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A REVIEW ON TREATMENT PATTERN OF ANTIBIOTICS AND STEROIDS USAGE IN COVID-19 PATIENTS

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ABSTRACT

Corona virus (COVID-19) pandemic due to the novel SARS Coronavirus (SARS-CoV-2) has resulted in a sudden, large and prolonged increase in hospitalizations of patients fulfilling the criteria for community-acquired pneumonia (CAP). SARS-CoV-2 can lead to a wide spectrum of disease, ranging from very mild symptoms of upper respiratory tract infection to life-threatening pneumonia. Corticosteroids are hormones that are naturally produced from the adrenal cortex and are involved in a variety of physiological processes, such as inflammatory regulation, stress, and immunological response, protein, and carbohydrate metabolism. As a result, corticosteroids are critical in the management of autoimmune, allergic, malignant, and many inflammatory disorders. In COVID-19-related severe acute respiratory syndrome, viral escape of cellular immune response and the cytokine storm is important in pathophysiology and clinical consequences. Dysregulation of cytokine and invasion of inflammatory myeloid cells results in lung inflammation and severe sequelae, such as acute respiratory distress syndrome, respiratory failure, sepsis, multi-organ failure, and death. Corticosteroids have significant anti-inflammatory and anti-fibrotic effects, which may play a role in reducing pulmonary inflammation, especially in severe pneumonia and in advanced stages of COVID-19 disease. The patient may be completely asymptomatic with a positive swab test, may present with a mild influenza-like illness or may present with serious symptoms that require hospitalisation. The effective vaccination, and oxygen therapy, antivirals, steroids, HCQS and antibiotics can minimize the COVID-19 clinical symptoms among affected patients.

KEYWORDS: Corona virus, respiratory distress syndrome, oxygen therapy, antivirals, steroids, HCQS.

INTRODUCTION

Coronavirus diseases 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2), is responsible for the global pandemic that originated from Wuhan in December 2019. Though the majority of patients undergo an uneventful recovery, in around 19% there is a progressive worsening leading to severe pneumonia in 14% and critical pneumonia in 5% of patients. There is a staged progression in the course of events after a median incubation period of 4 days (interquartile range 2–7 days). The adult respiratory distress syndrome (ARDS) usually develops from the second week onwards. This does not only happen because of uncontrolled viral replication but also because of an explosive immune response from the host. In presence of uncontrolled viral replication, the presence of an increased number of infected epithelial cells and cell debris triggers a massive cytokine release - the so-called 'cytokine storm' - with hyper-inflammation and immune suppression, characterized by decreased memory CD4 + T helper cells and increased CD8 cytotoxic activity.

In the first phase, the antiviral immune response leads to the elimination of the virus at the expense of the immune mediated pulmonary injury. At one end of the spectrum, a balanced immune response keeps the infection under control, but at the other end there is an exaggerated immune response with consequent lung injury. Lung injury initiates at the epithelial-interstitial-endothelial level, with exudation of neutrophils and macrophages, which, in its turn reduces the alveolar surfactant, thereby reducing the alveolar patency and the gas exchange. Infected cellular debris further augments the release of inflammatory cytokines like TNF-α, interleukin-1 (IL-1)

and IL-6, further accentuating the 'cytokine storm". The second phase begins with uncontrolled viral replication induced angiotensin-converting enzyme 2 (ACE2)-directed cytotoxicity, that triggers a vicious circle of immune activation with consequent worsening of the hyperinflammatory state. At this stage, patients exhibit lymphopenia with reduced B cells, CD4 and CD8 T cells and $CD16^+$ Natural Killer (NK) cells. This probably results because of an increase in extravasations of dysfunctional lymphocytes. The pathophysiological features of severe Covid-19 are dominated by an acute pneumonic process with extensive radiologic opacity and, on autopsy, diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis.[1-9]

