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Original Article

Exploring Fungal Rhinosinusitis-Epidemiological Profile, Expanding MALDITOF-MS Diagnostic Profiling, Therapeutic Responses, Failures and Learning's Over a Three-Year Period

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ABSTRACT

Introduction: Fungal Rhinosinusitis (FRS) is a growing concern in both immunosuppressed and immunocompetent patients and involves a broad spectrum of immune and pathological responses induced by different types of fungi. The aims of this study were to determine the type of fungi causing Rhinosinusitis and to correlate type of FRS with respect to the histopathological findings, causative fungi, immune status, clinical presentation, other co-morbid conditions, treatment and outcome **Materials and Methods:** This retrospective study on FRS was done on 92 non-duplicate specimens of suspected cases of FRS over three-year period. Samples from patients of suspected FRS were processed for fungal smear KOH examination and fungal culture. Identification of fungi was done by both conventional and automated methods using MALITOF-MS (Matrix Assisted Laser Desorption Ionization Time of Flight-Mass Spectrometry). **Results:** Out of 92 non-duplicate specimens of suspected cases of FRS received during study period; fungal smear or histopathological examination for fungal hyphae was positive in 43 cases and fungal culture was positive in 42 cases with 48 fungal isolates. *Aspergillus flavus* (43.75%) was isolated maximally followed by *Rhizopus* sp. (20.8%). Mixed infection with two types of fungi was also seen. *Aspergillus* FRS was mainly Allergic in immunocompetent host and Acute invasive in immunocompromised hosts. Infection with *Zygomycetes* was largely invasive and was seen in immunocompromised hosts with poor prognosis. Other fungi like *Schizophyllum commune, Bipolaris* and *Paecilomyces* were associated with Allergic FRS. *Scedosporium apiospermum* was associated with chronic non-specific FRS in immunocompetent patient. *Fusarium* infection was seen both as mere colonization and invasive sinusitis. *Candida* species were isolated mainly in mixture with mycelial fungi and were associated with invasive FRS. **Conclusion:** Our study depicts that a variety of fungi may cause FRS and the type of FRS caused by different types of fungi depend upon type of host. So, it is pertinent to monitor and study the types of fungi causing infections in different patient populations. Automated methods like MALDITOF -MS are an excellent tool in the definitive and timely identification of fungi resulting in timely and appropriate management.

Keywords: FRS, Immunocompetent, Immunocompromised, Automated.

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INTRODUCTION

Fungal Rhinosinusitis (FRS) is the fungal infection of nose and paranasal sinuses affecting 20% of population.[1] It is a growing concern in both immunosuppressed and immunocompetent patients. FRS involves a broad spectrum of immune and pathological responses. Broadly, FRS can be classified into Non-invasive and Invasive. Non-Invasive includes Allergic Fungal Rhinosinusitis, Eosinophilic Fungal Rhinosinusitis, Localized colonization and Fungal ball. Invasive includes Acute invasive (Fulminant), Chronic invasive and Granulomatous invasive. The consensus of terminologies and categorization of FRS were made by International Society for Human and Animal Mycology (ISHAM) working group on fungal rhinosinusitis.[1] There have been an increased prevalence of invasive cases of FRS due to increase in the number of immunocompromised/ immunosuppressed patients due to transplant, chemotherapy

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etc.[2] Poorly controlled diabetes and prolonged use of broad spectrum antibiotics are also risk factors for FRS.[3] Invasive Rhinosinusitis can be life-threatening and fatal in these patients. So, it is pertinent to know the clinicopathological type of FRS and the causative fungi for the optimum management of the cases. The fungi causing FRS mainly include *Aspergillus* sp., *Zygomycetes* and *Dematiaceous* fungi. *Aspergillus* sp. is involved in both Allergic and invasive type of FRS. With the increase in number of immunocompromised/immunosuppressed population and increased urbanization, other fungi of low virulence have also been found to be causing invasive or non-invasive FRS. So, keeping the newer aspects of FRS in mind, the aim of our study was to determine the type of fungi causing Rhinosinusitis and to correlate type of FRS with respect to the histopathological findings, causative fungi, immune status, clinical presentation, other co-morbid conditions, treatment and outcome.

