

EDITORIAL VIEW

CORONA EXPERIENCE

The COVID-19 babies are even more blue and lethal

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Abstract

This is a century of corona virus. The world is still coping up with the third wave of COVID-19, while the scientists have already warned that a fourth wave is imminent. This wave is expected to be more lethal due to multiple mutated variety of the corona virus, including one of the most lethal one known as Indian variant or delta variant. Meanwhile, the health staff has to deal with those patients who survived COVID-19, but continued to have a variety of new complaints, including respiratory distress, dysautonomia, intravascular thrombosis and endocardial myocarditis etc. Anti-corona therapy, in itself lead to multiple syndromes including acute kidney injury, bone marrow depression and deranged blood sugar levels. One of the more lethal complication is mucormycosis-a fungal disease. It has effected thousands of recovering or recovered corona patients in India. This editorial highlights the salient features of post-corona syndrome or long covid.

Key words: COVID-19; Genome; Mutation; Acute respiratory syndrome; Post-covid complications; Post-corona syndrome; Dysautonomia; Mucormycosis; COVID associated mucormycosis; Mortality

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For more than one and a half year, humanity has been ravaged by the corona virus disease of 2019 (COVID-19). The virus is constantly changing its genome (mutations) just like a chameleon and has spread the disease wave after wave the worldwide.¹ The mutations are also enhancing viral replication and transmission.² Although the infectivity of the virus has been documented to be much higher than the earlier versions, it is a matter of satisfaction that the mortality is not very high. Most of the COVID-19 infections are mild and can be managed in home isolation.³ Only the patients having moderate to severe disease leading to acute respiratory distress syndrome, requires hospitalization and ICU care.

The mortality is, however, higher in such patients. While the whole world is still searching for effective medication and looking for mass vaccinations hoping to cure the COVID-19 cases, the babies (post-covid complications) have started shaking human race. COVID-19 has been well reported with dysautonomia leading to different autonomic disturbances.⁴ Patients usually present with orthostatic intolerance syndrome with dizziness, fatigue, palpitation, presyncope episodes, chest pain, breathlessness, and panic attack, etc. The disease spectrum is also varied; postural tachycardia syndrome, autonomic neuropathy and gangliopathy are described among the patients who developed dysautonomia during and after the recovery of COVID-19.⁵

Although endomyocardial biopsy has found very minimal evidence of COVID-19 genome involving the myocytes directly,⁶ the virus has been well-reported to affect the myocardium indirectly, and COVID-19 associated myocarditis is also disabling the persons who have recovered from the illness.⁷ Patients usually complain of persistence of fever, shortness of breath and chest pain. COVID-19 associated hemostatic abnormalities are now a well-known complication.⁸ The mechanism is diverse; injury to the vascular endothelium, especially the microvessels causing endotheliitis, causes dysfunction of platelet, coagulation and fibrinolytic system, imbalance in angiotensin-converting enzyme-2 (ACE-2) regulation, hyper inflammation, host cell death and extracellular trap of neutrophils are a few of the contributing factors to the cascade. Both venous thromboembolism and arterial thrombotic events have been widely reported leading to many disabilities and mortality. The incidence of thromboembolism in COVID-19 patients is high. Meta-analysis of the data indicates that the 95% confidence interval for the overall venous thromboembolism rate was 17-26%, pulmonary embolism 11-19%, and arterial thromboembolic events 1-4%. The incidence was higher for patients requiring ICU treatment. The rate was also found to be higher in the studies that reported post-mortem data.⁹ These events increased the pooled mortality by an absolute number of 10%.⁹

While autonomic dysfunction, myocarditis is relatively common, their mortality was not very high. Recently, COVID-19 associated mucormycosis (CAM) has created havoc all over the world; India and neighboring developing countries can be regarded as the hub, especially after the devastating second wave.¹⁰ Cases from both active COVID-19 cases and recovered COVID-19 patients have been reported. A broad spectrum of anatomical locations, mainly within the head and neck area, is involved by the disease and frequently causes disabilities like loss of vision, loss of nasal structure, destruction of bony structures, paralysis, etc. Uncontrolled hyperglycemia, widespread use of steroids and the need of prolonged mechanical ventilation in ICU has been implicated as the causative factors for the CAM.¹¹ However, cases without ICU and even hospital admission have also been found.¹² The WHO advises against the use of antibiotics and steroids in home isolated patients.¹³