In other severe viral pneumonias, such as highly pathogenic avian influenza, SARS, and pandemic and seasonal influenza, the host immune response is thought to play a key role in the pathophysiology of organ failure. Inflammatory organ injury may occur in severe Covid-19, with a subgroup of patients having markedly elevated levels of inflammatory markers, including C-reactive protein, ferritin, interleukin-1, and interleukin-6. Several therapeutic interventions have been proposed to mitigate inflammatory organ injury in viral pneumonia, but the value of glucocorticoids has been widely debated. Although one small trial has reported improved clinical outcomes in patients with Covid-19 who were given methylprednisolone, the absence of reliable evidence from large-scale randomized clinical trials means there is uncertainty about the effectiveness of glucocorticoids in patients with Covid-19. Many guidelines for the treatment of such patients have stated that glucocorticoids were either contraindicated or not recommended, although in China, glucocorticoids have been recommended for severe cases. However, in the first 6 months of the pandemic, practice varied widely across the world: in some series, as many 50% of patients were treated with glucocorticoids.[10-15]

Treatment for COVID-19

Steroids

Steroids are the other class of medications that are commonly prescribed. They are given orally, intravenously or in the form of intra-articular injections for its anti-inflammatory properties. These include oral steroids for inflammatory conditions especially in the presence of NSAIDs allergy, intravenous steroids for inflammatory conditions or in the presence of spinal cord compression or cauda equina and intra-articular injections for diagnostic and therapeutic purposes. However, the evidence for the use of steroids in the management of COVID-19 patients is conflicting. These are derived largely from the previous studies for severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) as no clinical studies have been published on COVID-19. Potential advantages for the use of steroids include the ability of the steroids to reduce immunopathological damage and alleviate the early proinflammatory response, while potential disadvantages include delayed viral clearance and the adverse effects of avascular necrosis, diabetes and psychosis as evident from SARS and MERS, In view of the lack of survival benefit and possible harms, WHO, in their guidelines for the management of COVID-19 patients, therefore, has recommended against the use of systemic corticosteroids for the treatment of viral pneumonia. They further recommended for clinicians who are considering the use of steroids for COVID-19 patients with sepsis to balance the potential for a small reduction in mortality in surviving sepsis with the potential downside of the possible harms indicated. Based on the above, three recommendations are then made for the use steroids in COVID-19 patients. Firstly, orthopaedic surgeons prescribing steroids for COVID-19 patients are recommended to weigh the utility of the steroids against the potential risks. However, while WHO recommend against the use of systemic steroids for the treatment of viral pneumonia, WHO does not stop the usage of steroids for other evidence-based reasons. Therefore, patients with conditions where steroids are proven to have efficacious outcomes, such as that of spinal metastases with cord compression or cauda equina, can continue to receive their steroids. Secondly, WHO has also not issued a statement regarding intra-articular steroids, and the effects of intra-articular steroids on COVID-19 have also not been evaluated in other studies before; therefore, orthopaedic surgeons can continue using intra-articular steroids for pain relief when required after weighing the risks and benefits. Thirdly, it is also important for orthopaedic surgeons who are following up on COVID-19 patients with steroids usage to follow them long term and evaluate for the possibility of avascular necrosis. The excessive use of steroids for COVID-19 patients was likely the cause of the upsurge of this otherwise very rare fungal disease majorly black fungus.[16-19] The numbers of black fungus infections (or COVID-19 infection) of India must be put in the correct perspective, as the absolute numbers in a country of 1366 M people may appear incredibly high in countries with a dramatically smaller population such as the United Kingdom.

