

## Analysis of COVID-19-associated rhino-orbital-cerebral mucormycosis patients in a tertiary care center in Northern India

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**Purpose:** An unprecedented surge has been noted in rhino-orbital-cerebral mucormycosis (ROCM) in times of current COVID-19 pandemic. The present prospective study aims to evaluate clinico-epidemiological profile, risk factors, management, and outcome of the cases of ROCM that presented to our tertiary care center during the study period from April to June 2021. **Methods:** All patients were subjected to complete history taking, ophthalmological examination, and imaging studies. The patients were staged and were treated with intravenous liposomal amphotericin B (AMB) and sino-nasal debridement of local necrotic tissue. Transcutaneous retrobulbar AMB (TRAMB), orbital decompression, and exenteration were instituted as indicated. All patients were followed up for a minimum of 6 months before arriving at the final outcome. Statistical analysis was performed. **Results:** A total of 49 patients presented during the study period, with a mean age of 42.2 years. The major risk factors included uncontrolled diabetes (89.8%), COVID-19 positivity (51.02%), and concurrent steroid use (38.77%). The most common presenting symptom was facial pain/swelling (43.65%), while the most common presenting sign was deterioration in vision (75.51%). Intravenous liposomal AMB was given to all patients along with sino-nasal debridement (85.71%), TRAMB (57.14%), orbital decompression (14.28%), and exenteration (12.24%). Overall, mortality at 6 months was 22.45% (11 patients). Age more than 60 years, intracranial extension, and HbA1c of more than 8.0% were observed to be statistically significant indicators of mortality. **Conclusion:** Early suspicion and timely diagnosis of mucormycosis at rhino-orbital stage is warranted in order to salvage life as well as visual function. TRAMB may prove as potentially favorable treatment modality in cases with limited orbital involvement.

**Key words:** COVID-associated mucormycosis (CAM), rhino-orbital-cerebral mucormycosis (ROCM), transcutaneous retrobulbar amphotericin B (TRAMB)

The ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to health implications of unprecedented degree. We are still unravelling the far-fetched health implications and long-term complications associated with the coronavirus disease 2019 (COVID-19). Initial reports on ocular manifestations in patients with COVID-19 describe mainly self-limiting conjunctivitis and rare manifestations that include optic neuritis, vascular occlusions, ocular motor cranial neuropathies, and rhino-orbital-cerebral mucormycosis (ROCM).<sup>[1]</sup>

ROCM is a rare but life-threatening, invasive fungal infection that often occurs in immuno-compromised persons. Diabetic ketoacidosis remains the most common predisposing event, associated with around two-thirds of the cases of ROCM.<sup>[2]</sup> The condition originates in the nose and paranasal sinuses but is often undiagnosed until orbital spread, indicating its grave prognosis. The fungal hyphae invade the surrounding bone and soft tissue through vascular thrombosis causing subsequent tissue infarction and may eventually infiltrate the brain leading to fatal complications.<sup>[3,4]</sup>

During pre COVID-19 times, India had highest global burden of mucormycosis with about 140 cases per million populations.<sup>[5]</sup> The figures have increased exponentially with resurgence of COVID-19 cases in the country. COVID-19 produces a hypoxic milieu with high glucose levels, high ferritin levels, and impaired phagocytic activity of leukocytes due to immunosuppression by the virus as well as the rampant steroid use for the management. Also, hydroxychloroquin (HCQS) has been shown to impair autophagy and phagocytosis, further weakening host immune response.<sup>[6,7]</sup> COVID-19 in diabetics provided the most facilitatory condition for proliferation of fungal hyphae. Use of industrial grade oxygen to fill for shortage of medical oxygen, extended hospital stay with risk of nosocomial infection, use of targeted immunosuppressants like tocilizumab, and associated comorbidities contribute as other risk factors for rise in incidence of COVID-19-associated ROCM.<sup>[8,9]</sup>

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This study intends to report the clinic-epidemiological profile and treatment outcome of COVID-19-associated ROCM cases that presented at our center during April–June 2021.