MATERIALS AND METHODS

This study was conducted in a tertiary health care set-up between January 2015 to November 2017. The Samples from patients of suspected FRS were processed for Fungal smear KOH examination and Fungal culture. These samples mainly included tissue or debris from sinuses following Functional Endoscopic Sinus Surgery (FESS), mucopurulent exudates in sinus cavity, allergic mucin, nasal crust, fungal ball, oedematous mucosa, nasal polyp and purulent nasal discharge. Fungal culture was performed by inoculating the specimen on two tubes of Sabouraud's Dextrose agar (SDA) media (with and without antibiotics) which were incubated at 37°C and 25°C. Examination of SDA slants was done daily for three weeks. Identification of the fungi was done by growth characteristics and morphology, Lactophenol Cotton Blue mount (LPCB) examination of fungal growth, Slide culture and MALDI-TOF Vitek MS (Biomerieux Inc, France). Fungal isolates were correlated with fungal smear and histopathological examination (if available). Clinical details of the patients were collected from the medical record department of the hospital.

RESULTS

A total of 92 non-duplicate specimens of suspected cases of FRS were received during study period. Out of these 92 specimens, fungal smear or histopathological examination for fungal hyphae was positive in 43 cases and fungal culture was positive in 42 cases. The total numbers of fungal isolates from 42 culture positive cases were 48 (forty-eight). The total numbers of patients with FRS (Fungal smear positive or histopathology positive or fungal culture positive or all positive) were 53 (Fifty-three). Table 1 depicts the results of Fungal smear/histopathological examination and fungal culture.

Gender wise distribution of cases

Out of 92 specimens received from suspected cases of FRS patients, 60 were from male and 32 were from female patients (1.8:1). Out of 53 patients with lab confirmed diagnosis of FRS, 36 were male and 17 were female (2.1:1). Age of the patient varied from 4 years to 76 years. 36.9% of patients belonged to the age group 31 years to 50 years.

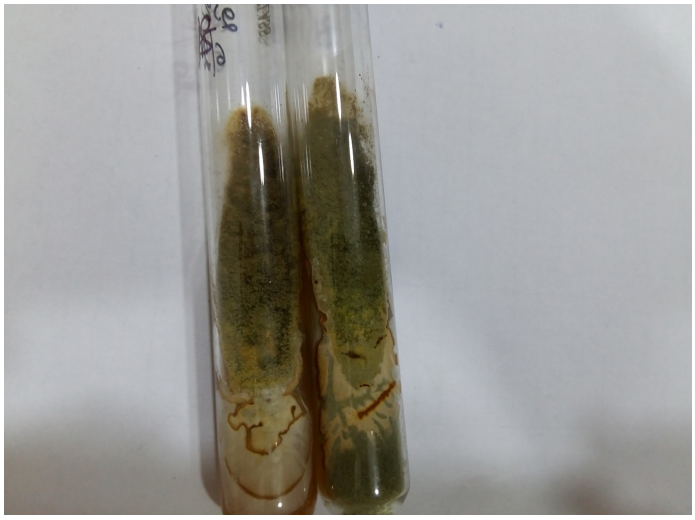

Figure 1: Growth of Aspergillus flavus on Sabouraud's Dextrose Agar.

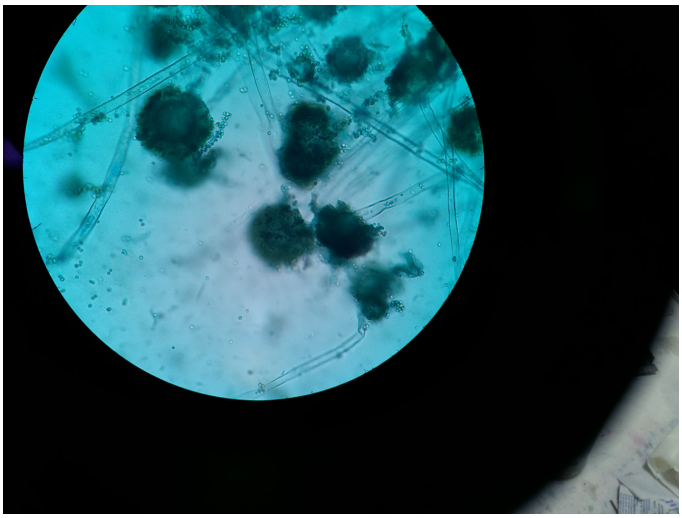

Figure 2: LPCB mount of culture growth showing Aspergillus flavus (400X).

Distribution of fungal species

The frequency of isolation of different types of fungi in patients with sinusitis is shown in Table 2. *Aspergillus flavus* (43.75%) was isolated maximally followed by *Rhizopus* sp. (20.8%).

The frequency of isolation of various types of fungi as mixed growth is shown in Table 3.

