

## LETTER TO EDITOR

### Antibiotic stewardship in COVID19 pandemic

Respected editor,

It is estimated that worldwide approximately 700000 deaths occur annually due to antibiotic resistance. The UN Interagency Coordination Group on Antimicrobial Resistance has warned that antibiotic resistance could cause 10 million deaths each year by 2050. History has witnessed a deadly pandemic of 1918, that affected 1/3rd of world population and resulted in nearly 50 million deaths, and most of the deaths were attributed to secondary bacterial infections based on post mortem studies<sup>1,2</sup>. During influenza pandemic in 2009, bacterial infections were reported in patients of H1N1 to the extent of 30% in some studies<sup>3</sup>. Likewise, possibility of co-infection or secondary bacterial infection in patients of COVID19 remains a driving stimulus for use of antibiotics; thus, rising concern of antibiotic resistance. Antibiotics are used in severe COVID19 illness worldwide with many guidelines advocating their use<sup>4</sup>. However, with nearly two years of journey into current pandemic, how much are we justified with the routine use of antibiotics in treatment of COVID19 illness?

Russell et al conducted a prospective cohort study to decipher the incidence of co-infection and super-infection in COVID19 patients admitted to 260 hospitals in UK<sup>5</sup>. More than 48000 patients were included in the study, with microbiological data available in 8649 patients. Positive results were rare (12.7%) among which majority had a secondary bacterial infection (positive culture after 2 days of hospitalization) and minority of patients had a co-infection (positive culture within 2 days of hospitalization). *Staphylococcus aureus* and gram negative bacteria were most commonly isolated. A meta-analysis reported similar results with bacterial co-infection reported in 3.5% of patients, and secondary bacterial infection in 14.3% of patients, with an overall 6.9% of patients having evidence of bacterial infection<sup>6</sup>. A study from India reported 13% and

15% of COVID19 patients admitted to wards and ICU respectively had associated bacterial infection. Multi drug resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii* were the most commonly isolated organisms<sup>7</sup>.

Although these studies infer that most of COVID19 patients do not harbor a bacterial pathogen, but what remains a concern is how efficiently these studies reflect the rate of bacterial infection in COVID19 patients. Such a concern arises from various factors. Firstly, even though only 6.9% of patients had a documented bacterial infection, 72 % of them had received antibiotics which would decrease chance of isolating an organism from the specimen studied. Secondly, there is reluctance in performing invasive diagnostic procedures in COVID19 patients due to risk of spread by aerosols. Thirdly, only blood culture and sputum culture was used to diagnose bacterial infections and antigen testing, blood markers, alveolar lavage were not used. Fourthly, a positive culture report could just mean bacterial colonization and the necessary clinical and temporal relation has not been studied.

To help rule out bacterial infection in COVID19 patients various other strategies have been tried with varying success. Elevated WBC count and rapid correction of elevated C reactive protein levels after antibiotics is one such approach<sup>8</sup>. The other strategy utilizes pro-calcitonin levels with a cut off of 0.25ng/ml. It has been observed that when antibiotics were withheld in patients with severe COVID and pro-calcitonin level of <0.25ng/ml it did not increase mortality<sup>9</sup>. However it is small retrospective observational study and may not serve as benchmark for decision making.

Moreover, if we talk of antibiotic use in mild COVID19 the situation is worse. Majority of COVID19 patients (85%) have mild or asymptomatic disease. Following initial reports of benefit of azithromycin and doxycycline in mild COVID19, subsequent well designed studies failed to

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replicate the result.<sup>10</sup> However, prescription of macrolide/quinolone antibiotics in mild/asymptomatic COVID19 continues to be a practice in our community and considering the proportion of such patients, it amounts to huge violation of antibiotic stewardship. These practices have to be avoided to prevent resistance against these antibiotics.

Antibiotic stewardship and preventing antibiotic resistance should be prioritized by responsible institutions; however, one must be cognizant of the fact that antibiotics save lives.<sup>11</sup> When compared to antibiotic resistance, it is the lack of antibiotics in resource constrained areas that costs more lives<sup>11</sup>. Thus, use of antibiotics cannot be denied in patients of COVID19 who require management in intensive care units or who receive immune-suppressants where chances of a bacterial infection have been reported higher.<sup>12</sup> Patients with suspicion of associated bacterial infection should receive antibiotics to cover the pathogens that are prevalent as per the local microbial ecology.

To conclude, we should have more studies to recognize and delineate the local bacterial spectrum affecting COVID19 patients, so that we can rationalize the use of antibiotics and apply brakes to emergence of multidrug resistant pathogens. In addition, alternate methods to diagnose bacterial co-infection and super-infections like pro-calcitonin, C-reactive protein should be utilized and their role defined by further studies.

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