

# Effect of a serum lactate monitoring recommendation policy on patients treated with linezolid

Jae Hyung Im, MD<sup>a</sup>, Jin-Soo Lee, MD<sup>a</sup>, Moon-Hyun Chung, MD<sup>b</sup>, Hea Yoon Kwon, MD<sup>a</sup>, Man-Jong Lee, MD<sup>c,\*</sup>, Ji Hyeon Baek, MD<sup>a,\*</sup> 

## Abstract

Lactic acidosis is one of the most fatal adverse effects of linezolid, an antibiotic used to treat serious infections caused by antibiotic-resistant bacteria. However, the measures to prevent lactic acidosis have not been well established.

We performed a retrospective study to analyze the impact of applying a serum lactate monitoring recommendation policy in patients treated with linezolid.

Since September 2011, we have recommended inpatient monitoring of serum lactate levels in patients treated with linezolid at our hospital. Patients were divided into two groups according to whether they were seen during the non-recommendation or recommendation periods. The frequency of serum lactate monitoring, linezolid-induced lactatemia, lactic acidosis, critical illness, and death were compared between the two periods.

After September 2011, adherence to the recommendation to monitor serum lactate increased from 6.1% to 60.1%. No difference was observed in the incidence of linezolid-induced lactatemia and lactic acidosis between the two periods. However, there was a significant difference in the incidence of linezolid-induced critical illness between the non-recommendation and recommendation periods (3 vs 0 cases,  $P = .044$ ).

In patients treated with linezolid, serum lactate monitoring led to early detection of lactatemia, thus enabling rapid rescue. We recommend regular monitoring of serum lactate in all patients treated with linezolid.

**Keywords:** acidosis, lactate, lactic acidosis, linezolid, mortality

## 1. Introduction

Linezolid is an oxazolidinone class antibiotic that has exceptional activity against most clinically-important gram-positive bacteria and

Editor: Duane R. Hospenthal.

This work was supported by a research grant from the Inha University Hospital.

All authors declare no conflicts of interest related to this study.

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

<sup>a</sup> Division of Infectious Diseases, Department of Internal Medicine, Inha University college of Medicine, Incheon, <sup>b</sup> Department of Internal Medicine, Seigui-po Medical Center, Jeju-do, <sup>c</sup> Division of Critical Care Medicine, Department of Hospital Medicine, Inha University School of Medicine, Incheon, Republic of Korea.

\* Correspondence: Ji Hyeon Baek, Division of Infectious Diseases, Department of Internal Medicine, Inha University college of Medicine, 7-206, Shinheung-Dong, Jung-Gu, Incheon, 400-711, Republic of Korea (e-mail: JHbaek@inha.ac.kr, likeavirgin@daum.net).

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How to cite this article: Im JH, Lee JS, Chung MH, Kwon HY, Lee MJ, Baek JH. Effect of a serum lactate monitoring recommendation policy on patients treated with linezolid. *Medicine* 2021;100:1(e23790).

Received: 3 May 2020 / Received in final form: 11 November 2020 / Accepted: 14 November 2020

<http://dx.doi.org/10.1097/MD.00000000000023790>

mycobacteria.<sup>[1]</sup> The use of linezolid is increasing due to emerging multidrug-resistant organisms, such as vancomycin-intermediate resistant staphylococci, vancomycin-resistant enterococci, and multi-drug-resistant tuberculosis, and an increased need for alternative drugs to glycopeptides.<sup>[2]</sup> The increasing use of linezolid has highlighted the development of frequent adverse effects, such as bone marrow suppression, neuropathy, and lactic acidosis,<sup>[3]</sup> which can be fatal as their early symptoms are not obvious and they are difficult to treat.<sup>[4]</sup>

In our previous study, we reported the risk of linezolid-induced lactic acidosis through comparison with a teicoplanin group, and recommended monitoring of serum lactate in patients treated with linezolid.<sup>[5]</sup> However, the impact of such generalized recommendations on patient outcomes has not yet been studied. Thus, we conducted a retrospective cohort study to investigate the incidence of linezolid-induced lactic acidosis and patient outcomes after recommending (from September 2011) serum lactate monitoring.

## 2. Methods

### 2.1. Overall design and study population

From January 2004 to July 2019, we monitored patients admitted to an 860-bed university hospital who were receiving either oral or intravenous linezolid (Zyvox; Pfizer, New York, NY, USA). Linezolid should be used at our hospital only after confirmation by an infectious disease specialist; however, children under the age of 15 were excluded from the study because they were supervised by the division of pediatric infectious diseases and not by the division of infectious diseases.

