



Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) Position Paper

Overview

Chronic Rhinosinusitis (CRS) is one of the most common chronic conditions worldwide.

CRS is generally subclassified into two dominant subgroups:

- CRS with Nasal Polyps (CRSwNP), and
- CRS sine (without) NP (CRSsNP).

CRSwNP is a Type 2 (T2) inflammatory disorder and has a significant impact on quality of life which is further reduced if other atopic diseases and asthma are also present.

The health-economic impact is significant, with direct costs to the US health care system regarding the care of CRS patients being more than 10 billion dollars yearly. Indirect costs from absenteeism and decreased productivity are additional and considerable.

Diagnosis of CRSwNP is based on symptoms and endoscopic or computed tomography (CT) scan findings. Patients with a higher number of symptoms (four or more) are more likely to have positive findings of CRS on CT scans.

Despite CRS's significant incidence and quality of life implications, there are relatively few large and well-conducted studies of current first-line therapies. Intranasal corticosteroids (INCS) and saline irrigation are safe and effective for long term use in patients with CRS. Many patients remain suboptimally controlled and require surgical management.

As new medical therapies are becoming available, we need a rational approach to appropriate, equitable, and cost-effective treatment. This position paper aims to provide an overview of this clinical entity and provide a framework for modern management that incorporates newer biological therapies.

This Position Paper was developed by the Australasian Society of Clinical Immunology and Allergy (ASCI) and the Australian Society of Otolaryngology Head & Neck Surgery (ASOHNS) Working Party, comprising: A/Prof Raewyn Campbell, Prof Richard Harvey, Prof Connie Katelaris AM (Chair), Prof Michaela Lucas, Dr Kathryn Patchett, A/Prof Janet Rimmer, Prof Ray Sacks.

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<https://www.allergy.org.au/hp/papers/references-crswnp-a-l>

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SECTION 1 - BACKGROUND

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is:

- **Inflammation of the paranasal sinuses for more than 12 weeks, localised or diffuse.**
- **Present in 2-4% of the adult population, increasing with age and other co-morbidities.**
- **Has a significant impact on quality of life especially when atopic diseases, asthma or other comorbidities are present.**

Understanding the aetiology and molecular endotype of each inflammatory condition is essential for targeted treatment.

Epidemiology

Chronic Rhinosinusitis (CRS) is one of the most common chronic conditions worldwide. CRS represents a **group of disease entities that present with chronic upper airway inflammation**. It is heterogeneous in its clinical presentation, with geographical, gender and ethnic differences.

CRS, with or without nasal polyps (NP), is estimated to affect approximately 9.8% of the Australian general population, 11% of the European, and 14% of the American population (Hastan et al., 2011; Jarvis et al., 2012; Kaliner et al., 1997; Habib et al., 2019) but can range between 5.5% to 28% worldwide (Fokkens et al., 2020). Based on data from the Australian National Health Survey 2017-2018, subjects self-reporting CRS were more likely to be female, over 60 years of age, cigarette smokers and consumed alcohol (Habib et al., 2019).

The prevalence of physician-diagnosed CRS in the community is much lower at 2% (Chaaban, Walsh & Woodworth, 2013) compared to the prevalence of 3-6% of Ear, Nose and Throat (ENT) specialist-diagnosed CRS when clinical symptomatology is combined with visualisation of disease by endoscopy or computed tomography (CT) scan (Fokkens et al., 2020). As most epidemiological studies are based on symptomatology without ENT assessment, they may therefore overestimate the prevalence of disease.

CRSwNP is present in 2-4% of the adult population (Fokkens et al., 2012) and is more common in smokers than in non-smokers (Hastan et al., 2011). It is often associated with other respiratory diseases, including asthma, aspirin exacerbated respiratory disease (AERD) and idiopathic bronchiectasis with approximately 25% of CRS patients having asthma (Fokkens et al., 2020). Involvement of the sinuses in AERD is almost universal, depending on the stage of disease, with an estimated prevalence of nasal polyposis in AERD patients up to 70% or more (Mullol & Picardo, 2013). AERD is present in 8-26% of patients with CRSwNP.

Overall, the prevalence of CRSwNP increases with age, with a mean onset of 42 years. Worldwide it is more common in men than women, except in the context of AERD (Chaaban et al., 2013). Alcohol hyperresponsiveness in subjects with CRSwNP has also been reported (De Schryver et al., 2017). The prevalence in children is associated with passive and active smoking (Sidell, Shapiro & Bhattacharyya, 2013; Reh, Higgins & Smith, 2013).

Economic and personal burden

CRSwNP has a significant impact on quality of life which is further reduced if other atopic diseases and asthma are also present (Alobid, Bernal-Sprekelsen & Mullo, 2008; Fokkens et al., 2020). It is estimated that 60-80% of people with CRS have some form of olfactory impairment (Ahmed & Rowan, 2020), which is known to be linked to depression (Kohli, Soler, Nguyen, Muus, & Schlosser, 2016). In line with these findings are reports that 11-40% of patients with CRS suffer from depression (Schlosser, Gage, Kohli & Soler, 2016). In addition to olfactory disturbances, 28% of CRS sufferers also have altered taste, or dysgeusia (Othieno et al., 2018).

The **health-economic impact is significant** with direct costs to the US health care system for the care of CRS patients more than 10 billion dollars annually (Bauer & Turner, 2020). The cost per patient is estimated at USD \$2609, GBP2974 and EUR 1501 per year. The indirect costs from absenteeism and

decreased productivity are additional and considerable (Fokkens et al., 2020). There is no Australian health-economic data for CRS readily available.

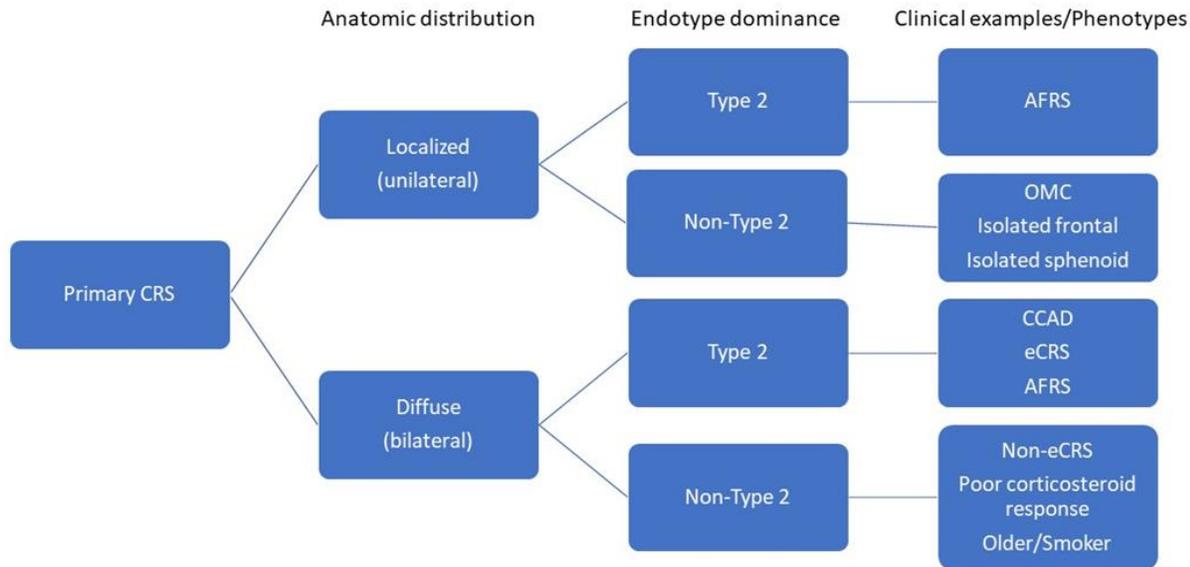
Classification

CRS is a complex disease that has previously been used to describe conditions ranging from unilateral single sinus disease, odontogenic sinusitis, fungal sinusitis, to widespread airway inflammation. The currently recognised definition of primary CRS is represented by chronic inflammation of the paranasal sinuses for more than 12 weeks. In clinical practice, treatment decisions are often based on observable findings including features from clinical history, examination findings and response to medications. The presumed disease and molecular pathophysiology is often inferred rather than carefully defined. This is especially true for CRSwNP.

