

Can Nasal Irrigation Serve as a Complementary Strategy for Preventing COVID-associated Mucormycosis?

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Mucormycosis is a highly aggressive angio-invasive disease caused mainly by the *Rhizopus* spp.¹ There was a rapid surge in the incidence of mucormycosis due to coronavirus disease-2019 (COVID-19).² The primary clinical presentations of “COVID-associated mucormycosis” (CAM) consist of the rhino-orbital–cerebral presentation.^{3–5}

As many as 50K cases were reported in India alone.^{6,7} The frequent causes of mucormycosis are high-dose steroid therapy, poorly controlled diabetes, renal failure, malignancy, and transplant cases.^{8,9} Mucormycosis frequently involves the male population, and indicators of risk include severe COVID-19, significantly elevated HbA1C, diabetic ketoacidosis (DKA) at admission, and prolonged ICU admission.^{8,9} Diabetic patients are particularly prone to infections like mucormycosis because of hyperglycemia-induced dysfunction of neutrophils.⁵ As cases have typically spiked in the second COVID wave, even the delta variant has been proposed in its genesis, but only limited literature supports this contention.^{6,7} Other unconventional risk factors like masking practices and nasopharyngeal swabbing were also highlighted, but more study is needed before their contribution is substantiated.^{6,7}

The prognosis of CAM is abysmal, with many succumbing to death. Those who survived lead a low quality of life due to gross disfigurement caused by radical surgical procedures. Gold standard drugs such as Amphotericin B can also lead to complications like nephrotoxicity. As CAM can recur again due to the likely emergence of newer viral variants, it is vital to reflect on the strategies that might aid in its prevention. Till-date, there is no knowledge concerning the methods that could prevent or manage this fatal condition.

Since CAM is more commonly observed in those with *uncontrolled diabetes* and *high-dose steroid therapy*, these comprise the vulnerable group. It would be interesting to ask if this vulnerable population can benefit from home-based interventions like saline irrigation procedures.

Saline Nasal Irrigation for COVID and CAM – A New Hypothesis

In the initial phase of the pandemic, some authors have hypothesized saline nasal irrigation as an effective intervention for preventing COVID-19 and managing nonhospitalized COVID-19 cases.^{10,11} The interim analysis by Kimura et al. added data in favor of this speculation.¹² The reason many supported it is that NaCl is known to possess a diverse antimicrobial profile, and irrigation, as such, could contribute to sinonasal clearance. Irrespective of the method used, saline irrigation generally eliminates thick mucus, clears the inflammatory mediators, and improves mucociliary

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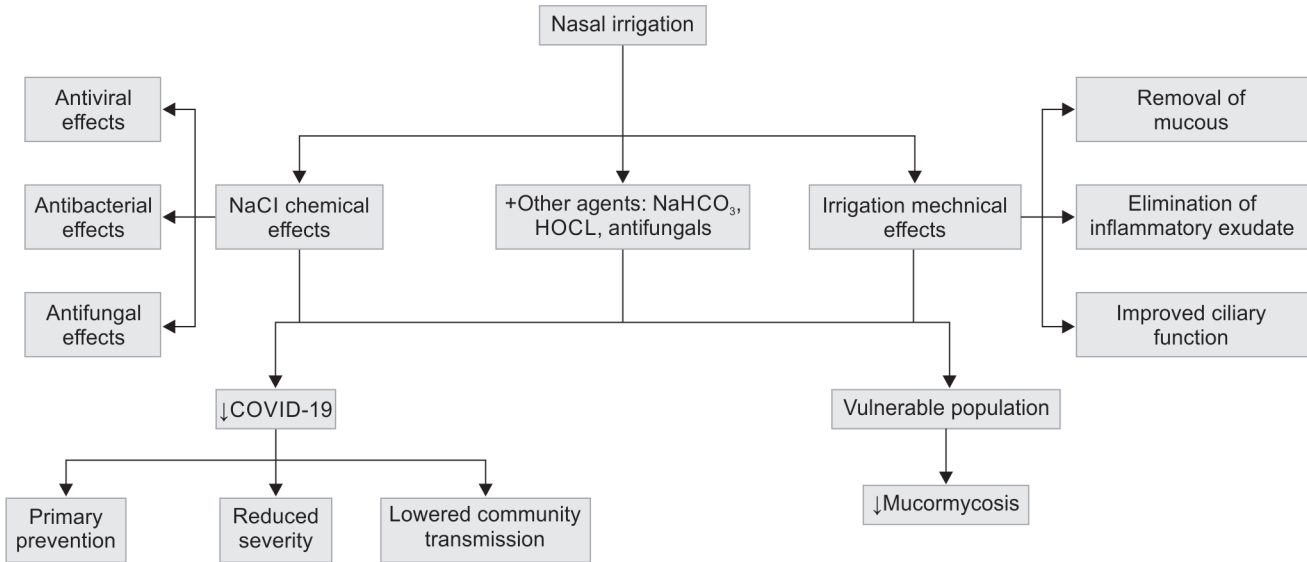
function.¹⁰ Its antiviral effect is well documented in the literature; it can also chemically act on bacteria and fungus.

