Dicle Tıp Dergisi / Dicle Med J (2022) 49 (4) : 541-549

www.diclemedj.org

Original Article / Özgün Araştırma

How Necessary Is Empirical Antibiotic Therapy in COVID-19 Patients before ICU infections develop? An Observational Study

Sirin Menekse[1], **Secil Deniz**[2]

1 Department of Infectious Diseases, Kosuyolu Kartal Heart Training and Research Hospital, Istanbul, Turkey

2 Department of Infectious Diseases, Pamukkale University School of Medicine, Denizli, Turkey

Received: 01.09.2022; Revised: 14.10.2022; Accepted: 15.10.2022

Abstract

Introduction: There have been few studies reporting empirical antibiotic use in Covid-19 patients, particularly in those admitted to the intensive care unit (ICU). This study evaluated empirical antibiotic use in patients admitted to the ICU with Covid-19

Methods: This two-center retrospective study included 79 consecutive patients who were admitted to the ICU due to Covid-19 infection between October 1 and December 31, 2020, and received empirical antibiotics. The patients were classified into two groups: those who developed ICU infections after 48 hours of ICU admission despite empirical antibiotic therapy (Group 1), and those who received empirical antibiotic therapy during the ICU stay, but were free of ICU infections (Group 2).

Results: In Group 1, 37 patients (46.8%) developed ICU infections after a median of 12 days (IQR 5.5-15.5) of ICU stay. The cumulative antibiotic use until the detection ICU infections was 395 antibiotic days corresponding to 1070 DOTs/1000 hospital days. The median antibiotic use was 9 days (IQR 4-15.5). In Group 2, 42 patients (53.2%) received empirical antibiotic therapy for a median of 5 ICU days (IQR 3-8.3) and for a total of 256 antibiotic days (1051 DOTs/1000 hospital days). Twenty–three patients received empirical antibiotic therapy during the entire ICU stay. The median ICU stay was 6.5 days (IQR 4-10) and the median antibiotic use was 5 days (IQR 3-8.2).

Discussion and Conclusion: Our findings are alarming and raise doubt about the potential role of antibiotics in the initial therapy of Covid-19 patients at the time of ICU admission and suggest the need to narrow or tailor antibiotic use based on clear laboratory and radiologic indications.

Keyword: SARS-CoV-2, empirical antibiotic use, Intensive Care Unit infections

DOI: 10.5798/dicletip.1220682

Correspondence / Yazışma Adresi: *Sirin Menekse, Department of Infectious Diseases, Kosuyolu Kartal Heart Training and Research Hospital, İstanbul, Turkey e-mail: meneksesirin@hotmail.com*

Ampirik Antibiyotik Tedavisi Yoğun Bakım Ünitesinde Takip Edilen COVID-19 Vakalarında Ne Kadar Gerekli? Gözlemsel Çalışma

Öz

Giriş ve Amaç: Yoğun bakım ünitesinde (YBÜ) takip edilen COVİD-19 vakalarında antibiyotik kullanımı ile ilgili az sayıda çalışma yapılmıştır. Bu çalışmada bu hasta gurubunda ampirik antibiyotik kullanımının değerlendirilmesini amaçlanmıştır.

Yöntemler: Çalışmaya 1.10.2020-31.12.2020 tarihleri arasında YBÜ'de takip edilen ve ampirik antibiyotik tedavisi alan 79 COVID-19 hastası dahil edilmiştir. Hastalar ampirik antibiyotik tedavisi altında hastane enfeksiyonu gelişen(Grup 1) ve hastane enfeksiyonu gelişmeyen(Grup 2) olmak üzere iki gruba alınmış, tanımlanmış günlük doz ve antibiyotik günleri incelenmiştir.

