

Hyperbaric Oxygen Therapy : A new Evolving Future Perspective for Management of Mucormycosis and COVID 19 in Children in Developing Countries

*Mahaveer Singh Lakra¹, Amar Taksande¹, Bhavana Lakhkar², Sachin Damke¹, Ashwini Lakra³

¹Department of Paediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (DMIMS), Sawangi Meghe, Wardha, Maharashtra, India.

²Department of Neonatology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (DMIMS), Sawangi Meghe, Wardha, Maharashtra, India.

³Senior Resident, Datta Meghe Medical College and SMHRC, Wanadongri, Nagpur, Maharashtra, India.

Article History

Received On : Jan 16, 2022

Accepted On : June 13, 2022

Funding sources: None

Conflict of Interest: None

Keywords: COVID 19; Hyperbaric oxygen; Mucormycosis; Oxygen tank; Tissue hypoxia

Online Access



DOI: <https://doi.org/10.3126/jnps.v42i1.42443>

*Corresponding Author

Mahaveer Singh Lakra
Assistant Professor
Department of Paediatrics
Jawaharlal Nehru Medical College
Datta Meghe Institute of Medical Sciences
Sawangi Meghe, Maharashtra, India.
Email: lakra.mahaveer@gmail.com

Abstract

The SARS COVID-19 virus has arisen as a major hazard to mankind, posing harm to the whole world population. During the second COVID wave, mucormycosis has emerged as one of the deadliest and most devastating illnesses. Mucormycosis is strongly associated with diabetes, prolonged use of steroids, prolonged hospitalisation and immunocompromised states. Children have also been affected by this badly. Hyperbaric oxygen therapy is a non-invasive, cost-effective and painless therapy where 100% oxygen is given to patients under high atmospheric pressure in small tents or chambers. It helps in tissue regeneration and angiogenesis. Hyperbaric oxygen has proved to be effective in the treatment of oculo-rhino-cerebral mucormycosis. Various studies have proved its role in the management of mucormycosis and acute respiratory distress syndrome associated with COVID-19 infection. The advantages of hyperbaric oxygen are same in children as in adults with minimum side effects. Hyperbaric oxygen therapy can be one of the good adjunctive therapies in the management of mucormycosis. It is found to be safe in the treatment of COVID-19 infection, but data is still limited on its use and further studies are needed. This article is all about its use, its efficacy, and future perspectives in the management of mucormycosis and COVID-19 in view of the arrival of the third COVID wave in developing countries like India.

Introduction

SARS 19 The COVID illness, which has created havoc on the global population, has been declared a public health emergency by the World Health Organization. Despite the fact that children are supposed to be affected less and with milder symptoms than adults, children have suffered greatly during the second wave. It has continued to disrupt people's lives and has significantly mitigated their health. India was the most severely

Copyrights & Licensing © 2022 by author(s). This is an Open Access article distributed under Creative Commons Attribution License (CC BY NC)



affected country in 2021 by the COVID-19 pandemic among the rest of the world.^{1,2} The pandemic is still continuing and creating a global threat, and now we have entered into the third wave caused by the new mutant strain, a concern of variance called Omicron. The first case of Omicron was discovered in South Africa, and it quickly has spread globally. Cases are steadily increasing in a step-by-step manner throughout the world, including India, causing concern among those who have recently escaped the second COVID epidemic. The rate of weekly cases is also rising. In light of the resurgence of COVID cases, the Ministry of Health and the Government of India have released updated travel guidelines.³

