Optimal management of allergic fungal rhinosinusitis

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Abstract

Introduction

Allergic fungal rhinosinusitis (AFRS) is a chronic disorder with significant morbidity & a high recurrence rate needing long term follow up. Even after its first description many decades ago, there is still considerable uncertainty about the management of this condition.

Description

In this chapter, we breakdown the topic – "Optimal management of allergic fungal rhinosinusitis" into sub-headings in order to discuss the latest research & available literature under each topic in great detail. Every attempt has been made to incorporate the highest level of evidence that was available at the time of writing.

Summary

Pre-operative diagnosis & further management prior is surgery is important -steroids help in reducing inflammation & help improve the surgical field. Surgery remains the mainstay in the management of this condition along with long term medical management. Oral steroids are reserved for acute flare-ups in the background of associated lung concerns. Oral and topical anti-fungal agents have no role in the control of the disease. Biological agents are being prescribed predominantly by respiratory physician colleagues, mainly for the control of the chest related issues rather than for sinus disease. Immunotherapy as an adjunct with surgery is promising.

Conclusion

AFRS is a disease with many variables and a wide range of symptomatic presentation. It takes a keen clinician to identify the disease & subsequently manage the condition. Treatment involves long term follow up with early detection of recurrence or flare-ups. Any of the mentioned modalities of management may be employed to effectively control the condition & treatment protocols will have to be tailor made to suit each individual patient. Various medications & drugs such as Manuka honey, antimicrobial photodynamic therapy, hydrogen peroxide and betadine rinses appear to be promising. More robust studies need to be undertaken to ascertain their routine use in clinical practice.

Keywords

Fungal, Allergic, Rhinosinusitis, eosinophilic, IgE, Immunotherapy.

Introduction

Allergic fungal rhinosinusitis (AFRS) was perhaps first described in 1976 by Safirstein et al[1] due to its similarities with allergic bronchopulmonary aspergillosis (ABPA). This condition is more commonly seen in geographic areas with higher humidity levels and amongst young adults with a mean age of presentation being about 22 years[2,3]. The classic presentation includes nasal polyps, presence of allergic fungal mucin and elevated IgE to at least one fungal antigen.

A Panel of international experts have defined some set criteria for the diagnosis of AFRS for research and clinical care as follows:[4]

Diagnostic criteria for AFRS

Symptoms	Requires ≥ one of the following:
	• Anterior and/or posterior nasal drainage
	• Nasal obstruction
	• Decreased sense of smell
• Facial pain-pressure-fullness	
Objective findings	Requires all of the following:
	• Presence of allergic mucin (pathology showing fungal hyphae with degranulating eosinophils)
	• Evidence of fungal specific IgE (skin test of *in vitro* test)
• No histologic evidence of invasive fungal disease	
Radiographic findings	Highly recommended:
	• Sinus CT demonstrating
	• Bone erosion
	• Sinus expansion • Double Density Sign
• Extension of disease into adjacent anatomic areas	
Other diagnostic measures	Possible, but *not* required:
	• Fungal culture
	• Total serum IgE

• Imaging by more than one technique (CT or MRI)	

Management of this condition has been ever evolving and thus necessitates the conglomeration of latest evidence and this document is an attempt to achieve the same.

Management of AFRS will be covered under the following headings

1. Surgical Management:
    a. Pre-operative Medication
    b. Surgical Technique details:
        i. Wide ethmoid doorway with wide max antrostomy, sphenoidotomy.
        ii. Wide frontal sinus ostial openings to include a frontal sinus rescue procedure or a Draf 2b.
    c. Revision surgery for AFRS
2. Post-operative Medical Management:
    a. Topical Steroids
        i. Low Volume vs High Volume rinses.
    b. Oral Steroids
    c. Oral Antifungals
    d. Topical Antifungals: is there a role?
    e. Advanced Therapies:
        i. Biologics
        ii. Immunotherapy
        iii. Other Research Therapies: aPDT, Betadine, Peroxide, Manuka Honey.

1: Surgical Management

1. a. Pre-operative medication

Oral Corticosteroids: The need for pre-operative medication, especially oral corticosteroids, in AFRS patients has been widely utilized. Pre-operative oral corticosteroids have shown a greater reduction in inflammation, radiological & endoscopic scores in AFRS when compared

to CRSwNP patients[5]. A meta-analysis of 1148 patients showed that pre-operative oral corticosteroids also reduced intra-operative blood loss & improved surgical field quality[6]. However, it must be kept in mind that the use of these medications in the preoperative period could impact any biopsies or mucous samples by under-staging the disease process at surgery.

