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Analysis of Antibiotic Usage in Critical COVID-19 Patients with Secondary Infections

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Abstract

Background: Infrequent data exist on the frequency of bacterial co-infections and secondary infection among COVID-19-infected patients admitted to intensive care units (ICU). **Objective:** To describe the quantity and the quality of antimicrobial usage in COVID-19 with secondary infection, multiple drug resistance organisms and the outcome of antimicrobial treatment. **Methods:** This study applies observational design with a cross sectional approach. All the patients with laboratory-confirmed severe COVID-19 pneumonia who were discharged from the Intensive Care Unit (ICU) Dr. Ramelan Navy Hospital from February 1st to June 30th 2022 included. The quantity of antibiotics usage was assessed by counting the Defined Daily Dose (DDD). **Result:** During the study period, 126 patients were referred to the ICU for COVID-19 with severe pneumonia. There were 70.6% (89 patients) treated with antibiotics and 29.4% (37 patients) untreated with antibiotics. Quantitative analysis of 89 patients revealed that levofloxacin was the most common antibiotic prescribed with 43 DDD, followed by Meropenem and Cefoperazone-Sulbactam, which were 17.76 DDD and 16.87 DDD, respectively. Meanwhile, qualitative analysis resulted in 81 antibiotics (43.55%) being used appropriately. No indications of the use of antibiotics were found in 53 antibiotics (28.49%). *Klebsiella pneumonia* was the main pathogen identified in the blood, sputum. While E. Coli was found to be the main pathogen in urine. **Conclusion:** A high death rate in patients treated with antibiotics compared to patients not treated with antibiotics.

Keywords

Bacterial Coinfection, Critical COVID-19, Intensive Care Unit, Antibiotics, Pneumoniae

1. Introduction

Confirmed bacterial infections in people with COVID-19 were not common, especially on the first day of admission to the hospital. Most of the bacterial infections were secondary infections that were diagnosed more than 48 hours after being admitted. Critical COVID-19 patients have an increased potential to gain secondary infections. Some possible entry points are mechanical ventilation, central venous catheters, and foley catheters, which possibly increase the risk of developing healthcare-associated infections [1]. Bacterial co-infection caused poor outcomes in patients with viral pneumonia, however, data on its role in the mortality of patients with COVID-19 is limited [2]. Although bacterial co-infections were rarely observed, representing 8.5% - 12% of cases [3] [4] [5], there remains a need to monitor hospitalized patients particularly following steroid use and other COVID-19 treatments. The use of a combination of antiviral and immunosuppressants to reverse the activation of the dysregulated immune system raises susceptibility to secondary infections [6] [7].

International guidelines recommend the initiation of antibiotic therapy for possible bacterial pneumonia in critical COVID-19 and suggest a rapid reassessment upon source documentation [8] [9]. The suspicion of concomitant bacterial pneumonia and the evidence of superinfection may become a reason behind this extensive use of antibiotics in COVID-19 [3] [4]. Several risk factors for secondary infection consist of the need for early care <48 hours after admission to the ICU, respiratory failure, severe lymphopenia [9].

The most common secondary infections were catheter-associated infections with coagulase-negative staphylococci (7.9%), lower respiratory tract infections by gram-negative nosocomial bacteria, and aspergillosis [6]. In addition, Sharifipour *et al.* reported superinfection of the lower respiratory tract in COVID-19 patients by *A. baumannii* and *S. aureus* which are resistant to extended-spectrum antibiotics and even to all classes of antibiotics [9]. This finding certainly invites all of our concerns because infections often go unresolved and cause death. The COVID-19 pandemic has the potential to drive an increase in the use of antibiotics when antimicrobial resistance is an increasing threat to global health.

Antibiotic Analysis in Hospital

The increasing use of antibiotics in the COVID pandemic has been described in hospital settings worldwide [10] [11]. High proportion of unnecessary or inappropriate prescriptions antibiotics are considered to be a pivotal force in the emergence of bacterial resistance [12].

Hospital antimicrobial usage evaluations were carried out by quantitative and qualitative analysis. Quantitative and qualitative analysis can be implemented accurately by patient-level surveillance. It includes a collection of data regarding the dose, dosage interval and duration of therapy. Meanwhile, other patient-specific data for qualitative analysis can be collected at the same surveillance, such as demographics, underlying disease states, pathogens documented and outcomes of antibiotic use. The appropriateness of antibiotic therapy was assessed by applying Gyssens flowchart to every patient [13].