FRS due to *Aspergillus* species

Table 4 shows the association of *Aspergillus flavus* with the type of FRS, associated risk factors and management. Figure 1 and 2 shows Fungal culture growth and LPCB mount examination findings from a sinonasal tissue examination respectively. *A. versicolor* was isolated from a 32 years immunocompetent

Table 1: Depiction of the results of fungal smear/histopathological examination and fungal culture of 53 specimens which were positive for fungus.

Comparative between Direct microscopic examination and Fungal culture	Number of cases
Number of fungal smear KOH or Histopathology positive but culture negative.	11
Number of fungal culture positive and fungal smear/histopathology negative.	10
Both fungal smear/histopathology and fungal culture positive.	32

Table 2: Frequency of isolation of various types of fungi in patients with FRS.

Type of fungal isolate	Number (%)
Aspergillus flavus	21 (43.75)
Aspergillus versicolor	01 (2.08)
Rhizopus sp.	10 (20.8)
Fusarium sp.	02 (4.16)
Syncephalastrum sp.	01 (2.08)
Schizophyllum commune	01 (2.08)
Bipolaris sp.	01 (2.08)
Scedosporium sp.	01 (2.08)
Exserohilum sp.	01 (2.08)
Acremonium sp.	01 (2.08)
Paecilomyces sp.	01 (2.08)
Candida species	07 (14.5)

Table 3: Mixed fungal growth in cases of FRS.

Type of fungi as mixed growth	Number of cases
Rhizopus sp.+*Candida tropicalis*	02
Rhizopus sp.+*Aspergillus flavus*	01
Rhizopus sp.+*Candida albicans*	01
Aspergillus flavus+*Fusarium* sp.	01
Aspergillus flavus+*Candida auris*	01

female with history of recurrent nasal polyps. Histopathological Examination (HPE) showed eosinophil rich chronic inflammatory cell infiltrate.

Zygomycetes and FRS

Amongst *Zygomycetes, Rhizopus* sp. (10, 20.8%) and *Syncephalastrum* sp. (01, 2.08%) were isolated in culture. In all these cases, Fungal smear KOH/Histopathological examination also showed fungal hyphae suggestive of *Zygomycetes. Syncephalastrum* sp. was isolated from a 59 years immunocompetent male patient with Sphenoid sinusitis (Clinically non-invasive FRS). FESS was done followed by Itraconazole. After culture report, patient was put on Posaconazole. Patient remained for follow up for two years with no relapse/recurrence.

Table 5 depicts the cases of FRS due to *Rhizopus* sp. with respect to type of FRS and other clinical correlates. Figures 3-5 shows HPE findings, Fungal KOH examination and culture growth respectively from a case of FRS due to *Rhizopus* sp.

Fusarium and FRS

Fusarium sp. was isolated in two cases. The details of these two cases are given in Table 6.

The other fungi which were also isolated in cases of FRS are described in Table 7.

Candida species and FRS

Candida species were isolated mainly in mixture with mycelial fungi (*Rhizopus* sp. or *Aspergillus flavus*) and were associated with invasive FRS. *Candida* species (*C. rugosa, C. glabrata* and *C. auris*) were the only causative agent of FRS in three cases. All these three cases were immunocompromised (post liver transplant, post kidney transplant and Chronic renal disease with diabetes mellitus respectively) and showed unfavorable outcome.

Fungal smear/HPE positive but culture negative

A total of 11 number of cases showed presence of fungal hyphae on Direct microscopic examination (Fungal smear KOH/ Histopathology) but their fungal culture remained sterile after 3 weeks of incubation. Out of these 11 cases, six showed broad, sparsely septate fungal hyphae suggestive of *Zygomycetes* and five showed thin, septate, fungal hyphae on direct microscopic examination.

DISCUSSION

A variety of fungi may cause different types of FRS. In our study, *Aspergillus flavus* (43.75%) was the commonest isolate followed by *Rhizopus sp.* (20.8%) and *Candida* species (14.5%). Krishnan KU *et al.* also reported the maximum isolation of *A. flavus* (52%) in their study.[4]

In our study, out of 21 cases of FRS due to *A. flavus*, 13 were cases of Allergic FRS or Nasal polyp with good response to treatment and eight were cases of Acute or Chronic invasive FRS in immunocompromised patients with mixed outcome. Khan MA *et al.* in their study found that out of 23 cases of *Aspergillus* FRS, non-invasive disease was seen in 13 (56.52%) and invasive in 6 (26.09) patients. In 4 (17.39%) patients,

