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Norepinephrine modified the interaction between *Escherichia coli* and levofloxacin, potentially affecting clinical outcomes and increasing the risk of bacterial colonization

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ABSTRACT

Background: Norepinephrine is the most used vasopressor in intensive care units. It can modulate gene expressions and metabolism pathways in *Escherichia coli.* As fluoroquinolone's bactericidal activity is affected by bacterial metabolism and growth rate, simultaneous exposure to these medications might alter the interaction between *E. coli* and levofloxacin. This study aims to investigate the effect of norepinephrine and levofloxacin given simultaneously on the in vitro growth of *E. coli*.
Methods: Ten clinical isolates of *E. coli* were grown in minimal nutrition media with and without norepinephrine, levofloxacin, or both. Bacterial growth was observed for 20 h, and viable cell count was done every 2 h. Growth curves and generation times for each study group were calculated. Statistical analysis compared the viable cell counts on the 4, 14, and 20 h observation time points and the generation times.
Results: Temporary inhibition of *E. coli* growth was observed until 4h of incubation when therapeutic concentrations of norepinephrine and levofloxacin were given simultaneously, followed by regrowth. The viable cell count of the norepinephrine–levofloxacin group was significantly lower than the control group by the 14 h and 20 h time points. Interestingly, the study group's average generation time of regrowth was 19.3 min, which was significantly faster than the control group ($p < 0.05$).
Conclusion: Norepinephrine caused alterations in the interaction between *E. coli* and levofloxacin, which may affect clinical outcomes and increase the risk of bacterial colonization in patients receiving simultaneous norepinephrine and levofloxacin therapy.

Keywords: antimicrobial susceptibility test, bacteremia, catheter-related bloodstream infection, drug–microbe interaction, gram-negative bacteria.
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INTRODUCTION

Norepinephrine is a sympathetic neurotransmitter synthesized by neurons from the amino acid tyrosine.[1,2] It exists in a very low concentration in human plasma under physiologic conditions.[3-5] It is used as medication in clinical settings, taking advantage of its inotropic and vasopressor activities. It is the most used vasopressor in intensive care units.[6-8] International guidelines recommend norepinephrine as the first-line vasopressor in septic shock.[9]

Previous studies revealed that norepinephrine plays a role not only in humans but also in bacterial physiology. It enhanced the in vitro growth of commensal and pathogenic bacteria such as Coagulase-negative staphylococci, *Escherichia coli*, and *Campylobacter jejuni*. Norepinephrine also modulates the expressions of genes related to the metabolic pathway, acid resistance, and SOS response.[10-16] *Escherichia coli* was the cause of most systemic infections globally. It ranks first as the cause of sepsis in 730 intensive care units from 84 countries, including Asia Pacific.[17-19] Infections via the multidrug-resistant strain of this bacteria caused high mortality and economic burden.[20,21] World Health Organization included the multidrug-resistant strain of *E. coli* as one of the pathogens critically targeted for antimicrobial research and development.[22]

Fluoroquinolone was one of the most used antimicrobials due to its broad spectrum of activity.[23-24] It acts mainly by binding to the deoxyribonucleic acid (DNA) gyrase of *E. coli* and blocking DNA replication.[25,26] Like most other bactericidal antimicrobials, fluoroquinolones also act secondarily by interfering with several other pathways in *E. coli*, such as the SOS pathway tricarboxylic acid cycle and hydroxyl radical formation. Unfortunately, due to its high usage, the resistance rate of fluoroquinolone in *E. coli* increased rapidly.[27-32] This increase is not followed by the discovery and development of new antimicrobial agents, raising concerns about the future clinical management of infectious diseases.

