Research Article

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Initial Empirical Antibiotic Treatment in Covid-19 Patients is Related with Excess Adverse Drug Reactions Without Clinical Benefit

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ABSTRACT

Objectives: Empirical antibiotic use is common in hospitalized patients with COVID-19 pneumonia because it is difficult to differentiate it from concurrent bacterial pneumonia. In this study, we investigated risk factors for concurrent bacterial community-acquired pneumonia (b-CAP) and the need for initial empirical antibiotic coverage when patients presented with pulmonary involvement caused by SARS CoV-2.
Materials and Methods: This study was conducted as a prospective observational study in a tertiary university hospital between March 2020 and April 2021. Patients over 18 years of age who were hospitalized with COVID-19 pneumonia were included. Risk factors and outcomes were compared between the patients who received initial empirical antibiotics and those who did not.
Results: The presence of respiratory viral pathogens other than SARS CoV-2 was investigated via a respiratory panel multiplex polymerase chain reaction in 295 patients, and potential bacterial respiratory pathogens in 306 patients on admission to the hospital. Although the co-infection rate was low (17.4%), half of the patients (205/409, 50.1%) were administered initial empirical antibiotics for suspected concurrent b-CAP. Antibiotic use was higher in patients with multiple comorbidities, severe to critical pneumonia, and patients over

65 years (p<0.001). The overall 30-day mortality was significantly higher (26.3% and 2.0%, p<0.001), and the duration of hospital stay was longer (median 13.0 and 5.5 days, p<0.001) in patients who received empirical antibacterial agents.
Conclusions: Initial empirical antibiotic treatment is common in patients infected with SARS CoV-2, although the co-infection rate is low. Empirical antibiotic(s) did not improve the clinical course in COVID-19 patients.
Key words: COVID-19, antimicrobial, empirical therapy, co-infections, community-acquired pneumonia

INTRODUCTION

Differential diagnosis of bacterial co-infections may be challenging in severe to critical coronavirus diseases 2019 (COVID-19) patients on hospital admission because the clinical presentation of COVID-19 may mimic atypical bacterial pneumonia, and pulmonary consolidates develop later during the disease.[1] In addition, physicians overwhelmed by the pandemic conditions might tend to cover all potential causes of community-acquired pneumonia (CAP) and leave no button unturned.[2,3]

World Health Organization guidelines recommend empirical antibiotic therapy based on local epidemiology for bacterial pneumonia in patients with severe COVID-19, older patients and long-term nursing home residents,[4] but a few studies have shown that the rate of antibiotic usage is high despite low microbiological evidence. In most of these studies, empirical antibacterial treatment of suspected hospital-acquired and ventilator-associated pneumonia was investigated.[5,6] A meta-analysis emphasized that co-infection incidence was low (8%) at hospital admission, yet, empirical antibacterial therapy was started in 48.6% to 72% of these patients.[7] During the COVID-19 pandemic in Turkey, antibacterial drug sales decreased by 24.30% in 2020 compared to 2019, which was probably associated with the quarantine.[8] However, a study conducted on SARS CoV-2 infected patients in Turkey showed that 71.2% of the patients were prescribed inappropriate antibiotics.[9]

Antibiotic misuse/abuse is well known to have a negative impact, such as increased antimicrobial resistance and adverse events related to the medication.[10] Therefore, we aimed to determine the risk factors for concomitant bacterial CAP (b-CAP) and the need for initial empirical antibiotic coverage in SARS-Cov-2 infected patients.

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MATERIALS AND METHODS

This prospective, observational, and single-center study was conducted at Hacettepe University Adult Hospital between March 20, 2020, and April 15, 2021. This study was conducted in accordance with the Declaration of Helsinki and the study protocol was reviewed and approved by the Local Ethics Committee and the Ministry of Health (GO 22/520). All the participants of the cohort provided informed consent.

In our hospital, authorization to use carbapenems, ceftazidime, cefepime, piperacillin-tazobactam, polymyxins, quinolones (except oral forms), glycopeptide antibiotics (vancomycin and teicoplanin), daptomycin and linezolid as well as more than three days of treatment with the 3rd generation cephalosporins and intravenous form of fluoroquinolones require infectious diseases (ID) approval because of reimbursement rules by the Social Security Institution. There is a close collaboration between the Department of Infectious Diseases and other clinical departments in the management of patients with any suspected infection. The routine clinical practice includes daily clinical rounds of patients treated with an antimicrobial agent by an ID specialist, residents, and a clinical pharmacist during the antimicrobial treatment.

Data on patient characteristics, diagnostic and clinical parameters such as changes in oxygen requirement and fever, and antimicrobial therapies were collected. Patients were followed until discontinuation of an antimicrobial agent and/or discharge from the hospital and/or demise.

Patients

Patients over 18 years of age admitted to the hospital who tested positive for SARS-CoV2 polymerase chain reaction (PCR) were included. Those with negative PCR tests but diagnosed presumptively based on characteristic findings in chest computed tomography (CT) and/or positive anti-SARSCoV2 IgM antibody were also included in the analysis.[11,12] Chest imaging and respiratory panel multiplex PCR test (Seegene, South Korea[6]) were used to diagnose concurrent b-CAP (Supplement 1). Patients younger than 18 years of age, those with nosocomial pneumonia (pneumonia that developed 72 hours or more after hospital admission) or without pulmonary involvement, were excluded.

