Treatment of Paranasal Sinus Fungus Ball: A Systematic Review and Meta-Analysis

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Gian Luca Fadda, MD^{1,2*}, Fabiana Allevi, MD, PhD^{2,3*}, Cecilia Rosso, MD⁴, Federica Martino, MD⁵, Carlotta Pipolo, MD^{2,4}, Giovanni Cavallo, MD¹, Giovanni Felisati, MD^{2,4+}, and Alberto Maria Saibene, MD, MA^{2,4+}

Abstract

Objectives: Paranasal sinus fungus ball is a common non-invasive mycosis with excellent long-term surgical treatment results. The present systematic review and meta-analysis were undertaken to define current treatment concepts and success rates in paranasal sinus fungus ball treatment.

Methods: Systematic searches were performed in multiple databases with criteria designed to include all studies published until May 2020 focusing on paranasal sinuses fungus ball treatment in humans. We selected studies including at least 10 patients, specifying treatment modalities, providing a minimum 6-month follow-up, and objectivating treatment success. After duplicate removal, abstract and full-text selection, and quality assessment, we reviewed eligible articles for treatment modalities and success rates. Success rates were pooled in a random effect meta-analysis and compared according to the use of intraoperative sinus lavages and postoperative antibiotics.

Results: Among 740 unique citations, 14 studies were deemed eligible. Most (n=11) were retrospective case series. All studies relied on endoscopic sinus surgery. Intraoperative lavages were proposed in 10 studies and postoperative antibiotics in 7 (for all patients in 5 studies and for selected patients in 2). No significant heterogeneity was observed between results (Cochran's Q P=.639, l^2 test=0). Treatment success rate was 98.4% (95% confidence interval 97.4%-99.3%). Intraoperative sinus toilette and postoperative antibiotics didn't significantly improve the success rate.

Conclusion: Endoscopic sinus surgery shows excellent results in fungus ball treatment. Further prospective studies might help further reducing antibiotics prescriptions in these patients and improve their management.

Keywords

endoscopy, computed tomography, maxillary sinus, mycosis, antibiotics

Introduction

According to the widely accepted classification proposed by DeShazo and colleagues,¹ paranasal sinus fungus balls (PSFBs) are considered a non-invasive mycosis.²

PSFB has, *per definition*, a benign behavior with rare invasive evolution in immunocompromised patients and/or immune-privileged anatomic sites. PSFB usually affects the maxillary sinus,³ though it can less commonly involve all paranasal sinuses and present with multiple lesions.⁴

PSFB can be completely asymptomatic and be discovered as incidentalomas in a radiological examination performed for other reasons.⁵ Nevertheless, they most often present with rhinosinusitis-like symptoms⁶ worsened by common bacterial superinfections.⁷

For unclear reasons, PSFB reporting has shown a significant increase in incidence over the last decade⁸ while its ¹Department of Otorhinolaryngology, San Luigi Gonzaga University Hospital, Università degli Studi di Torino, Turin, Italy
²ISGOS, The Italian Study Group on Odontogenic Sinusitis
³Department of Health Sciences, Maxillofacial Surgery Unit, Santi Paolo e Carlo Hospital, Università degli Studi di Milano, Milan, Italy
⁴Department of Health Sciences, Otolaryngology Unit, Santi Paolo e Carlo Hospital, Università degli Studi di Milano, Milan, Italy
⁵Department of Clinical Sciences and Translational Medicine, Unit of Otorhinolaryngology, University of Tor Vergata, Rome, Italy

*These authors contributed equally to this manuscript ⁺These authors contributed equally to this manuscript

Corresponding Author:

Alberto Maria Saibene, MD, MA, Department of Health Sciences, Otolaryngology Unit, ASST Santi Paolo e Carlo, Via Antonio di Rudini, 8, Milan, 20142, Italy. Email: alberto.saibene@gmail.com relationship with odontogenic sources of infection remains debated and not completely explained.⁹

Endoscopic sinus surgery (ESS) is the treatment of choice for PSFB and shows excellent treatment success rates without the need for antifungal treatment.³ On the other hand, the role of adjunctive sinus toilette techniques and postoperative antibiotic treatment is less consistent across the scientific literature and no randomized controlled trials addressed these issues.

The authors aimed, with this study, to systematically review the pertinent literature to aggregate mean success rates for PSFB treatment and to assess the influence of adjunctive sinus toilette techniques and postoperative antibiotic treatment on the overall treatment success rates.

