

Article

Effectiveness and Safety of Linezolid as Continuous Infusion Versus Intermittent Infusion in Critically Ill Patients: A Pilot Study

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Abstract

Introduction: Linezolid is a reserve antibiotic used to treat infections caused by Gram-positive bacteria with resistance genes. In critically ill patients, high intra- and interindividual variability has been observed, prompting the search for alternative methods to reduce this variability and achieve the pharmacokinetic/pharmacodynamic indices necessary for a favorable efficacy–safety balance. **Aim of the study:** We wished to compare the safety and effectiveness of a continuous infusion (CI) versus an intermittent infusion (II) of linezolid in patients requiring intensive care. **Materials and Methods:** This study, registered under the number NCT05801484, was a prospective, open-label, single-center, two-arm study. Data on hematologic safety and effectiveness were collected and compared between patients receiving CI and II, respectively, at the same daily dose of linezolid (1200 mg). **Results:** Twenty-nine patients from the intensive care unit were included, divided into two groups. No statistically significant difference was found in 30-day mortality between the groups, nor in the likelihood of post-treatment culture negativity. However, a significantly greater reduction in C-reactive protein levels was observed in the CI group compared to the II group. Regarding safety, at CrCl < 60 mL/min, the decrease in platelets was statistically significant in group II but not in group CI. Additionally, at the 30-day follow-up, recovery from thrombocytopenia was better in the CI group. **Conclusions:** Continuous infusion of linezolid proved to be non-inferior to intermittent infusion at the same daily dose in terms of effectiveness. Furthermore, a lower risk of adverse reactions was identified with continuous infusion.

Keywords: continuous infusion; critically ill patient; ICU; intermittent infusion; linezolid; thrombocytopenia; hematologic toxicity; effectiveness; safety



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1. Introduction

Linezolid is an oxazolidinone and a time-dependent antibiotic. It is used to treat community- and hospital-acquired pneumonia, as well as skin and soft tissue infections caused by Gram-positive bacteria (G+) [1]. Critical-care patients have been found to be unable to achieve the optimal concentration for a clinical response with the conventional intermittent intravenous (IV) infusion (II) of 600 mg every 12 h over a 1- to 2-h period, the approved dose and infusion duration [2]. The results of recent studies comparing continuous infusion (CI) with classic II in critically ill patients are promising and suggest that CI may increase the likelihood of achieving a clinical cure, enhance pharmacokinetic/pharmacodynamic (PK/PD) indices, and decrease the risk of side effects [3–5]. Less intra-individual concentration variations were observed, with a better percentage of time that the serum concentrations surpassed the minimum inhibitory concentration (%T > MIC > 80%) attained in the CI group than in the II group [6].

In this study, we aim to compare the effectiveness and safety of linezolid when administered as a continuous infusion versus an intermittent infusion regimen in critically ill ICU patients.

2. Materials and Methods

2.1. Setting

The study was conducted in accordance with the ethical standards outlined in the 2013 Declaration of Helsinki and approved by the local ethics committee. It was a prospective, open-label, single-center, two-arm study. The trial was registered with ClinicalTrials.gov on the 15 November 2022 under the unique identifier NCT05801484 (<https://clinicaltrials.gov/study/NCT05801484> accessed on 15 August 2025) and under the name: ‘Pharmacokinetics and Pharmacodynamics of Linezolid Continuous and Intermittent Administration’. It took place between July 2022 and March 2023 in the ICU of a tertiary hospital in Cluj-Napoca. Before enrolment in the study, written informed consent was obtained from participants or their family members.

2.2. Subjects

Eligible participants were ICU-admitted adults (≥ 18 years), with SOFA scores ≥ 2 , multiple comorbidities, and a suspected or confirmed Gram-positive infection requiring IV linezolid prescribed by the attending physician. The exclusion criteria included severe hepatic failure, classified as Child–Pugh C, refusal to sign the informed consent, and less than 24 h survival after linezolid initiation.

For administrative reasons, a convenience allocation was used, where patients enrolled during the first four-month phase of the study were assigned to the CI group, and those enrolled during the subsequent four-month phase were assigned to the II group. The decision to start with the CI group was made because this type of administration was the standard practice at the department level. Attending physicians initiated linezolid independently of the study, based solely on clinical judgment. The physicians did not participate in the study and, therefore, were not involved in the decision-making process for study inclusion. Investigators enrolled participants who met the inclusion criteria after prescription.

