

OPPORTUNISTIC INFECTIONS DUE TO OVERUSE OF STEROIDS

ABSTRACT

Background: Case reviews of rhino-orbital mucormycosis in sufferers with coronavirus sickness 2019 (COVID-19) are at the rise, specifically in India. Diabetes mellitus (DM) is a chance aspect for excessive COVID-19 and mucormycosis on its own. The purpose of this is to carry out a scientific review of the literature to decide the capabilities of Opportunistic Infections due to overuse of steroid.

Method: Using key phrases like COVID 19, Mucormycosis, Mucor, Novel corona virus, and SARS CoV-2, a scientific review was carried out on the subsequent databases: PubMed, Google Scholar, and Cochrane Library.

Result: Increased mucormycosis in India seems to be the end result of an unholy trinity of diabetes (excessive genetic occurrence), immoderate corticosteroid utilization (will increase blood glucose and results in opportunistic fungal contamination), and COVID-19 (cytokine storm, lymphopenia, endothelial damage). To lower the prevalence of lethal mucormycosis, all efforts must be taken to keep ideal hyperglycaemia, and best careful evidence-primarily based totally use of corticosteroids in sufferers with COVID-19 is suggested. Glucocorticosteroids (GC) play an critical position withinside the remedy of neuro-oncologic patients. GC are used for the control of malignant mind tumour's, both number one of secondary, neoplastic epidural spinal wire compression (NESC), as adjuvant chemotherapy of a few relevant worried device tumours and perioperatively in mind surgery. GC are believed to exert their effect on mind tumours especially through decreasing the tumor-related vasogenic edema, in all likelihood through lowering the extended capillary permeability of the blood-mind barrier (BBB),

Conclusion: Diabetes mellitus seems to result in a vicious cycle of hyperglycaemia and immunosuppression while coupled with the SARS COV 2 Virus and steroid treatment, which could cause excessive fungal colonization like mucormycosis.

Keywords: Covid-19, Mucormycosis, Novel corona virus, mucor, Diabetes Mellitus, SARS CoV-2 .

Introduction:

The severe acute respiratory syndrome (SARS-CoV-2) (COVID-19) has been related to a few opportunistic bacterial and fungal diseases. Because of the associated comorbidities (e.g., diabetes mellitus, persistent obstructive lung ailment) and immunocompromised states (e.g., diabetes mellitus, continual obstructive pulmonary ailment) (e.g., corticosteroid therapy, ventilation, full-size care unit live), sufferers are susceptible to boom immoderate opportunistic infections.

Mucormycosis is a number of the maximum fulminant shape of Zygomycosis because of (Mucorales species) phylum Zygomycota defined as a possibly deadly contamination taking location withinside the maximum essential in immunocompromised patients, specifically in people with DM, leukemia and lymphoma[1].

The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million population [2]. Whereas, in Indian population its prevalence is 0.14 per 1000, which is about 80 times higher than developed countries. The fatality price of mucormycosis is 46% globally [3] However, elements like intracranial or orbital involvement, irreversible immune suppression will boom fatality to as excessive as 50% to 80%[4] A excessive suspicion for this infection need to be taken into consideration in sufferers who have immunocompromised. A hallmark tissue necrosis of mucormycosis is usually a past due sign. In the context of the COVID-19 epidemic, in which corticosteroids are frequently administered, those findings want to be reconsidered. Mucormycosis case reviews/collection in mother and father with COVID-19 have multiplied dramatically, particularly in India. Many times have furthermore been recorded from fantastic areas of the world. In gray literature, which includes print and digital media, a few anecdotal examples have furthermore been recorded. These findings are not good and feature big public fitness regulations, manner to excessive death rate related to mucor-mycosis. Mucor-mycosis intracranial involvement, especially, will boom the mortality rate to as excessive as 90%[5]. Furthermore, the speed with which mucormycosis spreads is an uncommon phenomenon, or perhaps a 12-hour get rid of in analysis may be lethal, that is why 50 percentage of instances of mucormycosis have traditionally been detected pleasant in autopsy post-mortem collection[6]. This led us to carry out a scientific evaluation of posted case opinions/collection of mucormycosis in people with COVID-19 so that it will decide its temporal correlations with comorbidities, relationships with medicinal capsules implemented in COVID-19, and desired affected individual trends with prognosis. We furthermore proposed a mechanistic cause of why mucormycosis is turning into greater related to COVID-19 and is being said more and more extra from India.