Methods

Search Strategy

A systematic review was conducted between May 15 and October 10, 2020, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.¹⁰ We conducted systematic electronic searches for studies in the English, Italian, German, French, or Spanish language reporting original data obtained from humans and published until the search date which focused entirely or partly on PSFB.

On May 15, 2020, we searched the MEDLINE, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov databases with wide search strategies for fungus ball and all related terms in association with paranasal sinuses, nose, and related terms. The details of our full search strategies and the number of unique items retrieved from each database are available in Supplemental Resource 1.

We included any study dealing with the treatment of paranasal sinuses fungus ball in humans. We included only articles in which the diagnosis of fungus ball had been ascertained by the authors on the basis of radiological appearance, intraoperative findings and/or surgical pathology reports. We excluded meta-analyses, systematic and narrative reviews, and case reports, though references from review articles were hand-checked for additional potentially relevant studies. A minimum study population of 10 patients was required to minimize heterogeneity and publication bias.

Abstracts and full texts were reviewed in duplicate by different authors (C. R. and F. M. for abstracts and F. A. and G. F. for full texts). To maximize the rate of inclusivity in the early stages of the review, at the abstract stage, we included all studies deemed eligible by at least 1 rater. Then, at the full-text review stage, disagreements were resolved by consensus between raters. We included only studies that specified treatment modalities, provided a follow-up of at least 6 months and required an endoscopic, computed tomography, or magnetic resonance imaging evaluation to define therapeutic success.

PICO Criteria

The PICO criteria for the present review were as follows:

- Patients: Patients with PSFB.
- Intervention: PSFB treatment.
- Comparison: Use of intraoperative lavages; use of postoperative antibiotic treatment.
- Outcome: Treatment success (defined as no evidence of sinus pathology at endoscopic or radiological follow up).

Data Extraction and Quality Assessment

For each included article, we recorded the number of PSFB patients, the male to female ratio, patients' age, sinus location of PSFB (maxillary, ethmoidal, frontal, or sphenoidal), the presence of single or multiple PSFB in each patient, the main treatment of choice, the use of intraoperative sinus lavages or other intraoperative sinus toilette specific techniques, the use of postoperative antibiotics or antifungals, postoperative follow-up duration, choice of treatment success definition, and treatment success rate. Furthermore, we reported information on surgical pathology analysis and microbial cultures where available.

Selected studies were assessed for both quality and methodological bias according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).¹¹ Articles were rated in duplicate by 2 authors (A. M. S. and F. A.) and disagreements were resolved by consensus. Items were rated as good if they fulfilled at least 80% of the items required by the NHI-SQAT, fair if they fulfilled between 50% and 80% of the items, and poor if they fulfilled <50% of the items, respectively.

Also, the level of evidence was scored according to the Oxford Centre for Evidence-based Medicine (OCEBM) level of evidence guide.¹²

Articles with fair or good quality were used for metaanalysis. The pooled frequency of treatment success with 95% confidence intervals (CI) was assessed using the random effect model. Treatment success rates were compared also according to the use of intraoperative lavages and postoperative antibiotics administration. The between-study heterogeneity was assessed by Cochran's Q and *I*² statistics. Publication bias was assessed graphically via the funnel plot method.

All search results, abstract and article selection, and data extraction was performed with the Google Sheets web application (Google LLC, Mountain View, CA, US). The meta-analysis was performed with the freeware software Openmeta[Analyst] (Built 12/3/2013, Brown University,

Study	Study type	OCEBM rating	NHI-SQAT rating	Treated patients (n)	Male to female ratio (n)	Patients' age (years)
Castelnuovo et al ¹⁶	Case series	4	F	34	N/A	N/A
Costa et al ⁹	Case series	4	G	48	15:33	Avg 53.6, SD 11.9 (range 29-79)
Costa et al ¹⁷	Case series	4	F	13	N/A	Avg 56 (range 45-76)
Eloy et al ¹⁸	Case series	4	F	25	8:17	Avg 62 (range 24-83)
Fadda et al ⁶	Case series	4	F	40	11:29	Avg 52.8 (range 14-84)
Karci et al ¹⁹	Case series	4	F	10	3:7	Avg 43 (range 27-66)
Karkas et al ²⁰	Case series	4	F	28	10:18	Avg 64 (range 34-83)
Lai et al ²¹	Case series	4	F	90	21:69	Avg 61.1 (range 9-90)
Ledderose et al ²⁵	Prospective cohort study	2	G	40	15:25	Avg 56 (range 22-91)
Lee ²²	Case series	4	G	85	30:55	Avg 52 (range 22-74)
Nicolai et al ²³	Case series	4	F	160	42:118	Avg 52.7 (range 19-85)
Pagella et al ²⁴	Case series	4	F	56	15:46	Avg 62 (range 31-91)
Sawatsubashi et al ²⁷	Retrospective cohort study	3	G	28	5:23	Avg 60 (range 26-82)
Suresh et al ²⁶	Prospective cohort study	2	F	14	N/A	N/A

