The value of antifungal therapy in allergic fungal rhinosinusitis*

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Abstract

Background: Allergic fungal rhinosinusitis (AFS) is considered to part of the disease spectrum of chronic rhinosinusitis, which affects between five to fifteen per cent of the population. Currently, there is uncertainty relating to the pathological process and therefore optimal management of AFS. Studies assessing antifungal use have shown mixed results. The aim of this review is to assess the effect of antifungals on patients with AFS.

Methods: A systematic review of the literature to include all published trials searching Pubmed, Medline (Ovid), CINAHL (EBSCO) and the Cochrane central register of controlled trials (CENTRAL) databases.

Results: Sixteen studies (two systematic reviews, two meta-analysis, four randomised controlled trials, five prospective cohort studies and three retrospective studies) were included in this review. There was found to be no overall benefit of topical or oral antifungals upon endoscopic findings or patient reported outcome measures in AFS. There were no statistically significant differences in adverse effect profiles between treatment and control groups.

Conclusion: There is limited evidence to support the use of topical or oral antifungal agents in patients with AFS. Future research recommendations include large multicentre randomised trials with better matched patient groups and appropriate dosage and timing of antifungals.

Key words: rhinosinusitis, paranasal sinuses, antifungal agents, amphotericin b, endoscopy

Introduction

Rhinosinusitis in all of its forms (e.g. acute and chronic) is one of the most common conditions to affect the global population. There are estimated to be over 60 million sufferers within the European Union and the United States (US) alone [(1)].

Allergic fungal rhinosinusitis (AFS) is considered to be a subtype of chronic rhinosinusitis (CRS) and it is estimated that approximately 5-10 per cent of those with CRS actually carry a diagnosis of AFS [(2)].

There is much debate and controversy regarding AFS and the possible role that fungi may play in CRS. Rather than being a distinct entity, it has been argued that AFS falls within the large spectrum of sino-nasal inflammatory disease which includes the presence of nasal polyps. A growing body of experts now believe that fungi act as a primary stimulus within CRS and have therefore proposed the term "eosinophilic fungal rhinosinusitis". The consensus upon the effective management of AFS involves firstly removing the fungal stimulus (often surgical), followed by control of the immunological response and recurrence [(3)].

Antifungal therapy is believed to reduce the antigenic load and therefore reduce the hypersensitivity (allergic) response and recurrence. Several studies assessing systemic antifungal agents (e.g. Itraconazole and Ketaconazole) have shown mixed

results with regards to disease control and recurrence within this patient group [4]. As AFS is a non-invasive condition, it is considered that topical antifungal therapy should be more effective and safer in providing effective local disease control. Several investigators have shown support for the use of topical antifungal agents in AFS [5,6] as selected studies have reported some promising outcomes. However, there are also many studies that have shown no benefit. A previous Cochrane review (2011) has assessed the role of antifungals in CRS, however, there is little discussed with regards to the subgroup of AFS patients [7]. The major factor for this limited analysis was a lack of high quality evidence available in the literature regarding patients with AFS (did not fulfil inclusion criteria). Therefore, this review aims to assess the current evidence-base focusing on the use of antifungals in AFS.

Materials and methods

Objectives

To investigate the effect of antifungal therapy (topical and systemic) on the objective nasal endoscopic findings in patients with AFS.

Searching the literature

Types of studies

Following a review of the available literature a decision was made to include meta-analysis, systematic reviews, placebo controlled randomised control trials (RCT), open prospective studies and retrospective reviews within this study.

Types of participants

Studies that recruited both adults and children diagnosed with AFS as defined by the Bent and Kuhn (1994) criteria [8] (or modifications to Bent and Kuhn criteria [8]) were included (Table 1). Also due to the similarity in the disease process, secondary analysis included adults and patients diagnosed with CRS and its subtypes (with and without nasal polyposis) as described by the European Position Paper on Rhinosinusitis and Nasal Polyps (2012)[9], or by the American Academy of Otolaryngology – Head and Neck Surgery guidelines [10].

