International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1320-1326 www.ijprajournal.com ISSN: 2249-7781

Covid-19 Triggering Mucormycosis with Its Treatment And Management: A Review Of Cataclysmic Pandemic

Arpit Dwivedi*, Srishti Awasthi, Avanish Maurya, Arif Badar
Research Scholar, Department of Pharmacology, Institute of Pharmaceutical Sciences and Research, UnnaoUttar Pradesh- 209859, India
Research Scholar, Department of Pharmacology, Institute of Pharmaceutical Sciences and Research, Unnao Uttar Pradesh- 209859, India
Research Scholar, Department of Pharmacy, Saroj Institute of Technology and Management, Lucknow, Uttar Pradesh- 206002, India
Associate Professor, Department of Pharmacy, Avadh Institute of Medical Technology and Hospital, Lucknow Uttar Pradesh- 206026, India

Submitted: 17-01-2023 Accepted: 31-01-2023

ABSTRACT: In December 2019, an unidentified respiratory outbreak was reported in Wuhan, Hubei Province, China. Pneumonia cases were connected to the Huanan Seafood Wholesale Market.The Global Health Organization termed the disease caused by SARS-CoV-2 infection coronavirus disease 2019 on February 11, 2020. (COVID-19). COVID-19 causes a variety of clinical symptoms, including fever, persistent cough, and lethargy, often with respiratory involvement. SARS-CoV-2 is highly contagious, and most people in the general population are vulnerable to infection. Currently, wild animal carriers and sick patients are the primary routes of disease transmission via airborne droplets and close communication. Since the epidemic, the Chinese administration and research community have moved quickly to discover the causative agent, share the viral DNA sequence, and implement steps to contain the pandemic.The catastrophe (COVID-19) is still a major concern around the world. While numerous therapeutic approaches have been investigated, none have been demonstrated to increase survival in COVID-19. Unfortunately, the common use of glucocorticoids might result in secondary microbial or fungal infections. Although invasive bronchial aspergillosis complicates the course of COVID-19, mucormycosis is rarely noticed or diagnosed.This review aims to summarize and identify the consequences and treatment perspective of COVID-19-associated mucormycosis (CAM).

Keywords: Mucormycosis; Aspergillus niger; Candida albicans; SARS-Cov 2; Covid-19

I. INTRODUCTION

The pandemic coronavirus disease 2019 (COVID-19) is a prominent concern throughout the world. While numerous therapeutic alternatives have been investigated, none, except systemic glucocorticoids, have been demonstrated to increase survival in COVID-19. One such infectious sickness took place towards the end of 2019, shortly before the largest Chinese fest[(1).] This was highlighted by the large sets of multiple severe pneumonia cases with comparable findings in Wuhan, one of China's largest cities[(2-3)]. Later, using genome sequencing technology, the cause of the sickness was discovered as a novel kind of coronavirus known as severe acute respiratory crisis coronavirus 2 (SARS-CoV-2), and the condition was termed COVID-19[(4)]. (COVID-19) generated by the coronavirus that causes SARS (SARS-CoV-2) has been linked to a variety of uncontrolled bacterial and fungal infections. [(5)]Furthermore, Aspergillus niger and Candida albicans have been identified as the most common fungal strains

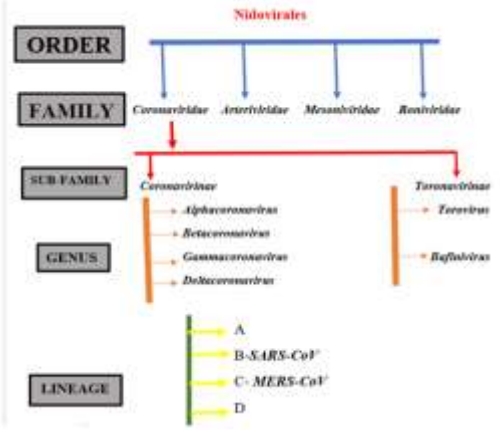

TABLE:1 SCHEMATIC CLASSIFICATION OF CORONAVIRUS

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1320-1326 www.ijprajournal.com ISSN: 2249-7781

associated with COVID-19 co-infection.As of 5 November 2020, a record of 48,539,872 affected individuals and 1,232,791 deaths reported from COVID-19 has been reported in 215 nations and regions worldwide [6]. Chronic sickness has generated a significant worldwide health burden as well as waves in the medical community. [7-8]

The major reason that Mucorales spores emerge to proliferate in people with COVID-19 is an ideal environment of oxygen depletion (hypoxia), elevated glucose (diabetes, new-onset impaired glucose tolerance, steroid-induced reactive hypoglycemia), acidic medium (metabolic acidosis, ketoacidosis [DKA]), high iron levels (increased ferritins), and reduced phagocytic activity of white blood cells combined with several other common risk factors, such as prolonged hospitalization accompanied by or without respiratory support.