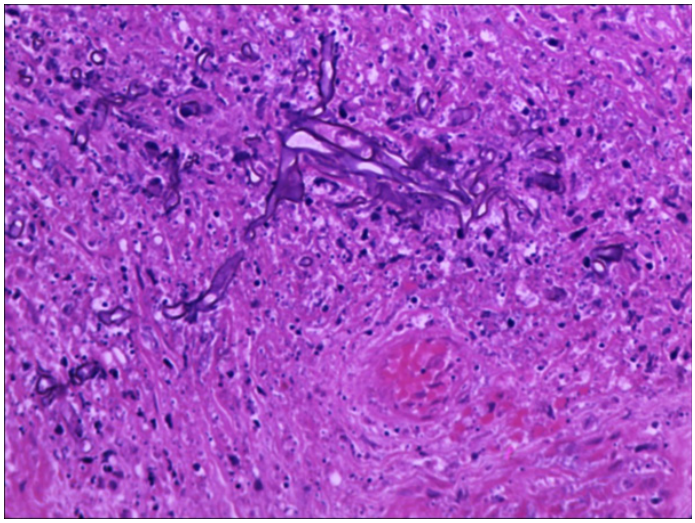

Figure 3: Histopathological examination of Sinonasal tissue suggestive of Zygomycetes.

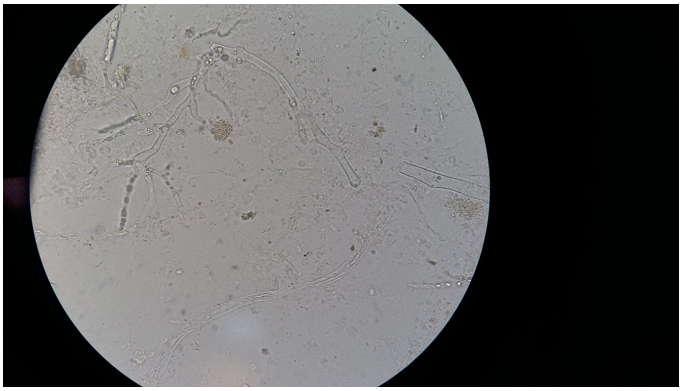

Figure 4: Fungal KOH examination of sinus tissue suggestive of Zygomycetes (400X).

Table 4: Details of cases with *Aspergillus* FRS.

Type of FRS	Number of cases	Underlying risk factors	Treatment	Type of FRS
Allergic	10	Immunocompetent (08) Diabetes mellitus (02).	FESS with /without Itraconazole/ Voriconazole and topical steroids/ saline irrigation.	Good
Nasal polyp	03	Immunocompetent	FESS with topical steroids/saline irrigation.	Good
Acute invasive	06	Post renal/liver transplant, on steroids, Carcinoma patient on chemotherapy, Diabetes mellitus.	Extended FESS with Amphotericin B and/or Voriconazole.	Expired: 03 Recovered: 03
Chronic invasive	01	Post renal transplant	FESS with Amphotericin B and Voriconazole.	Recovered
Granulomatous invasive	01	Diabetes mellitus	FESS with Voriconazole.	Expired

Table 5: FRS due to *Rhizopus* sp. with respect to type of FRS and clinical correlates.

Type of Sinusitis	Underlying illness	Treatment	Outcome
Necrotizing, tissue invasive fungal sinusitis	Post renal transplant.	FESS+Amphotericin B+Posaconazole	Expired
Invasive Fungal sinusitis (*Rhizopus* sp.+C.*tropicalis*)	Chronic kidney disease, cortical venous thrombosis, Diabetes.	Amphotericin B+Posaconazole	Poor outcome, LAMA
Invasive Fungal sinusitis	Carcinoma Ovary with metastasis-on chemotherapy.	Amphotericin B	Expired
Necrotizing angioinvasive Fungal sinusitis (*Rhizopus* sp. +A.*flavus*)	Crescentic glomerulonephrits-on steroids, Diabetes mellitus.	FESS+Amphotericin B	LAMA
Necrotizing, invasive fungal sinusitis	Chronic kidney disease, Diabetes mellitus.	Amphotericin B	LAMA
Chronic active sinusitis (*Rhizopus* sp.+C. *albicans*)	Diabetes mellitus, Lung infection, Pansinusitis and orbital cellulitis.	Amphotericin B	LAMA
Chronic fungal sinusitis	No risk factor.	FESS+ Amphotericin B	Recovered-Discharged.
Invasive fungal rhinosinusitis (*Rhizopus* sp.+C. *tropicalis*)	Bone marrow transplant patient.	Amphotericin B+Posaconazole.	Expired.
Invasive fungal rhinosinusitis	Post liver transplant.	Multiple Extensive debridement, Enucleation, Decrease in immunosupression, Amphotericin B +Posaconazole.	Recovered- No relapse since last six months.
Necrotizing invasive FRS	Post liver transplant.	FESS +Decreased immunosupression +Amphotericin B+Posaconazole.	No recurrence since last three months.