Traditionally, a coarse description of CRS was based on the presence or absence of nasal polyp formation. However, the formation of polyps is common to several well-defined CRS conditions and not an end result of a common or unique inflammatory pathway. In the European Position Paper on Rhinosinusitis and Nasal Polyps, known as EPOS 2020 (Fokkens et al., 2020), a classification system was put forward that is simple and practical. It proposed that the functional anatomical compartments involved create the first level of separation into localised (unilateral) disease, followed by diffuse (bilateral) distribution of disease (Fokkens et al., 2020). Diffuse does not imply ‘pan-sinusitis’ but simply that the disease does not confine to a known functional anatomical unit.

This classification takes into account first whether local anatomical factors are contributing to pathogenesis. Then the inflammatory endotype dominance separates into a T2 skewed inflammation as this has both aetiologic and treatment implications. Non-T2 encompasses everything else we do not know yet about inflammation and may change over time. The phenotypes, or clinical examples of CRSwNP, that have been described are shown below and include allergic fungal rhinosinusitis, ostiomeatal complex, central compartment atopic disease, eosinophilic rhinosinusitis and allergic fungal sinusitis.

Classification of Primary CRS



AFRS Allergic fungal rhinosinusitis
 CRS Chronic rhinosinusitis
 OMC Ostiomeatal complex occlusion

CCAD Central compartment atopic disease
 eCRS Eosinophilic rhinosinusitis

(adapted from Grayson et al., 2020)

Primary sinus disease is part of a process limited to the respiratory system only. Secondary sinus disease is secondary to a local process (dental infection, tumour, etc) or a condition not confined to the respiratory system (cystic fibrosis, immunodeficiency, eosinophilic granulomatosis with polyangiitis). Localised implies that the disease is limited to an anatomical area that drains or functions a single entity for mucociliary clearance and highlights local anatomy as a major part of pathogenesis. Conversely, diffuse disease implies an abnormal host-environment interaction and abnormal inflammatory response.

The term Primary CRS refers to a sinus condition in which no obvious secondary pathoetiologic event is occurring (fungal ball, neoplasia, odontogenic infection or immunodeficiency). Traditionally, Primary CRS has been separated into two major subtypes based upon phenotypic appearance: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) (Fokkens, Lund, & Mullol, 2007; Fokkens et al., 2012). The description of these different subtypes relies largely on observable clinical findings and lacks the inclusion of molecular differentiation and potential molecular diversity that exists within a subtype. Additionally, eosinophilic rhinosinusitis (eCRS), allergic fungal rhinosinusitis (AFRS) and aspirin exacerbated respiratory disease (AERD) have been proposed as subtypes of CRS.

In the era of biologic therapies, the treatment paradigm for CRS is largely driven by the presumed underlying etiology and molecular endotype of each inflammatory condition. This is also true for inflammatory disease of the lower respiratory tract, as the upper and lower airway are one unified tract and often exhibit similar molecular pathophysiology.

The phenotypes of CRS that have been classically associated with nasal polyps (CRSwNP) are part of the initial clinical presentation of eosinophilic chronic rhinosinusitis (eCRS). While some polypoid changes can occur with any prolonged inflammatory response, those conditions that are classically associated with the clinical features of nasal polyps are listed below:

Primary localized CRS (typically unilateral) T2 dominant: Allergic fungal rhinosinusitis (AFRS)
Primary diffuse CRS (typically bilateral) T2 dominant: Central compartment atopic disease (CCAD), Eosinophilic rhinosinusitis (eCRS) and Allergic fungal sinusitis (AFRS) Non-T2 dominant: Non-eCRS

Previous studies on the success of different treatment options in the lower respiratory tract have had varied results. This is likely due to vague clinical definitions and use of phenotype-only descriptions driving treatment decisions (Wenzel, 2012). Endotyping of both asthma and CRS has been the focal point of more recent studies, as well as categorizing endotypes with their associated phenotypic group (Anderson, 2008; Wenzel, 2012; Tomassen et al., 2016).

In the lower airway, asthma researchers became frustrated with the concept of asthma as a singular disease entity as it only describes a clinical condition and the associated wheeze, cough, and shortness of breath. To address this concern, these researchers described an endotype as a subtype of disease with a unique pathomechanism, functionally and pathologically different from others by the involvement of a specific molecule or cell. Unlike the immediately observable clinical characteristics noted in phenotypes, **endotypes define the underlying inflammatory pathophysiology to direct appropriate precision therapy for optimal patient outcomes.**

While all subtypes and etiologies of CRS have previously been lumped together on the basis of presence or absence of polyps, the current European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 classification defines CRS as indicative of primary or secondary sinus pathology, further delineated by their anatomic locations then, importantly, the endotype /inflammatory predominance, or etiological mechanism.

The traditional CRS phenotype of with and without nasal polyps has significant limitations. This is especially true when discussing the role of biologic agents in the management of CRS. The currently available biologics all target pathways of the T_H2 immune response. There are CRS entities that produce polyps, such as cystic fibrosis related CRS and non-eCRS that are unlikely to benefit from current biologic agents. Similarly, the AFRS phenotype, whether unilateral or bilateral is initially and predominantly managed with surgical intervention. Within the primary diffuse CRS group of conditions that produce a polypoid phenotype, four major disease entities exist: inhalant allergy driven central compartment atopic disease (CCAD), eosinophilic rhinosinuitis (eCRS), fungal associated CRS and non-eosinophilic form of CRSwNP.

Diffuse T2 dominant phenotypes of CRSwNP

Central compartment atopic disease (CCAD) /allergic (immunoglobulin E (IgE)-mediated) airway inflammation

Patients with allergic airway inflammation often have an earlier onset (<20 years) disease, and although there is eosinophilic T-helper 2 (T_H2) cell involvement, it is predominantly IgE driven and displays other signs of atopic disease such as allergic rhinitis (AR), allergic conjunctivitis, and dermatitis (Wenzel, 2012). They will also have a history of allergic asthma (asthma associated with childhood and not adult-onset) with similar triggers. Most patients with persistent asthma that had an onset in early childhood also have allergic airway inflammation (Wenzel, 2012).

Histopathologically, T_H2 cytokines dominate this condition. This leads to elevated total and serum specific IgE. These patients will rarely have an elevated serum eosinophil count (Wenzel, 2012) or sputum or tissue eosinophilia.

Eosinophilic airway inflammation

Eosinophilic CRS (eCRS) is an inflammatory condition due to T_H2 responses that is driven by eosinophilic inflammation. These patients tend to be older (30-50 years at onset) compared to those with early onset allergic disease (<20 years).

Although some of these adult onset eCRS patients may have had a history of allergic disease in their childhood, they often report that it quiesced for many years, with few symptoms in their early adult life, only to return in their 30s-50s. Any adult onset eCRS condition with a history of allergy that had previously become quiescent, is likely to be unrelated to their childhood atopy.