2.3. Antimicrobial Therapy

Following microbiological sampling, the patients were administered linezolid (Frese-nius Kabi AG, Homburg, Germany) in conjunction with a broad-spectrum antibiotic to target Gram-negative bacteria: amoxicillin + clavulanate (Antibiotice SA, Iasi, Romania)/ampicillin + sulbactam (Antibiotice SA, Iasi, Romania)/ceftriaxone (Antibiotice SA, Iasi, Romania)/

piperacillin + tazobactam (Fresenius Kabi AG, Homburg, Germany)/meropenem (Antibiotice SA, Iasi, Romania)/ceftazidime + avibactam (Pfizer, New York City, NY, USA).

The CI group received a one-hour IV loading dose of 600 mg, then 1200 mg per day via continuous infusion (50 mg/h), as described by Boselli et al. [7]. The II group was administered 600 mg IV over 1–2 h every 12 h, following the approved regimen [8]. The attending physician decided the treatment duration, which ranged from 2 to 13 days. The duration of the treatment was determined by the attending physician and ranged from 2 to 13 days.

2.4. Demographic and Clinical Data

Collected sociodemographic data included age, gender, origin, height, weight, BMI (calculated as weight divided by height squared), and comorbidities assessed with the Charlson Comorbidity Index (CCI) [9]. We also divided patients into two categories based on CCI, as moderate for $CCI \leq 4$ and as severe for $CCI \geq 5$ [10].

As part of the routine care procedure, several blood parameters were determined, including the number of white blood cells, platelets, neutrophils, and lymphocytes. These were documented at the commencement of linezolid therapy, and neutrophil-to-lymphocyte ratios (NLRs) and platelet-to-lymphocyte ratios (PLRs) were calculated.

The Simplified Acute Physiology Score II (SAPS II) and SOFA were calculated for each patient upon admission to assess the risk of mortality. Furthermore, data concerning infections, including the type of infection and the results of microbiological cultures, were collected and recorded to confirm the presence of G+ infections.

For the evaluation of side effects, we analyzed platelets as the primary outcome on the first day of treatment and before the first dose (Baseline), on the last day of treatment (Last), and at the 30-day follow-up after starting treatment (Final). As a secondary outcome we evaluated hemoglobin (Hb), red blood cell counts (RBC), hematocrit (Ht), red blood cell distribution width variation coefficient and standard deviation (RDW-CV and RDW-SD) on the first day of treatment and before the first dose (Baseline), on the last day of treatment (Last), and at the 30-day follow-up after starting treatment (Final).

For effectiveness, as a primary outcome we evaluated the clinical cure by measuring bacterial eradication at the infection site. As a secondary effectiveness outcome we assessed the reduction in CRP and leucocyte levels from Baseline to the Last assessment and 30-day survival.

When a patient did not have one of the mentioned parameters determined, it was mentioned as missing data during the analysis.

2.5. Data Analysis

Continuous variables are reported as mean, and standard deviation, while the absolute value and the percentage are used to describe categorical variables. The chi-squared test was employed to compare the categorical variables. We used the independent two-sample t-test to identify differences between groups, and the paired t-test for intra-group comparison of study parameters. Pearson's correlation measured linear relationships between continuous variables, while the Spearman rank test was used for other variables. A *p*-value of less than 0.05 was considered statistically significant. Data analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). For survival evaluation, we applied Kaplan–Meier methods.

3. Results

3.1. Subjects' Characteristics

This study is a secondary data analysis, and the selection flow chart and demographic extensive summary were published in a previous pharmacokinetic study [6].

Patients were divided chronologically: the first 14 were assigned to the continuous infusion (CI) group and the following 15 to the intermittent infusion (II) group. Ages ranged from 45 to 87 years, with body mass index (BMI) values spanning 15.7 to 41.7 kg/m². No significant baseline differences were observed between groups except for age, where patients in the II group were older (median: 75 vs. 72 years; $p = 0.046$).

Procalcitonin (PCT) levels were not significantly different between the groups. The median level of C-reactive protein (CRP) was higher in the CI group, but this difference was not statistically significant ($p = 0.08$).

Linezolid was used to treat septic shock, bacteremia, and urinary tract infections (UTIs), as well as skin, lung, and abdominal infections. There was no statistically significant difference between the two patient groups regarding the type of infection. A comprehensive summary of all patients' demographic, anthropometric, and prescription data was published in the previous pharmacokinetic study [6] before starting linezolid treatment.