Another method of surveillance is population-level surveillance. This method refers to the collection of antibiotic use data from the entire ward or hospital. Antibiotic dispensing data are readily from pharmacy computers. However, this surveillance requires Pharmacies to make appropriate administrative corrections for returns, disposals because of expiry, or exchanges among wards or third parties. Population-level surveillance is the only realistic alternative for ongoing and systematic monitoring of antibiotic use (MacKenzie FM, 2005).

We aim to analyse antibiotic prescribing and its impact on critical COVID-19 patients to document inappropriate use and its outcome as well as to determine the next step to take in the antimicrobial stewardship program.

2. Methods

2.1. Patients and Methods

The study is a single-center retrospective analysis of severe COVID-19 admitted to intensive care. Patients involved were those who were discharged from ICU Covid at dr Ramelan Navy Hospital (dr Ramelan Navy Hospital is a tertiary hospital with 700 beds and 49 ICU beds) from February 1st to June 30th, 2021.

2.2. Study Population and Participants

The inclusion criteria for this study were: 1) patients 18 years of age or older; 2) confirmed COVID-19 diagnosis, with procalcitonin number >1 ug/dl; 3) directly admit to ICU; 4) referral to ICU from other hospitals; 5) transfer from the ward, and 6) data on antibiotic use during hospitalization available. COVID-19 was confirmed by a positive real-time polymerase chain reaction (PCR) test of a nasopharyngeal exudate sample, sputum, or bronchoalveolar wash. The exclusion criteria were hospital readmissions. Secondary infections were judged from a clinical condition, CURB score, CPIS, thorax x-ray, and the presence of a positive culture of blood or sputum, and/or urine, Procalcitonin >1.0 ng/ml [14]. This study was approved by the Research Ethics Committee of dr. Ramelan Navy Hospital with certificate No: 43/EC/KEP/2021.

2.3. Statistical Analysis

Clinical data including age, gender, underlying disease history, patient demographics, hospital stay, results, and antibiotic regimen are collected. Categorical variables were expressed as absolute frequencies and percentages. Corrected *odds ratio* (OR), Kendal's Tau and 95% confidence intervals (CI) for all variables. Bilateral p-values below 0.05 were considered significant. Statistical analysis was performed using the SPSS version 25 software package (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

The other analysis carried out include Qualitative Analysis using the Gyssens

Scale [13] and Quantitative Analysis using DDD (Defined Daily Dose) calculations.

3. Results

3.1. Patient Characteristics

A total of 124 patients which were 77 males and 47 females had been included in the analysis. According to age, 94 patients were adults and 30 patients were elderly. Almost half of the patients that were 57 (46%) had an underlying disease such as hypertension, diabetes mellitus or both. The duration of ICU stay in average was 12.97 days. Patients in antibiotic side had 14.32 days and 9.47 days of Length of Stay (LOS). The patient's characteristics as shown in Table 1.

3.2. Antibiotic Use

Antibiotics were administered to 70.16% (n = 87) of the patients and 37 (29.84%) patients were not receiving antibiotics. There were 30 patients receiving single antibiotics, 57 and 19 of them were dead.

Qualitative analysis of antibiotic use revealed 43.55% (n = 81) of antibiotics prescribed appropriately, and 28.49% (n = 53) of antibiotics use without clear indications. Meanwhile, the quantitative analysis reported the use of levofloxacin was the highest 46.16 DDD, followed by meropenem 17.70 DDD and cefoperazone-sulbactam 16.87 DDD.

Table 1. Patient's characteristics.

Demography	Number
Female	47 patients
Male	77 patients
Adult	94 patients
Elderly	30 patients
ALOS	12.97 days
Total death	97 patients
Treated with Antibiotics	87 patients
Antibiotics	186 antibiotics
Comorbid on patients who had antibiotics	17 patients
Hypertension	17 patients
Diabetes Mellitus	13 patients
Hypertension & Diabetes Mellitus Others	10 patients

Note: ALOS = average length of stay in Hospital. how long a patient stays on average. This indicator not only shows how efficient something is, but it can also show how good the service is. When applied to certain diagnoses, it can be used as a sign that something needs more attention.