 Table I. Characteristics of the Included Studies.

Abbreviations: avg, average; F, fair; G, good; NI-SQAT, national heart, lung, and blood institute study quality assessment tools; OCEBM, oxford centre for evidence-based medicine; SD, standard deviation.

Providence, RI, US).¹³ The exception was the publication bias assessment, which was performed via the funnel plot method with the Statistical Process Control tool publicly distributed by the Information Services Division of Public Health Scotland¹⁴ and through Egger's and Begg's test performed with the freeware software Prometa (Version 3.0, IDoStatistics, Italy).¹⁵

Results

Search Results

Among the 729 unique research items initially identified, a total of 99 articles were selected for full-text evaluation, amongst which 14 relevant studies published between 1999 and 2019 were retained for further analysis (see Supplemental Resource 2). Most articles were retrospective case series (n=11),^{6,9,16-24} 2 were prospective cohort studies^{25,26} and 1 was a retrospective cohort study.²⁷ Concerning the level of evidence, 2 studies were rated as level 2 studies according to the OCEBM scale, 1 study was rated as level 3 study, and the remaining 11 studies were rated as level 4 studies. According to the NHI-SQAT, 4 articles were rated as good-, 10 articles were rated as fair- and no article was rated as poor-quality studies, respectively.

Most articles lacked ample information to support the comparability of patients. Table 1 reports the characteristics and demographics of the included studies.

The 14 included studies had 671 participants with single or multiple PSFB. All patients were treated with ESS. In selected cases, other accesses were coupled with ESS (trocar insertion through the canine fossa or access to MS anterior wall via a bony window). Female patients were the majority in all papers. Patients were on average in their 5th or 6th decade in 12 out of 14 studies (age range 9-90 years). Ten papers reported using sinus lavages during the surgical procedure and in 1 a gauze was used to clean the MS intraoperatively. Five papers reported postoperative antibiotic administration for all patients and 2 reported antibiotic administration in case of bacterial superinfection. The average follow-up was extremely heterogeneous, ranging from 6 to 341 months. A single article [6], which was coauthored by 1 of the authors of the present study, was implemented with missing follow-up data. Seven studies defined treatment success as endoscopic absence of PSFB recurrence and/or sinus infection, while a single study used only computed tomography (CT) scans. Another 3 studies used endoscopy coupled with CT scans and the last 3 used endoscopy coupled with CT scan in case of suspected recurrence. The overall treatment success rate in the reviewed articles was high, ranging from 92% to 100%. Detailed surgical, therapeutic, and follow-up data for each study are reported in Table 2. Most authors requested surgical pathology analysis of the specimens and performed fungal cultures, while only 2 papers reported data on bacterial cultures (see Table 3 for complete details on microbiological and surgical pathology analyses). No antibiogram results were reported, despite the antibiogram being indeed performed in a single study.⁶ The success rate after revision procedures was 100% in all studies reporting recurrences,

