A 10-Year Experience of Therapeutic Drug Monitoring (TDM) of Linezolid in a Hospital-wide Population of Patients Receiving Conventional Dosing: Is there Enough Evidence for Suggesting TDM in the Majority of Patients?

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Abstract: A retrospective study was conducted to assess our 10-year experience of therapeutic drug monitoring (TDM) of linezolid in a large patient population to establish whether conventional dosing may result in adequate drug exposure in the majority of patients. Patients included in this study underwent TDM of linezolid trough concentration (C_{min}) during treatment with conventional doses of 600 mg every 12 hr in the period between January 2007 and June 2016. The desired range of C_{min} was set between 2 and 7 mg/L (underexposure, $C_{min} < 2$ mg/L; overexposure, $C_{min} > 7$ mg/L). Multivariate logistic regression analysis investigated variables potentially correlated with linezolid C_{min}. One thousand and forty-nine patients had 2484 linezolid C_{min} assessed during treatment with conventional doses. Median (IQR) linezolid C_{min} was 5.08 mg/L (2.78–8.52 mg/L). Linezolid C_{min} was within the desired range in 50.8% of cases (1262/2484). Overexposure (n = 821; 33%) occurred much more frequently than underexposure (n = 401; 16.2%) and was severe (>20 mg/L) in 3.9% of cases (98/2484). Linezolid overexposure was significantly associated with $CrCL_{C-G}$ estimates ≤40 mL/min. (OR 1.463; 95% CI 1.124–1.904, $p = 0.005$). Linezolid underexposure was significantly associated with $CrCL_{C-G}$ estimates >100 mL/min. (OR 3.046; 95% CI 2.234–4.152, $p < 0.001$). Linezolid C_{min} was not correlated linearly with $CrCL_{C-G}$ ($R^2 = 0.061$). Variability in renal function explained only partially the very wide interindividual linezolid C_{min} variability. Our study suggests that TDM could represent a valuable approach in optimizing linezolid exposure in the majority of patients.

In the era of precision medicine and of emergence of antimicrobial resistance, therapeutic drug monitoring (TDM) is progressively gaining a major role in optimizing treatment with several antimicrobials [1,2]. Linezolid is an oxazolidinone antibiotic with time-dependent activity, which is licensed at the conventional dose of 600 mg every 12 hr for the treatment of pneumonia and of skin and soft tissue infections due to Gram positives [3]. Nowadays, the use of linezolid in daily clinical practice has been widened to include the treatment for other difficult infections, such as prosthetic and bone and joint infections, and multi-drug resistant (MDR) tuberculosis [4–6]. This has posed some safety concerns, considering that the duration of treatment is restricted to 28 days maximum due to the risk of drug-related adverse events [7,8].

Over the last couple of years, the interest on TDM of linezolid has consistently increased. Our group was among the first in observing that linezolid plasma exposure may vary greatly during treatment with conventional doses [9]. Subsequently, we and other authors suggested that maintenance of linezolid trough concentrations (C_{min}) within a pre-defined range may be helpful in preventing drug-related adverse events, while preserving therapeutic effectiveness [10]. We supposed that the interindividual variability of linezolid C_{min} may be related mainly to drug–drug interactions [9,11–14]. Other authors suggested that linezolid C_{min} may be influenced also by the degree of renal function [15], by the severity of critical illness [16,17] or even by some other factors [18,19].

The aim of this study was to assess retrospectively our 10-year experience of TDM of linezolid C_{min} in a large patient population while receiving conventional doses to establish whether the standard dosing regimen may result in adequate drug exposure or not in the majority of patients.

Methods

Study design. This retrospective observational study was carried out between January 2007 and June 2016 at the Santa Maria della Misericordia University Hospital, Udine, Italy. Patients included in this study were those admitted to intensive care units (ICUs) or to medical or surgical wards who were treated intravenously or orally with linezolid at the conventional dose of 600 mg every 12 hr because of documented or suspected MDR Gram-positive bacterial infections and who underwent TDM. The aim of this study was to assess the dimension of the interindividual variability of plasma linezolid C_{min} observed during the conventional dosing regimen. Consistently, we included in this analysis only the TDM carried out before the eventual application of TDM-guided dosage adjustments of linezolid, which usually are applied promptly by clinicians at our University Hospital [20].

