

## Main Article

Dr R Kurien takes responsibility for the integrity of the content of the paper



**Cite this article:** Kurien R *et al.* Revised workflow practices in the management of acute invasive fungal sinusitis during the coronavirus disease 2019 pandemic. *J Laryngol Otol* 2022;**136**:1314–1319. <https://doi.org/10.1017/S0022215122001888>

Accepted: 2 August 2022  
First published online: 16 August 2022

**Key words:**  
COVID-19; Paranasal Sinuses; Sinusitis; Mucormycosis

**Author for correspondence:**  
Dr Regi Kurien, Department of ENT,  
Christian Medical College, Vellore,  
Tamil Nadu, India – 632004  
E-mail: [regikurien@cmcvellore.ac.in](mailto:regikurien@cmcvellore.ac.in)

# Revised workflow practices in the management of acute invasive fungal sinusitis during the coronavirus disease 2019 pandemic

R Kurien<sup>1</sup> , L Varghese<sup>1</sup> , L M Cherian<sup>1</sup>, R Sundaresan<sup>1</sup>, M John<sup>1</sup>, M D Mammen<sup>1</sup>, R R Inja<sup>1</sup>, A Manesh<sup>2</sup>, H Paul<sup>3</sup>, P R Gurijala<sup>4</sup>, J S Michael<sup>5</sup>, M Thomas<sup>6</sup>, K P P Abhilash<sup>7</sup>, A M Varghese<sup>1</sup> and V Rupa<sup>1</sup>

Departments of <sup>1</sup>ENT, <sup>2</sup>Infectious Diseases, <sup>3</sup>Hospital Infection Control Committee, <sup>4</sup>Radiodiagnosis, <sup>5</sup>Microbiology, <sup>6</sup>Pathology and <sup>7</sup>Emergency Medicine, Christian Medical College, Vellore, India

## Abstract

**Objective.** To document changes in evaluation protocols for acute invasive fungal sinusitis during the coronavirus disease 2019 pandemic, and to analyse concordance between clinical and histopathological diagnoses based on new practice guidelines.

**Methods.** Protocols for the evaluation of patients with suspected acute invasive fungal sinusitis both prior and during the coronavirus disease 2019 period are described. A retrospective analysis of patients presenting with suspected acute invasive fungal sinusitis from 1 May to 30 June 2021 was conducted, with assessment of the concordance between clinical and final diagnoses.

**Results.** Among 171 patients with high clinical suspicion, 160 (93.6 per cent) had a final histopathological diagnosis of invasive fungal sinusitis, concordant with the clinical diagnosis, with sensitivity of 100 per cent, positive predictive value of 93.6 per cent and negative predictive value of 100 per cent.

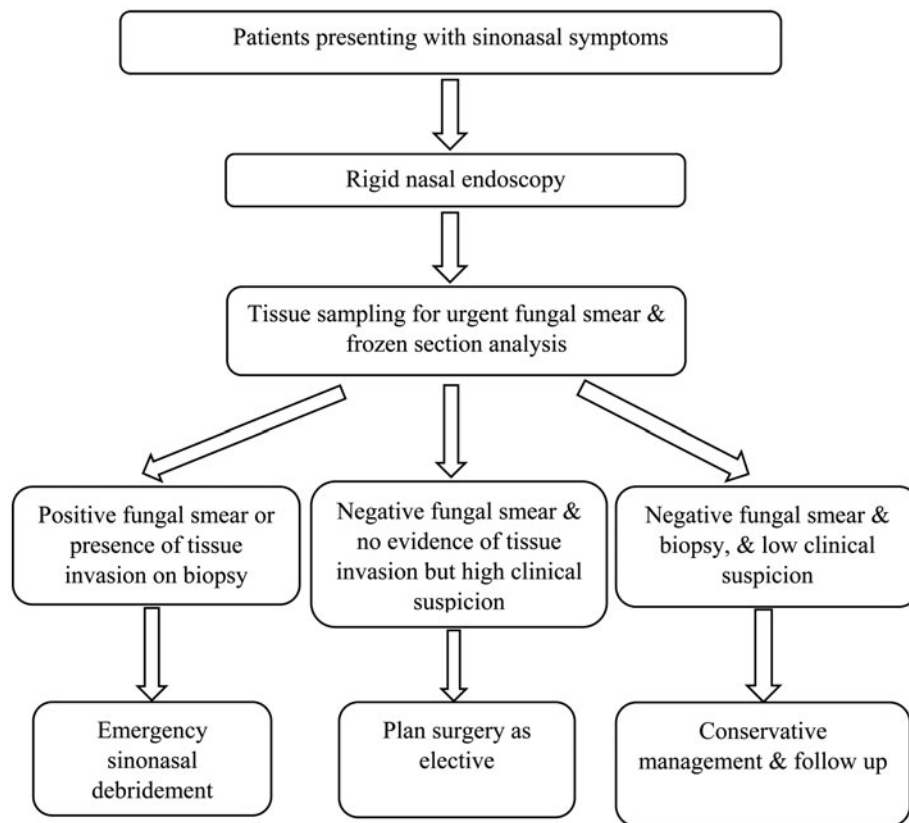
**Conclusion.** The study highlights a valuable screening tool with good accuracy, involving emphasis on 'red flag' signs in high-risk populations. This could be valuable in situations demanding the avoidance of aerosol-generating procedures and in resource-limited settings facilitating early referral to higher level care centres.

