META-ANALYSIS

The Use of Antimicrobial Drug in Patients During the COVID-19 Pandemic: A Meta-Analysis

Xu Jiao, MM; Mingfei Li, MM; Mengyue Zhang, MM; Xinyu Hu, MM; Lulu Li, MM; Fanlin Meng, MM; Kang Li, PhD; Yun Lu, PhD

ABSTRACT

Objective • To analyze the use of antimicrobial drugs in patients during the COVID-19 pandemic.

Methods • We searched for literature about antimicrobial treatment in COVID-19 patients through the Cochrane Library, Embase, PubMed, the Chinese biomedical literature database, CNKI, the Chinese journal full-text database, Wanfang, and Vipu. The quality evaluation of the literature was performed by Jadad's quality score.

Results • A total of three articles reported on ivermectin treatment in patients with COVID-19, and the Meta-analysis showed no clinical and statistical heterogeneity among the studies (I^2 = 15%, P = .31), a fixed effect model was used to incorporate effect sizes. The clinical effect of the observed group was not different from the control group (P = .16). None of the three ivermectin articles with clinical effect as the effect indicator showed a significant difference (P > .05), suggesting no publication bias. A total of four publications reported the treatment with azithromycin in patients with COVID-19, and the Meta-analysis showed no clinical and statistical heterogeneity between the studies (I^2 = 0%, P = .88), using a fixed-effect model to incorporate the effect sizes. The clinical effect of the observed group was not different from the control group (P = .57). None of the four azithromycin articles with a clinical effect as the effect index was statistically significant (P > .05), suggesting no publication bias.

Conclusion • During the COVID-19 pandemic, the patient's use of antibiotics does not significantly improve clinical efficacy, so antibiotic use is recommended only for patients with complicated bacterial infections. (*Altern Ther Health Med.* 2023;29(8):722-725).

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INTRODUCTION

Corona Virus Disease 2019 (COVID-19), which broke out in December 2019, is highly infectious, caused by the virus SARS-CoV-2 infection has imposed significant demand on all healthcare systems. Due to the long treatment time and hospitalization days of COVID-19 patients, some patients are prone to bacterial infections during the course of hospitalization.[1] The seventh version of the COVID-19 Diagnosis and Treatment Plan (Trial) released by the Chinese Health Commission recommends the implementation of antiviral and other supportive therapy for COVID-19 patients.[2]

The antibiotics are used either to resolve bacterial infections co-existing with COVID-19 infections or to exploit their potential antiviral activities.[3] Macrolide specifically azithromycin is the most common antibiotic used in the clinical management of COVID-19.[4] In patients with COVID-19, antibiotics are used for their immune-modulating, anti-inflammatory, and antiviral properties.[3] Moreover, the use of some of these antibiotics against SARS-CoV-2 infection remains highly controversial and not widely accepted. Chedid et al.[5] reviewed the major use of antibiotics among COVID-19 hospitalized patients, mainly in an empirical setting. There is no proven efficacy of this practice.

Clinically whether antimicrobial agents are administered to COVID-19 patients remains inconclusive.[4-5] In this study, by searching various literature platforms for the literature of antimicrobial treatment in COVID-19 patients, we conducted a meta-analysis to observe the antimicrobial use of COVID-19 patients. It will provide a theoretical basis for the clinical treatment of antimicrobial application in COVID-19 patients.

Table 1. Basic characteristics of the included literature

Order	First author	Publication year	Therapeutic method		Sample size (observation group/control group)	Outcome indicators	Jadad grade	Number of people
			Observation group	Control group				
1	Ravikirti	2021	ivermectin	placebo	56/58	death rate	5	(0/56)/ (4/58)
2	Vallejos J	2021	ivermectin	placebo	250/251	death rate	5	(4/250)/ (3/251)
3	Mahmud R	2021	ivermectin	placebo	200/200	Continuous positive rate	6	(14/183)/ (20/180)
4	RECOVERY Collaborative Group	2021	Azithromycin	placebo	2430/4881	death rate	5	(496/2430)/ (1028/4881)
5	Hinks TSC	2021	Azithromycin + Standard of Care	Standard nursing	145/147	death rate	5	(15/145)/ (17/147)
6	Furtado RHM	2020	Azithromycin	hydroxychloroquine	214/183	death rate	6	(34/214)/ (28/183)
7	Sivapalan P	2022	Azithromycin + hydroxychloroquine	placebo	61/56	death rate	6	(9/61)/ (6/56)

DATA AND METHODS

Literature search strategy

Using thematic words and free words, Cochrane Library, Embase, PubMed, Chinese biomedical literature database, CNKI, Chinese journal full-text database, Wanfang, Weipu, and other databases were searched. The Chinese search terms are: "COVID-19, antibacterial drugs", and the English search terms are: "COVID-19, antimicrobials", etc. The retrieval time limit will be for the database construction until October 2022. The retrieval languages are both Chinese and English.