Antibiotics are also common medications prescribed by orthopaedic surgeons for soft tissue and bony infections. Common antibiotics used by orthopaedic surgeons include penicillin and clindamycin. These antibiotics are not reported in publications to influence COVID-19 patients. The only antibiotics that are discussed with regard to COVID-19 are macrolides and tetracyclines. Macrolides and tetracyclines have been investigated and discussed in multiple publications in view of their potential therapeutic effect on COVID-19. Three observational studies, comprising of a total of 127 patients, have been published regarding the use of hydroxychloroquine and azithromycin in COVID-19 patients. Two of the studies are single arm observational studies, while the other study is a non-randomized observational study that compared between patients with hydroxychloroquine treatment alone and patients with

hydroxychloroquine and azithromycin treatment together and controls. The results from the studies are, however, non-conclusive as two studies reported positive outcomes with the use of hydroxychloroquine, especially when complemented with azithromycin, while one study did not demonstrate any antiviral activity with the medications. Tetracycline has been postulated to be a potential therapeutic agent for COVID-19 in view of its activity against matrix metalloproteinases and inflammatory cytokines, which are crucial for viral activity, but their effects have not been studied in any published studies thus far. Based on the above, two recommendations are then made for the use antibiotics in orthopaedic patients with COVID19. Firstly, common orthopaedic antibiotics including penicillin and clindamycin can continue to be used for soft tissue and bony infections in COVID-19 patients. Secondly, for COVID-19 patients, in the presence of organisms that can be managed with other antibiotics such as macrolides and tetracyclines, the antibiotics can potentially be switched to macrolides and tetracyclines to cover for the orthopaedic infections while potentially having therapeutic effects on the COVID-19 after the discussion with the infectious diseases specialist.[20-22]

Antibiotic treatment in covid-19

India is the largest consumer of antibiotics in the world. Broad spectrum antibiotics such as second- and third-generation cephalosporins, macrolides, and quinolones are overused for acute respiratory tract infections in India. There is a concern that symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, could lead to a substantial increase in antibiotic consumption (often inappropriately), thus promoting antibiotic resistance. In India, all antibiotics are included in Schedule H or H1. However, OTC dispensing of antibiotics is common in India.

In many countries, azithromycin and hydroxychloroquine (HCQ) are reportedly being used off label in prophylactic and therapeutic regimens either alone or in combination. In India, azithromycin is typically utilized to treat a range of conditions, including acute respiratory tract infections, bacterial dysentery, and enteric fever. This macrolide antibiotic was repurposed for the treatment of COVID-19 based on in its hypothetical anti-inflammatory and immunomodulatory properties.[23-24]

On the other hand, HCQ in India is mainly utilized for treatment of autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, and post-viral infectious arthritis, such as chikungunya arthritis, and is not part of national malaria treatment guidelines. It has been suggested that HCQ could have antiviral activity as well as indirect anti-inflammatory properties through the activation of CD8+ T cells and the reduction of pro-inflammatory cytokine response, thus leading to its widespread use in the management of COVID-19 as well as in pre- and post-exposure prophylaxis. However, an increasing number of studies have observed no beneficial effects from the use of azithromycin and/or HCQ, and a number of safety concerns have also been raised.

The WHO recommended that antibiotic therapy or prophylaxis should not be used in patients with mild/moderate COVID-19 unless it is justifiable. Some countries still recommended the use of antibiotics in the management of mild COVID-19. Most antibiotics recommended were from the "watch" (antibiotics that have higher resistance potential) and "reserve" (antibiotics that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms) such as polymyxin B and ceftazidime/avibactam, indicating the empirical use of these antimicrobials. Various antibiotics, such as azithromycin, doxycycline, clarithromycin, ceftriaxone, erythromycin, amoxicillin, amoxicillin-clavulanic acid, ampicillin, gentamicin, benzylpenicillin, piperacillin/tazobactam, ciprofloxacin, ceftazidime, cefepime, vancomycin, meropenem, and cefuroxime among others, were recommended for use in the management of COVID-19. This is worrisome in that COVID-19 is a viral disease and only a few COVID-19 patients would have bacterial co-infection. The national treatment guideline of Liberia recommended the use of antibiotics in sore throat, diarrhoea, and cough that are associated with COVID-19 symptoms. This highlights the need to ensure prudent use of antibiotics in COVID-19, being a viral disease.[25-29]

