

Prevention of chronic rhinosinusitis*

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Prevention of chronicity of disease and minimising its impact with individualized treatment is a fundamental tenet of precision medicine. A review of the literature has been undertaken to explore how this may apply to chronic rhinosinusitis (CRS).

Prevention may be thought of across 3 main domains.

Primary prevention of CRS focuses on the avoidance of exposure to environmental factors associated with increased incidence of disease. This includes avoidance of tobacco smoke and occupational toxins. Although allergic rhinitis, respiratory infections and gastro-oesophageal reflux have been shown to be risk factors, there is no evidence as yet that treatment of these conditions is associated with reduced incidence of CRS.

Secondary prevention of CRS is concerned with detecting a disease in its earliest stages, intervening to achieve disease and symptom control and preventing future exacerbations. Evidence based guidelines facilitate early diagnosis and appropriate use of medical and surgical interventions. In the future the use of endotypes to direct optimal is like to allow more clinically and cost-effective use of current and emerging treatments, such as monoclonal antibodies.

Tertiary prevention aims to minimise the impact of an ongoing illness or injury that has lasting effects. Anxiety and depression have been shown to be associated with symptom amplification and may require treatment. The role of disease-related factors such as the role of the microbiome and osteo-neogenesis in the development of chronicity, and the development of severe combined upper airway disease needs further research.

Key words: chronic rhinosinusitis, precision medicine, disease prevention

Introduction

Medicine has long tried to move from a model of 'illness management' to one of health or 'wellness'; encompassing the domains of physical, mental, and social well-being. Ideally, prophylactic measures would exist to prevent the development of illness; however the rising prevalence of many chronic diseases has shown this to be inadequate and that strategies to minimise the impact of disease are required. This approach is a fundamental tenet of precision medicine⁽¹⁾, which aims to tailor prevention and management of disease to the individual patient in order to optimise outcomes and minimise costs.

Chronic Rhinosinusitis (CRS), with nasal polyps (CRSwNP) and without (CRSSNP), is a highly prevalent chronic condition estimated by epidemiological studies to affect 5–15% of the general adult population⁽²⁾. CRS has been shown to have both a significant personal impact on patients' health-related quality of

life^(3,4), and economic cost to sufferers and to wider society^(5,6).

This, and the heterogeneous nature of the disease, means that CRS management is an ideal candidate to scrutinise under the microscope of precision medicine.

Prevention may be thought of in 3 main dimensions:

Primary prevention aims to reduce incidence of disease by reducing exposure to risk factors or triggers.

Secondary prevention aims to reduce disease prevalence by early detection and appropriate management, returning a patient to full health and preventing disease persistence. This aims to reduce severity and impact of disease from the outset.

Tertiary prevention aims to reduce the impact of ongoing chronic disease and its complications in order to maximise quality of life and restore normal functioning as much as possible. This review will consider where CRS may be prevented, based on current evidence and considering emerging treatments. Primary

CRS refers to the vast majority of patients that present to otolaryngologists with unexplained inflammation of the upper airway. Secondary CRS which occurs as a result of systemic disease will not be considered. A review of the literature using the terms 'prevention' and (sinusitis and rhinosinusitis) was supplemented by additional searches relating to factors identified.

Primary prevention

CRS is a heterogeneous disease, where inflammation, mucociliary dysfunction and changes in the microbial community interact with differing influence to cause disease⁽⁷⁾. The aetiology of CRS disease is multifactorial, and likely to be influenced by multiple genetic and environmental factors. Primary prevention measures that effectively target the specific causes and risk factors of CRS remains the ultimate goal for disease prevention. Promoting a healthy lifestyle, reducing unhelpful health behaviours, improving host immunity, and creation of an environment with minimal exposure to toxins are all factors which have been investigated as possible strategies to reduce the incidence of CRS^(2,5,8-12).

Environmental factors

Exposure to toxins, especially tobacco smoke, ozone and particulate air pollutants such as diesel exhaust particles, may exacerbate airway inflammation. However, the significance of most toxin exposures in development of CRS is unclear. Wolf found no correlation between CRS and outdoor air quality in Cologne⁽¹³⁾, similarly there was no difference in prevalence in rural or urban areas of South Korea⁽¹⁴⁾. In contrast weak correlations have been found in US studies⁽¹⁵⁾, where improvements in air quality were also associated with a decreased prevalence of both hay fever and sinusitis⁽¹⁵⁾.

