



COVID19 Associated Mucor (CAM): “Black Fungus Leading to Double Trouble in India”

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Abstract

With the huge numbers of COVID cases, India is witnessing an exceedingly high incidence of life-threatening Mucor mycosis infection with consequent morbidity, disability and mortality which is of serious concern considering the already stretched too thin medical health system and administration failure for the control and management of very high numbers of COVID cases.

Keywords: COVID19, Mucor Mmycosis in India, COVID Associated Mucor (CAM), Black Fungus.

Introduction:

During the COVID era, another strong nemesis has spurted out and spreading rampantly leading to the devastation of thousands of post-COVID patients, its none but black fungus or Mucor mycosis. It is a dangerous disease that is killing hundreds of people after successful recovery from the dreaded Covid-19. Covid Associated Mucor (CAM) can be fatal if left undiagnosed and untreated. India has never reported such high incidences of black fungus till mid-May 2021.

The incidence of Mucor mycosis has risen more rapidly during the second wave compared with the first wave of COVID-19 in India, with at least 14872 cases as of May 28, 2021. The state of Gujarat alone contributed to the highest number of cases, with at least 3726 cases of Mucor mycosis in patients with active and recovered COVID-19, followed by the state of Maharashtra. Since the communication from the Health Minister of Maharashtra on May 19, 2021, there have been 90 deaths attributable to Mucor mycosis. Other states have also shown a steady rise in the number of Mucor mycosis cases and deaths related to it; with multiple states already having declared it as an epidemic and a notifiable disease to the national health authorities. (1)

The Indian Council of Medical Research released guidelines for the screening, diagnosis, and management of Mucor mycosis in patients with COVID-19. (2)

Even though no official figures about Mucor mycosis in COVID-19 cases were released by the Union Health Ministry during the first wave of COVID-19, India contributed to approximately 71% of the global cases of Mucor mycosis in patients with COVID-19 based on published literature from December 2019 to the start of April, 2021. (3)

What is Mucor mycosis?

The infection is caused by mucoromycete mold, an organism present in the air, in leaves, piles of compost, soil and rotting wood. Mucor starts from the nostril, travels towards the eye and then towards the brain. It paralyzes the nerves it travels through. So, first, it's the eye that loses vision very swiftly and permanently. If not stopped, it enters the brain leading to paralyzes, multiple organ failure or sudden heart attack and dies*When exposed, the fungus can infect your central nervous system, eyes, sinuses, lungs, etc.

Mucor mycosis is a rare but serious fungal infection that occurs in people with weak immune systems. However, its not contagious, and does not spread from person to person. It catches on to those who have been on oxygen support for 5-7 days or more. So, the oxygen which gives your life, could become a double-edged sword leading to a death sentence.

Mucor mycosis, develops in the nasal tract due to the poor quality of water used for humidifier chambers for oxygen. For anybody on oxygen support in a hospital, it's crucial to keep looking around the nostrils for any black pigmentation. As soon as it's noticed even as the smallest dot, sirens should ring, and anti-fungal medication should start immediately with consult to ENT/ eye specialist.

The oxygen supply also needs to be sanitized immediately. While only distilled water should be used for humidified oxygen, in all hospitals, due to callosity, negligence or downright ignorance, tap water or any other water available around is used by the paramedical staff. These humidifier chambers are seldom cleaned leading to a concentration of viruses and bacteria in the piped supply system, causing abundant growth of "**Black Fungus**". Also, if tap water or even purified/boiled water is used in the humidifier, over a period of time, there will be deposits of impurities, including micro-metals, minerals/salts which make things worse. Sadly, this crucial aspect of the oxygen supply is missed by the majority.

Hundreds of people who were on oxygen support and had recently recovered from Covid are dying of mucor every day. Because of late diagnosis, underdiagnosis and lack of awareness about this fungal contamination in oxygen supply. Another postulated reason for high incidence of mucor could be sudden HUGE SURGE of COVID 19 cases with consequent oxygen supply shortage in hospitals and patients had to use industrial oxygen in an emergency situation which is not considered as pure and aseptic as medical oxygen used in hospital and this also could have contributed to the high incidence of Mucor during the second wave of COVID, because in the first wave of COVID when medical oxygen was used mucor cases were rare as suggested by experts. Another significant contributing factor could be rampant use of steroids during the second wave and uncontrolled hyperglycemia.