Another meta-analysis revealed that only 7.0% of hospitalized COVID-19 patients had a bacterial co-infection. A recent multi-centre study showed that only 86 out of 905 (9.5%) confirmed COVID-19 patients were clinically diagnosed with bacterial co-infection. This implies that only a few COVID-19 patients would need antibiotics for possible bacterial pneumonia and other superimposed/co-infections. For instance, an increase in the use of azithromycin, a broad-spectrum macrolide antibiotic, has been documented amid the pandemic in many countries usually with hydroxychloroquine in the management of COVID-19. Evidence has also shown that routine use of azithromycin for reducing time to recovery or risk of hospitalization for people with suspected COVID-19 in the community has been documented to offer no benefit. Azithromycin used alone was associated with TdP/QT prolongation events and should be used with caution. Studies showed that, among those COVID-19 patients that used antibiotics systematically, in about 90% of patients the prescription was empirical. This could aggravate the already serious problem of antibiotic resistance.[30]

WHO recommendations for clinical management of severe acute respiratory infection when novel coronavirus (nCoV) is suspected include the recommendation to 'Give empiric antimicrobials to treat likely pathogens causing SARI' and to give antimicrobials within one hour of critical patient

assessment for patients with sepsis. Blood cultures should be collected for bacteria that cause pneumonia, ideally before antibiotics but antibiotics should not be delayed to collect blood cultures. Antibiotics should be reserved for patients with the most severe presentations. Microbiological tests should be obtained beforehand. The treatment should be rapidly re-evaluated and stopped as soon as possible if the probability of bacterial super-infections considered low. If the treatment is continued, an oral switch should be performed rapidly if the patient is able to take oral medication, and the absence of fever should not be required as a criterion since patients with COVID-19 often show persistent fever over several days. Antibiotic duration should not exceed 5 days.

The WHO AWaRe classification makes it possible to visualize the antibiotics consumption that are considered the last line of treatment (World Health Organization, 2019b). A study involving twelve hospitals in Bangladesh drew attention to the Reserve group's high antibiotic consumption for patients admitted in wards. This increase, also found in this study, is alarming. High priority pathogens of the WHO list, such as MDR non-fermenting Gram-negative bacilli, can only be treated with antibiotics from the Reserve group. The increased consumption of these antibiotics raises concerns about the therapeutic options available to treat infections in the ICU. We also found an increase in consumption of first-generation cephalosporins, fluoroquinolones, and carbapenems. These are already the most commonly used antibiotic. Surgical sectors can consume more first-generation cephalosporins, as this class is used for surgical prophylaxis. In 2019, ANVISA issued a warning about the safety profile of fluoroquinolones, discouraging their use.

Among the antibiotics in this group, amoxicillin/clavulanate showed an increasing trend starting May 2020 that remained until the end of the analysed period. This association is commonly prescribed to treat community-associated pneumonia and while the prevalence of bacterial co-infection in patients affected by COVID-19 is still controversial, it cannot be ruled out. Thus, it is possible that the large number of COVID-19 patients boosted the consumption of amoxicillin/clavulanate. Cefuroxime was the only second-generation cephalosporin in the analysed period. The cefuroxime prescription in the studied ICU was negligible until April 2020. However, from May 2020, consumption increased significantly until the end of the period analysed. Another study found that using second-generation cephalosporins, such as cefuroxime, did not vary significantly in the pre-pandemic period in other. As cefuroxime, much like amoxicillin/clavulanate, is used to treat community-associated pneumonia, it may be that the sharp upward consumption trend is explained by a large number of COVID-19 patients in the ICU.