II. MATERIAL AND METHODS

By Nov 2022, this study was based on a substantial proof literature evaluation and was carried out by exploring databases such as Google Scholar, PubMed, and ScienceDirect. Keywords such as "Coronavirus," "COVID-19," "Black Fungus," "mucormycosis," and "prevention" were used in the search. The final article's reference list was also checked to identify items that were not found through the search. This study also made use of guidelines provided by prominent organizations such as the World Health Organization (WHO) and the Centers for Disease Control (CDC). For analysis, research published in English and done in various countries was chosen. The study omitted studies and research linked to therapy and clinical diagnostic symptoms.After eradicating duplicate instances, the findings were assessed individually byauthors based on the specific criteria, and the investigations that advanced to the final evaluation stage were extracted and analyzed.

III. ORIGIN OF SARS-COVID-19

Scientists have questioned the provenance of the new coronavirus, SARS-CoV-2, since its detection [9]. SARS-CoV-2 is thought to be the result of experimental research. However, genomic evidence contradicts this concept, indicating that SARS-CoV-2 didn't arise from a commonly identified virus core.[10]Intense infections of the airways are the most prevalent type of infection, affecting people of all ages and genders [11] Streptococcus pneumoniae, Hemophilus influenzae, Moraxella catarrhalis, Influenza A or B ("the flu"), respiratory syncytial virus (RSV), influenza, adenovirus, coronaviruses, and other microbes are commonly responsible for these disorders [12-13]. Conversely, in terms of contagiousness and medical problems, the most common infections are those caused by RSV, Flu, and retroviruses, which have caused multiple epidemics and pandemics [14].

IV. CLINICAL SYMPTOMS

Fever, chronic cough, dyspnea, and breathing difficulties are the most common first symptoms [15]. Although diarrhea was seen in around 20-25% of individuals harboring MERS-CoV or SARS-CoV exposure, gastrointestinal symptoms in COVID-19 patients are uncommon. Confusion, chest discomfort, vomiting, and nausea were also identified as COVID-19 symptoms in another study [16]. Difficulty swallowing, wheezing, rhinitis, mucus discharge, anosmia and heartburn, skin rash or coloring of the fingers and toes, and viral conjunctiva are some symptoms. Some laboratory experiments have revealed that COVID-19 suffers from cytokine storm, infection, and RNAanemia [17-18].

V. TRANSMISSION OF COV-19

SARS-CoV-2 potentially transmits through both direct (fluids and individual transmission) and contamination. In the meantime, personal protective attire (PPE) may be a source of airborne diseases [19]. As previously stated, person-to-person transmission of SARS-CoV-2 is thought to occur mostly through respiratory droplets produced when a person coughs, coughs or sneezes, or even speaks or sings [20]. Droplets often cannot travel over than 6 feet and can only stay in the air for a short period. SARS-CoV-2, on the other hand, stays unchanged and infectious in droplets (just under five microns diameter) and can circulate in the atmosphere for approximately three hours [21].

COVID-19 can be contracted if a person comes into close contact with mucosal membranes such as the conjunctiva, nostrils, or mouth after encountering a source affected with SARS-CoV-2 [22]. As a result, adequate hand cleaning with soaps and water or hand sterilizers is advised.SARS-CoV-2 has also been found to spread from asymptomatic persons (or those in the initial infection) without any diagnostic abnormalities [23-25]. As a result, advancements in speedy and sensitive diagnostic approaches for recognizing infected individuals are required.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1320-1326 www.ijprajournal.com ISSN: 2249-7781

VI. COVID-19 ACCOMPANIED BY MUCORMYCOSIS

Paltaufinitially identified phycomycotic or zygomycotic in 1885, and Bakeran American pathologist, created the term Mucormycosis in 1957 for an aggressive Rhizopus infection.[26-27] Mucormycosis is a sporadic but devastating fungal infection that typically affects patients with impaired immune systems.

Mucormycosis is anillness caused by mold fungi of the genus Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia of the Mucorales Order, Class Zygomycetes [28].

