**Research Article / Araştırma Makalesi**
doi: 10.18678/dtfd.1513307

*Duzce Med J, 2025;X(X):X-X*
*Düzce Tıp Fak Derg, 2025;X(X):X-X*

# The Effect of Antibiotic Use on Intensive Care Unit Admission and Mortality in Inpatients with COVID-19 Diagnosis

## COVID-19 Tanısıyla Yatan Hastalarda Antibiyotik Kullanımının Yoğun Bakım Ünitesine Yatış ve Mortalite Üzerine Etkisi

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Received / Geliş Tarihi : 09.07.2024
Accepted / Kabul Tarihi : 21.01.2025
Available Online /
Çevrimiçi Yayın Tarihi : 17.02.2025

**ABSTRACT**

**Aim:** The coronavirus disease 2019 (COVID-19) pandemic had and continues to directly impact antibiotic management. This study aimed to evaluate antibiotic use and its impact on intensive care unit (ICU) admission and mortality in COVID-19 patients.

**Material and Methods:** The medical records of 324 COVID-19 patients aged ≥18 years who had clinical signs of infection and were followed up in the service were retrospectively evaluated. Patients were divided into two groups, those who received antibiotics and those who did not. Patients transferred from the ICU to the ward, discharged on the first day, or had missing data were excluded from the study.

**Results:** Of the patients, 172 (53.1%) were male, 152 (46.9%) were female, and 212 (65.4%) received antibiotic treatment. Hospitalization longer than one week (p<0.001), pulse steroid use (p=0.011), ICU admission (p=0.002) and mortality (p<0.001) were significantly higher in patients receiving antibiotics. While CRP (p<0.001), PCT (p=0.001), and ferritin (p=0.017) values obtained at admission and 48-72 hours were also found to be higher in antibiotic-using patients, there was no difference in CRP value (p=0.052) at discharge. Duration of hospitalization, antibiotic use, pulse steroid use, and being 60 years and older were found to be risk factors for mortality and ICU admission.

**Conclusion:** Overusing antibiotics in COVID-19 patients did not have a positive effect on mortality and ICU requirements. Considering the harms of excessive antibiotic use, recommendations and practices that lead to rational antibiotic use are needed. Furthermore, factors predicting mortality and ICU can be used in clinical practice.

**Keywords:** Antibiotics; COVID-19; intensive care unit; mortality.

**ÖZ**

**Amaç:** Koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) pandemisinin antibiyotik yönetimi üzerinde doğrudan bir etkisi olmuştur ve olmaya devam etmektedir. Bu çalışmanın amacı, COVID-19 hastalarında antibiyotik kullanımı ve bunun yoğun bakım ünitesine (YBÜ) yatış ve mortalite üzerindeki etkisini değerlendirmektir.

**Gereç ve Yöntemler:** Enfeksiyonun klinik bulguları olan ve serviste takip edilen ≥18 yaş 324 COVID-19 hastasının tıbbi kayıtları geriye dönük olarak değerlendirildi. Hastalar antibiyotik tedavisi alanlar ve almayan olmak üzere iki ayrı gruba ayrıldı. YBÜ'den servise devredilen, birinci gün taburcu edilen veya eksik verisi olan hastalar çalışma dışı bırakıldı.

**Bulgular:** Hastaların 172'si (%53,1) erkek, 152'si (%46,9) kadın ve 212'si (%65,4) antibiyotik tedavisi almıştı. Bir haftadan uzun hastanede yatış (p<0,001), pulse steroid kullanımı (p=0,011), yoğun bakım yatışı (p=0,002) ve mortalite (p<0,001) antibiyotik kullanan hastalarda anlamlı olarak daha yüksekti. Antibiyotik kullanan hastalarda yatışta ve 48-72. saatlerde elde edilen CRP (p<0,001), PCT (p=0,001) ve ferritin (p=0,017) değerleri de daha yüksek bulunurken, taburculuktaki CRP değeri (p=0,052) açısından fark yoktu. Hastanede yatış süresi, antibiyotik kullanımı, pulse steroid kullanımı ve 60 yaş ve üzeri olmak mortalite ve YBÜ yatış için risk faktörleri olarak bulunmuştur.