Literature inclusion and exclusion criteria

Inclusion criteria. 1. All the included literature are randomized controlled experiments. 2. The study subjects included COVID-19 patients and took the reflected clinical effects as the observation indicators (such as mortality, positive rate, etc.). 3. The treatment methods involved include azithromycin, ivermectin, and other commonly used antiemetics.

Exclusion criteria. 1. Non-randomized controlled study. 2. Incomplete data in the article, and repeated published literature. 3. Animal experiments, case reports, reviews, etc.

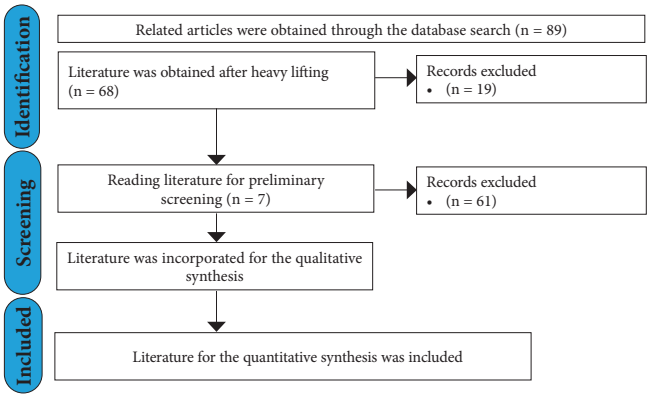
Data extraction and literature quality evaluation

All the literature was evaluated by the literature quality of two researchers according to the literature Evaluation criteria and the modified Jadad's Scale.[6] If the opinions of two researchers are inconsistent, the third researcher decided to extract the general information and basic information from all the included literature. The modified Jadad's scale score included the generation of random sequences, randomization concealment, blinding, and withdrawal versus withdrawal, with 1-3 scored as low quality and 4-7 scored as high quality.

Statistical analysis

Statistical analysis was performed using the Stata software version 2023 (StataCorp LLC, College Station, TX, USA), and the included literature results were tested for heterogeneity using Cochran's Q test, and the heterogeneity size passed the statistic I^2representation. Like $I^2 > 50\%$ or $P < .05$ indicates statistical heterogeneity among literature, the random effect model merges effect size; otherwise, the fixed effect model merges effect size. Weigh mean difference (WMD) and 95% confidence interval (95% CI) are used to calculate the combined effect size of measurement data, RR is used as the comprehensive effect, and 95% CI is used for interval evaluation. The publication bias test was performed using the funnel plot and Egger's test, with the test level of $\alpha = 0.05$.

Figure 1. Literature screening process



RESULTS

Basic characteristics of the included literature

Search for the keywords related to the topic in the relevant database, find the literature, and then read the abstract first, download the inclusion criteria and read carefully, and screen according to the exclusion criteria. The search yielded 5 articles in Chinese and 84 articles in English. The literature was downloaded and read, and 7 articles were finally screened.[7-13] The literature screening flow chart is shown in Figure 1. A total of 9132 patients were included in the 7 articles, including 3356 patients in the observation group and 5776 patients in the control group. Various treatments such as ivermectin, azithromycin, and hydroxychloroquine are involved (Table 1).

Meta-analysis results of Ivermectin

Clinical effects of ivermectin in COVID-19 patients. A total of three publications reported the treatment with ivermectin in patients with COVID-19, and the Meta-analysis showed no clinical heterogeneity and statistical heterogeneity among the studies ($I^2 = 15\%$, $P = .31$), a fixed effect model was used to incorporate effect sizes. The clinical effect of the observed group was not different from the control group [OR = 0.65,95% CI (0.35,1.19), $P = .16$]. See Figure 2.

Publication bias. Using funnel plot and Egger's test, none of the three ivermectin documents with clinical effect were significant ($P > .05$), suggesting no publication bias, as shown in Figure 3.