The Regional Ethics Committee approved the study, and informed written consent was waived according to the retrospective and observational nature of the study.

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Linezolid TDM is performed thrice weekly at our institution (on Monday, Wednesday and Friday), and the clinical pharmacological advice for dosage adjustment is provided via intranet within the same day to clinician. Dosage adjustment is recommended whenever linezolid C_{min} is outside of the desirable range of 2–7 mg/L, which was identified in a previous study [10]. Distributions of linezolid C_{min} were defined as follows: desired therapeutic range, when C_{min}s were between 2 and 7 mg/L; underexposure, when C_{min}s were <2 mg/L; overexposure, when C_{min}s were >7 mg/L. Linezolid overexposure was divided into three classes according to severity: mild, when C_{min}s ranged between 7.01 and 10 mg/L; moderate, when C_{min}s ranged between 10.01 and 20 mg/L; and severe, when C_{min}s were >20 mg/L.

The following data were retrieved from the patient data sheets stored at our institution: age, gender, total body-weight (TBW), height, body mass index (BMI), serum creatinine and linezolid C_{min}. Data on patient comedications were not included in the analysis because they were not collected systematically during TDM assessments in all of the cases. Creatinine clearance (CrCL) was estimated by means of the Cockcroft and Gault formula (CrCL$_{C-G}$).

Blood samples for TDM were collected immediately before dosing after at least 48 hr from starting linezolid therapy. Linezolid plasma concentrations were analysed by means of a validated high-performance liquid chromatography (HPLC) method with UV detection, as previously described [9,10]. Precision and accuracy were assessed by performing replicate analysis of quality control samples against calibration standards. Intra- and interassay coefficients of variation were always <10%. The lower limit of detection was 0.2 mg/L.

Statistical analysis. The Kolmogorov–Smirnov test was used to assess normal or non-normal distribution of data. Accordingly, means ± S.D. or medians with 25th and 75th interquartile range (IQR) were used for descriptive statistics. One-way ANOVA on ranks was used for comparing data among different groups. Univariate logistic regression analysis was used to investigate variables potentially correlated with linezolid C_{min}. All the independent variables associated with $p \leq 0.05$ at the univariate analysis were included in the multivariate logistic regression model. $p \leq 0.05$ was considered for statistical significance. Statistical analysis and plotting were performed with R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

One thousand and forty-nine patients who had 2484 C_{min} assessed during treatment with conventional doses of linezolid were included in the study (table 1). Median age was 65 years. The majority of patients were male (717/1049; 68.4%) and were admitted mainly in medical wards (470/1049; 44.8%). Median serum creatinine and estimated CrCL$_{C-G}$ were 0.9 mg/dL and 75.7 mL/min, respectively. The oral and the intravenous route for the administration of linezolid were almost equally distributed among the study population (50.2 and 49.8%, respectively). Overall, median linezolid C_{min} was of 5.08 mg/L during conventional dosing. Linezolid C_{min} fell within the desired range in around half of cases (1262/2484; 50.8%). Overexposure (n = 821; 33%) occurred much more frequently than underexposure (n = 401; 33% *versus* 16.2%) and was severe in 3.9% of cases (98/2484). Occurrence of linezolid under- or overexposure was unrelated to the duration of treatment and to the type of ward of admission. Histogram and Kernel density plot (fig. 1) showed that linezolid C_{min} had a log-normal distribution in the study population. Beeswarm plots of the individual linezolid C_{min} (fig. 2)

Table 1.

Patients' characteristics.

Total number of patients, n	1049
Total number of linezolid C_{min}, n	2484
Age (years), median (IQR)	65 (52–74)
Gender, male/female, n (%)	717/332 (68.4/31.6)
Body-weight (kg), median (IQR)	74 (64–85)
BMI (kg/cm^2), median (IQR)	25.0 (22.5–28.0)
Serum creatinine (mg/dL), median (IQR)	0.9 (0.7–1.2)
CrCL$_{C-G}$ (mL/min), median (IQR)	75.7 (35.3–124.3)
Linezolid route of administration, oral/iv, n (%)	527/522 (50.2/49.8)
Linezolid C_{min} (mg/L), median (IQR)	5.08 (2.78–8.52)
Linezolid C_{min} distribution, n (%)	
Desired therapeutic range (2–7 mg/L)	1262 (50.8)
Underexposure (<2 mg/L)	401 (16.2)
Overexposure (>7 mg/L)	821 (33.0%)
Mild (7.01–10 mg/L)	353 (14.2)
Moderate (10.01–20 mg/L)	370 (14.9)
Severe (>20 mg/L)	98 (3.9)
Ward of admission, n (%)	
Medical ward	470 (44.8)
Surgical ward	369 (35.2)
ICU	210 (20.0)