A better understanding of how bacteria respond to antimicrobial exposure in the presence of other medications used in clinical settings is of utmost importance. The evidence on whether

a high catecholamine concentration affects bacterial growth when given simultaneously with fluoroquinolone is lacking. Hence, this study aims to investigate the effect of norepinephrine and levofloxacin given at the same time on the growth of *E. coli*, using levofloxacin-susceptible clinical isolates of *E. coli* acquired from blood cultures of patients in a tertiary referral hospital in Indonesia.

METHODS

Bacterial isolates used in this study

This study received ethical approval from the research ethics committee of Dr. Soetomo General Academic Hospital, Surabaya. Isolates from blood cultures represented the strains associated with catheter colonization and bloodstream infection. Species identification and initial levofloxacin susceptibility were determined using the BD Phoenix™ system per CLSI 2021 breakpoints. Norepinephrine exposures before the withdrawal of blood specimens were traced from medical records. Samples were selected using consecutive sampling. Levofloxacin-susceptible *E. coli* from blood cultures of patients with no history of norepinephrine administration before specimen collections were included in the study. Those that failed to grow during the subculture step were excluded. *Escherichia coli* ATCC 25922 was used as the quality control.

Reagents and culture medium

The serum-SAPI medium was used as described in a previous study.[33-34] This medium contained minimal nutrition, supplemented with 30% (v/v) adult bovine serum and Hepes buffer (pH 7.5) to mimic the environment encountered by bacteria within the host. This culture medium also showed norepinephrine's growth enhancement effects on bacteria optimally.[34] The use of 10 µM of L-(—)-norepinephrine bitartrate (Sigma–Aldrich) was based on the range of its clinical doses and the concentration proven to enhance bacterial growth.[12,35-39] Levofloxacin (Sigma–Aldrich) concentration of 3 µg/ml was based on its representative MIC_{90} range for *E. coli* and the plasma concentration range achieved after intravenous or oral administration of the therapeutic doses.[40-43]

Growth assay

All isolates were grown overnight in ambient air at 35–37°C on a MacConkey agar medium. Colonies grown were suspended within a serum-SAPI medium until they reached 10^6 CFU/ml density with a volume of 2 ml. The bacterial suspensions were grown with or without 1 ml L-(—)-norepinephrine bitartrate, 1 ml levofloxacin, or both. All study groups were incubated in a 5% CO_2 incubator at 35°C–37°C. Bacterial growth was observed for 20 h, and viable cell count was done every 2 h. Each tube was vortexed for 5 s before the colony counting procedure. Serial dilution was conducted using sterile saline as a dilutant. A 50 µl from each dilution tube was inoculated on the nutrient agar surface by droplet. The agar plates were incubated at 35°C–37°C in ambient air for 24 h. Colonies grown on the agar were counted using a colony counter, and growth curves were generated. Generation times for each isolate were calculated. Statistical analysis compared the viable cell count and generation times on the 4, 14, and 20 h observation time points.

Post-exposure susceptibility test

Susceptibility to levofloxacin after the observation period of each group was determined using the disk diffusion method. Each tube was centrifuged at 3000x*g* for 10 min, and the pellets were washed in PBS (pH 7.4) (Oxoid). This process was repeated three times to minimize the carry-over effect of study drugs. Suspensions of bacteria were made from the pellets using Mueller Hinton (MH) broth (Sigma-Aldrich) as the diluent and incubated at 35°C–37°C in ambient air for 4h, the time estimated for the bacteria to reach exponential phase. The bacterial suspensions were adjusted to 0,5 McFarland standard turbidity and used as inoculants for the disk diffusion susceptibility test. Bacterial suspensions were inoculated and spread evenly onto MH agar (Sigma-Aldrich) using disposable sterile cotton swabs. The sterile applicator placed Levofloxacin 5 µg disk (Oxoid) on top of the agar surface. Plates were then incubated at 35°C–37°C in ambient air for 18h. Three operators measured inhibition zones using a caliper to minimize the manual measurement bias. The susceptibility categories were determined using CLSI 2021 diameter breakpoints of *Enterobacterales* for levofloxacin.