Mucormycosis, a name most doctors are acquainted with, refers to a group of different mycoses induced by one of the orders of Mucorales' ubiquitous saprophytic fungus. Even thoughnumerous Mucorales species are responsible.

Case studies reveal that strains of Mucorales that had been previously thought to be innocuous commensals may cause intrusive illness under the right conditions. The recognition of organisms retrieved from human illnesses has been made more challenging because the identities of the fungi have evolved throughout time as more aspects of their taxonomy have been revealed. [29]

In humans, the infection begins after inhaling Mucorales spores into the lower airways. This idea may settle in the nasal sinus passages or move into the respiratory airways. The events that lead to hyphal growth in tissue are mainly unclear. Experiments have revealed that alveolar macrophages derived from healthy mice can prevent Rhizopus spores from germinating [30-31]. The same macrophages derived from diabetic mice are unable to block the formation of Rhizopus spores, and these animals acquire quickly increasing mucormycosis after inhaling Rhizopus conidia.

The main distinguishing aspect of mucormycosis is the hyphal infiltration of blood vessels. This intrusion causes bleeding, thrombosis, infarction, and tissue necrosis. The causes for these fungi's affinity towards vasculature are unclear.

VII. DIAGNOSIS

A prognosis of mucormycosis is infrequently detected in hematology patients since most clinicians suspect expansive aspergillosis. Only 23-50% of hematology patients had an ante-mortem assessment of mucormycosis [32-36]. Ct scanning of the chest may detect infiltrates indicative of mucormycosis that are not visible on routine chest radiographs [37]. Sputum culture's low sensitivity (25%) makes diagnosis difficult [38]. Bronchoalveolar yield is not increased [37-38]. Direct imaging of bronchoalveolar lavage in conjunction with transrectal biopsy may improve yield.

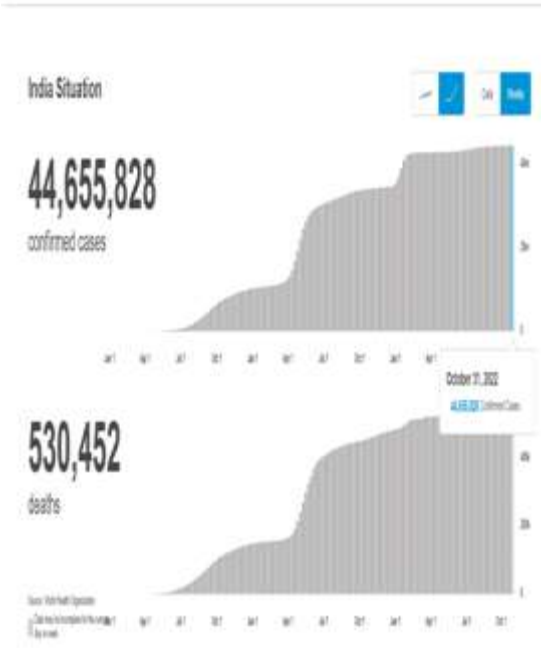

FIGURE 1: GRAPHICAL REPRESENTATION OF STATISTICAL DATA OF CONFIRMED CASES AND DEATH IN INDIA TILL OCT 31, 2022.
Source: WHO (World Health Organization) [47]

VIII. TREATMENTS FOR COVID-19 ASSOCIATED WITH MUCORMYCOSIS

The treatment of Covid-19 associated with pulmonary fungal infection involves the high spectrum antiviral agents, immunomodulators, and anti-inflammatory agents followed by some potent broad-spectrum anti-fungal drugs to achieve maximal relaxation in the severity of covid-19 triggering mucormycosis.

A significant range of antiviral medications, many of which are used to treat human immunodeficiency virus (HIV), hepatitis, and flu symptoms, are now being used off-label in patients with COVID-19 or are being studied for therapy. In this section, we review the most commonly used antiviral medications in terms of therapeutic effects and potential for COVID-19 therapy.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1320-1326 www.ijprajournal.com ISSN: 2249-7781

While it is uncertain if antifungal therapy forCOVID-19-related IPA improves mortality, identification should in most cases prompt early antifungal treatment.Voriconazole is still the first-line therapy for IPA outside of hematologic malignancies [39-40].