The clinical presentation in children varies, and the most common presentation is found to be fever and respiratory distress, which is almost considered a hall mark of COVID, and sometimes it is associated with the evidence of multisystemic inflammatory disorder.^{4,5} Less severity in children can be explained by poor representation of ACE inhibitors on mucosal cells and good adaptive immunity.^{5,6} Severe symptoms have been found in patients who are premature, have any underlying chronic illnesses and suffering from some immune-related disorders.⁷ Various modalities like social distancing, masks, sanitisation, antiviral drugs, oxygen therapy, use of antifungal drugs, surgical drainage and debridement for the management of mucormycosis have been advocated by the WHO and various other agencies.^{1,5,8} The updated and most trusted emergency treatment for COVID-19 includes the use of oxygen therapy, high-flow nasal canula, bilevel CPAP, and invasive ventilators. We should be very careful in the selection of oxygen therapy and oxygen delivery devices for children. It should be convenient, affordable, tolerable and have the minimum adverse effects without any risk of droplet spread.⁹ In India, mucormycosis has spread very fast during the second COVID wave, with the incidence being 80 times higher than in other developed countries. So mucormycosis was declared a notifiable disease by the WHO in India in May.¹⁰ Although adults are more prone for rhino orbito cerebral mucormycosis, cases have also been reported in children following COVID-19 infection.¹¹ The first case of rhino orbital cerebral mucormycosis was reported in a child by J. Diwakar et al, from Ahmedabad, India and they found that rhino orbital cerebral mucormycosis is a severe invasive fungal infection which can have a devastating course involving all body tissues.¹² The risk factor for this case was found to be type I diabetes mellitus. The treatment modalities are limited for mucormycosis. The role of hyperbaric oxygen is well documented as an adjunct therapy with antifungals and surgery in adults, but its role in children is still contentious. Various studies have shown that hyperbaric oxygen is found to be safe in the treatment of COVID-19 infection. However, data is still limited on its use in children and further studies are needed.

During the second COVID wave, stockpiling and black marketing of lifesaving drugs like Remdesivir and Tocilizumab, as well as antifungal drugs like liposomal Amphotericin B caused an

acute shortage and panic. The inadequate supply of oxygen, ventilators, anti-covid and antifungal drugs like Remdesivir and liposomal Amphotericin B and Posaconazole raises the question of the preparedness of our health system to handle a second COVID wave. Hyperbaric oxygen can be looked upon as a new therapeutic option for this highly infective and lethal disease, but the concerns may be about safety, high pressure required, infrastructure, cost, and duration of therapy required for treatment.¹³ Now we're dealing with the inevitable third wave, in which a modified new strain of Omicron has been declared a serious cause for worry by various authorities and is rapidly spreading.¹⁴ To deal with the increasing burden of COVID and mucormycosis in the third wave, these novel modalities might be a ray of hope in dealing with the growing burden of COVID patients and mucormycosis.

Definition and pathogenesis of Mucormycosis

Mucormycosis is an angioinvasive fungal infection. The most common species are *rhizopus*, *mucor* and *rhizomucor*, which grow in hyphae. It normally doesn't affect the healthy individual but affects the immunocompromised individual who has had some previous underlying illness.¹⁵ Mucormycosis generally grows on raw surface areas and is mostly found in homes. It is commonly seen in mouldy bread, wet dirty carpet areas, vacuum cleaners and other food items which are stored for a long time in homes.^{15,16} It is mainly angio-invasive and creates a hypoxic microenvironment at tissue level, which favours the hyphae's growth. *Mucor* infection can be fatal in children and can spread rapidly, resulting in necrosis of tissue.¹⁷ Many cases of fungal infections, invasiveness, bony dissemination and pulmonary spread have been reported. Clinical features and presentation vary depending upon the organ involved and extension of mucormycosis.¹⁵⁻¹⁷

One cause for the high number of mucormycosis cases in India might be that during the second COVID wave, the majority of the population was infected, and cases were significantly more prevalent in India than in other nations.

According to the WHO, the prevalence of mucormycosis in India is 140 per million people, nearly 80 times higher than in developed countries. The global incidence rate of mucormycosis varies from 0.005 to 1.7 per million people.¹⁸ Though the reasons are multifactorial, it has been thought that prolonged hospital stay, liberal use of steroids, diabetes, steroid-induced hyperglycaemia and low immunity are the reasons for getting so many mucor infections.^{17,18}