Definitions

The severity of COVID-19 disease was classified according to the World Health Organization-China Joint Mission definitions.[13] Patients with tachypnea, oxygen saturation ≤93% or PaO_2/FiO_2 ratio <300 mmHg, respiratory failure requiring mechanical ventilation, and septic shock was defined as severe to critical COVID-19 pneumonia. Patients with mild pneumonia were accepted as mild to moderate COVID-19 patients.

Fever was defined as a body temperature $\geq 38^0$C, whereas oxygen demand was determined as SaO_2 <90% and/or need for oxygen supplementation. Changes in fever pattern and oxygen demand were recorded. A leukocyte count less than 4.1 x 10^3/μL was defined as leukopenia, and greater than 11.2 x 10^3/μL was defined as leukocytosis. C-reactive protein (CRP) value greater than 0.8 mg/dl and a procalcitonin (PCT) value greater than 0.1 ng/ml were accepted as abnormal/high.

'The Kidney Disease: Improving Global Outcomes (KDIGO, 2013)' criteria were used to define drug-related nephrotoxicity. To summarize, nephrotoxicity was defined as an increase in serum creatinine (SCr) by ≥0.3 mg/dl within 48 h or an increase in SCr by ≥1.5 times the baseline within seven days after initiation of the antibacterial agent. According to KDIGO guidelines, an increase in SCr to 1.5-1.9 times the baseline or an increase in SCr of >0.3 mg/dl was considered 'Stage 1', and an increase in SCr to 2.0-2.9 times the baseline was considered 'Stage 2' and an increase in SCr to ≥3.0 times the baseline or >4.0 mg/dl or the initiation of renal replacement therapy was considered 'Stage 3'.[14] The Cancer Therapy Evaluation Program of the National Cancer Institute of the National Institutes of Health,

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accepted as Common Toxicity Criteria for Adverse Events, was used to determine drug-induced hepatotoxicity.[15] The Sanford Guide to Antimicrobial Therapy recommendations were used to determine the appropriateness of antimicrobial doses.[16] 'Drugs.com Drug Interactions Checker' (https://www.drugs.com/drug_interactions.html) database was used to detect potential drug-drug interactions (pDDIs) of antibacterial agents, and pDDIs were classified as 'minor', 'moderate' and 'major' interactions.

Statistics

Statistical analysis was performed on IBM SPSS Statistics 23 for patients given empirical antibiotic treatment for b-CAP within 72 hours (h) of admission and those who were not. In addition, SARS-CoV-2 PCR-positive patients were compared with those who tested negative but with highly suggestive CT findings or SARS-CoV2 IgM antibody positive. The Shapiro-Wilk goodness of fit test will test whether the distributions related to the numerical variables match the normal distribution. Descriptive statistics such as mean, standard deviation, minimum, and maximum were used for numerical variables that conform to normal distribution. Percentage values and frequency tables are given for categorical variables. Categorical variables were compared with the $\chi 2$ tests. Mann-Whitney U nonparametric test was used for comparing two independent groups. Univariable and multivariable logistic regression models were used to identify risk factors associated with antibiotic treatment. The logistic regression models included independent variables found to be significant predictors ($p<0.05$).

RESULTS

A total of 262 patients (262/409, 64.1%) with positive PCR for COVID-19 and 147 (147/409, 35.9%) PCR negative but diagnosed with COVID-19 infection according to the clinical and CT imaging findings were evaluated. The median age of the patients was 62 years (interquartile range, IQR: 48-75 years), and 58.7% were male. The most common comorbidity was hypertension, followed by diabetes mellitus and coronary artery disease (Table 1).

Four hundred and five patients received antiviral treatment in accordance with the recommendations of the Turkish Ministry of Health at the time of diagnosis: Favipiravir (76.8%, n=311), remdesivir (3.2%, n=13), and hydroxychloroquine (20%, n=81). Antiviral treatment was not prescribed in four patients due to severe liver failure. Oseltamivir was added in 14 (6.8%) patients empirically.

Pulmonary co-infection was detected in 71 (17.4%) patients. Among coinfecting agents, 83.1% (n=59) were bacteria and 16.9% (n=12) were respiratory viruses. The most common bacterial pathogen was *Haemophilus influenzae* (n=36, 60.0%) followed by *Streptococcus pneumoniae* (n=20, 33.3%) (Table 2). Urinary *Legionella* antigen was positive in one patient despite a negative respiratory multiplex PCR.