Meta-analysis results of azithromycin

Clinical effect of azithromycin in COVID-19 patients. A total of four publications reported the treatment with azithromycin in patients with COVID-19, and the Meta-analysis showed no clinical and statistical heterogeneity

Figure 2. Forest plot of the clinical effect analysis of ivermectin in COVID-19 patients

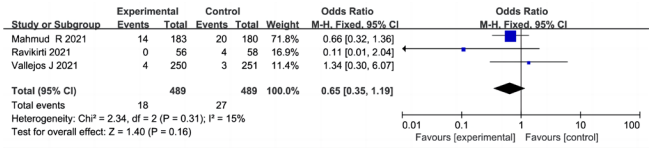


Figure 3. Funnel diagram of the clinical effect analysis of ivermectin in COVID-19 patients

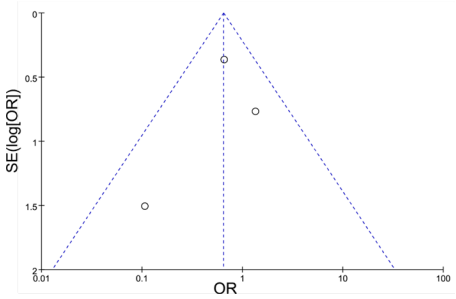


Figure 4. Forest plot of the clinical effect analysis of azithromycin in COVID-19 patients

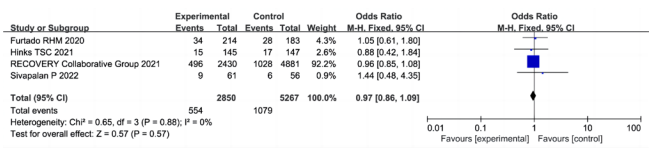
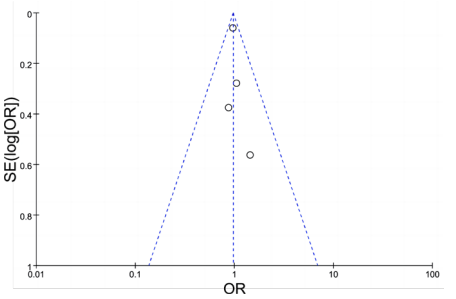


Figure 5. Funnel plot of the clinical effect analysis of azithromycin in COVID-19 patients



between the studies (I^2 = 0%, P = .88), using a fixed-effect model to incorporate the effect sizes. The clinical effect of the observed group was not different from the control group [OR = 0.97,95% CI (0.86,1.09), P = .57]. See Figure 4.

Publication bias. The included literature was tested for publication bias using the funnel plot and Egger's test, and none of the four azithromycin articles with clinical effect was statistically significant (P > .05), suggesting no publication bias, as shown in Figure 5.

DISCUSSION

In this meta-analysis including 7 studies, we demonstrated the use of antimicrobial drugs in patients does not significantly improve the clinical efficacy during the COVID-19 pandemic, so antibiotic drug use is recommended only for patients with complicated bacterial infections.

Since the outbreak of COVID-19 in Wuhan in December 2019, with the development and application of strong prevention and control measures, the epidemic in China has been initially brought under control, but the global number of incident cases has increased rapidly. By October 2022, more than 600 million people had been confirmed worldwide, with more than 6 million cumulative deaths reported. [14]

COVID-19 mainly focuses on supportive treatment, with no specific treatment.[15] Whether to use antimicrobial drugs based on symptomatic treatment has always been a topic of clinical controversy.[16-17] A web-based questionnaire in Malaysia revealed that in terms of antibiotics knowledge, 779 (36.8%) respondents in 1405 cases were aware that taking antibiotics could not speed up the recovery process of all infections.[16] Less than half of the respondents (49.0%) knew that antibiotics are effective against bacterial infection only.[16] That demonstrated that knowledge of antibiotic use and resistance was poor.[14] The other survey was completed by 166 participants from 23 countries and 82 different hospitals.[17] Local guidelines for antibiotic use in COVID-19 patients were reported by 61.8% of participants and for 82.9% they did not differ from local community-acquired pneumonia guidelines. Clinical presentation was recognized as the most important reason for the start of antibiotics. When antibiotics were started, most respondents rated as the highest the need for coverage of atypical pathogens, followed by Staphylococcus aureus. In the patients on the ward, 29.1% of respondents chose not to prescribe any antibiotics. A combination of β-lactams and macrolides or fluoroquinolones was reported by 52.4% of respondents. In patients in the ICU, piperacillin/tazobactam was the most commonly prescribed antibiotic. The mean reported duration of antibiotic treatment was 7.12 days.[17]

