

# Weaning of septic patients from the ventilator in the intensive care unit by attention approach to common antibiotic regimens

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## ABSTRACT

**Background:** Sepsis is a chronic blood infection that is more common in patients with ventilatory and disability. This study aimed to evaluate the effect of common antibiotic regimens on weaning sepsis patients from mechanical ventilator. **Methods:** In this prospective cross-sectional study, we classified 70 sepsis patients under mechanical ventilation which sedates with midazolam and do not take muscle relaxants into two groups: meropenem and levofloxacin versus meropenem, levofloxacin, and clindamycin. The duration of intubation and the number of patients who needed re-intubation (and their duration of extubation) were recorded. Data were analyzed using SPSS software. **Results:** In the present study, 68.6% were male and 31.4% were female. The mean age was calculated to be 37.98. The mean duration of mechanical ventilation and stay in the ICU in the group of two drugs (meropenem + levofloxacin) showed a significant decrease compared to the group of three drugs ( $P < 0.05$ ). But no significant difference was observed in terms of ventilator connection time ( $P < 0.05$ ). **Conclusion:** The differences in terms of mean duration of mechanical ventilation and ICU stay between the groups indicate that the two-drug regimen (meropenem + levofloxacin) is more efficient in bringing [sepsis] patients back to recovery.

**Keywords:** Antibiotics, clindamycin, mechanical ventilation, sepsis, ventilator

## Introduction

Sepsis is one of the most common causes of ICU mortality worldwide and remains a risk factor despite new supportive therapies and strong antibiotics.<sup>[1]</sup> It is a medical emergency requiring immediate treatment of the infection to restore hemodynamic and respiratory support.<sup>[2]</sup> Sometimes both antibiotic and non-antibiotic treatment regimens of these patients have adverse effects and increase the length of hospital stay. In severely ill septic patients, various antibiotics are prescribed,

including fluoroquinolones—a DNA topoisomerase inhibitor bactericidal<sup>[3]</sup>—and carbapenems which are strong beta-lactams.<sup>[4]</sup> Clindamycin is a macrolide used against gram-positive cocci and can inhibit *Staphylococcus aureus* toxins (because of its antitoxin effects).<sup>[5-7]</sup> However, rhabdomyolysis is a side effect seen with clindamycin and can worsen the patient's condition.<sup>[8]</sup>

Mechanical ventilation is an essential support to severely ill patients, such as those with sepsis.<sup>[9,10]</sup> The consequences of a prolonged mechanical ventilation include increased expenses of ventilation, increased risk of ventilator-associated pneumonia (VAP), respiratory tract trauma, muscle weakness, need for sedatives, the mental burden on patients and their families, and increase mortality.<sup>[11]</sup> Accordingly, weaning from

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mechanical ventilation as soon as possible is a priority.<sup>[12]</sup> Some patients with sepsis need mechanical ventilation due to respiratory problems, cerebral issues, etc., To wean them from the ventilator, all hemodynamic, cerebral, laboratory, and muscular conditions of the patient should be in the desired condition. Sometimes the adverse effects of the medications used to treat these patients cause problems that increase the duration of hospitalization.

It is important to provide solutions that can be effective in accelerating recovery and reducing the length of hospital stay. According to the said cases, this study aims to compare the efficiency of two common ICU antibiotic regimens in reducing the patients' need for intensive care and their time to recovery.

## Materials and Methods

### Study design

This prospective cross-sectional study compares the effect of two standard intensive care unit (ICU) antibiotic regimens on weaning patients from mechanical ventilation. We enrolled 70 patients from 501 Artesh of Islamic Republic of Iran (AJA) hospitals from 2019 to 2020. Patients were included if they were at least 18 years old, hospitalized in the ICU with sepsis, under mechanical ventilation which sedate with midazolam and do not take muscle relaxants, and receiving one of the following antibiotic regimens: fluoroquinolone (levofloxacin) and carbapenem (meropenem), or fluoroquinolone (levofloxacin), carbapenem (meropenem), and clindamycin. Patients with underlying neuromuscular problems (myopathies and muscular dystrophy), on muscle relaxant medications, psychiatric medications, and other antibiotics were not enrolled, and patients who expired during the study were excluded. IR.AJAUMS.REC.1399.087 2020-07-20

### Sampling

Based on the antibiotic regimen they received, we divided the participants into two groups: two-drug group (meropenem and levofloxacin) and three-drug group (meropenem, levofloxacin, and clindamycin). The nurse-in-charge of injections and data collection was not aware of the groups. The patients were followed until they met the criteria for weaning [Table 1] and duration of mechanical ventilation, those who required re-intubation (in each group), and duration of extubation in patients requiring re-intubation were recorded.