Statistical analysis

The viable cell counts of all study groups at 4, 14, and 20h time points were compared using Kruskal–Wallis and posthoc test. The generation time of the study groups, except for the levofloxacin group, was compared using analysis of variance and posthoc test. Statistical significance was indicated by a p-value of 0.05. Statistical analyses in this study were performed using IBM SPSS Statistic version 20.0 for Windows.

RESULTS

Characteristics of isolates

Five clinical isolates used in this study showed the phenotypic characteristic of extended-spectrum beta-lactamase (ESBL) producers. All isolates were detected as susceptible to ciprofloxacin, levofloxacin, and moxifloxacin via the BD Phoenix™ system. None of the isolates were detected as carbapenem-resistant, as seen in Table 1.

The effect of norepinephrine on the growth of *E. coli*

We found a prolongation of the lag phase in the norepinephrine-only group (4 h) compared to that in the control group (2 h), as seen in Figure 1. No significant difference was found between the viable cell count of norepinephrine-only and the control group after a 4 h observation period ($p = 0.33$). The average viable cell count at the end of the exponential phase (14 h) was significantly higher than that in the control group ($p = 0.03$) and stayed this way until the end of the observation period (20 h) ($p = 0.03$). The average generation time in this group (16.4 min) was significantly shorter when compared with that in the control group (24.4 min; $p = 0.00$), as seen in Figure 2. One of the 10 isolates in this group was categorized as having intermediate susceptibility to levofloxacin when tested post-exposure (data not presented).

Table 1. Susceptibility of the study isolates.

Isolate Number	Antimicrobial agents																
	AK	AMC	AMP	SAM	ATM	KZ	FEP	CTX	CAZ	C	CIP	CN	IMP	LEV	MEM	MXF	PIP	TZP	TE	SXT
1	S	S	R	I	S	S	S	S	S	S	S	S	S	S	S	S	R	S	R	S
2*	S	S	R	I	R	R	R	R	R	S	S	R	S	S	S	S	R	S	S	S
3*	S	S	R	S	R	R	I	R	R	R	S	R	S	S	S	S	R	S	R	S
4	S	S	R	R	S	S	S	S	S	S	S	S	S	S	S	S	R	S	R	S
5*	S	S	R	S	R	R	I	R	R	S	S	R	S	S	S	S	R	S	R	S
6	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
7*	S	S	R	S	R	R	I	R	R	S	S	S	S	S	S	S	R	S	S	S
8	S	R	R	R	S	S	S	S	S	S	S	S	S	S	S	S	R	S	S	S
9	S	S	R	I	S	S	S	S	S	S	S	S	S	S	S	S	R	S	R	S
10*	S	S	R	I	R	R	R	R	R	S	S	R	S	S	S	S	R	S	S	S

AK amikacin; AMC amoxicillin; AMP ampicillin; SAM ampicillin-sulbactam; ATM aztreonam; KZ cefazolin; FEP cefepime; CTX cefotaxime; CAZ ceftazidime; C chloramphenicol; CIP ciprofloxacin; CN gentamicin; IMP imipenem; LEV levofloxacin; MEM meropenem; MXF moxifloxacin; PIP piperacillin; TZP piperacillin-tazobactam; TE tetracycline; SXT trimethoprim-sulfamethoxazole

*Identified as *extended-spectrum beta-lactamase* (ESBL) producers by BD Phoenix™ system.

The effect of levofloxacin on the growth of *E. coli*

There was an immediate growth inhibition of *E. coli* when exposed to levofloxacin, reaching zero viable cell count at 8 h of the observation period, as seen in Figure 1. In this culture system, the reduction rate of levofloxacin was approximately 1.9 x 10^4 CFU/ml/min.

