

Efficacy of Different Modalities in Treatment of Different Types of Fungal Sinusitis

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ABSTRACT

Background: Fungal rhinosinusitis (FRS) includes a spectrum of disease processes that vary in clinical presentation, histologic appearances, and treatment options.

Objective: This systematic review was done to reach the effective and safe method in management of FRS.

Patients and Methods: Meta-analysis was performed in accordance to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This study used the published articles (from Jan1985 to Jan2018) in treatment of FRS via search in several databases.

Results: Finally, forty-five studies were included in this study. Fifteen of them assessed the treatment of fungal ball (FB) using mainly the functional endoscopic sinus surgery (FESS) the success rate was 98.1%. Twenty included studies have evaluated the management of allergic fungal sinusitis (AFS) via FESS, Systemic steroids, Antifungals and immunotherapy. The results showed that FESS represents the first-line, followed by aggressive medical therapies, the recurrence rate after postoperative steroids was 20.6%, postoperative antifungals was 40% and after immunotherapy was 9.1%. Ten included studies considered the Invasive Fungal sinusitis. The results showed that the combination of systematic antifungal therapy and aggressive surgical debridement was the treatment of the choice.

Conclusion: FESS is the treatment of choice for FB. AFS treatment consists of surgical extirpation of the allergic mucin and followed by anti-fungal therapy, Immunotherapy, and corticosteroids. Treatment of invasive fungal sinusitis includes surgical resection of necrotic tissues, systemic antifungal therapy and reversal of immune dysfunction.

Key Words: Allergic fungal rhinosinusitis, antifungal in AFS, aspergillus in FB, fungus ball rhinosinusitis, immunotherapy in AFS, invasive fungal rhinosinusitis.

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INTRODUCTION

The first step in treatment for any AFS patient is paranasal sinus surgery to both remove all obstructing inspissated allergic mucin and resect all diseased hypertrophic sinus mucosa. Failure to adequately surgically remove all sinus disease leads to higher AFS relapse rates^[1]. The addition of postoperative oral corticosteroids (OCS) in AFS play an important role to reduces overall disease activity, including decreasing both symptoms and surgical recurrence rates^[2]. The aim of management of fungal ball is to remove the allergic mucin and good aeration of the sinuses. The treatment of IFS requires reversal of the underlying predisposing condition, surgical debridement and appropriate systemic antifungal therapy^[3].

AIM OF THE WORK:

A systematic review of effective and safe method in management of different types of fungal sinusitis either by medical or surgical approaches or even combined.

PATIENTS AND METHODS:

We performed this systematic review and meta-analysis in accordance to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) statements. PRISMA and MOOSE are reporting checklists for Authors, Editors, and Reviewers of Meta-analyses of interventional and observational studies. According to International Committee of Medical Journal association (ICMJE), reviewers must report their findings according to each of the items listed in those checklists.

Study Selection and Eligibility Criteria:

The present review included studies that fulfilled the following criteria: Studies that included patients with different types of fungal rhinosinusitis whether it was invasive or non-invasive. Studies that assessed the efficacy and safety of different surgical and medical modalities

for the management of fungal rhinosinusitis Studies that compared those modalities with none or any comparison; Studies that reported any of the following outcomes: success rates, recurrence rates, and the incidence of complications. Studies that were either prospective or retrospective studies.

Search Strategy and Screening: Studies include published medical articles (from Jan1985 to Jan 2018) concerning the comparison between Different modalities for treatment of different types of fungal sinusitis through searching different databases such as Medline and PubMed using the following keywords in different combinations (treatment of fungal sinusitis) and (treatment of invasive fungal sinusitis) and (treatment of non invasive fungal sinusitis) and (Antifungal therapy for chronic rhinosinusitis) and (Immunotherapy in the treatment of allergic fungal sinusitis) and (role of surgical debridement in invasive fungal rhinosinusitis). Articles will be screened to fulfill the following criteria, restricted to English language, applied on humans.

Screening: Retrieved citations were imported into End Note X7 for duplicates removal. Subsequently, unique citations were imported into an Excel sheet and screened by two independent reviewers; the screening was conducted in two steps: title and abstract screening, followed by a full-texts screening of potentially eligible records.

Article inclusion criteria: Treatment of different types of fungal sinusitis. Published in English language (from Jan1985 to Jan 2018). Conducted on human subjects.

Article exclusion criteria: Published in other languages "not in English". Conducted on animals. Review articles and case reports.

Data Extraction: Data entry and processing were carried out using a standardized Excel sheet and reviewers extracted the data from the included studies. The extracted data included the following domains: (1) Summary characteristics of the included studies; (2) Baseline characteristics of studied populations; and (3) Study outcomes. All reviewers' independently extracted data from the included articles and any discrepancies were solved by discussion.

Dealing with Missing Data: Missing standard deviation (SD) of mean change from baseline was calculated from standard error or 95% confidence interval (CI) according to Altman^[4].

Data Synthesis: Continuous outcomes were pooled as mean difference (MD) or standardized mean difference (SMD) using inverse variance method, and dichotomous outcomes will be pooled as relative risk (RR) using Mantel-Haenszel method. The random-effects method was used

under the assumption of existing significant clinical and methodological heterogeneity. We performed all statistical analyses using Review Manager (RevMan) 5.3 or Open Meta-analyst for windows.

Assessment of Heterogeneity: We assessed heterogeneity by visual inspection of the forest plots, chi-square, and I-square tests. According to the recommendations of Cochrane Handbook of Systematic Reviews and meta-analysis, chi-square p-value less than 0.1 denote significant heterogeneity while The I-squared is interpreted as follows: 0% to 40%: unimportant heterogeneity. 30% to 60%: moderate heterogeneity. 50% to 90%: substantial heterogeneity. 75% to 100%: considerable heterogeneity.