Bulgular: Grup 1'de 37 hasta yer almakta olup, medyan 12 günde ampirik antibiyotik tedavisine rağmen enfeksiyon gelişmiştir. Bu grupta kümülatif antibiyotik kullanımı 395 antibiyotik günü, tanımlanmış günlük doz 1000 hasta gününe göre hesaplandığında 1070, medyan ampirik antibiyotik kullanımı ise 9 gün olarak bulunmuştur. Grup 2'de ise 42 hasta yer almakta olup, kümülatif antibiyotik kullanımı 256 antibiyotik günü, tanımlanmış günlük doz ise 1051/1000 hasta günü, medyan antibiyotik kullanımı ise 5 gün olarak saptanmıştır. Bu hastalardan yarıdan fazlası (23 hasta) tüm YBÜ yatışı boyunca ampirik tedavi almıştır

Tartışma ve Sonuç: Bulgularımız YBÜ'de takip edilen COVID-19 vakalarında ampirik antibiyotik kullanımı hakkında endişe vericidir. Bakteriyel enfeksiyonun kanıtlanamadığı durumlarda gereksiz antibiyotik kullanımından kaçınılmalıdır.

Anahtar kelimeler: Yoğun Bakım Ünitesi enfeksiyonları, ampirik antibiyotik kullanımı, COVID-19.

INTRODUCTION

The empirical use of antibiotics in patients with coronavirus disease 2019 (Covid-19) remains a controversial issue, particularly in those admitted to the intensive care unit (ICU). Although the guidelines clearly recommend against empirical use of antibiotics for mild-to-moderate Covid-19,[1,2] this is not the case for severe Covid-19 and there has been considerable uncertainty around the subject. World Health Organization (WHO) recommends prompt initiation, even within one hour of initial assessment, in patients with suspected or confirmed severe Covid-19. The WHO also warns that the duration of empirical antibiotic therapy should not be longer than 5-7 days[1]. On the other hand, the Surviving Sepsis Campaign Guidelines recommend empirical use of antibiotics in patients receiving mechanical ventilation due to Covid-19 and respiratory failure[2]. All guidelines also note that recommendations for empirical antibiotic use are based on insufficient data and low-quality evidence[1-4].

There have been few studies reporting empirical antibiotic use in Covid-19 patients[5-7], particularly in those admitted to the ICU[8,9]. After so much experience with Covid-19 patients, the authors of the present study feel that it is time to highlight the motto for antibiotic stewardship "the right drug at the right time and the right dose for the right bug for the right duration"[10] and to challenge the use of empirical antibiotic therapy, with particular concern about the detrimental consequences of unnecessary or inappropriate use of antibiotics.

This study evaluated empirical antibiotic use in patients admitted to the ICU with Covid-19, with particular focus on antibiotic administration throughout the period from ICU admission to the detection of ICU infections.

METHOD

We conducted a two-center retrospective study of Covid-19 patients admitted to the ICU between October 1 and December 31, 2020. The study was approved by the institutional review board (2021/9/517) and conformed to the Declaration of Helsinki.

Study design

The two study centers were a university ICU of the Department of Internal Medicine and a cardiovascular ICU of a dedicated tertiary center for cardiovascular surgery and diseases. The latter also served as a referral center for extracorporeal membrane oxygenation (ECMO) procedures for patients who had been hospitalized for Covid-19 at other health care facilities.

Study patients

During the study period, a total of 183 consecutive patients were admitted to the ICUs of the two centers due to severe Covid-19 infection, as diagnosed by the criteria recommended in the Interim Guidance of the WHO[1].Inclusion criteria were empirical use of antibiotics, an ICU admission of at least 48 hours for Covid-19, and age beyond 18 years. Exclusion criteria included the presence of nosocomial Covid-19 infection, a history of any bacterial infection before the diagnosis of Covid-19, a previous history of hospitalization within the past 6 months, the presence of any risk factor for multidrug-resistant infections and immunocompromised patients. After excluding 95 patients meeting the exclusion criteria, additional 9 patients who had not received antibiotic therapy before and after ICU admission were also excluded. The final analysis included 79 patients. The study design is shown in a flowchart in Figure 1.