Types of interventions

Studies involving the use of systemic and topical antifungals in patients with AFS were considered in the primary analysis. Systemic antifungals can be administered orally or intravenously. Topical antifungals can be administered via nasal inhalation, irrigation, drops, sprays and douching. Further analysis was performed on studies using systemic and topical antifungals in CRS and its sub-types.

Outcome measures

Objective endoscopic findings characterised by several endoscopic staging systems (e.g. Kupferberg staging system, modified Lund-Kennedy & Malm)[11-13] were used as the primary outcome measures. Secondary outcome measures included Patient Reported Outcome Measures (PROM), collated symptom scores and subjective symptom findings (e.g. improvement, no improvement or deterioration). Adverse events were also recorded.

Data collection and analysis

Literature search

An electronic database literature search was conducted with no date or language restrictions. This as well as other similar systematic searches are at risk of publication bias through non-inclusion of unpublished studies. A search strategy was performed with a combination of Medical Subject Headings (MeSH) and keyword items. Medical databases included Pubmed, Medline (Ovid) and CINAHL (EBSCO), the Cochrane central register of controlled trials (CENTRAL). Following initial search results, secondary hand-searches were performed. Search terms included "allergic fungal sinusitis", "fungal sinusitis", "sinusitis", "rhinosinusitis", "paranasal sinuses", "antifungal agents", "Amphotericin B", "Itraconazole", "Fluconazole", "Ketoconazole" and "Voriconazole". The evidence was individually analysed according to critical appraisal selection programme (CASP) data collection tools as highlighted by the Centre for Evidence Based Medicine (2009)[14]. The methods and quality (to include outcomes) were evaluated in turn.

Particular consideration was given to:

- Trial characteristics
- Methods of randomisation
- Methods of blinding
- Intention to treat analysis
- Duration of trial (to include follow-up)
- Number of participants
- Age of participants
- Exclusion criteria
- Diagnostic criteria
- Interventions – primary
- Interventions – secondary
- Duration of treatment
- Outcomes (primary and secondary)
- Adverse outcomes

Assessment for risk of bias from included randomised controlled studies

Critical Appraisal Skills Programme tools [14] were used to evaluate sequence generation, allocation concealment, blinding of participants, outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias.

Table 1. Bent and Kuhn Criteria (1994) for the diagnosis of allergic fungal sinusitis [8].

Bent and Kuhn Criteria
Evidence of Gel & Coombs type I hypersensitivity
Nasal polyposis
Characteristic Computer Tomography findings
Eosinophilic mucin
Positive Fungal Smear

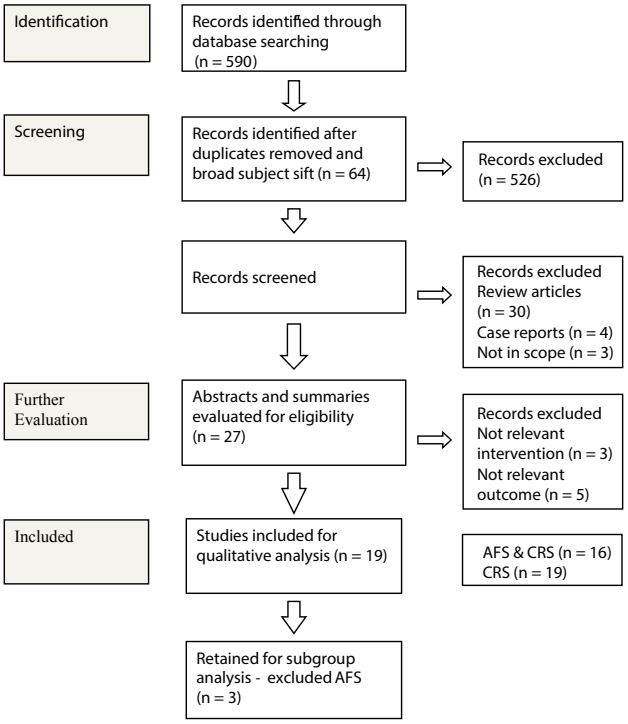

Figure 2. Flow diagram illustrating the literature selection process.