Levofloxacin was used singularly in 18 patients and combined with third-generation cephalosporin or meropenem in 14 patients. Levofloxacin use in 24 patients caused subsequent use of antibiotics and resulted in 23 patients' death, as listed in **Table 2**.

3.3. Outcome

Of 87 patients treated with antibiotics 71 patients died; meanwhile in the not-treated side there were 27 deaths. Out of 124 patients, there were 26 patients cured.

3.4. Microbiology Result

There were 80 positive cultures from the antibiotics side compared to 4 positive cultures on the no antibiotic side. Among them, 25 patients had positive blood culture in antibiotic treated side and 4 blood culture in non-antibiotic side. *Klebsiella pneumoniae* had been the most bacteria encountered in sputum and urine, 17.39% and 32.65% respectively. Meanwhile, in urine, 50% culture revealed *Escherichia coli*.

MDRO number reported every month by microbiologist showed an increasing trend during study period as shown in **Table 3**.

3.5. Statistical Analysis

To find out the association between mortality and the use of antibiotics, we conduct a regression analysis. The Odd Ratio OR was (3.21; 95% CI) indicating that cured in COVID-19 with secondary infection was affected 3.21 times by the use of antibiotics. To find out the further association between mortality and the use of appropriate antibiotics, we conduct a regression sub-analysis. The Odd Ratio (OR) was 0.39; with a confidence interval of less than 95%. It indicated that cured patients affected not significantly by 0.39 the use of appropriate antibiotics

We also analysed the relationship between numbers of antibiotics use with MDRO number by applying *Kendall's tau analysis* and found no significant corelation. The result as listed in **Table 4**.

4. Discussion

In the present study, we found high use of antibiotics, that is 70.16% (n = 87). This percentage is similar to what has been found in other cohorts [15] [16] and meta-analyses [3] [4]. The high number of patients who had positive cultures, justify why the number of patients treated with antibiotic is so high. In addition, difficulty to adjudicate on the presence of a co-infection in COVID-19 patients particularly in critically ill is well known. As a consequence, empirical antibiotic therapy is quasi-systematically initiated until pathogen documentation [16].

We conducted Odds ratio analysis between the use of antibiotics with the outcome and found a significant association that is 3.21 times patients with secondary infection being cured by antibiotics.

Table 2. Antibiotic use.

Antibiotic Used Parameter	Antibiotics Treated	No-Antibiotics
Number of patients	87 (70.16%)	37 (29.84%)
Death	71 (57.26%)	27 (21.77%)
ALOS	14.32 day	9.47 day
Single antibiotics:	30 (34.09%)	
Levofloxacin	18 (20.45%) Died14 (77.77%)	
Cefoperazone Sulbactam	9 (10.23%) Died 5 (55.55%)	
Cefotaxime	1	
Meropenem	1	
Ceftazidime	1	
Levofloxacin induces subsequent use of antibiotic	24 (27.27%) Died 23 (95.83%)	
Quantitative Analysis:		
Meropenem	17.70 DDD	
Cefo-Sulbactam	16.87DDD	
Ceftazidime	6.64 DDD	
Cefotaxime	0.41 DDD	
Ampi-Sulbactam	2.07 DDD	
Levofloxacin	46.16 DDD	
Moxifloxacin	1.58 DDD	
Amikacin	5.56 DDD	
Gentamicin	1.4 DDD	
Fluconazole	7.43 DDD	
Metronidazole	1.09 DDD	
Vancomycin	0.97 DDD	
Qualitative Analysis:		
Category 0	81 (43.55%)	
Category I	0	
Category II	0	
Category IIIA	2 (1.10%)	
Category IIIB	5 (2.69%)	
Category IVA	44 (23.65%)	
Category V	53 (28.49%)	
Category VI	1 (0.54%)	

Note: Cefo-Sulbactam = Cefotaxime-Sulbactam, Ampi-Sulbactam = Ampicillin-Sulbactam.

Table 3. Microbiology result.

Microbiology Parameter	Antibiotics Treated	No-Antibiotics
Bacteria on blood culture	25	4
Positive sputum culture	47	
Positive urine culture	8	
Klebsiella pneumoniae	21	-
Pseudomonas aeruginosa MDR	10	-
Bulkhorderia cepacia MDR	6	1
Acinetobacterbaumannii XDR	3	
E. coli	7	
MDRO isolated in entire ICU:		
February	10	
March	26	
April	8	
May	28	
June	43	

Note: MDR = multi drug resistance, XDR = extended drug resistance, MDRO = multi drug resistance organism.