Material and Method:

Aims and objectives

This article aimed to offer an outline of numerous studies findings on mucormycosis in put up covid 19 sufferers. The motive is to discover the etiology of mucormycosis in covid 19 sufferers.

Methods

A systematic literature are searching for changed into finished on database like PubMed, Google Scholar and Cochrane Library the use of key phrases like COVID 19, Mucormycosis, Mucor, Novel corona virus and SARS CoV-2. From all of the articles, those on mucormycosis with COVID-19 were retrieved. Each affected person's traits have been recorded and evaluated for diverse endpoints and consequences. The data's validity come to be double-checked with the useful resource of using writes.

RESULT

Mucormycosis is an angioinvasive fungus that develops on wet surfaces, useless and rotting vegetable materials, and is typically located withinside the surroundings. The name "black fungus" is incorrectly used to mucormycosis since "black fungus" refers to a tremendous

enterprise company of fungi referred to as dematiaceous fungi. Immunocompromised hosts, out of manage diabetes mellitus, in particular diabetic ketoacidosis, glucocorticoids, haematological malignancies, hematopoietic stem mobileular transplantation, iron chelating treatments, AIDS, trauma/burns, and so forth are all chance elements for mucormycosis [7].

While no person cause has been identified, it's far probably that a complicated mixture of variables, a few controllable and others out of control withinside the Indian context, is in rate for the growing mucormycosis epidemic. In India, out of manipulate diabetes isn't unusual place, and the bulk of sufferers do not have their blood sugar levels checked on a everyday basis. Furthermore, because of a full-size overcrowding in hospitals, medical scientific docs might not had been capped in a position to check all sufferers' blood sugar degrees. Furthermore, loads of those people have been taking an extended way more dexamethasone than the recommended quantity of 6.zero mg/day for 5–10 days. Another purpose is probably an attempt to adjust oxygen saturation with excessive doses of corticosteroids at the same time as hospitals have been experiencing an oxygen shortage[8].

Due to India's warm temperature and humid surroundings, we're in all likelihood to have a extra load of mucor spores withinside the indoor and outside air. Patients may also have neglected Mucormycosis symptoms (mainly pain), mistaking them with lingering COVID-19 symptoms, and so arrived on the medical institution late. Patients eventually confirmed with immoderate maxillary disorder at a later diploma of follow-up (1-three weeks). It is plain that the ROCM growth is being decided in India withinside the context of COVID-19. More affected organ concerned with mucormycosis became nostril and all sinuses (88.9%), discovered through rhino-orbital (56.7%) and ROCM type (22.2%). [9]

Evidence is for the cause that a malfunctioning immune gadget due to SARS-COV-2 and injudicious use of corticosteroids can be thru and massive liable for out of control diabetes in people .Diabetes mellitus seems to result in a generic cycle of increased blood sugar and immunosuppression on the identical time as coupled with the covid Virus and steroid treatment, which could result in extreme fungal colonization like mucormycosis.