Results

Description of studies

Results of the search

A literature search revealed 590 references, 526 references were initially removed by a primary screening process, which involved identifying and excluding clearly irrelevant material and duplicates from searches. The remaining 64 references underwent a secondary screening process and assessment. Following review of abstracts and summaries, 19 studies were selected for review. From these, 16 included participants with AFS, the remainder were included as they investigated CRS and the subtypes. A flow chart that details the study selection process can be found in Figure 2.

Methodological quality of included trials

Detailed information regarding the characteristics of each trial included within this review can be found in Table 2.
Overall, from the four RCTs included within this review, significant limitations in methodology leading to bias were identified from the study by Khalil et al. [15] (Table 3).

Exclusion of studies

Twenty-seven trials were identified as appropriate to the basic criteria for the review. Eight of these trials did not focus upon antifungals within AFS or CRS and its subtypes. This left 19 trials. A full text article review revealed that three of these trials actively excluded AFS from its analysis. As the outcomes of these three studies were relevant to several of the secondary outcome measures related to this study (i.e. antifungals in CRS), they have been included as a further sub-group analysis as indirect conclusions can be drawn from these studies. Excluding these studies from the primary analysis, the final search identified 16 studies that assessed the use of antifungals in AFS and CRS.

Outcome measures

Endoscopic outcomes - topical antifungals

Data extracted from an existing meta-analysis has shown there to be no overall evidence for improvement in endoscopic scores following the use of topical or oral antifungals in AFS and CRS [7]. The two trials that included AFS patients [16,17] interestingly marginally favoured the treatment groups (SMD -0.97 [-1.83 to -0.10 95% CI][16] and -0.13 [-0.62 to 0.36 95% CI][17]). However, although the overall meta-analysis reported no benefit, it must be noted that it included studies that actively excluded AFS [7]. Ponikau et al. included patients with both AFS and CRS [17]. As mentioned, the group reported improved endoscopic outcomes [11]. However, the group only enrolled a small number of participants (n = 30, both CRS and AFS) and suggested that factors including a poor uptake in the study and a national shortage of Amphotericin B (AMB) to be contributing factors for such low enrolment numbers. Although 20 per cent of participants did not complete the study, attrition bias is believed to be low as the group had calculated from previous studies that treatment effect was not expected until ten to twelve weeks, and as the participants withdrew prior to this they did not need to be included within the analysis.
Although the meta-analysis marginally favoured the treatment group in the study by Liang et al. [16], the authors reported no significant benefit upon endoscopic outcome following use of topical AMB. This high quality study included both AFS and CRS participants (n = 70). Despite robust methodology, the study only assessed the effect of topical AMB over a four week dura-

Table 2. Studies included in the review.

Author / Year	Study	Participants	Disease studied	Treatment	Duration	Outcomes	Adverse events	Risk of Bias
Meta-analysis & Systematic Reviews								
P. Sacks, Harvey, Rimmer, Gallagher, R. Sacks, 2012	Meta-analysis (RCT)	380 participants (6 RCTs)	AFS & CRS *3 studies excluded AFS	5 studies - Topical AMB (total daily dose range 4mg to 20mg) as spray, lavage or irrigation versus placebo 1 study - Oral Terbinafine 625mg versus placebo	4 to 52 weeks	Topical – Endoscopic: No significant benefit over placebo p=0.98 (4 trials, n=101 AMB group Vs n=103 controls; significant heterogeneity) Symptom scores: favoured controls p=0.01 (3 trials, n=101 AMB group Vs n=105 controls; acceptable homogeneity) Oral – Symptom scores: (n=23 antifungal Vs n=26 controls) no significant benefit p=0.82	Local irritation (AMB)	Low
P. Sacks, Harvey, Rimmer, Gallagher, R. Sacks, 2011	Systematic review of literature							
Thanasumpun & Batra, 2011	Systematic review of literature 1 RCT 27 (Retrospective studies, case series, case reports, expert opinions)	28 studies included	AFS & CRS (19 studies AFS as primary disease entity)	Oral Itraconazole Oral ketaconazole		No objective findings Symptom scores: improvement in 78% (n=64/82) p <0.001; significant heterogeneity	Elevation of hepatic enzymes, rash, lower extremity swelling, headaches	High
Isaacs, Fakhri, Luong, & Citardi, 2011	Meta-analysis 3 RCTs 3 Uncontrolled studies	284 participants (6 trials)	AFS & CRS 2 RCTs excluded AFS (total 176 participants AFS & CRS)	Topical AMB (0.1mg/ML to 10mg/ML)	4 to 52 weeks	Endoscopic scores: (4 studies n=157, where 2 excluded AFS) no significant difference versus control group (n=16) p =0.53. Symptom scores (SNOT-20; 2 studies): no significant difference versus controls p=0.33		Moderate
Randomised Controlled Trials (RCT)								
Khalil et al, 2011	Open prospective RCT	50 participants (9 lost to follow-up) Controls (n=10)	AFS	Oral Itraconazole (100mg daily) Topical Fluconazole (1mg daily) Oral Itraconazole and topical Fluconazole (as above) Irrigation of Fluconazole (1mg daily)	All regimens 3 months except irrigation of Fluconazole (6 weeks)	Endoscopic, radiological and clinical: Recurrence reduced in Topical Fluconazole, Topical Fluconazole and oral Itraconazole and Fluconazole irrigation where rates were 10% (n=1/10), 14.3% (n=1/7) and 28.6% (n=2/7) respectively.	Hepatotoxicity	High

