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Letter to the Editor

Underestimation of co-infections in COVID-19 due to non-discriminatory use of antibiotics

Dear Editor,

Coronavirus disease 2019 (COVID-19) pandemic is causing huge impacts on health and social care systems globally. Several health authorities have published their guidelines for COVID-19 diagnosis and treatment including the administration of antimicrobial agents. Both guidelines for COVID-19 management by the UK National Institute for Health and Care Excellence and by World Health Organization discourage antibiotic therapy or prophylaxis for suspected COVID-19 patients and confirmed patients with mild symptoms, but suggest to prescribe antibiotics for suspicious bacterial infections.^{1,2} The US National Institutes of Health guideline³ indicates that no sufficient data supports empirical antibiotic therapy, but acknowledges that some clinicians routinely administer broad-spectrum antibiotics to all patients with moderate or severe hypoxemia. The latest version of Chinese clinical guideline for COVID-19 diagnosis and treatment published in March 2020 only suggests to avoid inappropriate use of antibacterial drugs, especially the broad-spectrum ones, but without clear explicitness for empirical antibiotic therapy or prophylaxis.⁴ This suggests that the administration of antibiotics on suspected COVID-19 patients is heavily dependent on the judgement and experience of frontline clinicians, especially at the early stage of pandemic outbreak.

Learnt from the past influenza epidemics or pandemics, bacterial co/secondary infection is one of the major causes of fatalities. Antibiotic prophylaxis seems to be a reasonable approach to reduce potential morbidity and mortality in lower and upper respiratory infections such as pneumonia with unclear aetiological agents. Therefore, during the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 and the more recent Middle East Respiratory Syndrome (MERS) outbreak in 2012, most suspected patients were administered with potent broad-spectrum antibiotics even before the confirmation of the aetiological agents.^{5,6} This empirical procedure may be applied to treat COVID-19.

In the early outbreaks of COVID-19 in Wuhan, China occurred in late 2019, Chen et al. reported that 77 (71%) of their patients ($n=99$) received antibiotic treatment and only 1 (1%) patients developed bacterial co-infection.⁷ Later, Zhou et al. studied a bigger cohort ($n=191$) in Wuhan showing that 181 (95%) patients received antibiotics and 28 (15%) patients suffered secondary infections including 1 (1%) of 137 survivors and 27 (50%) of 54 non-survivors.⁸ A recent literature mining study on three coronavirus diseases revealed a very low identified/reported co-infection rate in SARS-1 (6%) and MERS (17%) patients. For the COVID-19, only 8% of patients with co-infections were reported, although 72% of the patients received antimicrobial therapy.⁹ Lansbury L and colleagues have written to this Journal for their systematically search from

literature between 1 January 2020 to 17 April 2020 for studying secondary infections in COVID-19 patients. From their results, only 7% of hospitalised COVID-19 patients had bacterial co-infections. Remarkably, Lansbury's analysis showed that 17 out of 30 studies, mainly in China, indicated the antibiotic usage and >90% of patients in 10 of these studies received empirical antibiotic treatments.¹⁰

It is unclear that the reported low co-infection rate is the result of large scales of empirical antimicrobial administration or the limitation of the overwhelmed clinical examinations in health systems during the pandemic. We concern the underestimation of the co-infections in COVID-19 patients, especially those on invasive mechanical ventilation support. However, we are also aware of the long-term impact of the development of antimicrobial resistance due to unnecessary usage of antimicrobial agents. We urge to re-establish the stewardship of antimicrobial therapy by systematic surveillance on antimicrobial usage and co-infections in COVID-19 patients. Future development in fast diagnosis for infectious agents based on genomics or proteomics identification will provide timely and accurate information for disease management. It is essential to develop evidence-based guidelines for responding the potential second wave of COVID-19 or future pandemics.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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References

- COVID-19 rapid guideline: managing suspected or confirmed pneumonia in adults in the community, 2020. Available at <https://www.nice.org.uk/guidance/ng165>. Accessed [June 24 2020].
- Clinical management of COVID-19, 2020. Available at <https://www.who.int/publications/i/item/clinical-management-of-covid-19>. Accessed [June 24 2020].
- COVID-19 Treatment Guidelines Panel. Coronavirus disease 2020 (COVID-19) treatment guidelines. National Institutes of Health, 2020. Available at <https://www.covid19treatmentguidelines.nih.gov/>. Accessed [June 24 2020].
- Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition in Chinese), 2020. Available at <http://www.nhc.gov.cn/jzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml>. [June 24 2020].
- Tsang K, Zhong NS. SARS: pharmacotherapy. *Respirology* 2003;**8**:S25–30.
- Rabaan AA, Alahmed SH, Bazzi AM, Alhani HM. A review of candidate therapies for Middle East respiratory syndrome from a molecular perspective. *J Med Microbiol* 2017;**66**:1261–74.

7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;**395**:507–13.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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.
9. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis* 2020:ciaa530. doi:[10.1093/cid/ciaa530](https://doi.org/10.1093/cid/ciaa530).
10. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect* 2020. doi:[10.1016/j.jinf.2020.05.046](https://doi.org/10.1016/j.jinf.2020.05.046). published online May 23.

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