# Antimicrobial Use in COVID-19 Patients

Subjects: Health Care Sciences & Services
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There is an urgent need for further research and guidance in this field, from producing evidence-based guidelines, reassessing biomarkers for antimicrobial stewardship in COVID-19 patients, understanding drivers, benefits, and disbenefits of antibiotic use, and assessing the wider impact of the pandemic on antimicrobial use (AMU) and AMR. In this scoping review, we aim to: add to the research evidence on prevalence and patterns of antimicrobial use in the treatment of COVID-19 patients; identify the most commonly used antibiotics and clinical scenarios associated with AMU; and to explore any impact of AMU on patient treatment outcomes.

Keywords: COVID-19 patients ; disease severity ; antibiotic use ; clinical justification ; secondary infections

## 1. Introduction

For example, in a multi-hospital cohort study in the USA, 56.6% of 1705 patients were prescribed early empiric antibacterial therapy, of which only 3.5% were confirmed to have bacterial infection [1]. Two systematic reviews found that, of the patients reported in the included studies, 72.0% received antibiotics, and 14.3% suffered a secondary bacterial infection [2][3]. The low proportion of COVID-19 patients having co-infection or secondary infection in these studies is consistent with other findings. In Spain, of 989 consecutive patients with COVID-19, only 72 (7.3%) had confirmed bacterial infections [4].

Overall, the pandemic may be accelerating the threat of AMR due to the increased use of antibiotics, increased exposure to hospital environments and invasive procedures used in COVID-19 treatment, while evidence for the benefits of antimicrobial use in such patients is limited. Many AMR experts have raised their concerns around the safety of using antibiotics in COVID-19 patients and called for strengthening antimicrobial stewardship (AMS) programs in the time of COVID-19 [5][6][7][8][9][10]. For example, the increased use of empirical antibiotics treatment increases the risks of Clostridioides difficile infection in COVID-19 patients and the emergence of multidrug resistant organism [11][12].

Guidelines have started to emerge around the use of antimicrobials in COVID-19 patients. For severe COVID-19, a daily assessment for de-escalation of antimicrobial treatment is recommended. For elderly patients and children under five with moderate COVID-19, WHO recommends use of antibiotics categorized in the WHO access list of medicines such as co-amoxicillin [6][13].The March 2021 UK National Institute for Health and Care Excellence (NICE) rapid guideline on managing COVID-19 provides the following consensus recommendations: (1) do not use antibiotics for preventing or treating COVID-19; (2) only use antibiotics if there is a strong clinical suspicion of additional bacterial infection [14]. Other guidelines such as those of the Dutch Working Party on Antibiotic Policy [12] and the Scottish Antimicrobial Prescribing Group [15] both advise avoiding routine antibiotic use in suspected COVID-19, the importance of obtaining sputum and blood samples as well as urinary antigen testing upon admission, and a cautious antibiotic treatment of short duration of five days in patients of COVID-19 when there is a clinical suspicion of secondary bacterial infection.

There is an urgent need for further research and guidance in this field, from producing evidence-based guidelines [12], reassessing biomarkers for antimicrobial stewardship in COVID-19 patients [9], understanding drivers, benefits, and disbenefits of antibiotic use, and assessing the wider impact of the pandemic on antimicrobial use (AMU) and AMR. In this scoping review, we aim to: add to the research evidence on prevalence and patterns of antimicrobial use in the treatment of COVID-19 patients; identify the most commonly used antibiotics and clinical scenarios associated with AMU; and to explore any impact of AMU on patient treatment outcomes.

## 2. Development and Findings

A total of 1216 records were identified through database searching. After duplicates were removed and irrelevant records of COVID-19 research not related to clinical treatment of COVID-19 patients were excluded, 223 records were screened for eligibility. A further 113 studies that reported neither antimicrobial use in treatment nor patients with co-infections were excluded. The remaining 110 articles and an additional eight articles that were identified by searching the reference lists of the retrieved articles and the authors' reference collections, led to a total of 118 full-text articles being included for review (**Figure 1**).

