

Review Article

One Health Bulletin

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Incidence and risk factors of myelosuppression of linezolid in patients with drug−resistant tuberculosis: A scoping review

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ABSTRACT

Background: Drug-resistant tuberculosis (DR-TB) poses a significant global health challenge, requiring prolonged treatment with multiple second-line anti-tuberculosis drugs. Among these medications, bedaquiline and linezolid have shown promising outcomes. However, the primary adverse effects of linezolid leading to dose reduction or early discontinuation is myelosuppression.

Methods: This study involved a comprehensive review to evaluate the incidence and risk factors of linezolid-induced myelosuppressionin patients with DR-TB in bedaquiline-based regimens. Furthermore, the procedure adhered to the Systematic Reviews and Meta-Analyses (PRISMA) guideline for a scoping review.

Results: The results showed that nine cohort studies met the inclusion criteria. Among the 3310 DR-TB patients in these studies, 661 (19.9%) had HIV. The incidence of myelosuppression ranged from 5.1% to 49.0%, with anemia being the most prevalent case, ranging from 2.9% to 39.0%. According to the reports, linezolid interruption, such as dose adjustments or complete discontinuation ranged from 20.5% to 23.6%. Myelosuppression occurred within a period less than three months on average. Several factors were identified as influencing myelosuppression (anemia) in DR-TB patients within these regimens, including age ≥ 60, concurrent treatment with zidovudine in HIV positive patients, and linezolid concentrations > 2 mg/L. No studies reported mortality cases associated with linezolid.

Conclusions: The incidence of myelosuppression was relatively high in DR-TB patients with regimen containing linezolid. Anemia was the most prevalent symptom of myelosuppression during treatment, leading to early discontinuation of linezolid. It indicates that hematologic parameter should be closely supervised, especially in patients with risk factors during linezolid treatment.

KEYWORDS: Myelosuppression; Bedaquiline; Linezolid; DR-TB

1. Introduction

Tuberculosis (TB) is one of the most infectious diseases with a high transmission rate worldwide. Indonesia stands out as one of the countries with the highest-burden of drug-resistant tuberculosis (DR-TB) which has a successful treatment rate of less than 57%[1]. This condition is likely to develop among patients who have previously received anti-TB medication. The treatment process takes a longer duration and is more costly than drug-susceptible TB[2]. The use of second-line injectable drugs, such as amikacin and kanamycin, for this condition, was significantly associated with poor outcomes because their severe adverse effects, including ototoxicity and renal impairment[3]. Therefore, regimens with high efficacy and tolerable adverse effects are needed to achieve a better outcome.

The WHO recommends the incorporation of bedaquiline in all oral medication to treat DR-TB patients with either shorter (9-11 months) or individual longer regimens (18-24 months)[4]. Bedaquiline, with an optimized background regimen, enhances the safety and efficacy of DR-TB treatment. Several studies have reported that the administration of regimens containing bedaquiline offers favorable outcomes, such as complete treatment and sputum conversion[5,6]. Bedaquiline is considered a core drug because of its exceptional bactericidal properties and excellent sterilizing activity.

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How to cite this article: Putra ON, Purnamasari T. Incidence and risk factors of myelosuppression of linezolid in patients with drug-resistant tuberculosis: A scoping review. One Health Bull 2024; 4(1): 1-8. https://www.doi.org/10.4103/ohbl.ohbl_43_23

Article history: Received 7 December 2023 Revision 31 January 2024
Accepted 27 February 2024 Available online 19 March 2024

Furthermore, it has the potential to prevent the development of cross-resistance to other second-line anti-TB drugs[7].

Linezolid, a repurposed drug, together with bedaquiline and levofloxacin, is classified as a group A drug that must be present in DR-TB treatment alongside group B drugs. It is licensed for an longer individual regimen and administered for 18-24 months[4]. Linezolid has shown potent activity against multidrug resistant(MDR) and extensively drug-resistant TB (XDR-TB) cases. It demonstrates weak early bactericidal activity and only slightly extended early bactericidal activity (2-7 days). However, it exhibits excellent sterilizing effect with AUC_{0-24}/MIC ratio is the best driver for this purpose. Furthermore, linezolid demonstrates good penetration into tuberculosis lung cavities. A meta-analysis study reported in regimens containing linezolid, 83% of DR-TB patients had favorable outcomes, including cure and treatment completion, and 89% had culture conversion at the end of treatment[8]. However, the increasing resistance rate of MDR *M. tuberculosis* to linezolid reduces its efficacy, particularly in subtherapeutic exposures[9].