The effect of norepinephrine and levofloxacin when given at the same time on the growth of *E. coli*

We observed an immediate inhibition of *E. coli* growth when given norepinephrine and levofloxacin simultaneously, comparable with the levofloxacin-only group. However, the inhibition stopped at 4 h of observation, whereas the levofloxacin-only group reached zero viable cell counts at 8 h, as seen in Figure 1. In the norepinephrine–levofloxacin group, this temporary inhibition was followed by regrowth. The regrowth in this group reached a considerably high viable cell count. However, it was still significantly lower than the norepinephrine-only and the control group by the 14 h ($p = 0.00$ and $p = 0.03$, respectively) and 20 h of the observation period ($p = 0.00$ and $p = 0.03$, respectively). The average generation time in the norepinephrine–levofloxacin group after the initial inhibition was 19.3 min, significantly shorter than the control group (24.4 min; $p = 0.00$), as seen in Figure 2. Two of the 10 isolates in this group were categorized as having intermediate susceptibility to levofloxacin post-exposure (data not presented).

DISCUSSION

Escherichia coli is the major cause of sepsis and bloodstream infections in many countries, contributing to a high disease burden over the years.[17,18,19,20,21] This problem is further complicated by the constant rise in antimicrobial resistance.[31,32] A slow and laborious drug development process does not match the bacterial evolution rate in developing a new survival mechanism. A better understanding of how bacteria respond to antimicrobial exposure under various environments relevant to clinical settings is necessary for a better clinical approach. Multiple studies have shown that norepinephrine increases

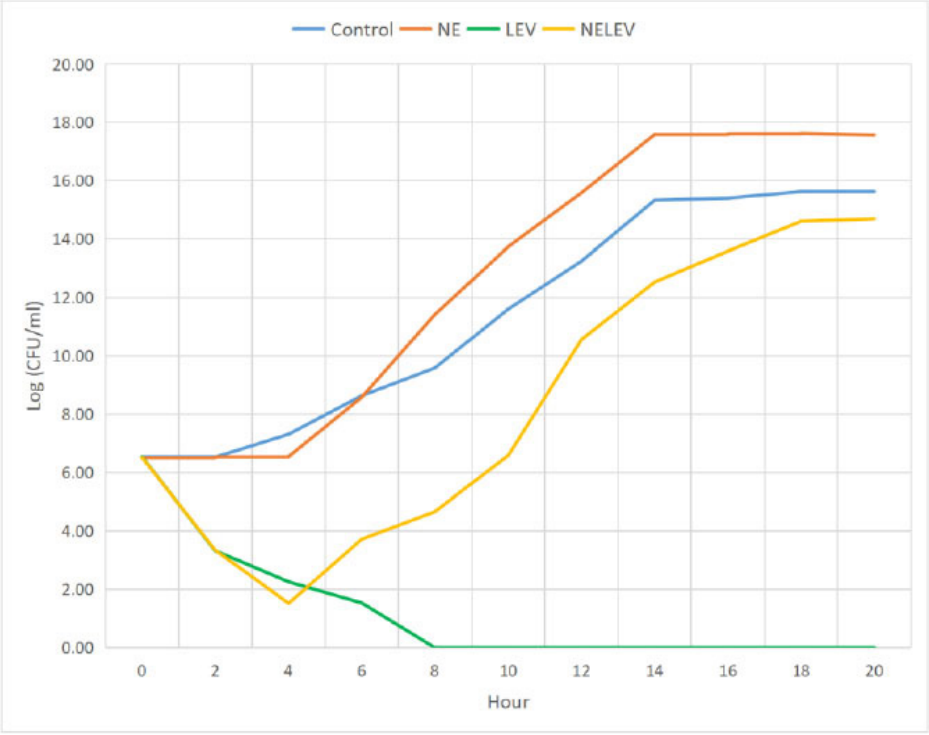

Figure 1. Growth curve comparison of study groups
NE norepinephrine, LEV levofloxacin, NELEV norepinephrine–levofloxacin.