The combined lopinavir/ritonavir, which is recommended in conjunction with other antiretroviral medications to treat HIV-1, is gaining popularity for the treatment of COVID-19. Lopinavir is a protease antagonist with good selectivity for HIV-1 and HIV-2, whereas ritonavir raises lopinavir plasma levels via cytochrome P450 inhibition [41].This combination was previously tried in patients with SARS infection and shown to be related tofavorable outcomes; it is now being studied in patients with MERS-CoV infection in conjunction with IFN- conducted a randomized, controlled, open-label experiment in 199 hospitalized SARS-CoV-2 patients. [42]

Remdesivir has recently been identified as a potential antiviral medication against a wide range of Viral pathogens (including MERS-CoV) infectious diseases in cultured cells, mice, and non-human primate models [43].A nucleotide analog can block RNA-dependent RNA polymerase (RdRp), which is required for viral replication[44]. The medicine was first created to treat Ebola and Marburg infections; however, it did not show clinical effectiveness. Antiviral activity against single-stranded RNA viruses, such as MERS and SARS-Cov, was also established [45]. A recent preclinical investigation found that the combination of remdesivir/chloroquine might successfully reduce SARS-Cov-2 infection in vitro.

Many different medications with various modes of action are being tested in COVID-19 patients. Camrelizumab, a PD-1 immune checkpoint blockade monoclonal antibody that recently got conditional clearance in China for the management of relapsed or resistant basic Hodgkin lymphoma, is being tested in a phase 2 research including individuals infected with SARS-Cov-2. PD-1 and its ligands (PD-L1) are important mediators of T cell suppression in sepsis patients. Preclinical research has shown that blocking PD-1 or PD-L1 can prevent T-cell & cell death, modulate cytokine production, and minimize organ failure [46].

IX. CONCLUSION

The entire review is around the technical aspects of the pandemic disorder originating from Wuhan, China. The reviewfocuseson the history and origin of the covid-19 and its clinical manifestations along with primary symptomatic approaches during the time of Pandemic.

On other hand, it also established the relations of fungal infection during the surge of Corona Virus, the patients suffering from mucormycosis or pulmonary zygomycetes infection commonly known as "BLACK FUNGUS". The review also includes graphical data and figures to get through the subject immensely and all the data are collected from recognized journals and research papers.

Further, the primary treatment methods are also been studied for the treatment of Covid-19 triggering mucormycosis. This review helps to understand and to establish the correlation between these two diseases.

FIGURE 2: SUMMARIZED DATA OF COVID-19 CASES AS PER NEWER DATA RELEASED BY WHO (WORLD HEALTH ORGANISATION)
Source: WHO (World Health Organization) [47]

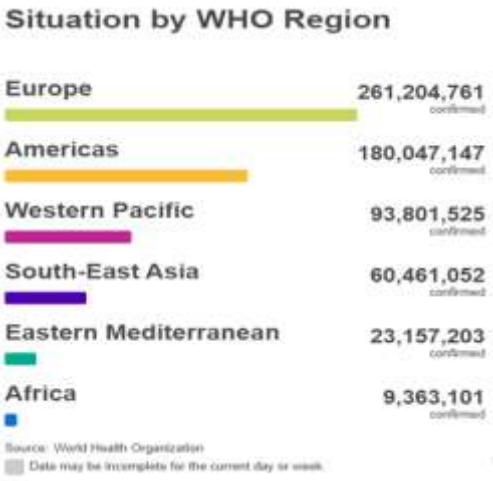

FIGURE 3: NUMBER OF COVID-19 CASES REPORTED WORLDWIDE

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1320-1326 www.ijprajournal.com ISSN: 2249-7781

REFERENCES

[1]. Wang, C.; Horby, P.W.; Hayden, F.G.; Gao, G.F. A novel coronavirus outbreak of global health concern. Lancet 2020, 395, 470–473.

[2]. Zhou, M.; Zhang, X.; Qu, J. Coronavirus disease 2019 (COVID-19): A clinical update. Front. Med. 2020.

[3]. Jiang, S.; Xia, S.; Ying, T.; Lu, L. A novel coronavirus (2019-nCoV) causing the pneumonia-associated respiratory syndrome. Cell. Mol. Immunol. 2020, 17, 554–554.

[4]. Yang, P.; Wang, X. COVID-19: A new challenge for human beings. Cell. Mol. Immunol. 2020, 17, 555–557.