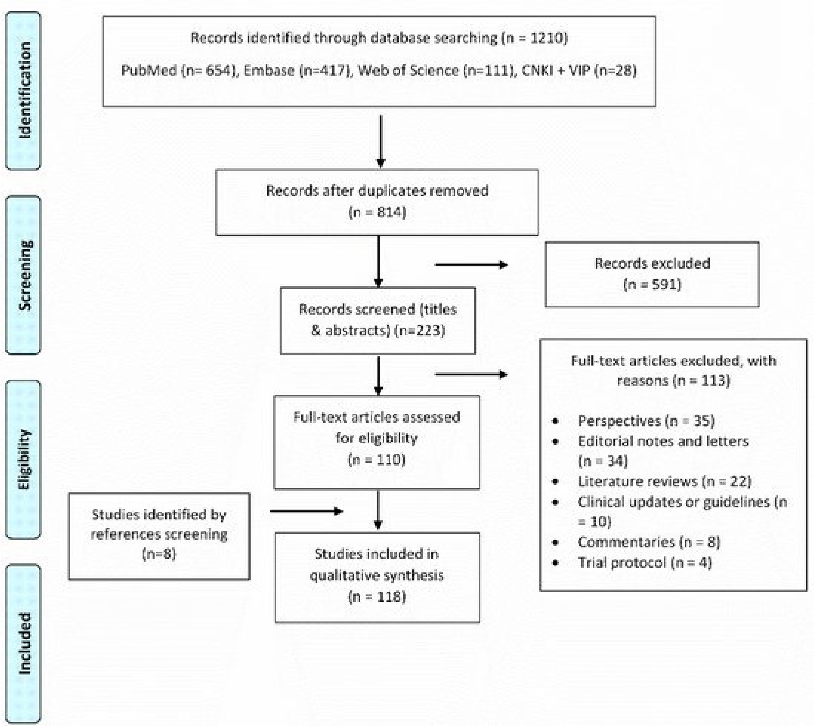


**Figure 1.** Prisma chart.

Of 118 included studies, 59 were case series or case reports, 47 were observational studies (all types of observational study except cohort studies), seven were randomized controlled trials, and five were cohort studies. Most of the studies were conducted in low- and middle-income countries, consonant with the trajectory of the pandemic at that stage, with the majority conducted in China (51.7%), followed by USA Italy and France Highest number of studies were from East Asia and Pacific (55.9%), followed by Europe and Central Asia (22.0%) and North America (14.4%). There were no reports of non-hospitalized COVID-19 patients in our results.

Severity of illness was not reported in all studies. Just over half reported the severity of illness using four categories (severe, critical, moderate, and mild) and the rest remainder used three groups (severe, moderate, and mild). In order to explore the potential role of severity of illness in decisions regarding antibiotic prescribing, we grouped severity of illness into two broader categories: severe or critical, and moderate or mild. A total of 2630 patients (41.9%) fell into the severe or critical group and 3649 patients (58.1%) into mild or moderate group.

In the included studies, 8501 out of 10,329 COVID-19 patients (82.3%) were prescribed antibiotics. There was little difference in the mean rates of antibiotic prescribing with 75.4% in severe or critical vs. 75.1% in mild or moderate groups (**Table 1**).

**Table 1.** Severity of illness and antibiotic prescribing.

| Illness Severity of COVID-19 Patients | Patient Size *n* (%) | Mean Antibiotic Prescribing (%) |
|---|---|---|
| **Severe and critical patients** | **2630 (41.9)** | **75.4** |
| **Mild and moderate** | **3649 (58.1)** | **75.1** |
| **Total** | **6279 (100.0)** | **75.2** |

We further explored the relationship between antibiotic prescribing and health outcomes (length of hospital stay (LOS), discharge rate, and mortality rate (all these health outcomes were calculated at the time of publication of those studies; some patients were still in hospital and these patients were not included in their calculation). The results show that patient mortality was higher in studies for patients all given antibiotics compared to studies that majority of patients were not given antibiotics (26.5% vs. 2.3%), LOS was longer (12.5 days vs. 10.3 days), and discharge rate was also higher (76.2% vs. 73.2%) (**Table 2**).