In addition to effectiveness, drug safety is an important factor in managing DR-TB patients. Several studies have reported that a daily dose of 600-1 200 mg of linezolid could be used for DR-TB patients with favorable outcomes[10,11]. However, the use of linezolid during DR-TB treatment is limited due to its moderate to severe adverse effects[12]. Among MDR and XDR-TB patients, myelosuppression, especially anemia occurs in a higher proportion than neuropathy. In addition, anemia can be life-threating and may require hospitalization and blood transfusion during treatment with linezolid. Moderate to severe anemia was associated with lower odds of treatment success in DR-TB patients[13]. Linezolid interruption was associated with longer duration of treatment and unfavorable outcomes. The dose and high linezolid exposure associated with myelosuppressive effects[8]. A recent study has reported that in DR-TB patients receiving linezolid medication, 18.4% stopped linezolid and 16.3% reduced the dose due to its adverse effects[14].

Studies reporting myelosuppression related to linezolid in DR-TB patients who received regimens containing bedaquiline showed heterogenous results[12,15,16]. These were attributed to variations in sample size, HIV status, dose, and duration of linezolid. A better knowledge of the factors associated with myelosuppression caused by linezolid can be used as a preventive action or policy-making to minimize the negative impact during treatment. Therefore, this study aimed to evaluate myelosuppression of linezolid in patients with drug-resistant TB receiving regimens containing bedaquiline and linezolid.

2. Methods

2.1. Search strategy and study selection

This study was a scoping review conducted according to the guideline of the Preffered Reporting Items for Systematc Reviews and Meta-Analysis (PRISMA) extension[17]. The procedures involved the inclusion of articles published from 2016 to May 2023 in PubMed and Science Direct databases. The studies have reported myelosuppression or its risk factors related to linezolid in patients with DR-TB who received bedaquiline-based regimens. Additionally, the search terms applied were “DR-TB”, “pre-XDR-TB”, “XDR-TB”, “MDR-TB”, “linezolid”, “hematologic”, “myelosuppression”, “toxicity”, and “bedaquiline”. Boolean operators with “OR”, “AND”, and “NOT” were used to combine these terms in databases.

The inclusion criteria in this study were as follows: 1) articles written in English as original articles with randomized controlled trial, cohorts, cross-sectional studies, or case-control studies; 2) patients treated with regimens containing bedaquiline and linezolid; 3) reporting myelosuppression including anemia, thrombocytopenia, or cytopenia during treatment, and 4) aged ≥ 18 years old. The risk factors of the included studies were assessed using binary logistic regression, as described in the method section. The exclusion criteria were articles written as reviews or opinions, case series, and animal studies.

2.2. Data extraction

Each study that met the inclusion criteria was summarized descriptively, based on the name of the author, year of publication, number of patients, study design, HIV status, type of DR-TB (MDR, pre-XDR, and XDR-TB), and summary of outcomes. The results of this study were presented as a narrative synthesis due to the heterogeneous nature.

2.3. Primary outcome

The severity of hematologic toxicity or myelosuppression was defined based on hemoglobin level, platelet count, white blood cell count, and absolute neutrophil according to Clinical and Programmatic Guide for Patient Management with New TB Drugs[18], as shown in Table 1. The regimen was considered linezolid-containing based on what appeared in the method of the selected studies.

3. Results

In a total of 175 articles were identified from PubMed and Science Direct using combined keywords, and 55 articles with duplicate records were removed. Of 120 articles remained, 65 of them were excluded. Furthermore, from 55 articles that eligible to be assessed, 46 articles were excluded since they did not report incidence or risk factors of hematologic toxicity related to linezolid. Finally, only 9 articles were included for scoping review according to the Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart (Figure 1). Characteristic of studies included in this scoping review is shown in Table 2. We retrieved 175 articles from the Pubmed and Science Direct Database with spesific keywords. Of them, 55 duplicates and 65 irrelevant articles were excluded, and 55 articles for eligibility were left. Upon further review, 46 of them were excluded for reasons including not reporting the incidence or risk factors of myelosuppression, being commentary articles, case reports or case series. Consequently, nine articles were suitable for the final analysis.