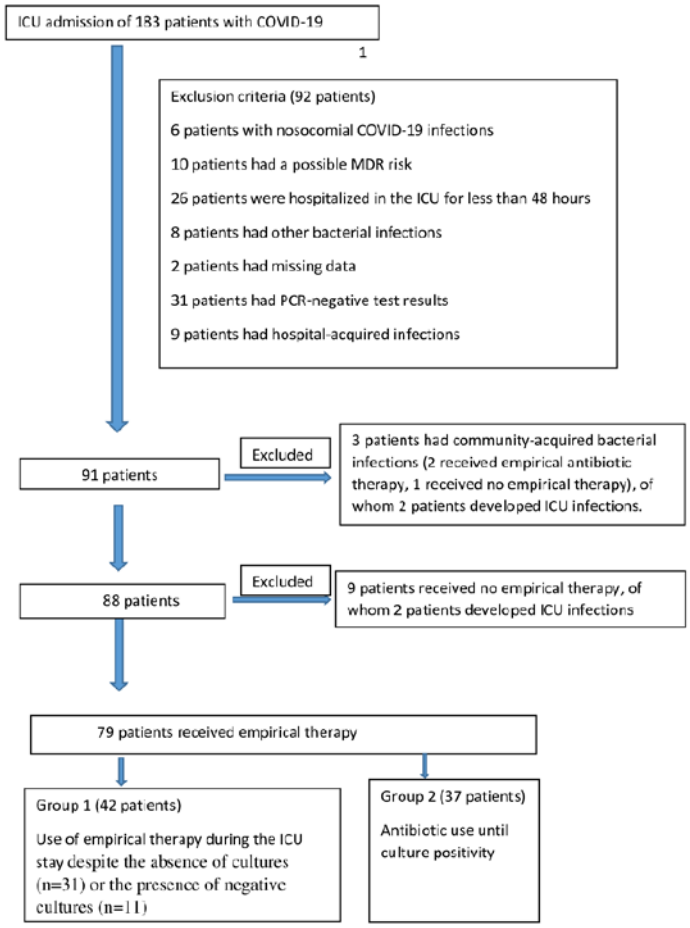

Figure 1. Flow diagram of COVID-19 patients admitted to the ICU

Data collection and definitions

Demographic, clinical and laboratory data of the patients as well as data on empirical antimicrobial use were retrieved from the hospital registry system and infection visit charts. Infections were classified into three groups: (i) community-acquired infections, identified prior hospitalization or within the first 48 hours after hospital admission; (ii) healthcare-associated infections, identified during hospitalization or within 48 hours after ICU admission; and (iii) ICU-acquired infections, identified based on positive cultures after 48 hours of ICU admission.

The analysis included two patient groups: those who developed ICU infections after 48 hours of

ICU admission despite empirical antibiotic therapy (Group 1), and those who met the inclusion criteria, received empirical antibiotic therapy during the ICU stay, but were free of ICU infections (Group 2).

Data on empirical antibiotic use were recorded covering all aspects, including timing, place and duration of antibiotic use, types of antibiotics and collection of blood, respiratory, and/or urine samples. Prescription of antibiotics was left at the discretion of treating physicians.

Risk factors for multidrug resistance included previous multidrug-resistant bacterial infections or colonization, a history of hospitalization, chemotherapy, or hemodialysis[11].

Antibiotic consumption was calculated and expressed as cumulative antibiotic use (total antibiotic days) and days of therapy (DOT/1000 patient days). The latter, represents the use of a single antibiotic on a given day irrespective of the number of doses given the same day, with each individual antibiotic taken into account as 1 DOT[12].

Statistical analysis

Demographic, clinical and laboratory data of the patients with and without ICU infections were compared. Data were processed using SPSS Statistics 20. For descriptive analysis, medians with the interquartile range (IQR) were used for continuous variables and categorical variables were expressed as number and percentages. The nonparametric Mann-Whitney U-test was used for comparison of numerical data, and the Fisher's exact test was used for comparison of categorical data. A P value of less than 0.05 was considered significant.

RESULTS

Demographic features, clinical and laboratory findings of Group 1 and Group 2 are summarized in Table 1. The median age of the whole patient population was 63 years (IQR 53-71). Of 79 patients, 56 died and 23 were discharged alive. Fifty-six patients had at least one comorbidity, including diabetes mellitus (n=32, 40.5%), hypertension (n=29, 36.7%), coronary artery disease (n=13, 16.5%) and others (n=38, 48.1%). Sixty-five patients (82.3%) required invasive mechanical ventilation. The median ICU stay was 10 days (IQR 6-23), the median time from PCR-positivity to ICU admission was 4 days (IQR 2-8).