Table 2. Studies included in the review, continued...

Author / Year	Study	Participants	Disease studied	Treatment	Duration	Outcomes	Adverse events	Risk of Bias
Liang et al, 2008	Prospective RCT	70 participants (5 lost to follow-up) Controls (n=35)	AFS & CRS	AMB Irrigation (20mg daily) Versus placebo	4 weeks	Endoscopic (Modified Lund): no significant difference between 2 groups at 2 or 4 weeks (p=0.375 and p=0.651 respectively) Symptom score (CRSOM-31: significant improvement between groups at 2 weeks (p=0.018) but not at 4 weeks	Skin itching – leading to 1 withdrawal	Low
Gerlinger et al, 2008	Prospective RCT	33 participants (3 lost to follow-up) Controls (n=17)	CRS *AFS excluded if suspected	AMB spray (4mg daily)	12 months	Endoscopic (Malm): more stage I,II & III changes seen but not statistically significant Symptom score (SNAQ II), CT score (Lund-Mackay): no significant differences	Nasal burning; 6 participants	Low
Ebbens et al, 2006	Prospective RCT	116 participants (17 lost to follow-up) Controls (n=57)	CRS *AFS excluded if suspected	AMB lavage (5mg daily each nostril) Versus placebo	13 weeks	Endoscopic scale: no significant difference p=0.64 Symptom score (VAS): no significant difference p=0.31		Low
Ponikau, Sherris, Weaver & Kita,, 2005	Prospective RCT	30 participants (6 lost to follow-up) Controls (n=15)	AFS & CRS	AMB lavage (20mg daily)	6 months	Endoscopy (modified Kupferberg): improved median scores at 3 and 6 months where p=0.047 and p=0.038 respectively. Symptom scores (SNOT-20): No significant difference	Nasal irritation – 2 patients withdrew, headache	Low
Kennedy et al, 2005	Prospective RCT	53 participants (9 lost to follow-up) Controls (n=28)	AFS & CRS	Oral Terbinafine (625mg daily)	6 weeks	CT scores (modified Lund Mackay) & Symptom score: no significant improvement		Low
Weschta et al, 2004	Prospective RCT	78 participants (20 lost to follow-up) Controls (n=39)	CRS *AFS excluded if fulfilled Bent & Kuhn criteria	AMB spray (4.8mg daily) versus placebo	8 weeks	Endoscopic (Malm): no significant difference CT (Lund-Mackay), Symptom score (VAS): no significant difference	Nasal burning	Low
Prospective Open Trials								
Chan, Genoway & Javer, 2008	Open pilot study	32 participants	AFS refractory to medical and surgical management (topical steroids, topical AMB, oral steroids)	Oral Itraconzaole (300mg daily tapered)	3 months	Endoscopic (Kupferberg): n= 12/32 (38%) improvement, however, the mean stage at pre-treatment, 1 and 2 months were stage 2. (no significant change) Symptom score (RSOM-31): significant improvement p=0.0156	Elevation in hepatic enzymes (one participant withdrawal)	High

Table 2. Studies included in the review, continued..