Discussion:

Although mucormycosis is enormously uncommon in wholesome human beings, it's far due to some of immunocompromised situations [8,9]. It can have an effect on the nostril, sinuses, orbit, CNS, lungs , gastrointestinal tract , joints, kidney, heart, jaw bones , skin, mediastinum , irrespective depending upon the truth that ROCM is the maximum now no longer unusual place model encountered in medical exercise sooner or later of the world. It's definitely well without a doubt nicely really well worth noting that the phrase "rhino-orbital-cerebral contamination" encompasses the overall spectrum, from restrained nasal cavity disorder (nasal cavity tissue invasion) to rhino orbital-cerebral sickness (CNS involvement).Due to the underlying sickness, the region of participation may additionally furthermore vary. For example, ROCM is typically related to out of control diabetic keto acidosis and diabetes, lung participation is often visible in sufferers with neutropenia, bone marrow and organ transplantation, and haematological cancers , and gastrointestinal involvement is extra now not unusual place in malnourished people[10].

Nonetheless there look like a number of of things which could purpose mucor-mycosis affecting people with COVID at the same time as corticosteroids are used. Some of those elements are as follow:

Mucormycosis is much more likely in those who don't have phagocytes \ have reduced phagocytic characteristic. Hyperglycaemia, as visible in sufferers with out of control diabetes mellitus, outcomes in phagocytic non-functioning, disabled chemotaxis and faulty within the cell killing via oxidative and nonoxidative mechanisms[9].

Insulin resistance is caused by interleukin-6 modulating the phosphorylation of the insulin receptor substrate -1 and insulin receptor, which is frequently high in patients with COVID-19[10]. Glucocorticoids, lopinavir, ritonavir, and remdesivir, which can be used to cope with COVID-19, can have an effect on glycaemic manage and predispose to mucormycosis[11]. Nucleoside drug remdesivir that suppresses SARS-CoV-2 replication property via inhibiting the proofreading exoribonuclease and viral RNA polymerase[12]. Remdesivir isn't always most effective for the remedy of CoV-2-SARS contamination in mobile and mouse lab modes[13]. However the profit of a short recuperation time in man or woman sufferers hospitalization with COVID-19. Due to the advantages of remdesivir have been first-rate visible on the identical time because it have become given earlier than and close to the onset of sickness and can little by little lower or disable if administered on the past due section of contamination[14].

Amazingly, a glucocorticoid namely dexamethasone with anti-inflammatory and immune-suppressive properties[15]. has in recent times been verified to lessen 28-day mortality in Britain sufferers hospitalization with COVID and required breathing help. A similar beneficial effect of the dexamethasone or methylprednisolone had been discovered in Brazilian COVID patients who have been affected by mild to severe acute respiratory misery group of symptoms[16] or who are over 60 years old [17].

India have documented more than one reviews, a precipitate upward push in {COVID-19} corona virus sickness 2019 related cerebello-rhino-orbito mucormycosis {CAROM} for the motive that March 2020 [18,19]. 1 in 400 to be currently anticipated in the famous danger of growing CAROM withinside the backdrop of COVID -19 [19].

From the onset of COVID-19, CAROM in India is usually stated 2-4 weeks . In India the reason of the abruptly excessive prevalence of CAROM has brought about extremely good hypothesis. Because of the dark shade of necrotic tissue, the CAROM has been classified as a "black fungus" by the urgent and public. Noticed, that mycelia (fungal spores) are not black. CAROM caused by fungi are omnipresent in our surroundings and it can be a piece of our sino-nasal flora .Infections due to fungus that are opportunistic together with CAROM most effective stand up whilst the host develops out of manipulate hyperglycaemia or terrific immunosuppression.

Through a huge change in Inborn immune tool and (CD4+) , CD8+ T cellular lymphopenia due to covid -19 can motive immunosuppression^[19]

Collection from India in CAROM is generally related to the triad of COVID-19-related immune suppression, uncontrol hyperglycaemia, and overuse of corticosteroids and unique immune-suppressive medications. The unlucky melding of those sports will boom susceptibility of host to CAROM and particularly infections that are opportunistic

The triad is however, also can inadequately offer an reason of the whole tale of CAROM , and in addition medical investigation is ongoing. Reviews which are unconfirmed and speculative withinside the press have delivered about alarm through describing the causation of CAROM to using business employer O₂ and nonsterile H₂O in O₂ humidifiers. Pre said that almost all sufferers with CAROM had mild or moderate or severe COVID infections and function in no way required oxygen, such hypothesis can be out of place and definitely mischievous. Nevertheless, there are a few particular populace and cultural elements applicable to the parts of India that would have facilitated this amazing upward push into CAROM. The review summarises our thoughts on CAROM in India[20].

