EDITORIAL

Prevalence of Bloodstream Infections and their Etiology in COVID-19 Patients: A Tale of Two Cities

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With 114,477,868 people affected worldwide and 2,539,290 deaths till now, coronavirus disease-2019 (COVID-19) is ravaging as the worst pandemic in human history. The unprecedented burden on the healthcare system as well as human resources has proven catastrophic and the world is still grappling with the seemingly relentless surges in cases. The search for effective antiviral therapy has so far been elusive with some steroids remaining the only class of drug that has shown any mortality benefit. Evidence regarding the use of anti-inflammatory drugs like baricitinib and tocilizumab, particularly in critically ill COVID-19 patients who need mechanical ventilation appears chimera for now, and their likely flip side in terms of impending secondary infections presents a clear danger.[1] In almost all severe cases, SARS-CoV-2 infection results in pneumonia and the inflamed fluid-filled alveolar tissue may turn into an ideal habitat for bacterial pathogens. Thus the causative agent resulting in further worsening of severe disease may be a bacteria or fungi rather than virus itself. Patients with COVID-19 are likely to stay on invasive mechanical ventilation for a long time (mean: 9·1 day), thereby increasing the chances of the hospital and ventilator-acquired infections.

While rationing of ventilators and ICU beds in overwhelmed health systems could have resulted in unusually high mortalities during the initial phase of COVID-19, what baffled medical community the most was nihilistic mortality figure of almost 100% amongst patients requiring mechanical ventilation, as reported from China. Half of these COVID-19 fatalities were believed to be due to a certain form of secondary infection (pulmonary or other).[2] The obvious answer to this problem in using early broad-spectrum antibiotics brings forth the risk of multidrug-resistant (MDR) pathogens. During the 2003 SARS-CoV outbreak, analyses of isolates collected from patients in the intensive care unit (ICU) in Prince of Wales Hospital (Hong Kong) showed increased rates of methicillin-resistant *Staphylococcus aureus* acquisition from 3.53% pre-SARS to 25.30%. This exponential rise despite adequate infection control practices was largely attributed to higher than usual antibiotic usage during the outbreak.[3] With almost all patients being treated with more than one antibiotic right from the time of hospital admission, this ongoing battle with COVID-19 is likely to worsen India's already dire situation regarding high incidence MDR pathogens.

The binary choice about not using antibiotics while awaiting etiology of secondary infection and risking increased mortality vs empirically starting them in severely ill COVID-19 gets confounded by lack of data regarding likely bacterial microbiology. Bacterial coinfection has huge geographic variations due to variability in the proportion of patients tested, the microbiology of bacterial infections, and antimicrobial stewardship policies. Langford et al. have tried to address this gap by adopting a concept of "living rapid review and meta-analysis: bacterial co-infection and secondary infection in patients with COVID-19", which periodically searches literature and updates findings in 3 monthly fashions. Their first published results from 24 studies representing 3,338 patients, identified bacterial co-infection (estimated on presentation) in 3.5% and secondary bacterial infection (during hospitalization) in 14.3% of the patients. Bacterial infection was more common (8.1%) in critically ill patients, this figure now stands grown up at 16.0% (11.6–20.4) (https://www.tarrn.org/covid). They also highlighted that majority of patients with COVID-19 (71.9%) received antibiotics despite most of the guidelines discouraging their use. The biggest shortcoming was specific species of bacterial co-pathogens being reported in 11/24 studies (45.8%), representing less than 14% of patients with reported infections. The most common organisms reported were *Mycoplasma* species, *Haemophilus influenzae,* and *Pseudomonas aeruginosa*.[4]

Initial studies from China although initiated by the world regarding outcomes related to secondary infections lacked microbiological details. A multicenter study that included 476 COVID-19 patients, revealed that critically ill ones had the highest percentage of bacterial coinfections (34.5%) compared to patients in the moderately ill and severely ill groups (3.9 and 8.3%, respectively). This higher rate of coinfections in critical patients was observed despite a majority of them (92.9%) receiving antibiotic treatments compared to 59.4 and 83.3% of the patients in the moderately ill and severely ill groups, respectively.[5] Zhou et al. observed that among 191 COVID-19 patients, bacterial coinfections occurred in 15% of the cases, including 50% of nonsurvivors, even though 95% of patients had received antibiotics; ventilator-associated pneumonia occurred in 31% of patients requiring invasive respiratory support. Even more troubling was the fact that 27/28 COVID-19 patients with coinfections succumbed.[2] These studies probably confirm the futility of prophylactic antibiotics when it comes to bacterial secondary infections.