## Introduction

Acute invasive fungal sinusitis is a rapidly progressive angio-invasive fungal infection associated with serious morbidity and mortality. The population most affected include individuals with uncontrolled diabetes mellitus, those with haematological malignancies, post-organ transplantation patients and individuals on immunosuppressive drugs.<sup>1</sup> Recently, the coronavirus disease 2019 (Covid-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a global pandemic.<sup>2</sup> Although the first wave of Covid-19 showed an increase in the incidence of mucormycosis, the second wave was associated with an exponential surge, with at least 14 872 cases in India as of 28 May 2021.<sup>3</sup>

Surgical debridement, systemic antifungal therapy and prompt correction of the underlying systemic disease are necessary for the treatment of acute invasive fungal sinusitis.<sup>4</sup> Until the onset of Covid-19 associated mucormycosis, the usual protocol for investigating patients suspected to have acute invasive fungal sinusitis included diagnostic nasal endoscopy, with sampling of tissues for fungal smear and histopathological examination. Surgical debridement was planned based on objective confirmation of the diagnosis. However, the Covid-19 pandemic brought out many changes at the institutional and personnel level in the way patients were triaged, and consultations were conducted in the emergency department, out-patient clinic and in-patient wards. Strict adherence to infection control practices, and the discontinuation of high aerosol-generating procedures (AGPs) such as pre-operative nasal endoscopy and tissue sampling, led to patients being enlisted for emergency surgery with a presumptive diagnosis based exclusively on a high index of clinical suspicion, without prior objective confirmation of the clinical diagnosis. Moreover, the implementation of stringent protective measures, and the segregation between coronavirus and non-coronavirus zones within the institution, led to changes in clinical practice guidelines during this Covid-19 pandemic.<sup>5</sup>

This study aimed to document the various changes formulated in the clinical workflow practice of evaluating and treating patients with acute invasive fungal sinusitis during the Covid-19 pandemic. We also aimed to analyse the concordance between the pre-operative clinical diagnosis based on the new practice guidelines and the final diagnosis.



**Fig. 1.** Pre-coronavirus disease 2019 pandemic workflow protocol.

## Materials and methods

### Study design

This retrospective study compared the methods of clinical evaluation, diagnosis and management of patients with acute invasive fungal sinusitis followed in our department during two time periods, namely the pre-Covid-19 era and during the Covid-19 pandemic mucormycosis surge. Relevant data, including demographics, initial clinical diagnosis and final diagnosis, were collected from institutional records.

### Participants

All patients seen in the emergency department, out-patient clinic and during in-patient consultations with sinonasal symptoms from 1 May to 30 June 2021 were included in the study.

### Statistical analysis

The concordance between the clinical and the final diagnosis based on microbiological and histopathological results using the revised workflow protocol was analysed using McNemar's chi-square test. The sensitivity, specificity, and positive and negative predictive values were also calculated for the new protocol.

### Protocols

#### Pre-pandemic workflow protocol

The pre-coronavirus pandemic workflow protocol is shown in Figure 1. Over the last decade, patients who presented with sinonasal symptoms suggestive of acute invasive fungal sinusitis underwent rigid nasal endoscopy, and representative samples from unhealthy appearing tissues were sent for fungal smear and histopathological examination. Frozen section analysis was performed in liaison with the pathologist whenever

this facility was available from 8am to 4pm. If the nasal mucosa appeared normal on endoscopy, tissue was taken from the middle turbinate.