lable 2. Da	ta on Patients Diagr	iosis and I reatm	lent of Included Studies.					
		Patients with single or		Use of lavages or sinus toilette	Use of antibiotics or	Follow up	Modality of treatment	Treatment
Study	FB location (n)	multiple FB (n)	Main treatment (n)	techinques (n)	antifungals	(months)	success definition	success rate (n)
Castelnuovo et al ¹⁶	M=24; E=15; S=12; F=3	s=31; m=13	ESS = 24	Saline + 3% H,O, lavage	٥	72	NE + CT in case of doubt	31/34
Costa et al ⁹	M=48	s=46; m=2	ESS = 11; ESS + CFA = 13; ESS + BW = 24	Saline lavage	Unspecified antibiotic treatment for all patients; no antifungals	12	NE + CT	46/48
Costa et al ¹⁷	M=13	s=13	ESS = I 3 (MMA = I 2; MMA + IA = I)	Unspecified lavage	S	Range 6 to 48	NE + CT	13/13
Eloy et al ¹⁸	S = 25	s = 20; m = 5	ESS = 25 (TRSE = 16; sphenoetmoidectomy = 4; TESE = 1, paraseptal sphenoid access = 4)	° 2	°Z	Avg 24 (range 6-120)	NE + CT in suspect of recurrence	23/25
Fadda et al ⁶	M=28; S=7; M + S=5	s=33; m=7	ESS=40 (MMA, TRSE)	Unspecified lavage	Antibiotics following and according to positive antibiogram; no antifungal	Avg 15.8 (range 6*-20)	В	40/40
Karci et al ¹⁹	M=3; E=2; S=4; F=1	s=10	ESS = 9 (MMA + EE = 2; EE = 2; SE = 4; FS = 1; ESS (MMA + EE) + CFA = 1	No	Unspecified antibiotic for 2wk; no antifungal	Range I5 to 32	NE + CT	01/01
Karkas et al ²⁰	S = 28	s=26; m=2	ESS = 28 (TRSE = 16; TESE = 12)	Saline lavage	No	Avg 13 (range 6-30)	NE	26/28
Lai et al ²¹	M=60; E=20; S=7; F=2	s=42; m=48	ESS = 90	Unspecified lavage	No	Avg 81 (range 31-341)	NE	87/90
Ledderose et al ²⁵	M=37; E=6; S=3; F=1	s=35; m=5	ESS = 40	oN	Unspecified antibiotic in 12 patients with visible bacterial superinfection; no antifungals	12	ЧZ	40/40
Lee ²²	M=67; M + E= 16; S=3	s=70; m=16	ESS = 85 (MMA; EE; TRSE; FS)	Unspecified lavage	Unspecified antibiotics in all patients	Avg 16.7 (range 6-22)	NE + CT in case of doubt	85/85
Nicolai et al ²³	M = I 35; E = 2; S = 23	s=158; m=2	ESS = 160 (MMA; EE; TRSE; TESE)	Saline lavage	Amoxicillin/clavulanate I g, b.i.d., for 7 d; no antifungal	Range 18-196	NE	158/160
Pagella et al ²⁴	S = 24	s=24	ESS = 56 (TRSE = 31, TESE = 25)	Saline lavage	Amoxicillin/clavulanate 1g, t.i.d., for 8d; no antifungal	Avg 70.7 (range 12-181)	NE	54/56
Sawatsubashi et al ²⁷	M=28	s=28	ESS = 28 (MMA = 14; MMA + 1A = 14)	Gauze toilette	oN	Avg 18 (range 12-60)	C	26/28
Suresh et al ²⁶	N/A	N/A	ESS = 14	No	°Z	Avg 11.06; SD 1.23	NE	14/14
Abbreviations: av	3, average; BW, anterior n	naxillary wall bone w	indow; CFA, canine fossa approach; CT	. computed tomograt		my; ESS, endoscopic s	sinus surgery; F, frontal; FS,	frontal

sinusotomy; IA, inferior antrotomy; M, maxillary; N/A, not available; NE, nasal endoscopy; TESE, trans-ethmoidal sphenoidotomy; TRSE, trans-sphenoethmoidal recess sphenoidotomy; S, sphenoidal; SD, standard deviation; SE, sphenoethmoidectomy. "Missing follow up data for this article was provided by Dr. Fadda, author of the referenced article and of this review.