Table 4. Statistical result.

Statistical Parameter		Value
Odds Ratio	Antibiotics treated vs. outcome	OR: 3.21 (p < 0.003)
Odds Ratio	Appropriate antibiotics vs. outcome	OR: 0.73 (p < 0.05)
Kendall's tau	Patients with antibiotics vs. number MDRO in ICU	τ: 0.200 (p > 0.05)

Note: τ = Kendall's tau.

The quantitative analysis indicates levofloxacin (46.16 DDD) followed by meropenem (17.70 DDD) being the most frequently used. Levofloxacin has been recommended in local or even international guidelines to treat suspected bacterial pneumonia in COVID-19 [8]. This recommendation drive to massive use of levofloxacin.

The qualitative analysis applying Gyssens [13] flowchart resulted in 43.55% of antibiotics being used appropriately and 55.91% of antibiotics being inappropriately prescribed consistent with larger number of studies [17]. The sub analysis between appropriate uses of antibiotics with the outcome revealed those appropriate antibiotics insignificantly will cure the secondary infection in COVID-19. This uncertain association with the use of appropriate antibiotics is consistent with other studies which found that concomitant bacterial infections were independently associated with increased inpatient mortality (OR: 5.838; 95% CI: 2.647 - 12.876) [17] [18]. Another possibility is the need to implement specific criteria for evaluation of antibiotic use in COVID-19 patients has previously been emphasized [19] [20].

Although the association of using antibiotics appropriately with the outcome is uncertain the impact of the overuse of antibiotic therapies on the spread of bacterial resistance is a matter of concern. This in turn which may be worse during the COVID-19 pandemic.

The mortality rate found in this study is higher compared to other world regions [21] [22]. However, the mortality is higher in patients receiving antibiotics (57% vs. 27%). Similarly, there was a significantly higher rate of inpatient mortality in patients who received antibiotics compared to those who did not (30% vs. 5%; $p < 0.0001$) [17]. The impact of these infections on mortality in patients with COVID-19 and its association with the use of antibiotics is still uncertain [18]. Several reasons are underlying high mortality incidence observed in this study. The first is approximately 35% of patients had positive blood cultures with nosocomial pathogen isolated. It indicates that the patient's conditions were severely co-infected on admission. The second reason is probably due to the increase in acquired resistance, because of pressure selection during the pandemic. International guidelines recommend the initiation of empirical antibiotics for possible associated bacterial pneumonia in COVID-19 critically ill [8]. The third reason is 46% of patients have comorbid which labelled them at high risk of death from COVID-19. Moreover, local and national management protocols advised physicians to prescribed levofloxacin or azithromycin empirically for pneumonia suspicion. This condition resulted in the high use of levofloxacin.

A closer look at levofloxacin as the most common antibiotic prescribed in this study shows that single use of levofloxacin therapy caused subsequent use of antibiotics. The mortality caused by levofloxacin failure was 95.83% (n = 23). Meanwhile, some patients died while on single levofloxacin 77.77% (n = 14). Those numbers indicating that levofloxacin has failed because of acquired resistance of the pathogen. Another reason why the mortality rate is high in this study is that bacterial coinfection in COVID-19 is associated with increased mortality as mention by other publications [16] [22] [23]. Some reports indicated that some COVID-19 patients were diagnosed with secondary infections with multidrug-resistant bacteria are among those microbes responsible for the development of these secondary infections [24] [25]. Further, Chen X pointed out that microbial coinfection is a non-negligible factor in COVID-19 and will exacerbate the processes of the occurrence, development, and prognosis of COVID-19, and the difficulties of clinical diagnosis and treatment. In addition, 65.5% of patients on antibiotics were admitted with comorbid that put them into high risk of death [26] [27].

The impact of antibiotics use on the ICU environment shows an increasing trend of multiple drug resistant organism (MDRO) number. It is well known that the spread of multidrug-resistant bacteria is closely related to antibiotic exposure [28] [29] [30].