According to some infectious disease experts, one of the causes of mucormycosis is contaminated industrial oxygen supply. The reason for this is that, owing to oxygen scarcity during the second COVID wave, hospitals used industrial oxygen instead

of medical oxygen. In terms of concentration, cleanliness and quality, industrial oxygen varies from medical oxygen. Because the cylinders used for transportation are not of medical grade and are frequently of poor quality, there is a greater danger of leakage during travel, which might lead to contamination. Due to unsanitary filling conditions, moisturization and dirt contamination, they are particularly sensitive to fungus overgrowth.¹⁹ Contaminated oxygen in pipe lines and a lack of water changes in bottles and humidifiers in ICUs should also be looked into. Mucor can infect any organ, but the most common sites of infection are the sinuses, nasal and oral mucosa, lungs, brain, eyes, and bloodstream. The initial symptoms may be headache, nasal congestion, nasal crusting, pain and loss of sensation and numbness over the face, black discolouration over the face or orbital pain and difficulty.^{10,11,15,17} When the dissemination occurs, it may result in paralysis, seizures, features of intracranial involvement, focal deficit, visual loss, osteomyelitis and necrosis of the bones involved.²⁰ Fungal infections are more common in tissues that have localised hypoxia, which creates a microenvironment of low oxygen level, leading to the growth of hyphae. The pathogenesis of mucormycosis has been depicted in figure 1.

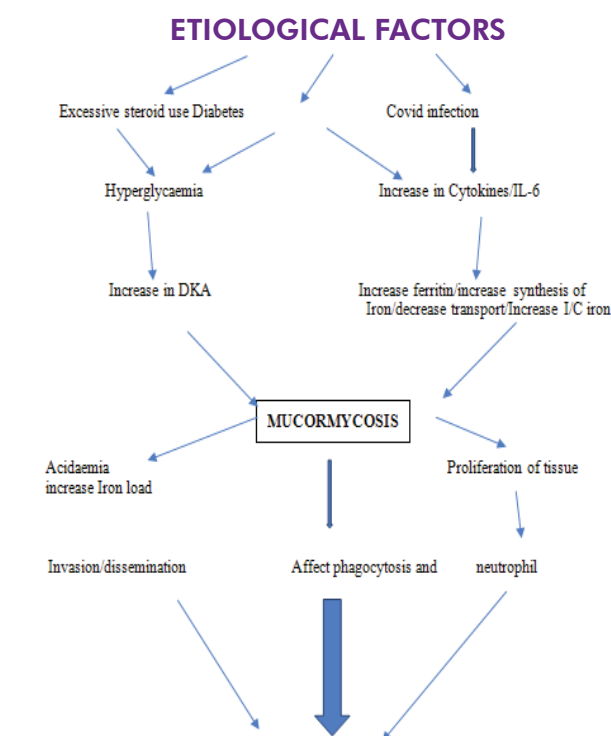


Figure 1. Fungal invasion lead to necrosis/haemorrhage Pathogenesis of mucormycosis

Spreading of infection to orbit and other tissues Affect Immune response Angioinvasion/tissue destruction When oxygen is given under high pressure, then there will be switch over of alternative pathway resulting in decrease in fungal invasion and prevention of

tissue hypoxia. The main modalities of treatment are debridement, curettage and anti-fungal treatment.²¹

Hyperbaric oxygen

Hyperbaric oxygen can be a lifesaver, revolutionising medical care and opening new possibilities in mucormycosis treatment. It is a non-invasive, cost-effective and painless therapy where 100% oxygen is given to patients under high pressure.²¹ This high pressure is two to three times the atmospheric pressure and given in a closed tank so that the body gets 100% oxygen, which diffuses into body tissue at the end level and helps in tissue healing by modifying oxidation and regeneration processes. Under this high oxygen pressure and concentration, the lungs and all body tissues get much more oxygen. This stimulates the release of some growth factors and stem cells, causing bacterial destruction and tissue healing.²² Hyperbaric oxygen has been used for a long time in the management of burns, tissue necrosis, for wound healing, cancers, and regeneration of tissues.²³ It causes vasoconstriction by acting on baroreceptors, resulting in a decrease in venous return and a lower load on the heart and cardiac contractility, assisting patients in combating low tissue hypoxia.²⁴ It is mostly used in medical conditions with resistant healing and where tissue destruction is severe and oxygen concentration is not reached at tissue level. The shortage of oxygen supply in the body during an infection state may lead to tissue hypoxia where fungus is more prone to growing in tissues in the human body. Hyperbaric oxygen reduces cell inflammation, resulting in a decrease in cellular oedema, which helps in improvement in oxygenation and tissue saturation. The mechanism of action of hyperbaric oxygen has been depicted in figure No. 2.