Author / Year	Study	Participants	Disease studied	Treatment	Duration	Outcomes	Adverse events	Risk of Bias
Helbling, Baumann, Haani, & Caversaccio, 2006	Prospective open trial	21 participants	AFS & CRS with nasal polyposis	AMB spray (3mg daily)	3 months	Endoscopic (Malm): no significant improvement p>0.05; n= 18/21 participants unchanged or deteriorated Symptom score: Improvement in n= 7/21 participants		High
Jen, Kacker, Huang & Anand, 2004	Open prospective Trial	16 participants	AFS	Fluconazole spray (100mg in 500ml saline; 5 sprays twice daily)	3 months	Endoscopic: no regression in polyps in n= 13/16 participants; n= 12/16 participants showed a stable reduction in oedema Symptom score: n= 12/16 participants showed stable or improvement		High
Ponikau, Sherris, Kita, & Kern, 2002	Prospective open label trial	51 participants	AFS & CRS	AMB irrigation (8mg daily)	Minimum 3 months (range 3-17 months)	Endoscopic (Malm):n= 38/51 improved by one stage; overall improvement significant p<0.001 Symptom score: n= 38/51 improved	Burning sensation (20% of participants)	Moderate
Richetti et al, 2002	Prospective trial	74 participants	AFS & CRS with nasal polyposis	AMB lavage (20mls 1:1000 twice daily)	4 weeks	Endoscopic (Malm): Those with stage I & II polyposis showed significant improvement p<0.0012; response to antifungal statistically significant p=0.033		Moderate
Retrospective reviews								
Lee, Przybyszewski, Montone, & Lanza, 2012	Retrospective chart review	20 participants	Fusarium associated CRS (positive fungal cultures)	Oral Voriconazole (unknown dose - 15 participants) Oral Posaconazole (unknown dose – 5 participants)	I month	Endoscopic score: improvement 66% (n= 10/15) and 60% (n= 3/5) for Voriconazole and Posaconazole respectively Symptom score: 80% (n= 16/20) improvement in sinonasal symptoms	erythematous rash, photosensitivity and elevation in hepatic enzymes	High
Sieberling & Wormald, 2009	Retrospective chart review	23 participants	AFS (Bent & Kuhn criteria)	Oral Itraconazole (100mg twice daily)	6 months	Endoscopic: 44% of AFS (n= 4/9) no recurrence	Elevation in hepatic enzymes; 3 participants withdrew due to elevated enzymes	High
Rains & Mineck, 2003	Retrospective case series review	137 participants	AFS (modified Bent & Kuhn criteria)	(1988-1992): Oral Itraconazole 400mg daily for 6 months (1992): Oral Itraconazole 200-300mg daily for 3-4 months (1994): Oral Itraconazole 400mg daily tapered over 3 months	12 year review Average duration of treatment 4.3 months	Recurrence rates: n= 69/137 participants; mean time to first recurrence 10.8+/-10.5 months	Elevated hepatic enzymes	High

Table 3. Methodology of included randomised controlled trials.

Study	Randomisation techniques	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Risk of bias (author judgement)
Kennedy et al., 2005	Computerised	Unclear	Double	Accounted	No	Unclear risk	Low
Ponikau et al., 2005	Block	Yes	Double	Accounted	No	Low risk	Low
Liang et al., 2008	Block	Yes	Double	Accounted	No	Low risk	Low
Khalil et al., 2011	Not described	No	No	Not accounted	Yes	Moderate risk	High

tion. It has been previously reported that this length of intervention is unlikely to yield meaningful outcomes [17].
Khalil et al. exclusively assessed AFS participants and reported evidence of objective improvement and reduced recurrence rates when assessing similarly matched groups [15]. However, several significant limitations were noted from the study, which can be seen in Table 3. In addition to these, it was not clearly stated how the recurrence was measured endoscopically (e.g. objective score / technique). Evidence derived from this study must be used with great caution due to the numerous failings and bias identified.