**Sonuç:** COVID-19 hastalarında aşırı antibiyotik kullanımının, mortalite ve YBÜ gereksinimi üzerinde olumlu bir etkisi olmamıştır. Aşırı antibiyotik kullanımının zararları göz önüne alınarak akılcı antibiyotik kullanımına yönlendiren öneri ve uygulamalara ihtiyaç vardır. Bununla birlikte mortalite ve YBÜ yatışı yordayan faktörlerin klinik pratikte kullanımı fayda sağlayabilir.

**Anahtar kelimeler:** Antibiyotik; COVID-19; yoğun bakım ünitesi; mortalite.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19), which has caused the deaths of millions of people since the day it was identified, was removed as an international health emergency by the World Health Organization (WHO) on 5 May 2023. Although the disease is not an emergency, the whole world is still experiencing the effects of the pandemic, both in health systems and economically. In the process, health systems have been put under unprecedented stress and have been experimenting with non-evidence-based practices. Since 2019, much literature has been published on COVID-19, including treatment protocols. Antimicrobial drugs were frequently used for anti-inflammatory effects and to treat secondary bacterial infections. The new guidelines do not recommend antibacterial agents for COVID-19 treatment unless there is strong evidence of super-infection or co-infection (1). However, in clinical practice, antibacterial drugs are still used in COVID-19 cases (1). As the rate of antibiotic use in COVID-19 patients has increased, studies on the collateral effects of this practice on the health system, especially antimicrobial resistance, have started to be published (2-4). Unnecessary antibiotic use was observed in many patients (5,6). Despite these publications, still some clinicians have started antibiotics in the treatment of COVID-19. The fact that super-infection and worsening of the course of COVID-19 show similar clinical and laboratory findings and the lack of tests that can be used in differential diagnosis leads many physicians to unnecessary antibiotic use. Elevated C-reactive protein (CRP) and procalcitonin (PCT) levels, which are frequently used in follow-up, are known to be predictive of bacterial infection rather than viral infection in clinical practice, but both tests can reach high levels in COVID-19 patients. Especially high CRP in COVID-19 patients may be misleading for antibiotic use (7). This study aimed to determine the characteristics of antibiotic use in COVID-19 patients and to investigate the effect of antibiotic use on intensive care unit (ICU) admission and mortality, which has a high rate of antibiotic use.

## MATERIAL AND METHODS

The study was designed as a retrospective, cross-sectional study. The medical records of patients aged 18 years and older who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) and had signs of COVID-19 infection (fever, fatigue, dyspnea, cough, digestive symptoms) and were followed up in the service between 01.04.2021 and 01.03.2022 in the 370-bed Fatsa State Hospital, a secondary care hospital, were retrospectively scanned from the hospital information system. The inclusion and exclusion criteria for the study were as follows.

Inclusion criteria:
- 18 years of age or older
- Positive SARS-CoV-2 PCR test
- To be followed up in the pandemic service

Exclusion criteria:
- COVID-19 patients hospitalized in ICU
- Patients admitted to the ward after ICU follow-up
- Patients discharged within the first 24 hours of admission
- Patients with incomplete treatment and clinical information in the epicrisis

According to the information obtained from the records and patient files, the patients were analyzed in two groups: patients who received antibiotics and patients who did not receive antibiotics. In patients requiring ICU, only the treatments and cultures administered in the ward were evaluated. The culture and blood values of the patients who were transferred to the ICU after service follow-up were not analyzed in the study. Since the primary outcome was determined as ICU requirement and mortality, only the pre-ICU processes of the patients were analyzed after transfer to the ICU. Mortality was evaluated as all causes of mortality regardless of ward and ICU.

Demographic information, comorbidities, treatments received, whether the patients received pulse steroid treatment during hospitalization (pulse steroid defined as methylprednisolone 250 mg or more at least once during hospitalization), duration of hospitalization, duration of antibiotic treatment, culture results if any, and clinical results were recorded. White blood cell (WBC), lymphocyte, platelet, PCT, CRP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ferritin, D-dimer values (taken during the first 48 hours of admission) were recorded. To evaluate CRP dynamics in the antibiotic and non-antibiotic group, patients' CRP values at 48-72 hours, on the 7$^{th}$ day of admission, and the last CRP value analyzed (before discharge, before ICU admission, or as the last value before mortality for cases with a mortal course during service follow-up) were noted. The first 28-day mortality in the service or ICU was analyzed. The duration of antibiotic use was recorded as the total duration of antibiotic use (e.g., for a patient who received ceftriaxone for 3 days and moxifloxacin for 2 days, the duration of antibiotic use was 5 days).