Indoor air quality is likely to be more important in the development of respiratory disease as pollutant levels may be substantially higher. Studies have shown strong links between occupational exposure to toxins and asthma and rhinitis, although there is a paucity of data for CRS. Gao et al. found a significant association between occupational and environmental factors and CRS⁽¹⁶⁾; more specifically exposure to industrial gases, fumes, dust and smoke have been shown to be associated with increased risk of CRS⁽¹⁷⁾. While a causal link cannot be clearly established, it seems sensible to counsel patients to reduce occupational exposure to irritants. Compliance with WHO standards for indoor air quality in the workplace must be monitored (http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf).

Evidence for both active and passive smoking leading to increased risk of CRS is much stronger. The GA2LEN survey of over 50,000 patients across Europe found that CRS was more common in smokers (OR1.7) compared with non-smokers⁽²⁾. There is a dose-dependent association between smoking and self-reported rates of CRS⁽¹⁸⁾, with a 1.5% increase in prevalence for each

additional year of smoking⁽¹⁹⁾. Berania et al. showed that active tobacco smoking is associated with an increase in systemic inflammatory markers of patients with CRS⁽²⁰⁾. There is direct evidence that tobacco smoke impairs mucociliary clearance and is a potential contributing or exacerbating factor in exposed individuals with chronic rhinosinusitis^(21,22). Passive smoking in childhood or adult life also seems to have a significant association with CRS^(23,24). Aggressive taxation on tobacco products, plain packaging with warning labels, and repeated counseling at every healthcare consultation are important to maintain the declining prevalence of smoking.

Allergy

It has been proposed that mucosal oedema within the osteomeatal complex in allergic rhinitis (AR) may compromise ventilation or even obstruct sinus ostia, leading to mucus retention and infection, however the causal role of allergy in CRS has been long debated^(5,10,25,26). On one hand; rates of positive skin prick tests are not statistically different between CRS patients and healthy controls, or between CRS sufferers with or without polyps⁽²⁵⁾ although patients with CRS had a higher number of different inhalant sensitivities when allergy was present. One recent systematic review evaluated 18 articles examining the relationship between allergy and CRSwNP: 10 articles found an association, 7 found no association, and 1 article showed a possible weak association. Of 9 articles which examined the relationship between allergy and CRSsNP, 4 articles found an association and 5 articles demonstrated no association⁽²⁷⁾. In a large population based study there was a significantly increased risk of AR prior to subsequent diagnosis of CRS (OR 2.4 for CRSsNP and 2.6 for CRSwNP)⁽²⁸⁾. No studies have assessed the effectiveness of management of AR on the outcome of established CRS or the risk of subsequent development of CRS, and further research in this area is needed before it can be recommended as a means of CRS prevention. However, early detection and management of AR has been shown to have a positive impact on the development of lower airway disease^(29,30), and is recommended for that aim.

Although patients often attribute their CRS to food allergies, there are only limited studies assessing the association between CRS and food allergies (with the specific exception of low salicylate diets in aspirin-exacerbated respiratory disease (AERD)). One study showed that milk allergy may be a predisposing factor for CRS⁽³¹⁾, however, overall the evidence is poor^(27,32,33), and certainly there is no evidence to support exclusion diets to prevent CRS. In AERD, CRSwNP typically develops after the onset of asthma, but again there are no studies evaluating the effectiveness of desensitisation in preventing CRSwNP.

Asthma

There is strong evidence to show that asthma and CRS, especi-

Table 1. Summary of factors involved in prevention of CRS.