Pre-epidemic occurrence of mucormycosis in India was previously thought to be significantly lower than global prevalence estimates.⁽²⁰⁾ The mild temperature conditions of recent months in India may have also led to a contaminant that has been recognised as having a seasonal predilection [19,20].

Diabetes [DM] is drastically well-known withinside the person Indian populace and sadly can also furthermore occasionally be poorly managed or recognized. Additionally, obstacles to getting access to medical institution treatment withinside the present day-day epidemic had aggravated the population of the not well treated or untreated hyperglycaemia/diabetes. In loads of city populations in India the incidence of heart and continual obstructive lung infection is likewise better; those situations may similarly aggravate to mortality and susceptibility to infections which are opportunistic [20].

The [ICMR] Indian Council of Medical Research advanced proofs-based fully definitely tips and procedures in a live overall performance with the [AIIMS] All India Institute of Medical Sciences [21]. Nevertheless, from a modern wave of COVID-19 the excessive deaths can also furthermore brought about panic caused due to overuse of more than one drugs at better doses and durations than encouraged. [22].

Glucocorticoids mainly dexamethasone might also additionally begin the onset of diabetes, suppress mobile immunoresponses, and reason immune suppression .Wide-spectrum antibiotics and use of antifungals in prophylactic way disrupt the healthful sino-nasal microbiome, likely facilitating opportunistic infections. Azithromycin which is macrolide antibiotics furthermore suppress IL-6. This is important to regular the antimicrobial immunoresponses. Interleukin-6 inhibitor, Tocilizumab is suggested to be used withinside the post infection cytokine storm; at the same time as used , this drug can hose down everyday immuno responses[22].

COVID-19 patients may also have immunosuppression, which is characterised by a natural killer cells, CD3+ T lymphocytes, T - lymphocytes+ T cells, and CD8+ T-cells are all decreasing. The reductions in suppressor CD8+ T-cells are higher than those in CD4+ T-cells, resulting in a considerable increase in the CD4/CD8 ratio within those cells. Patients[23]. Critically sick patients, particularly those admitted to critical care units (ICUs), who require positive pressure ventilation, or who have clinic stays of up to fifty days, are mostly have higher OIFIs. Therefore, it is far essential to do not forget that COVID infection sufferers can expand OIFIs at a few level withinside the center and latter ranges of the disorder, specially people with excessive COVID-19[24]. In the normal management of COVID-19 patients, regular helper (CD4+) and suppresser (CD8+) T-cell counts, similar to those conducted in patients with human immunodeficiency virus infection, could be beneficial. In patients suffering from severe COVID , increased Interleukin (IL-1 and IL-6)

production had observed. Following infections with the *Aspergillus fumigatus* method, similar changes were observed. As a result, differences in the levels of those cytokines can be linked to OIFIs in at least a few COVID-19 patients. sixteen IL-10 up-regulation can also suppress macrophage activity[25]. Immunosuppressive medications, corticosteroids, and broad-spectrum antibiotics, as well as ICU admission, intubation/mechanical ventilation, and surgical therapy are all connected to OIFIs. In the improvement of mucormycosis, unfastened unbound iron in serum performs a essential function. Endotheliosis's, endothelial damage, thrombosis, lymphopenia, and a decrease in CD4+ and CD8+ T-cell counts are all symptoms of COVID, putting the person at risk for secondary or opportunistic fungal infection. The presence of DM, whether or not or now no longer or now not without or with DKA, will boom the risk of growing mucormycosis, and DM is frequently related to better COVID-19 severity[26-30].