BMI, body mass index; C_{min}, plasma trough concentration; ICU, intensive care unit; iv, intravenous route.

showed that the distributions of linezolid C_{min} were similar among patients admitted to medical wards, surgical wards and the ICUs (median C_{min} 4.91 mg/L *versus* 5.16 mg/L *versus* 5.8 mg/L; $p = 0.128$).

Univariate and multivariate analyses of the variables tested for potential association with linezolid overexposure and underexposure are reported in tables 2 and 3, respectively. At multivariate logistic regression analysis, linezolid overexposure was significantly associated with the presence of CrCL$_{C-G}$ estimates ≤40 mL/min. (OR 1.463; 95% CI 1.124–1.904, $p = 0.005$) (table 2). Linezolid underexposure was significantly associated with the presence of CrCL$_{C-G}$ estimates >100 mL/min. (OR 3.046; 95% CI 2.234–4.152, $p < 0.001$) (table 3). However, linezolid C_{min} did not correlate linearly with CrCL$_{C-G}$ ($R^2 = 0.061$) (fig. 3). Neither BMI nor TBW was associated with the risk of linezolid under or overexposure.

Discussion

To our knowledge, this is the largest retrospective experience ever reported of linezolid C_{min} distribution during treatment with conventional doses of 600 mg every 12 hr in a hospital-wide population of adult patients.

Our group was among the first to show that linezolid exposure may vary widely during conventional therapy with linezolid in adult patients [9]. We also provided some initial understanding that maintenance of linezolid C_{min} in the range between 2 and 7 mg/L may optimize therapy and improve safety outcome of long-term treatment with linezolid in adult patients [10].