The medical fraternity was nearly completely ignorant about this dangerous "Black Fungus" lurking in the oxygen supply system itself due to tremendous pressure while treating COVID patients and the need for steroids.

As per ICU doctors, a significant rise in incidence and consequent complication including death by Mucor mycosis, among COVID-19 patients in India. The life-threatening infection often occurs in people with weak immune systems, such as severe diabetes. Although there is no evidence of direct linking of COVID-19 to Mucor mycosis, however, it has been observed that the recent Mucor mycosis epidemic caused by high dose or prolong period steroids use while treating COVID19 and has been seen primarily in recovering patients from COVID-19 and who have had high blood sugar during their hospital stay.

Typically, Prior to COVID-19, it has been reported primarily in immunocompromised hosts i.e uncontrolled diabetes mellitus, HIV and cancer patients, post organ transplant, etc. CDC estimated Mucor mycosis. annual incidence as 1.7 cases / 1 million population of with a mortality rate of 54% and high numbers of systemic complications.

However, since the pandemic, persons who have recovered from COVID-19 have been contracting the disease and the incidence has increased to 4-5 folds as compared to the pre-pandemic level and majority of patients have a history of COVID. In fact, various health Department issued an advisory to doctors over the recent rise of black fungus in COVID-19 treated patients.

Many of these cases of Mucor mycosis involves maxilla or upper jaw, which leads to the entire jaw detaching from the skull and which requires primary reconstruction of the jaw. The aggressive fungus is 'Angio invasive', which means it enters and blocks blood vessels and can cut off blood supply to the bone in the upper jaw leading to Jaw detachment. The infection is very so aggressive and can spread from jaw to eyes and brain within 3-4 weeks if left untreated.

From December onwards more than thousands of cases of black fungus have been reported in India, with loss of eyesight, a drop of nose jawbone and intracranial infection (rhino cerebral mucor) and deaths. Initially, it can be seen as black crust inside patients nose and often get ignored, Even if the crust is removed from the nose, the fungus can spread aggressively if not completely removed.

Predisposing Factors

COVID19 with uncontrolled diabetes mellitus, high dose or prolonged corticosteroids/ immunomodulators, mechanical ventilation, Long duration Oxygen therapy. The most common clinical presentations of Mucor mycosis are rhino-orbito-cerebral, pulmonary, cutaneous, and disseminated. The percentages reported in the review by Jeong et al. were 34%, 21%, 20%, and 14%, respectively, (4) while in the European study of the Working Group on Zygomycosis the corresponding numbers were 27%, 30%, 26%, and 15%.⁶ In patients with HM, the main clinical form of the disease is pulmonary. (5,6) In India rhino-orbito-cerebral presentation associated with uncontrolled DM was the predominant characteristic, and isolated renal Mucor mycosis has emerged as a new clinical entity. (7)

Salient clinical features: Early symptoms of the infection includes:

What do patients and their caretakers need to look out for?

No Worries!! Mucor mycosis has a typical set of symptoms

1. Bloody/ Abnormal black nasal discharge, or black crust, dryness, Nasal blockage
2. Facial swelling / numbness / Pain or tingling sensation, difficulty in chewing or opening the mouth
Sinus headache
3. eye pain Decreased / loss of vision, swelling around the eyes, double vision, redness of the eye, difficulty in the closing / to open the eye/ prominence of the eye

4.If neglected, it can even spread to the eyes and then the brain, making it fatal. If it entered the body via a cut or bruise in the skin, it could show up as blackened skin tissue.

Examination Findings:

Dental pain, Facial discoloration, Ptosis, Proptosis, Pan-ophthalmitis, Ophthalmoplegia, Palatal eschar, Nasal eschar Restricted /overacting extraocular muscle (**EOM**) Rhino-orbital Mucor mycosis Manifesting as Orbital Apex Syndrome with **Central retinal artery occlusion (CRAO)** in an otherwise Immunocompetent patient. Rhino-orbital Mucor mycosis (ROM) is an uncommon opportunistic infection affecting immunocompromised individuals.