Corticosteroid use is regularly related to out of control hyperglycaemia and the onset of DKA. Acidosis reasons a low pH, this is right for mucor spores to grow. Furthermore, steroid utilization impairs bronchoalveolar macrophage motility, ingestion, and phagolysosome fusion, in addition to decreasing WBC phagocytic activity (each first- and second-line shielding mechanisms). Putting a diabetic patient at a higher risk of mucormycosis.

The following steps can be taken to prevent covid 19-related mucor-mycosis:

1. To use corticosteroids withinside the advocated dose and to limitation length for which it is used.
2. Avoiding using iron and zinc for the dietary nutritional dietary supplements of covid -19 manage.
3. Voriconazole need to not be used as an antifungal prophylactic.
4. Maintain the blood sugar tiers of diabetic sufferers and to expose excessive chance sufferers.
5. Use of broad-spectrum antibiotics want to be prevented till truly necessary.
6. Maintenance of private hygiene in positioned up covid sufferers.
7. Decontamination of the health center surroundings must be completed properly.

Conclusion:

Increased mucormycosis in India seems to be the stop give up end result of an unholy trinity of diabetes (excessive genetic prevalence), immoderate corticosteroid utilization (will growth blood sugar and ends in opportunistic fungal infections), as well as COVID-19 (cytokine storm, lymphopenia, endothelial damage). To lower the superiority of lethal mucormycosis, all efforts need to be taken to preserve pinnacle of the road hyperglycaemia, and only careful evidence primarily based totally definitely absolutely use of corticosteroids in sufferers with COVID-19 is generally endorsed.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES:

1. Talmi YP, Goldschmied-Reouven A, Bakon M, Barshack I, Wolf M, Horowitz Z, et al. Rhino-orbital and rhino-orbito-cerebral mucormycosis. *Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg*. 2002 Jul;127(1):22–31.
2. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2019 Jan;25(1):26–34.
3. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. *Am J Emerg Med*. 2021 Apr;42:264.e5-264.e8.
4. Deutsch PG, Whittaker J, Prasad S. Invasive and Non-Invasive Fungal Rhinosinusitis- A Review and Update of the Evidence. *Med Kaunas Lith*. 2019 Jun 28;55(7):E319.
5. Maartens G, Wood MJ. The clinical presentation and diagnosis of invasive fungal infections. *J Antimicrob Chemother*. 1991 Jul;28 Suppl A:13–22.
6. Baldin C, Ibrahim AS. Molecular mechanisms of mucormycosis—The bitter and the sweet. *PLoS Pathog*. 2017 Aug 3;13(8):e1006408.
7. Sugar AM. Mucormycosis. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 1992 Mar;14 Suppl 1:S126-129.
8. Chinn RY, Diamond RD. Generation of chemotactic factors by *Rhizopus oryzae* in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis. *Infect Immun*. 1982 Dec;38(3):1123–9.
9. Rehman K, Akash MSH, Liaqat A, Kamal S, Qadir MI, Rasul A. Role of Interleukin-6 in Development of Insulin Resistance and Type 2 Diabetes Mellitus. *Crit Rev Eukaryot Gene Expr*. 2017;27(3):229–36.
10. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes Metab Syndr*. 2020 Aug;14(4):513–7.
11. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the

Viral Polymerase and the Proofreading Exoribonuclease. *mBio*. 2018 Mar 6;9(2):e00221-18.