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Study	Microbiological cultures	Fungal species	Bacterial species	Istological evaluation	Results
Castelnuovo et al ¹⁶	Fungal only (n=72)	Not reported analytically	N/A	Fungus ball and mucosa (n=72)	Not reported analytically
Costa et al ⁹	N/A	N/A	N/A	N/A	N/A
Costa et al ¹⁷	Fungal only (n = 13)	Aspergillus spp. (n=2)	N/A	Fungus ball (n = 13)	Hyphae from Aspergillus spp. (n = 13)
Eloy et al ¹⁸	Fungal only (n = 18)	Aspergillus fumigatus (N = 6)	N/A	Mucosa (n=25)	No mucosal invasion (n = 25)
Fadda et al ⁶	Fungal and bacterial	Aspergillus fumigatus (n=v4),	Staphylococcus spp. $(n = 5)$,	Fungus ball and	No mucosal invasion $(n = 40)$;
	(n=36)	Aspergillus flavus (n=2), Candida son (n=1)	Pseudomonas aeruginosa n = 5) Strentococcus son	mucosa (n=40)	hyphae from Aspergillus spp. (N = 31) Candida son (n = 1)
			(n = 2), Haemohilus influenzae (n = 2), other $(n = 5)$		Mucor spp. (n = 1) or from other uncharacterized mycetes (n = 3)
Karci et al ¹⁹	N/A	N/A	NA	N/A	N/A
Karkas et al ²⁰	Fungal only (n=28)	Aspergillus fumigatus $(n = 3)$,	N/A	Fungus ball and	No mucosal invasion (n = 28);
		Aspergillus nidans (n=1), Graphium spp. (n=1)		mucosa (n=28)	hyphae from Aspergillus spp. (n=26) or Graphium spp. (n=2)
Lai et al ²¹	Fungal only (n=53)	Aspergillus spp. (n=4), Candida spp. (n=1)	N/A	Fungus ball (n = 90)	Twisted hyphae $(n = 90)$
Ledderose et al ²⁵	Fungal and bacterial	Aspergillus fumigatus (n=4)	Bacterial growth $(n = 22)$, most	Fungus ball and	No mucosal invasion $(n = 40)$;
	(n = 40)		often S. aureus or mixed Gram- and Gram + bacteria	mucosa (n=40)	hyphae (n = 40)
22				E	
ree	¢ 2			rungus ball (n - 00)	Hypnae from Asperguius spp. (n = 62) or from other uncharacterizable mycetes (n = 26)
Nicolai et al ²³	Fungal only (n = 118)	Aspergillus fumigatus (n = 18),	N/A	Fungus ball and	No mucosal invasion (n = 160);
		Alternaria spp. (n = 3), Penicillum spp. (n = 1),		mucosa (n=160)	hyphae from Aspergillus spp (n=21), Mucor spp (n=1), and
		Bipolaris spp. (n= 1), and Paecilomyces variotii (n= 1)			Candida spp. (n= I)
Pagella et al ²⁴	Fungal only (n=56)	Aspergillus fumigatus (n = 22), Penicillum spp. (n = 3),	N/A	Fungus ball and mucosa (n=56)	No mucosal invasion (n=56); hyphae (n=56)
:		Paecilomycetes spp. (n = 1)			
Sawatsubashi et al ²⁷	N/A	A/A	N/A	Fungus ball (n=28)	Hyphae from Aspergillus spp. (n=20) or from other
, 12k		-			
Suresh et al ²⁰	Fungal only (n = 14)	Not reported analytically	N/A	Fungus ball (n = 14)	Not reported analytically

Abbreviation: N/A, not available.

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Table 3. Microbiological and Surgical Pathology Results of Included Studies.

Studies	Estir	nate (95% C.I.)	Ev/Trt
Castelnuovo et al, 2000	0.912	(0.816, 1.000)	31/34
Costa et al, 2008	0.958	(0.902, 1.000)	46/48
Costa et al, 2019	0.964	(0.867, 1.000)	13/13
Eloy et al, 2013	0.920	(0.814, 1.000)	23/25
Fadda et al, 2019	0.988	(0.954, 1.000)	40/40
Karci et al, 1999	0.955	(0.831, 1.000)	10/10
Karkas et al, 2013	0.929	(0.833, 1.000)	26/28
Lai et al, 2011	0.967	(0.930, 1.000)	87/90
Ledderose et al, 2012	0.988	(0.954, 1.000)	40/40
Lee, 2007	0.994	(0.978, 1.000)	85/85
Nicolai et al, 2009	0.988	(0.970, 1.000)	158/160
Pagella et al, 2011	0.964	(0.916, 1.000)	54/56
Sawatsubashi et al, 2015	0.929	(0.833, 1.000)	26/28
Suresh et al, 2016	0.967	(0.876, 1.000)	14/14
Overall (I^2=0% , P=0.630)	0.984	(0.974, 0.993)	653/671

Figure 1. The pooled success rate in patients undergoing treatment for paranasal sinus fungus ball. Effects and summaries were calculated using a random effect model weighted by the study population.

and no failure to complete the intended follow-up was reported in studies.