A total of 205 (50.1%) patients received initial empirical antibiotics for suspected b-CAP (Table 2). Antibacterial treatment with atypical coverage was given in 178 patients (86.8%). Chest CT did not suggest concurrent bacterial pneumonia in 66.8% (n=138) of these patients. Patients with high PCT and CRP values, leukocytosis, oxygen demand, and fever were more likely to receive initial empirical antibiotic therapy (Table 1). Corticosteroid use was also significantly more common in patients who received antibiotic treatment (61%, n=125) compared to those who did not (16.2%, n=33, $p<0.001$). Anti-inflammatory treatment was given to 3 patients due to cytokine storm (tocilizumab in 2 patients, pulse corticosteroid in one). All three also received empirical antibiotics at the time of admission to the hospital. Initial empirical antibiotic coverage was 5.338 (OR: 2.130-13.379) times more frequent in patients with chronic obstructive pulmonary disease (COPD), 4.457 (OR: 1.220-16.276) times with atrial fibrillation (AF), and 1.784 (OR: 1.060-3.004) times with diabetes mellitus. The pneumonia severity index (PSI) was higher in patients who received antibiotic treatment compared to those who did not [132 (range: 104.5-164.0) versus 54 (range:39.25-88.0);

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p<0.001]. However, discontinuation of oxygen supplementation, clinical improvement, and defervescence was similar who received antibiotics and those who did not (Table 3). 30-day mortality was much higher in patients who received initial antibiotics (26.3%) compared to those who did not (2.0%) (p<0.001). The mortality rate increased with older age (1.028-fold), severe to critical patients (3.411-fold), antibiotic therapy (5.726-fold) and nosocomial infection (3.557-fold) (Table 4).

Administration of antibiotics was comparable in SARS CoV-2 PCR positive (131/262, 50.0%) and negative patients (74/147, 50.3%) (p=0.947). In the severe to critical disease subgroup, empirical antibiotics were administered more frequently in patients with positive PCR than those with negative PCR (64.9% versus 59.5%, p<0.001). Corticosteroid usage (dexamethasone or methylprednisolone) was more frequent in the SARS-CoV-2 PCR-positive patients (43.1% versus 30.6%, p=0.013). Nosocomial infections were more common in the SARS-CoV-2 PCR-positive group compared to PCR-negative patients (29.0% versus 18.4%, respectively, p=0.017), and in those who received corticosteroids than those who did not (59.2% versus 40.8%, respectively, p<0.001). The median duration of antibiotic treatment did not differ in PCR positive and negative patients (p=0.999) (Table 2). Antibiotic treatment did not improve the clinical course in patients with positive SARS-CoV-2 PCR and negative results (data not shown).

Adverse events and pDDIs during follow-up

Acute kidney injury occurred in 11.2% of patients. Nephrotoxicity staging in patients was comparable between patients on and off antibiotics (p=0.247). Thirty-six patients who received antibiotic treatment experienced nephrotoxicity: 52.8% Stage 1, 36.1% Stage 2, and 11.1% Stage 3. Nephrotoxicity was significantly higher in patients with an antibiotic treatment than in antibiotic-free patients (18.0% versus 4.4%; p<0.001). Patients who received piperacillin-tazobactam experienced more nephrotoxicity than those treated with other antibiotics (31.3% versus 9.6%, p<0.001).

Elevated aminotransferase levels occurred in 60.9% (n=249) of the patients. Aspartate aminotransferase elevations were observed more frequently in patients receiving antibiotic treatment compared to antibiotic-free [58.0% (n=119) versus 46.6% (n=95), p=0.023]. However, alanine aminotransferase elevation was similar in patients who received or did not receive antibiotic(s) [52.7% (n=108) versus 46.6% (n=95), p=0.236].

Antibiotic-related pDDIs were detected in 77.1% of the patients treated with antibiotics: 30.7% minor, 68.3% moderate, and 15.1% major interactions (Supplement 2). The median number of pDDIs detected with antibiotics was 2 (1-3). The 30-day mortality was similar in patients with and without pDDIs (25.3% versus 29.8%, p =0.541) for antibiotic-related pDDIs.

DISCUSSION

Our results emphasize that initial empirical antibiotic treatment in COVID-19 patients is mostly unnecessary. We observed that empirical antibiotics did not make any difference in mortality regardless of the comorbidities and severity of pneumonia. In contrast, they led to drug-related problems such as nephrotoxicity and pDDIs. Although inflammatory markers improved, clinical parameters remained similar in patients receiving or not receiving antibiotics.

Several studies have reported an incidence of 2.0% to 17.2% bacterial co-infection rate in COVID-19 patients. However, antibiotic therapy was administered to 48.6% to 100% of patients.[2, 17-22] In our study (n=409) antibiotics were used in 50.1% of the COVID-19 patients for presumptive b-CAP. A cross-sectional study from our center found that respiratory bacterial co-infection was present in 26 (13.1%) of 198 outpatients with COVID-19 infection, and only 10.6% received.[23] This could be explained by the preference of the physician to administer antibiotics to the patient who needs to be hospitalized for pulmonary infection.

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Whether the patient was positive PCR for SARS-CoV-2 or diagnosed presumptively based on clinical and imaging findings did not affect the clinical decision making of the physicians to start antibiotics. Antibiotic treatment rate and antibiotic preference were similar in patients with positive and negative SARS-CoV-2 PCR (p=0.947). In a study by Beovic et al.,[24] clinical presentation was the most common indication for antibiotics in COVID-19 patients. It was also emphasized that laboratory markers and radiological evaluation were effective in the antibiotic therapy decision.[24] Similarly, in our study, antibiotic usage was related to supplemental oxygen therapy, fever, and elevated acute-phase reactants.