In addition to this, all patients underwent imaging in the form of contrast-enhanced computed tomography (CT) of the paranasal sinuses. If there was evidence of intracranial or intra-orbital involvement on contrast-enhanced CT, contrast-enhanced magnetic resonance imaging of the paranasal sinuses and brain was performed to determine the extent of involvement.

Patients with a positive fungal smear test result or with fungal tissue invasion on frozen section analysis subsequently underwent emergency sinonasal debridement under general anaesthesia followed by antifungal therapy. Although surgery was directed based on sinonasal involvement on imaging, a study performed from 2017 to 2019 led us to revise our surgical protocol, wherein all sinuses were widely opened and debrided irrespective of their involvement on imaging.<sup>6</sup> Patients with negative fungal smear and histopathological findings, and with significant findings on radiology, were selected electively for functional endoscopic sinus surgery.

#### Revised pandemic workflow protocol

With the emergence of the second wave of the Covid-19 pandemic, there was a tremendous surge in the number of patients with mucormycosis. The high level of infectivity associated with Covid-19 infection, and the aerosol-generating potential of procedures such as rigid nasal endoscopy, led to a review of our current diagnostic protocols. In view of the above, it was decided to revise the workflow protocol. Specifically, we discontinued the practice of performing diagnostic nasal endoscopy and tissue sampling for fungal smear and histopathological examination, and proceeded with surgical debridement based solely on the clinical diagnosis.

In addition to the regular conditions considered as indicating a high-risk status, any patients presenting with or

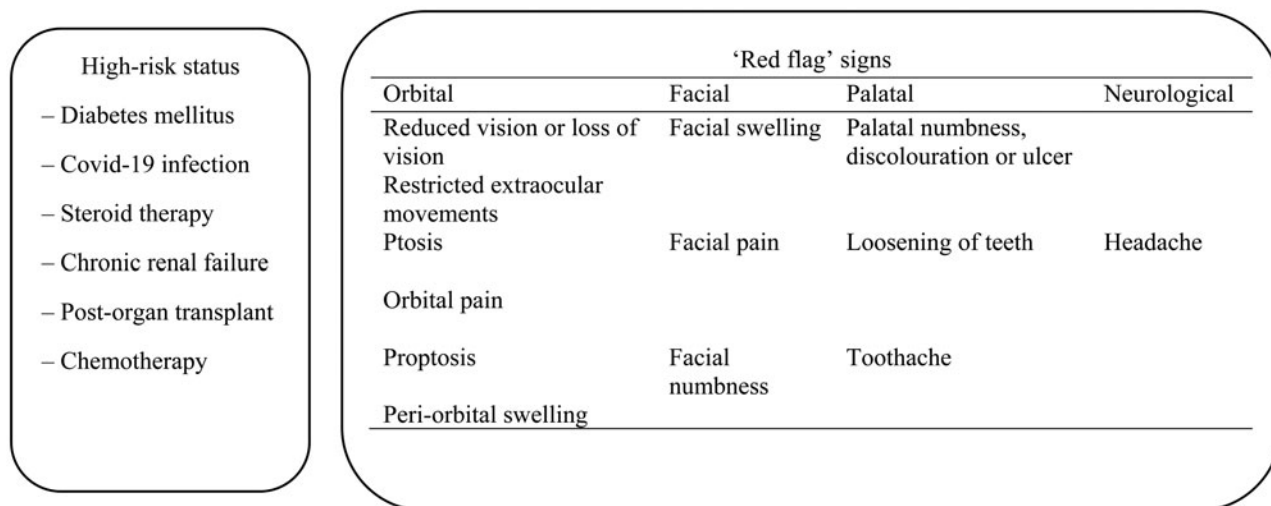


Fig. 2. Clinical criteria for high suspicion in the revised workflow protocol. Covid-19 = coronavirus disease 2019

recovered from Covid-19 infection, or who had received prior treatment with steroids, were also included in this category. Figure 2 depicts the sinonasal symptoms considered as ‘red flags’. The workflow protocol was revised, wherein the presence of one or more of these red flag symptoms in a patient with a high-risk status led to a high clinical suspicion of invasive fungal sinusitis. All patients underwent contrast-enhanced CT of the paranasal sinuses. Irrespective of the extent of radiological involvement, all patients in whom there was a high index of clinical suspicion were enlisted for emergency sinonasal debridement, as shown in Figure 3.

