COVID-19: A Chink in the AMR's Armor- Short Report

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The current pandemic COVID-19 has put the world perilously in a medical emergency state. Ramping up an aberrant cytokine storm by the deregulated immune system seems to be the leading cause of the pathophysiological state of the pandemic. Possibly, other bystander effects which hasn't been studied in details, can be fuelling up the present morbidity and mortality states. One of the most plausible possibility is the occurrence of secondary infections, leading to Antimicrobial Resistance (AMR) in COVID-19 patients.

A clinical study at Wuhan by Zhou et al reported 50% of the patients who died had secondary infections [1]. Interestingly, 98% of the non survivors (n=54) and 93% of the survivors (n=137) in the study were on empirical antibiotic regime. The secondary infections were observed towards later stages of COVID-19 infection, on day 17, with the patients put on mechanical ventilation on day 15. Another, smaller Wuhan clinical study (n=41) by Huang et al also reported 31% of ICU patients to develop secondary infections [2]. Here too, 100% of ICU/non ICU patients were on antibiotic therapy. The patients also had drastically reduced CD4/CD8 T cell counts, which increases the possibility for secondary infections [1]. Another Wuhan based study by He et al (n=65) reported the presence of *Staphylococcus* (27.9%), *Acinetobacter* (20.9%), *Pseudomonas aeruginosa* (PA)(14%), *Enterococcus faecium* (EF)(1.6%) and *Klebsiella pneumoniae* (KP)(9.3%) with Pneumonia (32.3%), Bacteraemia (24.6%) and Urinary tract infection (21%) as infection outcomes in COVID-19 patients [3].

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Secondary infections accounting to 42.8% were also reported by Wang et al (n=339), with 81.7 % of the patients succumbing due to infections [4]. A recent review article highlighted the presence of notoriously drug resistant gram negative bacteria as pan-drug resistant *Acinetobacter baumannii (*AB*)*, Carbapenemase producing (KP*)*, extended spectrum beta lactamase producing (PA) and fungi too (*Aspergillus fumigatus, Candida albicans*) in COVID-19 patients [5]. Evidences in China, France and Germany also reports some critically ill COVID-19 patients to be diagnosed with pulmonary aspergillosis [6]. Many of the said patients had high serum galactomanan. Galactomanan might not be detected in serum sometimes due to lower amount, requisitioning alternative detection means as- β-D-glucan and *Aspergillus* PCR. *Aspergillus* sp is known to colonise in the oral pharyngeal cavities, hence presence of *Aspergillus* sp in serum or brocheoalveolar lavage in these patients needed to be confirmed before starting anti-fungal interventions [6]. There is a high probability of COVID-19 predisposing to these secondary infections as they are observed towards the later stages of hospital admission with clinical manifestations like sepsis and ARDS preceding them. Possibly the patients get immunocompromised due to deregulated cytokine storm and become susceptible to these nosocomial bacterial/fungal infections from ventilators and ICU, exacerbating the pathophysiologies. Immunocompromised individuals are known to be more susceptible to these infections [7,8]. The other alarming issue is the possibility of generating and spreading novel deadly antimicrobial resistant superbugs as the patients are consistently under different antibiotic regime (Azithromycin,fluroquinolones, Cephalosporins, Carbapenems Vancomycin etc) [5]. The 14 membered macrolide Azithromycin (AZ) came into prominence as an intervention measure in combination with hydroxychloroquine against COVID-19[9].

Key words: COVID-19, Secondary Infections, Antimicrobial Resistance, Antibiotics, Gram positives, Gram negatives, Fungal Infections, Azithromycin.

AZ is used for treating respiratory tract lung infections, is classically a bacteriostatic translational inhibitor [10]. The bacteriostatic effects of AZ are attributed to inhibition of virulence factors, adhesion molecules , quorum sensing molecules even at sub-MIC dose (2µg/ml) to the resilient PA infections (with MIC- 8 µg/ml-128 µg/ml, depending on strains)[11]. Hence, the efficacy of AZ in a viral pandemic is interesting. Infact there was a massive usage of it which led to a shortage in the US. The macrolide is also known for immunomodulatory capacities (by downregulating inflammatory cytokines and chemotaxis) in managing infections [11]. AZ has MIC_{90} of ≥ 4µg/ml towards the gram negatives, however it has MIC_{90} of ≤ 1 µg/ml towards gram positives [12]. Hence gram positives like *Streptococcus* and *Staphylococcus* (arising typically in lung infections) would be susceptible, but with developing chances of resistance towards gram negatives. More so, lower ratios of AUC_{24}/MPC_{90} and C_{max}/MPC_{90} showed intrinsic tendency Of AZ (in comparison to other macrolides) towards resistance development [13]. AZ was also shown to have bacteriocidal activity against Multidrug resistant (MDR) PA (2log reduction), AB (6 log reduction) and KP (6 log reduction) in eukaryotic cell culture media (RPMI with 5% Luria Broth) [14].This effect was due to increased membrane permeability of AZ in eukaryotic media leading to nucleoid collapse and protein synthesis inhibition. The bacteriocidal effect was more prominent in presence of human sera [12, 14]. AZ also attenuated lung inflammation in MDR AB driven pneumonic model with far better survival data (89%), lower infiltration of neutrophils/macrophages and downregulation of IL1β, IL6 and MIP-2 [14,15] . Efficacy of AZ usage reemphasises the secondary infection involvement and perhaps fuelling up severity in COVID-19 patients. Historically, previous respiratory outbreaks of 1918 Flu and 2009 H1N1flu had reports of bacterial secondary infections too. Secondary infections due to *Streptococcus pneumonia* was one of the common cause of death in 1918 Flu [5].

In the current pandemic, there is a paucity of data regarding secondary infections as they have been under analysed, with clinicians focussing on immediate priorities. It's imperative to characterize the secondary infections [5] and have antibiotic resistome profiling of the COVID-19 patients in pressing exigency. Responsible antibiotic stewardship and the DISARM act would reduce the massive empirical usage of antibiotics, leading to better managing the present state and also greatly reduce the chances of spreading antibiotic resistant superbugs. Prior to COVID-19 onset, AMR infections were predicted to have 10 millions deaths per year worldwide by 2050 [5].With the current pandemic and massive antibiotic usage, the predictions would be scary. With a sharp decreasing trend of investigational new drug applications (IND) filings at FDA and new antibacterials being approved in last 40 years, coupled by lesser research investments by big pharmaceuticals [16], let's hope COVID-19 be not *coup de grace* to AMR.

Conflict of Interest

I declare that we have no conflict of interest.

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