Smell loss is a major feature early in the disease process for eCRS sufferers. Acute exacerbations, likely due to secondary obstructive or infective phenomena are common. These adult onset eCRS often receive antibiotics on multiple occasions prior to presentation (Ho et al., 2018).

A history of asthma is almost always reported by patients at around the same time as the onset of their upper airway symptoms. In those patients who do not present with asthma, they will likely become asthmatic.

Patients with eCRS will often report food induced and alcohol related exacerbations or flares of their condition. This is thought to be related to eosinophilic priming of the mucosa and leukotriene inducing triggers. Aspirin exacerbated airway disease (AERD), includes non-steroidal anti-inflammatory (NSAIDs) reactivity, is a subtype of adult-onset eCRS.

Corticosteroid responsiveness, including smell recovery, is a major feature of these patients. They often report a dramatic benefit within days of starting therapy and smell often returns quickly. Many patients seek corticosteroids and it is not uncommon to have patients wanting to be on them or self-medicating, although most are familiar with their side-effects. Patients who report that corticosteroids are a “magic pill” are often eCRS sufferers. This response is due to the systemic penetration of corticosteroid to the sinuses, unlike topical corticosteroid sprays which have little effect in most patients (Snidvongs et al., 2013).

Histopathologically, these patients will have tissue eosinophilia (>10 eosinophils/high power field or HPF) although this does not distinguish between CCAD and eCRS. Many patients have sinus tissue

biopsies with >100 eosinophils/HPF. A recent systemic review has demonstrated that a cut off of 55 eosinophils/HPF predicts the likelihood of recurrence following surgical intervention (McHugh, 2018; Snidvongs et al., 2018).

Systemic eosinophilia is a feature of eCRS. High levels of eosinophils in the blood have a positive likelihood ratio (LR) of 3.28 to predict high tissue eosinophilia (Ho et al., 2018). Tissue eosinophilia, however, is not significantly associated with total serum IgE (Ho et al., 2018)

Allergic fungal rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a subset of polypoid chronic rhinosinusitis that is characterised by the presence of eosinophilic mucin with non-invasive fungal hyphae within the sinuses and a Type I hypersensitivity to fungi. It was originally described by Safirstein (Safirstein, 1976) and Katzenstein (Katzenstein, Sale & Greenberger, 1983). It has a specific geographical distribution and so some clinicians, who work in parts of the world where AFRS is not so common, have questioned whether the condition really exists as a separate clinical entity, or is part of eosinophilic CRS or CRSwNP.

Although there is some controversy about the definition of AFRS, and even whether it is a distinct clinical phenotype of CRSwNP, the EPOS 2020 taskforce defines it as a unique and distinct phenotype (Peters et al., 2014; Dykewicz et al., 2018). Bent and Kuhn included IgE sensitisation as an inclusion criteria in their original description (Bent 3rd & Kuhn, 1994). AFRS is, for the most part, considered an IgE-mediated mucosal hypersensitivity directed against fungal antigens deposited on sinus mucosa (Kuhn & Javer, 2000).

The defining pathophysiology in AFRS is sensitisation to the causative fungus as a primary and requisite feature along with mucin colonised with non-invasive fungus (Hoyt et al., 2016). Although fungal sensitisation may exist in CRSwNP, typically IgE levels (both specific and total) are higher in AFRS (Bakhshaei et al., 2013; Bakhshaei et al., 2014).

Diffuse Non-T2 dominant phenotypes of CRSwNP

Unlike eosinophilic and allergic airway inflammation, patients with non-eosinophilic airway inflammation tend to be middle aged (~60s), female, obese, and have no significant history of atopic disease. These patients will have a history of broader airway inflammation that is often not completely controlled on inhaled corticosteroids. If they have a history of childhood atopy, they will no longer suffer from classic allergic symptoms.

They will less often have smell loss. However, when they do, corticosteroids will not be the “magic pill” that they are for eCRS patients. Even with adequate treatment and control, their sense of smell will be slower to return. If patients have been treated in the past with corticosteroids, they may report very mild to no improvement. These patients are often on classic preventative inhaled therapy for their lower airways symptoms and still have break through symptoms.

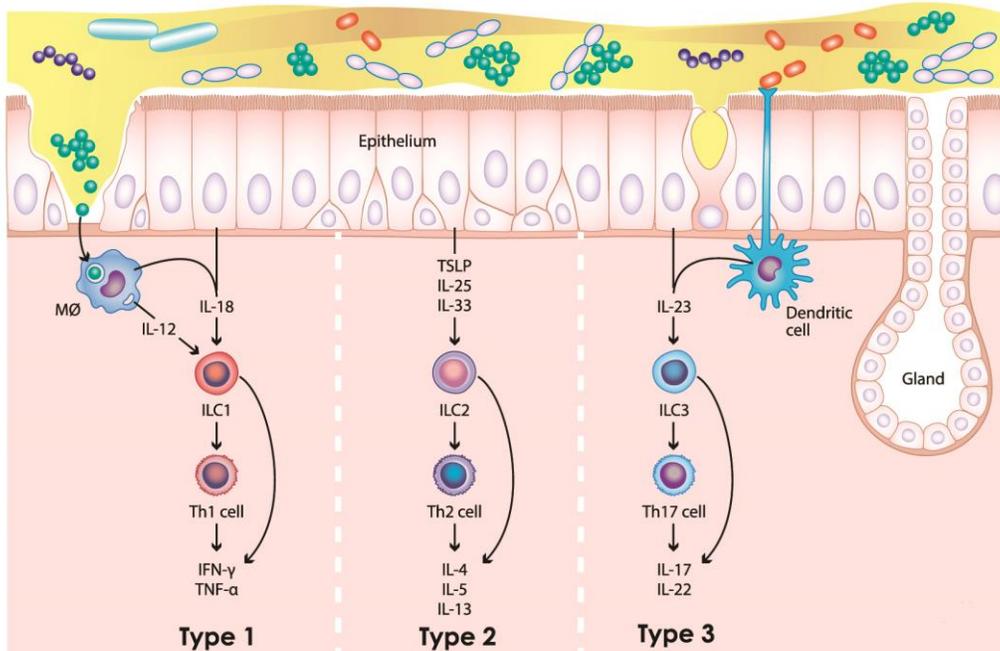
Inflammation is driven by neutrophils and tissue eosinophils will be low. Tissue neutrophilia is significantly correlated with the presence of pro-inflammatory cytokines (IL-1 β , 6, and 8) (Snidvongs et al., 2012; Morse et al., 2018). Increasing levels of the non-Th2 cytokines present in the mucus is correlated with higher bacterial culture positivity and age (Morse et al., 2018).

Pathophysiology

At the heart of most discussions on the origins of CRSwNP is an abnormal “host-environment” interaction. From the host standpoint, genetic and epigenetic variation of the mucosal immune system is believed to play a key role in CRS, but multiple genes are likely involved and, thus far, very few have been associated with a large effect size. The key environmental agents also remain largely uncertain, but cigarette smoke, fungi, viruses, bacteria, pollutants and allergens have all been implicated (Fokkens et al., 2020).