Overuse of antibiotics and inappropriately prescribed antibiotics in COVID-19 patients can induce an increase in antibiotic resistance, which has already been noted by some authors [5] [31]. We analyze the correlation between the number of antibioticsuses with the number of MDRO applying Kendall's tau analysis. The result shows insignificant corelation. This finding is consistent with other reports [32]. The relationship between antibiotic use and antimicrobial resistance is complex. Rafael Canton *et al.* stated that various factors affect this relationship such as antibiotic exposure and mutant selection windows, antimicrobial pharmacodynamics, the nature of the resistance (natural or acquired, including mutational and that associated with horizontal gene transfer) and the definition of resistance [32]. The main recommendation is to restrict the use of antibiotics, when bacterial infections are documented, procalcitonin high, and severe clinical condition. It even recommends early suspension of the antibiotic courses that may have been started in the emergency department. It may be challenging to discern which patients warrant antibiotic prescription and in which patients antibiotic use may be inappropriate. Another possible action should be to improve appropriate antibiotic therapy, stewardship principles, both in ICU or patient-level settings.

Our research has a number of limitations. First, this is a retrospective, single-centre study of a navy hospital located at the heart of the COVID-19 pandemic in Surabaya City, East Java Province, Indonesia, and the data obtained are limited. Consequently, our findings may not be applicable to other institutions with distinct bacterial ecologies. Second, molecular diagnostic methods (e.g., PCR) were not available throughout the study period to detect atypical organisms such as fungal pathogens. Therefore, it is possible that we missed the identification of atypical secondary bacterial infections and other respiratory pathogenic illnesses that are often detected by PCR. Because our hospital lacks a mycology laboratory, it is impossible to precisely identify a fungal illness. Therefore, the incidence of fungal infections remains uncertain. Finally, there was no therapeutic option for the ground-glass opacity (GGO) pattern.

5. Conclusion

To conclude, high antibiotic use was 70.16% found in this study and 43.55% of antibiotics were prescribed appropriately. However, the association between appropriate use with the outcome is uncertain. Although the correlation was not significant, high antibiotic use causes an increase in MDRO spread in the entire ICU. Concomitant bacterial infections in critical COVID-19 were independently associated with increased inpatient mortality.

Future Research

Future research can be directed to create a new tool for qualitative analyzis of antibiotics usage in secondary bacterial infection. Despite this, new research on implementing a new strategy for AMR during the pandemic COVID will be beneficial.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Giacobbe, D.R., Battaglini, D., Enrile, E.M., Dentone, C., Vena, A., Robba, C., *et al*. (2021) Incidence and Prognosis of Ventilator-Associated Pneumonia in Critically Ill Patients with Covid-19: A Multicenter Study. *Journal of Clinical Medicine*, **10**, Article No. 555. https://doi.org/10.3390/jcm10040555

[2] Alqahtani, A., Alamer, E., Mir, M., Alasmari, A., Alshahrani, M. M., Asiri, M., *et al*. (2022) Bacterial Coinfections Increase Mortality of Severely Ill COVID-19 Patients in Saudi Arabia. *International Journal of Environmental Research and Public Health*, **19**, Article 2424. https://doi.org/10.3390/ijerph19042424

[3] Langford, B.J., So, M., Raybardhan, S., Leung, V., Westwood, D., MacFadden, D.R., Soucy, J.P.R. and Daneman, N. (2020) Bacterial Co-Infection and Secondary Infection in Patients with COVID-19: A Living Rapid Review and Meta-Analysis. *Clinical Microbiology and Infection*, **26**, 1622-1629. https://doi.org/10.1016/j.cmi.2020.07.016

[4] Clancy, C.J. and Nguyen, H. (2020) Coronavirus Disease 2019, Superinfections and Antimicrobial Development: What Can We Expect? *Clinical Infectious Diseases*, **71**, 2736-2743. https://doi.org/10.1093/cid/ciaa524

[5] Rawson, T.M., Ming, D., Ahmad, R., Moore, L.S.P. and Holmes, A.H. (2020) Antimicrobial Use, Drug-Resistant Infections and COVID-19. *Nature Reviews Microbiology*, **18**, 409-410. https://doi.org/10.1038/s41579-020-0395-y

[6] Siddiqi, H.K. and Mehra, M.R. (2020) COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. *Journal of Heart and Lung Transplantation*, **39**, 405-407. https://doi.org/10.1016/j.healun.2020.03.012