All the recommendation methods for serum lactate monitoring, that is, education, documented recommendation, and verbal recommendation, were used; however, it is difficult to confirm it retrospectively. For this reason, patients were divided into two groups based on the time since we recommended routine testing of serum lactate levels: a non-recommendation period group (January 2004–September 2011) and a recommendation period group (October 2011–July 2019). Patients admitted to departments other than the Department of Infectious Diseases were divided into two groups (January 2004–April 2012 vs May 2012–July 2019) because the timing of the recommendation was different. The scheme of this study is shown in Figure 1.

**2.2. Event definition**

The weekly frequency of serum lactate monitoring was calculated as follows: [(number of serum lactate measurements during linezolid treatment/total days of linezolid treatment) x 7days]. Adherence to monitoring was defined as a patient undergoing more than one test every two weeks (weekly frequency > 0.5). Patients with linezolid treatment duration of less than one week were considered as having had no time to receive serum lactate monitoring and were excluded from the adherence analysis.

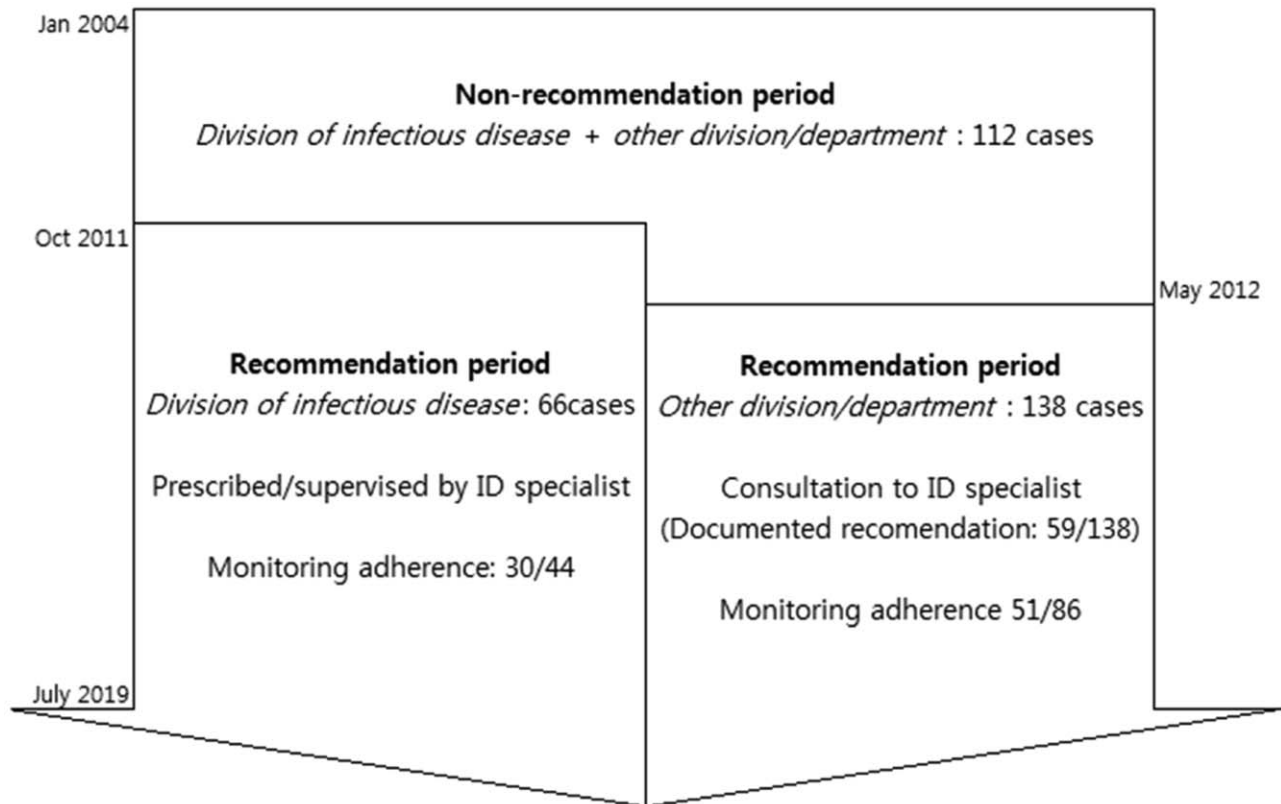
To assess the outcomes of serum lactate monitoring, linezolid-induced lactatemia, lactic acidosis, critical illness, and death were

compared between the two periods. Lactatemia was defined as serum lactate ≥4 mg/dL, and lactic acidosis was defined as serum pH < 7.25 plus lactatemia. If there was an apparent increase in anion gap due to linezolid (without ketoacidosis, other toxin-related, and renal failure), it was included in the case, even if serum lactate was not measured. Critical illness was defined as death, shock, or hemodialysis in patients with linezolid-induced lactic acidosis.