Prevention Type	Factor	Description / Examples
Primary	Environmental	Smoking, Air quality, Occupational toxins, Ozone
	Allergy	Allergic rhinitis, Food allergy
	Asthma	Aspirin Exacerbated Respiratory Disease (AERD)
	Genetic	Cystic Fibrosis (CF), Primary ciliary Dyskinesia (PCD), Youngs
	Microbial	Acute Rhinosinusitis (ARS), Upper Respiratory Tract Infections (URTIs)
	Socio-economic	Microbial exposure, Smoking Exposure, Access to Healthcare
	GERD	
Secondary	Diagnosis	History, Examination, Imaging
	Medical Treatment	Selection of optimal medical treatment by phonotype/ endotype Biomarkers, Biological treatments
	Surgical Intervention	Timing of surgery, Extent of Surgery, Post-operative care, Minimising risks of treatment
Tertiary	Patient-related	Technique, Compliance, Concomitant local/systemic disease, Immune deficiency, Anxiety/Depression
	Treatment-related	Inadequate treatment, lack of symptom orientated management
	Diagnosis	Incorrect diagnosis
	Disease-related	Bacterial biofilms, Osteitis/Osteoneogenesis, Severe combined uncontrolled airway disease (SCUAD)

ally CRSwNP, frequently coexist. Several studies have shown that patients with asthma have a higher likelihood of having CRS^(5,28,34-36), and the GA2LEN Survey showed that in all age groups, men and women, and irrespective of smoking behavior, asthma was associated with CRS⁽³⁵⁾. The Greisinger Health study⁽²⁸⁾ found higher rates of pre-existing asthma in those developing CRS compared with healthy controlled (OR 2.8 for CRSwNP and 1.7 for CRSsNP). Similarly, higher premorbid rates of bronchitis, pneumonia and bronchiectasis have been reported. Again, a causal relationship has not been confirmed, but it is postulated that acute infective exacerbations may modify susceptibility to developing CRS.

Genetic risk factors

A number of genetic disorders, including cystic fibrosis (CF) and primary ciliary dyskinesia are associated with a high prevalence of CRS, however these account for only a very small proportion of CRS cases. Currently over 70 genes have been associated with CRS, summarised by a number of recent reviews^(37,38). Genes

associated with CRS can be broadly categorised into: genes associated with ion channels (e.g. CFTR); immunological genes (HLA, CD, IL); genes involved in tissue remodeling and arachidonic acid metabolism^(10,37,38). Until recently, outside of CFTR, there were no replication studies validating the gene associations with CRS and no studies demonstrating their biological relevance⁽¹⁰⁾. Henmyr et al. found a significant association in only 7 genes of the previous 53 genes associated with CRS⁽³⁹⁾. There has been growing recent interest in the bitter taste receptor T2R38; polymorphisms are associated with an increased risk of CRS but additionally has been shown to be associated with improved prognosis, with significantly lower rates of 'super tasters' found amongst CRS patients undergoing surgery⁽⁴⁰⁻⁴³⁾, compared to expected levels in the normal population. Of course, genetic risk factors are immutable but identification of high risk genes would inform accurate screening programmes, targeted reduction of environmental exposure, and inform personalised prognostic factors which would all be vitally important in the era of precision medicine.

Microbial exposure

The natural history of CRS, and the relationship between acute rhinosinusitis (ARS) and CRS development have been very poorly studied. Using the definitions of ARS and CRS based on duration alone, all episodes of CRS must start as ARS. However, whether CRS is truly persistence of ARS or whether CRS is a completely different pathophysiology from the outset is little known. Tan et al found that premorbid ARS (OR 2.2 for CRSwNP, OR 3.2 for CRSsNP) and acute upper respiratory tract infections (URTIs) (OR 1.3 for CRSwNP, OR 1.6 for CRSsNP) were more prevalent in patients developing CRS compared to those who did not; however, this data was extracted from electronic health records, and may simply reflect the diagnostic dilemma above. One study followed patients with ARS using repeated aspirates; those that developed chronic symptoms transitioned from bacteria commonly associated with ARS (*Streptococcus pneumoniae*, *Moraxella catarrhalis*) to a mixed infection which involved anaerobes⁽⁴⁴⁾. However, there is no evidence to suggest that active management of ARS or URTIs may reduce the risk of subsequent development of CRS. Indeed, increased use of antibiotics may cause profound and detrimental effects on the microbiome⁽⁴⁵⁾. The balance of resident microbes is increasingly recognized as important in onset of CRS⁽⁴⁶⁾, and reduced diversity is found in patients with CRS compared to controls⁽⁴⁷⁾, and in CRS patients following antimicrobial therapy⁽⁴⁸⁾. Given that current evidence suggests that the human microbiome becomes established early in childhood⁽⁴⁵⁾, there may be only limited opportunity to influence this later in life. Unlike many chronic diseases, there is little data suggesting an increased risk of CRS in those with lower socio-economic status, which may be linked to both microbial exposure and higher

rates of tobacco exposure. Indeed, one study of CRS in children suggests that when compared to controls, children with CRS were more likely to be white and privately insured⁽⁴⁹⁾; this however may simply reflect inequality of access to healthcare.