Nose and sinuses showing mucor infection are the relatively early stages of the infection, it says; adding that timely detection at this stage can enable early treatment and minimize complications. At the moderately advanced stage comes the Eye/Orbital mucor infection. Intracranial infection is considered a very advanced disease when cavernous sinuses are involved and cranial nerve palsies occur.

Patients' relatives should be advised to help the patient for regular self-examinations including full face examination in daylight for facial swelling—especially of the nose, cheeks, around the eyes—or black discoloration, hardening, and pain on touch; as well as oral and nasal examinations using a torch to check for blackening and swelling inside the mouth or nose.

Postulated Mechanism for high incidence in COVID treated patients:

Altered immunity is the main cause of infection hence COVID induces suppressed immunity is the main trigger for the infection, not COVID19.

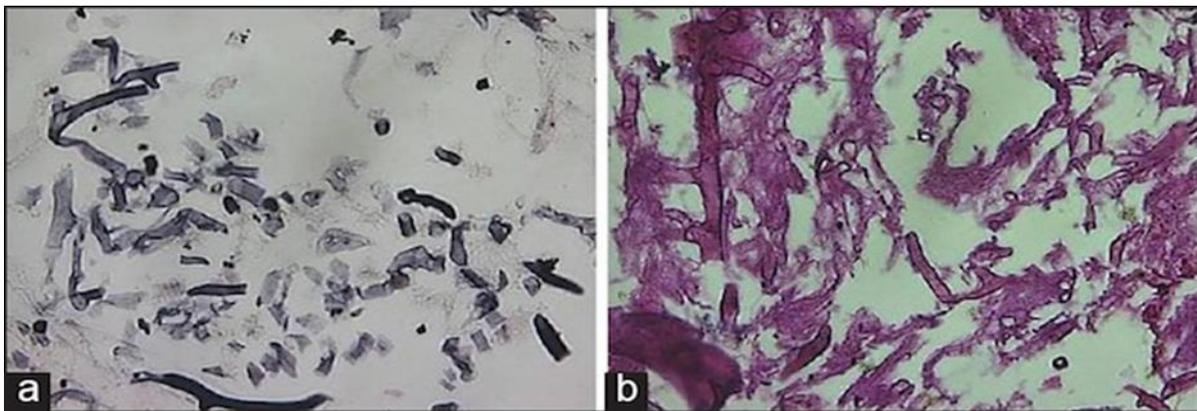
COVID-19 itself affects the immune system and has been found to alter the glucose metabolism in people. This is ideal ground for the fungus to grow, on top of that COVID-19 damage lung cells through vasculopathy and cytokine storms which requires steroids, which suppresses immunity and dysregulates blood sugar levels giving rise to the cellular predisposition for fungal growth. other reasons could be that during the lockdown months, several comorbid/immunocompromised patients had very little access to health care with worsening of their comorbidities and then COVID and steroids shots have made them more vulnerable to get black fungus infection. Lack of proper medical care coupled with poor dental hygiene (multiple cavities, bad odor, tartar on gums, mobile teeth) could be another trigger,

Three things are important for any infection to occur: classical triangle of host, pathogen & environment, Mucor is ubiquitous. You need supporting soil with fodder. Diabetes & steroids complement each other. Iron & local tissue acidosis fuels it. Mucor needs an acidic environment & neutrophilic dysfunction,

that's why more common in diabetics with acidosis or renal dysfunction. In certain predisposed individuals, covid is changing the local environment to the acidic side, uncontrolled DM and associated kidney disease and certain medication potentiates acidity and thereby predisposing to the development of this fungus and later on with local invasion & angioinvasion and distant complications.

COVID causes hyperglycemia due to the complex interplay of Remdesivir, Steroids, Viral pancreatic involvement, Stress, dehydration, and hypoxia-induced tissue acidosis. It's paradoxical to note that very few diabetics develop Mucor, it's only when they develop acidosis, as Mucor thrives in an acidic atmosphere. Now strangely very few of these patients have actually DKA, so diabetes alone cannot be blamed. Most of these patients receive an extremely high dose of vitamin C (1-3 gm TDS), this can cause metabolic acidosis, hyperglycaemia and a conducive atmosphere for Mucor. It is the combined effect of the COVID induced pathogenetic mechanism and its effect of body, contribution by various medicine for COVID treatment and comorbid conditions and environmental factors. Euglycemic ketosis can also contribute to mucor development.

