Will we ever cure nasal polyps?

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ABSTRACT

BACKGROUND Nasal polyposis is a benign hyperplastic growth of nasal mucosa. There is a paucity of evidence on the prevalence and incidence of nasal polyposis. Although nasal polyps can be asymptomatic, they can cause a spectrum of nasal problems including nasal obstruction, rhinorrhoea, nasal congestion, anosmia resulting in ageusia. Nasal polyps are mostly associated with chronic rhinosinusitis. The current management of chronic rhinosinusitis with nasal polyps is controversial and is not curative.

METHODS A Medline search was conducted, using the keywords 'rhinosinusitis', 'sinusitis', 'classification' and 'aetiology'.

FINDINGS The current treatment of nasal polyposis in chronic rhinosinusitis with nasal polyps is still challenging. Emerging research through endotypes profiling aims to better understand the complexities of this heterogeneous disease to personalise treatment and provide a cure. Randomised controlled trials aim to provide robust evidence for current management options.

KEYWORDS

Rhinosinusitis – Nasal polyposis – Management – Aetiology

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Introduction

Nasal polyposis is a benign hyperplastic growth of nasal mucosa.¹ It is thought to be common in the general population. However, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 has stated that there is a paucity of evidence on the prevalence and incidence of nasal polyposis, especially in European countries.² Although nasal polyps can be asymptomatic in some patients, they can cause a spectrum of nasal problems including nasal obstruction, rhinorrhoea, nasal congestion and anosmia resulting in ageusia. Nasal polyps are mostly associated with chronic rhinosinusitis with nasal polyps (CRSwNP), the current management of which is highly controversial and not curative.

This review discusses different aetiological hypotheses of nasal polyposis and innovative research in nasal polyposis treatment to assess whether we will ever cure nasal polyps.

Aetiology and current management of nasal polyposis

Understanding of the aetiology of nasal polyposis is crucial in treating it appropriately and effectively. Nasal polyposis should never be considered a definite diagnosis. It is only a pathological endoscopic description of sinonasal diseases. A finding of nasal polyposis should therefore always warrant further investigations into its aetiology.

The aetiology of nasal polyposis is poorly understood and is only explained by several proposed pathological associations. Classification of nasal polyposis based on different

aetiological hypotheses is indicated in Table 1. These uncertainties limit our ability not only to manage nasal polyps but also to cure them.

Localised nasal polyposis

A unilateral nasal polyp should be highly suspicious for sinonasal malignancy, especially in elderly patients with wood dust exposure. Conversely, it could be a more benign growth such as an antrochoanal polyp that arises within the maxillary sinus, passing into the nasopharynx through the sinus ostium and posterior nasal cavity, enlarging the latter two,³ or it could be a sinonasal inverted papilloma. A previous inflammatory event can cause obstructed sinus ostia with hypoxia leading to bacterial infection. Subsequently, this can cause a localised single nasal polyp.

To manage localised nasal polyposis, appropriate investigations including microbiology samples, sample biopsy and computed tomography (CT) of the sinus should be performed to understand its aetiology before the clinician can decide on an appropriate treatment plan.

Diffuse nasal polyposis – chronic rhinosinusitis with nasal polyps

Nasal polyps are often associated with chronic rhinosinusitis, which is classified coarsely into with and without polyps (CRSsNP). This classification of chronic rhinosinusitis is rudimentarily based on the presence or absence of nasal polyposis on endoscopic examination, inflammatory profiling and comorbidities such as asthma and aspirin-

Table 1 Classification of nasal polyps.