RESULTS:

A. Fungal Ball: Fifteen included studies (No. = 856 patients) assessed different modalities for the management of fungal ball infection. The majority of the included studies were retrospective studies, while only one study was prospective cohort. The sample size of the included studies ranged from 25 to 160 patients and the duration of follow up ranged from 12 months to 93 months. The success rate of FESS ranged from 91% to 100%. (Table 1). In terms of success rates of FESS, 9 studies reported the success rates. The overall effect estimate showed that FESS led to success rate of 98.1% (95% CI 96.6 – 99.6%). (Figure 1).

B. Allergic Fungal Sinusitis: (Table 2) showed twenty included studies (No=806 patients) that have assessed the efficacy and safety of different modalities for the management of allergic fungal sinusitis via FESS, Post-FESS Systemic steroids, Antifungals and immunotherapy. The results showed that FESS represents the first- line management strategy of AFS, followed by aggressive medical therapies, the recurrence rate after postoperative steroids was 20.6-% (95% CI 5.5 – 35.7%). (Figure 2). The incidence of recurrence was higher with postoperative antifungals was 40%. (Figure 3). While, after immunotherapy was 9.1% (95% CI 1.6 – 16.5%). (Figure 4).

C. Invasive Fungal Sinusitis: Ten studies (No=327 patients) recruited patients with Invasive Fungal Sinusitis. All included studies were retrospective studies with a sample size ranged from 11 to 90 patients. Most of the patients had hematological diseases with an age ranged from 34 to 82 years old. (Table 3). The results showed that combination of systematic antifungal therapy and aggressive surgical debridement are the treatment of choice. In addition, the reported mortality rates ranged from 18 to 60%. The overall effect estimate showed that the mortality rates of acute fungal sinusitis was 23.1% (95% CI 12.6 – 33.7%). (Figure 5).

Table 1: Summary Characteristics of the included studies which assessed the treatment of fungal ball

Author	Year	Study Design	Country	No	Age	Affected Sinus	Positive culture	Treatment Modality	Approaches	Follow-up (months)	Success Rate	Recurrence
Eloy <i>et al.</i> ^[5]	2004	Retrospective Study	Belgium	66	NA	Maxillary and sphenoid	Aspergillus fumigatus	surgery (mainly endonasal approach)	Middle antrostomy or sphenoidotomy; inferior antrostomy; a limited approach through the canine fossa.	NA	91%	10%
Montone <i>et al.</i> ^[6]	2012	Retrospective Study	USA	161	55 (18–90)	Maxillary sinus and sphenoid/ethmoid sinuses	Aspergillus sp. (66%)	surgery (mainly endonasal approach)	NA	NA	NA	NA
Pagella <i>et al.</i> ^[7]	2007	Retrospective Study	Italy	81	49.4 (19–90)	Maxillary sinus and sphenoid/ethmoid sinuses	Aspergillus sp. (34%)	Functional endoscopic sinus	Ethmoidectomy; Meatotomy; sinusoscopy via fossa canina was associated; trans-nasal sphenoidotomy; transethmoidal approach.	NA	95%	5%
Pagella <i>et al.</i> ^[8]	2009	Retrospective Study	Italy	33	NA	Maxillary sinus	Aspergillus sp. (34%)	Functional endoscopic sinus	Canine fossa approach.	93	95.4%	NA
Chobillon ^[9]	2004	Retrospective Study	France	9	NA	Maxillary sinus	Aspergillus sp. (100%)	Functional endoscopic sinus	Canine fossa approach.	93	100%	0
Suresh <i>et al.</i> ^[10]	2016	Prospective study	USA	14	(11–90)	Maxillary sinus and sphenoid/ethmoid sinuses	Aspergillus sp. (34%)	Functional endoscopic sinus	NA	12	100%	3%
Klossek <i>et al.</i> ^[11]	1997	Retrospective Study	France	109	(20–86)	Maxillary sinus and sphenoid/ethmoid sinuses	Aspergillus sp. (56%)	Functional endoscopic sinus	Middle antrostomy; combination of middle and inferior antrostomies; simple sphenoidotomies	29	96%	4%
Nicolai <i>et al.</i> ^[12]	2009	Retrospective Study	Italy	160	52.7 (19–85)	Maxillary sinus and sphenoid/ethmoid sinuses	NA	Functional endoscopic sinus	Middle antrostomy or sphenoidotomy; inferior antrostomy; a limited approach through the canine fossa.	24	100%	1%
Lee <i>et al.</i> ^[13]	2007	Retrospective Study	Korea	86	(20–79)	Maxillary sinus and sphenoid/ethmoid sinuses	Aspergillus sp. (72%)	Functional endoscopic sinus	Middle antrostomy or sphenoidotomy; inferior antrostomy; a limited approach through the canine fossa.		100%	0.6%

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Jiang <i>et al.</i> ^[14]	2018	Retrospective Study	Taiwan	91	57.51 (23-82)	Maxillary sinus and sphenoid sinuses	NA	Functional endoscopic sinus	NA	NA	NA	NA
Lop-Gros <i>et al.</i> ^[15]	2016	Retrospective Study	Spain	35	55 (22-79)	Maxillary sinus and sphenoid sinuses	NA	Functional endoscopic sinus	NA	NA	100%	1.4%
Garofalo <i>et al.</i> ^[16]	2016	Retrospective Study	Italy	25	55 (28-87)	Maxillary sinus	NA	Gauze technique	NA	96%	4%	
Chao, <i>et al.</i> ^[17]	2006	Retrospective Study	Taiwan	15	43 (21-65)	Maxillary sinus	NA	Gauze technique	NA	100%	0%	
Naros <i>et al.</i> ^[18]	2018	Retrospective Study	Germany	22	58.3 (14.7)	Maxillary sinus	NA	Osteoplastic Approach	29	100%	0	
Ferreiro <i>et al.</i> ^[19]	1997	Retrospective Study	USA	28	64 (28-68)	Maxillary sinus	Aspergillus Spec (76%)	variety of surgical procedures	NA	92%	8%	

