment group that compared patients who had <14 days of linezolid therapy with patients who had ≥14 days of linezolid therapy. As an exploratory analysis, univariate linear regression was used to assess the relationship between eGFR and absolute decrease in hemoglobin, neutrophils, or platelets.

All reported 95% CIs are 2-sided, and all tests are 2-sided, with a significance level of $P < .05$. All analyses were done with the statistical software R, version 3.6.3. IPTW based on propensity scores was done using the PSW package [25].

RESULTS

Of 1134 outpatients who were prescribed oral linezolid, 625 patients had a baseline creatinine and a complete blood count both at baseline and within 90 days of starting linezolid therapy.

Table 2. Comparison of Adverse Effects Related to Linezolid Between Patients With and Without Renal Impairment

	Renal Impairment (n = 98)	No Renal Impairment (n = 527)	Unadjusted Difference (95% CI)	Adjusted Difference (95% CI) *P* Value Based on Estimate and CI
Primary outcomes				
Platelet change, mean (SD), 10^9/L	−88.3 (108.4)	−76.5 (109.8)	Mean difference −11.8 (−35.5 to 11.8)	Mean difference −29.4 (−53.4 to −5.3) *P* = .0165
Platelet decreased to <50 × 10^9/L, No. (%)	9 (9.2)	31 (5.9)	Risk difference 3.3% (−2.8% to 9.4%)	Risk difference 2.7% (−3.1% to 8.6%) *P* = .3655
Secondary outcomes				
Noncritical bleeding, No. (%)	10 (10.2)	55 (10.4)	Risk difference −0.2% (−6.8% to 6.3%)	Risk difference −0.8% (−7.7% to 6.2%) *P* = .8420
Neutrophil change, mean (SD), 10^9/L	−1.6 (2.3)	−1.3 (3.1)	Mean difference −0.3 (−0.8 to 0.3)	Mean difference −0.4 (−0.8 to 0.1) *P* = .0945
Death within 30 d, No. (%)	7 (7.1)	25 (4.7)	Risk difference 2.4% (−3.0% to 7.8%)	Risk difference 2.3% (−3.0% to 7.6%) *P* = .4037
Other outcomes				
Hemoglobin change, mean (SD), g/L	−12.4 (16.0)	−11.2 (17.3)	Mean difference −1.2 (−4.7 to 2.4)	Mean difference −1.4 (−4.6 to 1.9) *P* = .4143
Hemoglobin decreased to <70 g/L, No. (%)	16 (16.3)	51 (9.7)	Risk difference 6.6% (−1.1% to 14.4%)	Risk difference 8.4% (−0.2% to 17.0%) *P* = .0538

The timing of bloodwork measurements is described in Supplementary Table 3. All patients included in the study had complete follow-up to 90 days. Baseline characteristics and known outcomes of the excluded patients with missing bloodwork compared with patients included in this study are described in Supplementary Table 4. The linezolid dose was 600 mg twice daily for all patients. The prescribed linezolid duration was ≥14 days for 260 (41.6%) patients. Of the 625 patients, 98 (15.7%) patients had renal impairment based on eGFR <30 mL/min/1.73 m^2. Thirty-seven (37.8%) of the 98 patients with renal impairment were receiving dialysis. In the comparison group, 527 (84.3%) patients had no renal impairment. Baseline characteristics for the 2 groups are described in Table 1. Notable differences included lower proportion of females, higher number of comorbidities, and lower baseline platelets in the renal impairment group (Table 1).

Outcomes

Adverse effects for patients with and without renal impairment are described in Table 2. Of note, the mean (SD) platelet change was −88.3 (108.4) 10^9/L in the renal impairment group and −76.5 (109.8) 10^9/L in the no renal impairment group (*P* = .3221). Severe thrombocytopenia occurred in 9.2% for the renal impairment group and 5.9% for the no renal impairment group (*P* = .2577). A similar proportion of patients had noncritical bleeding in both groups (Table 2).

Critical bleeding, severe neutropenia, peripheral neuropathy, acidosis, and serotonin syndrome occurred very rarely in both groups (Supplementary Table 5). No patient had a new diagnosis of optic neuropathy. The rates of adverse effect to cumulative linezolid days are described in Supplementary Table 6.

Adjustment Using Propensity Scores

The standardized differences of the mean before and after IPTW by propensity score are shown in Table 3. After adjustment, the maximum standardized difference was 0.0472, reflecting a good balance of matched variables.

The risk or mean differences for each adverse effect after adjustment by IPTW are described in Table 2 in the last column. Of note, there is a significantly larger decrease in platelet count in the renal impairment group, with an adjusted mean difference of −29.4 × 10^9/L (95% CI, −53.4 to −5.3; *P* = .0165). The adjusted risk difference for severe thrombocytopenia was 2.7% (95% CI, −3.1% to 8.6%; *P* = .3655). There was no significant difference between the 2 groups in terms of noncritical bleeding and death.