[7] Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S. and Manson, J.J. (2020) COVID-19: Consider Cytokine Storm Syndromes and Immunosuppression. *The Lancet*, **395**, 1033-1034. https://doi.org/10.1016/S0140-6736(20)30628-0

[8] Sharifipour, E., Shams, S., Esmkhani, M., Khodadadi, J., Fotouhi-Ardakani, R., Koohpaei, A., Doosti, Z. and Golzari, S.E. (2020) Evaluation of Bacterial Co-Infections of the Respiratory Tract in COVID-19 Patients Admitted to ICU. *BMC Infectious Diseases*, **20**, Article No. 646. https://doi.org/10.1186/s12879-020-05374-z

[9] Ripa, M., Galli, L., Poli, A., Oltolini, C., Spagnuolo, V., Mastrangelo, A., *et al*. (2021) Secondary Infections in Patients Hospitalized with COVID-19: Incidence and Predictive Factors. *Clinical Microbiology and Infection*, **27**, 451-457. https://doi.org/10.1016/j.cmi.2020.10.021

[10] Poston, J.T, Patel, B.K. and Davis, A.M. (2020) Management of Critically Ill Adults with COVID-19. *JAMA-Journal of the American Medical Association*, **323**, 1839-1841. https://doi.org/10.1001/jama.2020.4914

[11] Mustafa, L., Tolaj, I., Baftiu, N. and Fejza, H. (2021) Use of Antibiotics in COVID-19 ICU Patients. *The Journal of Infection in Developing Countries*, **15**, 501-505. https://doi.org/10.3855/jidc.14404

[12] Malacarne, P., Rossi, C. and Bertolini, G. (2004) Antibiotic Usage in Intensive Care Units: A Pharmaco-Epidemiological Multicentre Study. *Journal of Antimicrobial Chemotherapy*, **54**, 221-224. https://doi.org/10.1093/jac/dkh299

[13] Gyssens, I. C., van den Broek, P. J., Kullberg, B.-J., Hekster, Y.A. and van der Meer,

J.W.M. (1992) Optimizing Antimicrobial Therapy. A Method for Antimicrobial Drug Use Evaluation. *Journal of Antimicrobial Chemotherapy*, **30**, 724-727. https://doi.org/10.1093/jac/30.5.724

[14] Kritsotakis, E.I. and Gikas, A. (2006) Surveillance of Antibiotic Use in Hospitals: Methods, Trends and Targets. *Clinical Microbiology and Infection*, **12**, 701-704. https://doi.org/10.1111/j.1469-0691.2006.01415.x

[15] Vaughn, V.M., Gandhi, T.N., Petty, L.A., Patel, P.K., Prescott, H.C., Malani, A.N., *et al*. (2021) 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*, **72**, e533-e541. https://doi.org/10.1093/cid/ciaa1239

[16] Verroken, A., Scohy, A., Gérard, L., Wittebole, X., Collienne, C. and Laterre, P.F. (2020) Co-Infections in COVID-19 Critically Ill and Antibiotic Management: A Prospective Cohort Analysis. *Critical Care*, **24**, Article No. 410. https://doi.org/10.1186/s13054-020-03135-7

[17] Garcia-Vidal, C., Sanjuan, G., Moreno-García, E., Puerta-Alcalde, P., Garcia-Pouton, N., Chumbita, M., *et al*. (2021) Incidence of Co-Infections and Superinfections in Hospitalized Patients with COVID-19: A Retrospective Cohort Study. *Clinical Microbiology and Infection*, **27**, 83-88. https://doi.org/10.1016/j.cmi.2020.07.041

[18] Calderón-Parra, J., Muiño-Miguez, A., Bendala-Estrada, A.D., Ramos-Martínez, A., Muñez-Rubio, E., Carracedo, E.F., *et al*. (2021) Inappropriate Antibiotic Use in the COVID-19 Era: Factors Associated with Inappropriate Prescribing and Secondary Complications. Analysis of the Registry SEMI-COVID. *PLOS ONE*, **16**, e0251340. https://doi.org/10.1371/journal.pone.0251340

[19] Goncalves Mendes Neto, A., Lo, K.B., Wattoo, A., Salacup, G., Pelayo, J., DeJoy, R., *et al*. (2021) Bacterial Infections and Patterns of Antibiotic Use in Patients with COVID-19. *Journal of Medical Virology*, **93**, 1489-1495. https://doi.org/10.1002/jmv.26441