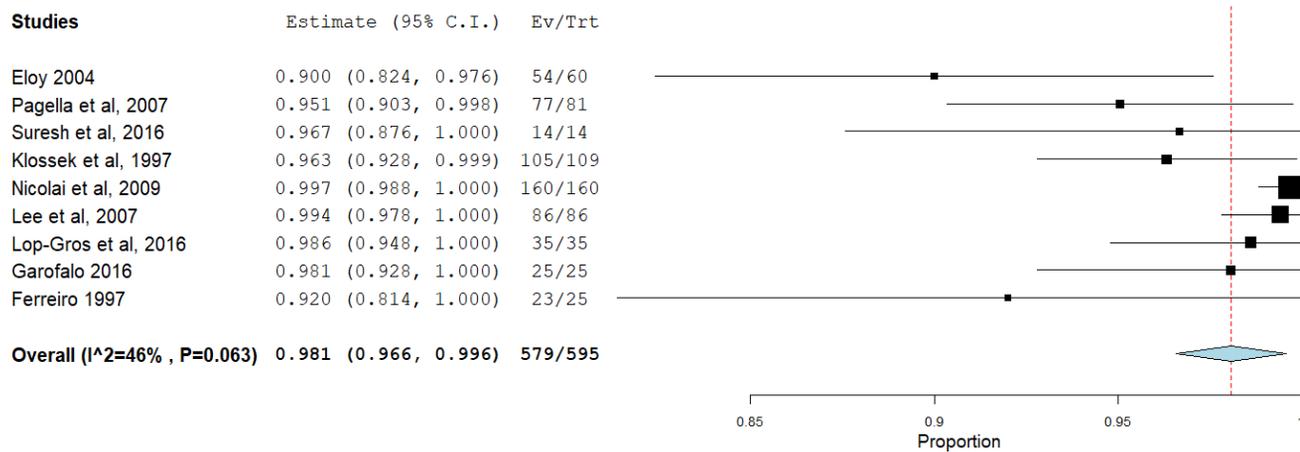


Fig. 1: Success rate of FESS in fungal ball.

Table 2: Summary Characteristics of the included studies which assessed the treatment of AFR.

Author	Year	Study Design	Country	Sample Size	Age	Treatment Modality	Follow-up (months)	Success Rate	Recurrence
Champagne <i>et al.</i> ^[20]	2010	Prospective cohort study		48	32 (12 - 68)	Endoscopic sinus surgery	12	NA	NA
Verma <i>et al.</i> ^[21]	2013	Prospective cohort study	India	40	27.8 (10-65)	Endoscopic sinus surgery	32	90%	NA
Masterson <i>et al.</i> ^[22]	2016	Retrospective study	USA	2	51 ±14	Endoscopic sinus surgery	12	100%	NA
Kupferberg <i>et al.</i> ^[23]	1997	Retrospective study	USA	26	NA	Oral steroids	14.5	92%	37.5%

Kuhn and Javer ^[24]	2000	Retrospective study	USA	11	NA	Oral steroids	27	NA	18.2%
Woodworth <i>et al.</i> ^[24]	2004	Prospective cohort study	USA	21	35	Systemic steroid treatment	NA	NA	NA
Landsberg <i>et al.</i> ^[25]	2007	Prospective cohort study	Israel	8	23 (14 -38)	Prednisolone 1 mg/kg for 10 days preoperatively	NA	NA	5.6%
Rojita <i>et al.</i>	2017	Prospective cohort study		30	(5-60)	Systemic steroid treatment	6	NA	16.6%
Gupta <i>et al.</i>	2007	Randomized Controlled Trial	India	24	31.1	Topical steroids	6	100%	23.5%
Kupferberg <i>et al.</i> ^[23]	1997	Retrospective study	USA	26	NA	Oral antifungals alone	14.5	NA	79.2%
Rains and Mineck	2003	Retrospective study	USA	139	42.8	Oral antifungals	NA	31.4	50.4%
Seiberling and Wormald	2009	Retrospective study	Australia	23	49 (23 -60)	Oral antifungals	15.7	NA	13%
Rojita <i>et al.</i> ^[26]	2017	Prospective cohort study		30	(5-60)	Oral antifungals	6	NA	31.2%
Khalil <i>et al.</i> ^[27]	2011	Randomized Controlled Trial	Egypt	50	35.4 (18 - 61)	Topical antifungals	9	100%	11.8%
Jen <i>et al.</i> ^[28]	2004	Prospective cohort study	USA	16	(39 -74)	Topical antifungals	3	NA	25%
Folker <i>et al.</i> ^[29]	1998	Retrospective study	USA	11	39 (19-72)	IT with fungal and nonfungal antigens, corticosteroids, antibiotics	30	NA	NA
Mabry <i>et al.</i> ^[30]	1997	Prospective cohort study	USA	9	NA	IT given weekly basis based on sensitivities to fungal and antifungal antigens up to 12 months	8.5	NA	5%
Mabry and Mabry ^[30]	1997	Prospective cohort study	USA	10	NA	IT given initially weekly for a year then extended to biweekly basis	NA	NA	10%
Bassichis <i>et al.</i> ^[31]	2001	Retrospective study	USA	60	42.7 (7 -75)	IT given for relevant antifungal and fungal antigens	12	NA	11%
Greenhaw <i>et al.</i> ^[32]	2011	Prospective cohort study	USA	14	36.6 (12.8)	IT given for relevant antifungal and fungal antigens	NA	NA	0%