Two open prospective trials [18,19] reported improved endoscopic scores [13] following their antifungal regimes. The two groups assessed participants with AFS and CRS with and without nasal polyposis. The heterogeneity of the patient groups (in terms of the disease stage) make results difficult to interpret. It was also reported that participant surgical state in the study by Richetti et al. influenced outcomes [19]. There was a significant difference (p = 0.033) in endoscopic findings post antifungal therapy between participants who did and did not receive surgery. Ponikau et al. used AMB irrigation for a minimum of three months (range 3-17 months) [18]. This significant difference between the regimen duration is a further limitation of this study.
Two further open prospective trials [20,21] failed to report any benefit from topical antifungal agents (Fluconazole and AMB) on endoscopic findings. Both studies lacked controls and randomisation. Despite mixed results, limitations of these open prospective trials include low numbers, high drop-out rates, surgical heterogeneity of participants, variability in regimens and inconsistent outcome measures [20].

Oral antifungals

From the studies included in this review, only four reported endoscopic outcomes following oral antifungal therapy.
Khalil et al. administered oral Itraconazole and topical Fluconazole within one study arm and reported lower disease recurrence rates (endoscopically)[15]. The oral Itraconazole group (further study arm) alone did not have reduced recurrence rates, therefore it may be deduced that the beneficial effect was potentially produced by the use of the Fluconazole. Further studies have also reported beneficial outcomes for oral antifungals.
Chan et al. [22] prospective pilot study showed an endoscopic improvement (38 % (n = 12) patients) following oral Itraconazole. However, these findings were reported not to be significant as the mean endoscopic stage was the same both pre- and post-treatment. The group studied AFS patients exclusively, however, the numbers were relatively small (n = 32). As this study did not have a control group or randomisation, methodological bias would be a major limiting factor.
Sieberling and Wormald also used oral Itraconzaole in AFS patients, but at a lower dose (200mg versus 300mg daily) [23]. Endoscopic findings revealed no recurrence in 44 per cent of participants (n = 23). Lee et al. also performed a retrospective chart review on a small number of participants treated with oral Voriconazole (n = 15) and oral Posaconazole (n = 5)[24]. Both treatments were reported to yield improved endoscopic scores. However, dosages of each treatment were not reported within their methodology and endoscopic outcomes were not quantified (i.e. validated scoring system). As both of these studies were retrospective chart reviews, it is difficult to draw any firm conclusions from their results, as the outcomes are likely to be subject to considerable bias within their methodology.

Symptom scores for both topical and oral antifungals

Validated – Patient Reported Outcome Measures (PROM)

Data extracted from meta-analysis reported there to be no overall difference between the topical AMB versus the placebo group in terms of PROM [1]. The pooled SMD was 0.21 [-0.02 to 0.44 95% CI], which favoured the control group. However, this study included three trials that actively aimed to exclude AFS [25-27]. Liang et al. [16] and Ponikau et al. [17] assessed AFS participants and did not report any statistically significant improvement in RSOM-31(Rhinosinusitis Outcome Measure) and SNOT-20 (Sinonasal Outcome Test) scores, respectively, when comparing their topical AMB treatment groups to their placebos over the full trial periods. Interestingly, Liang et al. did show an initial benefit of AMB at two weeks (p=0.018), however, this difference was

not reported at four weeks [16]. Data extracted from these two studies for the purpose of the meta-analysis revealed a SMD that favoured the treatment group.
Isaacs et al. showed there was no significant difference between SNOT-20 scores when comparing topical AMB versus controls (p = 0.33)[28]. Importantly, it must be noted that two studies from this meta-analysis aimed to exclude AFS patients [26,27] and therefore such results must be interpreted with caution considering their overall outcomes in the context of this review.
Kennedy et al. did not report any benefit using the RSDI (Rhinosinusitis Disability Index) score when comparing oral Terbinafine group to controls [29]. Critical appraisal tools identified a low risk of bias from this study.
Chan et al. reported that their RSOM-31 scores showed statistically significant improvement (p = 0.0156) following the use of oral Itraconazole [22]. Limitations of this open pilot study included a lack of randomisation and the use of controls.