Anti-fungal agents: A randomised control trial done in patients with AFRS treated with pre-operative itraconazole for 4 weeks in one arm & none in the other showed reduction in Clinical (SNOT 20), radiological (Lund Mackay) & endoscopic (Kupferberg) scores. 15 patients had complete resolution of disease endoscopically[7]. Unfortunately, the authors did not mention the dosage used in their study. Another study comparing the efficacy of oral itraconazole (200 mg BD for 2 days followed by 100 mg BD for 26 days) in the pre & postoperative period showed better disease control & lesser chances of recurrence with preoperative administration[8].

1. b. Surgery

Surgery remains the mainstay in the management of AFRS along with continued long-term medical management. It is the first and most vital step in the management of the disease process in most cases.

The goals of surgery include[9]

i. To completely clear fungal mucin & debris to reduce the antigen load.

ii. To create a wide opening for all sinuses in order to improve ventilation to all the sinuses, as well as allowing a pathway for ongoing postoperative topical therapy to the sinus cavities.

iii. To preserve mucosa for restoration of mucociliary health and motility.

iv. To create a wide sino-nasal corridor thereby allowing long term in-office endoscopic examination for the detection of early recurrence of disease and appropriate management.

v. To provide access to the sinuses for removal of fungal mucin and application of topical medication in the postoperative surveillance period.

Surgery usually involves a complete frontosphenoethmoidectomy with a wide maxillary antrostomy. Special attention is needed in those patients with extensively pneumatised sinuses. These deep cavities create areas of potential retention of fungal debris & allergic mucin that may not be amenable to post-operative long-term surveillance. Hence, areas such as retro-maxillary cells, frontal cells, lateral recess of sphenoid sinus etc., must be extensively marsupialised in order to allow for post-surgical topical medications. Care must be taken to avoid any inadvertent injury to critical structures such as the optic nerve, carotid artery, dura etc., which could have become dehiscent secondary to bone resorption. AFRS patients are reported to be 12 times more likely to have bony dehiscence than non-AFRS

patients needing surgery[10]. The normal anatomy is often grossly distorted due to bony remodelling caused by the expansion of the fungal debris within a closed space. This is most often seen in the anterior skull base and orbit[11].

Completion of all the bone work is essential to prevent pockets wherein fungal debris or allergic mucin could hide & act as an antigenic stimulus for the atopic patient. This also helps for easier clearance of debris in the office during the post-operative surveillance period.

The frontal sinus is one of the most difficult sinuses to keep patent. At our institute, we frequently utilize the frontal sinus rescue procedure, where the vertical process of the middle turbinate is removed to the level of the frontal ostium with preservation of a mucus membrane advancement flap. This is similar to a Draf 2b without the removal of the middle turbinate. It allows for a widely patent opening to the frontal sinus while still preserving the patients' sense of smell and the middle turbinate[12].

Over-enthusiastic surgery should be avoided in-order to preserve enough mucosa to have significant function as well as to avoid dryness and the possibility of an empty nose like syndrome. AFRS patients usually have a reduced sense of smell & poor muco-ciliary clearance to begin with. Undue tissue removal such as sacrificing the middle turbinate, superior turbinate or posterior septectomy to allow for a wide Sphenoidotomy, or performing a frontal sinus drill out will not necessarily help in controlling the disease. The surgeon must balance the benefits of aggressive surgery with loss of function such as hyposmia/anosmia or poor mucociliary function with mucous retention. It is important to remember that this is a physiologic problem that will need long term medical therapy and meticulous attention. It is not necessarily improved with over-aggressive surgery. The authors strongly suggest that each patient be treated individually & that the surgeon should never resort to use the "one size fits all" methodology to treat AFRS. It would not be justified to carry out extensive procedures in all patients, especially in the primary setting, as only a handful of patients may eventually need it.