## Methods

We conducted a prospective observational study on cases presenting with ROCM to our tertiary care from April to June 2021. Ethical approval for the study was sought from the institutional Ethics Committee. Evaluation at presentation included a detailed history, complete ophthalmic, oto-rhino-laryngeal and neurological examination, nasal endoscopy with biopsy, and haemato-radiological tests, to assess the extent of disease. History of COVID-19 vaccination was elicited and patients were categorized as unvaccinated (no dose received or less than 2 weeks of the first dose), partially vaccinated (more than 2 weeks of the first dose and/or less than two weeks of second dose), or fully vaccinated (more than two weeks of the second dose). History of COVID-19, past or concurrent, including diagnostic test for COVID-19 was recorded. The diagnosis of definite COVID-19 was based on either of the following: reverse transcription polymerase chain reaction (RT-PCR) test on nasopharyngeal or oropharyngeal swabs, rapid antigen test, or computed tomography (CT) chest scores in the absence of a positive RT-PCR test in a clinically symptomatic case. Suspected COVID-19 cases were the ones who were either kins of definite COVID-19 patients or had a recent history of fever and cough/cold in self or family members but had not undergone diagnostic tests for COVID-19. Medical records of hospitalization for COVID-19 treatment were reviewed, elucidating severity of disease, duration of hospital stay, use of steroids and other immune-suppressants, and requirement of supplemental oxygen or mechanical ventilation. History of any comorbid ailment and its treatment was also elicited. Imaging studies included magnetic resonance imaging (MRI) or CT scan of orbits, brain, and paranasal sinuses with or without contrast. Hematology included complete hemogram, blood sugar, glycosylated hemoglobin, and renal function tests. The patients were classified into Proven, Probable, or Possible Mucormycosis as per the case definition suggested by the European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) and modified by Honavar *et al.*<sup>[10,11]</sup> A patient with symptoms and signs of ROCM, in the clinical setting of concurrent or recently treated COVID-19, was labeled as possible ROCM. If clinical features were supported by diagnostic nasal endoscopy findings, contrast-enhanced MRI, or CT scan, patient was categorized as probable ROCM. Proven ROCM was defined as clinico-radiological features along with microbiological confirmation on direct microscopy and/or culture or histopathology.

All the patients were staged at admission, according to the staging system proposed by Honavar,<sup>[11]</sup> and were managed in accordance with the modified EORTC/MSG guidelines.<sup>[11]</sup> Intravenous liposomal amphotericin B (AMB) in recommended doses was the mainstay of treatment in all the patients. Therapeutic measures also included control of the general condition, underlying risk factors, and complications, together with antibiotics to prevent secondary bacterial infection. Functional endoscopic sinus surgery (FESS) was performed to debride sino-nasal necrotic tissue. Orbital intervention included transcutaneous retrobulbar AMB (TRAMB), orbital decompression, and orbital exenteration. Exenteration

was undertaken in patients with severe orbital disease (stages 3 and 4) after medicine and anesthesia clearance. TRAMB was employed as adjunctive treatment modality in patients who had limited orbital involvement or those who had extensive orbital involvement but were unfit or nonconsenting for exenteration. One millimeter liposomal AMB in a concentration of 3.5 mg/mL was used as one dose of TRAMB. A minimum of three and a maximum of nine alternate day injections were given. The patients were subsequently watched for possible side effects of retrobulbar injection such as neurotoxicity, compartment syndrome, and raised intraocular pressure. Orbital decompression and debridement instead of exenteration were performed in a few patients with severe orbital disease.

All the patients were followed up for a period of at least 6 months from presentation to record the final outcome.

The data was analyzed using SPSS (IBM SPSS Statistics 20, SPSS Inc., Chicago, IL, USA) and Microsoft Excel (Version 16.49).

**Table 1: Epidemiological profile of patients**

Patient characteristics (n=49)	Number (%)
Age, years	
≤ 40	13 (26.53)
41-59	20 (40.82)
≥ 60	16 (32.65)
Gender	
Male	32 (65.31)
Female	17 (34.69)
Association with COVID-19	
No COVID-19	24 (48.98)
Definite COVID-19	23 (46.94)
Suspected COVID-19	02 (4.08)
Vaccination status	
Unvaccinated	44 (89.79)
Partially vaccinated	05 (10.20)
Fully vaccinated	00
Comorbidities	
Diabetes mellitus	33 (67.34)
Hypertension	14 (28.57)
Coronary artery disease	01 (2.04)
Others	01 (2.04)
Glycosylated haemoglobin level at presentation	
<5.6 (Normal)	3 (6.1)
5.7-6.4 (Prediabetic)	2 (4.1)
≥ 6.5 (Diabetic)	44 (89.8)
History of oxygen therapy	
Yes	14 (28.57)
No	35 (71.43)
History of steroid use	
Yes	19 (38.77)
No	26 (53.06)
Unknown	04 (8.16)
No. of days from COVID-19 diagnosis to presentation for ROCM (n'=25)	
Concurrent	04
<1 month	18
>1 month	03