### Statistical analysis

We analyzed the collected information using SPSS version 20. For descriptive statistics, indicators such as mean ( $\pm$ SD<sup>1</sup>), frequency, and percentage of frequency were used. For inferential statistics, analysis of variance and independent *t*-test were used for the data with normal distribution and the non-parametric Friedman and Mann–Whitney tests were used for the data with non-normal distribution. Statistical significance was assessed at the 5% level.

<sup>1</sup>Standard deviation.

## Results

We studied 48 (68.6%) men and 22 were (31.4%) women [Table 2]. The mean age was calculated to be  $37.98 \pm 5.41$ . Mean ages were  $36.93 \pm 5.61$  and  $38.12 \pm 6.42$  years in the two-drug and three-drug groups, respectively ( $P = 0.2$ ); there is no significant difference between the mean two groups. Patient demographic data are shown in Table 2. The mean weight in the two-drug and three-drug groups was  $74.33 \pm 5.69$  kg and  $78.65 \pm 5.17$  kg, respectively ( $P = 0.6$ ). Overall, demographic findings were not significantly different between the two groups ( $P < 0.05$ ).

According to Table 3, about 89% in two-drug group and 88% in three-drug group needed a ventilator less than twice. In total, in the two groups, 90% of patients needed mechanical ventilation less than twice [Table 3].

The mean duration of mechanical ventilation and the duration of ICU hospitalization were both significantly higher in the three-drug group ( $P < 0.05$ ) [Table 4]. The average number of intubation times, however, was not significantly different ( $P = 0.22$ ).

Comparison of ventilation duration mean rank and duration of hospitalization in the ICU was significantly different in two-drug regimens. But the rank of connection number in two groups was not significantly different from each other [Table 5]. The number of unsuccessful extubations was also not significantly different.

**Table 1: Criteria required to separate patients from the ventilator**

Criteria required to separate from ventilator	Unit	Acceptable range
Respiratory rate	n/min	25<
Tidal volume	ml/kg	5>
Vital capacity	ml	10>
Minute ventilation	L/min	10<
FIO <sub>2</sub> /PaO <sub>2</sub>		200>
SHUNT fraction	%	20<
NIF	cmH <sub>2</sub> O	25<
F/VT respiratory frequency to tidal volume)		105<

**Table 2: Demographic findings in the two groups**

Parameters	Mean $\pm$ SD n (%)		P
	Two-drug group (n=35)	Three-drug group (n=35)	
Age (year)	36.93 $\pm$ 5.61	38.12 $\pm$ 6.42	0.24
Weight (kg)	74.13 $\pm$ 17.25	75.27 $\pm$ 11.92	0.6
Valid			
Male	23 (65.7)	25 (71.4)	0.09
Female	12 (34.3)	10 (28.6)	0.14
Systolic blood pressure (mmHg)	115.66 $\pm$ 11.06	112.66 $\pm$ 6.85	0.21
Diastolic blood pressure (mmHg)	74.33 $\pm$ 5.69	78.65 $\pm$ 5.17	0.19

## Discussion

Fear of pathogens not covered by experimental antibiotics is a major factor in treating overuse of a wide range of antibiotics in ICU and knowing the best antibiotics and better diagnostic data can be effective in removing barriers and improving the care of serious patients such as pneumonia and sepsis.<sup>[13,14]</sup>

We studied the application of two antibiotic regimens (meropenem + levofloxacin vs. meropenem + levofloxacin + clindamycin) on weaning septic patients from ventilator in the ICU. The present study showed that two groups were significantly different in terms of mean duration of mechanical ventilation and ICU stay. The differences in the two-drug group make the two-drug group (meropenem and levofloxacin) preferable over the three-drug group (meropenem + levofloxacin + clindamycin). In 2020, a similar study by Lertwattanachai *et al.*<sup>[15]</sup> showed that the use of meropenem in high experimental doses alone provided acceptable clinical results in patients with sepsis and septic shock.