Timing of empirical antibiotic therapy

Sixteen patients were directly admitted to the ICU from the emergency department. The remaining 63 patients were transferred from the clinical wards after a median of 2 days (IQR 1-4). In this group, based on clinical signs and laboratory findings, 38 patients (60.3%) had already started receiving empirical antibiotic therapy (30 patients at hospitalization), which was continued during the ICU stay. Antibiotic regimens of 16 patients were modified at ICU admission. The empirical antibiotic regimens administered in 38 patients are presented in Table 2. Antibiotic therapy was initiated at ICU admission in 25 patients.

Among 16 patients who were transferred to the ICU from the emergency department, antibiotic therapy was initiated at admission or within the first 24 hours of ICU stay in 10 patients and after 24 hours of ICU stay in 6 patients.

Table I: Demographic features, clinical and laboratory findings of ICU patients with Covid-19

	Group 1 Patients with ICU infections (n=37)	Group 2 Patients without ICU infections (n=42)	*p* value
Age, years – median (IQR)	60 (47-68)	65 (57-72)	0.09
Male sex – no. (%)	14 (37.8)	11 (26.2)	0.27
Comorbidities			
Diabetes mellitus – no. (%)	14 (37.8)	18 (42.9)	0.65
Arterial hypertension – no. (%)	9 (24.3)	20 (47.6)	0.03
Coronary artery disease – no. (%)	5 (13.5)	8 (19)	0.50
Chronic kidney disease – no. (%)	1 (2.7)	6 (14.3)	0.07
COPD – no. (%)	7 (18.9)	3 (7.1)	0.12
Congestive heart failure – no. (%)	2 (5.4)	3 (7.1)	0.75
Malignant neoplasia – no. (%)	1 (2.7)	5(11.9)	0.12
Body mass index > 30 kg/m^2 – no. (%)	5 (13.5)	0	0.01
Peripheral artery disease – no. (%)	1 (2.7)	1 (2.4)	0.91
Sarcoidosis – no. (%)	2 (5.4)	0	0.13
Rheumatic disease – no. (%)	1 (2.7)	0	0.21
Laboratory/clinical findings*			
White blood cell count, cells/mL	14470 (10500-20600)	15860 (12580-23990)	0.33
Lymphocyte count, cells/mL	500 (300-825)	520 (288-803)	0.80
C-reactive protein (mg/L)	182 (90-274)	144.5 (107.0-226.5)	0.42
Procalcitonin (ng/ml)	5.5 (1.5-9.5)	2.8 (0.5-9.3)	0.004
APACHE II score	24 (19-28)	27 (20-32)	0.07
SOFA score	4 (2-8)	6 (3-9)	0.21
Septic shock at ICU admission – no. (%)	10 (27)	18 (43)	0.14
Severe ARDS at ICU admission – no.(%)	22 (59.5)	27 (64.3)	0.66
Total length of ICU stay (days) – median (IQR)	23 (14-36)	6.5 (4-10)	0.001
ICU therapies / applications			
Cytokine filter – no. (%)	12 (32.4)	5 (11.9)	0.03
Convalescent plasma – no. (%)	6 (16.2)	4 (9.5)	0.37
Tocilizumab – no. (%)	7 (18.9)	4 (9.5)	0.23
Steroids – no. (%)	32 (86.5)	34 (81)	0.51
Invasive mechanical ventilation – no. (%)	35 (94.6)	30 (71.4)	0.007
ECMO – no. (%)	19 (51.3)	1 (2.3)	0.001
Mortality – no. (%)	28 (75.7)	28 (66.7)	0.38

**Laboratory data indicate values obtained at the time of detection of infection for Group 1, and the highest levels during ICU stay for Group 2.ICU: Intensive care unit; IQR: Interquartile range; COPD: Chronic obstructive pulmonary disease; ARDS: Acute respiratory distress syndrome; ECMO : Extracorporeal membrane oxygenation*

Table II: Antimicrobial agents initiated at clinical wards before ICU admission (n=38)

Antimicrobial agent	At hospitalization (1 to <24 hours)	24 to <48 hours	48 to <72 hours	72 to 96 hours
Piperacillin/tazobactam	10	2	2	1
Piperacillin/tazobactam+ Clarithromycin	1			
Piperacillin/tazobactam + anti-MRSA agents	1			
Piperacillin/tazobactam+ quinolone	1			
Ceftriaxone	7		1	
Antipseudomonal cephalosporins	2			1
Carbapenem				1
Quinolon	6			
Claritromycin	2			
Total	30	2	3	3

MRSA: Methicillin-resistant Staphylococcus aureus.