**Table 2: Clinical and radiological features (n=49)**

Feature	Number (%)
Presenting symptoms	
Facial pain/swelling	21 (42.86%)
Drooping of eyelid	18 (36.73%)
Nasal discharge/bleeding	18 (36.73%)
Decreased vision	17 (34.69%)
Double vision	10 (20.41%)
Protrusion of eye	09 (18.37%)
Altered sensorium	05 (10.20%)
Presenting signs	
Ptosis	21 (42.86%)
Ophthalmoplegia	21 (42.86%)
Visual deterioration	
No PL	09 (18.37%)
6/60 to PL+	15 (30.61%)
6/18 to 6/60	13 (26.53%)
Better than 6/18	12 (24.49%)
Proptosis	13 (26.53%)
Keratopathy	12 (24.49%)
Nasal/palatal eschar	02 (4.08%)
Periocular/Facial hypoesthesia	03 (6.12%)
Fundus changes	
CRAO*	02 (4.08%)
CRVO*	01 (2.04%)
Radiology	
Paranasal sinus	
Diffuse involvement	45 (22.4%)
Bilateral involvement	22 (44.90%)
Orbit	
Bilateral involvement	04 (8.16%)
Brain	
Cavernous sinus thrombosis	09 (18.37%)
ICA* Invasion	03 (6.12%)
Frontal lobe abscess	01 (2.04%)
Others	03 (6.12%)
Stage of disease at presentation	
1	01 (2.04%)
2	23 (46.94%)
3	11 (22.45%)
4	14 (28.57%)

\* CRAO, Central retinal artery occlusion; CRVO, central retinal vein occlusion; ICA, internal carotid artery

The Fisher's exact tests were used to compare outcomes. For all tests, *P* values  $\leq 0.05$  were defined as statistically significant.

## Results

A total of 49 cases of ROCM presented over a period of 3 months, 32 (65.31%) of which were male. The mean age of the cases was 42.2 ( $\pm 12.7$ ) years, with about two-thirds of the patients belonging to the productive age group of less than 60 years [Table 1]. A positive history of COVID-19 was elicited in only about half of the patients; with confirmed COVID-19 illness in only 23 patients. Three patients were concurrently

positive for SARS-CoV-2, had moderate to severe disease, and were treated for COVID-19 in isolation wards in accordance with the national guidelines for COVID-19 issued by Ministry of Health and Family Welfare (MoHFW) that included systemic steroids, HCQS, and oxygen supplementation.<sup>[12]</sup> History of partial vaccination was elicited in 5 (10.2%) patients, and none of the patients had undergone complete COVID-19 vaccination. History of preexisting diabetes mellitus was recorded in 33 (67.35%) patients, although glycosylated hemoglobin (HbA1c) levels at presentation were found in diabetic range in most of the patients. Comorbidities other than diabetes were present in 16 patients and included mainly hypertension. Coronary artery disease and chronic kidney disease were present in one patient each. Table 1 depicts the epidemiological profile and distribution of various risk factors among all the study patients.

Table 2 elucidates the clinico-radiological features of all the patients. Most common presenting symptom was facial pain/swelling (42.86%), followed by drooping of eyelid and nasal discharge/bleeding (37.5%). Significant deterioration in vision was recorded as the most frequent presenting sign, followed by ophthalmoplegia and ptosis. Forty-seven (95.9%) patients were categorized as proven cases of ROCM, while the rest two were probable cases.