Sensitivity Analyses

Comparison of adverse effects for patients with eGFR of <30 mL/min/1.73 m^2 vs ≥30 mL/min/1.73 m^2 based on creatinine taken only before starting linezolid is described in Supplementary Table 7, which showed similar results when compared to the main analysis results described above.

Comparison of adverse effects for patients with eGFR of >60 mL/min/1.73 m^2 vs 30 mL/min/1.73 m^2 to 60 mL/min/1.73 m^2 showed no significant difference between these 2 groups (Supplementary Table 8).

Table 3. Balance of Baseline Characteristics Before and After Inverse Probability of Treatment Weighting

Variables Adjusted by Propensity Scores	Std. Diff Before Adjustment	Std. Diff After Adjustment
Age		
66–69 y	0.0277	0.0136
70–79 y	0.0790	0.0472
≥80 y	0.1077	0.0373
Female	0.2458	0.0056
Rural home address	0.1927	0.0038
mCCI	0.2382	0.0158
Days of linezolid therapy	0.0777	0.0028
Baseline neutrophils	0.0385	0.0111
Baseline platelets	0.1974	0.0186

Abbreviations: mCCI, modified Charlson comorbidity index; Std. Diff = standardized difference.

In the renal impairment group with eGFR of <30 mL/min/1.73 m^2, the comparison of patients who received <14 days vs ≥14 days of linezolid therapy is shown in Supplementary Table 9. Longer linezolid therapy was associated with a larger drop in platelet count. There was no statistically significant difference between the 2 groups in terms of severe thrombocytopenia or other adverse events related to linezolid.

Univariate linear regression did not show any significant association of eGFR with change in hemoglobin, neutrophil count, or platelets (Supplementary Table 10).

DISCUSSION

This population-based retrospective cohort study compared adverse outcomes of linezolid treatment in 98 outpatients with renal impairment based on eGFR <30 mL/min/1.73 m^2 with 527 outpatients with no renal impairment. Linezolid led to a larger absolute decrease in platelet count by an average of $\sim 30 \times 10^9$/L in those with renal impairment. However, there was not a statistically significant increase in the risk of severe thrombocytopenia based on a platelet count $<50 \times 10^9$/L or risk of bleeding. Other adverse events including critical bleeding, severe neutropenia, optic neuropathy, peripheral neuropathy, acidosis, and serotonin syndrome occurred very rarely in both groups. The study did not detect any signal of a higher risk for these rare adverse events in renal impairment, but no definitive conclusion could be drawn due to the very small number of events. There were no statistically significant differences between the 2 groups with respect to mortality.

The mechanism of linezolid-induced thrombocytopenia is unclear [5]. Proposed mechanisms include phosphorylation of myosin light chain, which inhibits platelet release from mature megakaryoblasts, and destruction of platelets via oxidative damage or an immune-mediated pathway [5]. Interestingly, in our study, the risk of critical and noncritical bleeding was similar between those with renal impairment and those without renal impairment. It is well known that uremia causes platelet dysfunction and increases risk of bleeding in end-stage renal disease [26]. We hypothesize that the similar bleeding risk between the 2 groups could be due to 2 reasons. First, patients with an eGFR <30 mL/min/1.73 m^2 but not at end-stage renal disease were included in the renal impairment group, who may have less platelet dysfunction. Second, those with end-stage renal disease were on dialysis, which can correct platelet dysfunction [26]. The rare occurrence of adverse effects such as peripheral neuropathy, optic neuropathy, and lactic acidosis was likely due to the fact that these adverse effects occur after months of linezolid therapy [6, 7]. Renal impairment is unlikely to be a major contributing factor because the toxic effect of a cumulative dose over months likely far outweighed accumulation of metabolites in renal impairment.

Our study results are consistent with prior studies. In a meta-analysis of 24 observational studies published up to 2021, linezolid use in renal impairment increased the risk of thrombocytopenia, with an adjusted odds ratio of 2.51 (95% CI, 1.82–3.45) [5]. Similarly, our study showed that thrombocytopenia was more pronounced in individuals with renal impairment. Prior studies defined thrombocytopenia based on decrease to below the threshold of 100×10^9/L. Our study adds to the existing evidence by providing an absolute change in platelets on average and describing the risk for severe thrombocytopenia and bleeding. In our opinion, severe thrombocytopenia based on a threshold of 50×10^9/L was more clinically relevant because the risk of bleeding significantly increases when the platelet count is $<50 \times 10^9$/L [16]. Furthermore, the platelet count threshold to reconsider anticoagulation and platelet transfusion before a surgery or invasive procedure is typically $\leq 50 \times 10^9$/L [16, 27]. Our study did not find any signal of increased risk for adverse effects other than thrombocytopenia in renal impairment while on linezolid treatment. This was concordant with other studies that did not find renal impairment to be a significant predictor for linezolid-associated optic neuropathy [28], peripheral neuropathy [29], lactic acidosis [30], or serotonin syndrome [31].