the growth of *E. coli*.[11,12,33] Furthermore, sepsis-related immunoparalysis is hypothesized to be caused by increased norepinephrine levels.[44,45] Together, these could potentially increase the risk of colonization and subsequent infection. Increased sympathetic activity after stroke was associated with higher disease risk.[46] A study suggested that norepinephrine in the dialysates of patients receiving peritoneal dialysis increased bacterial growth.[47] Another study by Liu X et al. on patients requiring continuous renal replacement therapy showed that norepinephrine did not associate with increased catheter-related infections. However, the catheter-related colonization of Gram-negative bacteria was significantly higher in patients receiving catecholamine.[48] Clinical studies investigating the relationship between norepinephrine administration and catheter-related infections in other patient populations are still lacking.

In the present study, we found that simultaneous exposure to norepinephrine and levofloxacin resulted in a temporary inhibition followed by a regrowth of *E. coli*. These results were observed in the non-ESBL and ESBL phenotype of clinical isolates of *E. coli*, although more data are needed to produce a statistical conclusion. Similar results were found in a previous study using 4× minimal inhibitory concentration (MIC) of levofloxacin given in the presence of norepinephrine to resistant *E. coli* strains.[39] Another study showed that the exposure of tigecycline in the presence of norepinephrine on susceptible *Acinetobacter baumannii* strains resulted in a similar pattern but not when using colistin.[28] Higher survival of *Pseudomonas aeruginosa* to several tobramycin concentrations was also observed under the effect of norepinephrine, although the study did not present a growth curve.[49,50] Moreover, the post-exposure susceptibility test in the present study showed that only two out of 10 isolates shifted from susceptible to an intermediate category using the disk diffusion method. These findings suggest that the mechanism of how norepinephrine changes the interaction between antimicrobial agents and bacteria might not be directly related to specific resistant genes. Despite these findings, the investigation of the effect of norepinephrine on the clinical efficacy of antimicrobial therapy is still very limited.

The regrowth of *E. coli* after exposure to levofloxacin under norepinephrine might be caused by several mechanisms. Norepinephrine upregulated the expressions of genes related to the survival of *E. coli* under various stressors. Among these are the genes encoding DNA starvation proteins, universal stress proteins, cell division inhibitors, superoxide dismutase, and several genes involved in acid resistance pathways.[15,16] Another possible mechanism is enhancing gluconeogenic activity in *E. coli* by modulating several genes. Norepinephrine also switched the electron transport system toward nitrate/nitrite pathways which take part during anaerobic metabolism.[16] These changes in bacterial physiology by norepinephrine might, in turn, cause a change in the antimicrobials–bacteria interaction, as proven in previous studies.[28,30,51,52]

There were several limitations in our study. We used a conventional nonsteady-state culture system that did not represent a continuous infusion of norepinephrine administration in clinical settings. Other limitations in this study were the unavailable information of the exact MIC for each isolate to levofloxacin, as the initial susceptibility determination was done using a semi-automated BD Phoenix™ system. Future studies should investigate the effect of continuous exposure to norepinephrine and alternating exposure to norepinephrine and antimicrobial agents on the physiology of microbes. A continuous culture system with a chemostat can maintain and modulate the desired level of norepinephrine and antimicrobial agent concentrations. It is also essential to investigate how the result of this study translates to in vivo conditions and the impact on clinical outcomes by using animal models or clinical research methods.