[5]. Kubin CJ, McConville TH, Dietz D, et al. Characterization of Bacterial and Fungal Infections in Hospitalized Patients with COVID-19 and Factors Associated with Healthcare-associated Infections, Open Forum Infectious Diseases, 2021; ofab201,

[6]. . Song G, Liang G, Liu W. Fungal Co-infections Associated with Global COVID19 Pandemic: A Clinical and Diagnostic Perspective from China. Mycopathologia. 2020 Aug;185(4):599-606.

[7]. World Health Organization. Novel Coronavirus (2019-nCoV): Situation Report, 3. 2020.Available online: https://apps.who.int/ iris/bitstream/handle/10665/330762/nCoV sitrep23Jan2020-eng.pdf (accessed on 23 December 2020).

[8]. Lupia, T.; Scabini, S.; Pinna, S.M.; Di Perri, G.; De Rosa, F.G.; Corcione, S. 2019-novel coronavirus outbreak: A new challenge. J. Glob. Antimicrob. Resist. 2020, 21, 22–27.

[9]. Andersen KG, Rambaut A, Lipkin WI, et al. The proximal origin of SARS-CoV-2. Nat Med. 2020; 26:450–452.

[10]. Almazán F, Sola I, Zuñiga S, et al. Coronavirus reverse genetic systems: infectious clones and replicons. Virus Res. 2014;189:262–270.

[11]. Castagnoli, R.; Votto, M.; Licari, A.; Brambilla, I.; Bruno, R.; Perlini, S.; Rovida, F.; Baldanti, F.; Marseglia, G.L. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: A systematic review. JAMA Pediatrics 2020, 174, 882–889.

[12]. Gröndahl, B.; Puppe, W.; Hoppe, A.; Kühne, I.; Weigl, J.A.; Schmitt, H.-J. Rapid identification of nine microorganisms causing acute respiratory tract infections by single-tube multiplex reverse transcription-PCR: A feasibility study. J. Clin. Microbiol. 1999, 37, 1–7.

[13]. Bitskoitko, V.; Musiyenko, A.; Shulyayeva, O.; Barik, S. Inhibition of respiratory viruses by nasally administered siRNA. Nat. Med. 2005, 11, 50–55.

[14]. Brundage, J.F. Interactions between influenza and bacterial respiratory pathogens: Implications for pandemic preparedness. Lancet Infect. Dis. 2006, 6, 303–312.

[15]. Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. International Journal of Infectious Diseases. 2020;91:264-6.

[16]. N. Chen, M. Zhou, X. Dong, J. Qu, F. Gon g, Y. Han, et alEpidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study-The Lancet., 395 (10223) (2020), pp. 507-513.

[17]. M. Cascella, M. Rajnik, A. Cuomo, S.C. D ulebohn, R. Di Napoli Features, evaluation and treatment coronavirus (COVID-19). Statpearls [internet]StatPearls Publishing (2020).

[18]. (WHO) WHO. Q&A on coronaviruses (COVID-19) 2020 17 April [Available from: https://www.who.int/emergencies/diseases /novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses#:~:text=symptoms.

[19]. Liu Y, Ning Z, Chen Y, Guo M, Liu Y, Gali NK, et al. Aerodynamic characteristics and RNA concentration of SARS-CoV-2 aerosol in Wuhan hospitals during COVID-19 outbreak. bioRxiv. 2020.

[20]. N. van Doremalen, T. Bushmaker, D.H. Morris, M.G. Holbrook, A. Gamble, B.N. William son, et al. Aerosol and Surface Stability of

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1320-1326 www.ijprajournal.com ISSN: 2249-7781

SARS-CoV-2 as Compared with SARS-CoV-1 N. Engl. J. Med. (2020)

[21]. Santarpia JL, Rivera DN, Herrera V, Morwitzer MJ, Creager H, Santarpia GW, et al. Transmission Potential of SARS-CoV-2 in Viral Shedding Observed at the University of Nebraska Medical Center. medRxiv. 2020.

[22]. Santarpia JL, Rivera DN, Herrera V, Morwitzer MJ, Creager H, Santarpia GW, et al. Transmission Potential of SARS-CoV-2 in Viral Shedding Observed at the University of Nebraska Medical Center. medRxiv. 2020.

[23]. C. Rothe, M. Schunk, P. Sothmann, G. Br etzel, G. Froeschl, C. Wallrauch, et al.

[24]. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany N. Engl. J. Med. (2020).

[25]. P. Yu, J. Zhu, Z. Zhang, Y. Han, L. Huang A familial cluster of infection associated with the 2019 novel coronavirus indicates potential person-to-person transmission during the incubation period

[26]. J Infect Dis. (2020).

