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Antibiotics in the prophylaxis of COVID or in the treatment of mild COVID

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct and to assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical condition of each patient.

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Societies: Associação Médica Brasileira, Sociedade Brasileira de Infectologia and Sociedade Brasileira de Pneumologia e Tisiologia.

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CLINICAL QUESTION

In patients at risk or diagnosed with mild COVID-19, does the prophylactic use of antibiotics reduce the occurrence of infection (PCR positive), hospitalization, and mechanical ventilation or mortality, and does it not increase the risk of adverse events?

METHOD

Eligibility criteria for the studies to be included

PICO

Patient: risk of COVID or mild COVID confirmed by PCR

Intervention: antibiotics (not associated)

Comparison: no antibiotic or placebo

Outcome: infection (PCR+), hospitalization (ward or intensive care unit [ICU]), mechanical ventilation, mortality, and adverse events

Study design

Phase 3 randomized controlled trials (RCTs) and Phase 3 RCT systematic reviews meeting PICO

No limits on time consulted, language or full text availability.

Bases consulted with the respective strategies

Medline and EMBASE

#1 = COVID OR COV OR CORONAVIRUS OR SARS

#2 = (Anti-Bacterial Agents OR Antibacterial Agents OR Antibacterial Agent OR Anti-Bacterial Agent OR Anti Bacterial Agent OR Anti-Bacterial OR Anti Bacterial OR Bacteriocidal Agent OR Bacteriocide OR Bacteriocides OR Antibiotics OR Antibiotic)

#3 = #1 AND #2

#4 = #3 AND Random*

Clinical trials

COVID AND Antibiotics

Extracted data

Data on authorship, year of publication, description of patients, interventions (antibiotics and comparison), outcomes, and follow-up time will be extracted from the works.

Risk of bias and quality of evidence

The risk of bias will be assessed using the items in Rob 2[1], plus other fundamental elements, and expressed as very serious, serious, or not serious. The quality of evidence will be extrapolated from the risk of bias obtained from the study(s) (if there is no meta-analysis) using the GRADE[2] terminology in very

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low, low, and high and through the GRADEpro[2] software (if there is a meta-analysis) into very low, low, moderate, and high.

Analysis and synthesis of outcomes

The outcomes, when categorical, will be expressed by group (antibiotics and comparison) and through the number of events and the calculated risk (%) for each group (dividing the number of events by the total number of patients in each group). If the difference in risk (DR) between the groups is significant (95% confidence interval), it will be expressed accompanied by the 95% confidence Interval (95%CI) and the Number Needed to Treat (NNT) or to Produce Harm (NNH). If there is more than one study included with common outcomes, they will be aggregated through meta-analysis using the RevMan 5.4 software[3].

RESULTS

At the sources of scientific information, 288, 317, and 301 studies were recovered in Medline, Embase and Clinical trials, respectively. By eliminating duplicates and meeting the eligibility criteria, six studies were selected so that their full texts could be accessed, from which four works[4-7] were excluded (exclusion reasons in Table 1 worksheet – inclusion/exclusion reasons). Therefore, there are currently two randomized trials available to support this assessment, meeting the eligibility criteria adopted[8, 9]. It was not possible to aggregate the results of the two studies selected through meta-analysis because the primary outcomes analyzed were different, in addition to differences in the populations studied, in the form of the intervention and in the comparisons.

The Azithromycin for COVID-19 Trial study, Investigating Outpatients Nationwide (ACTION) was a 2:1 randomized clinical trial that evaluated the efficacy of a single 1.2 g oral dose of azithromycin compared to placebo on self-reported COVID-19 symptoms among outpatients[8].

Participants were eligible for the study if they had a documented positive SARS-CoV-2 test result (nucleic acid or antigen amplification) within 7 days prior to enrollment[8].

Participants were randomized in a 2:1 ratio to azithromycin or matching placebo. Randomization was unrestricted (no blocking or stratification), and the sequence was generated by the study's unmasked data team using a computer-generated pseudo-random number generator[8].

To facilitate allocation masking and concealment, letters were randomly assigned (e.g., A, B, and C; six letters total) to each study treatment (azithromycin or placebo). Study medication vial labeling was identical with the exception of the treatment letter to allow for masking of investigators, study staff, and participants. After randomization, participants received a single oral dose of 1.2 g of azithromycin suspension or matching placebo by overnight mail. The placebo was specifically formulated to combine with azithromycin. Allocation was concealed by not revealing the letter randomly assigned to the participant until enrollment and baseline assessments were completed[8].

Prespecified primary end point was the self-reported absence of symptoms of COVID-19 on day 14. The prespecified secondary end points included adverse events on day 3, hospitalization and/or death on day 21, emergency department and/or use of urgent care on day 21, household members who were diagnosed with or developed symptoms of COVID-19 on day 21, and patient-reported COVID-19 symptoms on day 21 (including fever, cough, diarrhea, abdominal pain, anosmia, conjunctivitis, pain sore throat, shortness of breath, myalgia, fatigue, dizziness, and an open "other" category). Participants completed online surveys on days 3, 7, 14, and 21 after enrollment to assess results[8].

A total of 263 participants were enrolled, of which 171 were randomized to azithromycin and 92 to placebo, with 76% completing the study visit on day 14 (77% in the azithromycin group and 76% in the placebo group)[8].