Our study has several strengths. First, our retrospective cohort study is the largest to date to characterize linezolid-induced thrombocytopenia and the only study to date to consider a wide array of serious adverse effects related to linezolid in renal impairment. The larger sample size allowed for more precise estimates. Second, we adjusted for multiple potential confounders including patient demographics, comorbidities, days of linezolid therapy, and baseline bloodwork values using propensity scores. Lastly, our databases had complete follow-up for all patients up to day 90, as all ambulatory care visits, ER visits, and hospitalization within the province, as well as deaths, would be captured by the administrative databases.

There are several limitations to the study that merit attention. First, a proportion of the patients treated with linezolid

were excluded from the study due to missing bloodwork. In clinical practice, patients prescribed a short course of linezolid would not necessarily need monitoring bloodwork. As such, it was expected that a proportion of outpatients would not have bloodwork. Prior observational studies have similarly excluded a significant proportion of patients due to missing bloodwork values [32, 33]. A comparison of baseline characteristics between excluded and included patients showed that the excluded patients were slightly older, with a higher proportion of females (Supplementary Table 4). There were no other significant differences between the excluded and included patients with respect to baseline characteristics and known outcomes.

Second, the constellation of ICD-10 codes did not perfectly capture linezolid-associated lactic acidosis or serotonin syndrome. The study could only capture acidosis as a proxy for lactic acidosis. Nevertheless, all lactic acidosis cases should be captured under this definition. For serotonin syndrome, the ICD-10 codes did not match perfectly with the diagnostic criteria. However, this is the most common method used in prior studies [34, 35]. We also used multiple definitions based on ICD-10 codes for serotonin syndrome (physician diagnosis, Sternbach's criteria, and Hunter's criteria) to be inclusive. It is reassuring that the incidence of serotonin syndrome observed in our study is similar to the reported incidence in prior studies [35], suggesting that we did not miss a significant number of cases.

Third, we defined baseline creatinine with a time frame up to 90 days after linezolid start date. This assumes stable renal function during linezolid use. We thought it was a reasonable assumption given the study population of outpatients being prescribed linezolid, but it may not necessarily be true. Sensitivity analysis using only creatinine before linezolid use to define renal impairment showed similar results (Supplementary Table 7).

Fourth, most linezolid-associated toxicity in prior studies appears to require longer-term use (eg, >14 days). For example, most myelosuppression occurred after 14 days of therapy [3]. Optic neuropathy, peripheral neuropathy, and lactic acidosis were usually observed after months of therapy [6, 7, 28–30]. In our study, the mean number of days on linezolid therapy was 11 days. This fact likely accounts for the low incidence of adverse events observed in our study. Still, a significant proportion (40%) of patients took linezolid for ≥14 days in our study. For patients who were on linezolid in the hospital and discharged home on linezolid, our database would have only captured linezolid days postdischarge. Therefore, the reported linezolid days may be an underestimate in some cases.

Our study has important implications. Prior studies led to proposals of dose reduction and trough monitoring for linezolid in renal impairment based on correlation between renal failure, higher linezolid plasma trough levels, and thrombocytopenia [36]. Subsequent studies used population pharmacokinetic modeling to determine the target trough level and dose reduction in renal impairment [32, 37]. While platelet count decreased more for renal impairment in our study, the proportion of patients who had severe thrombocytopenia or bleeding was not significantly different between those with and without renal impairment. Decrease in platelets does not necessarily require cessation of linezolid therapy as long as there is no severe thrombocytopenia or significant bleeding. For example, in a recent retrospective cohort study of 76 patients receiving long-term linezolid for multidrug-resistant tuberculosis, cytopenias occurred in 30 (39.5%) patients who received a median of 526 days of linezolid [38]. However, no patient required dose reduction or interruption due to cytopenia [38]. Therefore, linezolid-related thrombocytopenia in renal impairment is not likely to be clinically significant enough to require cessation of linezolid therapy. In addition, no significant difference in the risk for other adverse events was found for patients with and without renal impairment. Therefore, our study suggests that it is likely safe for patients to receive linezolid for a short duration without need for dose adjustment or drug level monitoring.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. Dr. Mark Loeb reports having served on advisory boards for Sanofi, Pfizer, Medicago, Merck, Seqirus, and Paladin Labs; Pan Data Safety and Monitoring Committees for Medicago, CanSino Biologics, the National Institutes of Health, and the WHO EML Antibiotic Working Group. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Data sharing. The data set from this study is held securely in coded form at the Institute for Clinical Evaluative Sciences (ICES). While data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential

access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Patient consent. As a retrospective study that reports de-identified data, patients' consent for participation was waived. The study was approved by the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB; project number 6035935).

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