Area covered	Type	Aetiology
Localised	Reactive polyps	Inflammatory Neoplastic
Diffuse	Host	Anatomical abnormality Atopy
	External factors	Staphylococcus super-antigen
	Combined host–external factor interaction	AFRS/EFRS/EMRS
Systemic	Cystic fibrosis, Churg–Strauss syndrome	

AFRS, allergic fungal hypersensitivity rhinosinusitis; EFRS, eosinophilic fungal rhinosinusitis; EMRS, eosinophilic mucin rhinosinusitis.

exacerbated respiratory diseases.⁴ Chronic rhinosinusitis affects 11% of the European Union population, causing a significant economic and disease burden to the health system, to patients and to the economy.^{5–7} CRSwNP has distinctive features of oedematous hyperplasia in the sinonasal epithelium, with albumin deposition, pseudocyst formation and subepithelial inflammatory cell infiltration.⁸

Despite classifying the potential pathological mechanisms behind polyp formation in CRSwNP into host factors, external factors and the combination of both (Table 1), these are only hypotheses and they largely overlap.

The first proposed aetiological mechanism involves bio-film and frank eosinophilia, both of which can exacerbate inflammatory process in CRSwNP. These mechanisms are postulated to be associated with host responses such as bacterial super-antigen response, fungal sensitisation and atopy. Allergic fungal rhinosinusitis (AFRD) and aspirin-exacerbated respiratory disease (AERD) should be considered in cases of bilateral nasal polyps with aspirin sensitivity and asthma. Pan-sinus opacification on CT and thick eosinophilic mucus are consistent with a diagnosis of

AFRD/AERD, which accounts for 15% of CRSwNP. If on CT, the sinus shows less opacification and less mucus, this could suggest a bacterial super-antigen aetiology. Regardless, salicylate desensitisation therapy is recommended.

In the West, the pathophysiology of CRSwNP is thought to be linked with a T-helper 2 (Th2) cell-driven eosinophilic, immunoglobulin E (Ig-E) inflammation, with high interleukin (IL-5) and eosinophil cationic protein concentrations in the nasal polyps.^{4,8} The current lack of evidence for any of these factors being solely responsible for pathogenesis indicates that this hypothesis is based on a multifactorial interaction between them. Conversely, nasal polyps are found to be mostly linked to Th1 and Th17 in Asia and Japan.⁹ In cystic fibrosis, nasal polyps show a neutrophilia.⁸ These conflicting findings emphasise the heterogeneity of the phenotypes of CRSwNP, which ultimately results in the overlapping clinical phenotypes (Table 2). Further understanding of CRSwNP endotypes will help to personalise therapies for CRSwNP-related nasal polyposis.

Another theory for the aetiology of CRSwNP involves anatomical abnormality or variation in the paranasal sinuses.

Table 2 Different CRSwNPs phenotypes and endotypes

Phenotype	Nasal Polyps in CRSwNPS and mucosal eosinophilia	Nasal Polyps in CRSwNPS and mucosal neutrophilia	Allergic fungal hypersensitivity rhinosinusitis (AFRS)
Endotypes	High Eosinophil counts Intensely oedematous nasal polyps High IL-4, 5,13 present No IL-10 present High Leukotrienes present High M2 (Th2 responding) macrophages counts Th2 dominant	No Eosinophil present High Neutrophils High INF- γ Negative IL-5 High IL-17 Th1 dominant Th17 dominant	High Eosinophil counts Positive fungal culture or histology High total IgE
Current proposed treatment implication	High dose intra-nasal corticosteroid or Oral corticosteroids Leukotriene modifiers Sinus surgery Aspirin/Salicylate desensitisation therapy ??? Biologics – Omalizumab, Mepoluziman, Reslizumab	High dose intra-nasal corticosteroid Sinus surgery ???Macrolides antibiotics	Oral corticosteroids Intra-nasal corticosteroid ??Antifungals ???Omalizumab

On CT of the sinuses of some patients, nasal polyps were found exclusively in the ostiomeatal complex with Haller cells indicating narrowing. The ostiomeatal complex is postulated to be a critical sinonasal anatomical structure, as anything impairing drainage through it contributes to CRSwNP.¹⁰ However, EPOS 2012 concluded that there is no evidence for a causal correlation between nasal anatomic variations in general and the incidence of CRSwNP.