This revised workflow was communicated to the physicians in the emergency department, who were encouraged to request appropriate imaging and refer patients early to ENT. These measures ensured minimal delay with regard to imaging, and enabled most patients to undergo surgery within 24–48 hours of arrival at our hospital. The changes made at the institutional and personnel levels to combat and manage the surge in mucormycosis cases are shown in Table 1.

**Results**

During the two-month study period, a total of 179 patients with sinonasal symptoms were screened for acute invasive fungal sinusitis in the emergency department, out-patient clinic and in-patient wards. The cohort consisted of 131 males and

48 females, with a mean age of 50 years (range, 18–80 years). Type 2 diabetes mellitus was the most common co-morbidity, seen in 148 patients (82.7 per cent). Of the patients, 139 (77.7 per cent) were diagnosed with concomitant Covid-19 infection or had recently recovered from it, and 68 patients (38 per cent) had received steroids as part of the treatment for Covid-19 infection.

Based on the revised workflow protocol, there was a high clinical suspicion of acute invasive fungal sinusitis in a total of 171 patients. Acute invasive fungal sinusitis was not suspected in eight patients. Most commonly, the patients suspected of having acute invasive fungal sinusitis had facial symptoms, followed by orbital and palatal symptoms (Table 2). Facial swelling (50.9 per cent), pain and numbness predominated the facial symptoms, while peri-orbital swelling, restricted ocular movements, orbital pain and ptosis were the predominant orbital symptoms. Palatal symptoms were seen in 76 patients (44.4 per cent), while nasal symptoms were seen in only 49 patients (28.7 per cent). Among the patients with palatal symptoms, palatal discoloration or ulceration was seen in 52 patients (30.4 per cent), while loosening of teeth and toothache were seen in 28 patients (16.4 per cent) and 20 patients (11.7 per cent) respectively.

Of the 171 patients, 164 underwent bilateral endoscopic sinonasal debridement with additional surgical procedures depending on the extent of the disease. Seven patients did not undergo surgery.

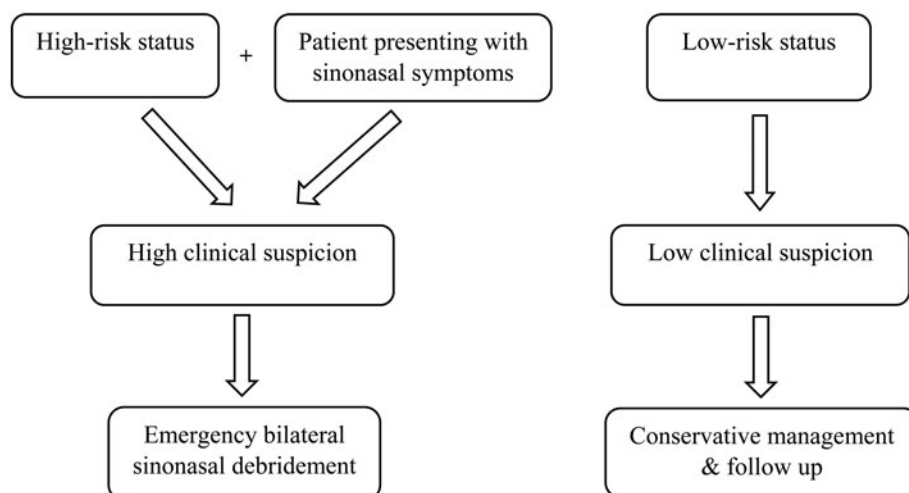


Fig. 3. Revised workflow protocol during coronavirus disease 2019 pandemic.