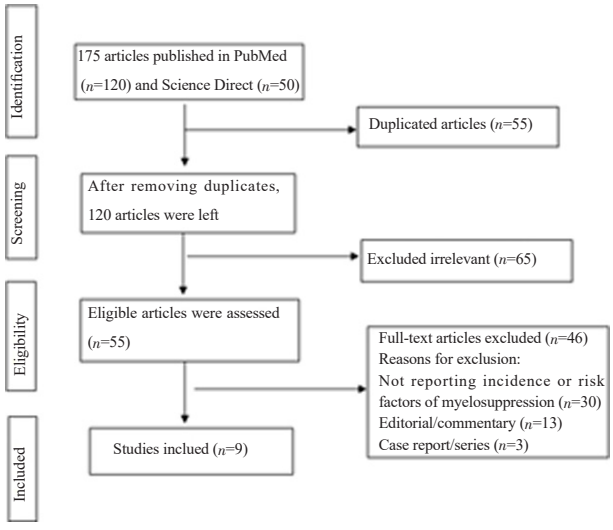

Figure 1. PRISMA flowchart of scoping review.

Table 1. Severity grade of hematologic toxicity or myelosuppression.

	Grade I (mild)	Grade II (moderate)	Grade III (severe)	Grade IV (life-threatening)
Platelet ($\times10^3$/mm^3)	75.0-99.9	50.0-74.9	20.0-49.0	< 20.0
Hb (g/dl)	9.5-10.5	8.0-9.4	6.5-7.9	< 6.5
WBC ($\times10^3$/mm^3)	3.0 to < LLN	2.0 to < 3.0	1.0 to < 2.0	< 1.0
ANC ($\times10^3$/mm^3)	1.0-5.0	0.75-0.99	0.5-0.749	< 0.5

Hb: Hemoglobin; WBC: White Blood Cells; LLN: Low Limit of Normal; ANC: Absolute Neutrophil Count.

4. Discussion

Linezolid demonstrates superior efficacy compared to standard regimens in a mouse tuberculosis model, with lower rates of relapse obsreved after 14 weeks of treatment. It indicates linezolid may be an effective treatment option for DR-TB patients[26]. Based on our review, we found two studies have reported that DR-TB patients with HIV who received treatment with zidovudine were associated with anemia and linezolid interruption[19,21]. Both linezolid and zidovudine may cause anemia and concurrent use may worsen this condition. Using other nucleoside reverse transcriptase inhibitors (NRTIs) that inhibit mitochondrial gamma polymerase may increase the mitochondrial toxicity of linezolid[27]. Anemia has been associated with disease progression and poor clinical outcomes in HIV/AIDS patients. Zidovudine is one of NRTIs used together with other antiretroviral drugs to slow the progression of HIV infection. However, due to initial long-term high-dose therapy, it is known to be associated with life-threatening hematological toxicity such as anemia[28].

Bone marrow toxicity seems more common in patients with advanced disease who have received a higher dose and longer duration of treatment. All of these conditions can be generally reversed after reducing the dosage. Mitochondrial disruption was associated with myelosuppression due to linezolid and zidovudine[27,29]. The incidence of anemia in HIV patients receiving zidovudine is not associated with CD4 cell counts. However, it is related to pre-treatment Hb levels. HIV patients with pre-treatment Hb levels lower than 10 g/dl are associated with anemia during zidovudine treatment[30]. Therefore, the first-line regimen of tenofovir/lamivudine/dolutegravir or lamivudine/tenofovir/efavirenz should be addressed in DR-TB patients with HIV to avoid anemia during treatment containing linezolid[31].

Linezolid binds to human mitochondria 16S rRNA and impairs oxidative phospholyration. In addition, mitochondrial dysfunction due to linezolid was associated with an elevated level of growth differentiation factor-15 (GDF-15). An increased GDF-15 level during follow-up could predict the development of anemia and represent mitochondrial dysfunction caused by linezolid. A case series study by Oehadian et al, demonstrated that a high level of GDF-15 was observed two weeks after initiation of linezolid and incidence of anemia occurred from four to twelve weeks[32]. It was

Table 2. Characteristic of studies included in this scoping review.