Another question, could high ferritin predispose for mucor, still, need to be answered. ? research needed to find out the answer.



The fungal organism causing Mucor mycosis. Image credit: NCIB

While the earlier prognosis of patients with Mucor mycosis was predictable, with COVID-19 it has become more complicated. Some patients have died or developed acute renal failure. Certain patients do not react well to Amphotericin B a potent but toxic drug that can cause side effects and reserved to treat potentially life-threatening fungal infections.

Investigation: FBS, PPBS, Hb1AC, RFT, Deep nasal swab for gram stain KOH and CFW + plate blood agar and fungal media (SDA or PDA)

Procedures to confirm diagnosis: Diagnostic nasal endoscopy, MRI orbit, PNS and brain with contrast, CT PNS

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A multidisciplinary approach is mandatory: Experts from three different disciplines (Maxillofacial, Ophthalmology and Neurology) should work together on advanced cases of mucor mycosis along with the intensivist to manage multi-organ failure.

How to prevent the infection: Old Dictum “Prevention is better than cure” holds absolutely true and becomes more relevant in the current situation when we have a scarcity of anti- mucor medicines in India

1.For immunosuppressed/immunocompetent patients: maintain oral hygiene, wearing fresh masks, etc. dental check-ups once in six months can help to reduce the risk of infection.

2.Blood sugar monitoring and control are crucial, especially for COVID-19 recovered patients or COVID pneumonia patients. Any doubtful lesion in the oral cavity should prompt the patient to consult an ENT doctor.

3.Checking for black fungus on patients on oxygen support should be made an essential part of the covid control protocol

4.Daily checklist during ward rounds: Daily ask new onset facial pain, black spots in oral cavity, eyes Pain, vision problem if your patient has been given high dose steroids

5.Maintain proper cleanliness and ventilation in ICU with regular cleaning of AC, humidifier, avoid overcrowding in ICU

6.Use of medical oxygen with frequent sampling of oxygen for mucor

Who are the “high-risk” patients in the Covid ward?

1.Patients with RT- PCR +ve at >10 days from onset of COVID representing immunocompromised status.

2.COVID patients on steroids especially Uncontrolled diabetes, diabetic ketoacidosis, and diabetics on steroids or tocilizumab (COVID- can worsen / precipitate diabetes) and cancer. medical experts have pointed to strong links between diabetes and infection.

3.On immunosuppressants or anticancer treatment / chronic debilitating illness

4.Severe Covid cases

5.Patients on oxygen support—nasal prongs, by mask, or on a ventilator

Ophthalmologists should conduct a baseline examination of these high-risk patients, followed by weekly examinations till the time of discharge. It has been stressed on follow-up examination, every 2 weeks for six weeks, or every month for 3 months.

Nose and sinuses showing mucor infection are the relatively early stages of the infection, it says; adding that timely detection at this stage can enable early treatment and minimize complications. At the moderately advanced stage comes the Eye/Orbital mucor infection.

Intracranial infection is considered a very advanced disease when cavernous sinuses are involved and cranial nerve palsies occur.

Patients' relatives or caretakers are advised to help the patient to do regular self-examinations for the above-mentioned signs and symptoms.

If a patient identifies any of these signs, what must they do?

immediately consult an ENT /Eye doctor for their treatment, and MUST NOT self-medicate with steroids, antibiotics, or antifungal. Apprise the doctor about your detailed medical conditions. An MRI/ CT contrast of paranasal sinuses and orbits needed to see the actual extent of mucor and then pan treatment.

Treatment of Covid associated Mucor mycosis (CAM):

1. Diabetes control
2. Reduce steroids, (judicial use in terms of dose and duration)
3. Discontinue immunomodulators
4. Medical therapy (maintain adequate hydration; put PICC or CVC)

Surgical Management:

In complicated patients surgical interventions such as Extensive surgical debridement (If eye involved, exenteration of the eye; in the lung, if localized or one lobe involved). **Early** surgical debridement Transcutaneous retrobulbar amphotericin B, Orbital exenteration with extensive orbital involvement are recommended based on the organ involvement.