Of the 29 patients included in this study, 19 were initiated on empiric therapy, while the remaining 10 had targeted therapy for G+ bacterial infection. Five *Enterococcus* spp. strains and one *Staphylococcus* spp. strain were identified in the CI group, and four *Enterococcus* spp. and five *Staphylococcus* spp. strains were identified in the II group, regardless of whether empirical or targeted therapy was initiated. These results did not consider screening strains from axillary, rectal, or nasal sites. Data regarding the site of infection and the identification status of G+ bacteria are presented in Table S1.

From Table S1, we note that nine patients with empiric treatment (64%) in the CI group and 10 patients (67%) in the II group were analyzed; 21% had UTIs in the CI group, and 20% had UTIs in the II group; 43% had G+ bacteremia in the CI group, compared to 27% in the II group; in the CI group, 7% of the patients had infections at other sites by G + bacteria, such as skin or pulmonary, versus 20% in the II group. There was no statistically significant difference between groups regarding the site of infection (data published in the pharmacokinetic study [6]). Regardless of whether linezolid therapy was initiated empirically or not, seven patients in the CI group and eight patients in the II group had at least one G+ bacteria identified (50% in the CI group vs. 53% in the II group). Five patients in each group had a negative control microbiological culture (71% in the CI group and 62% in the II group). In the remaining two patients in the CI group and three patients in the II group, no control microbiological testing was performed; however, these patients either survived 30 days after starting therapy or the cause of death was unrelated to therapeutic failure.

3.2. Effectiveness Data

Of the total number of treated patients, 3 (30%) had positive cultures for vancomycin-resistant *Enterococcus* spp. (VRE), and 2 (20%) had oxacillin-resistant *Staphylococcus* spp. (MRS). The remaining five patients (50%) had non-VRE cultures, but linezolid therapy was chosen for other reasons (e.g., moderate to severe kidney disease or unstable kidney function; previous treatment failure with another antibiotic; positive screening for VRE). Out of these 10 patients receiving targeted treatment, nine (90%) had negative control samples, while one patient (10%) did not have a control test, but that patient's infection was caused by an ampicillin-sensitive *Enterococcus* sp.

In Table 1, we can find a comparison of the mean values for leucocytes and CRP with no statistically significant differences between groups for Baseline, Last, and Final

evaluation. We assessed the variation in leucocytes and CRP variation from Baseline to Last for each group. In the CI group, from Baseline to the end of treatment (Last), we identified a statistically significant decrease in CRP ($p = 0.038$), while this decrease was not statistically significant in group II ($p = 0.132$). Regarding the reduction in leukocyte levels, this was statistically significant in group II ($p = 0.028$) and close to statistical significance in the CI group ($p = 0.057$).

Table 1. Comparison of CI group and II group: evaluation of mean values of effectiveness parameters.

Parameter	Group	N	Mean (SD)	<i>p</i>
C Reactive Protein_Baseline	CI	14	20.95 (11.54)	0.274
	II	15	16.4 (10.26)	
C Reactive Protein_Last	CI	14	11.69 (8.11)	0.814
	II	13	12.53 (9.94)	
CRP_Baseline vs. Last	CI	14	9.26 (15.03)	0.038 *
	II	13	5.27 (11.77)	0.132
Leucocytes_Baseline	CI	14	17.97 (12.93)	0.557
	II	15	15.69 (7.04)	
Leucocytes_Last	CI	14	11.13 (4.96)	0.543
	II	15	12.29 (5.16)	
Leucocytes_Baseline vs. Last	CI	14	6.85 (12.24)	0.057
	II	15	3.4 (5.37)	0.028 *
Leucocytes_Final	CI	14	14.53 (11.94)	0.373
	II	15	11.50 (4.86)	

Baseline—at the beginning of linezolid treatment, before first dose of linezolid; Last—at the end of linezolid treatment; Final—at the end of the monitoring period (30 days from the beginning of treatment); SD—standard deviation; * statistically significant p -value ≤ 0.05 .

3.3. Safety Data

Table 2 compares the mean scores for Hb, RBC, Ht, RDW-CV, RDW-SD, and platelets. Higher mean scores are observed in the II group compared to the CI group for Hb, RBC, and Ht at Baseline and after therapy for the same variables. For RDW-CV and RDW-SD, at Baseline and after Linezolid therapy, respectively, mean scores are higher in the CI group than in the II group. No statistically significant difference was found between the two groups for these variables. A borderline statistically significant difference ($p = 0.058$) exists at Baseline in the number of RBCs, with lower values in the CI group, but this difference is not statistically significant at the end of treatment. In the CI group, mean platelet scores at the 30-day follow-up were higher than at Baseline, while in group II, mean platelet scores were lower than at Baseline.