On radiological assessment, 32 (65.30%) cases demonstrated orbital infiltration with four cases (8.3%) having bilateral involvement. Of the 16 (33.3%) cases with central nervous system (CNS) involvement, 9 (18.4%) had developed cavernous sinus infiltration, three (6.1%) cases developed internal carotid artery infiltration, and one (1.9%) developed frontal lobe abscess.

FESS was performed in 42 (85.71%) of the patients. Table 3 depicts the stage-wise frequency of various orbital interventions. TRAMB was the most commonly employed orbital intervention, undertaken in 28 patients (57.14%). Of the 28 patients, 13 were the ones that were stage 2 at initial presentation but progressed during the course of disease and showed clinical/radiological sign of orbital involvement. Rest of the patients receiving TRAMB were stage 3 and stage 4 patients with significant orbital involvement. Orbital decompression and orbital exenteration were performed in four (8.16%) and six (12.24%) patients, respectively [Figs. 1 and 2].

Forty-two (85.71%) patients were discharged with either stable or improved status. The mean period of hospitalization was  $23 \pm 11$  days. Stepdown therapy with oral posaconazole could be instituted in 20 (40.81%) patients.

At 6 months follow-up, overall mortality was found to be 22.45% (11 patients), while complete loss of vision and ocular motility was noted in 11 and 16 surviving patients, respectively. Table 4 elucidates the final outcome in patients with severe orbital disease, but the numbers in each group are too less to arrive at any statistical relevance. Among the nonsurvivors, 81.82% had age more than 60 years ( $P < 0.05$ ), 90.90% had intracranial involvement ( $P < 0.05$ ), and all patients had HbA1c  $> 8.0\%$  ( $P < 0.05$ ).

## Discussion

Mucormycosis is an infrequent but fulminantly invasive, and potentially lethal infection caused by a group of aseptate filamentous fungi known as mucorales.<sup>[13]</sup> The clinical hallmark of mucormycosis is vascular invasion resulting in thrombosis

**Table 3: Stage-wise frequency of orbital intervention**

Stage of Disease <sup>[11]</sup>	No. Of Patients	TRAMB*	Orbital Decompression	Exenteration
Stage 2 (Paranasal sinus involvement with no/minimal orbital involvement)				
2a	02			
2b	07	03		
2c	10	07		
2d	04	03		
Stage 3 (Orbital involvement)				
3a	04	04		
3b	04	04		
3c	03	--	02	01
Stage 4 (Intracranial involvement)				
4a	03	01	01	01
4b	04	03	01	--
4c	07	03	--	04

\*Transcutaneous Retro-bulbar Amphotericin B

**Table 4: Outcome of various orbital treatment measures in patients with significant orbital involvement**

Orbital intervention (No. of patients)	Survivors at 6 months
Stage 3	
TRAMB (08)	06
Orbital decompression (02)	02
Exenteration (01)	00
Stage 4	
TRAMB (07)	06
Orbital decompression (02)	01
Exenteration (05)	01

**Table 5: Comparison of present study with that of other recent studies on ROCM**

Study (n)	Follow-up duration	Exenteration (%)	TRAMB (%)	Mortality (%)
Current (49)	6 months	12.24	57.14	22.4
Sen <sup>[28]</sup> (2826)	14.4±2.1 days	15.0	22.0	14.0
Dave <sup>[24]</sup> (58)	5 months	38.0	1.72	34.0
Ravani <sup>[20]</sup> (31)	2.5 months	13.0	--	10.0
Walid <sup>[30]</sup> (540)	3 months	5.0	51.85	9.25
Moorthy <sup>[31]</sup> (18)	--	39.0	--	33.0

and tissue infarction/necrosis. Apart from ROCM, there may be different clinical presentations depending upon the anatomic site involvement and associated defect in host defense. Diabetics in ketoacidosis typically develop the rhino-cerebral form of the disease and may rarely develop pulmonary or disseminated disease, while neutropenia and excessive steroid therapy predisposes a person to mainly pulmonary and disseminated mucormycosis.<sup>[14,15]</sup> Severe malnutrition is another risk factor that may predispose a person to gastrointestinal mucormycosis.<sup>[16]</sup> Cutaneous or subcutaneous mucormycosis may result from local trauma and skin maceration.<sup>[8]</sup> With unpredictable surge of COVID-19 cases in India and globally,