Dual antifungal (IV amphotericin B + oral Posaconazole) & surgery is the key. Plain or liposomal amphotericin B. Posaconazole & isavuconazole are expensive drugs.

In all patients with a CNS involvement high dose liposomal amphotericin B scores over all other agents. However, in patients with disease confined to the sinus with no CNS involvement probably both Posaconazole and isavuconazole can be used effectively.

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As per the latest Recommendation of Fungal Infection Study Forum (**FISF**) (8) on antifungal therapy in Covid associated Mucor mycosis when antifungal drug availability is limited are as follows:

- Antifungal prophylaxis is not recommended.
- Start calculated dose of amphotericin B from the first day, avoid dose escalation.
- Fluconazole, voriconazole, echinocandins (caspofungin, anidulafungin, micafungin) or 5 flucytosine is not active against Mucor mycosis.
- Combination of antifungal therapy is generally not recommended.

Actions taken by the ministry of health (MOH):

AIIMS has released new guidelines for early detection, prevention of CAM.(9). Stay vigilant even weeks after recovering from COVID-19 as Mucor infection may occur during COVID-19 infection, or after a few weeks of apparent recovery from it.

Various states have quickly undertaken measures to ascertain control over the situation by setting up special task forces, issuing guidelines, arranging separate wards in hospitals for the management of Mucor mycosis cases, and procuring the drugs required for treatment. Approximately 0.1 million vials of amphotericin B, have already been distributed to the states from May 1 to May 14, 2021, by the Union **MOH**. The shortage of amphotericin B has been noticed in multiple states and measures are being undertaken for the procurement and optimal allocation of the drug by ramping up domestic production; in addition to this, different methods of importing the drug are currently being explored by the **MOH**. The Ministry also needs to step up to monitor and analyze the situation; to disseminate information, education, and communication materials for the general public; and to undertake essential measures for preventing a further rise in the number of Mucor mycosis cases in patients with COVID-19 and mortality. (10)

Pearls of wisdom: Proptosis with loss of vision with black crust in nasal cavity consider Mucor. If vision remains intact - think of orbital cellulitis.

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Image 1- Swelling in both eyes, left side more and fullness of sinuses

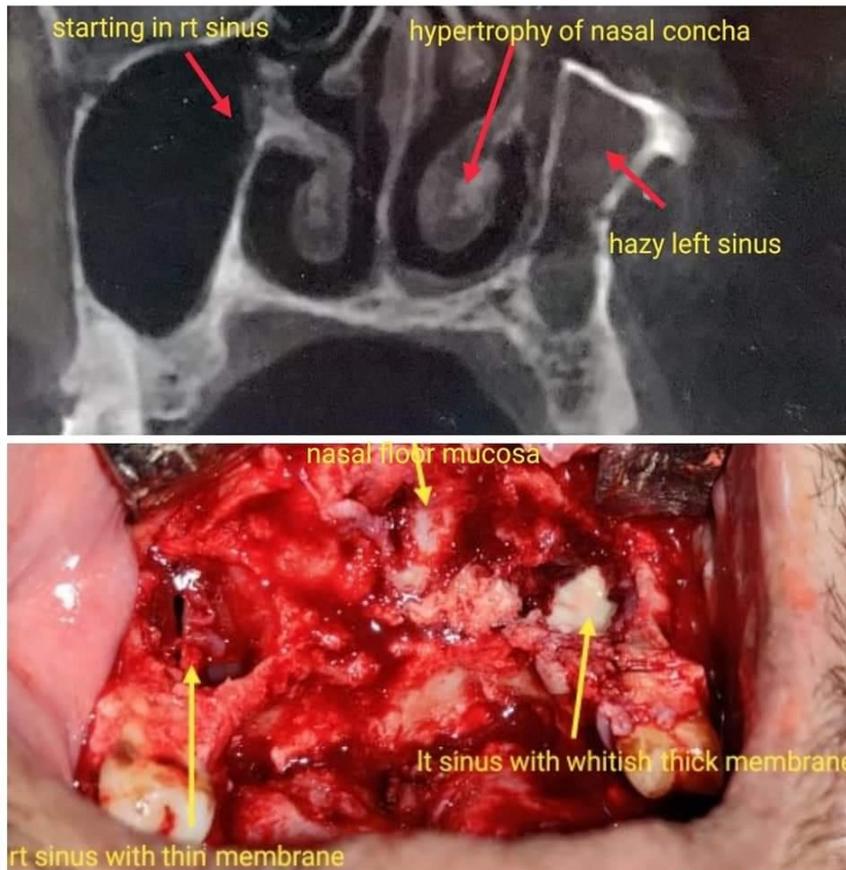


Image 2. Above CT scan showing hazy left sinus. Below left sinus with whitish thick membrane