The next hypothesis involves biofilm. It has been found that mucus sample cultures from nasal cavity of patients with CRSwNP show both Gram-positive and -negative bacteria.^{11–13} About 75% of cases of CRSwNP show biofilm;¹⁴ however, we are still uncertain if identifying bacteria in the nasal cavity is a sign of infection or purely colonisation. More research is needed to confirm the presence of biofilm in CRSwNP.

The super-antigen hypothesis postulates that a localised eosinophilic inflammatory response is triggered by non-invasive *Staphylococcus aureus* secreting exotoxins in the nasal mucosa. Two studies have demonstrated that there is a higher amount of exotoxin, specific super-antigen IgE, eosinophils and eosinophilic inflammation markers in CRSwNP than CRSsNP.^{15,16} Conversely, there is evidence suggesting that the super-antigens might have a role in some but not all cases of CRSwNP based on different levels of *S. aureus* (65%), super-antigen specific IgE (50%) and T-cell changes (33%).¹⁷ Taken together, the current evidence for this super-antigen hypothesis is conflicting.

The fungal hypothesis is highly controversial as it is difficult to provide evidence that fungi are the main causative organisms in CRSwNP. Studies with poorly selected cases with other comorbidities such as asthma are more likely to represent fungal aetiology leading to the conclusion that fungi do not play a part in the aetiology of CRSwNP. Consequently, anti-fungals do not work.¹⁸ Nevertheless, several studies have shown that patients with CRSwNP have a higher rate of fungi and eosinophilic mucus compared with a healthy control group. This demonstrates that there is a unique, T cell-driven hypersensitivity to fungi, independent of immunoglobulin-mediated/atopy in patients with CRSwNP.¹⁹ The reaction of peripheral blood mononuclear cells and eosinophils to *Alternaria* fungal extracts in patients with CRSwNP compared with healthy controls further supports the previous evidence.²⁰ However, it could be that a reaction to *Alternaria* was non-specific protease-based, as a T-cell receptor-mediated hypersensitivity response to fungal antigen has not yet been fully explained.

While there is support for the potential hypotheses discussed above, the conflicting evidence shows that there is a large poorly understood spectrum of pathophysiology and aetiology for CRSwNP, which demonstrates the complexities of this heterogeneous disease. The challenges of the current management of CRSwNP reflect this. Unsurprisingly, the current treatment for CRSwNP still amounts to a 'guess' rather than a treatment tailored to individual patients.

EPOS 2012 recommends that the first-line treatment for CRSwNP is medical, including topical intranasal corticosteroids and nasal douching. Systemic treatment includes

a short course of oral steroids and 12 weeks of low-dose macrolides. Sinus surgery is a last-resort option for suitable patients. The recommendation is based on our current understanding of the management of CRSwNP by modifying factors that are believed to contribute to the wide spectrum of the aetiology of nasal polyposis. Nasal douching is a safe and cheap way to clear mucus and increase ciliary activity, and to remove antigen, biofilms and inflammatory mediators. Intranasal corticosteroids target inflammation, improving nasal congestion, increasing drainage of the ostiomeatal complex and significantly reducing polyposis size in CRSwNP. Systemic steroids are useful for short-term symptom relief. Nonetheless, only two or three short course of oral steroids can be given in one year, as they have serious adverse effects. Low-dose macrolides have been shown to be effective in managing the symptoms of CRSwNP in conjunction with intranasal corticosteroids. It has been suggested that reslizumab, an anti-IL-5 monoclonal antibody, could help to reduce nasal polyp size in selected patients with CRSwNP.²⁰ There is limited conflicting evidence on the effectiveness of omalizumab, an anti-IgE monoclonal antibody in chronic rhinosinusitis.²⁰ There is insufficient evidence to show the benefits of biologics in the treatment of CRSwNP, and because of this and their cost, they will only be used in severe cases with recurrent nasal polyposis and uncontrollable asthma.²⁰ A systematic review demonstrated that endoscopic sinus surgery improves symptoms and has acceptable safety in chronic rhinosinusitis, especially CRSwNP. However, a revision rate up to 20% is found at long-term follow-up, with a higher recurrent nasal polyposis rate in CRSwNP.²¹ To prevent the recurrence of CRSwNP post-surgery, a sinus rinse and intranasal corticosteroids must be used postoperatively. There is an urgent need for large high quality multicentre randomised controlled trials (RCTs) of endoscopic sinus surgery compared with current medical treatment. The recommended CRSwNP management scheme from EPOS 2012 is shown in Figure 1.