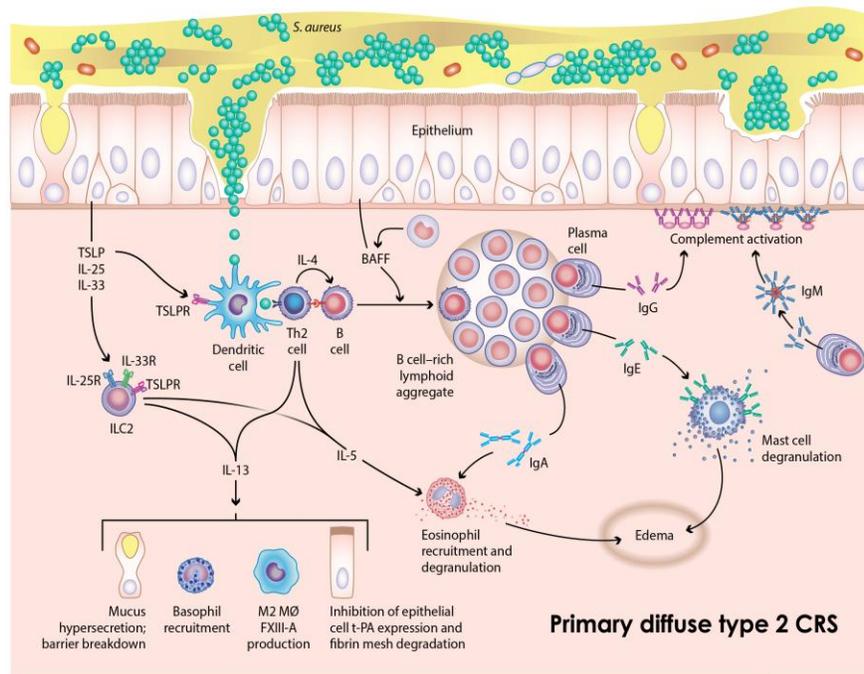
Inflammatory immune responses at mucosal surfaces are thought to offer advantages to manage differing classes of inciting pathogens. Type 1 (Th1) responses are directed against intracellular

pathogens, most commonly viruses. The recognised cytokine in this context is interferon (IFN- γ). T2 responses are directed against large, extracellular parasites and antigens and change pathogens to inciting agents. The established cytokines are IL-4, IL-5 and IL-13. Type 3 responses are directed against extracellular bacteria and fungi and the established cytokines are IL-17 and IL-22. Each type of response involves an immediate response mediated by an innate lymphocyte subset (ILC1, 2 and 3 respectively) that is linked to a corresponding delayed T helper subset (Th1, Th2 and Th17 respectively).



(reproduced with permission from Fokkens et al., 2020)

CRS with T2 cytokines are the most commonly associated with both the formation of nasal polyps and asthma. This endotype is the most recalcitrant to simple therapies and responsible for the majority of corticosteroid use by patients with CRS. Current biologic agents have been developed around the T2 immune responses observed in these patients. The tissue inflammation is often associated with remodeling patterns including fibrosis, polypoid oedema, fibrin deposition and barrier failure. The remodeling that comes about from fibrin deposition and crosslinking is what is thought to contribute to nasal polyp formation (Takabayashi & Schleimer, 2020). The T2 inflammatory endotype has been the most extensively studied pathway in Western countries, perhaps due to its association with allergic rhinitis, asthma, and CRSwNP (De Greve, Hellings et al., 2017).



(reproduced with permission from Fokkens et al., 2020)

Clinical manifestations

Chronic RSwNP means that symptoms have persisted for at least 12 weeks. As nasal polyp tissue obstructs the nasal cavity, symptoms of nasal obstruction or congestion are common, occurring in 95% of patients (Dietz de Loos, Hopkins & Fokkens, 2013). At least one other symptom should be present including nasal discharge, either anterior or posterior post nasal drip (89%), and reduction or loss of sense of smell (58%) due to occlusion of the olfactory nerve endings, and facial pain (60%). Facial pain rarely occurs as an isolated symptom. **Nasal obstruction and altered sense of smell are the most common and most severe symptoms** (Dietz de Loos et al., 2013). The role of headache is discussed in Section 2 - Clinical Diagnosis.

In children the same symptoms occur but they may not describe changes in smell and they may also have a cough (day and/or night).

Allergic rhinitis may co-exist and cause other symptoms such as nasal and ocular pruritis, sneezing, and watery rhinorrhoea. Acute sinusitis may also co-exist and cause facial pain, purulent secretions and fevers.

Co-morbidities

United or global airway disease recognises that upper and lower airway disease commonly co-exist with up to two thirds of patients with CRS affected by comorbid asthma, chronic obstructive pulmonary disease (COPD) or bronchiectasis (Yoo et al., 2016).

In relationship to asthma, there is a greater probability of having CRS (Shi, 2015) and asthmatics have an increased risk of developing CRS compared with healthy controls (OR 2.8 for CRSwNP) (De Sario, Katsouyanni & Michelozzi, 2013). CRS is associated with asthma, with a prevalence of asthma around 25% in patients with CRS compared to 5% in the general population.

The prevalence of allergy in CRS may vary by phenotype, with CCAD and AFRS having a stronger association than CRSwNP and CRSsNP (Hamizan et al., 2018; Phillipot et al., 2018).

Aspirin exacerbated respiratory disease (AERD/NERD)

Aspirin exacerbated respiratory disease (AERD), previously called Samter’s triad, consists of asthma, nasal polyposis, aspirin sensitivity and eosinophilic sinusitis (Samter & Beers, 1968). It is also called NERD or nonsteroidal exacerbated respiratory disease, recognising that aspirin is not the only trigger. It is an adverse reaction not an allergic or IgE-mediated reaction to the drug involving the arachidonic acid pathways which produce eicosanoids such as leukotrienes and prostaglandins, which act locally as pro/anti-inflammatory agents. Aspirin and many NSAIDs are COX1 inhibitors (see figure below). AERD has several phenotypes but the most common is a reduced cyclooxygenase-2 (COX2) expression and prostaglandinE2 (PGE2) production. The underlying reason for the development of AERD is unclear but a genetic basis has not been demonstrated (Taniguchi et al., 2019).

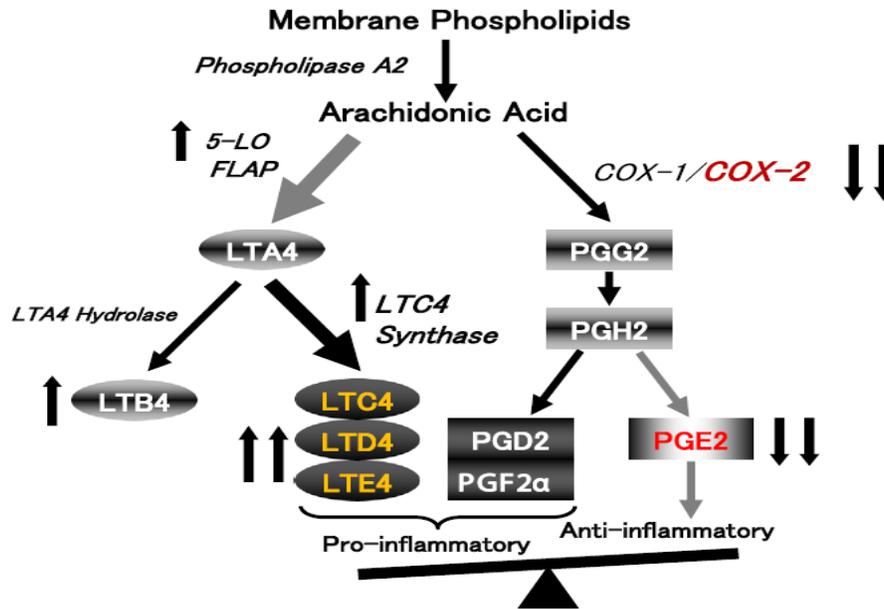


Fig. 2. Imbalance of arachidonic acid metabolites in patients with AERD (hypothesis). The COX-2 level decreases in patients with AERD and the production of endogenous PGE2 also decreases. With the addition of a COX-1 inhibitor, the amount of PGE2 further decreases, the suppression of 5-lipoxygenase (5-LO) activity disappears, and CysLT is overproduced.