Neuroinflammation, Decrease reduction in pro inflammatory.

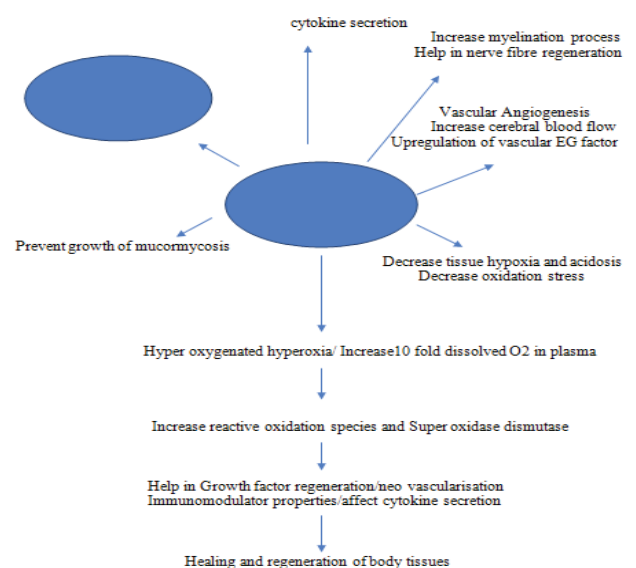


Figure 2: Showing mechanism of action of hyperbaric oxygen

The advantages of hyperbaric oxygen are the same in children as in adults, with minimal side effects. This is a safe, effective, and efficient method of treating some chronic illnesses. A prospective analysis at the Israel Naval Medical Institute studied 139 children with different illnesses like acute carbon monoxide poisoning, crush injury, traumatic ischemia, or compartment syndrome, clostridial necrosis, necrotizing fasciitis, and refractory osteomyelitis where hyperbaric oxygen was found to be useful. Out of 139 children, 129 (93%) had a favourable outcome.²⁵ Studies have shown that it is a useful modality of treatment for cerebral palsy and autism in children. In the management of cerebral palsy, it results in increase in cognitive function, vision, achievement of developmental milestones, attention, memory and improvement in daily routine activity.^{26,27} Hyperbaric oxygen reduces aspergillus growth both in vivo and in vitro. It is used as a stand-alone therapy, as an adjunct with amphotericin B, or surgery for the management of invasive aspergillosis.²⁸

Although hyperbaric oxygen has been explored for the treatment of rhino cerebral mucormycosis as it reduces tissue hypoxia and acidosis, it has been very effective in the management of rhino cerebral mucormycosis alone or in adjuvant with other treatment modalities like surgery and drugs. It acts by reducing tissue hypoxia and affecting vascularisation, thus arresting the growth of fungal hyphae in body tissues.²⁹ There was significant improvement in symptoms and a decreased need for intubation.³⁰ Studies have shown its efficacy in improving SpO₂ and d-dimer and leucocyte counts in patients who received hyperbaric oxygen therapy. The CT findings were also improved, showing its action as an anti-inflammatory in COVID.^{31,32} In previous studies, it has been found to be effective in adult COVID-19 patients.^{33,34} People have also started giving hyperbaric oxygen to overcome the post-COVID complications and problems like joint stiffness and lung fibrosis. Recently, a study by Robbins T et al over 10 patients having post-COVID fatigue showed promising results, saying that it can be a role-changer in the management of prolonged COVID and post-illness.³⁵