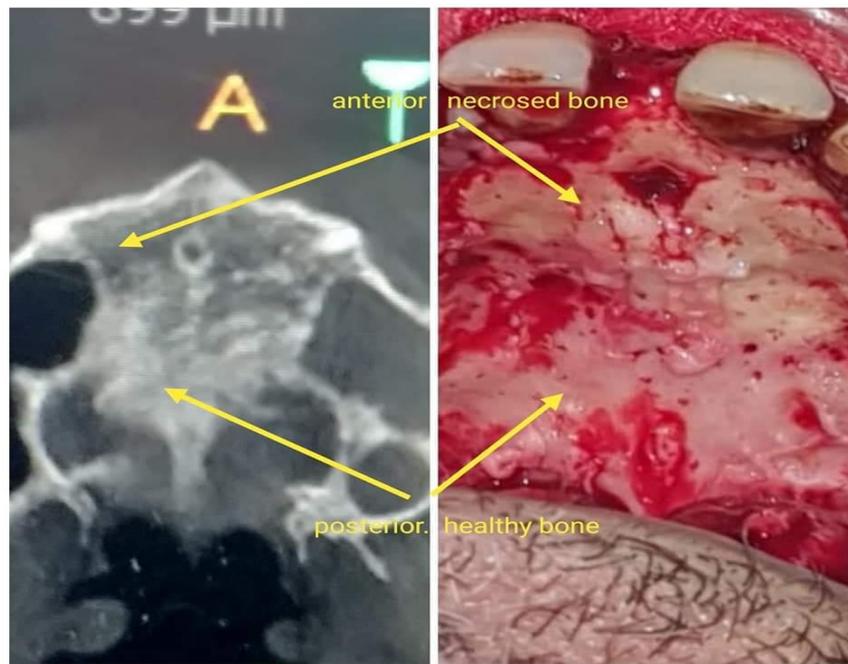


Image 3: Left side CT scan showing anterior necrosed bone and posterior healthy bone and same in the specimen after surgery



Image : Specimen showing demarcation between healthy and necrosed bone

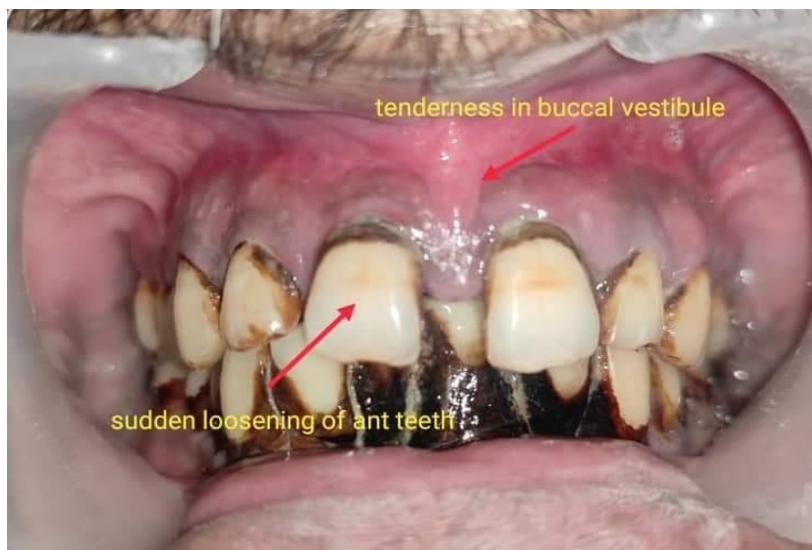


Image 4: Tenderness in buccal vestibule and sudden loosening of anterior teeth



Image 5: Early infection of buccal mucosa

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