In the last years, other authors provided further evidence in supporting the reliability of this range, either for therapeutic
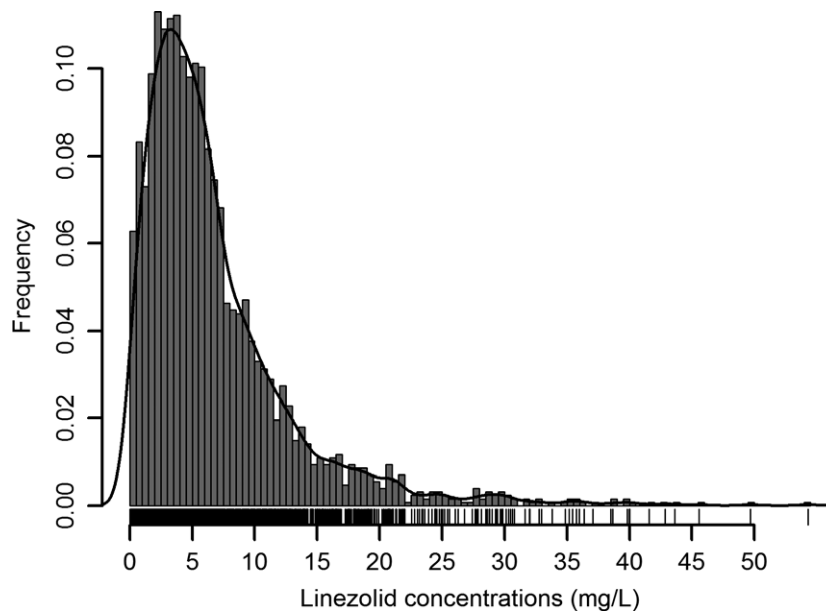
Fig. 1. Histogram and Kernel density plot of the distribution of linezolid trough concentrations. The rug plot along the *x*-axis illustrates the marginal distribution of the concentrations.
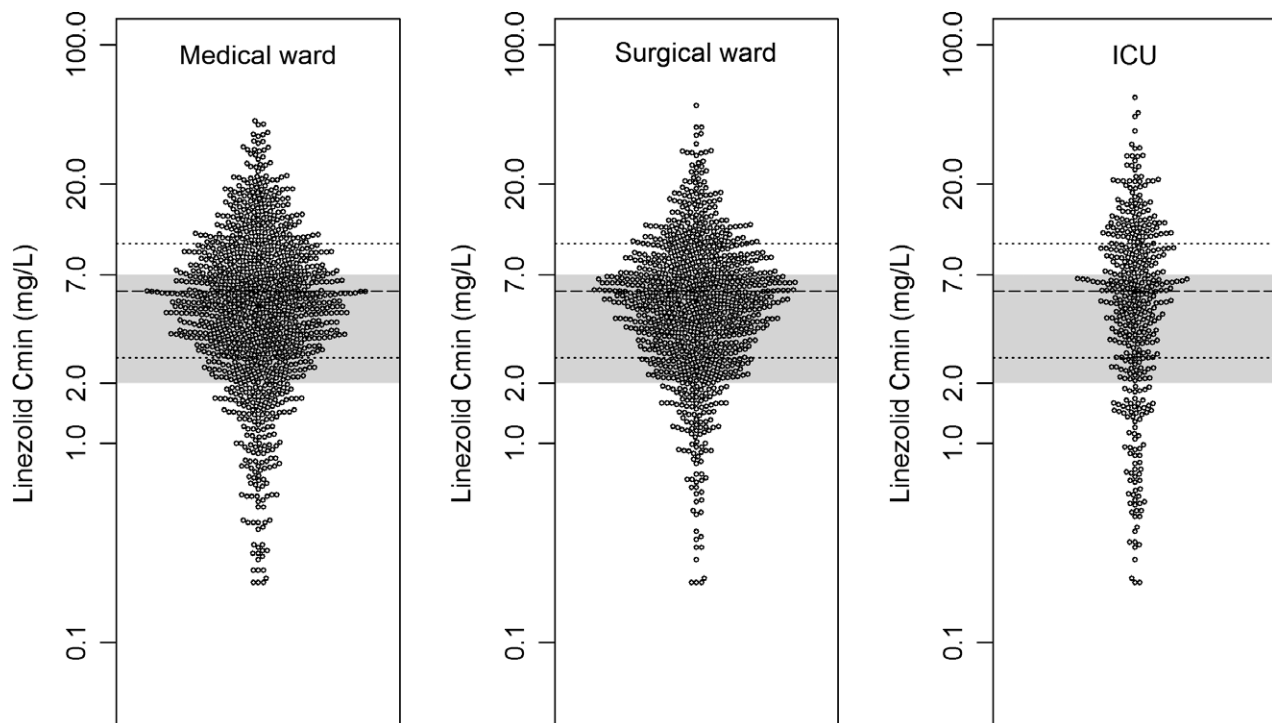

Fig. 2. Beeswarm plot of the distributions of each linezolid trough concentrations in patients according to the type of ward of admission. The grey shaded area identifies the desired therapeutic range (2–7 mg/L). Dashed line is the median. Dotted lines identify the 25th and the 75th percentile.

efficacy or for safety purposes. Linezolid C_{min}s ≥ 2 mg/L were associated with a probability higher than 80% of achieving bacterial eradication, and values > 6.3 mg/L were associated with a probability higher than 50% of developing thrombocytopenia [16]. Likewise, it was shown in a toxicodynamic model that linezolid concentration of 8.06 mg/L may

result in thrombocytopenia due to inhibition of the synthesis of platelet precursor cells by 50% [8]. This is in agreement with a recent study showing that mitochondrial toxicity risk may increase with increasing linezolid C_{min} [21]. Although thrombocytopenia is the most notable example of dose-dependent toxicity with linezolid, it should not be overlooked that

Table 2.
Univariate and multivariate analyses of variables tested for potential association with linezolid overexposure ($C_{min} > 7$ mg/L).

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
TBW < 60 kg	1.162 (0.918–1.472)	0.213	–	–
BMI ≤ 18 kg/m^2	0.899 (0.608–1.331)	0.595	–	–
CrCL$_{C-G}$ ≤ 40 mL/min	1.419 (1.095–1.838)	0.008	**1.463 (1.124 – 1.904)**	**0.005**

CrCL$_{C-G}$, creatinine clearance estimated by means of the Cockcroft & Gault formula; BMI, body mass index; TBW, total body-weight. Bold values relate to variables that resulted statistically significant at the multivariate analysis.