**Table 1.** Changes made at institutional and personnel levels during Covid-19 pandemic

Institutional level
– Separation of Covid-19 & non-Covid-19 services in emergency department
– Covid-19 testing for all patients before admission
– Separate ward for Covid-19 patients
– Zoning of operating theatres into green, orange & red for non-Covid-19, suspect & Covid-19 positive patients, respectively
– Provision of multiple simultaneous 24-hour, 7-day operating theatres for invasive fungal sinusitis cases
– High-pressure, laminar flow operating theatres for Covid-19 positive patients
– Provision for 24-hour fungal smear examination & reporting
– Commencement of 24-hour frozen section biopsy
– Commencement of multi-departmental clinic constituting infectious diseases, ENT & endocrinology departments
Personnel level
– Use of personal protective gear such as N95 masks, face shield & hazmat suit, with strict donning & doffing protocols

Covid-19 = coronavirus disease 2019

Among the 171 patients in whom there was a high clinical suspicion of acute invasive fungal sinusitis, 160 patients (93.6 per cent) had a final histopathological diagnosis of invasive fungal sinusitis, with acute invasive fungal sinusitis in 96 patients, chronic invasive fungal sinusitis in 1 patient and chronic invasive granulomatous fungal sinusitis in 3 patients. Mixed invasive fungal sinusitis was seen in 60 patients. The presence of a concomitant fungal ball was seen in 13 patients with acute invasive fungal sinusitis and in 8 patients with mixed invasive fungal sinusitis. Of the remaining 11 patients in whom there was a high clinical suspicion of acute invasive fungal sinusitis, 10 were proven to have chronic bacterial rhinosinusitis on histopathology and 1 patient had acute rhinosinusitis (Table 3).

Among the eight patients in whom there was no clinical suspicion of acute invasive fungal sinusitis, none had acute invasive fungal sinusitis as the final diagnosis. Three were proven to have chronic rhinosinusitis, two had acute rhinosinusitis and one patient had herpes zoster ophthalmicus. Two patients who did not have a biopsy proven diagnosis continued to be well at the last follow up.

On analysis, this new screening criteria for acute invasive fungal sinusitis, based purely on history and clinical examination, was statistically significantly associated with final histopathological diagnoses of invasive fungal sinusitis ( $p = 0.001$ ), with sensitivity of 100 per cent, a positive predictive value of 93.6 per cent and a negative predictive value of 100 per cent, though the specificity was only 42.1 per cent.

## Discussion

The current Covid-19 pandemic brought about a global change in the way in which medical consultations were performed at out-patient, in-patient and emergency levels. The surge in the Covid-19 pandemic witnessed a parallel escalation of mucormycosis cases during the first wave in India, followed by a much greater and sudden explosion of mucormycosis cases during the second wave. The discontinuation of AGPs such as nasal endoscopy, in accordance with infection control

**Table 2.** Demographics and clinical presentations\*

Parameter	Patients (n (%))
Gender	
– Male	131 (73.18)
– Female	48 (26.82)
Co-morbidities	
– Diabetes mellitus	148 (82.68)
– Covid-19 current	82 (45.81)
– Covid-19 recovered	57 (31.84)
– Steroids	68 (37.99)
– Chronic renal failure	7 (3.91)
– Hypertension	103 (57.54)
– Others	29 (16.20)
– No co-morbidities	4 (2.23)
Clinical presentation <sup>†</sup>	
Nasal symptoms	49 (28.65)
– Nasal obstruction	21 (12.28)
– Nasal discharge	9 (5.26)
– Blood-stained discharge	29 (16.96)
– No nasal complaints	122 (71.35)
Orbital symptoms	124 (72.51)
– Orbital pain	44 (25.73)
– Ptosis	56 (32.75)
– Peri-orbital swelling	69 (40.35)
– Proptosis	35 (20.47)
– Diplopia	5 (2.92)
– Restricted extraocular movements	64 (37.43)
– Decreased vision	25 (14.62)
– Loss of vision	30 (17.54)
– No orbital symptoms	47 (27.49)
Facial symptoms	134 (78.36)
– Facial numbness	59 (34.50)
– Facial swelling	87 (50.88)
– Facial pain	85 (49.71)
– Rash	1 (0.58)
– No facial symptoms	37 (21.64)
Palatal symptoms	76 (44.44)
– Loose tooth	28 (16.37)
– Toothache	20 (11.70)
– Palatal discolouration, swelling or ulcer	52 (30.41)
– Tooth numbness	4 (2.34)
– No palatal complaints	95 (55.56)
Headache	72 (42.11)
Neurological symptoms	34 (19.88)
– Hemiplegia	7 (4.09)
– Altered sensorium	10 (5.85)
– CN palsy other than II, III, IV, V, VI & VIII CN palsy	21 (12.28)