Table 2. Comparison of CI group and II group: evaluation of mean values of safety parameters.

Parameter	Group	N	Mean (SD)	<i>p</i>
Plateletes_Baseline	CI	14	185.5 (138.47)	0.153
	II	15	253.80 (111.10)	
	Overall	29	220.83 (127.60)	-
Plateletes_Last	CI	14	149.00 (89.94)	0.453
	II	15	177.86 (105.37)	
	Overall	29	163.93 (97.59)	-

Table 2. Cont.

Parameter	Group	N	Mean (SD)	p
Plateletes_Baseline vs. Last	CI	14	36.5 (93.5)	0.167
	II	15	75.93 (91.7)	0.006 *
Plateletes_Baseline Clcr > 60	CI	5	243.80 (156.96)	0.677
	II	6	280.33 (113.55)	
	Overall	11	263.73 (129.09)	0.131
Plateletes_Last Clcr > 60	Overall	11	204.00 (64.71)	
Plateletes_Baseline vs. Last Patients with CrCl > 60	CI	5	53.20 (150.90)	0.474
	II	6	65.16 (103.20)	0.182
	Overall	11	59.72 (120.30)	0.131
Plateletes_Baseline Clcr ≤ 60	CI	9	153.11 (124.65)	0.158
	II	9	236.11 (112.54)	
Plateletes_Last Clcr ≤ 60	CI	9	125.89 (102.18)	0.608
	II	9	153.00 (116.99)	
Plateletes_Baseline vs. Last Patients with CrCl ≤ 60	CI	9	27.22 (50.52)	0.144
	II	9	83.11 (89.02)	0.023 *
	Overall	18	55.16 (75.87)	0.07
Hemoglobin_Baseline	CI	14	9.31 (1.42)	0.216
	II	15	10.16 (2.08)	
Hemoglobin-Last	CI	14	8.56 (0.97)	0.618
	II	15	8.77 (1.25)	
Hb_Baseline vs. Last	CI	14	0.75 (1.19)	0.034 *
	II	15	1.39 (2.47)	0.047 *
Red blood cells_Baseline	CI	14	3.05 (0.44)	0.058
	II	15	3.47 (0.66)	
Red blood cells_Last	CI	14	2.84 (0.31)	0.252
	II	15	2.99 (0.37)	
RBC_Baseline vs. Last	CI	14	0.20 (0.37)	0.063
	II	15	0.47 (0.84)	0.049 *
Hematocrit_Baseline	CI	14	28.11 (3.91)	0.075
	II	15	31.69 (6.15)	
Hematocrit_Last	CI	14	26.15 (2.96)	0.289
	II	15	27.57 (3.97)	
Ht_Baseline vs. Last	CI	14	1.96 (3.35)	0.047 *
	II	15	4.12 (7.77)	0.059
RDW_CV_Baseline	CI	14	16.38 (2.10)	0.961
	II	15	16.34 (2.11)	
RDW_CV_Last	CI	14	16.61 (2.15)	0.683
	II	15	16.30 (1.82)	
RDW_CV_Baseline vs. Last	CI	14	0.22 (1.36)	0.541
	II	15	0.04 (0.96)	0.875
RDW_SD_Baseline	CI	14	54.70 (6.98)	0.800
	II	15	54.01 (7.46)	
RDW_SD_Last	CI	14	54.55 (6.53)	0.760
	II	15	53.79 (6.75)	
RDW_SD_Baseline vs. Last	CI	14	0.15 (5.65)	0.922
	II	15	0.22 (4.36)	0.844

Hb = hemoglobin; Ht = hematocrit; RBC = red blood cell count; RDW = red blood cell distribution width; CV = variation coefficient; Baseline = at the beginning of linezolid treatment; Last = at the end of linezolid treatment; SD = standard deviation; * statistically significant p -value ≤ 0.05 .

In the CI group, statistically significant positive correlations between the examined variables at Baseline and Last were identified for Hb ($r = 0.559$, $p = 0.038$), Ht ($r = 0.554$, $p = 0.04$), RDW_CV ($r = 0.795$, $p = 0.01$), and RDW_SD ($r = 0.652$, $p = 0.012$), respectively. Additionally, there was a statistically significant decrease in the values at the Baseline versus Last for Hb ($p = 0.034$) and Ht ($p = 0.047$). For RBC, RDW_CV, and RDW_SD, the decrease was not statistically significant. Mean platelet counts at discharge are higher than before treatment in the CI group. A statistically significant and strongly positive correlation was found between Baseline and Final platelet counts ($r = 0.730$, $p = 0.003$). However, no statistically significant differences were observed between the initial platelet values and those at the end of monitoring ($p = 0.167$) or when stratified based on CrCl in the CI group (Table 2).