Cost effectiveness, availability and feasibility

Hyperbaric oxygen was used to some extent in developing countries in the treatment of COVID-19 and mucormycosis during the second wave. If mucor cases still rise at the same frequency and do not respond to amphotericin and conventional treatment, then hyperbaric oxygen can be an important part of treatment in the third wave. However, we must be careful before recommending it to everyone, the reason being the availability, feasibility and affordability at every centre. In India, it is available in select metropolitan cities and only some hospitals are providing this facility. The cost of treatment varies, approximately 6000 Indian Rupees per session, costing almost 1.5 lac for the whole therapy, whereas in New Delhi, charges are somehow cheaper,

around Rs. 1800 per session, making it more effective. The cost of treatment is primarily determined by the type of setup, the capacity of the hyperbaric tank, the number of cycles available, the total duration of therapy, and the type of underlying illness. The cost of installation and infrastructure of the plant varies depending upon the capacity of the plant and the size and capacity of the chamber. In Western countries, the cost of an oxygen tank, installation, and staffing can range from 64000 pounds to one lac pounds.³⁶ The hyperbaric oxygen tank consists of a closed chamber with high atmospheric pressure inside it with the control panel and sitting arrangement for the patient as shown in figure 3.

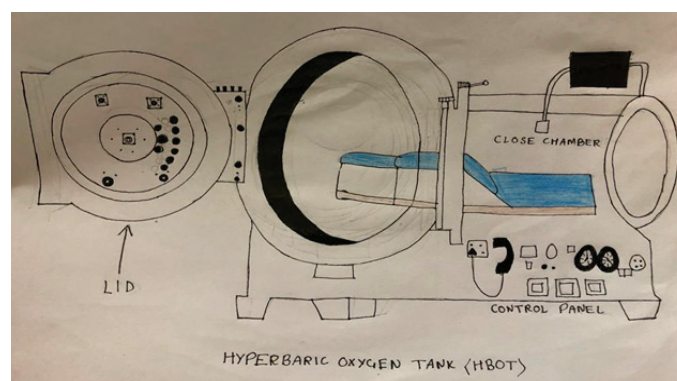


Figure 3. Hyperbaric oxygen tank with control panel.

Hyperbaric oxygen can be provided in two different types: either in monoplace or in polyplace forms, where many people can be treated at a single time. In the polyplace type, either a room with multiple beds or a large-sized sitting chamber is made. It can be given for two to three hours sitting on a single day. The schedule recommended by various studies is 90 minutes a day for a total of five days or 60 minutes a day for a total of seven days. Some studies have used 90 minutes followed by 60 minutes for five days.³⁴ The polyplace chambers and rooms for multiple people proved to be economical, but will be difficult to use when a patient is COVID positive. So many patients, if they are infectious, can't be allowed to stay for one hour in a closed chamber in view of the increased risk of infection and contamination. The cost of treatment of post-Covid mucormycosis is very high. The drug lyophilised amphotericin has come up as one of the lifesaving drugs in the treatment of mucormycosis. In the second COVID wave epidemic, a single vial of 50 mg cost around Rs 6000 - 8000. The overall treatment needed will be for at least three weeks, raising the cost to nearly 8 -10 lacs.³⁷ Black marketing, illegal stocking, and reduced production of liposomal Amphotericin B resulted in an acute shortage of the drug.³⁸ On this issue, the Delhi High Court lamented the drug shortage issue and ordered the Government to maintain an adequate supply and procure drugs to make them available for treatment.^{38,39} By keeping in mind the total cost of treatment and the scarcity of drugs, hyperbaric oxygen can be used as one of the adjunctive treatment therapies for severe cases of mucormycosis. Plant cultivation can be more cost-effective, as it can treat a large number of patients for the same price as

the total cost of antifungals and hospitalisation. As we are in the initial phase of an epidemic, the behaviour of omicron is not fully known at this stage.^{14,40} According to Union Health Minister data on Friday, January 14, 2022, India has reported a single day jump of 2,64,202 new corona cases in the current year 2022 amid third wave, the highest in the last 239 days, making a total of 3,65,82,129 cases in India, out of which 5753 belong to omicron variants, making situation more grievous.⁴¹ A lot of work has been going on hyperbaric oxygen in developed countries on its role in the management of COVID illness and mucormycosis, but there is very limited data about its use in India. Though it has not proved to be an alternative to surgery or anti-fungal treatment, if combined with other modalities, the results are excellent.^{28,29} Several studies have yielded promising results.^{42,43}

We need to investigate the potential of this novel therapy in India so that we can better address the issue if we come across more serious forms of mucormycosis and covid 19.⁴³ If additional data on hyperbaric oxygen's utility, infrastructure requirements, cost effectiveness, feasibility and treatment were accessible from all developing countries, we might better plan the installation of future hyperbaric oxygen facilities. It will also assist the Government and other health authorities in developing strategies to battle new COVID and mucormycosis cases, as well as procuring appropriate equipment. We need further detailed studies to analyse the efficacy, affordability and feasibility of this new therapeutic modality.

