ejpmr, 2021,8(9), 216-220

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SECONDARY INFECTIONS ASSOCIATED WITH STEROID USE IN COVID 19 PATIENTS

Nazish Fathima, Soniya M., Tani Elsa Thomas and *[1]Teena Elsa Tigi

Department of Pharmacy Practice, Bapuji Pharmacy College, Davangere (577004), Karnataka, India.

***Corresponding Author: Teena Elsa Tigi**

Department of Pharmacy Practice, Bapuji Pharmacy College, Davangere (577004), Karnataka, India.

Article Received on 30/06/2021 **Article Revised on 19/07/2021** **Article Accepted on 07/08/2021**

ABSTRACT

COVID-19 is an acute respiratory syndrome produced by SARS-CoV-2. It is transmitted through droplets from infected individuals while talking, coughing or sneezing. Patients who are affected with coronavirus usually present with symptoms like fever, cough, shortness of breath, fatigue, muscle aches, headache, loss of smell or taste, sore throat, congestion, nausea/vomiting and diarrhoea. It is diagnosed using RT-PCR and serology testing. COVID-19 patients are associated with the risk of developing secondary bacterial and fungal infections such as mucormycosis and aspergillosis. Uncontrolled diabetes, immunocompromised conditions or use of steroids are the risk factors of secondary infections. Dexamethasone used at an early stage can change the pulmonary and systemic inflammatory response and thereby reduces mortality. But the overuse of steroid may suppress the immunity and leads to secondary infections and hence should be carefully administered. Infection controlling practices such as removing gloves after taking care of a patient, avoiding hand rubs over gloves and adherence to device care bundles are the ways to prevent secondary infections in COVID-19 patients.

KEYWORDS: COVID-19, SARS-CoV-2, mucormycosis, aspergillosis.

1.1 INTRODUCTION

COVID-19 which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) initially came out in late 2019 in Wuhan, China and spread quickly across the world.[1]

1.2 Pathophysiology of COVID-19

SARSCoV-2 is evolving and hence information regarding the pathogenesis of bacterial co-infection is also limited. For influenza, it is assumed that viral damage of epithelial cells in the lower airway along with mucociliary dysfunction allow pathogenic bacteria aspirated from the nasopharynx to bind to cell surfaces. Establishment of bacterial infection causes further damage by hindering repair and regeneration of the epithelial cell layer.[2]

When the SARS-CoV-2 (Covid 19) invades the respiratory epithelium and binds to angiotensin converting enzyme 2 (ACE2) receptors, it is manifested as an upper respiratory infection followed by pneumonia. The second stage of this disease, which is more severe, is caused by the systemic inflammation and coagulopathy resulting in direct damage to blood vessels, in addition to hepatic, renal and cardiac injuries. The coagulopathy is more of complement-mediated thrombotic microangiopathies (TMA), instead of sepsis-induced coagulopathy or disseminated intravascular coagulation (DIC), resulting in damage to endothelium and microvascular thrombosis. Other than diffuse alveolar damage with severe inflammatory exudation and coagulopathy, COVID-19 patients also possess immunosuppression with a decline in CD4 + T and CD8 +T cells.[3]

1.3 Clinical presentation of covid-19

The range of Covid-19 symptom has broadened since the beginning of the disease, which initially comprised of a dry cough and high grade fever, to additional multisystem problems including shortness of breath, anosmia, ageusia, diarrhoea, generalised malaise, acute cardiac injury and secondary infections.[4]

Symptoms as well as the severity and duration of COVID-19 differ widely. COVID-19 initially affects the human respiratory system, with the most common symptoms like fever, cough, shortness of breath, fatigue, muscle aches, headache, loss of smell or taste, sore throat, congestion, nausea/vomiting and diarrhoea.[5]

1.4 Diagnosis of COVID-19

Rapid antigen detection tests are useful to detect the presence of SARS-CoV-2 proteins, made by replicating viruses within the secretions of the respiratory tract.[6] Reverse transcription-PCR (RT-PCR) of respiratory samples is the standard test used for diagnosis of

COVID-19, which magnifies the genetic material of virus collected through nasal swab. Saliva can be used as an alternative source of specimen. IgM antibodies can be quantified within 5 days of infection, where it will be higher during weeks 2–3 of disease and IgG response is initially seen within 14 days after the onset of symptoms.[7]