[27]. Y. Bai, L. Yao, T. Wei, F. Tian, D.-Y. Jin, L. Chen, et al.Presumed asymptomatic carrier transmission of COVID-19JAMA (2020).

[28]. Paltauf A. Mycosis mucorina. Virchows Arch PatholAnatPhysiolKlin Med 1885;102:543–64.

[29]. Baker RD. Mucormycosis-a new disease? J Am Med Assoc. 1957;163:805-808.

[30]. Eucker J, Sezer O, Graf B, Possinger K. Mucormycoses. Mycoses. 2001;44(7):253-260.

[31]. Sugar, A. M. (1992). Mucormycosis. Clinical Infectious Diseases, 14(Supplement_1), S126–S129.

[32]. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against Rhizopus. J Clin Invest 1984;74:150-60.

[33]. Waldorf AR, Levitz SM, Diamond RD. In vivo bronchoalveolar macrophage defense against Rhizopus oryzae and Aspergillus fumigants. J Infect Dis 1984;150:752-60.

[34]. Nosari A, Oreste P, Montillo M, et al. Mucormycosis in hematologic malignancies: an emerging fungal infection. Haematologica 2000; 85: 1068–71.

[35]. Funada H, Matsuda T. Pulmonary mucormycosis in a hematology ward. Intern Med 1996; 35: 540– 4.

[36]. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston VI. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis 2000; 30: 851– 6.

[37]. Maertens J, Demuynck H, Verbeken EK, et al. Mucormycosis in allogenic bone marrow transplant recipients: report of five cases and review of the role of iron overload in the pathogenesis. Bone Marrow Transplant 1999; 24: 307– 12.

[38]. Pagano L, Ricci P, Tonso A, et al. Mucormycosis in patients with hematological malignancies: a retrospective clinical study of 37 cases. GIMEMA infection program (Gruppo ItalianoMalattieEmatologicheMaligneDell' adulto). Br J Haematol 1997; 99: 331– 6.

[39]. McAdams HP, Rosado de Christenson M, Strollo DC, Patz EF Jr. Pulmonary mucormycosis: radiologic findings in 32 cases. AJR Am J Roentgenol 1997; 168: 1541– 8.

[40]. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston VI. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis 2000; 30: 851– 6.

[41]. Patterson, T.F.; Thompson, G.R., III; Denning, D.W.; Fishman, J.A.; Hadley, S.; Herbrecht, R.; Kontoyiannis, D.P.; Marr, K.A.; Morrison, V.A.; Segal, B.H.; et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin. Infect. Dis. 2016, 63, e1–e60.

[42]. Ullmann, A.; Aguado, J.; Arikan-Akdagli, S.; Denning, D.; Groll, A.; Lagrou, K.; Lass-Flörl, C.; Lewis, R.; Munoz, P.; E Verweij, P.; et al. Diagnosis and management of Aspergillus diseases: Executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin. Microbiol. Infect. 2018, 24, e1–e38.

[43]. Soliman, E. Z., Lundgren, J. D., Roediger, M. P., Duprez, D. A., Temesgen, Z., Bickel, M., … INSIGHT SMART Study Group. (2011). Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. Aids, 25(3), 367– 377.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1320-1326 www.ijprajournal.com ISSN: 2249-7781

[44]. Arabi, Y. M., Alothman, A., Balkhy, H. H., Al-Dawood, A., AlJohani, S., Al Harbi, S., … Al-Hameed, F. (2018). Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): Study protocol for a randomized controlled trial. Trials, 19(1), 81.

[45]. Sheahan, T. P., Sims, A. C., Leist, S. R., Schäfer, A., Won, J., Brown, A. J., … Baric, R. S. (2020). Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature Communications, 11, 222.

[46]. De Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T., … Feldmann, H. (2020). Prophylactic and therapeutic remdesivir (GS-5734) treatment in the Rhesus Macaque model of MERS-CoV infection. PNAS Latest Articles, 117(12), 6771– 6776.

[47]. Agostini, M. L., Andres, E. L., Sims, A. C., Graham, R. L., Sheahan, T. P., Lu, X., … Denison, M. R. (2018). Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. MBio, 9(2), e00221–e00218.

[48]. Markham, A., & Keam, S. J. (2019). Camrelizumab: First Global Approval. Drugs, 79(12), 1355–1361.

[49]. WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/