At present, there are more reports of antimicrobial use in COVID-19 patients, but few controlled studies, mainly in foreign countries.[18] Bacterial co-infection was uncommon among COVID-19 patients, yet the use of antibiotics was high. There is insufficient evidence to support the widespread use of empiric antibiotics in these patients. Most may not require empiric treatment and if they do, there is promising evidence regarding azithromycin as a potential COVID-19 treatment.[14]

Although there has been a rapid increase in COVID-19-related publications recently, none are specific to the use of procalcitonin (PCT) to guide antimicrobial de-escalation in critically unwell patients with COVID-19 pneumonia. A meta-analysis concluded that PCT > 0.5 ng/mL is associated with an increased risk of progression to critical illness particularly when the white blood cell is initially normal or reduced.

The current review explored that most of the studies used antibiotics such as azithromycin or ivermectin.[19-20] To further understand the therapeutic effect of antibiotics in COVID-19 patients, this study further clarified the clinical effect of antibiotics in COVID-19 patients through meta-analysis, to provide a basis for the clinical use of antibiotics for COVID-19. During the search process, only 5 Chinese documents and 84 English documents were found. After extensive reading of the literature, it has been found that most doctors may apply

antibiotics in COVID-19 patients for the following considerations: (1) unknown etiology, bacterial infection and empirical use of drugs cannot be excluded; (2) clear etiology and preventive use; (3) use of drugs with nosocomial infection.[19] In India, a significant increase in non-CAF antibiotic sales, particularly azithromycin, occurred during the peak phase of the first COVID-19 epidemic wave, indicating the need for urgent antibiotic stewardship measures.[21]

In the present study, a total of seven control study experiments were finally selected through preliminary reading and screening. The commonly used drugs are ivermectin and azithromycin. According to the different experimental drugs, the clinical effect of the two antimicrobial drugs on COVID-19 patients with COVID-19 was observed. The results showed that there were three articles using ivermectin, with no clinical heterogeneity ($I^2 = 15\%$, $P = .31$). Select a fixed-effect model to incorporate the effect sizes. The results showed that the clinical effect of the observed group was not different from the control group [OR=0.65,95% CI (0.35,1.19), $P = .16$]. The results suggest that ivermectin does not improve treatment efficacy in COVID-19 patients. For observing azithromycin application, there were four articles with no clinical heterogeneity ($I^2 = 0\%$, $P = .88$). Select a fixed-effect model to incorporate the effect sizes. The results showed that the clinical effect of the observed group was not different from the control group [OR = 0.97, 95% CI (0.86, 1.09), and $P = .57$]. The results suggest that azithromycin administration also does not promote the clinical effect in COVID-19 patients.

Compared with study,[5] nineteen clinical studies reporting data from 2834 patients were included. The mean rate of antibiotic use was 74.0 % of cases. Half the studies reported the occurrence of a bacterial co-infection or complication. Among the latter, at least 17.6 % of patients who received antibiotics had secondary infections. Pooled data from 4 studies show that half of the patients receiving antibiotics were not severe nor critical. The study demonstrated a major use of antibiotics among COVID-19 hospitalized patients, mainly in an empirical setting. There is no proven efficacy of this practice.[5] The results were consistent with the current meta-analysis.

In summary, it is believed that the use of antimicrobials for COVID-19 will not improve the treatment effect of patients, so prophylactic medication is not recommended, as prophylactic medication may lead to various adverse reactions. For novel COVID-19 patients with clear evidence of bacterial infection or hospital-acquired infection, they can be combined with antimicrobials to provide antimicrobial treatment.[22]

The present study must be interpreted within the context of its potential limitations. Firstly, the number of included studies is relatively small. Secondly, sensitivity analyses: As a result of the limited number of included studies for each outcome, we couldn't precisely perform sensitivity analyses. Thirdly, the included studies did not have the same criteria for disease stages, which may have been substantially detrimental to the explanation of the pooled results. Fourthly, the included studies are mainly observative, partially hindering the explanation of the causation and effect.

CONCLUSION

In conclusion, the use of antimicrobial drugs in patients does not significantly improve clinical efficacy during the COVID-19 pandemic, so antibiotic drug use is recommended only for patients with complicated bacterial infections.

COMPETING INTERESTS STATEMENT

There are no competing interests for any author.

FUNDING STATEMENT

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DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request. No additional unpublished data are available.

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