No	Author/Year/Country	Sample size	HIV/DR-TB profile	Dose and duration of linezolid	Summary of findings
1	Dayyab *et al*. 2021/Nigeria[12]	39	HIV: 3(7.7%) MDR-TB: 30(76.9%) Pre-XDR TB: 9(23.1%)	600 mg daily for six months	1) 13 of 39 cases (33.3%) were hematological disorders. 2) 12 of 39 cases (30.8%) had severe anemia (Hb<8 g/dl) at a median of 9.9 weeks (IQR 8.0-12.7 weeks). 3) 8 of 39 patients (20.5%) had linezolid interruption. 4) Those with linezolid interruption significantly had more incidence of severe anemia (5/8, 62.5%) than those without linezolid interruption (7/31, 22.6%), *P*=0.029. 5) None patients had a history of other drugs related to anemia.
2	Wasserman *et al*. 2022/South Africa[15]	151	HIV: 95(62.9%) MDR-TB: 12(7.9%) Pre-XDR TB: 68 (45.0%) XDR-TB: 61(40.4%)	148 patients and 3 patients were administered 600 mg and 300 mg daily of linezolid as a starting dose, respectively. The median time of linezolid therapy was 336 days (IQR 159-506).	1) 58/151 (38.4%) had anemia, 24 of them (41.4%) with grade 1 anemia. 2) 10/151 (6.6%) had thrombocytopenia, 8 of them (80.0%) with grade 1 thrombocytopenia. 3) 6/151 (4.0%) had leukopenia, 5 of them (83.3%) with grade 1 leukopenia. 4)32/151 (21.2%) had early discontinuation of linezolid, with median time until first interruption was 69 days. 5) Linezolid concentration, male, and age were independently associated with anemia, aOR 1.4 (95% *CI* 1.1-1.8, *P*=0.001), 3.4 (95% *CI* 1.5-8.1, *P*=0.001) , and 1.7 (95% *CI* 1.2-2.3, *P*=0.021), respectively. 6) HIV positivity was not associated with anemia.
3	Olayanju *et a*l. 2019/South Africa[19]	63	HIV: 37(58.7%) XDR-TB: 63(100%)	600 mg daily The median duration of linezolid treatment was 231.5 *vs*. 365.0 days in patients with or without linezolid interruption, respectively.	1) 22/63 (34.9%) patients experienced linezolid interruption. 2) 17/22 (77.3%) patients with linezolid interruptions had anemia,compared to 3/41(7.3%) without linezolid interruptions (*P*< 0.001). 3) 16/63 (25.4%) patients experienced anemia. 4) Anemia occurred at a median of 5 weeks. 5) HIV co-infection was significantly associated with linezolid interruption (aHR 4.83; 95% CI 1.52-15.29, *P*= 0.001).
4	Hewison *et al*. 2022/ 16 countries[20]	2296	HIV: 316(13.8%) MDR-TB: 738 (32.1%) Pre-XDR TB: 1231 (53.6%) XDR-TB: 683 (29.7%)	Not available	1) Myelosuppression occurred in 136/2296 patients (5.9%). 2) Median time to first myelosuppression was 2.5 months (IQR 0.9-5.2).
5	Letswee *et al*. 2019/South Africa[21]	27	HIV:15(55.6%) MDR-TB: 13(48.1%) XDR-TB: 14(51.9%)	600 mg of linezolid Duration: Not available	1) 6/27 patients (22.2%) experienced anemia and 1 patient with macrocytosis. All patients who experienced hematologic toxicity of linezolid were living with HIV and treated with zidovudine. 2) The hematologic toxicity occurred at mean of 30 days after initiation of linezolid.
6	Padayatchi *et al*. 2020/South Africa[22]	151	HIV: 116(76.8%) Pre XDR-TB: 45(29.8%) XDR-TB: 106(70.2%)	600 mg of linezolid	38/151 (25.2%), 26/151 (17.2%), and 6/151 (4.0%) patients experienced anemia, leukopenia/neutropenia, and thrombocytopenia, respectively.
7	Gracia *et al*. 2022/Georgia[23]	76	HIV: 2(2.6%) MDR-TB: 76(100%)	600 mg of linezolid	1) 1/76 (1.3%), 23/76 (30.3%), and 11/76 (14.5%) experienced leukopenia, anemia, and thrombocytopenia, respectively. 2) Cytopenias were significantly associated with linezolid pharmacokinetic parameters (C_{min} > 2 mg/L and $AUC_{0\text{-}24}$ > 160 mg.h/L).
8	Huerga *et al*. 2022/14 countries[24]	472	HIV: 7(16.3%)	Not available	1) 24/472 patients (5.1%) had myelosuppression or 5.6 incidence/1000 person-month. 2) Median time to first myelosuppression was 2.8 months (IQR 1.3-7.8).
9	Gao *et al*. 2021/China[25]	35	MDR-TB: 14(40.0%) XDR-TB: 5(14.3%) Pre-XDR TB: 16(45.7%)	Not available	1) 29/35 patients (82.9%) had any adverse events and 4/35 patients (11.4%) had myelosuppression. 2) 2/35 (5.7%), 1/35 (2.9%), and 1/35 (2.9%) patients experienced leukopenia, anemia, and thrombocytopenia, respectively and all patients discontinued of linezolid.