Systematic Review and Meta-Analysis

All articles of fair or good quality according to the NHI-SQAT rating were included as no significant methodological bias emerged. Neither the visual analysis via funnel plot (see Supplemental Resource 3) or Egger's and Begg's (respectively P=.11 and .78) suggested the presence of a publication bias. A meta-analysis was therefore performed across all 14 reviewed studies.

The mean treatment success rate in patients with PSFB was 98.4% (95% confidence interval [CI] 97.4%-99.3%) (see Figure 1). No significant heterogeneity was observed between studies (Cochran's Q P=.63, I^2 test=0). The estimated rate of treatment success in patients with PSFB. The use of sinus toilette techniques improved the success rate (98.4%, [CI 97.4%-99.4%] against 97.9% [CI 94.9%-100%]) (see Figure 2). Use of postoperative antibiotics improved the success rate (98.8% [CI 97.7%-99.9%] against 95.3% [CI 92.6%-98%]). This difference was analogous, but with wider confidence intervals, if antibiotics were used only in specific patients subgroups (ie, with positive bacterial cultures and following antibiogram or when purulence was recorded) (success rate 98.8% [CI 96.4%-100%]) (see Figure 3). Both for sinus toilette techniques and antibiotics use, the reported moderate improvement in success rate was nevertheless not statistically significant, as confidence intervals for success rates are largely overlapping between all subgroups. Last, the lack of complete information on antibiotic regimens and antibiograms determined a too heterogeneous scenario to be further analyzed in a meta-analysis.

Discussion

This is the first meta-analytic study to address the treatment of PSFB and it confirms ESS as the only current treatment for the condition, with an excellent overall treatment success rate, higher than success rates for chronic rhinosinusitis surgery,²⁸ which employs similar techniques. It has to be noted that we chose to include only articles objectively demonstrating fungus ball treatment success as we felt that patients' satisfaction or symptoms resolution was not a reliable index in such a commonly asymptomatic disease. Our hypothesis was that basing success rates on less objective parameters could have led to a biased greater success rate for all studies.

This systematic review included a total of 14 studies involving 671 patients diagnosed with PSFB, allowing for a comprehensive evaluation of the pertinent literature. Most of the included studies were of good or fair methodological quality, albeit marred by a lack of prospectively collected data and the absence of randomized controlled trials.

In the context of such outstanding treatment rates, it is understandable that nuances in the management of these patients have not been addressed systematically to date. Specifically, our meta-analytic work shows that the use of more thorough sinus toilette techniques (lavage with either saline or oxygen peroxide) and selective use of postoperative antibiotics do not significantly improve the success rate in



Figure 2. The pooled success rate in patients undergoing treatment for paranasal sinus fungus ball. Results are separately evaluated and pooled for patients in which a sinus toilette technique was used intraoperatively (subgroup "sinus toilette") and for patients in which it wasn't (subgroup "no sinus toilette"). Effects and summaries were calculated using a random effect model weighted by the study population.



Figure 3. The pooled success rate in patients undergoing treatment for paranasal sinus fungus ball. Results are separately evaluated and pooled according to the postoperative antibiotic treatment: no postoperative antibiotic treatment ("No ABx treatment" group), postoperative antibiotic treatment to all patients ("ABx in all patients" group), or postoperative antibiotic treatment in a selected group of patients ("ABx in selected patients" group). Effects and summaries were calculated using a random effect model weighted by the study population.

these patients. In both cases the better pooled success rates despite being modestly higher, have largely overlapping CI. It has to be noted though that the lack of prospective randomized studies focused on these ancillary treatments and procedures doesn't allow a direct comparison of results or performing a nested analysis. Therefore the modest shift in the pooled average treatment success rate observed in our meta-analysis definitely requires further studies to be confirmed.

For what specifically concerns postoperative antibiotic treatment, we have to take into account that the reviewed articles either propose a first-line antibiotic therapy (Amoxicillin clavulanate), do not specify antibiotic treatment, or follow the antibiogram results, making their results too heterogeneous to compare. Therefore, despite the overall good general results following postoperative PSFB antibiotic treatment, it is not possible to conclude this aspect. It is nevertheless important to recall also that, based on current evidence, indiscriminate use of antibiotic therapy following PSFB remains questionable.⁶ It has to be noted that articles not employing lavages and/or antibiotics didn't explicitly state so, so the allocation to the meta-analysis subgroups was an inference agreed upon during data extraction, extrapolated from careful analysis of the papers. While this doesn't alter the overall quality of the results, this is a significant inherent limitation that deserves mention.