Table 1. Antibiotics COVID prophylaxis or treatment of mild COVID.

PMID	First author	Journal/book	Publication year	DOI	Included/excluded (reasons)
33676597	PRINCIPLE Trial Collaborative Group	*Lancet*	2021	10.1016/S0140-6736(21)00461-X	Excluded (trial phase ii)
32853672	Sekhavati E	*Int J Antimicrob Agents*	2020	10.1016/j.ijantimicag.2020.106143	Excluded hospitalized
32706953	Cavalcanti AB	*N Engl J Med*	2020	10.1056/NEJMoa2019014	Excluded association
32205204	Gautret P	*Int J Antimicrob Agents*	2020	10.1016/j.ijantimicag.2020.105949	Excluded association
34269813	Oldenburg CE	*JAMA*	2021	10.1001/jama.2021.11517	Included
34252378	Hinks TSC	*Lancet Respir Med*	2021	10.1016/S2213-2600(21)00263-0	Included

	Absence of symptoms Number/total (%) Azithromycin	Placebo	Difference in prevalence % (95%CI)
All participants	66/131 (50)	35/70 (50)	0 (–14 to 15)
Asymptomatic	9/10 (90)	3/4 (75)	15 (–46 to 76)
Symptomatic	57/120 (48)	32/66 (48)	–1 (–17 to 15)

On day 3, more participants reported gastrointestinal adverse events in the azithromycin group compared to placebo, including diarrhea (azithromycin: 41%; placebo: 17%), abdominal pain (azithromycin: 17%; placebo: 1%), and nausea (azithromycin: 22%; placebo: 10%). There were no significant differences in self-reported specific COVID-19 symptoms reported at day 14. No serious adverse events were reported and there were no deaths in any of the study groups. Among the participants followed up to day 21, five reported being hospitalized, all in the azithromycin group. Emergency/urgent care visits in the azithromycin group were significantly higher than in the placebo group (azithromycin: 14%; placebo: 3%; difference, 12%; 95%CI 3%–20%; p=0.01)[8].

ATOMIC 2 was a prospective, open-label, two-arm, randomized superiority study of standard care and azithromycin compared to standard care alone[9].

Eligible participants were adults aged at least 18 years assessed at an acute care hospital with a clinical diagnosis of highly probable or confirmed COVID-19 infection made by the clinical staff, with onset of symptoms within the last 14 days and assessed by the attending physician and clinical staff as appropriate for initial outpatient (i.e., outpatient) management[9].

Patients were randomly assigned (1:1) to azithromycin plus standard care or standard care alone using an automated web-based service, with a minimization algorithm to ensure balanced allocation between treatment groups, stratified by center, sex, and attendance of hypertension and diabetes. To ensure the unpredictability of treatment allocation, the first 30 participants were randomly assigned by simple randomization and the minimization algorithm included a probabilistic element (participants had an 80% chance of being allocated to treatment, which minimized imbalance between groups). Patients, investigators, and health care professionals were not masked to study drug assignment[9].

Patients in the azithromycin group received 500 mg of azithromycin once daily orally plus standard care for 14 days, and those in the control group received standard care as per local guidelines[9].

The primary end point was the proportion of participants with hospital admission or death from any cause within 28 days of randomization. Secondary outcomes were the proportion of participants admitted to hospital with respiratory failure requiring noninvasive mechanical ventilation (level 2) or invasive mechanical ventilation (level 3) or death from any cause within 28 days of randomization[9].

Of the 295 participants, 147 were randomly assigned to azithromycin plus standard care and 148 were randomly assigned to standard care alone. Of the 295 patients, 3 withdrew consent after randomization; thus, data on the primary outcome were available from 292 participants[9].

Mortality from all causes	1/145 (1%)	1/147 (1%)
Hospitalization or death (ITT)	15/145 (10%)	17/147(12%)
Level 2 or 3 ventilation or death	2/145 (1%)	2/147 (1%)

Risk of bias

The risk of bias in both included studies is high, giving consequently a low quality of evidence to the results (Table 2).

SUMMARY OF THE EVIDENCE (CONCLUSION)

The evidence based on RCTs available at the moment does not support the indication of prophylactic antibiotic therapy or specific therapy for patients with mild COVID-19, because when compared with conventional treatment or placebo, there are no differences in the presence of symptoms, hospitalization rates, mortality, or the need for ventilation. In addition,

Table 2. Risk of bias.

First author	Year	Randomization	Blind allocation	Double blind	Outcome researcher blind	Lost	Prognostic characteristics	Appropriate outcomes	Intention to treat analysis	Sample size calculation	Early interruption
Oldenburg CE	2021										
Hinks TSC	2021										
LEGENDA		High risk			Not informed			Low risk			

the group of intervention had more adverse effects and a low quality of evidence.

AUTHORS' CONTRIBUTIONS

ANB: study concept and design, critical review and approval of the final version. **AS:** data collection, statistical analyses and interpretation of data, drafting of the manuscript. **HB:** study concept and design. **IF:** data collection, statistical analyses and interpretation of data, drafting of the manuscript. **ST:** study concept and design, data collection, statistical analyses and interpretation of data, drafting of the manuscript, critical review and approval of the final version. **WB:** study concept and design, data collection, statistical analyses and interpretation of data, drafting of the manuscript, critical review and approval of the final version.

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