In the II group, negative correlations were found for Hb, RBC, and Ht without statistical significance, while highly positive correlations were noted for RDW_CV ($r = 0.889$, $p < 0.001$) and RDW_SD ($r = 0.816$, $p < 0.001$). Also, in the II group, there was a statistically significant decrease from Baseline to Last in Hb ($p = 0.047$), RBC ($p = 0.049$), platelets ($p = 0.006$), and platelets in patients with CrCl < 60 mL/min ($p = 0.023$). For the other parameters, the decrease was not statistically significant. Mean platelet counts were lower at the end of the 30-day monitoring than at Baseline in the II group. A statistically significant and moderate positive correlation was identified between Baseline and Last platelets ($r = 0.517$, $p = 0.048$). No statistically significant differences were identified between the mean values of initial platelets and those at the completion of monitoring in the II group ($p = 0.489$).

3.4. Survival Data

Table 3 displays the overall and stratified mortality data for the two studied groups. There is no statistically significant difference in overall mortality between these groups. The same lack of significance is observed when comparing mortality among patients with UTIs versus those without ($p = 0.866$), as well as between patients with and without G+ bacteria in the urinary tract ($p = 0.839$). Likewise, the difference in patients with and without G+ bacteremia is not statistically significant ($p = 0.944$). Overall and when comparing the two groups, no statistically significant difference in survival was found when stratifying by targeted versus empiric therapy.

Table 3. Comparison of survival rates.

Parameter	Total N	N of Deceased	Survivors		Mean Days of Survival (SD)	<i>p</i> Value
			N	Percent		
CI group	14	7	7	50.0%	22.67 (2.20)	0.4
II group	15	5	10	66.7%	23.33 (2.55)	
Overall	29	12	17	58.6%	23.12 (1.69)	-
Overall—patients without UTI	17	7	10	58.8%	23.59 (2.19)	0.866
Overall—patients with UTI	12	5	7	58.3%	22.39 (2.65)	
Overall—without G+ UTI	23	10	13	56.5%	22.94 (1.90)	0.839
Overall—with G+ UTI	6	2	4	66.7%	24.25 (3.47)	
Overall—without G+ bacteriemia	19	8	11	57.9%	22.81 (2.08)	0.944
Overall—with G+ bacteriemia	10	4	6	60.0%	23.80 (2.81)	

Table 3. Cont.

Parameter	Total N	N of Deceased	Survivors		Mean Days of Survival (SD)	p Value
			N	Percent		
CI group—Targeted therapy	5	2	3	60.0%	26.00 (2.12)	0.557
CI group—Empirical therapy	9	5	4	44.4%	21.05 (2.97)	
II group—Targeted therapy	5	2	3	60.0%	23.00 (4.04)	0.773
II group—Empirical therapy	10	3	7	70.0%	23.50 (3.24)	
Overall—Targeted therapy	29	12	17	58.6%	24.54 (2.36)	0.864
Overall—Empirical therapy	19	8	11	57.9%	22.47 (2.22)	

CI—continuous infusion group; II—intermittent infusion group; SD—standard deviation; UTI—upper or lower urinary tract infection as a diagnosis for Linezolid therapy; G+—a sample positive for Gram-positive bacteria; N—number.

Figure 1 shows the overall survival comparison of the two groups, and Figure 2 presents the survival comparison based on the type of therapy. Analysis of 30-day outcomes revealed no statistically significant differences in mortality between CI and II groups ($p = 0.4$).

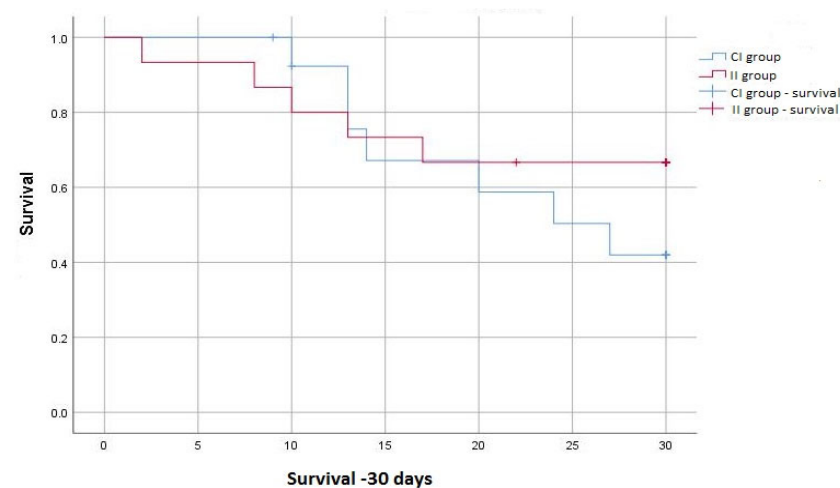


Figure 1. Comparison of overall survival at 30 days between the two groups.

