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LETTER TO THE EDITOR

Use of Azithromycin in COVID-19: A Cautionary Tale

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The novel coronavirus disease 2019 (COVID-19) pandemic has seen many drugs being repositioned or repurposed for the treatment of COVID-19. Among the repurposed drugs, azithromycin has caught the limelight, where it is frequently administered to patients with COVID-19 alongside chloroquine or hydroxychloroquine. We appreciate the efforts by Bleyzac and colleagues, who comprehensively summarised the pharmacological and therapeutic properties of azithromycin in the treatment of COVID-19, including the concerns regarding prolongation of the QT interval, which may lead to fatal cardiac events [1]. However, we are also concerned about the emergence of microorganisms resistant to azithromycin and related macrolides, such as clarithromycin and erythromycin, in relation to the unrestricted use of azithromycin amid the COVID-19 pandemic.

Azithromycin and other macrolides have been largely used to treat infections from Gram-positive microorganisms, including *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, and group A, B, C, and G *Streptococcus*, but azithromycin also possesses satisfactory activity against different gram-negative microorganisms, including *Haemophilus* spp., *Moraxella catarrhalis*, *Escherichia coli*, *Salmonella* spp., *Yersinia enterocolitica*, *Shigella* spp, *Campylobacter jejuni*, *Vibrio cholerae*, *Neisseria gonorrhoeae*, and *Helicobacter pylori* [2]. In fact, azithromycin is active against atypical pneumonia pathogens, including *Legionella pneumophila*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* [2].

Nevertheless, acquired macrolide resistance is an increasingly recognised problem. The development of acquired resistance towards azithromycin and other related macrolides is associated with active macrolide efflux pumps produced by the bacteria [3]. Active macrolide efflux pumps are encoded by the macrolide efflux genes *MSRA* and *MSRB*. These efflux pumps are part of the bacterial systems involved in the extrusion of molecules from bacteria to the environment, including bacterial products such as siderophores, as well as toxic compounds and macrolide antibiotics.

Similar to resistance with other antimicrobial agents, widespread and unrestricted use has been associated with the development of resistance towards azithromycin and other related macrolides. Such association was directly illustrated in a controversial randomised, double-blind trial in which 224 healthy volunteers were assigned to either azithromycin, clarithromycin, or placebo to determine the development of pharyngeal carriage of macrolide-resistant streptococci [4]. At baseline, the proportion of macrolide-resistant streptococci was 26–30%. Both macrolides significantly increased the proportion of macrolide-resistant streptococci compared with placebo, peaking at days 4–8, with a mean increase of approximately 50% (to an absolute proportion of more than 80%), compared with 4% with placebo. Indeed, the increase in resistance was greater with azithromycin compared with clarithromycin, possibly due to its much longer half-life.

We have observed increasing resistance of azithromycin towards *Treponema pallidum*, the causative pathogen of syphilis, which therefore renders azithromycin out of favour as the treatment option for this infection [5]. History may repeat itself if we do not practice judicious use of azithromycin. With the possible more widespread use of azithromycin to treat COVID-19, we may lose azithromycin in our antimicrobial armamentarium to treat bacterial infections, for which the role of azithromycin has been well-established, including community-acquired pneumonia, non-tuberculous mycobacterial infections, and Group A streptococcal pharyngitis. We urge clinicians managing patients with COVID-19 to factor into consideration the possible development of acquired resistance when prescribing azithromycin, especially in regions where azithromycin resistance is already a concern.

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Declarations

Conflicts of Interest Chia Siang Kow and Syed Shahzad Hasan declare no potential conflicts of interest.

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