In AERD the upper airway disease commonly predates the development of asthma and aspirin sensitivity. It first develops between ages 20-40 years, more commonly in females, and is associated with an increased rate of polyp recurrence and more severe asthma. Identification of this phenotype may lead to the selection of specific therapies such as aspirin desensitisation.

Frequency of aspirin sensitivity

General population	0.6-2.5%
Asthmatics	4.3 – 11%
Severe asthmatics	14%
Asthmatics with challenge	21%
Asthmatics with CRSwNP	30%

(Rajan et al., 2015)

There are a number of systemic diseases that predispose to CRS as outlined in the classification section. These include the inherited disorder cystic fibrosis, ciliary diseases such as primary ciliary dyskinesia, Kartageners syndrome, immunodeficiencies which predispose to recurrent sinus infections. Also CRS can be part of the united airways disease spectrum and associated with asthma, COPD, and bronchiectasis.

AFRS is a particular entity due to IgE-mediated reactivity to fungal antigens resulting in unilateral or bilateral noninvasive sinuses disease often requiring a surgical approach.

CRSwNP in children

A detailed discussion of paediatric chronic rhinosinusitis (PCRS) with nasal polyposis is beyond the scope of this paper. However, a brief description of the epidemiology, clinical presentation, pathophysiology and treatment of CRS in children is provided.

Epidemiology

Rhinosinusitis is prevalent in children and is poorly understood. Of the three to eight annual viral upper respiratory tract infections experienced by children, up to 10% of these will progress to acute bacterial rhinosinusitis (Brietzke et al., 2014; Wald et al., 2013; Hamilos, 2015; Leiser & Derkey, 2005; Aitken & Taylor, 1998). The overall prevalence of PCRS is up to 8% and tends to reduce around the ages of 7-9 years (Leo & Incorvaia, 2010). Whilst PCRS with nasal polyposis is a distinct patient subgroup with a unique pathophysiology, the exact prevalence of PCRS with nasal polyposis is not known (Brietzke et al., 2014).

CRS has a more complex pathophysiology compared to acute rhinosinusitis and PCRS has a different pathophysiology to adult CRS (Sidell, Shapiro & Bhattacharyya, 2013; Benson & Marano, 1993). Contributing factors in PCRS include familial risk, age, environmental exposures (cigarette smoking, etc), atopy, asthma and adenoiditis (Neff & Adil, 2015; Belcher & Virgin, 2019; Orb et al., 2016; Anfusio et al., 2015). Further, the microbiome in PCRS differs to that of adult CRS (Stapleton, Shaffer, Morris Fitch & Methe, 2021). Paediatric CRS can significantly impact quality of life, concentration and academic performance (Cunningham, Chiu, Landgraf & Gliklich, 2000).

Symptoms

To formally diagnose PCRS, a child must have two or more symptoms of nasal congestion, rhinorrhoea, facial pressure/pain or cough plus endoscopic signs of sinonasal disease (such as mucosal oedema or polyps) or relevant findings on a CT scan over a 90 day continuous time frame (Brietzke et al., 2014).

Unlike adults, **cough is one of the most significant symptoms in PCRS and rhinorrhoea is one of the strongest predictors of PCRS** (Leo & Incorvaia, 2010; Sami & Scadding, 2014). The combination of rhinorrhoea plus halitosis, cough, facial pain and nasal obstruction results in a near 100% probability of PCRS (Leo & Incorvaia, 2010).

Pathophysiology

The paranasal sinuses in children continue to develop until early adulthood and reach maturity at different rates (Keith, 1921). Pathologic processes that occur during these developmental stages can impact paranasal sinus development (Lawson, Patel & Lin, 2008). Whilst paranasal sinus development begins in the second to third month of gestation, only the maxillary and ethmoid sinuses are present on imaging at birth (Lawson, Patel & Lin, 2008; Badr, Gaffin & Phipatanakul, 2016; Pohunek, 2004). The maxillary sinuses rapidly pneumatise starting at the age of 12 months (Vaid & Vaid, 2015). The sphenoid sinuses are not really appreciable before the age of 3 years and the frontal sinuses only start to significantly pneumatise by the age of 4-7 years (Pohunek, 2004; Vaid & Vaid, 2015). Therefore, clinically, frontal sinusitis is unlikely prior to the age of 4 years and the sphenoid sinus does not become clinically relevant until the age of 10 years (Vaid & Vaid, 2015).

The sinonasal mucosa differs between adults and children (Coffinet et al., 2009; Chan et al., 2004). The mucosa in children with CRS is thinner, more lymphocytic and has less eosinophils and submucosal mucous glands than adults with CRS (Chan et al., 2004; Berger et al., 2011). Adenoiditis is also a contributing feature of PCRS (Neff & Adil, 2015; Belcher & Virgin, 2019). However, the adenoids start to involute by the age of 12 years and therefore, are less likely to be a contributing feature in CRS in older children (Fujioka, Young & Girdany, 1979). Similarly, allergic rhinitis is less common in younger children (Brietzke et al., 2014).

Overall, due to these differences, CRS in children under 12 years often differs to that in children over 12 years (Brietzke et al., 2014; Badr et al., 2016).

Investigations

Children who do not respond to initial medical therapy or who present with complications of CRS should be referred for further investigations and examination. These investigations may include nasendoscopy (in children who will tolerate it), pathology, imaging, olfactory testing and measurements of nasal airflow and patency.

Magnetic resonance imaging (MRI) scans may be indicated as an initial radiologic investigation (avoiding radiation) or in complicated sinus disease which has extended beyond the limits of the paranasal sinuses. However, MRI scans do not provide the detailed sinonasal bony anatomy and anatomic variants required prior to any sinus surgery. CT scans provide a high specificity and sensitivity for PCRS and are essential to assess sinonasal anatomy, extent of sinus development as well as the extent and severity of disease (Brietzke et al., 2014; Bhattacharyya, Jones, Hill, & Shapiro, 2004). Low radiation CT scans are available which expose children to doses as low as 0.1-0.2mSv. (Al Abdulwani, ZilinSkienes, Colley, & Ahmed, 2016). Some in-office scanners provide CT scans with even lower doses (0.04-0.18mSv) of radiation (Xoran). These doses are comparatively low when compared to the annual radiation exposure due to background radiation of approximately 3.1mSv (US Nuclear Reg Comm, 2017). Whilst CT scans are a recommended aid to diagnosis of PCRS, the radiation risks must be considered on an individual basis.

Lateral airways x-rays to assess adenoid size are not recommended as adenoid size does not correlate with the adenoids functioning as a bacterial reservoir (Shin et al., 2008).

Pathology investigations may include a full blood count, vitamin D and IgE levels, biopsies, allergy testing and studies to exclude immunodeficiencies.

Measures of nasal airflow and patency are described in the investigations section for adult CRS with nasal polyposis. Measures of peak nasal inspiratory flow, rhinomanometry and acoustic rhinometry are all possible in children with normative data available (Prescott & Prescott, 1995; Papachristou et al., 2008; Da Cunha Ibiapina et al., 2011; van Spronsen, Ebben & Fokkens, 2012; Laine-Alava et al., 2012; Peksis et al., 2018).