**Table 2.** Antibiotic prescribing categories and outcomes.

| SN | Category of Antibiotic Prescribing | LOS (Mean Days) | Discharge (Mean%) | Mortality (Mean%) |
|---|---|---|---|---|
| 1 | **All given abs (58 studies)** | **12.5** | **76.2** | **26.5** |
| 2 | **Majority are given abs (37 studies)** | **14.3** | **57.9** | **13.1** |
| 3 | **Majority not given abs (11 studies)** | **10.3** | **73.2** | **2.3** |

We extracted the details of prescribed antibiotics from all the included studies where this information was available. Further, 33.9% of included studies did not report the details of antibiotics but only mentioned that antibiotics or empirical antibiotics were used in treatment.

Among the 78 studies that reported type of antibiotics used in the treatment of COVID-19 patients, (**Figure 2**) azithromycin (macrolides and ketolides) was the most frequently prescribed antibiotic (accounting for 28.0% of studies); followed by ceftriaxone (17.8%), moxifloxacin (14.4%), meropenem (14.4%), and Piperacillin/tazobactam (12.7%). It is not possible to tabulate prescribing percentages of these frequently prescribed antibiotics for the treatment of hospitalized COVID-19 patients as most studies, except case report or case series, did not report the percentage of each prescribed antibiotic in the treatment of COVID-19 patients. Notably, the frequently prescribed antibiotics are all broad-spectrum antibiotics.

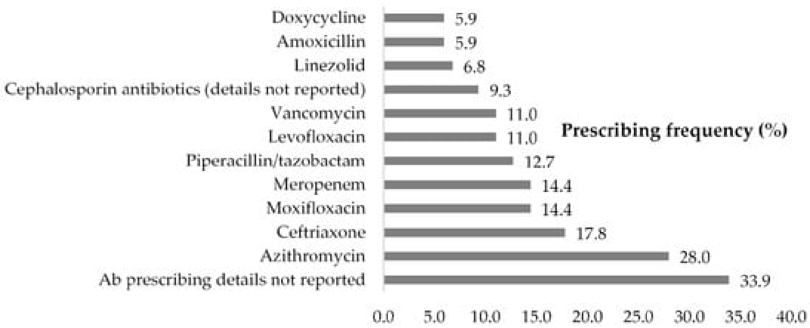


**Figure 2.** Frequently prescribed antibiotics for hospitalized COVID-19 patients.

We asked two experienced clinicians in infectious diseases with expertise in AMS practices to classify each antibiotic prescribing scenario as: (1) with clinical justifications; (2) without clinical justifications; (3) not sure. In addition to microbiological analysis; sepsis, elevated white blood cells or procalcitonin are also signs of bacterial infection and antibiotics prescribed under those circumstances were considered as “with clinical justifications”. There were some ambiguous cases (around 30% of scenarios) on which both experts found difficult to make judgements regarding whether antibiotics should be prescribed or not; we categorized those as “not sure”. A relatively high proportion (around 45%) of scenarios described in the included studies were categorized by both experts as “without clinical justifications”.

We also categorized the frequency of each antibiotic prescribing scenario by illness severity (Supplementary Table S2). We found that only 12.9% of severe or critically ill patients were prescribed antibiotics with clinical justifications, and this proportion was 13.6% for mild or moderate patients. The proportion of patients prescribed antibiotics without clinical justification was 51.5% vs. 41.9% for patients with mild or moderate illness and those with severe or critical illness.

All studies with all severe or critical patients had a higher mortality rate than all studies with mild or moderate patients (53.1% vs. 0.2%), similarly with lower discharge rate (96.2% vs. 36.6%) and higher LOS (17.4% vs. 8.7%) (**Table 3**).