Table 6: Details of cases with *Fusarium* FRS.

Age/Gender	Type of sinusitis	Underlying illness	Treatment	Outcome
63years/Male	Invasive sinusitis	Diabetes, Chronic Lymphocytic Leukaemia.	FESS+Amphotericin B followed by Voriconazole.	Symptoms resolved completely.
70 years/Female	Colonization	Diabetes, Nasal Myiasis.	Amphotericin B and Voriconazole.	Discharged in stable condition.

simple inflammatory polyps were seen.[5] *A. versicolor* is rarely encountered as a pathogen. In our study, it was isolated from an immunocompetent patient with recurrent nasal polyps. Like our study, Ghadage DP also reported isolation of *A. versicolor* in an immunocompetent patient presenting with nasal polyposis.[6]

Infection with *Zygomycetes* is usually associated with underlying predisposing conditions like uncontrolled Diabetes, haematological malignancy and in immunocompromised patients.[7] In our study, out of 11 cases of FRS due to *Zygomycetes*, 10 were caused by *Rhizopus* and 1 was caused by *Syncephalastrum*. Except one, all the cases of FRS due to *Rhizopus* occurred in immunocompromised patients (Post transplant/Malignancy/ uncontrolled diabetes) with poor outcome. One case of *Rhizopus* FRS which occurred in patient with no underlying risk factor showed good response to endoscopic sinus surgery followed by Amphotericin B (1 mg/Kg/day) for 15 days. *Syncephalastrum racemosum* is widely found in the environment and has been described to have low pathogenic potential. There are reports of rhino-orbital-cerebral rhinosinusitis by *Syncephalastrum racemosum* in immunocompromised patients.[8] However, in our study, one case of FRS was caused by *Syncephalastrum* in immunocompetent patient with favorable outcome to endoscopic sinus surgery followed by initially Itraconazole followed by Posaconazole for 2 weeks.

Table 7: Association of other mycelial fungi with different types of sinusitis.

Name of the fungi	Type of sinusitis	Clinical history	Treatment	Outcome
Schizophyllum commune	Allergic Fungal sinusitis	34 years /Male, immunocompetent.	FESS with septoplasty followed by topical steroids and saline irrigation.	No recurrence of symptoms for one year.
Bipolaris sp.	Allergic Fungal sinusitis	32 years/ Female, immunocompetent.	FESS followed by Itraconazole.	Good
Scedosporium apiospermum	Chronic nonspecific sinusitis	35 years/ Female, immunocompetent.	FESS with septoplasty followed by Itraconazole.	Good
Paecilomyces sp.	Allergic fungal sinusitis	31 years/ Female, Immunocompetent.	FESS	Good
Exserohilum rostratum	Invasive Fungal sinusitis	41 years/Male, Immunocompromised.	-	Poor (Patient left against medical advice).

Figure 5: Growth of Rhizopus on Sabouraud's Dextrose Agar.

Fusarium is a known cause of FRS in both immunocompetent and immunocompromised patients. It is difficult to distinguish between *Aspergillus* FRS from *Fusarium* FRS. In our study, *Fusarium* was associated with both Invasive sinusitis and with mere colonization of sinus cavity respectively. Rajmane VS *et al.* reported a case of chronic rhinosinusitis with cavernous sinus thrombosis by *Fusarium* sp. in a 55-year-old diabetic male.[9] Radulesco T *et al.* reported two cases of maxillary fungus ball due to *Fusarium proliferatum*.[10] *Fusarium* is known for its intrinsic multi drug resistance. with standard antifungal therapy. In our study both the patients of *Fusarium* infection were treated with Amphotericin B and Voriconazole for 2 weeks. In 2014, the European Fungal Infection Study Group and the European Confederation of Medical Mycology recommended voriconazole or a lipid formulation of amphotericin B with strong (AII) and moderate (BII) support, respectively, as optimal management for invasive fusariosis.[11]

