Antibiotic misuse during COVID-19 Pandemic: A Recipe for Disaster

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The abrupt and brutal disruption by the COVID-19 pandemic has thrown the healthcare professionals into a frenzy, forcing them to not only deal with the strained healthcare system but trying to manage a disease that was unknown to the world. It has catapulted healthcare professionals onto the frontlines in response to the crisis without any clear guidelines for the management of the disease for obvious reasons, impelling them to deal with it in a varied and ambiguous manner.

The subsequent publications of guidelines on the management of the disease, especially the use of steroids, have paved the way for managing critically ill patients. A significant emphasis has been given to infection control also; however, the guidelines were inconspicuous initially on antibiotics due to lack of sufficient data. When first reported in Wuhan in December 2019, more than 90% of hospitalized patients with COVID-19 received antibiotics with little supporting evidence of bacterial infection.[1] The International Severe Acute Respiratory Infection Consortium study reported prescribing antibiotics in 72% of those hospitalized.[2] While the antibiotic usage was much higher, the rate of secondary bacterial infection from COVID-19 cases in Wuhan was reported in 15% of hospitalized patients.[3] In another retrospective observational study, only 3.2% had early confirmed bacterial isolates identified, which rose to 6.1% throughout hospitalization.[4]

Langford et al. published results of a meta-analysis designed to determine the prevalence of bacterial coinfection (at presentation) and secondary bacterial infection (occurring after presentation) in patients with COVID-19. A total of 28 studies met eligibility criteria. Bacterial coinfection was identified in 3.5% and secondary bacterial infection in 15.5% of patients. Notably, 71.3% of the patients received antibiotics.[5] Vaughn et al. reviewed 1705 hospitalized patients and found that the majority (56%) were prescribed early empiric antibacterial therapy. There were only 3.5% of patients with confirmed bacterial coinfections. Nori et al. published results from a retrospective observational study of 4267 patients with COVID-19.[6] Approximately 3.6% had a bacterial or fungal infection. The most common respiratory isolates were *Staphylococcus aureus*, *Pseudomonas* spp., and *Klebsiella* spp., and the most common blood culture isolates were *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus* spp. Despite the low (3.6%) incidence of confirmed coinfection, 98% of hospitalized COVID-19 patients received inpatient antimicrobial therapy.[7]

There are challenges to antibiotic prescription in a patient with COVID-19. The presentation of fever, tachypnea, and hypoxia together with lung infiltrates on chest imaging and a rise in biomarkers, such as C-reactive protein (CRP), present a challenge to the rational use of antibiotics as it is difficult to exclude bacterial infection with certainty.[8] Given the lack of widespread access to

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accurate and rapid COVID-19 point of care diagnostics particularly in the emergency department, it is difficult to differentiate COVID-19 from other acute respiratory conditions for which antibiotics are generally indicated.[9] The increased prevalence of early hypoxia and progression to respiratory failure reported for COVID-19 compared to other infectious respiratory conditions is another potential factor underlying high rates of antibiotic utilization. Additionally, early guidelines for critically ill patients with COVID-19 recommended consideration of antibiotics due to the possibility of bacterial coinfection, despite a lack of evidence demonstrating improved outcomes.[10,11]

The administration of steroids can mask the presence of fever and lead to neutrophilic leukocytosis, making the situation complex to understand regarding secondary bacterial infection. While steroids and tocilizumab both are given as a part of COVID-19 management in severe and critically ill patients, the risk of secondary infection is also higher.[12]

Moreover, it is important to differentiate between contamination, colonization, and true infection. In a study done by Hughes et al. on COVID-19 patients, out of 60 positive blood cultures, only 21 were identified as true pathogens, while the rest were contaminants.[4] Microbiological culture is a relatively insensitive technique, especially during antibiotic treatment. It can be difficult to differentiate between infection and colonization in nonsterile sites, and the mere presence of bacterial isolate from the lower respiratory tract should not be viewed as infection only. On the contrary, even in patients with sepsis, only 30–50% will have a positive blood culture.[13] Therefore, reliance on positive culture alone as an indicator of infection is not worthwhile. The presence of purulent secretions from the lower respiratory tract or increasing quantity raises the high suspicion of secondary bacterial infection and should be read in context to the patient overall clinical picture.

The utility of multiplex polymerase chain reaction panel for respiratory pathogens in diagnosing coinfection or secondary

bacterial infection in COVID-19, though appears promising because of its rapid turnaround time and detection of multiple respiratory pathogens at once, may be of limited value for antimicrobial stewardship, since it tests only for viruses and few atypical bacteria that are not found to cause infection in COVID-19 patients requiring antibiotic therapy.