Odontogenic sinusitis

Dental disease is a well-recognised cause of chronic rhinosinusitis, accounting for 25% of cases in one series of CRS⁽⁵⁰⁾. Restrictions in access to dental care have been proposed to lead to an increase in the incidence of odontogenic disease in the UK⁽⁵¹⁾. Good dental hygiene, caution during exodontia to avoid fistula formation and loss of dental roots into the antrum may prevent the development of odontogenic disease.

GERD

The relationship between gastroesophageal reflux disease (GERD) and upper and lower airway diseases has been debated in the past. However, recent epidemiologic studies using electronic health registries and systematic reviews report that GERD and CRS often coexist^(10,52). Wong et al. describe a possible vagal reflex existing between the oesophagus and the paranasal sinuses⁽⁵³⁾. A causal relationship between GERD and CRS has yet to be firmly established, but GERD does appear to be a risk factor for development⁽⁵⁴⁾. Few studies specifically assess whether treatment of GERD has an impact on development of CRS or severity of symptoms, and there is insufficient evidence to consider anti-reflux therapy as standard for refractory CRS in adults⁽⁵⁵⁾.

Secondary prevention

Secondary prevention of CRS is concerned with detecting a disease in its earliest stages, and intervening to achieve disease and symptom control, thus preventing future exacerbations. Implicitly, secondary prevention takes place when primary prevention fails. Early diagnosis and selection of the optimal treatment paradigm is central to secondary prevention. Recent data suggest that there is still a large portion of the population with CRS not receiving treatment; as stated above, it is estimated epidemiologically that CRS affects approximately 5–15% of the general population both in Europe and the USA, in contrast with 2–4% prevalence of doctor-diagnosed CRS^(8,56). It is unclear whether this discrepancy arises because patients effectively self manage symptoms of CRS or are unable to access care.

Early establishment of diagnosis

State-of-the-art guidelines like EPOS⁽⁸⁾ provide clinicians with evidence-based diagnostic and treatment algorithms for CRS based on symptom duration and severity. However, a symptom based definition alone is likely to over-estimate disease⁽⁵⁷⁾, and consistent findings on endoscopy or radiological imaging are

required to support the diagnosis. It is likely that the diagnostic criteria will be further refined as biomarkers for disease are identified. The Finnish allergy programme⁽²⁹⁾ has shown the effectiveness of screening for inflammatory airway disease, however current financial constraints in healthcare are a barrier to rolling out of widespread similar schemes. However, symptom-based screening of patients at high risk of secondary CRS, such as those with systemic vasculitides, eosinophilic airway disease, or AERD is likely to be beneficial.

Selection of optimal treatment

Currently CRS is broadly categorised into 2 subgroups; CRS with and without nasal polyps. However, clinical phenotypes do not provide full insight into underlying cellular and molecular pathophysiologic mechanisms of CRS⁽⁵⁸⁾ and further differentiation or “endotyping” of CRS is needed. Endotypes, which are defined by distinct pathophysiologic mechanisms and characterised by corresponding biomarkers, might demonstrate differences in the natural course of disease and prognosis in terms of recurrence after surgery and risk of comorbid asthma but also in responsiveness to different treatments, including topical intranasal corticosteroids, surgical interventions, and biological agents. For example: noneosinophilic nasal polyps, which are more prevalent in Asia compared with Europe or the United States, do not show the same response to topical and oral corticosteroids as eosinophilic polyps⁽⁵⁹⁾. Some antibiotics, such as macrolides, demonstrate better efficacy in neutrophilic CRS, while tetracyclines demonstrate superior efficacy in patients with eosinophilic CRS⁽⁶⁰⁾.