\*Total n = 179. <sup>†</sup>n = 171. Covid-19 = coronavirus disease 2019; CN = cranial nerve

**Table 3.** Final diagnoses

Final diagnosis	Patients (n (%))
Invasive fungal sinusitis	160 (93.56)
AIFS	156 (91.22)
– AIFS alone	83 (48.54)
– AIFS + CGFS	47 (27.49)
– AIFS + CIFS	4 (2.34)
– AIFS + fungal ball	13 (7.60)
– AIFS + CIFS + CGFS	1 (0.58)
– AIFS + CGFS + fungal ball	7 (4.09)
– AIFS + CIFS + fungal ball	1 (0.58)
CGFS	3 (1.75)
CIFS	1 (0.58)
Chronic rhinosinusitis	13 (7.60)
Acute sinusitis	3 (1.75)

AIFS = acute invasive fungal sinusitis; CIFS = chronic invasive fungal sinusitis; CGFS = chronic invasive granulomatous fungal sinusitis

practices, meant that the routine practice of endoscopic tissue sampling for histopathological and fungal culture testing, to diagnose invasive fungal sinusitis before embarking on definitive surgical procedures, could not be performed. This necessitated a change in the protocols for evaluating suspected invasive fungal sinusitis cases. Rather than objective confirmation of the clinical diagnosis by nasal endoscopy and tissue sampling, treatment decisions in our institution were based on patients' clinical presentations. This study investigated the accuracy of this pre-operative clinical diagnosis.

Our study showed a high level of agreement between clinical suspicion and the final histopathological diagnosis, with 100 per cent sensitivity. None of the patients in whom there was a low clinical suspicion later had evidence of invasive fungal sinusitis on histopathology. Among the patients with histopathologically proven invasive fungal sinusitis, 48.5 per cent had acute invasive fungal sinusitis alone, while 35.1 per cent had mixed fungal sinusitis. Concomitant association with fungal ball presence was seen in 12.3 per cent of patients.

Acute invasive fungal sinusitis is often associated with an immunocompromised host, with the most common immunocompromised state being diabetes mellitus.<sup>7</sup> The presence of Covid-19 infection causes impairment of cell-mediated immunity, causing immune dysregulation and decreased cluster of differentiation 4 and 8 counts, thereby increasing vulnerability to fungal infections.<sup>8</sup> The high prevalence of diabetes mellitus in India, combined with the surge in Covid-19 cases and the widespread use of steroids during the study period, are thought to be the common predisposing factors behind the unprecedented number of mucormycosis cases.<sup>9,10</sup> In our study cohort too, diabetes mellitus was the most common immunocompromised state, followed by active and recovered Covid-19 infection. A history of steroid treatment was present in 37.9 per cent of patients.

Facial (78.4 per cent) and orbital (72.5 per cent) symptoms were the predominant presenting symptoms in most patients in this cohort. This was followed by palatal symptoms (44.4 per cent) and headache (42.1 per cent). These findings are in contrast to our previous study from the same institution during the pre-Covid-19 era, where headache (66.7 per cent) was the commonest symptom.<sup>6</sup> It was also noted that the incidence of

facial and orbital symptoms was much higher during the Covid-19 pandemic compared to the pre-Covid-19 period.

Although sinonasal in origin, the disease process showed a conspicuous paucity of nasal symptoms in the cohort, with only 28.7 per cent of patients presenting with nasal symptoms. The importance of not disregarding non-specific subtle signs in high-risk patients is highlighted by the fact that a high proportion of patients presented with symptoms such as facial pain (49.7 per cent), facial swelling (50.9 per cent), facial numbness (34.5 per cent), peri-orbital swelling (40.4 per cent) and headache (42.1 per cent). Clinicians such as ophthalmologists and neurologists may be the first to see these patients in view of the high rates of non-sinonasal symptoms. Hence, it is necessary to create greater awareness among these clinicians, and at the emergency department level, regarding the presentation of acute invasive fungal sinusitis during the Covid-19 pandemic.