Conclusions

Mucormycosis and COVID 19 has emerged as a challenging task to the world. Hyperbaric oxygen works by correcting tissue hypoxia, creating a microenvironment of high oxygen pressure and resulting in good tissue perfusion. Amid of the third wave, it can be a good future perspective supportive adjunct therapy in refractory cases of mucormycosis, but further large-scale studies and robust data are needed. Setting up and maintaining a hyperbaric oxygen plant will be really a challenging task.

References

- Center for Disease Control and Prevention. COVID-19: information for pediatric healthcare providers. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html>. Accessed March 26, 2021.
- World Health Organisation. COVID-19. Weekly Epidemiological Update. Edition 41, published 25 May 2021.
- Ministry of health and family welfare. Covid 19- Omicron update. January 7,2022.
- Jurado Hernandez JL, Alvarez Orozco IF. COVID-19 in Children: Respiratory Involvement and Some Differences With the Adults. *Front Pediatr*. 2021 Mar 29;9:622240. DOI:10.3389/fped.2021.622240. PMID: 33855003; PMCID: PMC8039144.
- Indian Academy of Pediatrics. COVID-19 Bulletin 2nd Edition. Accessed July 28,2020. Available from <https://iapindia.org/pdf/Final-Edited-Version-of-IAP-COVID-19-Bulletin.pdf>.
- Swann OV, Holden KA, Turtle L. Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ*. 2020 Aug 27;370:m3249. DOI: 10.1136/bmj.m3249. PMID: 32960186; PMCID: PMC7488201.
- Freeman MC, Rapsinski GJ, Zilla ML, Wheeler SE. Immunocompromised Seroprevalence and Course of Illness of SARS-CoV-2 in One Pediatric Quaternary Care Centre. *J Pediatric Infect Dis Soc*. 2021 Apr 30;10(4):426-431. DOI: 10.1093/jpids/piaa123. PMID: 33049042; PMCID: PMC7665604.
- World Health Organisation. Living guidance for clinical management of COVID-19.23 November 2021. <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2>
- Lakra M, Taksande A, Lakhkar B. Oxygen therapy and respiratory support in SARS COVID 19 infection in children. *J Pediatr Neonatal Care*. 2021;11(3):4956. DOI: 10.15406/jpnc.2021.11.00444
- World Health Organisation. Covid-19 and mucormycosis. <https://www.who.int/india/emergencies/coronavirus-disease>.
- Saied AA, Metwally AA, Dhama K. Our children are at risk of COVID-19- associated rhino-orbito-cerebral mucormycosis (ROCM). *Ann Med Surg (Lond)*. 2021;72:103058. DOI:10.1016/j.amsu.2021.103058.
- Diwakar J, Samaddar A, Konar SK. First report of COVID-19-associated rhino-orbito-cerebral mucormycosis in pediatric patients with type 1 diabetes mellitus. *J Mycol Med*. 2021;31(4):101203. DOI:10.1016/j.mycmed.2021.101203.
- Moon RE, Weaver LK. Hyperbaric oxygen as a treatment

