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Original Article

Internal Medicine Section

Factors Influencing the Prescription of Antibacterial Drugs in COVID-19 Patients: An Antibacterial Surveillance Study

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ABSTRACT

Introduction: The empiric use of antibiotics in Coronavirus Disease-2019 (COVID-19) infection is not routinely recommended unless a secondary bacterial infection is suspected or confirmed. However, there have been reports of widespread antibiotic use in COVID-19 patients, despite a low rate of secondary bacterial co-infection. Therefore, this study aims to understand the factors influencing the empirical prescription of antibacterial drugs in Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) confirmed COVID-19 patients in Indian settings, as the available data is sparse and conflicting.

Aim: To determine the factors associated with antibacterial prescription in patients with proven COVID-19 infection at a tertiary care hospital.

Materials and Methods: An antibacterial surveillance study was conducted at Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. The study duration was two months, from September 2020 to October 2020. The study included COVID-19 patients admitted to critical and non-critical COVID-19 Care Units. Patient data, including demographics, general and systemic examination details, biochemistry, pathological and microbiological reports, and treatment details, were collected using a specially designed form. Patients who were prescribed antibacterial drugs (other than repurposed antibacterial drugs for COVID-19 treatment) were considered as cases, while the rest were classified as controls. The Hazard Ratio (HR) for factors associated with antibacterial prescription was estimated using Cox regression analysis with the Statistical Package for Social Sciences (SPSS) version 20.0.

Results: The study included 200 patients, of whom 45 (22.5%) received antibacterial drugs and were classified as cases, while the remaining 155 (77.5%) received antibacterial drugs and were classified as controls. The median age of cases and controls was 59 and 46 years, respectively. Cox regression analysis showed that procalcitonin >1 ng/mL (HR: 1.074, 95% Confidence Interval [CI]: 1.009-1.142, p-value=0.02) and admission to the critical care unit were independent predictors of antibacterial prescription. Additionally, high-dose steroid use (>120 mg/day of Methylprednisolone [MPS]) was associated with a 20% higher risk of antibacterial prescription, although the values were statistically non-significant (HR: 1.203, 95% CI: 0.503-2.879, p=0.678).

Conclusion: Admission to critical care units and procalcitonin levels >1 ng/mL were identified as independent predictors of antibacterial prescription in COVID-19 patients. Compliance with hospital-based standard treatment guidelines promotes the rational use of antibacterial drugs.

Keywords: Antibiotic prescription, Antimicrobial stewardship, Antimicrobial resistance, Coronavirus disease-2019, Methylprednisolone, Procalcitonin, Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

COVID-19 is a viral infection caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and there is a limited role for antibiotics in its management, unless a secondary bacterial infection is confirmed or suspected. However, during the early phase of the pandemic, widespread use of antibiotics for the management of COVID-19 was reported, despite the low rate of secondary bacterial infection or co-infection in RT-PCR confirmed COVID-19 patients (2%-8%) [1,2]. This suggests a discrepancy between antibiotic prescribing and the rate of bacterial co-infection. In the past, infections with the influenza virus were known to alter the respiratory environment and increase susceptibility to bacterial infections [3]. However, current evidence does not indicate that SARS-CoV-2 promotes secondary bacterial infections [4]. Antibiotics must be used judiciously to avoid the growing threat of nosocomial infections in patients with COVID-19 and other viral infections.

According to the interim guidance for clinical management of COVID-19 released in May 2020 by the World Health Organisation (WHO), the empiric use of antibiotics in patients with mild and moderate COVID-19 disease is not recommended unless there is clinical suspicion of bacterial infection, as it can contribute to increased rates of antimicrobial resistance [5]. However, the guideline does recommend empiric use of antimicrobials to treat all likely pathogens in COVID-19 patients admitted to critical care units with suspected bacterial infections, after obtaining samples for culture susceptibility testing. The Antimicrobial Stewardship Programme (AMSP) is a program that promotes the rational use of antimicrobials. The goal of the AMSP is to optimise clinical and healthcare outcomes while minimising the unintended consequences of antimicrobial use. The AMSP helps ensure that antibiotics are appropriately used for the correct patient, at the correct dose, and for the correct duration [6,7].