In this regard, novel biological treatments would be ideally suited for patients who can be predicted to have an otherwise recalcitrant path, based on their biomarkers, rather than undergoing ineffective cycles of treatment with corticosteroids and surgery. Typically, recalcitrant CRS patients are defined by the failure of treatment to adequately control disease. In an ideal world it would be possible to identify these patients early in the course of disease and offer tailored treatment from the outset. There are a growing number of monoclonal antibodies, targeting type 2 inflammatory cytokines (including IL-4, IL-5, IL-13) and IgE and studies have demonstrated proof of concept in the patients with CRSwNP⁽⁶¹⁾. We now need to identify biomarkers that will allow accurate selection of patients and the ideal monoclonal to achieve maximum benefit. Guidelines have traditionally attempted to drive all patients through the same pathway; in reality multiple interconnected pathways are likely to be required to facilitate precision medicine.

Optimising the outcome of surgical intervention

i) Timing of surgery

Once the diagnosis of CRS is made, EPOS advocates surgical

treatment when optimal medical management has made no improvement in symptoms after 12 weeks⁽⁸⁾.

Current evidence fails to show clear benefit of surgery over medical treatment at first presentation, supporting a role for primary medical treatment^(62,63). However, after failed medical therapy, patients who elected to continue with medical therapy achieved poorer outcomes than those choosing surgery⁽⁶⁴⁾. Furthermore, delayed surgery in the setting of persistent CRS after failed medical therapy has been shown to be associated with higher ongoing healthcare utilisation postoperatively^(65,66). Early surgical intervention after a trial of medical therapy may also deliver better symptomatic outcomes that are sustained for as long as five years⁽⁶⁷⁾.

Appropriate indications for endoscopic sinus surgery (ESS) are currently poorly defined and the lack of clear indications for ESS likely contributes to the large geographic variation in surgical rates. Recent study by Rudmik et al. clearly states that ESS can only be indicated after medical treatment has failed with patients still having significant symptoms (SNOT-22 \geq 20) and at least some abnormalities at CT scan⁽⁶⁸⁾. Pre- and post-operative measures of patient rated outcome scores such as the Sinonasal Outcome Test-22 may be used to predict benefit from surgery and identify early failure^(69,70). Improved patient selection for surgery is likely to optimise outcomes and reduce risk of harm.

ii) Extent of surgery

There is little comparative evidence to direct surgeons as to whether a conservative, aggressive or tailored approach to sinus surgery should be taken⁽⁷¹⁾. Data from the UK audit of ESS found no additional benefit of additional sinus surgery over simple polypectomy in terms of symptomatic benefit, and only a small benefit in terms of revision rates⁽⁷²⁾. However, the additional sinus surgery performed in most cases was very conservative, and less than 2% of the surgical cohort had complete frontoethmoidectomy and sphenoidotomy. The effectiveness of intranasal steroids has been shown to be increased in the post-operative state, suggesting improved access to topical therapy is an important aspect of the benefits of surgery⁽⁷³⁾. Furthermore, eosinophilic CRS has been shown not to be associated with osteomeatal occlusion⁽⁷⁴⁾, and therefore simple measures to address the osteomeatal complex are unlikely to be effective. There is some evidence to support a more extensive approach, particularly in eosinophilic disease or CRSwNP^(75,76).

iii) Postoperative care

Patients should be encouraged to continue to use intranasal corticosteroids (INCS) after surgery as continued use has been shown to improve post-operative endoscopic scores in all CRS patients⁽⁷⁷⁾ and, in those with CRSwNP, reduce risk of recurrence⁽⁷⁸⁾. Mucosal eosinophilia has been shown to be highly correlated with risk of polyp recurrence, more so than the basic phenotype

of CRSwNP, and in future this may provide a better indicator of the need for long term INCS⁽⁷⁹⁾.

Saline douching has been shown to improve symptoms after surgery^(80,81), and may reduce need for nasal cavity debridement. The value of post-operative debridement remains controversial; although systematic reviews have shown benefit in terms of early symptom scores and endoscopic appearances⁽⁸²⁾, there is no significant impact on long-term outcomes, and current trials have not compared debridement to high-volume saline irrigation alone. Routine use of antibiotics in all patients after ESS is not supported by the literature and increasing bacterial resistance must be considered, but may be used in selected cases⁽⁸²⁾. There are a growing number of drug-eluting stents and topical dressings that may promote early healing and restoration of mucociliary function. A recent systematic review studied steroid-eluting bioabsorbable intranasal devices, and demonstrated improved objective and subjective outcomes following ESS⁽⁸³⁾. Currently, cost of such devices may restrict widespread usage, although cost-effectiveness may be enhanced by reduced attendances for post-operative debridement.