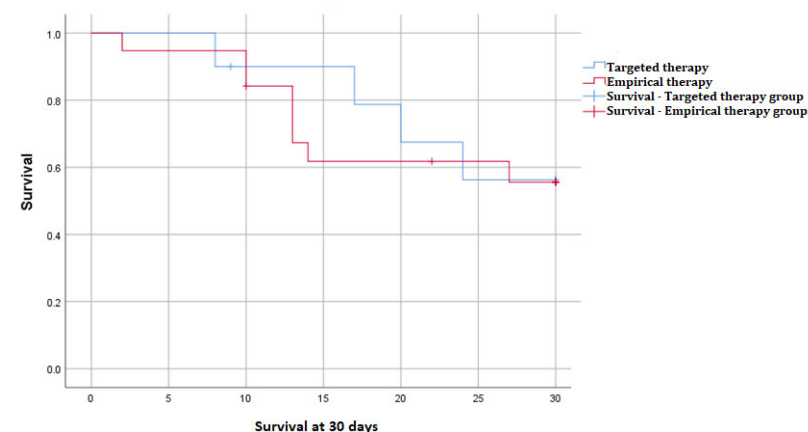


Figure 2. Comparison of survival at 30 days stratified by type of therapy.

Regarding survival outcomes, no significant difference was observed when stratifying by: UTI status—patients without UTI had a 58.8% survival rate ($p = 0.866$), while those with UTI had a 58.3% survival rate; Gram-positive bacteriuria—patients without G+ had a 56.5% survival rate ($p = 0.839$), and those with G+ had a 66.7% survival rate; Gram-positive bacteremia—patients without G+ had a 57.9% survival rate ($p = 0.944$), and those with G+ had a 60.0% survival rate.

When comparing targeted vs. empirical therapy, neither the CI nor the II groups showed statistically significant differences. In the CI group, targeted therapy had 60% survival vs. 44.4% with empirical therapy ($p = 0.557$), and in the II group, 60% vs. 70% ($p = 0.773$).

Regarding the impact of comorbidities (Table 4), no significant differences in mortality were observed between patients grouped by CCI. Patients with moderate CCI (≤ 4), representing 31% of the sample, had a 77.8% survival rate, while those with severe CCI (≥ 5), making up 69%, had a 50% survival rate. Although the difference was not statistically significant ($p = 0.234$), the relative risk indicates that patients with $CCI \geq 5$ were 2.25 times more likely to die, and survival probability was 3.5 times higher in those with $CCI \leq 4$. Additional correlations identified between CCI and age were positive correlations ($r = 0.679$, $p < 0.000$) between CCI and pulmonary infection ($r = 0.450$, $p = 0.014$) and between CCI and septic shock ($r = 0.397$, $p = 0.033$). These findings confirm that higher comorbidity burden is linked with advanced age and increased likelihood of severe infections.

Table 4. Survival Stratification Based on the Charlson Comorbidity Index.

CCI Stratification	N (%)	<i>p</i>	30-Day Survival			Age		Pneumonia		Septic Shock	
			N	%	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Moderate (2–4)	9 (31)	0.197	7	77.8	0.234	-	-	-	-	-	-
Severe (>5)	20 (69)		10	50.0		-	-	-	-	-	-
Total	29 (100)	-	17	58.6	-	0.679	0.000 *	0.450	0.014 *	0.397	0.033 *

CCI—Charlson Comorbidity index; *r* = correlation coefficient; * statistically significant *p*-value ≤ 0.05 .

4. Discussion

By comparing the two groups that received the same daily dose but through different infusion methods, we found a statistically significant difference only in the patients' ages. Additionally, in terms of effectiveness, we observed a more notable decrease in CRP in the CI group. From a safety standpoint, the risk of thrombocytopenia was higher in patients with CrCl below 60 mL/min in group II.