The role of inflammatory markers in determining the efficacy of antibiotic therapy is limited. In our study, a significant improvement was achieved in these parameters, but not in the clinical course. The use of anti-inflammatory agents (corticosteroids or tocilizumab) and the rate of concomitant nosocomial infection are confounding factors in determining the impact of antibiotic treatment on the serum levels of inflammatory markers alone. In our study, more patients who received empirical antibiotics were also treated with corticosteroids (61.0% versus 16.2%; p<0.001). This could explain the improvement in inflammatory markers observed in the antibiotic-treated group despite no clinical improvement.

Empirical antibacterial therapy may have unwanted consequences. Contrary to other studies[18, 19, 21], we found that the nosocomial infection rate was significantly higher in patients treated with antibiotics for CAP (39.0% versus 11.3%, respectively, p<0.001). In addition, hospital stay was longer in patients treated with antibiotics (p<0.001). This could also be related to a more severe initial clinical presentation, the presence of certain comorbidities such as COPD and diabetes mellitus known to have a negative effect on the hospital stay of COVID-19 patients, and more frequent use of corticosteroids in this patient population.

Pettit et al.[2] reported the mortality rate in COVID-19 patients receiving empirical antibiotic therapy for CAP was 13.8%.[2] A retrospective study by Ng et al.[25] on COVID-19 patients showed that mortality was higher in patients receiving antibiotic treatment (13.3% versus 0.5%, p<0.001). Furthermore, their study did not associate antibiotic therapy with lower mortality [adjusted odds ratio 14.492, (95% CI 0.533– 393.875)].[25] We found that initial empirical antibacterial treatment was an independent risk factor for increased mortality (Table 4).

Study Limitations

This is a single-center and observational study; thus, results may not be applicable to other centers. In some patients with positive CT imaging but negative PCR, the absence of antibody testing makes the definitive diagnosis for COVID-19 unclear. We did our best to rule out other viral/bacterial infections and non-infectious causes such as congestive heart failure leaving us with a COVID-19 diagnosis during the pandemic.

CONCLUSION

Attending physicians tend to prescribe antimicrobials to prevent adverse outcomes in high-risk COVID-19 patients, i.e. patients with older age, severe disease, comorbidities such as COPD, AF and diabetes mellitus, and high inflammatory markers, fever, and the necessity for oxygen supplementation even when there is no microbial evidence of co-infection. Irrational use of antibiotics may cause drug-related problems and negative effects by disrupting the gut microbiota in COVID-19 patients, including altered metabolic activity and increased antibiotic-resistant organisms. This study further provides evidence for antimicrobial stewardship efforts and recommends discontinuing empirical antibiotics, even not starting them.

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References

1. Sieswerda E, de Boer MGJ, Bonten MMJ, Boersma WG, Jonkers RE, Aleva RM, Kullberg BJ, Schouten JA, van de Garde EMW, Verheij TJ, van der Eerden MM, Prins JM, Wiersinga WJ. Recommendations for antibacterial therapy in adults with COVID-19 - an evidence based guideline. *Clin Microbiol Infect.* 2021;27(1): 61-6. doi:10.1016/j.cmi.2020.09.041
2. Pettit NN, Nguyen CT, Lew AK, Bhagat PH, Nelson A, Olson G, Ridgway JP, Pho MT, Pagkas-Bather J. Reducing the use of empiric antibiotic therapy in COVID-19 on hospital admission. *BMC Infect Dis.* 2021;21(1): 516. doi:10.1186/s12879-021-06219-z
3. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng OT, Marimuthu K, Ang LW, Mak TM, Lau SK, Anderson DE, Chan KS, Tan TY, Ng TY, Cui L, Said Z, Kurupatham L, Chen MI, Chan M, Vasoo S, Wang LF, Tan BH, Lin RTP, Lee VJM, Leo YS, Lye DC; Singapore 2019 Novel Coronavirus Outbreak Research Team. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA.* 2020;323(15): 1488-94. doi:10.1001/jama.2020.3204
4. World Health Organization (WHO) Living Guidance for Clinical Management of COVID-19: Living Guidance. Nov 23, 2021. [(accessed on 23 July 2022)]. Available online: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2
5. Evans TJ, Davidson HC, Low JM, Basarab M, Arnold A. Antibiotic usage and stewardship in patients with COVID-19: too much antibiotic in uncharted waters? *J Infect Prev.* 2021;22(3): 119-25. doi:10.1177/1757177420976813
6. Calik Basaran N, Uyaroglu OA, Telli Dizman G, Ozişik L, Sahin TK, Tas Z, Inkaya AC, Karahan S, Alp S, Alp A, Metan G, Zarakol P, Sain Guven G, Oz SG, Topeli A, Uzun O, Akova M, Unal S. Outcome of noncritical COVID-19 patients with early hospitalization and early antiviral treatment outside the ICU. *Turk J Med Sci.* 2021;51(2): 411-20. doi:10.3906/sag-2006-173