The primary objective of this antibacterial surveillance study was to determine the factors associated with antibacterial prescription in patients with proven COVID-19 infection. The secondary objective was to estimate the rate of antibacterial prescription and the rate of microbiologically confirmed bacterial co-infection in patients with RT-PCR confirmed COVID-19 infection admitted to COVID care units.

MATERIALS AND METHODS

An antibacterial surveillance study was conducted at Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. The study duration was two months, from September 2020 to October 2020. The study was conducted under the Indian Council of Medical Research (ICMR) sponsored Antimicrobial Stewardship

Programme (AMSP), which was approved by the Institutional Ethics Committee (EC/NIMS/2426/2020 dated-09/06/2020).

Inclusion criteria: The study included RT-PCR confirmed COVID-19 patients aged 18 years and above, of either gender.

Exclusion criteria: Patients with pre-existing antibacterial prescriptions at the time of admission into COVID Care Units were excluded from the study.

Study Procedure

Data was collected from the patients' case sheets using a specially designed case record form. This included demographic details, clinical history and examination details, data from biochemical, pathological, and microbiological reports, as well as, treatment details, including prescribed antibacterial drugs. Data was collected on a daily basis for the entire duration of hospitalisation from patients admitted to COVID care units at the hospital. Routine investigations ordered by treating clinicians for all COVID-19 patients included Complete Blood Count (CBC) with Differential Cell Count (DLC), complete urine examination, Liver Function Test (LFT), renal function tests, random blood sugar, C-reactive Protein (CRP), serum ferritin, lactate dehydrogenase, procalcitonin, and D-dimer. Chest X-ray and, if required, High-resolution Computed Tomography (HRCT) chest were also performed.

Out of the total patients, 45 (22.5%) were prescribed antibacterial drugs and were considered as cases, while 155 (77.5%) received antibacterial drugs and were classified as controls. The repurposed antiviral drugs recommended by the National COVID-19 guideline [8], including azithromycin, hydroxychloroquine, and doxycycline [9,10], were not classified as antibacterial drugs for the purpose of this study. Patients who were not prescribed antibacterial drugs were classified as controls. The primary outcome measures were: (i) Association of admission to critical care units, fever, steroid use, DM, CRP>12 mg/100 mL, procalcitonin >1 ng/mL with antibacterial prescription. The secondary outcomes were: (ii) Percentage of patients with antibacterial prescription as per WHO AWaRe (Access, Watch, Reserve) [10] criteria; (iii) Percentage of patients with microbiologically confirmed bacterial infection.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarise the data as proportions for categorical variables. The outcome measures were compared for association with cases using Fisher's exact test for categorical variables. The HR associated with different factors and antibacterial prescription was estimated by Cox regression analysis using SPSS version 20.0. A p-value of <0.05 was considered statistically significant.

RESULTS

Data was collected from 205 patients using purposive sampling. Out of these, 200 patients were included, while the remaining five patients were excluded as they were already on antibiotics upon admission. Among the enrolled patients, 45 (22.5%) were prescribed antibacterial drugs and considered as cases, while the control group included 155 (77.5%) patients.

Risk factors for antibacterial use were analysed using Fisher's exact test. Factors such as older age (>61 years), admission to critical care units, Diabetes Mellitus (DM), co-morbidities, procalcitonin level >1 ng/mL, Total Leucocyte Count (TLC) >11000 cells/mm^3, CRP level >12 mg/1000 mL, steroid use (MPS >120 mg/day), oxygen requirement, and invasive ventilation requirement were found to be significantly associated with cases. The demographic and clinical characteristics of cases and controls are shown in [Table/Fig-1].