Li et al. in a retrospective analysis of about 1500 patients, tried to explore etiology and antimicrobial resistance of secondary bacterial infections (SBI) in patients hospitalized with COVID-19.[6] They confirmed high mortality (49.0%, 50/102) in those with SBI while the overall percentage who acquired SBI was 6.8% (n = 102) only. Among the 159 strains of bacteria isolated from the SBIs, 85.5% were gram-negative bacteria. The top three strains were *Acinetobacter baumannii* (35.8%), *Klebsiella pneumoniae* (30.8%), and *Stenotrophomonas maltophilia* (6.3%). The isolation rates of carbapenem-resistant *A. baumannii* and *K. pneumoniae* were 91.2 and 75.5%, respectively. Methicillin resistance was present in 100% of *S. aureus* and coagulase-negative staphylococci. The high antimicrobial resistance rates of major isolated bacteria highlight that the optimizing choice of antibacterial agents is necessary for SBIs in patients hospitalized with COVID-19. An Italian study analyzed 731 patients and reported that an overall 28-day cumulative incidence of 16.4% bloodstream infections (BSI) was much higher (7.9 vs 3.0%) than presumed lower respiratory tract infections (pLRTI).[7] Most of the BSIs were due to gram-positive pathogens specifically coagulase-negative staphylococci (69.7%), while among gram-negatives (21.7%) *A. baumannii* (30.4%) and *Escherichia coli* (21.7%) predominated. pLRTIs were caused mainly by gram-negative pathogens (53.8%). Eleven patients were diagnosed with putative invasive aspergillosis, again reminding that geographic variations are a rule rather than an exception.

In terms of risk factors male gender, older age, heart diseases, hypoproteinemia, corticosteroid and proton-pump inhibitors, early need for ICU, respiratory failure are reported most frequently.

Several studies have shown that sustained and substantial reduction of the peripheral lymphocyte counts, especially CD4 T and CD8 T cells, is representative of the immune suppression stage after the cytokine storm activation phase. The dysregulated immune response may be associated with a high risk of developing a secondary bacterial infection.[7,8]

Current high antibiotic use in COVID-19 patients admitted to intensive care units, renders culture-based microbiological testing less sensitive. Hence, early diagnosis of co-infection is required, preferably using methods capable of detecting potential pathogens and antimicrobial resistance. This brings to centerstage that we still lack good understanding regarding clinical risk factors for concomitant bacterial infections in COVID-19 patients, and India-specific data on how demographics and medical comorbidities influence bacterial infection risk are much needed. One such study from AIIMS, New Delhi, analyzed positive cultures from hospitalized COVID-19 patients. 15% of ICU patients and 12% of non-ICU patients developed secondary infections.[9] *K. pneumoniae* (33.3%) was the most common pathogen, followed by *A.baumannii* (27.1%), *E. coli* (16.7%), and *P.aeruginosa* (11.5%). Overall resistance to third-generation cephalosporins and carbapenems was found to be 64–69%. Amongst gram-positive pathogens isolated were MR-CONS and MSCONS which were sensitive to vancomycin, teicoplanin, tigecycline, linezolid, and daptomycin. The AMR genes encoding for carbapenemases-NDM (71%), OXA-48-like (61%), and extended-spectrum beta-lactamases CTX-M (61%) were found highly prevalent in the respiratory samples tested by FilmArray. While it is understandable that neither European nor Chinese microbiota will have many similarities with Indian ones, a study undertaken in a tertiary care center in Jaipur underscores regional variations likely to be encountered within.[10] The low rate of secondary bloodstream infection (9.4%) has prompted authors to raise a red flag against prophylactic use of antibiotics as well as prompt discontinuation in case they were already started. In contrast, they had a much higher incidence of coagulase-negative staphylococci (CoNS) out of which almost 90% were methicillin-resistant, while pseudomonas species were pan drug-sensitive. This wide variation in local microbiology is of utmost significance since the risk factor including age, gender, and severity of illness in both studies are almost mirror images. The USA is the other country that has reported a higher incidence of these otherwise skin commensal CoNS in COVID-19 patients.[11] One probable reason could be poor sampling technique and unless a pathological role is confirmed, treating such isolates is another conundrum that clinicians are likely to face. The possibility of antibiotics administered at admission altering the microbiological and clinical milieu is another way of explaining these findings. To diagnose co-infections early in COVID-19, patients should be screened on admission at the intensive care unit and subsequently sampled throughout the disease course.

The use of interleukin 6 (IL-6) inhibitors, such as tocilizumab for COVID-19-related cytokine activation syndrome is going to presents a unique challenge by suppressing common signs of sepsis. Acute-phase reactants including white blood cell count and C-reactive protein may also not rise in response to a secondary bacterial infection after tocilizumab use.[1] Duration of this effect likely to last with 1 or 2 doses is also unclear. Procalcitonin may be less affected by IL-6 inhibitors, but the data to identify secondary bacterial infections in this context are in a nascent stage. Lastly, fungal infections including *Candida albicans* as well as non-albicans and invasive pulmonary aspergillosis are also being reported in patients with COVID-19-associated acute respiratory distress syndrome.[12] This further necessitates discretion when it comes to the use of broad-spectrum antibiotics in COVID-19 patients.

Global pandemics from emerging viruses are inevitable in a world with interconnected societies, transcontinental travel, and intuitive tourism. In order to stay well-prepared for the next pandemic, we must be well informed regarding bacterial pathogens commonly observed in secondary infections to avert a healthcare crisis due to antibiotic-resistance.

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