**Table 3.** Severity of illness and health outcomes.

| Severity of Illness (Categories) | LOS (Mean Days) | Discharge (Mean%) | Mortality (Mean%) |
|---|---|---|---|
| **All severe/critical (16 studies)** | **17.4** | **36.6** | **53.1** |
| **Majority were severe/critical (4 studies)** | **18.0** | **77.9** | **5.8** |
| **Majority were mild/moderate (33 studies)** | **12.0** | **60.5** | **4.8** |
| **All mild/moderate (20 studies)** | **8.7** | **96.2** | **0.2** |

Mortality rate was lower for those patients who were provided antibiotics with clinical evidence of infections compared to those who were given without clinical justifications (9.5% vs. 13.1%), discharge rate was higher (80.9% vs. 69.3%) and LOS was lower (9.3 days vs. 12.2 days) (**Table 4**).

**Table 4.** Antibiotic prescribing justifications and health outcomes.

| Antibiotic Prescribing Justified or Not | LOS (Mean Days) | Discharge (Mean%) | Mortality (Mean%) |
|---|---|---|---|
| A-with clinical justifications” (*n* = 14) | 9.3 | 80.9 | 9.5 |
| B-without clinical justifications (*n* = 49) | 12.2 | 69.3 | 13.1 |
| C-not sure (*n* = 47) | 14.1 | 61.1 | 24.8 |

Nine of the 118 studies reported on secondary infections. Out of a total sample size of 820 in these studies, 74.4% patients had diagnosed secondary infections (n= 610) and 51.3% of these patients were serious or critically ill (n= 313). In perspective to our total sample size across all studies (6279 patients), the percentage of patients with confirmed or diagnosed secondary infections was 9.7%. Compared to total patients (n= 6279), patients with secondary infections had higher LOS (20.4 days vs. 12.4 days), lower discharge rate (54.8% vs. 65.6%), and higher mortality rate (43.7% vs. 16.3%) (**Table 5**).

**Table 5.** Secondary infections and health outcomes.

| Descriptions | Severe/Critical *n* (%) | Mild/Moderate *n* (%) | Mean Length of Stay (Days) | Mean Discharge Rate (%) | Mean Mortality Rate (%) |
|---|---|---|---|---|---|
| Total patients with secondary infections (*n* = 610) | 313 (51.3%) | 297 (48.7%) | 20.4 | 54.8 | 43.7 |
| Total sample size (*n* = 6279) | 2630 (41.9%) | 3649 (58.1%) | 12.4 | 65.6 | 16.3 |

We found that male patients compared to female patients had a higher mortality rate (37.7% vs. 20.0%), lower discharge rate (75.2% vs. 91.7%), and longer LOS (13.4 days vs. 11.4 days) (Supplementary Table S3). These findings are in line with other recent studies conducted with COVID-19 patients across the world [16][17].

We conducted a stratified analysis of antibiotic prescribing rate, length of hospital stay, discharge rate, and mortality rate by study design and incomes of the countries where studies originated. There was little variation in antibiotic prescribing rate, length of hospital stay, and discharge rate by study design. Reported antibiotic prescribing rates, length of stay, and mortality rates were also similar between low-and-middle income countries (LMICs) and high-income countries (HICs) based on World Bank Classfication. However, discharge rates were considerably lower in LMICs (60.2%) compared to HICs (81.9%)

## 3. Conclusions

This review and evidence synthesis suggest that during the first six months of the COVID-19 pandemic, antibiotic prescribing in hospitals was not associated with illness severity. A large proportion (40–50%) of antibiotic prescribing for COVID-19 patients did not have clinical indications of a bacterial co-infection; around half of COVID-19 patients with mild or moderate illness, had been prescribed antibiotics in the reports and studies we reviewed. Patients without clinical evidence of a bacterial co-infection should not receive antibiotics treatment according to international guidelines.

The evidence reviewed suggests that where secondary bacterial infection is absent, antibiotic prescribing may not be beneficial to treatment outcomes for COVID-19 patients. Until more clinical data become available to verify these findings, considerable caution is warranted when considering antibiotic treatment in COVID-19 cases, even for severe and critically ill patients. The widespread use of antibiotics for COVID-19 may not only magnify the problem of antibiotic resistance globally and render currently available antibiotics ineffective, but also provide little or no benefit for COVID-19 patients. A further scoping review to capture changes in global prevalence and patterns of antibiotic prescribing for COVID-19 patients in hospital settings from June 2020 to Aug 2021 is currently underway.

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