CONCLUSION

Simultaneous exposure of norepinephrine and levofloxacin caused a temporary inhibition and markedly faster regrowth of levofloxacin-susceptible *E. coli* in vitro. This can potentially affect the clinical outcomes and increase the risk of bacterial colonization in patients receiving norepinephrine and levofloxacin, such as those in septic shock conditions or under

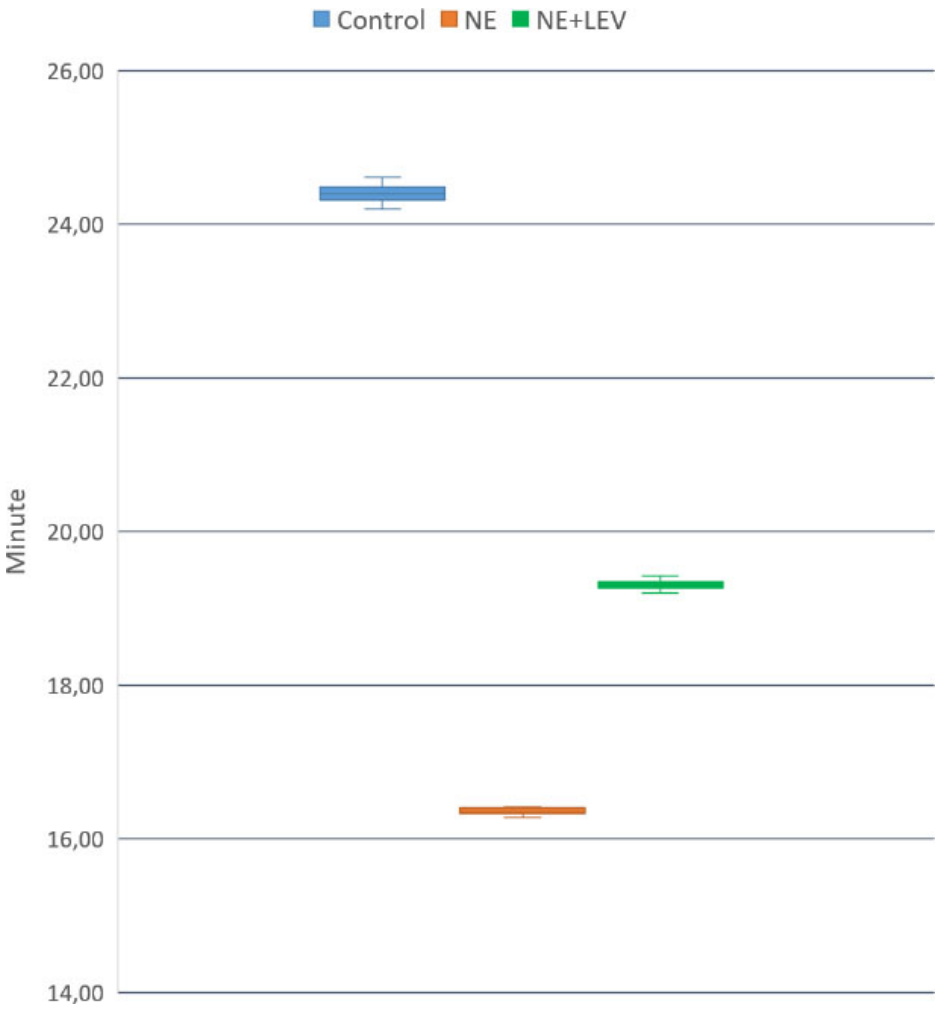

Figure 2. Generation time comparisons of study groups
NE norepinephrine, LEV levofloxacin, NELEV norepinephrine–levofloxacin.

intensive care. Thorough and continuous infection prevention and control are imperative in this patient population. Further study is needed to investigate the best clinical approach that will gain the most benefit from antimicrobial therapy in patients receiving life-saving norepinephrine.

CONFLICTS OF INTEREST

None.

ETHICAL CLEARANCE

This study received ethical approval number 0699/LOE/301.4.2/XI/2021 from Dr. Soetomo General Academic Hospital, Surabaya.

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None.

AUTHOR CONTRIBUTIONS

Amina Thayyiba: Conceptualization, investigation, data collection, data analysis, paper writing-original draft. Eddy Bagus Wasito: Conceptualization, data analysis, paper writing-editing and reviewing, supervision. Lindawati Alimsardjono: Conceptualization, data analysis, paper writing-editing and reviewing, supervision.

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