supported by the several included studies that a median time of four to ten weeks was associated with anemia[19,21,24]. It indicates that an increased level of GDF-15 was associated with anemia. GDF-15 could be used as a promising biomarker to predict mitochondrial toxicity. Further studies with larger sample sizes were needed to clarify this finding.

Moreover, linezolid has been reported to cause pancytopenia. A case report reported a significant decrease in hematological parameters, including erythrocytes, leukocytes, Hb, and platelets, after 14 days of treatment with linezolid at a dosage of 600 mg twice daily for soft tissue infection. The hematological parameters gradually improved after the discontinuation of linezolid[33]. It indicates the importance of periodic complete blood counts, especially in patients with a history of myelosuppression and those taking other drugs that suppress the bone marrow.

Linezolid trough plasma concentrations and $AUC_{0\text{-}24}$ are linearly related and trough concentrations can predict linezolid exposure. A daily dose of 600 mg of linezolid is recommended by WHO[2]. A study by Gracia *et al*.[23] demonstrated that with linezolid at a dose of 600 mg daily, cytopenias were significantly associated with $C_{min} > 2$ mg/L and $AUC_{0\text{-}24} > 160$ mg.h/L and at a median of four months. Of 76 patients, 7 (9.2%) and 10 (13.1%) of them had $C_{min} > 2$ mg/L and $AUC_{0\text{-}24} > 160$ mg.h/L as a critical parameter of mitochondrial toxicity. For those with $C_{min} > 2$ mg/L and $AUC_{0\text{-}24} > 160$ mg.h/L, the incidence of cytopenia and anemia was 71.4%, 60%, 57.1%, and 50.0%, respectively. However, cytopenia and anemia had minimal clinical impact since they did not limit long-term treatment. It was supported by Kumar *et al*., demonstrating that anemia was not associated with sputum conversion during six months of treatment[34]. Therefore, DR-TB patients with HIV, those who have received immunosuppressant drugs, and those who have experienced of recurrent anemia should regularly monitor their Hb levels[35].

A recent study suggests that the CYP450 2J2 enzyme is responsible for primary linezolid hepatic metabolism[36]. Therefore, concomitant drugs inhibiting this enzyme should be avoided to prevent high linezolid exposure. The utility of therapeutic drug monitoring is recommended to improve its safety. Conversely, a study by Wasserman *et al*.[15] reported that HIV was not associated with anemia but was associated with reduced hemoglobin. It was more likely because only two DR-TB patients with HIV on zidovudine.

Duration of linezolid treatment was associated with anemia leading to its interruption, as reported by Dayyab *et al*.[12] and Wassserman *et al*.[15]. A median time of four to ten weeks was associated with anemia in the included studies. Anemia reported in most studies led to the temporary discontinuation of linezolid. Higher incidence of anemia was observed in patients whose linezolid treatment was interrupted compared to those without linezolid interruption[12,19]. Futhermore, patients with linezolid interruption experienced a lower favorable outcome (cured/completed treatment) than those without linezolid interruption. This indicates the significant role of linezolid in the therapeutic success of DR-TB patients[19]. A study by Fang *et al*. demonstrated that the duration of linezolid was significantly longer in patients with myelosuppression than in those without[37]. A hemoglobin level that decreases more than 10% after administration of linezolid for four weeks confers sensitivity and specificity of 82% and 84%, respectively, to predict severe anemia. Reducing the dose of linezolid from 1200 to 600 mg daily can prevent up to 60% of severe anemia while preserving its effiacy[38]. A study by Mase *et al*. reported that patients who have received 300 mg daily of linezolid or intermittent dose experienced significantly fewer adverse events with better treatment outcomes than those with 600 mg of linezolid. It demonstrates that linezolid was better tolerated at a lower dose[39].