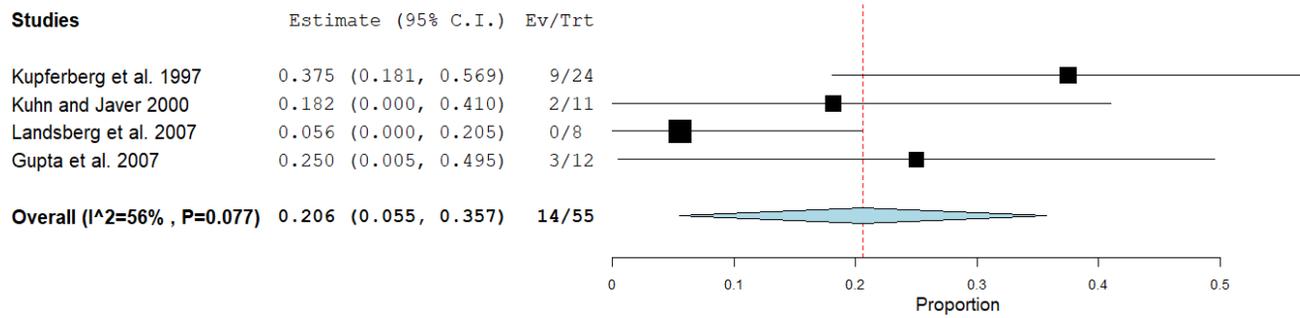


Fig. 2: Recurrence rates after steroids in AFS.

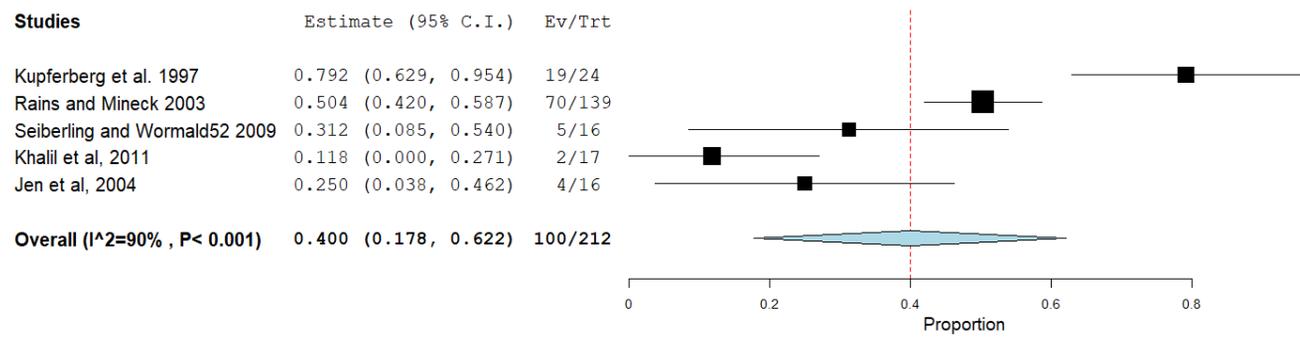


Fig. 3: Recurrence rates after anti-fungal in AFS.

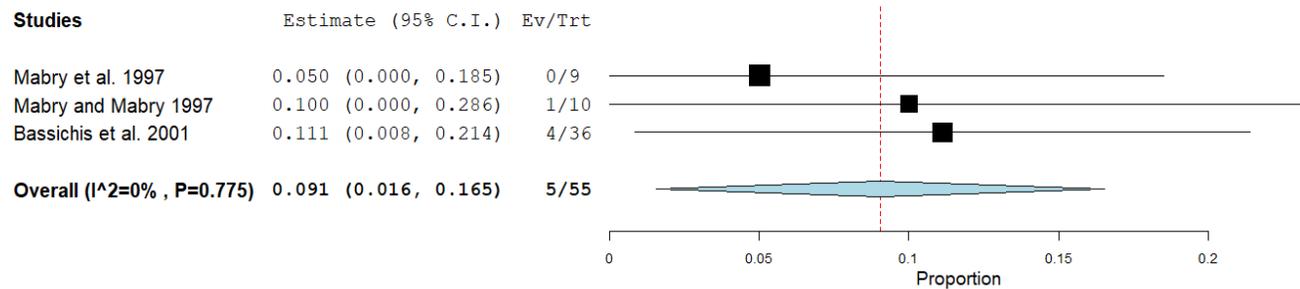


Fig. 4: Recurrence rates after immunotherapy in AFS.

Table 3: Summary Characteristics of the included studies which assessed the treatment of invasive fungal sinusitis.

Author	Year	Study Design	Country	Population	Sample Size	Age	Treatment Modality	Mortality rates
Chen et al. ^[33]	2011	Retrospective study	Taiwan	patients with 3 hematological disease	46	NA	antifungal combination therapy and/or aggressive surgical debridement,	41%
Saedi et al. ^[34]	2011	Retrospective study	Iran	Patients with infection limited to the nose and sinuses were selected	30	49±19.3	antifungal combination therapy and aggressive surgical debridement,	60%

Sun et al. ^[35]	2010	Retrospective study	USA	SOT recipients with rhino-orbital-cerebral zygomycosis	90	NA	antifungal combination therapy and/or aggressive surgical debridement,	52.30%
Kara et al. ^[36]	2007	Retrospective study	Turkey	patients with hematological disease	20	25	Antifungal treatment and radical surgical debridement	55%
Khor et al. ^[37]	2003	Retrospective study	Taiwan	patients with invasive fungal sinusitis	21	60 (34-82)	antifungal combination therapy and aggressive surgical debridement,	23%
Bhansali et al. ^[38]	2004	Retrospective study	India	Patients with rhino-orbital-cerebral mucormycosis	35	47.3 (18-70)	antifungal combination therapy and aggressive surgical debridement,	32%
Butugan et al. ^[39]	1996	Retrospective study	Brazil	Patients with rhino-orbital-cerebral mucormycosis	11	31	antifungal combination therapy and aggressive surgical debridement,	28%
Parikh et al. ^[40]	2004	Retrospective study	USA	patients with invasive fungal sinusitis	45	41.6 (17- 82)	antifungal combination therapy and/or aggressive surgical debridement,	18%
Alrajhi et al. ^[41]	2001	Retrospective study	Saudi Arabia.	Cases of paranasal invasive aspergillosis	23	20; (9-61)	Surgical debridement followed by antifungal therapy	5%
D'Anza et al	2016	Retrospective study	USA	patients with chronic invasive fungal sinusitis	6	(25-77)	antifungal combination therapy and/or aggressive surgical debridement,	NA