Development of ICU infections

During the ICU stay, ICU infections developed in 37 patients (46.8%) after a median of 12 days (IQR 5.5-15.5) of ICU stay.

Empirical therapy in patients who developed ICU infections (Group 1)

At least 48 hours after ICU admission, blood, respiratory and/or urine samples for cultures were collected from 48 patients based on worsening clinical signs and laboratory findings, yielding ICU-acquired infections in 37 patients. A total of 44 isolates were recovered, with Gram-negative bacteria accounting for 79.5%. The most commonly isolated pathogen was Acinetobacterbaumanii followed by Klebsilla pneumoniae, with 14 and 13 isolates, respectively (Table 3). Susceptibility testing for isolated pathogens showed carbapenem resistance in 28 isolates (63.6%). Out of 35 Gram-negative isolates recovered from 32 patients, 28 isolates of 25 patients were found to be resistant to carbapenem.

Table III: Isolated strains in 37 patients

Isolates	No.	Carbapenem resistance
Gram-negative bacteria		
Acinetobacter spp.	14	13
Klebsiella spp.	13	12
Pseudomonas spp.	5	3
E.coli	1	0
Enterobacter spp.	2	0
Total	35	28
Carbapenem-resistance – no. (%)	–	28 (80%)
Gram-positive bacteria		
MRCoNS	5	
MRSA	2	
Enterococcus spp.	1	
Candida spp.	1	

MRCoNS: Methicillin-resistant coagulase negative staphylococcus;

MRSA:Methicillin-resistant Staphylococcus aureus

The cumulative antibiotic use until the detection ICU infections was 395 antibiotic days corresponding to 1070 DOTs/1000 hospital days. The most frequently used empirical antibiotic was piperacillin/tazobactam in 46% of the patients (Table 4). The median antibiotic use until detection of ICU infections was 9 days (IQR 4-15.5).

Overall empirical therapy in infection-free patients during the ICU stay (Group 2)

Despite the absence of cultures or the presence of negative cultures, 42 patients (53.2%) received empirical antibiotic therapy for a median of 5 ICU days (IQR 3-8.3) and for a total of 256 antibiotic days (DOT: 1051 antibiotic

days/1000 hospital days) (Table 4). The most frequently used antibiotic was piperacillin/tazobactam in 50% of the patients (Table 4). Twenty–three patients received empirical antibiotic therapy during the entire ICU stay. The median ICU stay in this group was 6.5 days (IQR 4-10). The median antibiotic use was 5 days (IQR 3-8.2).

Table IV: Antibiotics administered and rates of antibiotic use

	Group 1 Patients with ICU infections (n=37)		Group 2 Patients without ICU infections (n=42)	
Antibiotics	n (%)	Antibiotic days	n (%)	Antibioticdays
Piperacillin/tazobactam	17 (46)	127	21 (50)	124
Tigecycline	12 (32)	77	10 (23.8)	55
Carbapenem	12 (32)	120	6 (14.3)	39
anti-MRSA agents*	8 (22)	69	8 (19)	56
Antipseudomonal cephalosporins**	6 (16)	32	1 (2.4)	5
Ceftriaxone	6 (16)	32	8 (19)	36
Quinolon	5 (13.5)	38	1 (2.4)	3
Claritromycin	0	0	3 (7)	11
Colistin	1 (2.7)	1	0	0
Fosfomycin	1 (2.7)	7	0	0
Length of ICU stay (days)#		470		313
Cumulative antibiotic use (days)#		395		256
Days of therapy (DOT/1000 patient days)#		1070		1051
Median antibiotic use (days, IQR)#		9 (4-15.5)		5 (3-8.2)

**Anti-methicillin-resistant Staphylococcus aureus (anti-MRSA) agents: vancomycin, daptomycin, linezolid, and teicoplanin.*

***Antipseudomonal cephalosporins: ceftazidime, cefepime.#Until detection of ICU infections for Group 1.*

Time to ICU infections in relation to the application of ECMO

Of 37 patients in Group 1, 19 patients received ECMO. Of these, 12 patients (63.2%) developed ICU infections before the initiation of ECMO (Table 1).