Non-validated symptom scores

One non-randomised prospective study showed no significant improvement in symptom scores upon AFS and CRS patients following the use of topical AMB [21].
Three studies reported symptomatic improvement, however, were limited by their methodological quality. Ponikau et al. reported that 38/51 participants had improved symptoms following topical AMB in their prospective open study [18]. A symptomatic improvement was also shown to occur following the prospective use of topical Fluconazole in 12/16 participants with AFS [20]. Finally, the retrospective study by Lee et al. reported that symptoms improved in 80 per cent of participants following oral Voriconazole and oral Posaconazole [24].
Disease specific QOL scores were collated within a meta-analysis [1], which reported no significant improvement in QOL with the use of topical AMB when compared to the placebo. When assessed individually (without the studies which excluded AFS) there was still no benefit reported.

Adverse effects of topical and oral antifungals

Despite the well documented side effect profile of antifungal agents, no studies have reported any statistically significant adverse effects when compared to control groups. However, individual studies have reported common adverse effects (e.g. hepatic enzyme derangement). Meta-analysis assessing adverse events associated with topical AMB versus a placebo, reported no statistically significant difference between the two groups [1]. A risk ratio for adverse events was calculated at 3.36 [0.86 to 13.07 95% CI] [1], thus favouring the controls. The remainder of the individual trials reported adverse events inconsistently and failed to show any statistically significant associations with the therapeutic intervention. Four studies which utilised topical antifungal therapy reported nasal irritation / burning with AMB [17,18,26,27], with one study reported skin itching [16]. The use of systemic antifungals were associated with elevation of hepatic enzymes in five studies [15,22,24,30].

Discussion

It is clear that due to the different quality of studies, inclusion criteria, methodology and treatment regimens comparisons and conclusions are difficult to establish. Within the review, sixteen of the included studies reported objective outcomes in the form of endoscopic findings. The endoscopic findings were either reported as part of validated scoring scales [1,7,16-19,21,22,25-28] or non-validated systems [15,20,23,24,30]. Seven studies reported endoscopic improvement [15,17-19,22-24], whereas the remainder of the studies reported no benefit (endoscopic) from antifungal agents. When the outcomes were taken into context of the methodology of individual studies, there appears to be no high quality evidence that supports the benefit of topical or oral antifungal agents in improving endoscopic outcomes in patients with AFS.
Patient Reported Outcome Measures (PROM) are important to consider when assessing the effect of an intervention as they relate to the perceived benefit recorded by the patient and therefore reflect upon the quality of life (QOL). Only one study reported statistically significant improvement in PROM following antifungal therapy [22], the remainder of the studies showed no benefit. Therefore, due to a lack of high quality evidence in the literature, this review reports that antifungals do not appear to improve symptoms in patients with AFS.

This review identified that twelve studies assessed the use of topical antifungal therapy in AFS and CRS participants, with only two studies [15,20] exclusively including AFS patients. Therefore, it is clear that there are only very few studies that assess AFS patients alone in the literature. This may be related to the complexity within the diagnosis of the condition and the uncertainty surrounding the disease process, or possibly due to the relatively low incidence in comparison to the other subtypes of CRS. As a result, there proved to be a large degree of heterogeneity in the participant profile within the included studies. It can be argued that this factor may be limited by the reported similarities between the conditions (especially CRS with nasal polyposis and AFS). It must also be noted that it is estimated that 10 per cent of CRS patients carry a diagnosis of AFS. Despite this, it remains to be a challenge to draw accurate conclusions from studies that do not specifically recruit this particular group. Without the presence of large methodologically robust studies that assess AFS participants (through strict diagnostic inclusion criteria), it must be stressed that the current evidence-base must be handled with care.

From analysing the results of this review, it has been identified that a significant influence upon the outcomes of both meta-analysis and the systematic reviews in the literature [1,7,28] are the findings reported by three RCTs of high methodological quality

(Table 2) [25-27]. All of these three studies reported no statistical benefit for the use of topical antifungals in CRS. However, a major limitation with respect to this review relates to their active exclusion of AFS. Therefore, despite the similarities of the disease states (e.g. CRS with polyps and AFS), direct conclusions cannot be drawn from these studies regarding the benefit of antifungals in patients with AFS. In addition to this, overall results of any included meta-analysis [1,28] must be interpreted with caution when considering the AFS patient subgroup alone.