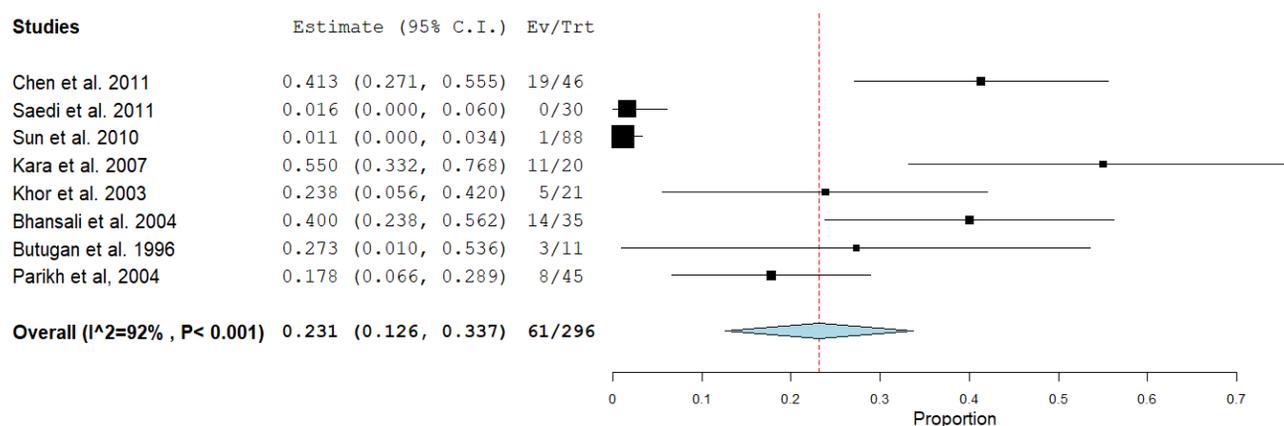


Fig. 5: Motility rates of acute fungal sinusitis.

DISCUSSION

Among causes of sinonasal inflammatory disease, fungal sinusitis is a relatively uncommon but well-established clinical entity. Fungi are ubiquitous in the environment, and can colonize the upper respiratory tract mucosa when fungal spores are inhaled. In people with normal immune function, the fungal growth is kept in check. With impaired host immunity, fungi can invade host mucosa and cause invasive disease. Fungal sinusitis consists of a heterogeneous group of disorders, with diversity in the affected

patient population, mechanism of disease, clinical presentation, histopathology, imaging appearances, treatment, and overall prognosis^[43].

Fungal ball is one of the most common form of noninvasive fungal sinusitis that is usually preceded saprophytic fungal infestation. The fungal ball is characterized by an extramucosal, entangled mass of fungi usually associated with minimal mucosal inflammation^[44]. In the present systematic review and meta-analysis, 15 included studies (No = 856 patients) assessed the efficacy and safety of different

modalities for the management of non-invasive fungal ball infection with a sample size ranged from 9 to 160 patients and the duration of follow up ranged from 12 months to 93 months.

The current body of evidence shows that fungal balls are more common in middle-age or older women, while maxillary sinus is the most commonly involved sinus^[45]. In line with our findings, Nicolai and colleagues^[46] performed a retrospective study that included 160 patients with fungal ball of the paranasal sinuses who underwent endoscopic surgery. They found that the majority of patients were females; in addition, the maxillary sinus was the most commonly involved (84%), followed by the sphenoid sinus (14%) and, rarely, the ethmoid or frontal sinus.

On the other hand, surgical opening of the natural sinus ostium with evacuation of fungal debris is the treatment of choice. After removal of fungal hyphae, the sinus mucosa generally returns to a normal state of health and no additional treatment is usually necessary. In the present systematic review, all of the included studies utilized functional endoscopic sinus surgery for the management of fungal ball. Our analysis showed that that functional endoscopic sinus surgery led to success rate of 98.1% (95% CI 96.6 – 99.6%) and recurrence rate of 2.3% (95% CI 0.8 – 3.8%). Moreover, the reported perioperative complication and recurrence rates were very low among the included studies.

In terms of the surgical approaches, the removal of maxillary sinus fungal ball may be long and difficult, in particular when the anterior and/or inferior recesses are involved, as they are notoriously more difficult to manage with the classic endoscopic technique. Therefore, some authors have advocated a combination of the pure endoscopic technique and a complementary endoscopic canine-fossa approach, using a trocar in the canine fossa (the so-called “double approach”) so as to arrive at a complete resection of the fungus ball^[47].

Nevertheless, canine fossa approach may make fungal ball surgery in the long. This leads to an increase in the surgical procedure time, a higher risk of complications due to the difficulty of the technique and, consequently, a higher cost. Consequently, numerous authors have proposed various techniques without intervening on the canine fossa. Chao and Liu in 2006^[48] proposed the so-called “gauze technique.” The merits of this technique do not only lie in its simplicity and the high learning curve but also include a higher speed of execution and lower costs than the technique without gauze, as the materials used are part of the standard supplies in any operating theatre.

Moreover, this atraumatic technique has potentially no complications other than those related to the classic endoscopic technique. In order to avoid recurrence, there are two cornerstones, to widen the maxillary sinus ostium as much as possible and to take care of pushing the gauze very gently so as to preserve the periosteum of the maxillary sinus; even if the mucosa is injured, it will heal as long as the periosteum is intact^[48].