In a study by Strich *et al.*, meropenem was identified as an effective antibiotic in patients' recovery. In their study, comparing empiric meropenem and ciprofloxacin versus meropenem alone for suspected VAP showed that there was no difference in outcomes between the two groups in a setting of low resistance. However, those that had infection due to *Pseudomonas* species, *Acinetobacter* species, and multidrug-resistant gram-negative bacilli were more likely to receive adequate initial therapy and have microbiological clearance if they received meropenem and ciprofloxacin.<sup>[16]</sup> Other studies in 2020 also examined various antibiotics such as meropenem, levofloxacin, and clindamycin in ventilator patients and found the use of effective antibiotics to reduce the length of hospital stay of patients.<sup>[16,17]</sup>

**Table 3: Number of mechanical ventilation connections per drug group**

Drug		Frequency	Percent	
Two-drug group (meropenem and levofloxacin)	Valid	1.00	24	68.6
		2.00	8	22.9
		3.00	2	5.7
		4.00	1	2.9
	Total	35	100.0	
Three-drug group (meropenem, levofloxacin, and clindamycin)	Valid	1.00	18	51.4
		2.00	13	37.1
		3.00	2	5.7
		4.00	1	2.9
		5.00	1	2.9
Total	35	100.0		

Prolonged mechanical ventilation can cause various problems and complications for patients. Minimizing exposure to mechanical ventilation is an important issue in preventing and reducing patient mortality and should be considered.<sup>[18]</sup>

Timely weaning from mechanical ventilation is an essential step in the treatment of patients under mechanical ventilation. The two-drug regimen in this study achieved a shorter duration of mechanical ventilation and ICU hospitalization, perhaps by omitting clindamycin. Clindamycin is a bacteriostatic antibiotic that inhibits protein synthesis by binding to the 50S subunit of the bacterial ribosome.<sup>[8,19]</sup> Its common side effects include skin rash, hepatotoxicity, diarrhea,<sup>[20]</sup> rhabdomyolysis, and mitochondrial damage,<sup>[8]</sup> which may cause muscle weakness. In a study on a 49-year-old man with mitochondrial myopathy,<sup>[8]</sup> the patient's fatigue began immediately after starting clindamycin for the first time. Lest a reaction to clindamycin, his cellulite treatment was switched to vancomycin. Therefore, they suggested physicians to consider clindamycin as a potential cause of drug-induced rhabdomyolysis in patients with underlying mitochondrial myopathy. Consistently with other studies, adding clindamycin to the treatment regimen in the present study increased the duration of ventilation, treatment failure, and rate of [indicated] re-intubation.<sup>[8,19,20]</sup> Therefore, we recommend physicians to use clindamycin less frequently in the ICU for weaning septic patients from ventilator.

Kenaa *et al.*<sup>[21]</sup> in 2021 show that the use of effective antibiotic therapy is effective in management of ventilator-related infectious diseases in the ICU and in reducing the length of stay in the ICU.

Recent studies have found that injecting antibiotics is effective in increasing their effectiveness. In fact, many studies show that time-dependent antibiotics and drug concentrations are needed to increase the interval between doses to increase the minimum inhibitory concentration (MIC) and for best performance and effectiveness. Consequently, continuous injection is preferred to long-term injection of beta-lactam antibiotics, which is associated with clinical benefits such as reduced hospital stay, cost of treatment, and mortality.<sup>[22]</sup>

Overall, the findings of our study recommend the use of a two-drug regimen, and it is suggested that future studies conduct similar studies on other patients in other wards for reliable results.

## Conclusion

Decreased duration of mechanical ventilation and ICU stay in the two-drug (meropenem + levofloxacin) group compared to the

**Table 4: Mean of ventilation duration, number of connections, and duration of hospitalization in the intensive care unit**

Parameters	Mean±SD		P
	Two-drug group (n=35)	Three-drug group (n=35)	
Duration of mechanical ventilation	5.31±1.12	7.85±1.18	0.003
Number of times to connect the ventilation	1.42±0.19	1.68±0.21	0.16
The length of the patient's stay in the intensive care unit	7.20±1.78	10.00±1.38	0.002

**Table 5: Comparison of the average rank of ventilation duration, number of connections, and duration of hospitalization in the intensive care unit in two-drug regimens**

Parameters	Mean±SD		P
	Two-drug group (n=35)	Three-drug group (n=35)	
Duration of mechanical ventilation	28.43±3.38	42.57±5.12	0.04
Number of times to connect the ventilation	32.56±4.66	38.44±7.01	0.22
The length of the patient's stay in the intensive care unit	28.11±2.99	42.89±5.46	0.01

three-drug group (meropenem + levofloxacin + clindamycin) indicates that the two-drug regimen helps patients return to the desired condition faster, which was achieved by eliminating clindamycin from the regimen. Therefore, our recommendation on weaning septic patients from ventilators in the ICU is avoiding the prescription of clindamycin as far as possible.

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### Conflicts of interest

There are no conflicts of interest.

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