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7. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, Satta G, Cooke G, Holmes A. 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
8. İEİS - İlaç Endüstrisi İşverenler Sendikası - Temel Göstergeler / Türkiye İlaç Pazarı: - n.d. [(accessed on May 26, 2023)]. Available online: http://ieis.org.tr/ieis/tr/indicators/33/turkiye-ilac-pazari
9. Sencan I, Cag Y, Karabay O, Kurtaran B, Guclu E, Ogutlu A, Agalar C. Antibiotic use and influencing factors among hospitalized patients with COVID-19: a multicenter point-prevalence study from Turkey. Balkan Medical Journal. 2022; 39(3), 209. doi: 10.4274/balkanmedj.galenos.2022.2021-11-62
10. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf*. 2014;5(6): 229-41. doi:10.1177/2042098614554919
11. Kipritci Z, Keskin AU, Ciragil P, Topkaya AE. Evaluation of a Visually-Read Rapid Antigen Test Kit (SGA V-Chek) for detection of SARS-CoV-2 virus. *Mikrobiyol Bul.* 2021;55(3):461-4. doi:10.5578/mb.20219815
12. Beavis KG, Matushek SM, Abeleda APF, Bethel C, Hunt C, Gillen S, Moran A, Tesic V. Evaluation of the Euroimmun Anti-SARS-CoV-2 Elisa Assay for detection of IgA and IgG antibodies. *J Clin Virol.* 2020;129: 104468. doi:10.1016/j.jcv.2020.104468
13. Gomes C. Report of the WHO-China joint mission on Coronavirus Disease 2019 (COVID-19). *Brazilian Journal of Implantology and Health Sciences*. 2020;2(3).
14. Kellum JA, Lameire N, Group KAGW. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care.* 2013;17(1): 204. doi:10.1186/cc11454
15. LiverTox: Clinical and research information on drug-induced liver injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Severity grading in drug induced liver injury. May 4, 2019. [(accessed on 25 November 2023)]. Available online: https://www.ncbi.nlm.nih.gov/books/NBK548241/
16. Gilbert DN, Robert C, Moellering JMD, Eliopoulos GM, Sande MA. The Sanford guide to antimicrobial therapy: Antimicrobial therapy, Incorporated; 2011.

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17. Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020;180(7): 934-43. doi:10.1001/jamainternmed.2020.0994
18. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. 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
19. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223): 507-13. doi:10.1016/S0140-6736(20)30211-7
20. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with Coronavirus Disease 2019 in Wuhan, China. *Clin Infect Dis.* 2020;71(15): 769-77. doi:10.1093/cid/ciaa272
21. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. 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
22. Lehmann CJ, Pho MT, Pitrak D, Ridgway JP, Pettit NN. Community-acquired coinfection in Coronavirus Disease 2019: A retrospective observational experience. *Clin Infect Dis*. 2021;72(8): 1450-2. doi:10.1093/cid/ciaa902
23. Telli Dizman G, Metan G, Ayaz Ceylan CM, Altunay H, Uzun M, Gursoy G, Tas Z, Karahan G, Ahmadova F, Saricaoğlu T, Caliskan ZC, Alp A, Sonmezer MC, Inkaya AC, Er AG. A COVID-19 First evaluation clinic at a university hospital in Turkey. *Turk J Med Sci.* 2021;52(1): 1-10. doi:10.3906/sag-2104-152
24. Beovic B, Dousak M, Ferreira-Coimbra J, Nadrah F, Rubulotta M, Belliato M, Berger-Estilita J, Ayoade F, Rello J, Erdem H. Antibiotic use in patients with COVID-19: a 'snapshot' Infectious Diseases International Research Initiative (ID-

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IRI) survey. *J Antimicrob Chemother*. 2020; 75(11): 3386-90. doi:10.1093/jac/dkaa326

25. Ng TM, Ong SWX, Loo AYX, Tan SH, Tay HL, Yap MY, Lye DC, Lee TH, Young BE. Antibiotic therapy in the treatment of COVID-19 pneumonia: Who and When? *Antibiotics*. 2022;11(2): 184. doi:10.3390/antibiotics11020184

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Table 1. Demographic and clinical characteristics of patients with COVID-19 pneumonia

	Total (n=409)	**Receiving initial antibiotic therapy (n=205)**	**Not initial receiving antibiotic therapy (n=204)**	**p**
Age				
Age (years), median (IQR)	62 (48-75)	70 (57.5-80.0)	54 (40.50-67.0)	**<0.001**
>65 years, n (%)	184 (45.0)	126 (61.5)	58 (28.4)	**<0.001**
Sex, n (%)				
Male	240 (58.7)	134 (65.4)	106 (52.0)	**0.006**
Vaccination, n (%)				
Influenza vaccine	17 (4.2)	9 (4.4)	8 (3.9)	0.085
Pneumococcal vaccine	9 (2.2)	7 (3.4)	2 (0.98)	0.692
Comorbidities, n (%)				
Hypertension	166 (40.6)	103 (50.2)	63 (30.9)	**<0.001**
Diabetes mellitus	111 (27.1)	73 (35.6)	38 (18.6)	**<0.001**
Coronary artery disease	106 (25.9)	66 (32.2)	40 (19.6)	**0.004**
Malignancy	63 (15.4)	48 (23.4)	15 (7.4)	**<0.001**
Neurological disease	56 (13.7)	48 (23.4)	8 (3.9)	**<0.001**
Chronic obstructive pulmonary disease	44 (10.8)	38 (18.5)	6 (2.9)	**<0.001**
Congestive heart failure	37 (9.0)	29 (14.1)	8 (3.9)	**<0.001**
Benign prostatic hyperplasia	30 (7.3)	19 (9.3)	11 (5.4)	0.133
Chronic kidney disease	25 (6.1)	19 (9.3)	6 (2.9)	**0.008**
Asthma	25 (6.1)	8 (3.9)	17 (8.3)	0.061
Atrial fibrillation	23 (5.6)	20 (9.8)	3 (1.5)	**<0.001**
Rheumatological diseases	19 (4.6)	8 (3.9)	11 (5.4)	0.474