Linezolid-induced events were based on probable cases according to the Naranjo criteria for adverse drug reactions.<sup>[6]</sup> The exclusion criteria for linezolid-induced events were shock, lactic acidosis, hypoxemia, bleeding, cancer progression, or exposure to other medications.

**2.3. Data analysis**

Because the Shapiro–Wilk test did not provide a normal distribution, the duration of antibiotic administration and number of patients for whom serum lactate levels were monitored were presented using median and interquartile range. Student’s *t* test and chi-squared test were used to compare general characteristics between the non-recommendation and recommendation period groups. Fisher’s exact test and Mann–Whitney test were used to compare outcomes between the two periods. Two-tailed *P* values < .05 were considered statistically significant. Data analysis was performed using SPSS statistical software (v.20; SPSS Inc., Chicago, IL).



**Figure 1.** Scheme of the present study. Figure 1 shows the non-recommendation and recommendation periods in this study. Monitoring adherence was analyzed only for patients who used more than 7 days.

**Table 1**  
**Comparisons of general Characteristics Pre-recommendation and recommendation period.**

Variables	Pre-recommendation	Recommendation	P value
Total Number	112	204	
Gender: male	53	115	.128
Age, years	60.2 (SD 16.8)	62.3 (SD 16.0)	.277
Comorbidities			
Cardiovascular diseases	11	22	.850
Diabetics	32	57	.897
Liver cirrhosis	5	8	.776
Chronic kidney disease	9	23	.438
Antibiotics duration, days	13.0 [IQR 6.0-25.8]	11.0 [IQR 5.0-16.0]	.031

IQR=interquartile ranges, SD=standard deviation.

**2.4. Ethics statement**

Ethical approval from the Inha University Hospital Institutional Review Board (Incheon, Republic of Korea) was obtained prior to the study. All patient records were anonymized.

**3. Results**

**3.1. General characteristics of patients treated with linezolid**

A total of 316 patients treated with linezolid were monitored between January 2004 and July 2019. Of these, 112 were in the non-recommendation period group and 204 in the recommendation period group (Table 1). Median linezolid treatment duration was reduced from 13 days to 11 days after the recommendation for serum lactate monitoring ( $P < 0.031$ ) because linezolid administration was often interrupted due to the monitoring results. Lactic acid levels were measured during linezolid treatment in 111 patients at least once, and linezolid-induced serum lactate elevation was identified in 11 patients. Of these patients, four were identified in  $\leq 2$  weeks, three in 2 to 4 weeks, and four in  $\geq 4$  weeks (Table 2).

**3.2. Comparison between the non-recommendation and recommendation period groups**

Mean weekly frequency (number of serum lactate monitoring events per week) increased from 0.07 in the non-recommendation period group to 1.08 in the recommendation period group ( $P < .001$ ). Only 6.1% of patients were adequately monitored before the recommendation, with the ratio increasing to 60.1% after the recommendation ( $P < .001$ ).

Although the incidence of linezolid-induced lactatemia was higher in the recommendation period group than in the non-recommendation period group, the difference was not statistically significant. However, the incidence of critical illness related to linezolid-induced lactic acidosis decreased from 3/112 patients to 0/204 patients ( $P = .044$ ). There was no rescue from linezolid-induced events during the non-recommendation period - two patients died and one patient experienced shock and hemodialysis. During the recommendation period, all eight patients with lactatemia were rescued after early discontinuation of linezolid (Table 3).

**4. Discussion**

Because lactic acidosis is fatal and has no effective treatment, early detection of linezolid-induced lactic acidosis is impor-

**Table 2**  
**Cases of linezolid-related events.**

No.	Age	Sex	Period	Duration of linezolid, days	frequency of serum lactate	Serum lactate, mg/dL	Linezolid-related events			Comorbidity
							Lactic acidosis	Critical illness	Death	
1	77	M	Non rec-period	30	2	20.0	Yes	Yes	Yes	—
2	64	M	Non rec-period	42	2	16.0	Yes	Yes	Yes	Diabetics
3	52	F	Non rec-period	5	—*	—*	Yes*	Yes	—	Cancer
4	76	F	Rec-period	7	1	4.5	—	—	—	Diabetics
5	69	F	Rec-period	39	8	4.8	—	—	—	Diabetics
6	60	M	Rec-period	33	3	4.1	—	—	—	—
7	89	M	Rec-period	27	2	10.4	Yes	—	—	Heat failure
8	56	M	Rec-period	22	3	4.1	—	—	—	Diabetics and chronic kidney disease
9	69	F	Rec-period	20	4	4.7	—	—	—	—
10	61	F	Rec-period	12	1	4.0	—	—	—	—
11	76	F	Rec-period	11	1	7.1	—	—	—	Diabetics

Non rec-period=Non-recommendation period, Rec-period=recommendation period.