12. Pruijssers AJ, George AS, Schäfer A, Leist SR, Gralinski LE, Dinnon KH, et al. Remdesivir Inhibits SARS-CoV-2 in Human Lung Cells and Chimeric SARS-CoV Expressing the SARS-CoV-2 RNA Polymerase in Mice. *Cell Rep*. 2020 Jul 21;32(3):107940.
13. Vandewalle J, Luypaert A, De Bosscher K, Libert C. Therapeutic Mechanisms of Glucocorticoids. *Trends Endocrinol Metab TEM*. 2018 Jan;29(1):42–54.
14. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021 Feb 25;384(8):693–704.
15. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial | *Critical Care Medicine* | *JAMA* | *JAMA Network* [Internet]. [cited 2021 Oct 27]. Available from: <https://jamanetwork.com/journals/jama/fullarticle/2770277>
16. Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2021 May 4;72(9):e373–81.
17. Paul SS, Kumar R, Meena VP, Ramprasad A, Garg P, Keri VC, et al. Clinical Characteristics And Outcomes of 16 Cases With COVID19 and Mucormycosis: Experience From A Tertiary Care Center In India and Review of Literature [Internet]. 2021 [cited 2021 Oct 27]. Available from: <https://www.researchsquare.com/article/rs-533347/v1>
18. Where Mucormycosis Comes From | *Mucormycosis* | *CDC* [Internet]. 2021 [cited 2021 Oct 27]. Available from: <https://www.cdc.gov/fungal/diseases/mucormycosis/causes.html>
19. Prakash H, Chakrabarti A. Epidemiology of Mucormycosis in India. *Microorganisms*. 2021 Mar 4;9(3):523.
20. CLINICAL GUIDANCE FOR MANAGEMENT OF ADULT COVID-19 PATIENTS | *AIIMS Covid Information Portal* [Internet]. [cited 2021 Nov 15]. Available from: <https://covid.aiims.edu/clinical-guidance-for-management-of-adult-covid-19-patients/>
21. Havey J. A year and a half later: The biopharmaceutical industry remains committed to beating COVID-19 [Internet]. [cited 2021 Nov 15]. Available from: <https://catalyst.phrma.org/a-year-and-a-half-later-the-biopharmaceutical-industry-remains-committed-to-beating-covid-19>

22. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect.* 2020 Jun;80(6):607–13.
23. Coronavirus disease (COVID-19) – World Health Organization [Internet]. [cited 2021 Nov 15]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
24. Apostolopoulou A, Esquer Garrigos Z, Vijayvargiya P, Lerner AH, Farmakiotis D. Invasive Pulmonary Aspergillosis in Patients with SARS-CoV-2 Infection: A Systematic Review of the Literature. *Diagnostics.* 2020 Oct 10;10(10):807.
25. Webb BJ, Ferraro JP, Rea S, Kaufusi S, Goodman BE, Spalding J. Epidemiology and Clinical Features of Invasive Fungal Infection in a US Health Care Network. *Open Forum Infect Dis.* 2018 Aug;5(8):ofy187.
26. Acharya S, Shukla S, Acharya N. Gospels of a pandemic-A metaphysical commentary on the current COVID-19 crisis. <https://doi.org/10.7860/JCDR/2020/44627.13774>.
27. Arora D, Sharma M, Acharya S, Shukla S, Acharya N. India in "Flattening the Curve" of COVID-19 Pandemic-Triumphs and Challenges Thereof. *Journal of Evolution of Medical and Dental Sciences.* 2020 Oct 26;9(43):3252-6. <https://doi.org/10.14260/jemds/2020/713>.
28. Bawiskar N, Andhale A, Hulkoti V, Acharya S, Shukla S. Haematological Manifestations of Covid-19 and Emerging Immunohaematological Therapeutic Strategies. *Journal of Evolution of Medical and Dental Sciences.* 2020 Nov 16;9(46):3489-95. <https://doi.org/10.14260/jemds/2020/763>.
29. Burhani TS, Naqvi WM. Telehealth--A Boon in the Time of COVID 19 Outbreak. *Journal of Evolution of Medical and Dental Sciences.* 2020 Jul 20;9(29):2081-5. <https://doi.org/10.14260/jemds/2020/454>.
30. Butola LK, Ambad R, Kute PK, Jha RK, Shinde AD, DMIMS W. The Pandemic of 21st Century-COVID-19. *Journal of Evolution of Medical and Dental Sciences.* 2020 Sep 28;9(39):2913-9. (September 28, 2020): 2913–18. <https://doi.org/10.14260/jemds/2020/637>.