Liver failure	7 (1.7)	4 (2.0)	3 (1.5)	1.000
Presence of comorbidity	308 (75.3)	189 (92.2)	119 (58.3)	**<0.001**
Number of comorbidities**,** median (IQR)	2 (1-3)	3.0 (1.0-4.0)	1.0 (0.0-2.0)	**<0.001**
Severity of the disease for COVID-19, n (%)				
Severe to critical patient	168 (41.1)	129 (62.9)	39 (19.1)	**<0.001**
Mild to moderate patient	241 (58.9)	76 (37.1)	165 (80.8)	
Corticosteroid therapy, n (%)				
Yes	158 (38.6)	125 (61.0)	33 (16.2)	**<0.001**
No	251 (61.4)	80 (39.0)	171 (83.8)	
Presence of risk factors for CAP, n (%)				
Present of risk factors	239 (58.4)	167 (81.5)	72 (35.3)	**<0.001**
Number of patients monitored for biochemical markers, n (%)				
Procalcitonin	348 (85.1)	191 (93.2)	157 (77.0)	**<0.001**
C-reactive protein	383 (93.6)	195 (95.1)	188 (92.2)	0.219
Erythrocyte sedimentation rate	302 (73.8)	157 (76.6)	145 (71.1)	0.205
Development of nosocomial infections during hospitalization, n (%)				
Presence of nosocomial infections	103 (25.2)	80 (39.0)	23 (11.3)	**<0.001**
Hospital stays, [median (IQR)]				
Duration of hospital stay, day	9.0 (5.0-17.0)	13.0 (8.0-27.5)	5.5 (4.0-10.0)	**<0.001**
Criteria for evaluating the severity of the disease, [median (IQR)]				
CURB-65 score	2.0 (0.0-2.0)	2.0 (1.0-3.0)	0.0 (0.0-1.0)	**<0.001**
Pneumonia severity index	94 (51.0-139.0)	132 (104.5-164.0)	54 (39.25-88.0)	**<0.001**
Adverse events				
Acute kidney injury	46 (11.2)	37 (18.0)	9 (4.4)	**<0.001**
ALT elevation	203 (49.6)	108 (52.7)	95 (46.6)	0.236
AST elevation	214 (52.3)	119 (58.0)	95 (46.6)	**0.023**
Mortality, n (%)				
30-day mortality	58 (14.2)	54 (26.3)	4 (2.0)	**<0.001**
Mortality (in hospital)	79 (19.3)	70 (34.1)	9 (4.4)	**<0.001**

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, CAP: Community-acquired pneumonia, IQR: interquartile range

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Table 2. Initial empirical antibiotic treatment for CAP in patients with COVID-19 confirmed with a positive PCR for SARS CoV-2 and those with suggestive clinical and radiological findings