1. c. Revision surgery for AFRS

AFRS is associated with a very high probability of revision surgery & studies have identified it as the greatest risk factor for revision surgery[13,14]. There are many reasons for this. The authors believe that it is due to the ubiquitous nature of the fungal spores and hyphae in the environment that the patient invariably breathes. The fungal spores and hyphae then enter the already opened sinus cavities which are dark, deep and moist spaces; especially the maxillary & sphenoid sinuses. This in turn activates an inflammatory response at the level of the sinus mucosa, thereby creating polypoid edema, which further walls off the fungus and re-propagates the cycle. The fungal debris and mucin then become inaccessible to topical rinses or medication & provide continued antigenic stimulation, thereby making the situation worse. This inflammation spreads contiguously & involves other sinuses, which is when symptoms start to become evident. Interestingly, symptoms occur at a much later

stage when the disease has advanced fairly significantly and after several sinuses have become involved.

Revision surgery usually involves complete removal of all the fungal debris and residual cells in order to allow complete visualization of the frontal, maxillary & sphenoid sinuses through the sino-nasal corridor. This can be achieved again by principles similar to the primary surgery mentioned above. In certain cases, larger openings such as wide antrostomies or mega antrostomies or even a modified medial maxillectomy may become necessary.

2. Post-operative medical management

a. Topical steroids

i. Low Vs High Volume steroid rinses - Post operative irrigation of the operated sinuses is one of the main modalities for clearing and adequately controlling the fungal spores that the patient breathes in during the post-operative period and for controlling the mucin build up within the sinus cavities. The irrigant distribution depends on various factors such as patient anatomy, inflammatory load & type of irrigation device used. In many cases, it might be very difficult to clear sinus mucin as it is thick & tenacious. Topical rinses aim to improve inflammation, infection & muco-ciliary dysfunction which accompanies the disease process[15]. A comparative study between 9 post-operative patients & 3 un-operated patients comparing metered nasal spray, nebulization & nasal douching showed that douching had good penetration into the maxillary & frontal recess but not so much into the sphenoid & frontal sinuses[16]. A prospective randomised control trial with 121 patients comparing low volume high pressure devices such as nasal sprays vs high volume, low pressure devices showed that the latter had better reduction in the SNOT 20 scores[17]. Mucosal atomization devices (MAD) help deliver low volume high concentration steroid into the frontal recess and sinuses. It is preferred that it be used in the head hanging posture (Mygind or Regan position) in order to target the frontal recess areas. It is important to instruct the patient to stay in the head hanging position for at least 4-5 minutes so that there is good penetration of the topical steroid into the frontal recess and sinus mucus membrane. Mechanism of action is by droplet distribution & retention which can deliver the medication to the dependent sinuses in high concentrations[18].

A cadaveric study reported that the maxillary sinuses seem to be best irrigated with heavy rinses despite the presence of mucin or polyps whereas the frontal & sphenoid sinuses are more difficult to reach in the presence of post-surgical recurrence of disease[19].

Topical budesonide, despite being used off label in the management of AFRS, has become a game changer in the control of mucosal inflammation in these patients. A randomised control trial comparing 1 mg nasal budesonide nebulization against topical nasal sprays (n=15) found that patients using budesonide had no recurrence of disease compared to 26.67% of patients who had recurrence of disease in the second group over a mean follow up period of 18.5 months[20]. There are 2 studies that have studied the safety of budesonide in the nasal cavity. One reported the effects of short-term use of Budesonide (up to 2

months) & found no implications of regular use of budesonide. The other studied the effects of long-term use of budesonide (>6 months) and found a 3% incidence of asymptomatic adrenal suppression in these patients[21,22].

b. Oral corticosteroids

Oral corticosteroids are widely used in the management of AFRS and can be used either as the sole management of the condition in mild cases, or pre- and post-operatively in patients needing surgery. At the moment there are no randomised control trials comparing the use of systemic steroids in AFRS.

A retrospective chart review of 26 patients by Kupferberg et al. showed maximum improvement in the post-operative period with the use of steroids for a month after surgery. The authors found a reduction in mucosal grading scores, incidence of fungal mucin & polyps[23].

A retrospective review of 15 patients by Kinsella et al. showed that all the patients on oral steroids did not have any recurrences but those needing revision surgery did not get oral steroids in the post-operative period[24].