COX regression analysis was conducted to determine the likelihood of association between six factors (steroid use MPS >120 mg, procalcitonin >1 ng/mL, CRP >12 mg/dL, DM, fever, and critical care) and empirical antibacterial drug prescription. The results,

Parameters	Cases n=45 n (%)	Controls n=155 n (%)#	p-value
Age (in years)			
18-30	5 (11.1)	40 (25.8)	0.04
31-45	4 (8.9)	34 (21.9)	0.05
46-60	17 (37.7)	60 (38.7)	0.73
>61	19 (42.2)	21 (13.5)	0.0001
Gender			
Females	14 (31.2)	71 (45.8)	0.081
Males	31 (68.8)	84 (54.2)	
Non critical units	8 (17.8)	126 (81.3)	0.001
Critical units	37(82.2)	29 (18.7)	
Presented with fever	34 (75.5)	97 (62.6)	0.113
Co-morbidities#	35 (77.8)	73 (47.1)	0.003
DM	21 (46.7)	36 (23.2)	0.004
Long term immunosuppressants	2 (4.4)	9 (5.80)	1.000
Procalcitonin >1 ng/mL	8 (17.8)	4 (2.6)	0.009
TLC >11,000/µL	19 (42.2)	9 (5.8)	0.009
CRP >12 mg/dL	28 (62.2)	22 (14.2)	0.001
Steroid (MPS >120 mg/day)	20 (44.4)	19 (12.3)	0.001
Invasive ventilation	14 (31.1)	1 (0.6)	0.001

[Table/Fig-1]: Characteristic of the study population. (n=200, Fisher's-exact test).
*-Percentages for each parameter in the cases group is calculated with total number of cases (45) as denominator
#-Percentages for each parameter in the control group is calculated with total number of controls (155) as denominator, TLC: Total leucocyte count; CRP: C-reactive protein; MPS: Methylprednisolone

presented in [Table/Fig-2], identified admission to critical care as a significant independent predictor, increasing the likelihood of antibacterial prescription by five times. Procalcitonin >1 ng/mL also significantly increased the likelihood by 7%. Although, high-dose steroid prescription (>120 mg/day of MPS) was associated with a 20% higher risk of antibacterial prescription (HR: 1.203, 95% CI, 0.503-2.879, p=0.678), this was not statistically significant. Fever, elevated CRP, and DM were not associated with antibacterial prescription in the present cohort of patients.

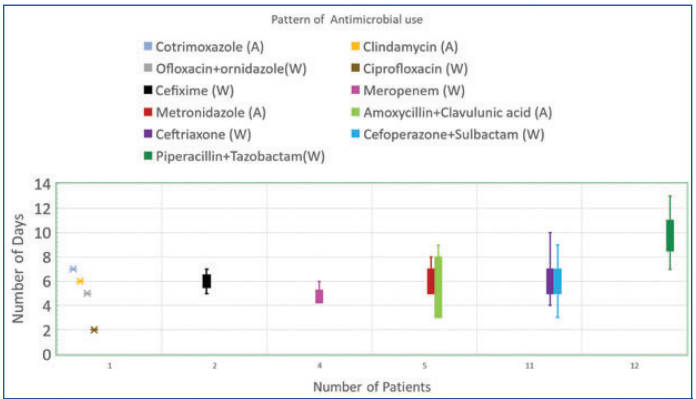
Variables	Hazard ratio	95% CI	p-value
Steroid (MPS >120 mg/day)	1.203	0.503-2.879	0.678
Procalcitonin >1 ng/mL	1.074	1.009-1.142	0.02
CRP >12 mg/dL	1.011	0.996-1.027	0.148
DM	1.090	0.523-2.273	0.818
Fever	1.064	0.485-2.335	0.876
Critical care	5.771	2.373-14.035	0.001

[Table/Fig-2]: Predictors of antibacterial use using COX regression.
*Methylprednisolone, MPS: Methylprednisolone; CRP: C-reactive protein; CI: Confidence interval

The overall rate of antibacterial prescription was 22.5% (45/200 patients) for empirical use. Nine patients were started on a combination of two antibacterial drugs, while 36 patients were prescribed a single antibacterial drug empirically. The pattern of empirical antimicrobial therapy is presented in a box and whisker plot in [Table/Fig-3], where the Y-axis represents the number of days of antibiotic.

use and the X-axis represents the number of patients prescribed each antibiotic. Furthermore, the choice of antibiotics used empirically belonged to the 'Access and Watch' group of the WHO AWaRe classification. No drugs from the 'Reserve' group were used empirically. Among the cases, appropriate cultures were sent for 21/45 (46%) patients, with 10/21 (48%) cultures yielding positive results. Antibiotic therapy was reviewed and rationalised in 7/10 (70%) patients with positive cultures.