Diseases such as atopy, cystic fibrosis, primary ciliary dyskinesia, allergic fungal sinusitis and immunodeficiencies should always be considered in children with CRS, especially in those with nasal polyposis. It is also important to assess the ears in children with CRS as there is a high concurrence of chronic otitis media with effusion and PCRS (Brook, 2017).

Treatment

Medical therapy is the mainstay of treatment for PCRS with surgery reserved for those resistant to medical therapy or for complications such as periorbital abscesses. Yet, what constitutes optimal medical therapy for PCRS is yet to be determined. Immunotherapy should be considered in children with persistent allergic rhinitis. Saline irrigations or sprays are safe and effective in children as is the long-term use of second-generation intranasal corticosteroid sprays, such as mometasone or fluticasone (Schenkel et al., 2000; Wei et al., 2011; Pham et al., 2014).

The bacteriology of CRS is controversial, however, antibiotics may also be indicated for acute exacerbations of PCRS or for complications of PCRS (Brietzke et al., 2014). Antibiotics alone are rarely

beneficial in the treatment of PCRS and most recommendations are based on data from acute paediatric sinusitis studies (Brook, 2017; Chandy, Ference & Lee, 2019; Garbutt et al., 2001). The risk of development of antimicrobial resistant bacteria increases in children who have had recent treatment with antibiotics and in those who attend day care (Brook, 1984). When indicated, antimicrobial therapy should include antibiotics effective against anaerobic and beta-lactamase producing bacteria (Brook, 2017). Amoxicillin-clavulanate, a cephalosporin or clindamycin (for anaerobes) should be considered as first-line oral antibiotics when indicated in immunocompetent children (Brook, 2017; Chandy et al., 2019; Chow et al., 2012). There is no consensus on the duration of antibiotic therapy, however, 20 days has been shown to be superior to ten days (Brietzke et al., 2014). Parenteral therapy is reserved for children with significant complications or comorbidities. There is limited evidence or consensus supporting the routine use of antibiotic nasal irrigations in children and they are not recommended (Chandy et al., 2019). Post-operative use of antibiotic irrigation may be of benefit in specific paediatric populations (such as the immunocompromised).

Systemic corticosteroids are reserved for severe disease or for complications of PCRS.

The use of other therapies such as antihistamines, leukotriene receptor antagonists or imidazolines for PCRS is not routinely recommended unless warranted for concomitant disease such as allergic rhinitis or asthma. The use of imidazolines in children can cause toxicity and overdose in rare instances with doses of more than 2.5mL or 0.4mg/kg. (van Velzen et al., 2007; Eddy & Howell, 2003). Whilst children with gastroesophageal reflux disease do have an increased risk of sinusitis, empiric treatment of undiagnosed gastroesophageal reflux disease or extra-oesophageal reflux disease in PCRS is not recommended (Brietzke et al., 2014; El-Searg, Gilger, Kuebeler & Rabeneck, 2001).

When indicated, paediatric endoscopic sinonasal surgery (ESS) is safe, improves quality of life and should include adenoidectomy in children with CRS, particularly those aged under six years (Fokkens et al., 2020; Bettadahalli & Chakravarti, 2017; Brietzke & Brigger, 2008; Vlastarakos, Fetta, Segas, Maragoudakis, & Nikolopoulos, 2013; Bothwell, Piccirillo, Lusk, & Ridenour, 2002; Lusk, Bothwell, & Piccirillo, 2006; Makary & Ramandan, 2013).

Endoscopic sinonasal surgery does not impair facial growth in children (Bothwell et al., 2002; Senior et al., 2000).

Summary

CRS in children differs to that of adults and can differ throughout the stages of childhood. Much is still not known about the pathophysiology and management of PCRS. Classic T2 diffuse CRS with polyp formation is uncommon in children.

SECTION 2 - CLINICAL DIAGNOSIS

- **A full clinical history will accurately diagnose CRS in 88% of patients with CRSwNP.**
- **Nasal obstruction and loss of smell have high specificity for diagnosing CRS.**
- **Diagnosis is based on symptoms, endoscopic examination and imaging.**
- **Atopic disease should be identified and managed in patients with CRSwNP.**
- **Scoring systems aim to measure disease control and quality of life measures.**
- **Disease control is an important concept for assessing a patient before and after treatment.**

Clinical History

The diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP) is based on symptoms and endoscopic or CT findings (Fokkens et al., 2020). The correlation between symptoms, examination findings and imaging results in CRS has a high sensitivity but low specificity for diagnosing CRS unless endoscopy is included (Amine, Lininger, Fargo & Welch, 2013; Bhattacharyya & Lee, 2010). Based on symptoms alone, the sensitivity, specificity, positive predictive value and negative predictive value are 88.7, 12.3, 39.9 and 62.5 respectively for diagnosing CRS (Bhattacharyya & Lee, 2010). However, **taking a full history has been shown to accurately diagnose CRS in 88% of patients with CRS with nasal polyposis** (Hughes & Jones, 1998).

A patient's clinical history should include documentation of symptoms such as: nasal obstruction (unilateral/bilateral, fluctuating/alternating or constant, circadian rhythm and whether it changes with position), rhinorrhoea (watery, blood-stained or mucopurulent, unilateral or bilateral) and hyposmia/anosmia. A history of head trauma, significant or repeated infections or underlying neurological conditions is vital if a patient has hyposmia or anosmia as is a detailed list of current medications. A history of smoking, radiation therapy or chemotherapy and intranasal cocaine use should also be taken. In any patient with smell disturbance, an occupational history of exposures to fuels, toxins, solvents, formaldehyde, pesticides or metal compounds such as cadmium, chromium and nickel is recommended (Werner & Nies, 2018; Shrestha et al., 2020; Genter & Doty, 2019).

Patients should also be asked if they have any sensitivity to non-steroidal anti-inflammatory drugs or alcohol and also about any comorbidities such as asthma (childhood or adult-onset) and if they have had any previous sinonasal surgery.

Patients with a higher number of symptoms (four or more) are more likely to have positive findings of CRS on a CT scan (Amine et al., 2013). Nasal obstruction is very sensitive for CRS and hyposmia/anosmia has a very high specificity for diagnosing CRS. Symptoms of headache, facial pain and postnasal drip (PND) correlate poorly with objective findings in CRS (Rosbe & Jones, 1998; Hseuh et al., 2013).

Most patients with CRSwNP do not report headaches except during an acute exacerbation or due to barotrauma (Kamani & Jones, 2012). However, rhinogenic and neurogenic headaches share many clinical similarities. Many neurogenic headaches cause pain in the region of the paranasal sinuses and are associated with rhinorrhoea, nasal obstruction or the sensation of nasal congestion (Kaymakci, Cikriklar & Pay, 2013).

Many rhinogenic headaches are actually neurogenic when appropriately investigated using criteria established by the International Classification of Headache Disorders (Lipton et al., 2001; Cady and Schreiber, 2004; Eross, Dodick, & Eross, 2007; International Headache Society)

CRSwNP patients will have higher nasal domain and lower sleep and aural/facial domain scores on the sinonasal outcome test, known as the SNOT-22 test, than those with neurogenic headaches (Sharbel et al., 2021). In particular, an aural/facial score ≥ 4 , a Lund Kennedy endoscopic score of ≤ 4 and a Lund Mackay score of ≤ 2 are strong predictors of primary headache rather than rhinogenic headache (Sharbel et al., 2021).