Minimising risks of treatment

As a general rule, any treatment should have benefits that always outweigh the risks. When considering medical and surgical interventions we must consider the risk of harm to the patient.

Short courses of oral corticosteroids are widely used, and may result in insomnia, mood and gastrointestinal disturbances⁽⁸⁴⁾. There is a paucity of data on the threshold of dose that may expose patients to major complications such as avascular necrosis and osteoporosis, and repeated courses should be used judiciously⁽⁸⁵⁾. In contrast, topical corticosteroids are safe and adverse effects are minor. A recent Cochrane review found no difference in the reported side effects between topical corticosteroids and placebo⁽⁸⁶⁾, except for an increase in reported epistaxis. Moreover, there seems to be no clinically relevant impact on ocular pressure, glaucoma, lens opacity, or cataract formation⁽⁸⁷⁾.

The use of prolonged courses of anti-inflammatory antibiotics needs to be balanced with the potential gastrointestinal disturbances and serious adverse effects of rhabdomyolysis and prolonged QT⁽⁸⁸⁾, effects on bacterial resistance, and the potential consequences to the sinus microbiome which are as yet largely unknown.

In comparison with the medical therapy, there are more data reporting the rate of surgical complications. The National Sinonasal Audit reported a total adverse event rate of 6.6%, most of which was related to minor bleeding. This rate of major

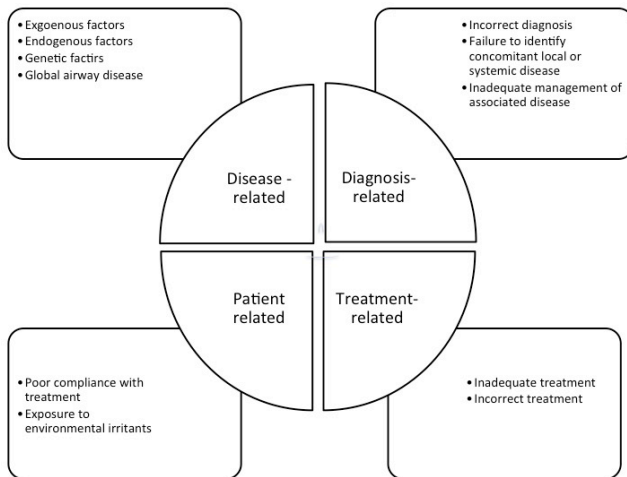


Figure 1. Severe combined uncontrolled airway disease, from Hellings et al. ⁽⁹⁰⁾.

complications from the UK (0.4 %) compares with a rate of 1.1 % reported in a meta-analysis from 10 years previously of 4691 patients who underwent ESS in the US ⁽⁸⁹⁻⁹¹⁾.

Tertiary Prevention

Tertiary prevention aims to minimise the impact of an ongoing illness or injury that has lasting effects. This is done by helping people manage long-term, often-complex health problems (e.g. chronic rhinosinusitis) in order to improve their ability to function, quality of life, and life expectancy. Ongoing poorly controlled upper airway disease may result from disease-related factors, inadequate treatment, poor compliance, or failures in the diagnostic pathway that incorrectly diagnose primary CRS or fail to identify secondary CRS (Figure 1) ⁽⁹²⁾. A recent study found that at least 40% of CRS patients would be considered to have uncontrolled disease within 3 – 5 years of endoscopic sinus surgery ⁽⁹³⁾.