- for COVID-19 infection? Undersea Hyperb Med. 2020 Second-Quarter;47(2):177- 179.
DOI: 10.22462/04.06.2020.1. PMID: 32574432.
14. World Health Organisation. Update on Omicron. 28 November, 2021.
 15. Sasaki T, Mineta M, Kobayashi K, Ando M, Obata M. Zygomycotic invasion of the central nervous system. Jpn J Radiol. 2010 Jun;28(5):376-80.
DOI: 10.1007/s11604-010-0435-z. PMID: 20585927.
 16. Jain D, Kumar Y, Vasishtha RK, Rajesh L, Pattari SK, Chakrabarti A. Zygomycotic necrotizing fasciitis in immunocompetent patients: a series of 18 cases. Mod Pathol. 2006 Sep;19(9):1221-6.
DOI: 10.1038/modpathol.3800639. PMID: 16741524
 17. Swain SK, Jena PP, Das S, Gupta A. COVID-19 Associated Mucormycosis in Head and Neck Region: Our Experiences at a Tertiary Care Teaching Hospital of Eastern India. Siriraj Med J. 428–423 ,(7)73.
DOI: <https://doi.org/10.33192/Smj.2021.56>
 18. World Health organisation. Mucormycosis-Emergency. [https://www.who.int/india/emergencies/coronavirus-disease-\(covid-19\)](https://www.who.int/india/emergencies/coronavirus-disease-(covid-19))
 19. Abhishek DE, Sinha S. Can spurt in black fungus cases be blamed on industrial oxygen cylinders, dirty water in humidifiers? India Today. May 26, 2021. New Delhi. <https://www.indiatoday.in/coronavirus-outbreak>.
 20. Hosseini SM, Borghei P. Rhinocerebral mucormycosis: pathways of spread. Eur Arch Otorhinolaryngology. 2005 Nov;262(11):932-8.
DOI:10.1007/s00405-005-0919-0. PMID: 15891927.
 21. Francis JR, Villanueva P, Bryant P, Blyth CC. Mucormycosis in Children: Review and Recommendations for Management. J Pediatric Infect Dis Soc. 2018 May 15;7(2):159-164.
DOI: 10.1093/jpids/pix107
 22. Halbach JL, Prieto JM, Wang AW, Hawisher D, Cauvi DM, Reyes T, et al. Early hyperbaric oxygen therapy improves survival in a model of severe sepsis. Am J PhysiolIntegr Comp Physiol 2019;317:R160-8.
DOI: 10.1152/ajpregu.00083.2019. PMID: 31091156; PMCID: PMC6692752.
 23. Leach RM, Rees PJ, Wilmshurst P. Hyperbaric oxygen therapy. BMJ.1998;317(7166):1140-1143.
DOI:10.1136/bmj.317.7166.1140.
 24. Demchenko IT, Zhilyaev SY, Moskvina AN, Krivchenko AI, Piantadosi CA, Allen BW. Baroreflex-mediated cardiovascular responses to hyperbaric oxygen. J Applied Physiology. (1985). 2013 Sep;115(6):819-28.
DOI: 10.1152/jappphysiol.00625.2013. PMID: 23823147.
 25. Waisman D, Shupak A, Weisz A, Melamed Y. Hyperbaric Oxygen Therapy in the Pediatric Patient: The Experience of the Israel Naval Medical Institute. Paediatrics. November 1998;102 (5):53.
DOI: <https://doi.org/10.1542/peds.102.5.e53>
 26. Sakulchit T, Ladish C, Goldman RD. Hyperbaric oxygen therapy for children with autism spectrum disorder. Can Fam Physician. 2017 Jun;63(6):446-448.
PMID: 28615394; PMCID: PMC5471082.
 27. Collet JP, Vanasse M, Marois P, Amar M, Goldberg J, Lambert J, et al. Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. HBO-CP Research Group. Lancet. 2001 Feb 24;357(9256):582-6.
DOI: 10.1016/s0140-6736(00)04054-x. PMID: 11558483.
 28. Dhingra S, Buckley JC, Cramer RA. Hyperbaric Oxygen Reduces Aspergillus fumigatus Proliferation In Vitro and Influences In Vivo Disease Outcomes. Antimicrob Agents Chemother. 2018 Feb 23;62(3):e01953-17.
DOI: 10.1128/AAC.01953-17. PMID: 29229641; PMCID: PMC5826133.
 29. Ferguson BJ, Mitchell TG, Moon R, Camporesi EM, Farmer J. Adjunctive Hyperbaric Oxygen for Treatment of Rhinocerebral Mucormycosis. Rev Infect Dis. 1988;10 (3) :551–559.
DOI: <https://doi.org/10.1093/clinids/10.3.551>
 30. Thibodeaux K, Speyrer M, Raza A, Yaakov R, Serena TE. Hyperbaric oxygen therapy in preventing mechanical ventilation in COVID-19 patients: a retrospective case series. J Wound Care. 2020 May 1;29(Sup5a):S4-S8.
DOI: 10.12968/jowc.2020.29.Sup5a.S4. PMID: 32412891.
 31. Guo D, Pan S, Wang M, Guo Y. Hyperbaric oxygen therapy may be effective to improve hypoxemia in