Parameters		**Total (n=409)**	**COVID-19 patients with positive PCR (n=262)**	**COVID-19 patients with suggestive CT imaging & negative PCR (n=147)**	**p value**
Antibiotic usage, n (%)					
Rate of antibiotic use		205 (50.1)	131 (50.0)	74 (50.3)	0.947
Coverage of atypical pathogens in treatment		178 (86.8)	112 (85.5)	66 (89.2)	0.453
Antibacterial treatment duration (day), median (IQR)		7 (6-10)	7.5 (6.0-10.0)	7 (6.75-10.0)	0.999
Antibiotic preference in the treatment of CAP, n (%)					
Cefuroxime		5 (2.4)	2 (1.5)	3 (4.1)	0.354
Ceftriaxone		73 (35.6)	48 (36.6)	25 (33.8)	0.682
Amoxicillin-clavulanic acid		10 (4.9)	5 (3.8)	5 (6.8)	0.501
Ampicillin-sulbactam		45 (22.0)	26 (19.8)	19 (25.7)	0.333
Piperacillin-tazobactam		81 (39.5)	50 (38.2)	31 (41.9)	0.600
Meropenem		51 (24.9)	37 (28.2)	14 (18.9)	0.138
Fluoroquinolones		9 (4.4)	5 (3.8)	4 (5.4)	0.725
Macrolides		23 (11.2)	15 (11.5)	8 (10.8)	0.889
Doxycycline		147 (71.7)	92 (70.2)	55 (74.3)	0.532
Respiratory Multiplex PCR at admission, n (%)					
Bacteria (n=295)		59 (20.0)	33 (18.0)	26 (23.2)	0.280
Detected pathogens (n=60)					
	H. influenzae	36 (60.0)	18 (52.9)	18 (69.2)	
	S. pneumoniae	20 (33.3)	14 (41.2)	6 (23.1)	
	Dual pathogen[†]	4 (6.7)	2 (5.9)	2 (7.7)	
Virus (n=306)		12 (3.9)	8 (4.2)	4 (3.5)	1.000
Deteceted viruses (n=12)					
	Human rhinovirus	3 (25.0)	1 (12.5)	2 (50.0)	
	Influenza A	2 (16.7)	2 (25.0)	0 (0.0)	
	Influenza B	2 (16.7)	1 (12.5)	1 (25.0)	
	Bocavirus	2 (16.7)	1 (12.5)	1 (25.0)	
	Adenovirus	2 (16.7)	2 (25.0)	0 (0.0)	
	Dual pathogen[‡]	1 (8.3)	1 (12.5)	0 (0.0)	
COVID-19 severity, n (%)					
Severe to critical		168 (41.1)	112 (42.7)	56 (38.1)	0.359
Mild to moderate		241 (58.9)	150 (57.3)	91 (61.9)	
Nosocomial infections during hospitalization, n (%)					
Presence of nosocomial infections		103 (25.2)	76 (29.0)	27 (18.4)	**0.017**
Mortality, n (%)					
30-day mortality		58 (14.2)	41 (15.6)	17 (11.6)	0.256
Mortality (in hospital)		79 (19.3)	58 (22.1)	21 (14.3)	0.054

CAP: Community-acquired pneumonia, IQR: interquartile range, PCR: Polymerase chain reaction,
[†]Dual pathogens in bacterial respiratory PCR: *H. influenzae* and *S. pneumoniae*,
[‡]Dual pathogens in viral respiratory PCR: *Human rhinovirus and Influenza B*

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Table 3. Antibiotic treatment & clinical, biochemical, and microbiological parameters

		Total	Receiving initial antibiotic therapy	Not intitial receiving antibiotic therapy	p value
Baseline inflammatory markers, n (%)					
Procalcitonin (n=397)	≥0.1 ng/ml	167 (42.1)	133 (65.5)	34 (17.5)	**<0.001**
	<0.1 ng/ml	230 (57.9)	70 (34.5)	160 (82.5)	
CRP (n=405)	≥0.8 mg/dl	345 (85.2)	197 (97.0)	148 (73.3)	**<0.001**
	<0.8 mg/dl	60 (14.8)	6 (3.0)	54 (26.7)	
Leukocyte count (n=409)	<4.1 x 10^3/μL	53 (13.0)	20 (9.8)	33 (16.2)	**<0.001**
	4.1-11.2 x 10^3/μL	269 (65.8)	114 (55.6)	155 (76.0)	
	>11.2 x 10^3/μL	87 (21.3)	71 (34.6)	16 (7.8)	
Inflammatory markers at antibiotic discontinuation, n (%)					
Procalcitonin (n=147)	No change	47 (32.0)	34 (28.3)	13 (48.1)	**0.046**
	Improved	100 (68.0)	86 (71.7)	14 (51.9)	
CRP (n=321)	No change	97 (30.2)	42 (22.8)	55 (40.1)	**0.001**
	Improved	224 (69.8)	142 (77.2)	82 (59.9)	
Leukocyte (n=136)	No change	61 (44.9)	36 (39.6)	25 (55.6)	0.078
	Improved	75 (55.1)	55 (60.4)	20 (44.4)	
Baseline clinical parameters, n (%)					
Oxygen saturation (n=409)	SaO_2 ≥90 mmHg	200 (48.9)	35 (17.1)	165 (80.9)	**<0.001**
	SaO_2 <90 mmHg	209 (51.1)	170 (82.9)	39 (19.1)	
Fever (n=409)	<38^{0}C	130 (31.8)	48 (23.4)	82 (40.2)	**0.001**
	≥38^{0}C	279 (68.2)	157 (76.6)	122 (59.8)	
Clinical parameters at antibiotic discontinuation, n (%)					
Oxygen saturation (n=209)	No change	96 (45.9)	77 (45.3)	19 (48.7)	0.699
	Improved	113 (54.1)	93 (54.7)	20 (51.3)	
Fever (n=279)	No change	95 (34.1)	48 (30.6)	47 (38.5)	0.164
	Improved	184 (65.9)	109 (69.4)	75 (61.5)	
Respiratory PCR monitoring, n (%)					
Bacterial multiplex PCR (n=295)	Positive	59 (20.0)	28 (17.9)	31 (22.3)	0.351
	Negative	236 (80.0)	128 (82.1)	108 (77.7)	
Viral multiplex PCR (n=306)	Positive	12 (3.9)	8 (5.0)	4 (2.8)	0.320
	Negative	294 (96.1)	153 (95.0)	141 (97.2)	
Bacterial cultures within 72 hours of hospitalization, n (%)					
Growth in sputum culture (n=52)	Yes	9 (17.3)	8 (17.8)	1 (14.3)	1.000
	No	43 (82.7)	37 (82.2)	6 (85.7)	