Migraine is the most common cause of non-rhinogenic headache (Eross et al., 2007). The ID-Migraine questionnaire, a self-administered screener for migraine in primary care (Lipton et al., 2003), comprises three questions:

- In the last three months, how disabling are your headaches? Do they interfere with your ability to function? (Are you missing work; school; family activities?)
- Are your headaches ever associated with nausea?
- Are your headaches ever associated with sensitivity to light?

The questionnaire has an 81-92% sensitivity, a 60-75% specificity and a 93% positive predictive value for diagnosing migraine (de Mattos et al., 2017; Lipton et al., 2003). If a patient's symptoms do not appear to correlate with the examination findings, neurogenic or primary headache should be considered.

Diagnostic Criteria for Rhinogenic Headache

Criteria	Signs and symptoms
A	Frontal headache accompanied by pain in one or more regions of the face, ears or teeth and fulfilling criteria C and D
B	Clinical, nasal endoscopy, CT and/or MRI and/or laboratory evidence of acute or acute-on-chronic rhinosinusitis
C	Headache and facial pain develop simultaneously with onset of acute exacerbation of CRS
D	Headache and/or facial pain resolve within seven days after remission or successful treatment for acute or acute-on-chronic rhinosinusitis

(Kamani & Jones, 2012)

Examination

A complete head and neck examination should be performed in any patient with sinonasal symptoms. Specific rhinologic examination procedures are discussed below.

Observation

Assess for the following:

- Mouth breathing.
- Collapse of the external nasal valve (observe the patient's nasal breathing and then ask them to sniff).
- Collapse of the internal nasal valve (as above).

A Cottle manoeuvre is a common component of the nasal examination and involves widening the nasal valve by tensioning the skin lateral to the nasolabial fold whilst the patient inspires via the nose. If the patient reports improved nasal airflow, this is considered a positive test. However, Cottle's manoeuvre is not recommended as it is not validated, nor is it a useful assessment tool to assess nasal valve function (Bonaparte & Campbell, 2018).

Anterior rhinoscopy

Anterior rhinoscopy assesses the anterior nasal airway, in particular, the caudal septum, the internal nasal valves and the size of the inferior turbinate heads. Occasionally, the middle turbinate may also be visualised during anterior rhinoscopy. The size and appearance of the inferior turbinates can be very helpful. Oedematous and pale turbinates or turbinates with a bluish discolouration can be indicative of allergic rhinitis. Large nasal polyps may also be visualised using anterior rhinoscopy.

Anterior rhinoscopy alone has been shown to have an accuracy of 74% in diagnosing rhinosinusitis and up to 77% when combined with the clinical history (Bhattacharyya & Lee, 2010; Hughes & Jones, 1998). Anterior rhinoscopy is also best combined with endoscopy to improve accuracy (Bhattacharyya & Lee, 2010; Hughes & Jones, 1998). Anterior rhinoscopy is performed using the Killian, Cottle or Thudichum nasal speculum and a head light.

Endoscopy

Endoscopy permits visualisation of anatomy not possible with anterior rhinoscopy. Endoscopy enables visualisation of the entire nasal cavity, inferior, middle and superior meati and postnasal space. Endoscopy can be used to assess response to treatment, for surveillance, for biopsies or directed cultures and for post-operative debridement. A three-pass technique is recommended for full evaluation which involves passing the endoscope along the floor of the nasal cavity to assess the inferior meatus, posterior septum and post-nasal space/nasopharynx, above the inferior turbinate to assess the middle meatus and then medial to the middle turbinate to assess the sphenoid-ethmoidal recess (Rimmer et al., 2019). Flexible nasendoscopy can also be used to assess the laryngopharynx if required.

An endoscopic scoring system may be used as an objective measure of disease burden and to describe endoscopic findings (Psaltis et al., 2014). The Lund-Kennedy endoscopic scoring system is an objective measure of disease burden based on the degree of scarring, crusting, oedema, polyposis and discharge noted during an endoscopic exam (Lund & Kennedy, 1995). It was designed for patients who had undergone endoscopic sinus surgery. A Modified Lund-Kennedy (MLK) endoscopic scoring system has been developed (which does not include scores for crusting or adhesions) for patients irrespective of their surgical status (Psaltis et al., 2014). The MLK system has been shown to correlate with symptom-based measurements such as the sinonasal outcome test or SNOT-22 score (see below).

The Lund-Mackay score is a validated radiologic scoring system based on CT scans and has high inter-observer and intra-observer agreement (Oluwole et al., 1996). It involves scoring mucosal inflammation in the sinuses and osteomeatal complexes bilaterally from 0-2.

The addition of endoscopic examination to symptom criteria improves the accuracy of diagnosing CRS (Bhattacharyya & Lee, 2010). Endoscopic examination has a sensitivity of 36%-92% and specificity of up to 95% (Amine et al., 2013; Bhattacharyya & Lee, 2010; Hughes & Jones, 1998). Endoscopy alone cannot exclude CRS however, in patients with positive symptom criteria and endoscopic findings of nasal polyposis or mucopurulence, a diagnosis of CRSwNP can be made confidently (Shargorodsky & Bhattacharyya, 2013).

Assessment tools

Imaging

CT scanning is vital to assess sinonasal pathology (and to confirm the diagnosis of CRS), the air cell configuration in mucociliary drainage pathways and also to delineate the presence of anatomic variants such as Onodi cells. CT scans are generally recommended after failure of an appropriate course of medical therapy (Fokkens et al., 2020; Orlandi et al., 2016). A CT scan is also vital prior to any sinonasal surgery. CT scans correlate well with endoscopic findings but not necessarily with symptoms (Rimmer et al., 2019; Stankiewicz & Chow, 2002; Hopkins et al., 2007; Brooks et al., 2018). CT scans have a 94% sensitivity and up to 59% specificity for diagnosing CRS (Rimmer et al., 2019). It must be noted that inflammatory changes will remain present on imaging for many weeks after an acute viral upper respiratory tract infection (Gwaltney, Phillips, Miller & Riker, 1994; Leopold et al., 1994). For details regarding the radiation exposure from CT scans, refer to the paediatric section.

Magnetic resonance imaging (MRI) scans are recommended when more detailed soft tissue information is required. This may be indicated in complex CRS which has extended beyond the paranasal sinuses, in fungal disease, when visualisation of the olfactory pathway is indicated or where a neoplasm or meningocele/meningoencephalocele is suspected.

Microbiologic assessment

The role of culture-directed antibiotic therapy in CRSwNP is recommended for acute exacerbations only as there is no evidence to support their long-term impact on outcomes of CRSwNP (Rimmer et al., 2019). Nasal lavage and undirected nasal/nasopharyngeal swabs are not recommended as they correlate poorly with endoscopically-directed middle meatal swabs (Rimmer et al., 2019). Endoscopically-directed swabs do, however, demonstrate high concordance with maxillary sinus cultures (Dubin et al., 2005; Joniau et al., 2005, Vogan, Bolger & Keyes, 2000). However, maxillary sinus cultures do not necessarily reflect the microbiota in the remaining sinuses. Next-generation sequencing techniques have been shown to identify previously unidentifiable micro-organisms and to have stronger concordance with resident sinus microbiota than directed sinus cultures (Hauser et al., 2015). Overall, microbial assessment is not routinely recommended in the diagnosis of CRSwNP as the role of microbes in the aetiology of this condition is uncertain (Fokkens et al., 2020; Rimmer et al., 2019).