Nasal endoscopy does play a key role in the pre-operative assessment of patients with invasive fungal sinusitis, enabling visualisation of intranasal lesions, and aiding the procurement of representative tissue samples for fungal smear and histopathological examination to establish a reliable pre-operative diagnosis.<sup>11</sup> Endoscopy guided biopsies for frozen section analysis have been shown to be highly reliable in establishing a confirmatory diagnosis.<sup>12</sup> Although not performed in many centres worldwide, the pre-coronavirus protocol of pre-operative frozen section analysis, whenever feasible, helped us better counsel the patients and plan a one-staged definitive surgery. In extensive cases, with involvement of the orbit requiring orbital exenteration, a pre-operative confirmatory diagnosis was also mandatory. Furthermore, in patients not willing or unfit for surgery, a pre-operative histopathological diagnosis can aid earlier initiation of antifungal therapy. As the frozen section reports were available in 1 hour at our institution, there was no substantial delay in surgery, which thereby prevented causing additional harm to the patients. However, our study shows that, in demanding situations with AGP restrictions, pre-operative nasal endoscopy and biopsy can be substituted with a highly sensitive screening approach, whereby clinical suspicion is determined based purely on history and clinical findings.

- The coronavirus disease 2019 pandemic was associated with a sudden surge in mucormycosis
- Most patients presented with facial followed by orbital and palatal symptoms, with inconspicuous sinonasal symptoms
- The revised protocol based on identification of subtle 'red flag' symptoms in high-risk patients enabled accurate clinical diagnosis of acute invasive fungal sinusitis
- The revised algorithm can be used to screen high-risk patients in demanding situations with restrictions on pre-operative endoscopy and tissue sampling

Our study indicates that good history and clinical evaluation, with emphasis on the above described 'red flag' signs in a high-risk population, are sufficient to arrive at an accurate clinical diagnosis of invasive fungal sinusitis. The finding that all patients who were diagnosed clinically as negative for invasive fungal sinusitis were also negative on histopathology is encouraging. A clinical diagnosis based on the above algorithm could be useful not only in situations where facilities for nasal endoscopy, frozen section analysis and fungal smear testing are not available, but also among general practitioners and non-ENT physicians dealing with such patients. The revised workflow protocol that we adopted during the

Covid-19 pandemic period enabled early diagnosis, prompt and complete debridement of affected areas, and efficient utilisation of personnel and other resources.

**Acknowledgements.** We would like to thank all the faculty and residents in the Department of ENT for their participation and encouraging support towards this project. We would also like to thank Dr Grace Rebekah for her kind input towards the statistical analysis.

**Competing interests.** None declared.

## References

- deShazo RD, O'Brien M, Chapin K, Soto-Aguilar M, Gardner L, Swain R. A new classification and diagnostic criteria for invasive fungal sinusitis. *Arch Otolaryngol Head Neck Surg* 1997;**123**:1181–8
- Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020;**5**:536–44
- Raut A, Huy NT. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? *Lancet Respir Med* 2021;**9**:e77
- Turner JH, Soudry E, Nayak JV, Hwang PH. Survival outcomes in acute invasive fungal sinusitis: a systematic review and quantitative synthesis of published evidence. *Laryngoscope* 2013;**123**:1112–18
- Indian Council of Medical Research. Evidence based advisory in the time of COVID-19 (screening, diagnosis & management of mucormycosis). In: [https://www.icmr.gov.in/pdf/covid/techdoc/Mucormycosis\\_ADVISORY\\_FROM\\_ICMR\\_In\\_COVID19\\_time.pdf](https://www.icmr.gov.in/pdf/covid/techdoc/Mucormycosis_ADVISORY_FROM_ICMR_In_COVID19_time.pdf) [9 September 2022]
- Mallesappa V, Rupa V, Varghese L, Kurien R. Avoiding repeated surgery in patients with acute invasive fungal sinusitis. *Eur Arch Otorhinolaryngol* 2020;**277**:1667–74
- Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B *et al*. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. *Med Mycol* 2006;**44**:335–42
- Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. *Mycopathologia* 2020;**185**:599–606
- John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. *J Fungi (Basel)* 2021;**15**:298
- Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr* 2021;**15**:102146
- Fernandez IJ, Crocetta FM, Demattè M, Farneti P, Stanzani M, Lewis RE *et al*. Acute invasive fungal rhinosinusitis in immunocompromised patients: role of an early diagnosis. *Otolaryngol Head Neck Surg* 2018;**159**:386–93
- Ghadiali MT, Deckard NA, Farooq U, Astor F, Robinson P, Casiano RR. Frozen-section biopsy analysis for acute invasive fungal rhinosinusitis. *Otolaryngol Head Neck Surg* 2007;**136**:714–19