1.5 Treatment of COVID-19

Broad-spectrum antibiotics, fluid replacement with normal saline and ringer's lactate and vasopressors in order to prevent or manage shock and peripheral hypoperfusion are used. Dobutamine is the drug of choice for the management of poor perfusion and cardiogenic shock. Azithromycin prevents pulmonary infections and also have a remarkable anti-inflammatory effect on the airways. Lopinavir is used to prevent the activity of coronavirus protease at a dose of 400 mg orally every 12 h. It works by modulating the inflammatory response in COVID-19 patients. Monoclonal antibodies like tocilizumab and sarilumab prevent organ damage by targetting the overactive inflammatory response following SARS-CoV-2 infection. Chloroquine, administered at a dose of 500 mg, every 12 h, can block the virus infection by increasing the endosomal pH needed for virus or cell fusion. Low doses of methylprednisolone are indicated in patients with worsening oxygen saturation. Dexamethasone has also been found to be effective in reducing mortality in serious and critically ill patients.[7] Remdesivir is a phosphoramidate prodrug, whose triphosphate form is analogous to adenosine triphosphate (ATP), prevents RNA-dependent RNA-polymerases from distinct Coronaviridae like SARS-CoV-2. Remdesivir was approved by the Food and Drug Agency (FDA) for COVID-19 patients, regardless of the seriousness of their disease.[8]

1.6 Secondary infections in COVID-19

Bacterial and fungal infections are the common complications developed in hospitalized COVID-19 patients. COVID-19 patients who require prolonged stay in hospitals are at a greater risk to develop hospital-acquired bacterial and fungal infections. This is because of the damaged ability of the host to get rid of bacterial pathogen resulting in discharge of certain cytokines like IL-10, IL-6, IL-17 and IL-23; decreased function of dendritic cells, macrophages, natural killer cells, CD4+ and CD8+ T-cells; and also some phagocyte-independent mechanisms through which virus infection may promote secondary bacterial infection. The most common sites of secondary infection in COVID-19 patients were blood and respiratory sites. Gram negative pathogens were predominant in respiratory infections whereas in bloodstream infections, Gram-positive pathogens were significant. Gram-negative pathogens are predominant due to the invasive device-related infections during hospitalization as they require mechanical ventilation and central venous catheter implantation in these patients.

Hand hygiene practices are more impaired at the time of COVID-19 pandemic as the health professionals wear gloves along with PPE and think it isn't necessary to perform hand hygiene, and there is a lack of awareness on the chances of transmission of infections in patients. Gloves can get contaminated with pathogens and can lead to transmission between persons, and hence glove hygiene practices such as removing gloves after care of a patient, avoiding hand rubs over gloves and adherence to device care bundles have to be reinforced in every health care sectors. Highly drug resistant pathogens can evolve as a result of poor infection control practices and empirical excessive use of broad-spectrum antimicrobials. Improving infection control practices will help to reduce the incidence of secondary infections, mainly nosocomial infections. Drug pressure can be reduced by strict practice of antimicrobial stewardship which in turn reduces drug resistance.[9]

1.7 Pathophysiology of secondary infections in COVID-19 patients

The pathophysiology of secondary infection in severe and critical COVID-19 cases is dependent on the interactions between host and pathogens, including severity of pathogens, unbalanced immune responses, and interrupted microbiota in viral pneumonia. Viral pneumonia and secondary infection are mutually supporting factors in promoting the evolution of COVID-19. Severe SARS-CoV-2 infection can decrease the oxygen and carbon dioxide diffusion capacities by causing multiple injuries in the lungs. The destruction of surfactant and the sloughing of cells into the airways may promote fast bacterial growth due to an abundant source of nutrients. The immune responses to SARS-CoV-2 can be altered by the influence of microbiome change and bacteria virulence factor, resulting in the rebound of concentration of infectious viral particles and high mortality in extremely serious patients.[10]

1.8 Symptoms of fungal infection

Sinusitis with mucosal thickening of maxillary and ethmoid sinuses, facial swelling, headache, proptosis, oedema of the extraocular muscles, orbital cellulitis, ophthalmoplegia, etc. were few of the symptoms of invasive fungal infection.[3]

1.9 Mucormycosis

Mucormycosis or zygomycosis, also called phycomycosis, is a type of life-threatening invasive fungal sinusitis that usually occurs in individuals who are immunocompromised and have a disrupted neutrophilic response. It is described by the presence of hyphal entry into sinus tissue and a time period of less than four weeks. Mucor is a saprophytic fungus, whose spores exist extensively in nature, spread in air, soil, food and decomposing organic material. It may exist in the nasal mucosa of healthy people as a commensal, because of its low virulence potential. When the patient becomes immunocompromised, this fungus may germinate inside the paranasal sinuses, and spread intracranially or to

other close by structures such as the orbit. Signs and symptoms of rhinocerebral mucormycosis can be similar to complicated sinusitis, which include nasal congestion, crusting, proptosis, pain and oedema in the face, ptosis, ophthalmoplegia, chemosis, along with headache and fever and several neurological signs and symptoms in the presence of intracranial extension. A black eschar may be present in the nasal cavity or above the hard palate region, but is not a characteristic feature. Microanatomical features such as mycotic infiltration and inflammation of the blood vessels with thrombosis, tissue death due to inadequate blood supply, haemorrhage and acute neutrophilic infiltrate. There may be rapid progression of the disease when the diagnosis and treatment are delayed, with 50-80% of reported mortality rates from intra-orbital and intracranial complications. The management of mucormycosis is usually ineffective, resulting in the extension of the infection and ultimately death, even with quick and appropriate diagnosis, treatment of the underlying diseases and aggressive medical therapy and surgical intervention.