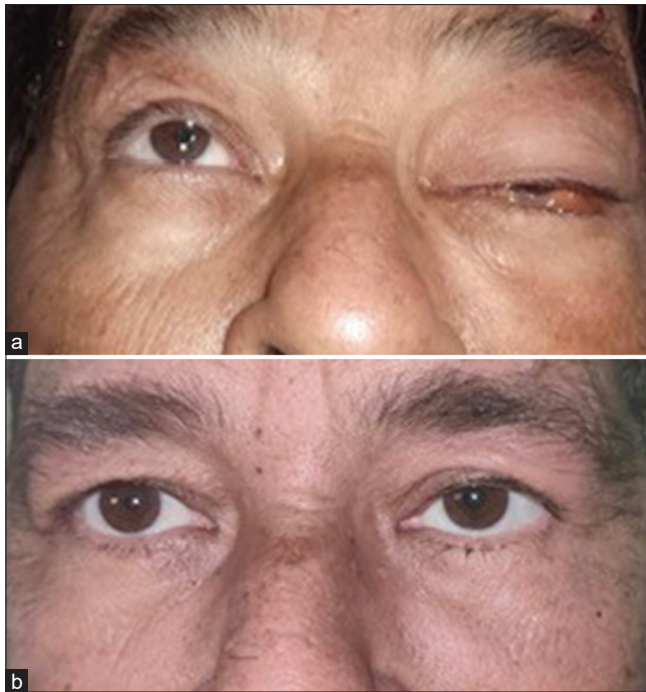
a monumental rise in the cases of mucormycosis has been noted. A systematic review and meta-analysis by Masuza *et al.*<sup>[17]</sup> observed that COVID-associated mucormycosis (CAM) constitutes 0.3% of COVID-19 coinfections.

The average incidence of mucormycosis reported from different case series in India during the pre-COVID-19 era has ranged from 9.5 to 24.5 cases per year with a clear male preponderance.<sup>[18]</sup> We report a much higher rate of ROCM cases presenting to our hospital during the COVID-19 pandemic in comparison to the same period in the previous years. Male gender predominance, similar to that reported in previous studies, may be due to their greater involvement in outdoor chores. Two-thirds of our patients belonged to productive age group, indicating significant loss of man-days due to high mortality and morbidity associated with the disease.

Only about half of our cases had a positive association with SARS-CoV-2 infection, similar to that in a case series from Egypt by Fouad and co-workers.<sup>[19]</sup> Ravani *et al.*<sup>[20]</sup> also reported that a total of 38.70% patients in their series of 31 cases had no positive history of COVID-19 and steroid use. We cannot rule out a prior undocumented, untreated, or asymptomatic infection with SARS-CoV-2 in rest of our patients. Possible implication of COVID-19 in the development of ROCM may include impaired host defenses against the fungus by virus-induced lymphopenia or the therapeutic use of corticosteroids and/or HCQS, both likely to impair phagocytic immune-cell response, which is the major defense mechanism against mucormycosis.<sup>[8]</sup>

The national guidelines by MoHFW recommended prophylactic and therapeutic use of HCQS during both first and second wave of SARS-CoV-2, despite the United States Food and Drug Administration declaring its use unsafe outside of a hospital.<sup>[12,21]</sup> Self-medication with HCQS was fairly common practice as a preventive and treatment agent against SARS-CoV-2 without any strong evidence for its use.<sup>[22]</sup> It is worth noting that the widespread use of HCQS as measure against SARS-CoV-2 infection may be among the few factors responsible for surge in mucormycosis cases during the pandemic.

Deranged blood sugar was observed to be the most common risk factor, present in about 90% of our patients. Various other



**Figure 1:** (a) A stage 3b patient at presentation with proptosis and complete ophthalmoplegia. (b) At discharge, complete resolution of proptosis and ophthalmoplegia with TRAMB (five injections)



**Figure 2:** A stage 4c patient, 34 years male, underwent radical exenteration with maxillectomy. The patient succumbed at day 6 of surgery

studies from India have reported the presence of diabetes in 54–76% cases of CAM.<sup>[18,23]</sup> Known history of diabetes was found in lesser patients signifying an undiagnosed diabetes load in the community. With overwhelmed healthcare facilities during the second wave and the inadvertent use of systemic steroids as over-the-counter drug in patients treated for COVID-19 at home and undesignated centers may have led to derangement of blood sugars. Other liable factors for increased cases of ROCM during COVID-19 era may include loss of stringent blood sugar control in diabetics and late seeking or inaccessibility of medical care during lockdown.