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Growth in blood culture (n=272)	Yes	11 (4.0)	10 (6.0)	1 (1.0)	0.055
	No	261 (96.0)	157 (94.0)	104 (99.0)	
PCT: Procalcitonin, CRP: C reactive protein, PCR: Polymerase chain reaction					

Table 4. The factors influencing mortality in logistic regression

	Univariable analysis		**Multivariable analysis**	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Male	2.485 (1.314-4.701)	**0.005**	1.997 (0.963-4.142)	0.063
Age	1.057 (1.034-1.079)	**<0.001**	1.028 (1.003-1.053)	**0.030**
Presence of comorbidities	7.101 (2.171-23.231)	**0.001**	1.366 (0.276-6.768)	0.702
Presence of risk factors for CAP	6.317 (2.789-14.305)	**<0.001**	1.653 (0.533-5.126)	0.384
Severe to critical patient	10.614 (5.042-22.344)	**<0.001**	3.411 (1.506-7.724)	**0.003**
Initial antibiotic therapy	17.881 (6.337-50.456)	**<0.001**	5.726 (1.866-17.569)	**0.002**
Nosocomial infection	6.936 (3.832-12.556)	**<0.001**	3.557 (1.826-6.930)	**<0.001**

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Supplement 1. Respiratory pathogens tested by microbiological culture and respiratory panel multiplex PCR (Seegene, South Korea)	
Viral pathogens	**Bacterial pathogens**
Respiratory Panel Multiplex PCR	
Adenovirus *Bocavirus* *Enterovirus* *Humanrhinovirus* *Influenza A* *Influenza B* *Metapneumovirus* *Coronavirus OC43* *Coronavirus HKU1* *Coronavirus 229E* *Coronavirus NL63* *Parainfluenza 1* *Parainfluenza 2* *Parainfluenza 3* *Parainfluenza 4* *RSV A* *RSV B*	*Streptococcus pneumoniae* *Haemophilus influenzae* *Mycoplasma spp.* *Legionella spp*
Microbiological culture (deep tracheal aspirate or sputum)	
-	Meticillin-sensitive *Staphylococcus aureus* *Streptococcus parasanguinis* *Haemophilus influenzae* *Klebsiella pneumoniae* *Klebsiella aerogenes*

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Supplement 2. Classification of antibiotic-drug interactions

Major Antibiotic-Drug Interactions (n=42)*		**Moderate Antibiotic-Drug Interactions (n=221)***	
Clarithromycin – Atorvastatin	14.3%	Doxycycline – Piperacillin	21.7%
Clarithromycin – Methylprednisolone	9.5%	Doxycycline – Calcium carbonate	20.8%
Moxifloxacin – Dexamethasone	9.5%	Doxycycline – Insulin	16.3%
Clarithromycin – Fentanyl	7.1%	Doxycycline – Ampicillin	10.4%
Clarithromycin - Haloperidol	4.8%	Clarithromycin – Dexamethasone	6.3%
Clarithromycin – Quetiapine	4.8%	Ceftriaxone – Furosemide	5.9%
Clarithromycin – Tamsulosin	4.8%	Clarithromycin – Lactulose	2.3%
Clarithromycin – Midazolam	4.8%	Doxycycline – Digoxin	1.8%
Clarithromycin – Amiodarone	4.8%	Clarithromycin – Amlodipine	1.8%
Clarithromycin – Silodosin	4.8%	Clarithromycin – Lansoprazole	1.4%
Meropenem – Tramadol	4.8%	Doxycycline – Warfarin	0.9%
Clarithromycin – Warfarin	2.4%	Doxycycline – Rocuronium	0.9%
Clarithromycin – Colchicine	2.4%	Clarithromycin - Insulin	0.9%
Clarithromycin – Escitalopram	2.4%	Clarithromycin – Propofol	0.9%
Clarithromycin – Hydroxychloroquine	2.4%	Levofloxacin – Quetiapine	0.9%
Levofloxacin – Methylprednisolone	2.4%	Levofloxacin – Lactulose	0.9%
Levofloxacin – Dexamethasone	2.4%	Ceftriaxone – Warfarin	0.5%
Levofloxacin – Haloperidol	2.4%	Cefuroxime – Pantoprazole	0.5%
Levofloxacin – Insulin	2.4%	Piperacillin – Warfarin	0.5%
Moxifloxacin – Granisetron	2.4%	Moxifloxacin – Aspirin (low strength)	0.5%
Moxifloxacin – Insulin	2.4%	Moxifloxacin – Famotidine	0.5%
Meropenem – Valproic acid	2.4%	Moxifloxacin – Ibuprofen	0.5%
		Levofloxacin – Aspirin (low strength)	0.5%
		Levofloxacin – Mirtazapine	0.5%
		Doxycycline – Sucralfate	0.5%
		Doxycycline – Primidone	0.5%
		Doxycycline – Carbamazepine	0.5%
		Clarithromycin – Clopidogrel	0.5%
		Clarithromycin – Sertraline	0.5%

(*) indicates the total number of interactions.

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