In patients with poor disease control, a careful review of ongoing treatment, technique and compliance with medication should be undertaken. A recent study found only 20% of CRS patients to be actively utilizing an intranasal corticosteroid spray, with both under-prescription and poor compliance likely implicated ⁽⁹⁴⁾. Growth in digital healthcare and patient apps may encourage self-management and increase compliance. Encouraging health behaviours such as smoking cessation may be beneficial: although the evidence of the impact of ongoing tobacco exposure on quality of life outcomes of CRS treatment is conflicting ^(95,96), higher rates of revision surgery are seen in smokers ⁽⁹⁷⁾, and cessation should therefore be encouraged. Management of individuals with recalcitrant CRS is based on the understanding that this is a chronic condition, and that “cure,” as achieved in acute bacterial infections such as tonsillitis, cannot and should not be expected. Caregivers and allied

health personnel all share in the task of educating the patient to understand the chronic, ongoing nature of the disorder, and to adjust their expectations accordingly.

The diagnosis should be reconfirmed, particularly when facial pain is the ongoing primary symptom, and systemic diseases should be considered and excluded when indicated. Conditions such as granulomatosis with polyangiitis (formerly Wegener’s granulomatosis) or eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) may present with sinonasal disease and the systemic nature of disease may not be apparent in the early stages. Underlying immune deficiency should be considered, particularly where there is a history of concomitant lower airway, ear or skin infections. Up to 10% patients with refractory CRS were found to have chronic variable immunodeficiency disorder (CVID): 20% had decreased IgG, IgA or IgM, and 11-67% had an inadequate functional response to pneumococcal vaccine ⁽⁹⁸⁻¹⁰⁰⁾, (however, all these studies were conducted at tertiary institutions and thus it is likely that there is significant selection bias).

Higher levels of anxiety and depression are found in patients with CRS, although it is often undiagnosed ^(101,102). It is unclear if this is a causative relationship; however it appears likely that co-existing depression results in both higher rates of symptom reporting and amplifies symptom severity, particularly in CRSsNP ⁽¹⁰³⁾. Patients with co-existing depression report poorer disease specific health related quality of life both before and after treatment for CRS ⁽¹⁰⁴⁾. Although treatment for CRS has been shown to reduce depression scores, there is no evidence on whether treatment of depression may result in improvement of CRS-related QOL.

Disease related factors

A number of factors have been shown to be associated with poorer long-term outcomes in CRS, however there is a paucity of evidence regarding prevention or management of these factors.

Bacterial biofilms may cause recurrent acute exacerbations in CRS through the periodic release of free-floating bacteria ⁽¹⁰⁵⁾ and are associated with unfavourable outcomes post-surgery ⁽¹⁰⁶⁾.

Osteitis has been shown to be associated with poorer post-operative endoscopic appearances and HRQOL. It is unclear whether osteitic bone acts as an innocent bystander becoming secondarily involved in the inflammatory process, or whether diseased bone plays a more active role in propagating inflammation ^(107,108). However, its association with the number of revision surgeries, which itself is surrogate marker for recalcitrant disease, could also suggest that osteitis is an adverse consequence of mucosal stripping during surgery.

SCUAD has been introduced as a definition of those patients with chronic severe upper airways disease despite evidence-

based treatment schemes⁽¹⁰⁹⁾ (Figure 1). It is estimated that up to 30% of CRS patients remain uncontrolled despite evidence-based treatment⁽⁹²⁾. After having excluded patient-related, diagnosis-related and treatment-related factors for failure of adequate control in CRS patients, we can only speculate on the percentage of patients having severe disease recalcitrant to prolonged medical and surgical treatment. Immune deficiencies, heterozygote CF patients, and primary ciliary dyskinesia are rare conditions but may account for the severity and chronicity of SCUAD. Further work is required to better define this population and to develop effective treatment strategies for those patients with recalcitrant disease.

Conclusions

There is currently little research on the prevention of CRS. Current evidence supports anti-smoking advice, optimal management of asthma and allergic rhinitis and improving both internal

and external air quality in order to reduce the incidence of CRS. Early diagnosis and timely introduction of treatment in order to achieve disease control may minimise chronicity and severity of the disease. More research is needed to define both best medical and surgical management, and the role of endotyping to choose different interventions. Patients with SCUAD remain one of the greatest challenges in CRS management, and novel treatments are much needed.

Authorship contribution

CH, PH: concept of paper, design, final review of manuscript, CH: drafting of manuscript, PS: review of primary prevention literature, FB: review of secondary prevention literature, RH, AW: review of tertiary prevention literature.

Conflict of interest

No conflicts of interest or relevant financial interests to disclose.

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