In the present systematic review and meta-analysis, two included studies assessed the “gauze technique” to clean out the fungal ball from the sinus without resorting to any destructive procedures. The earlier study by Chao *et al.*^[48] reported that neither recurrence nor complication was noted among 15 adults with FB of the maxillary sinus.

More recently, Garofalo and colleagues^[49] performed a retrospective, cross-sectional, and descriptive study of 25 patients affected by maxillary fungus ball: 19 were treated by the “gauze technique” and 6 were treated without “gauze technique”. The authors reported a success rate of 96% (24/25 patients) with the gauze technique.

In the present review, 20 included studies (No. = 608 patients) assessed the efficacy and safety of different modalities for the management of allergic fungal sinusitis.

Surgical therapy represents the first-line management strategy of AFRS. Most clinical series describe surgical therapy to remove polyps, open sinus ostia, and clear eosinophilic fungal mucin, followed by aggressive medical therapies. From the literature, it appears that surgery in combination with other medical treatments leads to improved outcomes^[45].

In the present systematic review, a wide range of post-surgical medical therapies were investigated by the included studies. The efficacy of systemic steroids has been studied in 6 included studies with a sample size ranged from 8 to 30 patients (oral steroids = 2 studies; and systemic steroids = 3 studies). The included studies agreed that postoperative steroids significantly reduce postoperative mucosal disease, improve symptoms by endoscopic grading, and reduce inflammatory markers. In addition, two study assessed the efficacy of topical steroid in form of low-volume metered-dose steroid spray (0.25 mg/2 mL or 0.5 mg/2 mL in 240 mL saline or higher concentration). The results of the meta-analysis showed that the recurrence rates after postoperative steroids was 20.6% (95% CI 5.5 – 35.7%). Moreover, the post-surgical steroids improved the Sino-nasal Outcome Test (SNOT-20) by 24.09% (95% CI 11.52 – 36.6%).

On the other hand, limited evidence reported benefits of oral antifungal therapies in patients with AFRS. In the present systematic review and meta-analysis, the use of systemic antifungal therapy in patients with AFRS has been studied in four studies. Itraconazole at 200 mg to 400 mg PO daily in divided doses were used with an average duration of follow-up ranged from 6-15.7 months. Oral antifungals were reported to lead a significant reduction in symptoms, reduction in dependence on oral steroids and prevention of disease recurrence. While, two included studies explored the use of topical antifungals in the management of AFRS patients. The antifungal regimens included fluconazole nasal spray irrigation with a fluconazole solution through the nasal fossa. The results of the present meta-analysis showed that the recurrence rates after postoperative antifungals was 40% (95% CI 17.8 – 62.2%); while the rate of symptoms improvement after postoperative antifungals was 57.7% (95% CI 33 – 82.5%).

Finally, Rains and colleagues^[50] conducted a retrospective chart review in 139 patients with AFRS and cited findings using their protocol including high dose itraconazole, low-dose oral steroids, and topical corticosteroids. The authors reported a 50.3% recurrence rate, with 20.5% of those patients requiring reoperation. They concluded that their regimen, with its use of itraconazole, was safe.

AFRS is defined by a Type 1 hypersensitivity to fungus, so it stands to reason that immunotherapy (IT) could feasibly blunt the immune response to fungus and decrease disease burden^[51]. Allergen IT was used to treat allergic fungal sinusitis in five included studies in the present systematic review. Those studies supported that indicates IT may be beneficial in AFRS patients. However, all studies used IT in conjunction with other medical therapies. Despite case-control studies, none of the comparison groups were placed on the same medical regimen to decipher the true effect of IT. The results of the meta-analysis showed that the recurrence rates after immunotherapy was 9.1% (95% CI 1.6 – 16.5%).

Gan and colleagues^[52] conducted a systematic review of the available literature regarding IT in AFRS. This review identified and assessed 6 medical modalities for AFRS in the literature: oral steroids; topical steroids; oral antifungals; topical antifungals; immunotherapy; and leukotriene modulators. The results showed that IT potentially reduces mucosal inflammation and the amount of topical/systemic corticosteroids required.

Treatment of invasive fungal sinusitis includes surgical resection of necrotic tissues, systemic

antifungal antibiotics, and reversal of immune dysfunction. The goal of surgical therapy is to remove necrotic tissue. The treatment employed in all studies was a combination of systematic antifungal therapy and aggressive surgical debridement. The included studies use a variety of topical and intravenous antifungals including (amphotericin B plus caspofungin and amphotericin B plus voriconazole or amphotericin B alone. The results of the meta-analysis showed that mortality rate of acute fungal sinusitis was 23.1% (95% CI 12.6 – 33.7%).

CONCLUSION

Our meta-analysis assessed different modalities for management of fungal ball, via classic endoscopic technique, Canine-fossa approach, gauze technique and osteoplastic approach for FB of the maxillary sinus. The results showed that functional endoscopic sinus surgery led to success rate of 98.1%.