There are certain risk factors including diabetes mellitus, presence of any previous respiratory pathology, immunosuppressive therapy, sources of nosocomial infection and systemic immune alterations caused by Covid-19 infection itself that can lead to secondary infections, which are immediately considered due to their impact on morbidity and mortality. Covid-19 patients present an increase in inflammatory cytokines and impairment in cell-mediated immunity with decreased CD4+ T and CD8+ T cell counts, showing susceptibility to fungal co-infections. Critically ill patients, who were admitted to ICUs and those who needed mechanical ventilation, or who had a longer period of hospital stays, as much as 50 days, were more susceptible to fungal co-infections. Using steroids extensively in managing Covid-19 can also reduce immunity, causing colonisation of opportunistic fungal infections. Covid-19 patients can develop fungal infections during the middle and latter stages of this disease, especially critically ill individuals.

Usually the first investigation of choice is non-contrast computed tomography of the paranasal sinuses whereas gadolinium-enhanced magnetic resonance imaging is preferred when intra-orbital or intracranial extension is suspected. Focal bony erosions and extrasinus spread are strong indications of the diagnosis. Once the diagnosis is confirmed, it is recommended to perform surgical debridement of the infected area as soon as possible. Surgery alone is not considered to be curative, but it can improve survival. The antifungal treatment of choice is Amphotericin-B deoxycholate, with its liposomal preparations selected because of reduced nephrotoxicity. Posaconazole is considered a suitable alternative option, in cases refractory or intolerant to amphotericin therapy.[4]

Mucormycosis may occur in patients with diabetes mellitus, malignancy, organ or hematopoietic stem cell transplant, or neutropenia. Pulmonary mucormycosis is observed in patients with a predisposing state of neutropenia or use of corticosteroid. AmB formulations, posaconazole and iron chelation therapy are the present recommendations for effective treatment of mucormycosis. Use of AmB and an echinocandin have shown improved outcomes, even though monotherapy with echinocandins is not effective against mucormycosis. However, its use in mucormycosis is not recommended due to the lack of literature about combination therapy.[11]

1.10 Aspergillosis

Aspergillosis intruding into the sinuses also occur in immunocompromised individuals. Computed tomography (CT) is the first diagnostic tool employed to assess the condition of sinuses and the extent of extra-sinus growth is best interpreted with magnetic resonance imaging (MRI). Histologic examination of the biopsy specimen is performed to diagnose the causative fungal species and culture and KOH examination may be used to detect the presence of mucormycosis. Aspergillosis of the head and neck is also detected by histological examination.[3]

Invasive pulmonary aspergillosis (IPA) has been highly reported in seriously ill patients, including patients without any risk factors of immunosuppression. Approximately, 12.5% of the acute respiratory distress syndrome (ARDS) patients had IPA as shown by random post-mortem histopathological examination of lung tissue. If it is the use of immunomodulatory agents such as corticosteroids and antibiotics to treat or prevent bacterial superinfections is behind the high susceptibility of COVID-19 patients to invasive pulmonary fungal disease continues to remain unstudied.[12]

1.11 Treatment of secondary infections

Prescribing of antibiotic in suspected or documented COVID-19 patients are aimed at a variety purpose as they are futile in the treatment of COVID-19. To be precise, the difficulty to rule out bacterial co-infection and also the possibility of secondary bacterial infection during the course of the illness. The empirical use of antibiotics has been advocated by several guidelines from the growing concerns about the mortality of patients with bacterial superinfection during influenza pandemic. This at the same time raises concerns about the overuse of antibiotic and the ensuing harm associated with bacterial resistance.[2]

1.12 About corticosteroids

Systemic corticosteroids are regularly prescribed to patients outside clinical trials, unless otherwise they are indicated for another reasons, although WHO does not recommend it. During the outbreak in China these were the drugs that were widely used. Wu et al. have shown in a retrospective cohort study, that the administration of

methylprednisolone appears to have reduced the risk of death in COVID-19 patients with ARDS. Even then, it still lies short of evidences about the application of corticosteroids (virus shedding and immunological function) in the management of COVID-19 pneumonia. The clinical evidence neither in favour nor in disapproval of the corticosteroid application for COVID-19 pneumonia exists. Many potential risks such as secondary infections and other long-term complications accompany the corticosteroid application in treating viral pneumonia. Early use of corticosteroid for a short period could prolong the SARS-CoV-2 shedding in patients with COVID-19 pneumonia, especially in the patients without acute respiratory failure, as a result of suppression of the immune cells. It was suggested not to add corticosteroids to the standard therapy as a general treatment.[13]