- patients with severe COVID-2019 pneumonia: two case reports. *Undersea Hyperb Med.* 2020 Second-Quarter;47(2):181-187.
DOI: 10.22462/04.06.2020.2.
PMID: 32574433.
32. Senniappan K, Jeyabalan S, Rangappa P, Kanchi M. Hyperbaric oxygen therapy: Can it be a novel supportive therapy in COVID-19? *Indian J Anaesth.* 2020 Oct;64(10):835-841.
DOI: 10.4103/ija.IJA_613_20.
PMID: 33437070; PMCID: PMC7791429.
 33. Gorenstein SA, Castellano ML, Slone ES, Gillette B, Liu H, Alsamarraie C, et al. Hyperbaric oxygen therapy for COVID-19 patients with respiratory distress: treated cases versus propensity-matched controls. *Undersea Hyperb Med.* 2020 Third-Quarter;47(3):405-413.
DOI: 10.22462/01.03.2020.1. PMID: 32931666.
 34. Oliaei S, Alinaghi S, Mehrtak M. The effects of hyperbaric oxygen therapy (HBOT) on coronavirus disease-2019 (COVID-19): a systematic review. *Eur J Med Res.* 26, 96 (2021).
DOI: <https://doi.org/10.1186/s40001-021-00570-2>
 35. Robbins T, Gonevski M, Clark C, Baitule S, Sharma K, Magar A, et al. Hyperbaric oxygen therapy for the treatment of long COVID: early evaluation of a highly promising intervention. *Clin Med (Lond).* 2021 Nov;21(6):629-632.
DOI: 10.7861/clinmed.2021-0462.
PMID: 34862223.
 36. Treweek S, James PB. A cost analysis of monoplace hyperbaric oxygen therapy with and without recirculation. *J Wound Care.* 2006 Jun;15(6):235-8.
DOI: 10.12968/jowc.2006.15.6.26921.
PMID: 16802558.
 37. Shainu M. Black fungus treatment: Up to 70000 per day for liposomal Amphotericin B in Kerala. *Expressed News Services | Published: 07th June 2021.India.*
 38. Times Of India. Black marketing of Covid-19 drugs condemnable attempt to exploit peoples' misery: Supreme court . PTI | May 3, 2021, 18:42 IST.
 39. Richa Banka. 'Everyone is living this hell': Delhi high court on antifungal shortage. *Hindustan times.* New Delhi. May 29,2021.
 40. UNICEF. What we know about the Omicron variant. 7-Dec-2021 <https://www.unicef.org/coronavirus>.
 41. The Hindu Bureau .Corona virus updates: January 14,2022. <https://www.thehindu.com/news/national/coronavirus-live-updates-january-14-2022/>
 42. Ferguson BJ, Mitchell TG, Moon R, Camporesi EM, Farmer J. Adjunctive hyperbaric oxygen for treatment of rhinocerebral mucormycosis. *Rev Infect Dis.* 1988 May-Jun;10(3):551-559.
DOI: 10.1093/clinids/10.3.551. PMID: 3393782.
 43. El Hawa AAA, Bekeny JC, Phillips NW, Johnson-Arbor K. Hyperbaric oxygen therapy for paediatric patients: an unintended consequence of the COVID-19 pandemic. *J Wound Care.* 2021 Sep 1;30 (Sup9):S24-S28.
DOI: 10.12968/jowc.2021.30.Sup9.S24.
PMID: 34554855.