Facial pain and puffiness was seen as the most common presenting symptom followed by drooping of eyelid and nasal discharge and/or bleeding. Early suspicion and timely diagnosis of mucormycosis is imperative to minimize morbidity and mortality associated with the disease. If subtle facial pain and nasal blockage is neglected by the patient and

the primary healthcare provider, the diagnosis may be missed until the orbit is involved. Most common presenting signs in our study were those related to orbital involvement, that is, visual deterioration, ptosis, and ocular motility restriction. Nasal or palatal black eschar clinches the diagnosis but was seen in a few of our patients compared to one-third of the cases in multi-centric case series by Dave *et al.*<sup>[24]</sup> Further, intracranial involvement occurs from invasion of superior orbital fissure, ophthalmic vessels, cribriform plate, and not uncommonly, through carotid artery. One-third of the patients in our study showed intracranial extension, mainly in the form of cavernous sinus infiltration. One of the cases developed frontal lobe abscess. Hoenigl and co-workers have evaluated data from 18 countries and have reported intracranial involvement in 37% of the cases.<sup>[25]</sup>

The current standard of care involves reversal of immunosuppression, debridement of devascularized tissue, and systemic antifungal therapy.<sup>[26]</sup> Systemic antifungals alone are typically inadequate for eliminating the infection due to its angioinvasive nature, which leads to obliteration of local blood supply and rapid tissue necrosis that, in turn, limits the penetration of systemic drugs. Therefore, removal of devitalized tissue plays a key role in the management of ROCM.<sup>[26]</sup>

From 2015 onwards, a therapeutic algorithm incorporating transcutaneous retrobulbar amphotericin B (TRAMB) for moderate orbital disease has been employed in the routine management of invasive fungal rhino-orbital sinusitis (IFROS) cases.<sup>[26]</sup> Ashraf *et al.*<sup>[27]</sup> have found that IFROS patients who were treated with a modified treatment protocol including TRAMB had a lower risk of disfiguring exenteration without a perceptible increase in the risk of mortality. Sen *et al.*<sup>[28]</sup> observed usage of intraorbital AMB in 22% cases for a median of two (range, 1–9) injections. Dave and co-workers have reported use of TRAMB in one of their 58 cases, which had localized orbital apex involvement and resulted in complete regain of ocular motility.<sup>[24]</sup> Safi reports resolution of ptosis and ophthalmoplegia in a case of ROCM with associated cerebritis with adjuvant TRAMB therapy.<sup>[29]</sup> Walia *et al.*<sup>[30]</sup> instituted TRAMB in 51.8% cases and reported an overall mortality of 9.25%. The current study observed favorable outcome in cases with mild orbital disease in terms of function recovery with TRAMB. In cases of severe orbital disease with or without cranial extension, the current study noted a better survival, with TRAMB therapy, although statistically unrelated. There is paucity of data on efficacy and safety profile of TRAMB, and well-designed prospective randomized studies are advocated to impart better clarity on the topic.

Mortality rates have varied considerably in recent Indian studies on CAM. Table 5 depicts the comparison of orbital intervention, follow-up, and mortality in the current study with that reported in other recent literature. With TRAMB having better survival benefits and being globe-salvaging option, the call for orbital exenteration needs to be reviewed especially in patients with compromised lung function due to COVID-19 and resultant anesthesia risks. In our experience, orbital decompression and debridement appear to be a better alternative to exenteration in cases of extensive orbital involvement.

## Conclusion

CAM has emerged as an enormous threat to life and vision of patients. Uncontrolled diabetes mellitus and multifactorial immune suppression associated with COVID-19 plays

the pivotal role. Further research should aim to explicate whether a causal link exists between COVID-19 and ROCM. Early suspicion and timely diagnosis of mucormycosis at rhino-orbital stage is warranted in order to salvage life as well as visual function. TRAMB may serve as a favorable treatment modality in cases with limited orbital involvement.

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### Conflicts of interest

There are no conflicts of interest.

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