Other fungi like *Schizophyllum commune, Bipolaris* and *Paecilomyces* were associated with Allergic FRS. *Schizophyllum commune* and *Paecilomyces* are the rare cause of FRS and may be misinterpreted as *Aspergillus* on histopathological examination. Hence, it is prudent to perform Fungal culture for the definitive identification and management. Liu X *et al.* reported a case of Allergic FRS due to *Schizophyllum commune* in a 56 years old woman.[12] *Paecilomyces* and *Bipolaris* may be lab contaminants but in all these two cases fungal smear were suggestive of *Hyalohyphomycetes* and *Phaeohyphomycetes* respectively. Wong G *et al*. reported a case of debilitating sinusitis due to *Paecilomyces lilacinus* in a case of 20 year old immunocompetent female.[13] Taguchi A *et al.* reported two cases of Allergic FRS caused by *Bipolaris spicifera* and *Schizophyllum commune* in a 70 year old male and 55 years old female respectively.[14] It is important to definitively identify these fungi not only for epidemiological purpose but also for devising strategy to prevent recurrence and to remain vigilant for any feature of invasive infection especially in immunocompromised patients.

Scedosporium apiospermum was associated with chronic nonspecific rhinosinusitis and *Exserohilum rostratum* was associated with invasive FRS. Association of *Scedosporium apiospermum* with FRS was seen in the year 2016 in our study. During that time, not much cases were reported in literature. Now, the reports are coming up from India and abroad implicating *Scedosporium* as a cause of FRS in both immunocompetent and immunocompromised patients.[15,16] Vasikasin V *et al.* reported a case of Sphenoid sinusitis due to *Scedosporium apiospermum* complex in a 56 years old immunocompetent male.[17]

Like *Bipolaris, Exserohilum* is a *dematiceous* fungus and is usually associated with wide spectrum of diseases ranging from less invasive to more invasive. The infections are usually seen in immunocompromised patients particularly associated with haematological malignancy and transplant patients.[18] In our study, *Exserohilum* was isolated in an immunocompromised patient with poor prognosis.

Candida sp. were associated with invasive FRS and were isolated in immunocompromised patients either alone or as mixed fungal growth with *Aspergillus flavus* or *Rhizopus* sp. Reports of non-*albicans Candida* in fungal sinusitis is rare. *C. tropicalis, C. krusei and C. kefyr* have been reported as a cause of FRS.[19,20] In our study we have seen the association of *C. auris, C. glabrata* and *C. rugosa* with FRS also. All these were associated with immunocompromised hosts with unfavorable outcome.

The dictum to diagnose fungal infection should be a combination of Fungal KOH examination, Fungal culture along with clinical correlation. In certain cases, Fungal culture may be negative like in our study, 11 cases were fungal smear positive (6 corroborating to *Zygomycetes* and 5 fungi with thin and septate hyphae). Negative culture in case of *Zygomycetes* is a known fact due to coenocytic nature of their hyphae which may get damaged easily during tissue processing.[21] The other reason behind sterile culture may be the use of antifungal drugs prior to collection of samples.

CONCLUSION

FRS may occur in both immunocompetent and immunocompromised population. Different fungi behave differently with respect to type of FRS and antifungal susceptibility. With the increase in immunocompromised/ immunosuppressed population, fungi with low virulence are increasingly being associated with invasive infections. So, it is pertinent to monitor and study the types of fungi causing infections in different patient populations. Apart from *Aspergillus* and *Zygomycetes* causing FRS other fungi like *Fusarium, Schizophyllum commune, Scedosporium apiospermum, Paecilomyces, Exserohilum, Bipolaris* and *Candida* may also be associated with FRS. So, it is very important to know the epidemiology of various fungi causing Rhinosinusitis for the proper management of the patients. The response to treatment depends upon type of FRS, type of fungi and its antifungal susceptibility pattern. Our study details about the epidemiological profile of fungi in different patient population. Automated methods like MALDITOF -MS are an excellent tool in the definitive and timely identification of fungi to save lives and contain the extent of morbidities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FESS: Functional Endoscopic Sinus Surgery; **FRS:** Fungal Rhinosinusitis; **HPE:** Histopathological Examination; **KOH:** Potassium Hydroxide; **LAMA:** Leave Against Medical Advice; **LPCB:** Lactophenol Cotton Blue; **MALDITOF-MS:** Matrix Assisted Laser Desorption Ionisation Time of Flight-Mass Spectrometry.

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