The rate of confirmed bacterial co-infection was 10 (5%). Out of the 10 isolated bacteria, seven were gram-negative and three



[Table/Fig-3]: Pattern of empirical antimicrobial use.

were gram-positive bacteria. Among the gram-negative isolates, four were Klebsiella pneumoniae (K. pneumoniae), one was Escherichia coli (E. coli), and two were Acinetobacter baumanii (A. baumanii). Carbapenem resistance was found in three isolates of K. pneumoniae and one isolate of A. baumanii, while extended-spectrum β-lactamase resistance was seen in one isolate each of K. pneumoniae, E. coli, and A. baumanii. In patients with carbapenem-resistant isolates, injection colistin was started in combination with injection meropenem. For patients with ESBL-producing organisms, antibiotic therapy was changed to injection meropenem. Among the gram-positive bacteria isolated, two were Enterococcus faecium and were sensitive to vancomycin and linezolid, while the remaining one was methicillin-resistant Staphylococcus haemolyticus. Injection linezolid, belonging to the reserve group as per WHO AWaRe, was started in all three patients.

DISCUSSION

The present prospective study has demonstrated that admission to critical care units and procalcitonin >1 ng/mL were independent factors that increased the likelihood of empiric antibiotic prescription in RT-PCR proven COVID-19 patients. The rate of antibacterial use was found to be 22.5%, and the antibiotics used belonged to the 'Access' and 'Watch' group of the WHO AWaRe classification. The rate of confirmed bacterial infection was 5% in the present cohort of patients.

For COX regression analysis, the authors selected six factors based on previous literature that showed an association with antibacterial prescription in COVID-19 patients. These factors included age, invasive ventilation, co-morbidity, severity of COVID-19, Intensive Care Unit (ICU) admission, corticosteroid use, and procalcitonin use. Age, Invasive ventilation were not included as separate factors as it was observed majority of the patients admitted in critical care were elderly, with severe disease and only patients who were admitted in critical care were administered invasive ventilation. Co-morbidities, apart from DM, were not included in the analysis due to the small number of cases for each individual co-morbidity.

A cross-sectional study on the Malaysian population found that the severe stage of COVID-19, elevated inflammatory blood parameters (neutrophils, lymphocytes, and CRP), corticosteroid use, and ICU/High Dependency Unit (HDU) admission were associated with higher odds of antibiotic use [11]. A study from Bangladesh in COVID-19 dedicated wards showed that severe COVID-19 and DM were associated with higher odds of antibacterial prescription [12]. A retrospective study in the Indian population found that disease severity and CRP were significantly associated with antimicrobial prescription in COVID-19 patients. Although age >60 years was associated with antimicrobial prescription on univariate analysis, it was no longer significant on multivariable analysis [13]. These results align with the findings of the present study regarding admission to critical care units and high corticosteroid use. However, in the present study, the likelihood of empiric antibiotic prescription was not associated with DM or elevated CRP.

Among the cohort of patients in this study, a majority of those prescribed antibacterial drugs were elderly (>60 years) (42.2%), compared to 3.5% in the control group. This can be explained by a large meta-analysis that found older age (>60 years) to be associated with a higher risk of severe COVID-19 disease and a greater need for intensive care.

The present study's results were also in line with WHO guidelines, which recommend the use of empiric antibiotics in severe COVID-19 infection based on clinical judgment, patient host factors, and local epidemiology [14].

The rate of empiric antibacterial prescription in this study was only 22.5%, compared to national and international statistics ranging from 57% to 95% [1,2]. The majority of empiric antibacterial drugs prescribed in this study were from the 'Watch' group, guided by the previous six months' antibiogram of the hospital's ICU units, which justified their use. Furthermore, this prescription may be justified in the critical care setting, as these patients had suspected COVID-19-induced cytokine storm, were on immunosuppressives including tocilizumab and steroids, and had undergone invasive procedures. Antibacterial drugs from the 'Reserve' group were only used definitively in patients with confirmed in-vitro sensitivity reports. This rational pattern of antibacterial drug prescription can be attributed to compliance with the local hospital-based guideline for the treatment of COVID-19, released by the COVID-19 task force of the Institute, which was adapted from WHO and national COVID-19 guidelines and based on the principles of AMSP. The use of antibacterial drugs in severe COVID-19 infection is recommended as preliminary evidence shows that pneumonia causing fluid and pus-filled pulmonary alveoli create a conducive environment for bacteria such as Pseudomonas aeruginosa and Staphylococcus aureus. Additionally, cytokine storm in severe COVID-19 induces a proinflammatory response, which promotes immune dysregulation, tissue damage, and predisposition to bacterial co-infection [15].