Allergic fungal sinusitis treatment consists of surgical extirpation of the allergic mucin and polyps with maintenance of adequate sinus drainage followed by medical therapy consists of topical intranasal steroids nasal irrigations, anti fungal therapy Immunotherapy, and systemic corticosteroids. The use of Post-ESS Steroids significantly reduces postoperative mucosal disease, improves symptoms by endoscopic grading, and reduces inflammatory markers. The use of systemic antifungal therapy in patients with AFRS has been reported to lead to a significant reduction in symptoms and a reduction too in dependence on oral steroids, but recurrence rate is higher than steroids. However, possible harms may include renal failure, elevated liver enzymes, rash, headache, malaise and fatigue. Treatment of invasive fungal sinusitis includes surgical resection of necrotic tissues, systemic antifungal therapy, and reversal of immune dysfunction. The mortality rates of invasive fungal sinusitis was 23.1%.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Schubert MS. Allergic fungal sinusitis, *Clin Rev Allergy Immunol*, 2006; 30: 205-216.
2. Kuhn FA and Javer AR. Allergic fungal rhinosinusitis: perioperative management, prevention of recurrence, and role of steroids and antifungal agents. *Otolaryngol Clin North Am*. 2000;33(2):419-433.
3. Chakrabarti A, Denning DW, Ferguson BJ, Ponikau J, Buzina W, Kita H, Marple B, Panda N, Vlaminc S, Kauffmann-Lacroix C, Das A. Fungal rhinosinusitis:

- a categorization and definitional schema addressing current controversies. *The Laryngoscope*. 2009; 119(9):1809-18.
4. Altman DG and Bland JM. Treatment allocation by minimisation. *Bmj*. 2005; 330(7495):843.
 5. Eloy P, Mardyla N, Bertrand B, Rombaux P. Endoscopic endonasal medial maxillectomy: case series. *Indian Journal of Otolaryngology and Head & Neck Surgery*. 2004; 62(3):252-7.
 6. Montone KT. Pathology of Fungal Rhinosinusitis: A Review. *Head Neck Pathol* 2012;10:40–6, doi.org/10.1007/s12105-016-0690-0.
 7. Pagella F, Matti E, De Bernardi F, *et al*. Paranasal sinus fungus ball: diagnosis and management. *Mycoses* 2007; 50:451–456, doi.org/10.1111/j.1439-0507.2007.01416.x.
 8. Pagella F, Matti E, Giourgos G, Colombo A, De Bernardi F, Castelnovo P. Is canine fossa access necessary for successful maxillary fungus ball treatment? *Rhinol J* 2009; 47:385–8, DOI:10.4193/Rhin08.234.
 9. Chobillon MAJ, Jankowski R. What are the advantages of the endoscopic canine fossa approach in treating maxillary sinus aspergillomas? *Rhinology* 2004;42:230–5.
 10. Suresh S, Arumugam D, Zacharias G, Palaninathan S, Vishwanathan R, Venkatraman V. Prevalence and clinical profile of fungal rhinosinusitis. *Allergy & Rhinology*. 2016; 7(2): 16, doi.org/10.2500/ar.2016.7.0156.
 11. Klossek JM, Serrano E, Peloquin L, Percodani J, Fontanel JP, Pessey JJ. Functional endoscopic sinus surgery and 109mycetomas of paranasal sinuses. *Laryngoscope* 1997;107:112–117, doi.org/10.1097/00005537-199701000-00021.
 12. Nicolai P, Lombardi D, Tomenzoli D, Villaret AB, Piccioni M, Mensi M, *et al*. Fungus ball of the paranasal sinuses: Experience in 160 patients treated with endoscopic surgery. *Laryngoscope* 2009;119:2275–9, doi.org/10.1002/lary.20578.
 13. Lee KC. Clinical features of the paranasal sinus fungus ball. *J Otolaryngol* 2007;36:270–3.
 14. Jiang J, Tang ZH, Zhong YF, Qiang JW. Diffusion kurtosis imaging for differentiating between the benign and malignant sinonasal lesions. *J Magn Reson Imaging*. 2018; 45(5):1446-54.
 15. Lop-Gros J, Gras-Cabrerizo JR, Bothe-González C, Montserrat-Gili JR, Sumarroca-Trouboul A, Massegur-Solench H. Fungus Ball of the Paranasal Sinuses: Analysis of Our Serie of Patients. *Acta Otorrinolaringol*. English Ed 2016;67:220–5, doi.org/10.1016/j.otoeng.2016.07.002.
 16. Garofalo P, Griffa A, Dumas G, Perottino F. “Gauze Technique” in the Treatment of the Fungus Ball of the Maxillary Sinus: A Technique as Simple as It Is Effective. *Int J Otolaryngol* 2016; 2016:1–6, doi.org/10.1155/2016/4169523.
 17. Chao TK, Liu CM. Gauze-Assisted Technique in Endoscopic Removal of Fungus Balls of the Maxillary Sinus. *Am J Rhinol* 2006. doi:10.2500/ajr.2006.20.2872.
 18. Naros G, Grimm F, Weiss D, Gharabaghi A. Directional communication during movement execution interferes with tremor in Parkinson's disease. *Movement Disorders*. 2018; 33(2):251-61.
 19. Ferreiro JA, Carlson BA, Thane Cody D. Paranasal sinus fungus balls. *Head & Neck: Journal for the Sciences and Specialties of the Head and Neck*. 1997; 19(6):481-6.
 20. Champagne VK, Helfritch DJ, Trexler MD, Gabriel BM. The effect of cold spray impact velocity on deposit hardness. *Modelling and Simulation in Materials Science and Engineering*. 2010; 18(6):065011.
 21. Verma V, Prateek S, Banerjee G, Gupta P, Singh M, Goel MM. Fungal rhinosinusitis: a prospective study in a University hospital of Uttar Pradesh. *Indian journal of medical microbiology*. 2013; 31(3):266.
 22. Masterson SA, Kennelly MM, Janke RR, Rivard CL. Scion shoot removal and rootstock cultivar affect vigor and early yield of grafted tomatoes grown in high tunnels in the central United States. *HortTechnology*. 2016; 26(4):399-408.
 23. Kupferberg SB, Bent III JP, Kuhn FA. Prognosis for allergic fungal sinusitis. *Otolaryngology—Head and Neck Surgery*. 1997; 117(1):35-41.
 24. Woodworth BA, Joseph K, Kaplan AP, Schlosser RJ. Alterations in eotaxin, monocyte chemoattractant protein-4, interleukin-5, and interleukin-13 after systemic steroid treatment for nasal polyps. *Otolaryngology—Head and Neck Surgery*. 2004; 131(5):585-9.
 25. Landsberg R and Friedman M. A computer-assisted anatomical study of the nasofrontal region. *Laryngoscope*. 2007; 111(12):2125–2130.
-