The linezolid dose in our review is approximately 300-600 mg per day. A daily dose of 600 mg of linezolid was recommended by WHO. An $AUC_{0\text{-}24}/MIC > 125$ was proposed as critical threshold for successful outcome of linezolid treatment. The median time to sputum conversion was faster (2 months) in patients with $AUC_{0\text{-}24}/MIC > 125$ than those < 125 (24 months). Interestingly, an $AUC_{0\text{-}24}/MIC > 125$ could be achieved with linezolid dose of 600 mg[40].

Moreover, a dose of 600 mg of linezolid had a probability of target attainment (PTA) > 90% for all susceptible samples. However, more patients had toxicity thresholds than those who have received 300 mg of linezolid[41]. This indicates the importance of linezolid dose individualization to maximize the therapeutic effect and minimize adverse effects.

The incidence of anemia is correlated with the dose of linezolid and occurs within a predictable time frame. Administration of iron and folic acid can be considered to maintain Hb levels in DR-TB patients with risk factors for anemia[42]. This predictability of events can inform patient care, guide physicians and healthcare workers in patient management, and inform dose adjustments at critical time

points to prevent the occurrence or severity of adverse events[19]. Therefore, hematologic monitoring during linezolid treatment, including complete blood count (platelet, hemoglobin, neutrophil) within two weeks of initial treatment and then monthly until treatment is complete.

Elderly patients, especially those aged over 60 years, are associated with anemia due to the use of linezolid as reported by Wasserman *et al*.[15]. It is more likely because they often coincide with decreased liver function and kidney, which affects the pharmacokinetics of linezolid, thereby increasing the serum concentration of linezolid which causes adverse drug reactions. The probability of Hb reduction by 2 g/dL is high in patients aged over 60 years[15]. It indicated that Hb levels should be closely supervised in elderly patients during linezolid treatment. Furthermore, nearly 50% of patients aged over 65 years had supra-therapeutic linezolid trough concentration with a dose of 600 mg every 12 hours. Linezolid accumulation in elderly patients may be associated with progressive impairment in the functional reserve of some organs (*e.g.* liver) or changes in body composition, resulting in changes in the volume of distribution that may affect the drug's pharmacokinetics. Linezolid dose should be reduced in elderly patients to limit drug overexposure[43]. Further studies related to covariates, including renal and hepatic function, and drug-drug interactions related to P-glycoprotein, especially in DR-TB patients may help explain variability and improve linezolid dosing regimens.

Furthermore, elderly patients had a higher incidence of renal impairment. The elderly, especially those with renal impairment, are at a high risk of overexposure on linezolid if treated with a conventional dose. A meta-analysis study reported a high frequency of hematologic toxicity in patients with renal impairment during linezolid therapy[44]. It demonstrates that linezolid-related toxicity is associated with creatinine clearance (CrCl). Patients with hematologic toxicity had significantly lower CrCl than those without[37]. It warrants us to monitor renal function regularly during linezolid treatment. However, no studies measuring CrCl during linezolid were found in our review.

Although our review indicated a high incidence of myelosuppression related to linezolid, no death cases were reported in our included studies. This review provided evidence of the incidence and some risk factors associated with myelosuppression related to linezolid. Active pharmacovigilance is required for reporting any possible adverse effects to strengthen the safety of its use.

5. Conclusions

In conclusion, among DR-TB patients receiving regimens that include bedaquiline and linezolid, the incidence of myelosuppression was relatively high. Anemia was the most prevalent form of myelosuppression, leading to early discontinuation of linezolid. Several factors were identified as independent risk factors for myelosuppression during treatment, including being HIV-positive, elderly, and high exposure of linezolid. It indicates that hematologic parameter level should be regularly monitored, especially in those with risk factors during linezolid treatment.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

This study received no extramural funding.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Putra ON searched for articles, designed the study, collected and interpreted the data, created tables and figures, and wrote the manuscript. Purnamasari T analyzed and interpreted the data, wrote the manuscript, reviewed and revised the manuscript. All authors approved the final version of the manuscript.

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Edited by Qi Y, Liang TC