However, oral steroids, with all their concomitant side effects, should be reserved only for patients with severe SNOT 22 scores along with pulmonary worsening during acute exacerbations in the post-surgical period. In the absence of an acute worsening, the authors are of the opinion that the involved sinus cavities can be flushed & debrided in the clinic to get the inflammation back under control. 1 ampule (1.0mg/2ml) of budesonide is then applied to the affected sinuses topically under endoscopic guidance. If steroids become absolutely necessary as a last resort, the authors prefer a tapering course of prednisone starting at 40mg per day bringing it down by 10 mg over 5-day intervals & then stopping it while at the same time continuing with topical budesonide treatment. Documentation of the number of times the patient needs oral steroid rescue is necessary in order to look out for adrenal (HPA axis) suppression. All potential therapies such as repeated flushing, topical application of medications and other medical therapies listed below are attempted prior to succumbing to the use of oral steroids, especially in patients with osteoporosis, diabetes mellitus, hypertension, peptic ulcer disease, cataracts or glaucoma.

c. Oral antifungals

Proponents for oral antifungals in the management of AFRS argue that these patients have a hypersensitivity response to fungal antigens & that oral antifungals could help reduce the fungal load in these patients, thereby reducing the immune mediated response. Oral antifungals have been inadequately studied in the management of AFRS[25,26,27]. Of the three studies in the literature, one used oral terbinafine whereas the other 2 used oral Itraconazole. There are mixed opinions about the inferences drawn from these studies but the results have limitations due to small sample sizes. One of the studies recruited 6 patients, in which 3 patients received itraconazole & 3 received placebo. The study arm group showed improvement in CT scores and reduction in eosinophil counts, while there

was worsening of the same in the control group. 2 patients apparently dropped out due to skin rashes with Itraconazole but no liver dysfunction was reported in this study[15].

Another study by Javer et al. included a cohort of 32 patients refractory to oral prednisone, steroid & amphotericin B nasal sprays. These patients were treated with oral itraconazole for 3 months. There was no significant improvement in endoscopic or subjective scores. There was an increase in the post treatment IgE as compared to the pre-treatment levels. However, they did find that there was a small cohort (38%) within their study group that responded well to the itraconazole. One patient developed elevated liver enzymes and had to stop treatment[16].

Kennedy et al. did a randomised control trial with high dose oral terbinafine in 26 patients compared to a similar group on placebo & found no radiological or symptom improvement at the end of 6 weeks.

In conclusion, from this small group of published studies, it appears that oral antifungals do not seem to drastically improve symptom scores or radiological scores, but could be tried in some recalcitrant cases as adjunctive therapy together with topical steroids. From our experience, it appears that there is a distinct cohort of patients who respond much better than others, indicating that further endotyping and cytokine profiling of these patients may help identify this unique group of patients that respond to antifungal treatment. At this point, the evidence is limited to a few studies with small sample sizes. Caution must be practised in terms of monitoring for adverse effects such as skin rashes, elevated liver enzymes and cardiac side effects, etc.

d. Topical antifungals

There were many more research studies focussing on topical antifungals compared to oral antifungals in the early 2000's[28,29,30,31,32,33,34, 35,36,37,38,39,40,41]. Most of these studies used topical amphotericin B in the management of AFRS. Two meta-analysis studies eventually showed that there was no benefit with the use of intranasal amphotericin B either in the form of a rinse or nasal spray[42,43]. Some studies have reported a higher incidence of adverse events in patients with intra-nasal amphotericin B, the most common ones being nasal burning, itching, acute pain, bleeding etc. Intranasal Amphotericin B was eventually abandoned as a treatment for AFRS due to its in effectivity and its side effects.

e. Advanced therapies

i. Biologic agents

Biologic agents are an exciting and upcoming group of adjunctive therapies in the management of chronic rhinosinusitis, especially in the presence of comorbidities such as asthma. They are popular due to their specific action at the receptor level, which helps reduce the gross systemic side effects that corticosteroids have. They slow down and even reverse the inflammatory process, thereby reducing the dependency on steroids & anti-fungal agents. Although there are many trials which have been conducted with various biologic agents in the management of chronic rhinosinusitis, only one agent has been