\* This case presented increased an-ion gap (23 mg/dL) and pH 7.19, without other cause except LZD.

#Case 1-5 were described in a previous study.

**Table 3**  
**Comparisons of outcomes between Pre-recommendation and Recommendation period.**

Variables	Pre-recommendation	Recommendation	P value
Total number	112	204	
Adherence to serum lactate monitoring	5/82 (6.1%)	86/143 (60.1%)	<.001
Linezolid-related event			
Lactatemia	3	8	.752
Lactic acidosis	3	1	.129
Lactic acidosis-related critical illness*	3	0	.044*
Death	2	0	.125

\* Critical illness includes shock, hemodialysis and death.

tant.<sup>[7,8]</sup> However, early recognition of the condition is difficult because the initial signs are nonspecific symptoms such as vomiting, aura, and dizziness.<sup>[9]</sup> Several reports exist of linezolid-induced lactic acidosis, and some articles recommend monitoring lactic acid,<sup>[10]</sup> but it is unknown whether such monitoring is necessary only for patients with comorbidity and receiving long-term linezolid therapy. In addition, there have been no studies about the outcomes of routine monitoring of patients treated with linezolid.

In the present study, after recommendation of serum lactate monitoring in patients treated with linezolid, we compared the recommendation and non-recommendation period groups instead of directly comparing monitored and unmonitored patients. Because this was a retrospective study, lactate monitoring did not exclude physician interventions due to patient condition. Physicians may prescribe more frequent lactate monitoring in severely ill patients; conversely, they may tend not to use monitoring if patients who are in good condition or if the expected duration of linezolid treatment is short. We recommended serum lactate measurement in various ways, including by educating physicians, oral instruction, and documentation. However, the intensity or frequency of our recommendation was not constant. We analyzed the groups divided by periods as it was not possible to correct these limitations in a retrospective study.

The recommendation for serum lactate monitoring in linezolid-treated patients led to early detection of elevated lactate levels. In the non-recommendation period group, the two patients with linezolid-induced lactatemia died from severe acidosis, and one patient had shock and hemodialysis. In the recommendation period group, 8 patients with lactate elevation were identified before severe acidosis occurred and linezolid administration was halted at the appropriate time. There was no significant difference in the mortality rate; however, this may have been due to the low number of patients in the study, and more research with a larger sample population may provide statistical significance.

Previous studies have shown that lactic acidosis is more common when linezolid is used for a long time.<sup>[5,11]</sup> In this study, 3 of 10 patients with increased serum lactate levels had an increase in lactate when linezolid was administered for > 4 weeks, although four patients showed an increase in  $\leq 2$  weeks and three patients in 2 to 4 weeks. Therefore, we suggest lactate monitoring during linezolid therapy within day 7. Elevation of serum lactate was more prevalent in patients with other comorbidities,<sup>[12,13]</sup> but in our study, such elevation also occurred in patients without comorbidities. Therefore, we suggest lactate monitoring for all patients, and not the at-risk group alone.

The rate of adherence to serum lactate monitoring was 60.1%, which was lower than expected. Nevertheless, many patients were rescued before experiencing critical complications. We suggest increasing adherence to serum lactate monitoring. Lack of education or the absentmindedness of attending physicians may be the main cause of low adherence. It may be possible to increase adherence to serum lactate monitoring by repeatedly educating physicians about its importance, and by introducing automatic lactate-test prescribing in computer systems for patients treated with linezolid.

This study has some limitations. First, it was conducted as a retrospective, single-center trial, such that the personal opinion of one physician may have been involved in several lactate-test prescriptions. Therefore, we divided the groups into different time periods to reduce these potential confounding factors. Second, the study results did not show a significant difference in mortality between the two periods. However, this was probably due to the small patient population, and further research is needed. Third, despite the recommendation period, the documented recommendation was only 59/138. The main reason for non-compliance with monitoring was an oral approval. In an emergency, the prescription was orally approved without any documentation. In this oral approval, we were unable to review if the serum lactate monitoring recommendations were followed.

Conclusively, the recommendation for serum lactate monitoring led to early detection of lactic acidosis in patients in this study. Thus, we recommend routine serum lactate monitoring for all patients treated with linezolid.

### Author contributions

**Conceptualization:** Jae Hyoung Im, Man-Jong Lee, Ji hyeon Baek.

**Supervision:** Man-Jong Lee, Ji hyeon Baek.

**Writing – original draft:** Jae Hyoung Im.

**Writing – review & editing:** Jin-Soo Lee, Moon-Hyun Chung, Hea Yoon Kwon.

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