This review included several trials that were found to have varying methodology, which would make interpretation of results and direct comparison difficult. Firstly, it was noted that the duration of treatment significantly differed (range 4 to 68 weeks). As mentioned earlier, Ponikau et al. calculated that a short treatment duration (less than 10 weeks) could be associated with a limited treatment effect [17]. Another important study design factor that must be recognised is the mode of application of topical therapy employed in each study. Studies included within this review used topical antifungals in the form of spray, lavage and irrigation. It is believed that nasal lavage may confer a treatment benefit versus other forms of application. Ferguson et al. reported that nasal irrigation in patients with CRS had a therapeutic effect on improving outcomes versus the application of AMB [31]. Therefore, outcomes in studies that use irrigation / lavage may be confounded by this effect. Two of the included studies that reported an endoscopic improvement administered their topical therapy by irrigation [18] and lavage [19]. In addition to the mode of application, it is also clear that there is a significant degree of variation upon the dosage of topical antifungal delivered between studies included within this review. It has been shown that this may have an effect upon fungal growth. In-vitro studies indicate that fungal growth may not be reduced at concentrations of AMB at 100µg/ML, whereas impedance is considered to occur at concentrations of 200-300µg/ML [32]. Helbling et al. used a total daily dose of 3mg AMB, which was the lowest treatment dose when compared to the other studies included in this review (range 3mg to 20mg daily) [21]. The group reported no significant benefit of antifungals on endoscopic outcome, which may be partly due to the lower dosage used. The type of topical antifungal studied varied within the literature. AMB was the most commonly used topical antifungal therapy within the included studies (10 trials), however, topical Fluconazole via a spray or lavage was also studied [15]. Bent and Kuhn assessed antifungal activity against AFS organisms during an in vitro study and reported that AMB and Ketoconazole to be the most effective antifungals in vitro [5]. It has been reported that Fluconazole has limited antifungal activity in those with AFS. However, in vitro studies have shown mixed results. Current evidence suggests that the type of antifungal agent may also impact on the outcome in AFS, however, further in vivo studies are needed.

Review of the literature for both topical and systemic antifungal therapies identified significant surgical heterogeneity between the studies. Several studies specified within their inclusion criteria for participants to have recently undergone FESS prior to the study [17-20,25] or as part of the study [15,22,23,26,30]. However, a number of studies specifically excluded participants whom had recent FESS prior (range 3 to 12 weeks) to the medical intervention [16,21,27,29]. The studies that excluded FESS prior to intervention argued that surgery would positively influence outcomes. Several studies have reported that FESS improves the delivery of topical preparations compared to pre-operative states [33,34]. This evidence therefore implies that the surgical heterogeneity described within the review may influence outcomes of individual studies especially in the setting of topical application (e.g. spray, irrigation, drops).

Recommendations for future studies

This review has identified that the current literature has limited high quality evidence that specifically assesses the use of antifungal treatment in patients with AFS. Several factors contributing to the paucity of good quality evidence have been discussed in this review in relation to limitations of existing studies. Therefore, to yield better quality of evidence in the future, trials must be double-blind and randomised which enrol larger numbers of participants who are diagnosed with AFS specifically. It is also important that these participants should be well matched in terms of demographics and surgical state (e.g. previous FESS) to reduce heterogeneity. There should be consideration into the adequate delivery, dosage and duration of antifungal therapies (e.g. sufficient to cause treatment effect). Finally, to obtain consistent objective data for analysis, the use of validated scoring systems (e.g. endoscopic, PROM) must be used within the studies.

Conclusion

Based upon the findings of this review, there is no convincing evidence to support the routine use of topical or oral antifungals in the treatment of patients with AFS (or CRS). However, it is also clear that there remains to be limited numbers of high quality studies focusing specifically on the use of antifungals in AFS. Therefore, to draw accurate conclusions about the benefit of antifungals within this particular group, recommendations for future research include enrolment of AFS patients into further large multi-centred double-blinded RCTs. These studies should aim to address factors such as the heterogeneity in the surgical state of participants, mode of application, dose and timing of antifungal therapy.

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Authorship contribution

SGM: Researcher, author and BNK: Supervisor, editor.

Conflict of interest

None.

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