A power analysis was conducted using G*Power v.3.1. The study's power was calculated to be 98.9% for an independent samples t-test, conducted post hoc, with an effect size of 0.5, a type-1 error (α) level of 0.05, and sample sizes of 212 in the antibiotic-using group and 112 in the non-using group (8).

The study was conducted by the Declaration of Helsinki. Approval for the study was received from the Ordu University Ethics Committee (27.10.2022, 21/235).

### Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, v.20.0. Descriptive statistics were presented as frequency, percentage, mean, standard deviation, median, quartile, minimum, and maximum values. The conformity of the variables to the normal distribution was evaluated by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Group comparisons were done with an independent samples t-test when data were distributed normally and a Mann-Whitney U test when data were non-normally distributed. The chi-square test or Fisher's exact test was used for categorical variables. A multivariable logistic regression model was used to assess independent variables. In logistic regression analysis, two different models were created by considering the need for ICU and death as the dependent variables. The multivariate model included variables found to be statistically significant in univariate analyses and known to be related to mortality and ICU admission. Final models were computed with the enter

procedure. Clinically relevant variables and those with p<0.05 were incorporated through a backward step-wise approach. The Hosmer-Lemeshow test was applied to evaluate the goodness of fit of the model. The results were evaluated within a 95% confidence interval and the statistical significance level was accepted as p<0.05.

## RESULTS

A total of 324 COVID-19 patients, 172 (53.1%) male and 152 (46.9%) female, were included in the study. Of the patients, 212 (65.4%) received antibiotic treatment. The mean age was 65.14±15.91 years in the antibiotic-using group and 62.99±14.98 years in the non-using group. Mean age (p=0.239) and gender (p=0.565) were not found statistically significantly different between the two groups. Hospitalization longer than one week (p<0.001), pulse steroid use (p=0.011), ICU admission (p=0.002), and mortality (p<0.001) were found statistically significantly higher in the group receiving antibiotics than in the group non-using. Demographic and clinical data of the patients and characteristics of the antibiotic-using and non-using groups were presented in Table 1.

When the cases were evaluated in terms of comorbidity, there was no difference between the two groups (p=0.559). There were patients with more than one comorbid disease. Hypertension 156 (48.1%), diabetes mellitus 76 (23.5%), and chronic obstructive pulmonary disease 67 (20.7%) were the most common comorbidities (Table 2).

When the laboratory parameters of the cases were compared according to the antibiotic use, it was found that CRP (p<0.001), PCT (p=0.001), ferritin (p=0.017), and D-dimer (p=0.018) values obtained at admission and 48-72 hours were statistically significantly higher in the group receiving antibiotics. No significant difference was observed in terms of other parameters (Table 3).

When the antibiotics used by the patients were analyzed, it was found that 212 (65.4%) patients used at least one antibiotic and 112 (34.6%) patients had received combined antibiotic treatment. The median duration of antibiotic use was 6 (interquartile range, 4-9) days. The most commonly used antibiotics were ceftriaxone at 112 (34.6%) patients and moxifloxacin at 93 (28.7%) patients (Table 4).

When the factors affecting the need for ICU were analyzed, logistic regression analysis revealed that being over 60 years of age (p=0.002), hospitalization duration of more than one week (p<0.001), pulse steroid use (p<0.001), and history of antibiotic use (p=0.002) were independent risk factors (Table 5).

When the associated factors with mortality were analyzed by logistic regression analysis, again being over 60 years of age (p=0.002), hospitalization duration of more than one week (p=0.002), pulse steroid use (p<0.001), and history of antibiotic use (p=0.001) were detected as the factors affecting mortality (Table 6).