Table 3.
Univariate and multivariate analyses of the variables tested for potential association with linezolid underexposure ($C_{min} < 2$ mg/L).

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
TBW > 100 kg	1.532 (1.040–2.256)	0.031	1.183 (0.676–2.073)	0.556
BMI > 25 kg/m^2	0.948 (0.765–1.173)	0.621	–	–
CrCL$_{C-G}$ ≥ 100 mL/min	3.091 (2.275–4.199)	<0.001	**3.046 (2.234–4.152)**	**<0.001**

CrCL$_{C-G}$, creatinine clearance estimated by means of the Cockcroft & Gault formula; BMI, body mass index; TBW, total body-weight. Bold values relate to variables that resulted statistically significant at the multivariate analysis.
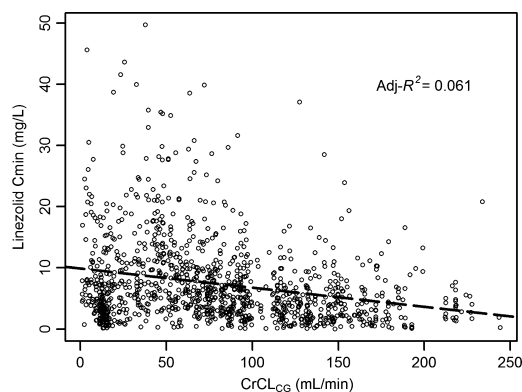

Fig. 3. Relationship between linezolid trough levels (C_{min}) and creatinine clearance estimated by means of the Cockcroft and Gault formula (CrCL$_{C-G}$).

also hyperlactacidaemia may be another dose-dependent toxic effect occurring during linezolid treatment, which sometimes may be life-threatening [11].

In the last year, several authors further supported the hypothesis that TDM might represent the way forward for optimizing linezolid therapy in specific subpopulations of patients [17,18,20,22,23].

In this study, we had the opportunity of documenting the distribution of linezolid C_{min} during treatment at conventional doses in more than one thousand adult patients admitted hospital-wide. Noteworthily, linezolid C_{min} fell within the desired range only in half of the cases. In the other half, we found that the risk of drug overexposure was much higher than that of drug underexposure. The distribution of linezolid C_{min} among the study population was not associated with TBW and/or with BMI. This is in agreement with the findings of Bhalodi *et al.* [24] showing that linezolid exposure in obese volunteers with BMI of 30–54.9 kg/m^2 receiving the fixed 600 mg every 12-hr intravenous dose was similar overall to that of non-obese

patients, implying that dosage adjustments based on BMI alone are not required. Likewise, distribution of linezolid C_{min} in our study population was not influenced by admission to medical wards, surgical wards or the ICUs. This suggests that no specific condition related to the type of ward of admission (i.e. critical illness or surgery) may imply *per se* dosage adjustments. It is worth mentioning that in our study, most of the TDM instances came from the medical wards. This is in line with the hospital-wide extension of our TDM linezolid programme and may reflect the improved perceived usefulness of clinical pharmacological advice for personalized drug dosing even outside of the ICUs, thanks to the educational interventions that we carried out in recent years [20,25]. Among the tested variables, CrCL$_{C-G}$ was the only one that independently predicted the risk of inappropriate linezolid exposure. CrCL$_{C-G}$ estimates >100 mL/min. predicted the risk of drug underexposure, whereas those <40 mL/min. predicted that of drug overexposure. This is in agreement with the findings of other authors who showed that CrCL estimates >80 mL/min. were associated with the risk of linezolid $C_{min} < 2$ mg/L [15], and those <40 mL/min. were associated with that of $C_{min} > 8$ mg/L [26].

Overall, these data suggest that TDM might be valuable for linezolid especially in patients with severe renal impairment or in those with augmented renal clearance. However, it should not be overlooked that renal function seems to explain only partially the very wide interindividual C_{min} variability that we observed in the study population. Noteworthily, no linear relationship between linezolid C_{min} and CLCr$_{C-G}$ estimates was observed. Additionally, it is worth mentioning that only 32% of the patients with linezolid overexposure had also CLCr$_{C-G}$ estimates ≤40 mL/min. This is in agreement with the finding that renal clearance should account for around 30–40% of the total linezolid clearance [27].