DISCUSSION

The present study primarily aimed to examine and report the practice of empirical antibiotic use among ICU patients with Covid-19 by the time of the development of secondary infections. The overall incidence of empirical therapy among patients admitted to the ICU with Covid-19 was 89.8%. Of note, in the vast majority of patients (92.4%), empirical antibiotic therapy was initiated within the first 24 hours of ICU admission. Despite the high rate of empirical therapy, nearly half of the patients (46.8%) developed secondary infections, of whom 67.6% also had carbapenem resistance.

At the beginning of the Covid-19 pandemic, both the WHO and professional societies strongly recommended early prophylactic antibiotic use in Covid-19 patients primarily based on previous experiences with the 1918 Influenza pandemic[1,2]. However, over time as reports on Covid-19 and clinical results in ICU settings accumulated, it gradually became apparent that the incidences of co-infections at the time of admission and during the first days of ICU stay were not so high as expected[5,11-13]. Consequently, excessive prophylactic antibiotic use, particularly broad-spectrum antibiotics, has aroused concerns about antimicrobial resistance, the likelihood of adverse patient outcomes due to inappropriate antibiotic use and overall public health, prompting professional societies to recommend not only to narrow or restrict indications for antibiotic use in ICU patients based on daily assessments of more specific disease parameters, but also to discontinue antibiotics if there is no evidence of bacterial infection after 48 hours[3,4].

This small experience of the two centers highlights the fact that adherence to guidelines about empirical antibiotic use in critically ill Covid-19 patients is sacrificed to a great extent due to the inherent ICU conditions that fuel fear of a missing infection among intensivists and to strenuous working conditions amid the pandemic.

The authors of the present study mainly aimed to challenge the use of empirical antibiotics in Covid-19 patients, with concerns that the present antimicrobial practices weaken the efforts to strengthen antibiotic stewardship strategies. It is clearly emphasized in the American Thoracic Society Consensus Report that the critical care practitioners serve as the front line antibiotic stewardship and that antibiotic stewardship should be a core competency of the critical care clinicians[10]. Therefore, given the absence of evidence about the high incidence of coexistent bacterial pneumonia in Covid-19 patients and the potential benefits of antibiotics to protect patients against ICU infections, justification of the empirical use of antibiotics in Covid-19 patients remains critical. To better address this problem, we conducted a meticulous exclusion to rule out any possibility of bacterial infections at the time of ICU admission and any predisposing bacterial co-infections. In addition, the analysis was restricted to the time of the first positive cultures rather than evaluating the overall antibiotic use throughout the whole hospitalization period. The findings of the present study are thus clear and refined. The authors found that empirical use of antibiotics in Covid-19 patients at the time of ICU admission and during the first few days of ICU stay did not prevent ICU infections in 46.8% of patients, with a resultant resistance rate of 67.6%. Moreover, the duration of antibiotic use was strikingly prolonged in patients who did not develop ICU infections, with 1051 antibiotic days/1000 hospital days. These findings are alarming and raise doubt about the potential role of antibiotics in the initial therapy of Covid-19 patients at the time of ICU admission and suggest the need to narrow or tailor antibiotic use based on clear laboratory and radiologic indications.

Based on this limited experience, the authors propose the following considerations for Covid-19 patients admitted to the ICU: (i) Given that all clinicians involved in critical care are both causes of, and potential solutions to the inappropriate antibiotic use, empirical antibiotic use can be dealt with by institutional evaluations rather than individual decisions. (ii) When there is a need for empirical antibiotic use, narrow-spectrum antibiotics can be preferred until culture results. Continuation of antibiotics after obtaining a negative culture result should be reassessed and stopped upon the absence of worsening clinical, laboratory and radiological findings. (iii) Given the low incidence of bacterial co-infections at admission in Covid-19 patients, the indications for empirical antibiotic use can be refined based on an individualized approach. (iv) Prompt initiation of empirical antibiotic use can be avoided in certain patients whose clinical picture does not suggest a bacterial infection despite suggestive laboratory findings.