**Table 1.** Comparison of cases according to antibiotic use

| | Using (n=212) | Non-using (n=112) | p |
|---|---|---|---|
| **Age** (year), mean±SD | 65.14±15.91 | 62.99±14.98 | 0.239 |
| **Age group**, n (%) | | | |
| 23-39 years | 14 (6.6) | 8 (7.1) | |
| 40-59 years | 56 (26.4) | 38 (33.9) | 0.333 |
| ≥60 years | 142 (67.0) | 66 (59.0) | |
| **Gender**, n (%) | | | |
| Male | 115 (54.2) | 57 (50.9) | 0.565 |
| Female | 97 (45.8) | 55 (49.1) | |
| **Duration of hospitalization** (day), median (Q1-Q3) [min-max] | 7 (5-10) [1-30] | 5 (3-6) [1-21] | **<0.001** |
| **Hospitalization ≥1 week**, n (%) | 116 (54.7) | 27 (24.1) | **<0.001** |
| **Comorbidity**, n (%) | 156 (73.6) | 79 (70.5) | 0.559 |
| **ICU admission**, n (%) | 37 (17.5) | 6 (5.4) | **0.002** |
| **Pulse steroid treatment**, n (%) | 61 (28.8) | 18 (16.1) | **0.011** |
| **Presence of culture**, n (%) | 73 (34.4) | 9 (8.0) | **<0.001** |
| **Blood culture positivity*** (n=39 vs n=2), n (%) | 6 (20.7) | 1 (50.0) | 0.406 |
| **Urine culture positivity*** (n=58 vs n=6), n (%) | 16 (27.6) | 0 (0.0) | 0.323 |
| **Mortality**, n (%) | 37 (17.4) | 4 (3.6) | **<0.001** |

SD: standard deviation, ICU: intensive care unit, *: there were 29 antibiotic-using and 2 non-using patients with blood culture, and 58 antibiotic-using and 6 non-using patients with urine culture, percentages for these comparisons were calculated accordingly

**Table 2.** Comorbid diseases of the cases

| Comorbidity | n (%) |
|---|---|
| Hypertension | 156 (48.1) |
| Diabetes Mellitus | 76 (23.5) |
| Chronic Obstructive Pulmonary Disease | 67 (20.7) |
| Coronary Artery Disease | 51 (15.7) |
| Congestive Heart Failure | 23 (7.1) |
| Cerebrovascular Disease | 16 (4.9) |
| Alzheimer | 8 (2.5) |
| Malignancy | 6 (1.9) |
| Epilepsy | 5 (1.5) |
| Thyroid Disease | 4 (1.2) |
| Other Disease | 39 (12.0) |

**Table 3.** Comparison of laboratory parameters according to antibiotic treatment status

| | Using (n=212) | Non-using (n=112) | p |
|---|---|---|---|
| **WBC (µl)** | 7445 (5498-10445) [770-29050] | 6800 (5500-8990) [1100-84700] | 0.127 |
| **Lymphocyte (µl)** | 1075 (728-1423) [200-22300] | 1130 (810-1610) [220-3320] | 0.072 |
| **Platelet (µl)** | 198500 (158000-239250) [11000-498000] | 196000 (161000-249000) [59000-465000] | 0.584 |
| **CRP (mg/L)** | | | |
| First arrival | 108 (53-171) [2-370] | 68 (31-113) [0-239] | **<0.001** |
| Third day | 66 (35-128) [0-320] | 29 (13-59) [0-142] | **<0.001** |
| Seventh day | 17 (6-49) [1-233] | 5 (2-16) [1-179] | **0.006** |
| At discharge | 11 (5-36) [0-219] | 8 (3-25) [0-343] | 0.052 |
| **PCT (µg/L)** | 0.11 (0.06-0.24) [0.01-4.21] | 0.06 (0.04-0.14) [0.01-1.62] | **0.001** |
| **AST (IU/L)** | 29 (20-41) [8-165] | 26 (21-38) [11-133] | 0.579 |
| **ALT (IU/L)** | 20 (13-32) [5-201] | 20 (15-29) [6-440] | 0.771 |
| **Ferritin (ng/mL)** | 331 (166-607) [16-3140] | 252 (133-454) [8-1863] | **0.017** |
| **D-dimer (ng/mL)** | 548 (293-1067) [84-8858] | 420 (256-803) [70-6331] | **0.018** |