Since irrigation techniques have potent antimicrobial effects, it seems logical to presume nasal irrigation is a complementary technique for mucormycosis (Flowchart 1). Another critical reason to extrapolate its role for mucor is that mucor organisms primarily involve the paranasal air sinuses, which are well within reach of the irrigation procedure.

Large-volume Irrigation Techniques can Aid in the Clearance of Nasal Pathogens

In particular, large-volume nasal irrigation methods like “Jala-Neti” (JN) could be helpful due to their (possibly) superior irrigation impact compared with saline nasal sprays or saline nasal drops, which only result in mucosal wetting. While “mucosal wetting with hypertonic saline” may be sufficient to control viral and/or bacterial infection, to control fungal colonization, there is a need to consider high-volume irrigation techniques (like JN).

Jala-Neti is pertinent to the mucormycosis scenario. The spores carried from the environment to the nasal cavity could be easily flushed out through routine irrigation in the initial stages. Because of the accentuated mechanical cleansing action, JN may also have

Flowchart 1: Nasal irrigation with saline and other agents supports COVID management in mild cases and might aid in mucor prevention in vulnerable populations

the potential to disengage the subsequently formed hyphae and attachment elements. Large-volume nasal irrigation techniques like JN may be superior at eliminating fungal colonies.

Past Evidence That Informs Us about Saline's Potential in Mucor

To date, only one case report (of suspected rhino-cerebral-orbital mucormycosis) by Rastogi and Verma reveals the possible value of saline irrigation.¹³ In this report, the clinical and MRI-PNS findings suggested mucormycosis, but the patient could not be admitted due to a lack of bed availability. The patient was prescribed JN by an Ayurveda consultant (about six times in 4 days), after which symptoms slowly subsided. It is essential to recognize that the authors recommended saline practice mainly due to existing delays in conventional management and after obtaining patient consent. It is worth noting that, besides this case report-level evidence, no further data indicates saline's added advantage in mucormycosis.¹³ There is a need for more evidence; similar reports may be available with ENT clinicians and those that frequently recommend irrigation, such as Ayurveda and Naturopathy practitioners.

Other Agents in Irrigation

It is also essential to look into other alternative agents supporting nasal irrigation. In this context, *sodium bicarbonate* is a valuable addition. Patients with diabetic ketoacidosis (DKA) and renal failure have increased nasal pH. The acidic nasal pH is known to increase the *availability of free iron*, which might lead to fungal growth.^{14,15} So, adding sodium bicarbonate could modulate the nasal pH and potentially mitigate the growth of *Mucor* spp. Kim et al. showed that a low-concentration HClO could be used against a spectrum of organisms, including a *Rhizopus oryzae*; their cell-line-based research demonstrated substantial neutralization.¹⁶ Therefore, HClO (hypochlorous acid) may also be a potential addition to nasal irrigation.