Even if there is variability between the two patient groups regarding age, the manufacturer's specifications recommend the same dose of 1200 mg/day, regardless of a patient's age [11], which aligns with the dose we used in our study.

In terms of effectiveness, treatment with continuously infused linezolid significantly reduced CRP levels, whereas intermittent infusion did not. To our knowledge, no other study has reported changes in CRP levels. This may be due to the low variability in the linezolid concentration during therapy in CI, unlike II, where the concentration variability is much higher. This concentration variability difference was confirmed in the same population and published in a previous study [6].

Of the 29 patients treated with linezolid, 19 received empiric treatment, of whom only one had G+ bacteria, which was a VRE that actually benefited from linezolid (5%). The remaining 18 patients (95%) could have been treated with a penicillin-class antibiotic since all the identified strains showed sensitivity to ampicillin. Regardless of whether

the treatment was targeted or empirical, out of the 29 patients, 21% could have been treated solely with linezolid based on the antibiograms. For the remaining 79% of patients, linezolid therapy was not supported by antibiograms, as no G+ microbiological samples with resistance genes to ampicillin and vancomycin were identified. In any case, linezolid is also effective against Gram-positive bacteria that are sensitive to ampicillin or vancomycin, so the effectiveness of the therapy is not compromised. Also, since microbiological results have limitations and are not always obtained in time before starting the antibiotic treatment, the decision was made based on clinical judgment, considering the severity of infection and individualizing treatment for each patient.

Furthermore, empiric linezolid therapy is unnecessary in institutions with a history of low VRE or MRS rates. It is not needed to cover VRE and MRS species in patients with septic shock who have no previous infections or colonization with these bacteria. Encouragingly, no linezolid-resistant bacterial strain was identified.

Bacterial cultures should be obtained before the first dose of an antibiotic to identify cases that require coverage for ampicillin- and vancomycin-resistant Gram-positive bacteria. Using MALDI-TOF, PCR, or other rapid detection methods for bacterial species and resistance genes is crucial in guiding clinicians when initiating linezolid therapy. Another essential point is the use of proper techniques for performing antibiograms to detect vancomycin sensitivity (such as the microdilution method or VITEK for *Staphylococcus* spp.) [12].

Protti et al. and Alvarez-Lerma et al. evaluated effectiveness in their case reports through microbiological sample negatation and found that linezolid brought microbiological negatation, but only in the CI group was a clinical positive course also observed [13,14]. We did not obtain statistically significant differences in terms of culture negatation, possibly due to the small number of patients included who underwent bacteriological evaluation at the end of therapy.

De Pacale et al. evaluated effectiveness through alveolar diffusion and clinical improvement by day 4. These parameters had higher values in the CI group than in the II group (98.8% vs. 87.1% and 81.8% vs. 72.7%) [4]. Given the small number of patients and the hematological toxicity of linezolid, we decided to examine the patients' blood counts more thoroughly to identify other blood components that could be affected by linezolid therapy. To our knowledge, no other study has reported data on changes in other blood components in such detail.

In terms of safety, as observed in the CI group, Hb and Ht show a statistically significant decrease during treatment, while RDW decreases in a non-statistically significant manner. Also, in the II group, Hb and RBC decrease following intermittent linezolid infusion. In contrast, in the CI group, platelets correlate with a statistically significant increase and in the II group decreased from the first day of treatment to the 30-day follow-up, although the mean value differences were not statistically significant. Using a larger sample size could potentially reveal a statistically significant difference. When comparing the overall Baseline with the Last platelets, we found a statistically significant decrease in the II group but not in the CI group. We did not find significant differences between the groups for Hb, Ht, RBC, and RDW, even though we observed a decline, which is in line with Warda et al.'s study. Furthermore, when stratified based on CrCl, in patients with $\text{CrCl} \leq 60$ mL/min, the decrease was statistically significant in the II group but not in the CI group, which is again in line with Warda et al.'s study [5]. This may be due to the more stable concentration achieved through continuous infusion, without peaks exceeding the maximum acceptable concentrations that are likely responsible for linezolid-induced thrombocytopenia. In patients with renal impairment, these peaks may be more frequent and higher.