The rate of confirmed bacterial infection in COVID-19 patients was found to be 5% in this study, while other studies have reported rates ranging from 5% to 27% in severe COVID-19 patients [1,16,17]. A multi-hospital cohort study in Michigan-based hospitals found the incidence of community-onset bacterial co-infection to be 3.5% (59/1705 patients) in those with confirmed COVID-19 infection [18]. Another retrospective study reported that the rate of secondary bacterial infections in critically ill COVID-19 patients was 68% [19]. The low rate of bacterial infection in this study may be attributed to the inclusion of COVID-19 patients across all spectrums of disease severity, as studies indicate that severe illness is a risk factor for secondary infection [15,17-18]. The majority of organisms isolated were carbapenem-resistant in four patients, followed by Extended-spectrum Beta-lactamase (ESBL) producing organisms in three patients, and vancomycin-sensitive Enterococcus faecium in two patients, and methicillin-resistant Staphylococcus haemolyticus in one patient, indicating that the majority of infections were hospital-acquired. A retrospective cohort study in critically ill COVID-19 patients found gram-negative bacilli to be the most frequent (82%), followed by gram-positive cocci (66%), and gram-negative cocci (24%) [19].

A study conducted in moderate to severe COVID-19 patients from India reported Klebsiella pneumoniae and Escherichia coli in four and two isolates, respectively, from nine urine culture positive reports, and one patient had Enterococcus in blood culture. This finding is consistent with the bacterial isolates found in the present cohort of patients [20]. The study further reported that patients with co-infections had higher mortality. Additionally, studies have reported that the median time to secondary infection in critically ill COVID-19 patients was 10-12 days, and the median time to death was 19 days, indicating that secondary infections leading to sepsis and septic shock may be an important cause of mortality in critically ill COVID-19 patients [21,22]. It is crucially important to identify

such patients and initiate empirical antibacterial therapy as early as possible, especially in the setting of sepsis due to bacterial co-infection in COVID-19 patients.

Distinguishing between exacerbation of viral pneumonia and secondary bacterial infection in a COVID-19 patient is difficult due to similar clinical presentation, radiological findings, and the absence of specific biological markers. Additionally, isolating bacteria is challenging in COVID-19 patients due to the scarcity of sputum production and the modest yield of sputum samples, which limits the ability to obtain satisfactory samples for bacterial identification and other microbiological studies [23]. Furthermore, the administration of exogenous steroids increases neutrophil count mainly through two mechanisms: glucocorticoids increase the migration of neutrophils from the bone marrow to the blood and increase their overall survival [24,25]. This steroid-induced neutrophilia creates a perplexing clinical picture, further complicating the decision regarding the initiation and discontinuation of antibiotics despite negative blood cultures. In such scenarios, procalcitonin may prove to be a useful marker for distinguishing between viral and bacterial pneumonia. Procalcitonin levels are usually expected to be low in viral infections since macrophages secrete interferon-γ, which inhibits the secretion of procalcitonin. However, in bacterial infections, procalcitonin is typically elevated, with higher values seen in systemic compared to localised infections and with more pathogenic organisms [26-28]. However, some studies have reported that elevated procalcitonin is associated with severe COVID-19, which is a hyperinflammatory state [29].

Thus, there is an urgent need to develop a rapid diagnostic test to differentiate between bacterial and viral infections. This would help maintain the balance between over-prescribing empirical antimicrobial prescriptions in mild to moderate viral illnesses and early initiation of antibacterial therapy in suspected bacterial sepsis during a viral illness. Such a test could guide AMSP practices in the future and play a role in preventing the unnecessary use of antibacterial drugs in patients with viral infections.