The fluoroquinolones use trend was downward in 2019, possibly due to discouraged prescription by regulatory agencies, given its severe adverse effects. Nevertheless, in 2020 the consumption of fluoroquinolones increased again. It might be related to the risk of ventilator-associated pneumonia (VAP) due to mechanical ventilation needed by the COVID-19 critical cases.[31] Fluoroquinolones have a broad spectrum of action, including against *Stenotrophomonas maltophilia*, an important VAP etiologic agent, and COVID-19 is associated with an increased risk of VAP. The treatment of Corrective and Preventive Action (CAPA) includes antifungals like voriconazole, Posaconazole, and Isavuconazole. Voriconazole is an azole antifungal recommended to treat invasive aspergillosis, associated with critically ill patients with COVID-19. The risk of COVID-19-associated Mucor mycosis may be decreased by encouraging vaccination against COVID-19, prescribing steroids for COVID-19 treatment based on guidelines. Daptomycin and linezolid are intended to treat infections caused by MDR Gram-positive cocci. At the end of the analysed period, it was suggested that many patients have received these without microbiological proof of infection. Statins have been commonly used for primary and secondary cardiovascular prevention. We hypothesized that statins may improve in-hospital outcomes for hospitalized patients with COVID-19 due to its known anti-inflammatory effects.

Phage Therapy

Consequently, the use of antibiotics to treat COVID-19 patients must be rationalized, or an alternative treatment must be sought that does not risk contributing to AMR development and positively impacts the treatment outcomes. Phage therapy, a century-old concept, is one of the most promising approaches that can be adapted to serve this purpose. Targeted killing (narrow spectrum) and anti-inflammatory (which can target the primary cause of mortality in COVID-19) properties of phages can be an effective alternative to antibiotics. Bacteriophages or phages are viruses that infect and kill bacteria.[32-39] Bacteriophages consist of a nucleic acid molecule surrounded by a capsid. The bacteriophage that is found in the River Ganges, especially at its origin, shows the ability to infect several kinds of bacteria.

The impact of bacteriophages on SARS-CoV-2, especially concerning phage therapy (PT), several studies have confirmed that in addition to their antibacterial abilities, bacteriophages also show antiviral and antifungal properties. It has also been shown that PT is effective for building immunity against viral pathogens by reducing the activation of NF kappa B; additionally, phages produce the antiviral protein phagicin. Recent evidence also suggests that phages may have therapeutic potential against several diseases, including the seasonal flu and avian influenza. Influenza viruses infect lung tissue similar to SARS-CoV-2. Chemically modified phage capsids which enveloped the influenza virus in such a way that it could no longer infect lung tissue.[40-42] This phenomenon was studied in a preclinical study

using human lung tissue and is being explored against coronavirus infection. Since currently available antiviral drugs attack influenza and coronavirus after they have already infected the lung cells, it is important to target the virus and prevent infection in the first stage of viral infection. Phage therapy (PT) was primarily developed to kill bacteria, to help prevent the overuse of antibiotics and the development of antibiotic resistance. Phages mediate immunoregulatory and immunotherapeutic activities that are relevant in balancing the immunological homeostasis of human subjects.

CONCLUSION

Paracetamol is the first line of analgesia and antipyretic for COVID-19 patients. Opioids have the potential for immunosuppression in addition to respiratory depression and, therefore, should be prescribed with care in COVID-19 patients, with buprenorphine appearing to be the safest for use in the immunocompromised or elderly patients susceptible to infections.[43-45]

Oral anticoagulation should be converted to parental heparin to minimize overtreatment or under treatment with oral anticoagulation. Seventhly, common orthopaedic antibiotics including penicillin and clindamycin are safe to continue for COVID-19 patients. However, for COVID-19 patients, the antibiotics can potentially be switched to macrolides and tetracyclines if the organisms are sensitive to these antibiotics, so as to cover for the orthopaedic infection while potentially having therapeutic effects on the COVID-19 infection as well. Vitamins B, C and D potentially have therapeutic benefits for COVID-19 patients, and therefore, prescription for these vitamins should continue as per usual clinical practice. In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. In hospitalized hypoxic COVID-19 patients, methylprednisolone demonstrated better results compared to dexamethasone. The use of an antiviral such as Ivermectin in early stages, coupled to one antibacterial, plus vitamins and minerals, has been the best therapeutical approach against COVID-19 infection and indirectly against the Black fungus infection.

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