The utility of PCT in diagnosing infection as bacterial and managing antibiotic therapy in an appropriate clinical situation has always remained on the forefront of critical care physicians. It rises in response to bacterial infection and falls in response to appropriate antibiotic therapy. It has greater sensitivity and specificity for bacterial infection than CRP.[14] PCT has been proven useful in the early diagnosis of lower respiratory tract infections of bacterial origin.[15] In the intensive care unit (ICU) setting, serial measurement of PCT can guide the safe withdrawal of antibiotic therapy.[15] In patients with COVID-19, CRP is usually increased on presentation while PCT is often low.[15] PCT has been identified as a marker of poor prognosis in COVID-19 infection, and it appears to increase in COVID-19 patients with the severe disease when the hyperinflammatory phase sets in later in the disease process or those presenting with a secondary bacterial infection.[14,15] It is only later in the disease process the chances of secondary bacterial infections are more. Williams et al. described a retrospective analysis of PCT use in COVID-19 patients, concluding that PCT led to a reduction in antibiotic use without impacting on 28-day outcomes.[16] Van Berkel et al. measured PCT and CRP in ICU patients with COVID-19 diagnosed with a secondary bacterial infection. They concluded that low PCT could be used to exclude secondary bacterial infection.[15] In another study by Williams et al. on the dynamics of PCT in COVID-19 patients, they identified elevated PCT in the first 48 hours of admission was rare in COVID-19 patients. They concluded that dynamics of PCT in COVID-19 patients is consistent with a response to secondary bacterial infection and is not consistent with an inflammatory response to COVID-19 alone. It was also concluded that PCT appears to be a useful biomarker in identifying COVID-19 patients with superadded bacterial infection and supports antibiotic treatment in COVID-19 patients with a significantly raised PCT, including those without positive microbiological cultures.[14]

While NICE guidelines recommend that "Do not use antibiotics for preventing or treating COVID-19 patients and it should be used only when there is strong clinical suspicion of bacterial infection," treatment guidance from the National Institutes of Health recommends that "in patients with COVID-19 and severe or critical illness, there are insufficient data to recommend broad-spectrum antimicrobial therapy in the absence of other indications. If antimicrobials are initiated, their use should be reassessed daily to minimize the adverse consequences of unnecessary antimicrobial therapy."

Once antibiotic therapy is given to COVID-19 patients based on strong clinical suspicion of infection, the empirical therapy should be chosen on the same criteria as for other critically ill patients, which include the most likely site of infection, likely organism, and local antimicrobial sensitivity pattern. In one study done in a Scottish hospital, the predominant organisms identified were *Enterobacteriaceae* species, *Staphylococcus aureus,* and pseudomonal species typical of a hospital or ventilator-associated pneumonia occurring at a median of 14 days following admissions.[17] In another study, there was no case of concomitant pneumococcal, legionella, or influenza infection.[4]

The consequences of overuse of antibiotics are well known. The immediate concern includes antibiotic pressure to select resistant pathogens, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, multidrug-resistant Gram-negative bacteria, and the acquisition of nosocomial infection, such as *Clostridioides difficile*. Patients may likely develop a secondary bacterial infection that is resistant to multiple antibiotics if the antibiotics are started inappropriately in a patient when no antibiotic was required. There are larger, theoretical level impacts that remain under careful research scrutiny, but more and more becoming a reality. A good example includes the antibiotic influence on microbiome dysfunction.

Although empiric antibiotic therapy is often initiated upon presentation, particularly in those with severe COVID-19 pneumonia, consideration can be given to antibiotic discontinuation at 48–72 hours for patients with a positive test for SARS-CoV-2, no evidence of bacterial pathogen, and early clinical stability.

It is important to consider the collateral effects of COVID-19 on antimicrobial resistance. Optimizing antibiotic stewardship during COVID-19 will likely require a combination of traditional stewardship approaches and effective implementation of host-response biomarkers and rapid COVID-19 diagnostics. The unnecessary use of antibiotics is a prime driver of antimicrobial resistance, a global public health crisis. In one recently published review article, the author reiterated that overzealous use of broad-spectrum antibiotics in patients with mild to moderate COVID 19 should be avoided and the likelihood of secondary bacterial or fungal pneumonia in a patient with worsening respiratory failure or sepsis should be considered.[18]

The COVID-19 pandemic is teaching us that SARS-CoV-2 is going to stay with us as a long-term member of the respiratory viral microbial ecosystem, making it critically important to have all possible answers regarding antimicrobial use very soon. One such RCT, ProSAVE, is currently underway that is investigating the role of PCT-guided antibiotic stewardship in COVID-19 patients. Till then, it is prudent not to use antibiotics in mild to moderate cases of COVID-19. COVID-19 patients who are severe or critically ill should be followed closely for secondary bacterial infection by clinical assessment, cultures, and PCT, and empirical antibiotic therapy should be started and deescalated as we do in other critically ill patients. Otherwise, the COVID-19 pandemic has immense opportunity to bring another pandemic of antimicrobial resistance.

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