However, the use of steroids and antibiotics is not uncommon even in home isolated patients.¹² This might be attributed to the after-effect of the widely publicized 'Randomized Evaluation of COVID-19 Therapy' trial (RECOVERY Trial), which showed the mortality benefit with the use of steroids.¹⁴ Therefore, using steroids and broad-spectrum antibiotics in the face of de-arranged immunology and deranged glycemic control might be the underground mechanism for such CAM cases among non-hospitalized patients. COVID-19 affects blood-sugar metabolism. A bi-directional relationship between COVID-19 and diabetes mellitus, including evidence of new diabetes mellitus in patients without predisposing factors, has been reported due to adipose tissue dysfunction and insulin resistance.^{15,16}

The mortality of CAM is very high. A study by Singh Y et al. has reported an overall mortality of 64.3%. Although the study reported survival data of only 14 patients, they also found that the mortality odds were higher with the old age and diabetes mellitus.¹⁷ Another multi-centre study conducted between September-December 2020 found that the prevalence of CAM was 27 per 10000 hospitalised COVID-19 patients. However, the authors noted an increasing trend in the incidence over the study period. The case-fatality rate at 12 weeks reported in this study was 45.7%.¹⁸ Similar to Singh Y et al., the study by Patel A et al. also noted age as a risk factor for mortality. They noted that brain involvement and ICU admission led to increased mortality. The disease usually starts from the sino-nasal cavities and gradually involves the orbital cavity followed by an extension to the brain cavity.¹⁹ In the author's (HMRK) institute, cases of brain infarcts without clear communication from the sino-nasal area to the brain cavity or without the involvement of the orbital cavity have been noted in several cases.

Management of the CAM usually requires both surgical debridement and medical management with antifungals.²⁰ Liposomal amphotericin B is recommended to be started as the first-line antifungal treatment.^{20,21} The drug is usually advised to be started in the recommended high-level dose, and escalation therapy is not recommended. Even a combination antifungal therapy is not recommended unless the disease is progressing clinically and radiologically. In such a scenario, isavuconazole or posaconazole can be

added.²¹ However, there are some practical limitations in following such recommendations. With the sudden surge in the cases, amphotericin B shortage has become another adverse factor.

Further, intolerance to amphotericin B therapy in terms of frequent reactions, presenting as fever, shivering, hypotension and even desaturation, has been noted in the clinical practice. Acute kidney injury (AKI) and electrolyte imbalance add up to the problems. Therefore, in clinical practice posaconazole has been used (practised in many institutes) to overcome these problems. Amphotericin B often needs pre and post-infusion fluid therapy, which is again a double-edged sword in critically ill patients. Therefore, it is high time to rationalize the use of amphotericin B in CAM patients; healthcare institutions in collaboration with local administration can prepare an individualized protocols as per the problems faced.

Along with the focus on the treatment of CAM cases, we should also focus on preventing such cases. Although the incidence of CAM is still low, the healthcare professionals need to keep the predisposing factors in view and take appropriate measures urgently once the early signs are recognized in any patient. The Fungal Infection Study Forum and the European Confederation of Medical Mycology recommend good glycemic control and judicious use of steroids (only in hypoxemic patients, administered in low dose for 5-10 days only) during the management of COVID-19. Further, patient education regarding the symptoms and signs of CAM at the time of discharge is also advocated.²¹

To conclude, COVID-19 is with us and probably will stay with us for an unknown period of time. While we learn to survive with COVID-19, we need to find a way to tackle the COVID-19 babies, i.e. post-covid complications, and prevent them. Meanwhile, judicious use of steroids, avoiding unnecessary broad-spectrum antibiotics, and better glycemic control appear as the cornerstone of preventive measures, while being treated for COVID-19; patient education at discharge and follow-up of COVID-19 recovered patients, either in the hospital or at home for early detection might help us in reducing the burden of disabilities and mortality from the CAM. The shortage and complications associated with the administration of liposomal amphotericin B are also a concern. Till we

achieve a better demand-supply status for this drug, we need to use it judiciously. A multi-disciplinary team including anesthesiologists, critical care physicians and nephrologists should be formed to rationalize drug therapy and associated fluid management. Alternative antifungals like posaconazole with better availability and tolerability might play a crucial role in the crisis.

1. Conflict of interest

None declare by the authors.

2. Authors' contribution

HMRK: Literature search, manuscript writing, editing

THK: Concept, manuscript editing, references correction and hyperlinking.

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