studied for the treatment of AFRS – Omalizumab. AFRS is predominantly an IgE mediated disease & hence, Omalizumab, an anti-IgE monoclonal antibody may theoretically be the best one for use in this condition. It binds to its Fc receptor & thereby blocks the IgE mediated inflammatory pathway[44]. Additionally, it downregulates the Fc receptors on other cells such as Mast cells, dendritic cells & basophils[45]. Since 2003, the US food & drug administration (FDA) has approved its use in patients ≥12 years with moderate to severe allergic asthma not controlled by a combination of inhaled corticosteroids & long acting bronchodilators[46]. There is only one report of a retrospective chart review by Javer et al. which included seven patients with refractory AFRS & asthma, who were studied over a 2 year period. These patients had received an average of 287mg of Omalizumab & showed a 31% improvement in their SNOT 22 scores & 61% improvement in the endoscopic grading[47]. The evidence for routine use of Omalizumab in AFRS is scant & there is certainly a need for further studies with longer follow up periods before it can be recommended. At the moment, it is only approved for patients with uncontrolled allergic asthma & therefor cannot be prescribed in patients unless they have this comorbidity. Dupilumab is a new drug which has recently been approved for use in patients with CRSwNP. It has shown some promise in some RCTs which show reduction in polyp size, sinus opacification and symptom severity[48]. However, there are no RCTs at this point in time, where it has been studied in AFRS patients, to draw any conclusions in this specific patient group.

ii. Immunotherapy

Since the allergic mechanisms involved in AFRS are thought to be IgE mediated Gel & Coombs type I reaction & IgG mediated type III hypersensitivity reaction, the mechanism of action of immunotherapy is hypothesized to reduce the production of allergen-specific IgE and to increase the production of IgG4 blocking antibodies which are intended to interfere with the IgE antigen reaction. However, opponents of immunotherapy argue that it could induce an immune complex mediated reaction & cause disease progression or worsening.

One of the better reports utilizing immunotherapy in AFRS was published by Mabry et al. who carried out the first prospective trial on 11 patients who underwent sinus surgery at least 1 month prior to the initiation of fungal antigen immunotherapy. At the end of 1 year they found a significant reduction in the production of allergic mucin, fungal debris & crusts, reduced use of intra-nasal steroids & completely negated the need for systemic steroids. In the 2nd year of their study two patients needed a course of rescue steroids, but these were patients that already had residual disease prior to the start of immunotherapy[49]. In the third year, they reported that none of the patients in the treatment arm needed further surgical intervention or systemic steroids[50]. At the end of 4 years, they reported that even after stopping immunotherapy for upto 7 to 17 months, there was no recurrence of disease. However, their report on long term outcomes (from 4-10 years) in AFRS management failed to show any additional benefit from immunotherapy as compared to the non-immunotherapy group[51]. This may have been a result of the fact that immunotherapy loses its potency after being stopped for a longer duration.

Other studies have reported similar results indicating that immunotherapy reduces the need for oral & nasal steroids, the need for revision procedures & improved patient outcomes[52,53]. One study also highlighted that these patients needed fewer follow up visits in the post-surgical period[54]. With regards to adverse effects, none of the studies reported greater adverse effects with fungal antigen immunotherapy. Of note is one study by Greenhaw et al. with 14 subjects which showed no greater risk of local or systemic reactions with high dose immunotherapy[55].

One of the disadvantages of immunotherapy is that it works in conjunction with surgery & other modalities of management. It may not be successful in the presence of fungal antigen load not addressed by surgery & in such a situation may potentially worsen the disease[56].

iii. Advanced and Research Therapies

Anti-microbial photodynamic therapy (aPDT)

This is a newer modality of a non-antibiotic broad-spectrum antimicrobial treatment which can eradicate 99.99% of organisms in-vitro after a single treatment session[57]. Although there are no reports specific to AFRS in humans, there is one report of aPDT being used in rabbits after inoculation of Aspergillus fumigatus in their maxillary sinuses. Compared to control rabbits, the Sinuwave™ antimicrobial photodynamic therapy was able to kill 99.99% of recoverable fungus[58]. Although the initial animal studies are encouraging, there is a need for a well-designed prospective randomised control trial in order to ascertain the role of aPDT in the management of AFRS. The authors have recently conducted a retrospective data review of their aPDT experience & found 14 AFRS patients in whom aPDT was conducted. At the end of 6 months they found significant improvement in endoscopic scores (MLK) in 9 of the 14 patients (64.2%). They also reported that 3 of these 14 patients had minor adverse events such as stinging or slight bleeding but these were transient & did not last more than 3 months. However, this data is yet to be published.