Unfortunately, there is limited evidence concerning the consequences of inappropriate use or overuse of antibiotics in relation to antibiotic resistance in Covid-19 patients. The most recent updated version of the Coronavirus Disease 2019 (COVID-19) Treatment Guidelines emphasizes the fact that there have been no clinical trials to evaluate empirical antimicrobial use in patients with COVID-19[3]. In the present study, 67.6% of patients who developed ICU infections were found to have carbapenem resistance. Since antibiotics are the most important and indispensable armaments against bacterial infections, inappropriate use or overuse not only gives rise to adverse consequences but also inevitably deprives us of this invaluable weapon.

Limitations

The gravity of unnecessary antimicrobial use in Covid-19 patients receiving ICU care could have been better reflected if data from a larger number of centers could have been incorporated into the analysis. In the light of our findings concerning

Covid-19 patients receiving critical care, the authors undertook a pivotal role in the evaluation, criticism and steering of institutional antibiotic use, with particular emphasis on antibiotic stewardship.

Ethics Committee Approval: The study was approved by the institutional review board (2021/9/517).

Conflict of Interest: The authors declared no conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. World Health Organization. Clinical management of COVID-19: interim guidance, 27 May 2020. World Health Organization. 2020. https://apps.who.int/iris/handle/10665/332196. License: CC BY-NC-SA 3.0 IGO. Accessed 8 Oct 2021.

2. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Medicine 2020; 48(6):854-887. https://doi.org/10.1007/s00134-020-06022-5.

3. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/. Accessed 8 Oct 2021.

4. Sieswerda E, de Boer MGJ, Bonten MMJ, et al. Recommendations for antibacterial therapy in adults with COVID-19 - an evidence based guideline. Clinical microbiology and infection 2021; 27(1):61-66. https://doi.org/10.1016/j.cmi.2020.09.041.

5. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. ClinicalInfectious Diseases 2020; 71(9):2459-2468. https://doi.org/10.1093/cid/ciaa530.

6. Vaughn VM, Gandhi TN, Petty LA, et al, Empiric Antibacterial Therapy and Community-onset Bacterial Coinfection in Patients Hospitalized With Coronavirus Disease 2019 (COVID-19): A Multi-hospital Cohort Study. Clinical Infectious Diseases 2021;72(10):e533-e541. https://doi.org/10.1093/cid/ciaa1239.

7. Karami Z, Knoop BT, Dofferhoff ASM, et al. Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID-19: results from a multicentre retrospective cohort study in The Netherlands. Infectious diseases (Lond) 2021;5382):102-110. https://doi.org/10.1080/23744235.2020.1839672.

8. Mustafa L, Tolaj I, Baftiu N, Fejza H. Use of antibiotics in COVID-19 ICU patients. Journal of infection in developing countries 2021; 15(4):501-505. https://doi.org/10.3855/jidc.14404.

9. Abu-Rub LI, Abdelrahman HA, Johar AA, et al. Antibiotics Prescribing in Intensive Care Settings during the COVID-19 Era: A Systematic Review. Antibiotics (Basel) 2021;10(8):935. https://doi.org/10.3390/antibiotics10080935.

10. Wunderink RG, Srinivasan A, Barie PS, et al. Antibiotic Stewardship in the Intensive Care Unit. An Official American Thoracic Society Workshop Report in Collaboration with the AACN, CHEST, CDC, and SCCM. Annals of the American Thoracic Society 2020;17(5):531-540. https://doi.org/10.1513/AnnalsATS.202003-188ST

11. Nseir S, Grailles G, Soury-Lavergne A, et al. Accuracy of American Thoracic Society/Infectious Diseases Society of America criteria in predicting infection or colonization with multidrug-resistant bacteria at intensive-care unit admission. Clinical Microbiology and Infection 2010; 16(7):902-8. https://doi.org/10.1111/j.1469-0691.2009.03027.x

12. The National Healthcare Safety Network. Antimicrobial Use and Resistance (AUR) Module. February 2021. https://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf. Accessed 8 Oct 2021.

13. Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clinical Microbiology and Infection 2020;26(10):1395-9. https://doi.org/10.1016/j.cmi.2020.06.025

14. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. The Journal of infection 2020; 81(2):266-75. https://doi.org/10.1016/j.jinf.2020.05.046