

Too many antibiotics for patients with COVID-19 despite low bacterial infections



Although low rates of bacterial infections have frequently been reported in patients hospitalised with COVID-19, excessive use of antibiotics has also been described in this population since the beginning of the COVID-19 pandemic.¹⁻⁵

In this issue of *The Lancet Infectious Diseases*, Justin Chen and colleagues⁶ report the results of a non-inferiority, pragmatic, cluster-randomised trial, with randomisation at the bed level, in three hospitals in Edmonton, AB, Canada. The authors aimed to assess the efficacy and safety of an antimicrobial stewardship prospective audit and feedback intervention in patients admitted to hospital for the treatment of COVID-19. The primary endpoint was clinical status on postadmission day 15, defined using a seven-point ordinal scale from 1 (not hospitalised and able to resume normal daily activities) to 7 (death). Overall, 886 patients were enrolled between March 1 and Oct 29, 2021, of whom 429 in the intervention group and 404 in the standard of care group completed the study. The characteristics of patients were similar between groups, with a mean age of 56.7 years and a median baseline clinical status of 4 (hospitalised and on supplemental oxygen). 124 (15%) of 833 patients were directly admitted to the intensive care unit. Overall, 438 (53%) of 833 patients were treated with antibiotics, despite a low burden of culture-positive bacterial co-infections (15 [2%] patients with positive blood cultures and 15 [2%] with positive respiratory cultures). A total of 301 prospective audit and feedback audits were conducted in the intervention group. The majority of interventions pertained to the discontinuation of antibiotics or to a reduction in the duration of antibiotic therapy. The acceptance rate of antimicrobial stewardship recommendations in the intervention group was 84%, and antibiotic use was eventually lower in the intervention group than in the standard of care group (length of therapy 364.9 vs 384.2 days per 1000 patient days). With a predefined margin of 0.5, non-inferiority was achieved on the basis of a median clinical status at postadmission day 15 of 2.0 (IQR 2–3) in the intervention group and 2.0 (2–4) in the standard of care group ($p=0.37$, Mann-Whitney U test). Secondary, exploratory endpoints were similar

between the intervention group and the standard of care group (11% vs 13% for in-hospital mortality, 11% vs 12% for 30-day mortality, 7 days vs 7 days for median acute length of stay, 4% vs 5% for 30-day readmission rates, <1% vs 0% for *Clostridioides difficile* infection, and 3% vs 3% for isolation of multidrug-resistant organisms), as were adverse events, measured as neutropenia (3% vs 5%) and acute kidney injury (18% vs 19%).⁶

Some notable limitations preclude a firm generalisation of results. For example, a possible bias towards non-inferiority could result from factors not accounted for in the study that could favourably affect the prognosis of patients with COVID-19 (and, indirectly, their risk of superinfections), such as improvements in the prevention and treatment of moderate or severe COVID-19 due to the availability of vaccines, antiviral agents, monoclonal antibodies, and anti-inflammatory drugs.⁷⁻⁹ The lack of information about COVID-19 vaccination rates in enrolled patients is also a major limitation of the study. Furthermore, the very low rate of infectious diseases consultations during the study period (10 [1%] of 833 patients) should be noted, as whether the favourable effect of the antimicrobial stewardship intervention would be similar in other settings with higher baseline rates of consultations with antibiotic therapy experts is uncertain.

Nonetheless, to the best of our knowledge, this is the first randomised trial assessing the efficacy and safety of an antimicrobial stewardship intervention in patients hospitalised with COVID-19, and provides a higher-than-usual certainty of evidence that reducing antibiotic use in such patients is possible without substantial harm. Despite the mentioned limitations, this message remains crucial in light of the discrepancy observed between the high frequency of patients who were treated with antibiotics (53%) and the low frequency of culture-confirmed bacterial infections (4%).⁶ Although not reaching the very high rates of antibiotic prescriptions registered at the beginning of the pandemic (70–100% of patients in most studies),^{2,3} the frequency of antibiotic use recorded by Chen and colleagues⁶ still remains uncomfortably high from an



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Lancet Infect Dis 2023

Published Online
January 27, 2023
[https://doi.org/10.1016/S1473-3099\(22\)00866-0](https://doi.org/10.1016/S1473-3099(22)00866-0)
See Online/Articles
[https://doi.org/10.1016/S1473-3099\(22\)00832-5](https://doi.org/10.1016/S1473-3099(22)00832-5)

antimicrobial stewardship perspective, and strikingly similar to the pooled value reported in a recent meta-analysis (62%), again despite a low pooled frequency of bacterial infections in this meta-analysis (6%).⁴ Although some encouraging steps forward have been made, a lot of ground is still left to cover.

MB reports research grants and personal fees as an advisor, consultant, and speaker from BioMérieux, Cidara, Gilead, Menarini, MSD, Pfizer, and Shionogi, all outside the submitted work. DRG reports investigator-initiated grants from Pfizer, Shionogi, and Gilead Italia; personal fees as a speaker from Pfizer; and personal fees as a speaker and advisor for Tillotts Pharma; all outside the submitted work.

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- 1 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054–62.
- 2 Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis* 2020; **71**: 2459–68.
- 3 Lansbury L, Lim B, Baskaran V, et al. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect* 2020; **81**: 266–75.
- 4 Alshaikh FS, Godman B, Sindi ON, et al. Prevalence of bacterial coinfection and patterns of antibiotics prescribing in patients with COVID-19: a systematic review and meta-analysis. *PLoS One* 2022; **17**: e0272375.
- 5 De Waele JJ, Derde L, Bassetti M. Antimicrobial stewardship in ICUs during the COVID-19 pandemic: back to the 90s? *Intensive Care Med* 2021; **47**: 104–06.
- 6 Chen JZ, Hoang HL, Yaskina M, et al. Efficacy and safety of antimicrobial stewardship prospective audit and feedback in patients hospitalised with COVID-19 (COVASP): a pragmatic, cluster-randomised, non-inferiority trial. *Lancet Infect Dis* 2023; published online Jan 27. [https://doi.org/10.1016/S1473-3099\(22\)00832-5](https://doi.org/10.1016/S1473-3099(22)00832-5).
- 7 Watson OJ, Barnsley G, Toor J, et al. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis* 2022; **22**: 1293–302.
- 8 Närhi F, Moonesinghe SR, Shenkin SD, et al. Implementation of corticosteroids in treatment of COVID-19 in the ISARIC WHO Clinical Characterisation Protocol UK: prospective, cohort study. *Lancet Digit Health* 2022; **4**: e220–34.
- 9 Cohen MS. Early treatment to prevent progression of SARS-CoV-2 infection. *Lancet Respir Med* 2022; **10**: 930–31.