WBC: white blood cell, CRP: C-reactive protein, PCT: procalcitonin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, descriptive statistics were presented as median ($25^{th}$-$75^{th}$ percentile) [minimum-maximum]

**Table 4.** Antibiotics used in order of frequency

| Antibiotics | n (%) |
|---|---|
| Ceftriaxone | 112 (34.6) |
| Moxifloxacin | 93 (28.7) |
| Piperacillin-tazobactam | 55 (17.0) |
| Levofloxacin | 27 (8.3) |
| Meropenem | 21 (6.5) |
| Ertapenem | 16 (4.9) |
| Clarithromycin | 9 (2.8) |
| Amikacin | 6 (1.9) |
| Vancomycin | 5 (1.5) |
| Azithromycin | 5 (1.5) |
| Ciprofloxacin | 5 (1.2) |
| Metronidazole | 4 (1.2) |
| Other | 8 (2.5) |

**Table 5.** Associated factors with ICU admission

| Independent Variables | p | OR | %95 CI |
|---|---|---|---|
| Age ≥60 years | **0.002** | 5.989 | 1.961 - 18.286 |
| Hospitalization ≥1 week | **<0.001** | 5.075 | 2.130 - 12.091 |
| Pulse steroid treatment | **<0.001** | 6.954 | 3.086 - 15.672 |
| Antibiotic treatment | **0.002** | 4.650 | 1.748 - 12.372 |

ICU: intensive care unit, OR: odds ratio, CI: confidence interval

**Table 6.** Associated factors with mortality

| Independent Variables | p | OR | %95 CI |
|---|---|---|---|
| Age ≥60 years | **0.002** | 5.507 | 1.822 - 16.643 |
| Hospitalization ≥1 week | **0.002** | 3.554 | 1.569 - 8.051 |
| Pulse steroid treatment | **<0.001** | 4.449 | 2.014 - 9.829 |
| Antibiotic treatment | **0.001** | 6.728 | 2.215 - 20.434 |

OR: odds ratio, CI: confidence interval

## DISCUSSION

This study found that mortality did not increase significantly in the group that did not receive antibiotics, but on the contrary, antibiotic treatment was found to be 6.728 and 4.650 times higher in terms of mortality and ICU admission in logistic regression, respectively. In addition to antibiotic use, pulse steroid use, being 60 years of age or older, and long hospital stays were found to be other factors predicting mortality and ICU admission. Although antibiotics were used in 65.4% (n=212) of all patients, culture was ordered in only 25.3% (n=82) of patients, and growth was detected in any culture in only 10.4% (n=22) of the patients who received antibiotics. These data show that there is a high rate of inappropriate antibiotic use in COVID-19 management in the study center.

Similar to this study, studies have shown that antibiotic use in COVID-19 patients is associated with the severity of the disease and the need for mechanical ventilation (9-11). In a study to detect co-infections during hospital admission for COVID-19, co-infections were detected in less than 4% of cases. In addition, the efficiency of routine diagnostic testing for pneumonia was low (12). In the present study, the causative agent was detected in the culture of only 10.4% (n=22) of the patients in total (at the time of admission or during hospitalization). This is an indication of how low the co-infection rate is in the first presentation of COVID-19 cases. Although ICU patients were excluded from the study, it was observed that broad-spectrum antibiotics such as piperacillin-tazobactam, meropenem, and vancomycin were preferred at a considerable rate. In addition, while atypical agents were expected less frequently, it was observed that quinolone group antibiotics were preferred at a high rate in the study center despite the cautions regarding the use of quinolone group antibiotics.

In the COVID-19 patient group, the lack of a clear indicator to differentiate between bacterial co-infection or super-infection and deterioration due to COVID-19 results in a high rate of unnecessary antibiotic use. Incorrect or unnecessary use of antibiotics may have multifaceted results. One of these is the increasing antimicrobial resistance (13-17). Another result is the worsening of the clinic in COVID-19 patients due to the disruption of the microbiota (18).