26. Rojita M, Samal S, Pradhan P, Venkatachalam VP. Comparison of steroid and itraconazole for prevention of recurrence in allergic fungal rhinosinusitis: a randomized controlled trial. *Journal of Clinical and Diagnostic Research: JCDR*. 2017; 11(4):MC01, doi: 10.7860/JCDR/2017/23488.9610.
27. Khalil Y, Tharwat A, Abdou AG, Essa E, Essawy AH, Elnakib O, Elnaidany NF. The role of antifungal therapy in the prevention of recurrent allergic fungal rhinosinusitis after functional endoscopic sinus surgery: a randomized, controlled study. *Ear, Nose & Throat Journal*. 2011; 90(8):1-7, doi.org/ 10.1177/ 014556131109000815.
28. Jen A, Kacker A, Huang C, Anand V. Fluconazole nasal spray in the treatment of allergic fungal sinusitis: A pilot study. *Ear, nose & throat journal*. 2004; 83(10):692-5.
29. Folker RJ, Marple BF, Mabry RL, Mabry CS. Treatment of allergic fungal sinusitis: a comparison trial of postoperative immunotherapy with specific fungal antigens. *Laryngoscope*. 1998;108(11 Pt 1):1623-1627, doi.org/10.1097/00005537-199811000-00007.
30. Mabry RL, Manning SC, Mabry CS. Immunotherapy in the treatment of allergic fungal sinusitis. *Otolaryngol Head Neck Surg*. 1997; 116(1):31–35, doi.org/10.1016/S0194-59989770348-6.
31. Bassichis BA, Marple BF, Mabry RL, Newcomer MT. Use of immunotherapy in previously treated patients with allergic fungal sinusitis. *Otolaryngol Head Neck Surg*. 2001; 125: 487-490, doi.org/10.1067/ mhn.2001.119585.
32. Greenhaw B, deShazo RD, Arnold J, Wright L. Fungal immunotherapy in patients with allergic fungal sinusitis. *Annals of Allergy, Asthma & Immunology*. 2011; 107(5):432-6.
33. Chen CY, Sheng WH, Cheng A, Chen YC, Tsay W, Tang JL, Huang SY, Chang SC, Tien HF. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. *BMC infectious diseases*. 2011; 11(1):250, doi.org/10.1186/1471-2334-11-250.
34. Saedi B, Sadeghi M, Seilani P. Endoscopic management of rhinocerebral mucormycosis with topical and intravenous amphotericin B. *The Journal of Laryngology & Otolaryngology*. 2011; 125(8):807-10.
35. Sun X, Guo LD. Endophytic fungal diversity: review of traditional and molecular techniques. *Mycology*. 2010; 3(1):65-76.
36. Kara IO, Tasova Y, Uguz A, *et al.* Mucormycosis-associated fungal infections in patients with haematologic malignancies. *Int J Clin Pract* 2007; 2013:134–9
37. Khor R, McElroy LJ, Whittaker GR. The ubiquitin-vacuolar protein sorting system is selectively required during entry of influenza virus into host cells. *Traffic*. 2003; 4(12):857-68.
38. Bhansali A, Bhadada S, Sharma A, Suresh V, Gupta A, Singh P, Chakarbarti A, Dash RJ. Presentation and outcome of rhino-orbital-cerebral mucormycosis in patients with diabetes. *Postgraduate medical journal*. 2004; 80(949):670-4.
39. Butugan O, Sanchez TG, Goncalvez F, Venosa AR, Miniti A. Rhinocerebral mucormycosis: predisposing factors, diagnosis, therapy, complications and survival. *Revue de laryngologie-otologie-rhinologie*. 1996;117(1):53-5.
40. Parikh SL, Venkatraman G, DelGaudio JM. Invasive fungal sinusitis: a 15-year review from a single institution. *Am J Rhinol* 2004;18(2):75–81, doi. org/ 10. 1177/ 194589240401800202.
41. Alrajhi AA, Enani M, Mahasin Z, Al-Omran K. Chronic invasive aspergillosis of the paranasal sinuses in immunocompetent hosts from Saudi Arabia. *The American journal of tropical medicine and hygiene*. 2001; 65(1):83-6.
42. D'Anza B, Tien D, Stokken JK, Recinos PF, Woodard TR, Sindwani R. Role of lumbar drains in contemporary endonasal skull base surgery: Meta-analysis and systematic review. *American journal of rhinology & allergy*. 2016; 30(6):430-5.
43. Perfect JR. Fungal Rhinosinusitis (Noninvasive). *Rhinology*, 2014, p. 1–9.
44. Suresh S, Arumugam D, Zacharias G, Palaninathan S, Vishwanathan R, Venkatraman V. Prevalence and clinical profile of fungal rhinosinusitis. *Allergy & Rhinology*. 2016; 7(2): 16.
45. Soler ZM, Schlosser RJ. The role of fungi in diseases of the nose and sinuses. *Am J Rhinol Allergy* 2012;26:351–8.
46. Nicolai P, Lombardi D, Tomenzoli D, Villaret AB, Piccioni M, Mensi M, *et al.* Fungus ball of the paranasal sinuses: Experience in 160 patients treated with endoscopic surgery. *Laryngoscope* 2009;119:2275–9.

47. Costa F, Polini F, Zerman N, Robiony M, Toro C, Politi M. Surgical treatment of *Aspergillus* mycetomas of the maxillary sinus: review of the literature. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2007; 103(6):e23-9.
48. Chao TK, Liu CM. Gauze-Assisted Technique in Endoscopic Removal of Fungus Balls of the Maxillary Sinus. *Am*.