The present study was conducted during the first wave of COVID-19 in India, between September 2020 and October 2020. Only a few frontline workers with mild COVID-19 were admitted for isolation purposes. This allowed the authors to analyse the pattern of antibacterial prescription across the spectrum of disease severity, factors associated with empirical antibiotic use, the choice of empiric antibiotics, and the pattern of secondary bacterial infection.

Limitation(s)

The present study was a single-centre study, limiting the generalisability of the findings. The authors focused on assessing changes in process measures rather than outcomes such as microbial resistance levels and clinical outcomes.

CONCLUSION(S)

The present study has shown that admission to the ICU and procalcitonin levels were independent predictors of antibiotic prescription in COVID-19 patients. The rate of antibacterial use was found to be 22.5%, with antibiotics from the "Access and Watch" group of the WHO AWaRe classification being prescribed. The rate of confirmed bacterial infection in this cohort of patients was 5%. Compliance with hospital-based standard treatment guidelines promotes the rational use of antibacterials. Understanding patterns and predictors of antibacterial prescribing can help identify opportunities for interventions and target antimicrobial stewardship strategies to improve the rational use of antibacterials.

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Declaration: The study was carried out as part of ICMR-AMSP, in which the center was selected by the ICMR. Therefore, a grant number is not applicable. However, the authors have received fund sanction number AMR/139/2018-ECD-II.

REFERENCES

[1] Rawson TM, Moore LS, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020;71(9):2459-68. Doi: 10.1093/cid/ciaa530.

[2] Cong W, Poudel AN, Alhusein N, Wang H, Yao G, Lambert H. Antimicrobial use in COVID-19 patients in the first phase of the SARS-CoV-2 pandemic: A scoping review. Antibiotics (Basel). 2021;10(6):745. Available at: https://Doi.org/10.3390/antibiotics10060745.

[3] Rowe HM, Meliopoulos VA, Iverson A, Bomme P, Schultz-Cherry S, Rosch JW. Direct interactions with influenza promote bacterial adherence during respiratory infections. Nat Microbiol. 2019;4(8):1328-36. Doi: 10.1038/s41564-019-0447-0.

[4] Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: A systematic review and meta-analysis. J Infect. 2020;81(2):266-75. Doi: 10.1016/j.jinf.2020.05.046.

[5] World Health Organisation. (2020). Clinical management of COVID-19: Interim guidance, 27 May 2020 (Internet). Available from: https://apps.who.int/iris/handle/10665/332196.

[6] World Health Organisation. WHO report on surveillance of antibiotic consumption: 2016-2018 early implementation. Geneva: World Health Organization; 2018 (Internet). Available from: https://www.who.int/publications/i/item/who-report-on-surveillance-of-antibiotic-consumption.

[7] Indian Council of Medical Research. Antimicrobial Stewardship Programme Guideline 2017 (Internet). Available from: https://iamrsn.icmr.org.in/index.php/amsp/amsp-guidelines.

[8] Ministry of Health and Family welfare Government of India. Revised Guidelines on Clinical Management of COVID-19 [Internet]. Mar 2020. Available from: RevisedNationalClinicalManagementGuidelineforCOVID1931032020.pdf (mohfw.gov.in).

[9] Hussman JP. Cellular and molecular pathways of COVID-19 and potential points of therapeutic intervention. Front Pharmacol. 2020;11:1169. Doi: 10.3389/fphar.2020.01169.

[10] World Health Organisation. AWaRe Classification. 2019 (Internet). Available from: https://www.who.int/publications/i/item/2021-aware-classification.

[11] Mohamad IN, Wong CK, Chew CC, Leong EL, Lee BH, Moh CK, et al. The landscape of antibiotic usage among COVID-19 patients in the early phase of pandemic: A Malaysian national perspective. Journal of Pharmaceutical Policy and Practice. 2022;15(1):4. https://doi.org/10.1186/s40545-022-00404-4.

[12] Molla MM, Yeasmin M, Islam MK, Sharif MM, Amin MR, Nafisa T, et al. Antibiotic prescribing patterns at COVID-19 dedicated wards in bangladesh: Findings from a single center study. Infect Prev Pract. 2021;3(2):100134. Doi: 10.1016/j.infpip.2021.100134.