The long duration of hospitalization, pulse steroid treatment, and high baseline CRP and PCT values, which were found to be significantly higher in the group receiving antibiotics, are factors defined in COVID-19 patients in terms of ICU admission and mortality. Therefore, mortality was found to be high in this group. The estimated relative risk of antibiotic treatment in patients with a mortal course was high. This may be due to clinicians' suspicion of bacterial infection secondary to COVID-19 when initiating antibiotics or empirical antibiotic initiation practices in patients with severe progression. During the pandemic, due to the disease burden, many branch physicians have followed primary COVID-19 patients, and the principles and perspectives of antibiotic use of each branch physician have been different. This makes the reasons and patterns of antibiotic use in COVID-19 patients heterogeneous and makes it difficult to distinguish whether the high use of antibiotics in the mortality group is due to inappropriate use or a genuine need for antibiotics. The independent impact of antibiotic-related adverse effects on mortality is difficult to determine in this complicated patient group. In COVID-19 patients, elevated levels of PCT as well as CRP without bacterial infection have been reported with clinical severe progression (19). CRP and PCT may contribute to the diagnosis of lower respiratory tract infection, but it is not possible to make a definitive distinction (20,21). Because inflammation, which is a natural consequence of COVID-19 pathophysiology, can also increase acute phase parameters (22). Nevertheless, studies show that PCT values are particularly useful in shortening the duration of antibiotic treatment (23-25). A cohort study showed that PCT-guided antibiotic prescription reduced antibiotic prescription rates in hospitalized COVID-19 patients (26). However, baseline and third-day CRP were higher in the group receiving antibiotics, while there was no difference in seventh-day and discharge CRP. This supports the inappropriateness of antibiotic treatment based on CRP. The similar decline in seventh-day and discharge CRP in the group not receiving antibiotics indicates that elevated CRP should not be an indication for antibiotics alone in COVID-19 patients. It is noticeable that antibiotic use is higher in the group with high acute-phase reactants. However, as can be understood from the studies, acute phase reactants alone are insufficient to diagnose co-infection or super-infection in COVID-19 cases (19-22). Studies are showing that CRP trajectory in the first week of hospitalization is an important factor in predicting microbiology culture positivity and outcome in patients hospitalized with COVID-19 (27). For the prediction of clinical outcome and co-infection, the dynamism of CRP over time as well as the absolute value of CRP should be interpreted.

The main limitation of the study is that the results represent more regional data since it is a single-centered study. Secondly, the study was limited to 324 cases so this reduces the strength of the study. Thirdly, patients hospitalized in the ICU and pediatric age group were not included.

## CONCLUSION

As a result, the present study center was found to have a very high rate of antibiotic use during the COVID-19 pandemic. Although the number of cultures gained was relatively small, it was observed that a considerable amount of broad-spectrum antibiotics were used. Since the COVID-19 pandemic has been managed according to the guidelines of the Ministry of Health in Türkiye from the beginning, we guess that similar results will be obtained throughout the country. The high acute phase values in COVID-19 cases contributed to this result. The lack of a definitive algorithm for antibiotic management in COVID-19 cases and the limitations in microbiologic detection of bacterial pneumonia agents are other factors of this problem. It is possible to predict that the rates of antibiotic use will be much higher in retrospective studies, especially in cases followed up in ICUs in Türkiye. During the COVID-19 pandemic, many negative consequences of high antibiotic use in this patient group in Türkiye, especially resistance, will be revealed more clearly in the future. These effects should be investigated with further analyses such as antibiotic resistance, side effects of treatments, and cost. In addition, the principles of antibiotic use in the COVID-19 patient group should be presented in a way to guide clinicians with clear and applicable recommendation articles based on Türkiye.

**Ethics Committee Approval:** The study was approved by the Clinical Research Ethics Committee of Ordu University (27.10.2022, 21/235).

**Conflict of Interest:** None declared by the authors.

**Financial Disclosure:** None declared by the authors.

**Acknowledgments:** None declared by the authors.

**Author Contributions:** Idea/Concept: TK; Design: TK, OA; Data Collection/Processing: TK, AD; Analysis/ Interpretation: TK, OA; Literature Review: TK, AD; Drafting/Writing: TK, AD, OA; Critical Review: TK, AD.

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