Tascini et al. reported a 12.5% versus 0% risk of thrombocytopenia in the II group compared to the CI group, but the statistical significance was not calculated [15]. Albadry et al.'s study, which included 70 patients in each group (continuous vs. intermittent infusion), identified that there was no statistically significant difference in platelet levels in the CI group between patients with $\text{Clcr} \leq 60 \text{ mL/min}$ versus those with $\text{Clcr} \geq 60 \text{ mL/min}$, but in group II, it was significant, with patients with $\text{Clcr} \leq 60 \text{ mL/min}$ having a higher risk of thrombocytopenia [16]. These data are in line with our results. Warda et al., who included 92 patients in the CI group and 87 patients in the II group, found a statistically higher risk of thrombocytopenia in the II group. They also found that three cumulative conditions increase the risk of thrombocytopenia: baseline platelets $\leq 200,000 \text{ mm}^3/\text{mc}$, $\text{CrCl} \leq 30 \text{ mL/min}$, and intermittent infusion [5]. Wicha et al. identified that for CI, the risk of grade 3 thrombocytopenia (platelets $\leq 50,000 \text{ mm}^3/\text{mc}$) is 10.4%, and if $\text{Clcr} \leq 20 \text{ mL/min}$ is associated, it increases to 15.2%. Still, by using TDM with a target Css of 7 mg/L, the risk is reduced to 6.3% [17].

We did not find any statistically significant differences in 30-day mortality between the two groups in the overall analysis or groups stratified by type of infection, empiric/targeted treatment, or CCI categories. Warda et al. and Albadry et al. did not find statistically significant differences between the groups either. However, their results were closer to significance, with a p -value of 0.076, indicating a higher value in the II group [5,16].

Although the length of stay in the ICU and hospital was longer in group II, the difference was not statistically significant compared to group CI, likely due to the limited number of patients included in the study. These results align with Warda et al.'s study, but Albadry et al. found a statistically significant shorter stay in the ICU and hospital in the CI group ($p < 0.001$) [5,16].

As far as we know, in the largest comparative study of the two proposed modes of infusion that evaluated safety and efficacy, Warda et al. concluded that CI is superior to II in terms of clinical response and presents a lower risk of adverse reactions (thrombocytopenia) [5]. Based on our data and supporting studies [3,18], in critically ill patients, linezolid administered via continuous infusion (CI) may be more effective than intermittent infusion (II), as indicated by CRP reduction, and cause fewer adverse events, such as less thrombocytopenia. These factors support the potential benefits of using linezolid as a continuous infusion, especially in critically ill patients with impaired renal function, similar to experience with other antibiotics like vancomycin and beta-lactams.

4.1. Study Limitations

The two groups were not enrolled simultaneously for administrative reasons, which could bring some bias to our results' interpretation. Since this was a real-life study, the groups were heterogeneous, including both empirically treated patients and those receiving targeted treatment. Because many patients were treated empirically, the effectiveness of linezolid could be overestimated or underestimated, representing a potential bias. To address this, we performed a stratified analysis by group. Our findings are limited by the relatively small sample size, which reduces statistical power and increases the likelihood of failing to detect subtle effects. Incomplete data for some parameters, group heterogeneity, and loss to follow-up in some patients may also have introduced bias. Furthermore, the potential impact of older age among patients with II compared to those with CI was not assessed, representing an additional limitation of this study.

4.2. Future Directions

Larger-scale studies are needed to confirm the observed benefits of CI in terms of effectiveness and safety. These studies should include pharmacokinetic modeling, investigate

the links between comorbidities and drug exposure, and evaluate adverse outcomes based on renal clearance, platelet levels, and other risk factors. Using real-time diagnostic tools (such as MALDI-TOF and rapid PCR) and TDM protocols will help tailor and optimize antibiotic therapy. Ultimately, this approach will improve linezolid dosing strategies and enhance treatment results in the ICU.

5. Conclusions

The increasing microbial resistance to antibiotics and the rising prevalence of resistant G+ bacteria, which present a significant financial burden and a public health issue [19,20], highlight the need for alternative strategies to prevent antibiotic resistance. The CI of linezolid may represent a cost-effective approach for this purpose. The association between CI and TDM may prove to be the optimal combination for the successful therapeutic use of linezolid in critically ill patients with pathological alterations.

Based on our analyzed data, we can conclude that linezolid CI is safer than linezolid II for critically ill patients and is non-inferior to linezolid II regarding effectiveness.

Considering the current approval of II of linezolid and the growing number of studies exploring CI of antibiotics based on the duration during which the concentration exceeds the minimum inhibitory concentration, evaluating linezolid administration through CI is of interest. Given the relatively small number of studies conducted on linezolid's safety and effectiveness as a continuous infusion so far, the findings of this study may be relevant. Due to limitations such as the small sample size, larger population studies are necessary to apply the results to a broader population.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/futurepharmacol5040061/s1>. Table S1: Site of infection and status of Gram-positive bacteria identification.

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