[20] Copaja-Corzo, C., Hueda-Zavaleta, M., Benites-Zapata, V.A. and Rodriguez-Morales, A.J. (2021) Antibiotic Use and Fatal Outcomes among Critically Ill Patients with Covid-19 in Tacna, Peru. *Antibiotics*, **10**, Article No. 959. https://doi.org/10.3390/antibiotics10080959

[21] Huttner, B.D., Catho, G., Pano-Pardo, J.R., Pulcini, C. and Schouten, J. (2020) COVID-19: Don't Neglect Antimicrobial Stewardship Principles! *Clinical Microbiology and Infection*, **26**, 808-810. https://doi.org/10.1016/j.cmi.2020.04.024

[22] Metlay, J.P. and Waterer, G.W. (2020) Treatment of Community-Acquired Pneumonia during the Coronavirus Disease 2019 (COVID-19) Pandemic. *Annals of Internal Medicine*, **173**, 304-305. https://doi.org/10.7326/M20-2189

[23] Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., *et al*. (2020) Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA-Journal of the American Medical Association*, **323**, 1574-1581. https://doi.org/10.1001/jama.2020.5394

[24] Gupta, S., Hayek, S.S., Wang, W., Chan, L., Mathews, K.S., Melamed, M.L., *et al*. (2020) Factors Associated with Death in Critically Ill Patients with Coronavirus Disease 2019 in the US. *JAMA Internal Medicine*, **180**, 1436-1447. https://doi.org/10.1001/jamainternmed.2020.3596

[25] Silva, D.L., Lima, C.M., Magalhães, V.C.R., Baltazar, L.M., Peres, N.T.A., Caligiorne, R.B., *et al*. (2021) Fungal and Bacterial Coinfections Increase Mortality of Severely Ill COVID-19 Patients. *Journal of Hospital Infection*, **113**, 145-154.

https://doi.org/10.1016/j.jhin.2021.04.001

[26] Bardi, T., Pintado, V., Gomez-Rojo, M., Escudero-Sanchez, R., Azzam Lopez, A., Diez-Remesal, Y., *et al*. (2021) Nosocomial Infections Associated to COVID-19 in the Intensive Care Unit: Clinical Characteristics and Outcome. *European Journal of Clinical Microbiology & Infectious Diseases*, **40**, 495-502. https://doi.org/10.1007/s10096-020-04142-w

[27] Musuuza, J.S., Watson, L., Parmasad, V., Putman-Buehler, N., Christensen, L. and Safdar, N. (2021) Prevalence and Outcomes of Co-Infection and Superinfection with SARS-CoV-2 and Other Pathogens: A Systematic Review and Meta-Analysis. *PLOS ONE*, **16**, e0251170. https://doi.org/10.1371/journal.pone.0251170

[28] Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., *et al*. (2020) Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. *The Lancet*, **395**, 1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3

[29] Kun'ain, U.I.A., Rahardjo, S.S. and Tamtomo, G. (2020) Meta-Analysis: The Effect of Diabetes Mellitus Comorbidity on the Risk of Death in Covid-19 Patients. *Indonesian Journal of Medicine*, **5**, 368-377. https://doi.org/10.26911/theijmed.2020.05.04.12.

[30] Chen, X., Liao, B., Cheng, L., Peng, X., Xu, X., Li, Y., *et al*. (2020) The Microbial Coinfection in COVID-19. *Applied Microbiology and Biotechnology*, **104**, 7777-7785. https://doi.org/10.1007/s00253-020-10814-6

[31] Rawson, T.M., Moore, L.S.P., Zhu, N., Ranganathan, N., Skolimowska, K., Gilchrist, M., Satta, G., Cooke, G. and Holmes, A. (2020) Bacterial and Fungal Coinfection in Individuals with Coronavirus: A Rapid Review to Support COVID-19 Antimicrobial Prescribing. *Clinical Infectious Diseases*, **71**, 2459-2468. https://doi.org/10.1093/cid/ciaa530

[32] Lynch, C., Mahida, N. and Gray, J. (2020) Antimicrobial Stewardship: A COVID Casualty? *Journal of Hospital Infection*, **106**, 401-403. https://doi.org/10.1016/j.jhin.2020.10.002