It is interesting to observe that all authors agree on selectively treating with ESS only the paranasal sinuses directly affected by PSFB, except for Karci et al.¹⁹ In their paper, notably the eldest in our selection, they coupled antrostomy with ethmoidectomy even in cases with isolated maxillary involvement. Regarding the use of extended accesses to the diseased sinus, inferior antrotomy was shown to be the most frequent and appears to have a shared indication for specific fungus ball locations (eg, lateral or anterior maxillary wall for inferior antrotomy). Though shared, the indications for these accesses have not been explored methodically in the reviewed articles. Furthermore, only 2 articles separately reported results for ESS-only patients and extended-access patients.9,27 This makes a direct comparison of standard ESS and endoscopic approaches impossibile in the context of our meta-analysis and this represents a limitation of our work. Specific indications for these accessory approaches and discussion of their advantages over "conventional" ESS techniques fall therefore outside the scope of this paper and are a matter of debate in contemporary literature.²⁹ The comparison between different endoscopic approaches for PSFB definitely represents a research area for future prospective studies.

In the context of this meta-analysis, we strived to minimize bias in selecting articles and extracting data. With this in mind, we didn't choose time limits for our searches and included all treatment modalities. Nevertheless, eligible included articles were all published in the endoscopic era (no later than 1999) and ESS emerged as the only current treatment for PSFB. Choosing to include only articles proposing imaging or endoscopy for treatment success definition may appear as a considerable bias in selecting articles. Nevertheless, we chose to include articles that objectivated the treatment success over a sufficient follow-up to avoid misclassifying asymptomatic recurrences as successes. It's been recently indeed demonstrated in prospective studies that a significant rate of patients undergoing surgery for PSFB show signs of mucostasis, which can negatively affect the long term results.³⁰

It remains still open to debate whether or not PSFB should be surgically treated also in asymptomatic patients,³¹ since the excellent treatment success rate should be always adequately balanced with the anesthesiological risk and the overall benefit for the patients. Further studies are nevertheless required to explore this important question.

Conclusion

Our findings, therefore, confirm ESS as the treatment of choice for PSFB, with excellent success rates. Despite improving these rates would be extremely difficult, further prospective, and hopefully randomized, study of the ancillary procedures and treatments that we discussed which might lead to the reduction of unnecessary further antibiotic treatments and revision surgeries and a better management of PSFB patients.

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ORCID iDs

Cecilia Rosso D https://orcid.org/0000-0002-2187-0799 Alberto Maria Saibene D https://orcid.org/0000-0003-1457-6871

Supplemental Material

Supplemental material for this article is available online.

References

- deShazo RD, O'Brien M, Chapin K, et al. A new classification and diagnostic criteria for invasive fungal sinusitis. *Arch Otolaryngol Head Neck Surg.* 1997;123(11): 1181-1188.
- Kim YK, Kim HJ, Kim HY, et al. Extrasinonasal infiltrative process associated with a sinonasal fungus ball: does it mean invasive fungal sinusitis? *Diagn Interv Radiol*. 2016;22(4): 347-353.
- 3. Liu X, Liu C, Wei H, et al. A retrospective analysis of 1,717 paranasal sinus fungus ball cases from 2008 to 2017. *Laryngoscope*. 2020;130(1):75-79.
- Vinciguerra A, Saibene AM, Lozza P, Maccari A. Unusual case of bilateral maxillary fungus ball. *BMJ Case Rep.* 2016;2016:bcr2016217930.
- Johnson K, Parham K. Nasal and paranasal sinus infections. In: Hupp J, Ferneini E, eds. *Head, Neck, and Orofacial Infections*. Amsterdam, The Netherlands: Elsevier; 2016: 248-270.