The current management strategy is only focused on modifying relevant factors to lessen symptoms instead of curing CRSwNP. In addition to the uncertainties in the current management of the condition, it has been suggested that there is also a wide spectrum of responses to treatment for chronic rhinosinusitis. First, the multiple poorly understood pathophysiology and aetiologies lead to 'guessing' rather than targeting treatment. Additionally, compliance with medication, including nasal douching and intranasal corticosteroids, is low in chronic rhinosinusitis.²² This should be addressed by clinicians to encourage good compliance to improve response to treatment.

Systemic nasal polyposis

Churg–Strauss syndrome and cystic fibrosis are the two key systemic disorders that commonly present with nasal polyposis. Nasal polyposis can occur in up to 76% of patients with Churg–Strauss syndrome, so those with nasal polyps and positive anti-neutrophil cytoplasm antibodies should be suspected of necrotising granulomatous vasculitis affecting small vessel wall.²³ Nasal polyps are found in

up to 45% of patients with cystic fibrosis, often with clear radiological evidence.²⁴ Cystic fibrosis should be suspected in young patients testing positive in the sweat test, together with a sinus CT showing total opacification, hypoplastic frontal and sphenoid sinuses. Nasal polyposis in Churg–Strauss syndrome and cystic fibrosis can be treated by managing the underlying systemic conditions, which is beyond the remit of this review.

Research in nasal polyposis treatment

There is emerging research to better understand the complexities of this heterogeneous disease, specifically its wide spectrum aetiology and pathophysiology, as discussed above. Work in the UK involving analysis of cytokine responses and inflammatory signatures in material isolated from patients selected on the basis of clinical parameters aims to define the core set of biomarkers in chronic rhinosinusitis.²⁵ Research in chronic rhinosinusitis endotype profiling could identify different groups, which might help towards the provision of personalised medical treatments. This might not cure CRSwNP but could minimise ‘guessing’ in current management regimens.

RCTs evaluating current medical and surgical treatment for chronic rhinosinusitis are in progress. The Defining best Management for Adults with Chronic Rhinosinusitis (MACRO) trial is a UK-based multicentre RCT assessing

endoscopic sinus surgery compared with medical treatment and placebo in 600 patients with CRSwNP and CRSsNP.²⁶ PolypESS is a Dutch multicentre RCT in 258 patients with CRSwNP assessing the effectiveness of endoscopic sinus surgery compared with medical treatment.²⁷ More research into understanding the inflammatory pathway is required to provide more robust evidence supporting the use of biologicals in treating nasal polyps.

Conclusion

Curative treatment of nasal polyposis should arise from understanding the complex aetiology of this common nasal endoscopic finding. Localised polyposis can be managed medically and surgically according to its inflammatory or neoplastic origin. Systemic disease-related nasal polyposis should be managed by controlling the underlying cause. Diffuse nasal polyposis in CRSwNP remains difficult to manage. The challenges of CRSwNP management reflects the multiple poorly understood aetiological and pathophysiological hypotheses in this condition. Currently available treatments are largely based on clinical experience and are not supported by evidence-based-medicine. Until we fully understand the underlying mechanism of disease, we will only manage CRSwNP symptomatically without ‘curing’ the condition.

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