Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Macrolides for patients with COVID-19 and concurrent pertussis infection

Dear Editor,

We read with interest the study by He et al. (He et al., 2020) which compared the type and frequency of bacterial co-infections between patients with coronavirus disease 2019 (COVID-19) and patients with other viral pneumonia. The authors (He et al., 2020) observed that the rate of pertussis co-infection was significantly higher in patients with COVID-19 pneumonia compared to patients with other viral pneumonia. Therefore, pertussis co-infection should be one of the differential diagnoses in patients with COVID-19 demonstrating persistent coughing.

Macrolides are the preferred antibiotic therapy for pertussis infection (Kilgore et al., 2016). In a Cochrane review which included 13 randomized controlled trials to evaluate the effectiveness of antimicrobial treatment for pertussis infection, it was observed that macrolide antibiotics (azithromycin, clarithromycin, and erythromycin) were effective for the eradication of *Bordetella pertussis* from the nasopharynx, either with the short-term or the long-term duration of antibiotic therapy (Altunaiji et al., 2012).

Nonetheless, we are concerned with the use of macrolides among patients with COVID-19 and concurrent pertussis infection. One of the macrolides, azithromycin, has been repurposed for the treatment of COVID-19, with or without combination with the antimalarials, chloroquine, and hydroxychloroquine. While the effectiveness of azithromycin has yet to be conclusively proven, there have been safety concerns with its use in COVID-19. A recent systematic review and meta-analysis reported an increased risk of death with the use of azithromycin in combination with hydroxychloroquine though this was not the case for the use of hydroxychloroquine alone, among patients with COVID-19 (Fiolet et al., 2020).

Though some may believe that prolongation of the QTc interval with the use of azithromycin in combination with hydroxychloroquine may be the cause of increased death in this patient population, such prolongation does not increase the risk of arrhythmia since azithromycin prolongs the action potential instead of prolongs repolarization which tends to cause torsades de pointes (Milberg et al., 2002). Instead, azithromycin (and possibly clarithromycin) could induce a novel proarrhythmic syndrome characterized by rapid, polymorphic ventricular tachycardia in the absence of QTc prolongation, due to intracellular loading of sodium ions with subsequent potentiation of sodium current in the cardiac cells and dysregulation of cardiac calcium homeostasis (similar to digoxin therapy) (Yang et al., 2017).

In fact, an analysis of more than 1 million azithromycin exposures (before the COVID-19 pandemic) reported that the use of azithromycin significantly increased the hazard of cardiovascular death (Zaroff et al., 2020). Likewise, a follow-up study of a randomized trial evaluating 4,373 patients with stable coronary heart disease who received either clarithromycin or placebo for the treatment of atherosclerosis reported an increased risk of cardiovascular mortality with the use of clarithromycin during the first three years of follow-up (Winkel et al., 2015).

These findings warrant further exploration, but in the meantime, macrolides should be administered with caution in patients with COVID-19 since COVID-19 has been associated with myocardial injury, and administration of macrolides may add to the cardiac insult. This may be the reason for the increased risk of death with the use of azithromycin in combination with hydroxychloroquine in this patient population. Trimethoprim-sulfamethoxazole is an acceptable alternative to macrolides; in the aforementioned Cochrane review, trimethoprim-sulfamethoxazole was also effective for the eradication of *Bordetella pertussis* (Altunaiji et al., 2012).

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Conflict of interest

The authors have no conflicts of interest to declare.

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