- Fadda GL, Succo G, Moretto P, et al. Endoscopic endonasal surgery for sinus fungus balls: clinical, radiological, histopathological, and microbiological analysis of 40 cases and review of the literature. *Iran J Otorhinolaryngol* 2019;31(102):35-44.
- Saibene AM, Vassena C, Pipolo C, et al. Odontogenic and rhinogenic chronic sinusitis: a modern microbiological comparison. *Int Forum Allergy Rhinol.* 2016;6(1):41-45.
- Kim DW, Kim YM, Min J-Y, et al. Clinicopathologic characteristics of paranasal sinus fungus ball: retrospective, multicenter study in Korea. *Eur Arch Otorhinolaryngol*. 2020;277(3):761-765.
- 9. Costa F, Emanuelli E, Franz L, et al. Fungus ball of the maxillary sinus: retrospective study of 48 patients and review of the literature. *Am J Otolaryngol.* 2019;40(5):700-704.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
- Study Quality Assessment Tools. National Heart, Lung, and Blood Institute (NHLBI). Accessed September 2, 2020. https://www.nhlbi.nih.gov/health-topics/study-qualityassessment-tools
- The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine. Accessed September 2, 2020. https://www.cebm.net/index.aspx?o=5653
- Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: ras a computational back-end. *J Stat Softw.* 2012;49(5):1-5. doi:10.18637/jss.v049.i05
- Quality Indicators. ISDS Scoltand. Accessed October 1, 2020. https://www.isdscotland.org/Health-Topics/Quality-Indicators/Statistical-Process-Control/
- 15. ProMeta 3. IDoStatistics. Accessed September 10, 2020. https://idostatistics.com/prometa3/
- Castelnuovo P, Gera R, Di Giulio G, et al. Paranasal sinus mycoses. *Acta Otorhinolaryngol Ital*. 2000;20(1):6-15.
- Costa F, Polini F, Zerman N, et al. Functional endoscopic sinus surgery for the treatment of Aspergillus mycetomas of the maxillary sinus. *Minerva Stomatol.* 2008;57(3):117-125.
- Eloy P, Grenier J, Pirlet A, et al. Sphenoid sinus fungall ball: a retrospective study over a 10-year period. *Rhinology*. 2013;51(2):181-188.

- Karci B, Bilgen C, Gunhan O. Endoscopic sinus surgery in the isolated paranasal sinus aspergilloma. *Rev Laryngol Otol Rhinol (Bord)*. 1999;120(5):327-330.
- Karkas A, Rtail R, Reyt E, Timi N, Righini CA. Sphenoid sinus fungus ball. *Eur Arch Otorhinolaryngol.* 2013;270(3):893-898.
- Lai J-C, Lee H-S, Chen M-K, Tsai Y-L. Patient satisfaction and treatment outcome of fungus ball rhinosinusitis treated by functional endoscopic sinus surgery. *Eur Arch Otorhinolaryngol.* 2011;268(2):227-230.
- 22. Lee KC. Clinical features of the paranasal sinus fungus ball. J Otolaryngol. 2007;36(5):270-273.
- Nicolai P, Lombardi D, Tomenzoli D, et al. Fungus ball of the paranasal sinuses: experience in 160 patients treated with endoscopic surgery. *Laryngoscope*. 2009;119(11):2275-2279.
- Pagella F, Pusateri A, Matti E, et al. Sphenoid sinus fungus ball: our experience. *Am J Rhinol Allergy*. 2011;25(4):276-280.
- Ledderose GJ, Braun T, Betz CS, Stelter K, Leunig A. Functional endoscopic surgery of paranasal fungus ball: clinical outcome, patient benefit and health-related quality of life. *Eur Arch Otorhinolaryngol.* 2012;269(10):2203-2208.
- Suresh S, Arumugam D, Zacharias G, et al. Prevalence and clinical profile of fungal rhinosinusitis. *Allergy Rhinol*. 2016;7(2):115-120.
- Sawatsubashi M, Murakami D, Umezaki T, Komune S. Endonasal endoscopic surgery with combined middle and inferior meatal antrostomies for fungal maxillary sinusitis. J Laryngol Otol. 2015;129(Suppl 2):S52-S55.
- Chowdhury N, Smith TL, Beswick DM. Measuring success in the treatment of patients with chronic rhinosinusitis. *Immunol Allergy Clin North Am.* 2020;40(2):265-279.
- Felisati E, Saibene AM, Borloni R, Prades JM, Felisati G. Miniinvasive endoscopic approaches to the maxillary sinus floor: a comparative anatomical study. *Am J Rhinol Allergy*. Published online October 6, 2020. doi:10.1177/1945892420964096
- Cavada MN, Wong E, Orgain CA, et al. Fungal ball of the maxillary sinus and the risk of persistent sinus dysfunction after simple antrostomy. *Am J Otolaryngol.* 2020;41(4):102541.
- Bulfamante AM, Pipolo C, D'Agostino Fiorenza U, et al. Spontaneous healing in maxillary fungus ball: beware of asymptomatic patients. *Clin Case Rep.* Published online November 28, 2020. doi:10.1002/ccr3.3665