We hypothesise that the ideal host for mucormycosis is provided by the immunocompromising effects of corticosteroids with microangiopathy of diabetes and possible peripheral microthrombi in COVID-19, which because of its inherent angioinvasive nature bring forth an increased incidence. It might be necessary to revisit a standard blanket protocol of steroid administration for Covid-19 infection and play up on tight glycaemic control during and after Covid-19 infection should be laid.[3]

2. CONCLUSION

The two main factors that are aggravating the illness are uncontrolled diabetes and fanatical use of steroids, and must be checked properly with equal importance. As a prognosis, if infected, early surgical intervention and intravenous anti-fungal treatment should be sought for management and it is achievable to have a fairly less fulminant disease course in cases of post-coronavirus mucormycosis. Boundlessly using steroids in Covid-19 can also suppress immunity, which pave way for the colonisation of fungal infections. Therefore, it is crucial to be aware of the fungal infections that can be developed in COVID-19 patients during the middle or latter stages of this disease, especially severely ill individuals. It is extremely important to understand the proportion of COVID-19 patients with acute respiratory bacterial co-infection, and the culprit pathogens as it is crucial for treating patients with COVID-19 and to ensure empirical use of antibiotics and to limit negative results of overuse. Furthermore, this knowledge could cause a significant impact in refining antibiotic management guidelines for patients with COVID-19.

REFERENCE

1. Ananthalakshmi V. The current situation of COVID-19 in India. Brain, Behavior, & Immunity-Health, 2021 Feb 1; 11: 100200.
2. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, Soucy JP, Daneman N. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clinical Microbiology and Infection, 2020 Jul 22.
3. Moorthy A, Gaikwad R, Krishna S, Hegde R, Tripathi KK, Kale PG, Rao PS, Haldipur D, Bonanthaya K. SARS-CoV-2, Uncontrolled Diabetes and Corticosteroids—An Unholy Trinity in Invasive Fungal Infections of the Maxillofacial Region? A Retrospective, Multi-centric Analysis. Journal of maxillofacial and oral surgery, 2021 Mar 6; 1-8.
4. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. The Journal of Laryngology & Otology, 2021 May; 135(5): 442-7.
5. Klein H, Asseo K, Karni N, Benjamini Y, Nir-Paz R, Muszkat M, Israel S, Niv MY. Onset, duration and unresolved symptoms, including smell and taste changes, in mild COVID-19 infection: a cohort study in Israeli patients. Clinical Microbiology and Infection, 2021 May 1; 27(5): 769-74.
6. Merino P, Guinea J, Muñoz-Gallego I, González-Donapetry P, Galán JC, Antona N, Cilla G, Hernáez-Crespo S, Díaz-de Tuesta JL, Gual-de Torrella A, González-Romo F. Multicenter evaluation of the Panbio™ COVID-19 rapid antigen-detection test for the diagnosis of SARS-CoV-2 infection. Clinical Microbiology and Infection, 2021 May 1; 27(5): 758-61.
7. NEELA B, JAKKULA S, GAUR RP. Corticosteroids and secondary infections: An insight into coronavirus disease-2019. Asian Journal of Pharmaceutical and Clinical Research, 2021 Jan 5; 36-47.
8. Touafchia A, Bagheri H, Carrié D, Durrieu G, Sommet A, Chouchana L, Montastruc F. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns. Clinical Microbiology and Infection, 2021 May 1; 27(5): 791-e5.
9. Vijay S, Bansal N, Rao BK, Veeraraghavan B, Rodrigues C, Wattal C, Goyal JP, Tadepalli K, Mathur P, Venkateswaran R, Venkatasubramanian R. Secondary Infections in Hospitalized COVID-19 Patients: Indian Experience. Infection and drug resistance, 2021; 14: 1893.
10. Zhang H, Zhang Y, Wu J, Li Y, Zhou X, Li X, Chen H, Guo M, Chen S, Sun F, Mao R. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerging Microbes & Infections, 2020 Jan 1; 9(1): 1958-64.
11. Cook S, Confer J. Assessment and treatment of fungal lung infections. US Pharm., 2011; 36(7).
12. Dellière S, Dudoignon E, Fodil S, Voicu S, Collet M, Oillic PA, Salmona M, Dépret F, Ghelfenstein-Ferreira T, Plaud B, Chousterman B. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. Clinical Microbiology and Infection, 2021 May 1; 27(5): 790-e1.

13. Tang X, Feng YM, Ni JX, Zhang JY, Liu LM, Hu K, Wu XZ, Zhang JX, Chen JW, Zhang JC, Su J. Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial. Respiration, 2021; 100(2): 116-26.