[13] Chindhalore CA, Dakhale GN, Gajbhiye SV, Gupta AV. Prescription pattern for antimicrobials and the potential predictors for antibiotics among patients with COVID-19: A retrospective observational study. J Clin Diag Res. 2022;16(9):FC15-FC19. Doi: 10.7860/JCDR/2022/56961.16874.

[14] Pijls BG, Jolani S, Atherley A, Derckx TR, Dijkstra JI, Franssen GH, et al. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: A meta-analysis of 59 studies. BMJ Open. 2021;11:e044640. Doi: 10.1136/bmjopen-2020-044640.

[15] Manohar P, Loh B, Nachimuthu R, Hua X, Welburn SC, Leptihn S. Secondary bacterial infections in patients with viral pneumonia. Front Med (Lausanne). 2020;7:420. Doi: 10.3389/fmed.2020.00420.

[16] Clancy CJ, Nguyen MH. COVID-19, Superinfections and antimicrobial development: What can we expect? Clin Infect Dis. 2020;71(10):2736-43. Doi: 10.1093/cid/ciaa524.

[17] Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, et al. Antibiotic prescribing in patients with COVID-19: Rapid review and meta-analysis. Clin Microbiol Infect. 2021;27(4):520-31. Doi: 10.1016/j.cmi.2020.12.018.

[18] Vaughn VM, Gandhi TN, Petty LA, Patel PK, Prescott HC, Malani AN, et al. Empiric antibacterial therapy and community-onset bacterial coinfection in patients hospitalised with Coronavirus Disease 2019 (COVID-19): A multi-hospital cohort study. Clin Infect Dis. 2021;72(10):e533-41. Doi: 10.1093/cid/ciaa1239.

[19] De Bruyn A, Verellen S, Bruckers L, Geebelen L, Callebaut I, De Pauw I, et al. Secondary infection in COVID-19 critically ill patients: A retrospective single-center evaluation. BMC Infect Dis. 2022;22(1):207. Doi: 10.1186/s12879-022-07192-x.

[20] Jalandra R, Babu A, Dutt N, Chauhan NK, Bhatia P, Nag VL, et al. Co-infections in hospitalised COVID-19 patients- A prospective observational study. Cureus. 2022;14(10):e30608. Doi: 10.7759/cureus.30608.

[21] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. Doi: 10.1016/S0140-6736(20)30183-5.

[22] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-62. Doi: 10.1016/S0140-6736(20)30566-3.

[23] Lucien MA, Canarie MF, Kilgore PE, Jean-Denis G, Fénélon N, Pierre M, et al. Antibiotics and antimicrobial resistance in the COVID-19 era: Perspective from resource-limited settings. Int J Infect Dis. 2021;104:250-54. Doi: 10.1016/j.ijid.2020.12.087.
[24] Cox G. Glucocorticoid treatment inhibits apoptosis in human neutrophils. Separation of survival and activation outcomes. J Immunol. 1995;154(9):4719-25.
[25] Liles WC, Dale DC, Klebanoff SJ. Glucocorticoids inhibit apoptosis of human neutrophils. Blood. 1995;86(8):3181-88.
[26] Schuetz P, Batschwaroff M, Dusemund F, Albrich W, Burgi U, Maurer M, et al. Effectiveness of a procalcitonin algorithm to guide antibiotic therapy in respiratory tract infections outside of study conditions: A post-study survey. Eur J Clin Microbiol Infect Dis. 2010;29(3):269-77. Doi: 10.1007/s10096-009-0851-0.
[27] Williams EJ, Mair L, de Silva TI, Green DJ, House P, Cawthron K, et al. Evaluation of procalcitonin as a contribution to antimicrobial stewardship in SARS-CoV-2 infection: A retrospective cohort study. J Hosp Infect. 2021;110:103-07. Doi: 10.1016/j.jhin.2021.01.006.
[28] Pink I, Raupach D, Fuge J, Vonberg RP, Hoeper MM, Welte T, et al. C-reactive protein and procalcitonin for antimicrobial stewardship in COVID-19. Infection. 2021;49(5):935-43. Doi: 10.1007/s15010-021-01615-8.
[29] Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta. 2020;505:190-91. Doi: 10.1016/j.cca.2020.03.004.

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