Intranasal betadine rinses

Betadine is proposed to be a broad spectrum anti-microbial which has proven to be effective against various bacteria, fungi, spores, protozoa & amoebic cysts[59]. In Vitro it also has some anti-inflammatory effects created by pathogens & by host responses[60]. The clinical relevance of this property of betadine has been studied previously[61,62]. Javer et al. reported a study involving patients with recalcitrant sinusitis being treated with 0.08% povidone iodine rinses & assessed pre & post treatment improvement in MLK scores & SNOT 22 scores. They found a statistically significant improvement in both parameters. They also monitored thyroid hormone levels which remained within normal limits in these patients[63]. In another report, they found a 17% decrease in the inflammatory mediators after rinsing with betadine[64]. There are some reports that betadine has ciliotoxic effects on the nasal mucosa but the concentration needed for causing ciliary dysfunction is much higher than that needed for antimicrobial activity[65,42]. At the moment, there is limited evidence for the efficacy of betadine in AFRS patients & a more extensive trial focusing specifically on AFRS patients would pave the way for its routine use in these patients.

Manuka honey rinses

Honey has been used since ancient times in the management of wounds & injuries[66,67]. The microbicidal action of Manuka honey is by 3 mechanisms – Firstly, the high glucose content of honey is thought to provide energy for the phagocytes to act against microbes. Secondly, the acidic pH is known to directly kill the organisms & thirdly, Manuka honey was thought to produce a chemical compound known as "inhibin" initially, which is now known to be hydrogen peroxide[68,69]. The most potent honey is apparently Manuka honey (Leptospermum scoparium) which has a 100-fold concentration of the active component – Methylglyoxal as compared to normal honey[70].

Yabes et al. compared the anti-fungal properties of Manuka honey & polyhexamethylene biguanide (PHMB). They found that anti-fungal activity of both agents correlated with exposure time rather than dose. They reported that Manuka honey managed to completely supress the growth of fungi at 6 hours[71]. Another study by Irish et al. found that Jarrah honey was most active against Candida species as compared to other forms of honey[72]. Clinically however, there is very limited data regarding the success of its use in AFRS. As per one study by Thamboo et al., there wasn't much improvement in endoscopic scores or culture results from the ethmoid sinuses after 30 days of Manuka honey use, but the SNOT 22 scores did show improvement after its use[73]. The conclusion drawn is that honey would not be effective on its own as it needs a surgically opened sinus with reduced fungal load to work as topical therapy, but it may be used as an adjunctive therapy with other modalities of treatment.

Hydrogen peroxide rinses

Hydrogen peroxide is thought to be the world's safest natural sanitizer as it is primarily composed of 2 elements only – hydrogen & water. It predominantly works by means of oxidisation when it comes in contact with organic material. This is mainly due to the production of hydroxyl ions which can damage cell membrane walls. Many plant based research studies have effectively proven the anti-fungal properties of hydrogen peroxide in low doses[74]. In humans, hydrogen peroxide has been studied in the sinuses for invasive fungal sinusitis as an adjuvant along with surgery in order to destroy Mucor & kill the supporting dead tissue on which the fungus flourishes[75]. There are also reports of successful inhibition of Catalase producing Candida species with the use of Hydrogen peroxide[76]. However, at the moment there are no reports of the use of Hydrogen peroxide in the management of AFRS. There are ongoing prospective studies at our centre regarding the use of hydrogen peroxide in post-operative AFRS patients. It will be interesting to see the results of such a randomised control trial in the near future.

Conclusion

To summarize, allergic fungal rhinosinusitis is a chronic disorder with a very high propensity for recurrence or flare-up of disease, thus necessitating repeated surgeries. In these cases, it is prudent to keep a watchful eye by means of endoscopic assessments at regular intervals

as the symptoms lag behind endoscopic appearances. At the time of writing this article, there is evidence for surgery by creating large ostial openings to allow topical medications such as steroids to enter the sinuses. There is no definite evidence in the role of topical or oral anti-fungals in the management of AFRS. Immunotherapy is effective as per some studies, as an adjunctive to surgery. There are some new novel research therapies which are upcoming & need some more evidence before they can be incorporated into treatment protocols.

Disclosures

None

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