Interestingly, the landmark paper by Ramalingam et al. reveals that epithelial cells generate intracellular HClO once they

are exposed to a chloride (Cl⁻²) source.¹⁷ This means intracellular HClO (or endogenous HClO) primarily takes part in the epithelial defense against viruses. There are also some wound management studies that showed that HClO-generating scaffolds could help manage fungal infections like *Candida*.¹⁸ The naturally releasing HClO, following saline irrigation, could have a similar effect. Some *in vitro* toxicity studies, like the one by Kim et al., also simulated the benefits of low-concentration hypochlorous acid on many fungal organisms, including (and not limited to) *R. oryzae*.¹⁶ There are also interesting clinical studies using a low concentration of HClO, which corroborate with the *in vitro* evidence and inform us of good tolerance.¹⁹

Specific Pharmacological Agents for Precise Targeting

We should also explore antifungal agents like Amphotericin B in nasal irrigation systems for those in the early stages of mucormycosis.²⁰ Intranasal Amphotericin B may help reduce the adverse effects (like nephrotoxicity and hepatotoxicity) that are strongly associated with systemic delivery. Localized Amphotericin B irrigation was implemented by Khafagy et al. in a leukemia patient with mucormycosis.²¹ The authors mention that Amphotericin B was well tolerated.²² It is noteworthy that no inflammation, irritation, pain, discharge, or epistaxis were observed.²²

Once the COVID patients are to be discharged, they could be motivated to perform SNI/JN and be asked to return if red-flag symptoms like nasal congestion, facial swelling, and headache that are consistent with mucormycosis are reported. While follow-ups are highly warranted in vulnerable populations, simple prophylaxis options like SNI may go a long way (if proven beneficial). We must understand that past evidence points out that JN practice with isotonic and hypertonic saline was not associated with adverse effects. It is thus a relatively safe intervention. Previous studies also point to a robust protective effect of SNI due to the wide-spectrum antimicrobial actions of NaCl. Local antifungals may also be a valid therapeutic option in mild mucor cases when medical management cannot be instituted.

Need for *In Vitro/In Vivo* Investigations

Since clinical–interventional studies cannot be warranted due to the aggressive course of mucormycosis, preclinical investigations can be carried out in murine models. We could also design *in vitro* studies with variable concentrations of NaCl separately and jointly with other agents on the mucor cultures (e.g., *Rhizopus* spp.). Insights drawn through such investigations would improve our understanding of the clinical feasibility of saline-irrigation prophylaxis in mucor cases.

The optimal frequency of irrigation and ideal concentration of hypertonic saline (2% or more) that has the potential to counter settlement and colonization of *Mucor* spp. is still unknown, and there is a need for studies to determine this. Whether antifungal agents provide a higher impact than hypertonic saline is also worthy of a deeper inquiry.

Potential Drawbacks of Nasal Irrigation

Overuse of saline irrigation could lead to “water retention” issues. Another possible complication is that hot water could injure the mucosa, or sometimes the sharp tip of the neti pot’s spout could also lead to thermal or mechanical injury of the delicate nasal mucosa.^{10,11}

There is also a possibility of infection if unclean vessels and/or contaminated water is used, but this is extremely rare. A small number of reports of infection with neuropathogenic bacteria also exist in the literature.¹¹ However, using thoroughly filtered and/or boiled water effectively eliminates such issues. It is also vital to speculate further if regular use of saline is acceptable in patients with diabetes who display elevated secondary infection rates. However, in general, ample literature states that it is a well-tolerated practice.

Concluding Remarks

Mucormycosis is a fatal condition that requires prompt medical and surgical management. Judicious use of pharmacological agents and glycemic control in people with diabetes is vital for preventing this condition in COVID-19 patients. Our effort in this paper was to provide insight into the plausibility of prevention. We believe advocating “nasal irrigation” via low-cost irrigants like hypertonic saline could be a supportive measure during the “COVID and/or post-COVID” phase. We want to reiterate that nasal irrigation cannot be considered part of the “mucormycosis-management protocol” but only as a potential “risk-mitigation approach” relevant to the high-risk groups. As nasal irrigation has shown value in fungal infections like “rhino-sinusitis,” further studies could be planned to validate the utility of this approach for more challenging and complex conditions like mucormycosis.

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