Consistently, the wide interindividual variability of linezolid C_{min} should also be related to other causes. It has been

postulated that linezolid may be a substrate of P-glycoprotein [28]. P-gp inhibitors, such as omeprazole, amiodarone and amlodipine, were associated with the risk of linezolid overexposure [9,14]. Conversely, P-gp inducers, such as rifampin, levothyroxine and venlafaxine, were associated with that of underexposure [10,12,13,29,30]. Unfortunately, in this study, we did not have the chance to retrieve data on patients' comedications. We had no opportunity to check all the clinical folders, and the study data were retrieved from the patient TDM data sheets stored at our institution. However, we believe that a significant amount of the variability of linezolid C_{min} might be explained by drug–drug interactions. This is in line with the huge 2-log degree of interindividual variability in linezolid C_{min} that was observed, suggesting that linezolid clearance could have been nonlinear in the study population, as typically may occur in the presence of inhibition or induction of the metabolic/elimination pathways. This is in agreement with a recent population pharmacokinetic study carried out among 20 ICU patients showing that coadministration of P-gp inhibitors (i.e. proton pump inhibitors) was associated with a trend to linezolid overexposure, whereas that of P-gp inducers (i.e. levothyroxine) caused exceedingly low drug exposure [18]. We are aware of the importance of this, and we are planning a specific study in order to address this issue in clinical practice.

Recently, other additional causes have been advocated. It has been shown that the presence of acute respiratory distress syndrome (ARDS), by increasing linezolid clearance, might be a strong predictor of insufficient linezolid concentrations in critically ill patients [19]. Prospective studies could clarify whether other pathophysiological conditions could be involved in affecting linezolid clearance.

While waiting for a better definition of the leading causes of the linezolid variability, these data should further strengthen the conviction that TDM might be a great opportunity for personalizing linezolid therapy in the majority of patients. This could be especially valuable in preventing toxicity among patients who are experiencing drug overexposure [11,31] and in preventing therapeutic failure among patients who are experiencing drug underexposure [19]. TDM might be of utmost importance for preventing drug-related toxicity during long-term treatment with linezolid, as, for example, for prosthetic and/or bone and joint infections [4,32] and/or for MDR tuberculosis [5,7,21].

A recent retrospective study of a TDM programme carried out among patients admitted to infectious disease units showed that the adherence of clinicians to the TDM-guided dosage adjustments recommended in the presence of linezolid overexposure was very low (<10%) [22]. This is in contrast to our personal experience, and we agree with the authors' claims that this is a missed opportunity for clinicians. Since 2007, we are providing clinicians with well-articulated and explanatory clinical pharmacological advice for personalizing linezolid therapy, and since then, the majority of feedback has been positive. A recent 1-year retrospective audit of quality indicators of clinical pharmacological advice for personalized linezolid dosing carried out at our university hospital confirmed that in 2014, the clinicians' adherence to TDM-guided dosage adjustments of linezolid was very high (94.7%, 356/376) [20]. The very high clinician adherence rate to TDM-guided linezolid dosage adjustments has probably been favoured by the educational and organizational interventions that we carried out in recent years to improve the usefulness of clinical pharmacological advice for personalized drug dosing based on TDM [25].

We acknowledge that our study has several limitations. The retrospective nature, the lack of data on clinical outcome on the occurrence of adverse events and on comedications are probably the most relevant. However, the study was focused on dimensioning the interindividual variability of linezolid exposure during conventional dosing regimens in routine clinical practice, and the very large sample size of the study population is a strength of this work.

In conclusion, our study provides evidence that linezolid C_{min} may vary widely in a large population of hospital-wide adult patients. This variability is partially dependent on variability in renal function, but it is probably related also to other factors such as drug–drug interactions and/or other pathophysiological conditions. This suggests that TDM could represent an opportunity to optimize therapy with linezolid in several patients, especially when dealing with long-term treatment. Prospective clinical studies are currently ongoing to provide further evidence that this approach may be valuable in obtaining therapeutic efficacy while preventing dose-dependent drug-related adverse effects even in long-term treatments.

Acknowledgement

Competing Interests

Federico Pea has received funds for speaking at symposia organized on behalf of Pfizer and served on scientific advisory boards for Pfizer. All other authors have no competing interests to declare.

Ethical Approval

The study was approved by the Regional Ethics Committee. Informed consent was waived due to the observational and retrospective nature of the study.

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