Biopsy

A biopsy should only be performed after imaging and examination has confirmed the absence of a skull base defect or lesion and when a vascular lesion is not suspected to avoid a cerebrospinal fluid leak or catastrophic haemorrhage. It is best performed under endoscopic guidance by an ENT surgeon. Biopsies are used to confirm the diagnosis of CRSwNP and to endotype the inflammation which is then used to guide therapy and prognosis.

In CRSwNP, biopsies are generally performed intraoperatively. A structured histioathologic report provides information on key markers that impact diagnosis, prognosis and treatment (Snidvongs et al., 2012; Pan et al., 2021). Examples of these markers include tissue eosinophilia, inflammatory cell predominance, subepithelial oedema, squamous metaplasia, Charcot-Leyden crystals and mucin eosinophil aggregates. An eosinophil count >10 per high powered field defines eosinophilic CRS which correlates with worse endoscopic and CT scores, higher corticosteroid requirements and a higher likelihood of recurrence or recalcitrance (Soler et al., 2010; Snidvongs et al., 2012; Tajudeen et al., 2019; Pan et al., 2021). These biopsy results can then guide post-operative therapy and permit more precise management. For example, a patient with a high neutrophil count may benefit more from macrolide treatment than from corticosteroids (Harvey et al., 2009; Wen et al., 2012).

Allergy testing

The role of allergic rhinitis to the pathophysiology of CRSwNP is controversial (Fokkens et al., 2020; Wilson, McMains & Orlandi, 2014). Further, the prevalence of positive allergy testing is higher than the prevalence of allergic rhinitis (Rimmer et al., 2019). Many studies have found a higher prevalence of atopy in patients with CRS, especially in patients with nasal polyposis (Green et al., 2014; Benjamin et al., 2019). Perennial allergy is also a risk factor for CRS, particularly house dust mite sensitisation (Green et al., 2014; Houser & Keen, 2008; Philpott et al., 2018).

Certainly, allergy has a likely association in certain phenotypes or endotypes of CRSwNP such as allergic fungal sinusitis and central compartment atopic disease (Hamizan et al., 2018; Marcus et al., 2019). Finally, patients with CRS and atopic disease have been found to be younger and to have more severe symptoms scores (Ho, Alvarado, Rimmer & Sewell, 2019; Li, Cheng, Wang & Zhou, 2016).

Allergy testing typically involves either in-vitro serum-specific IgE tests or in-vivo skin prick tests (SPT), and should be supervised by a clinical immunology/allergy specialist. The correlation between serological tests for allergen-specific IgE and skin testing is high (Rimmer et al., 2019).

In-vitro tests are not affected by patient medications, are easily available and carry no risk of systemic reactions. However, SPT is more sensitive than serum testing (Fokkens et al., 2020). A positive skin prick or serological test does not necessarily imply a clinically relevant allergy as approximately 60% of sensitisations to aero-allergens are actually clinically relevant (Burbach et al., 2009). Therefore, allergy testing results must be interpreted in clinical context. Nasal or conjunctival allergen provocation tests

are mostly indicated when occupational allergies or local allergic rhinitis are suspected or in patients that prove difficult to diagnose.

It is often difficult to delineate between symptoms of allergic rhinitis and those of CRS, especially in those with perennial sensitisations (Fokkens et al., 2020). Therefore, it would seem reasonable to undertake allergy testing in any patient with CRSwNP and to optimally manage atopic disease if present.

Quality of life instruments

CRSwNP has a significant impact on quality of life (QOL) and the degree of QOL impairment has been shown to drive patients' choice of treatment (DeConde, Mace, Bodner, Hwang, Rudmik, & Soler, 2014; Gliklich & Metson, 1995). Quality of life measures evaluate the degree of impairment due to CRS, can assist in guiding treatment recommendations and are one tool used to monitor response to treatment.

Quality of life measures involve both generic and disease-specific patient-rated outcome measure instruments (PROMs).

Generic PROMs allow comparisons of the QOL of different diseases, however, they are not useful to assess changes in health-related QOL. (Passalacqua et al., 2006; Rudmik et al., 2015). The short form 36 (SF-36) measures eight domains of health and has been used in multiple medical conditions. Normative values are available however the highest quality generic PROM for CRS is the EuroQOL five-dimensional questionnaire (EQ-5D) (Rudmik et al., 2015). The EQ-5D has been validated for the CRS population and provides values capable of generating quality-adjusted life-years and calculating healthy utility (Remenschneider, et al., 2015).

Disease-specific PROMs are more sensitive to small but clinically relevant changes in outcomes. Many PROMs have been developed for adults with CRS, however, in a systematic review, the highest quality validated PROMs for CRS were found to be the 22-item sinonasal outcome test (SNOT-22), the questionnaire of olfactory disorders (QOD) and the sinusitis control test (SCT) (Rudmik et al., 2015).

The SNOT-22 evaluates health-related QOL and symptoms of CRS, the QOD evaluates olfaction (see section on olfaction) and the SCT evaluates disease control. It has a score range of 0-110 (Morley & Sharp, 2006). A minimum clinically important difference (MCID) of 12 has been proposed for patients undergoing medical therapy and 8.9 for patients undergoing surgical treatment (Fokkens et al., 2020; Pham, Sykes & Wei, 2014). The SCT has been found to be a reliable tool to monitor changes in CRS control levels (Brook, 2017; Chandy et al., 2019).

Measures of nasal airflow and patency

Nasal obstruction is a common complaint in patients with CRSwNP. Objective measures of nasal airflow and patency are not necessary to diagnose CRS, however, they may serve as an adjunct to assess the impact of treatment and to assist in treatment decision making. Pre- and post-decongestion measures can distinguish the nature of the obstruction (fixed or dynamic), which aids in the choice of surgical candidates and in surgical procedure selection.

Measures of nasal airflow and patency are also useful in the evaluation of treatment outcomes. Measures include peak nasal inspiratory flow (PNIF), rhinomanometry (RM) and acoustic rhinometry (AR). PNIF and RM have been evaluated as tests for the presence and severity of nasal obstruction (Garbutt et al., 2001).

PNIF is fast, inexpensive, reproducible and simple and normal values are available for adults and children (Ottaviano et al., 2006; Chaves, et al., 2012; Ottaviano, 2012). PNIF does require patient cooperation but can produce reliable, meaningful and repeatable measures (Starling-Schwanz et al., 2005). It is important to evaluate nasal valve collapse during PNIF measures as this can occur during high flow rates (Barnes, 2007).

Rhinomanometry measures nasal airflow and nasal airway resistance and can be used in adults and children with reference values available (Rimmer et al, 2019; Clement, 1984). Rhinomanometry is more

expensive and time consuming compared to PNIF, however, it provides information regarding the nature of the nasal obstruction and can assess the contribution of nasal valve collapse.

Acoustic rhinometry (AR) assesses the geometry of the nasal cavity and can localise the site of obstruction. Results are impacted by septal perforation therefore endoscopic examination is vital prior to AR use. Rhinomanometry and acoustic rhinometry are both impacted by the nasal cycle and correlate poorly with subjective nasal obstruction (Rimmer et al., 2019).

Olfaction

Reduction or absence of olfaction is a common symptom of CRS, affecting up to 80% of patients, yet many patients are not completely aware of their olfactory impairment or its severity (Soler, Kohli, Storck & Schlosser, 2016).

Olfactory tests include subjective assessments and objective or psychosocial tests of identification, threshold and discrimination. The subjective questionnaire of olfactory disorders (QOD) survey is a validated tool that analyses the impact of changes in olfaction on a patient's daily life (Simopoulos et al., 2012). The QOD also differentiates between normosmia and hyposmia (Hummel et al., 2017; Nordin, Bramerson & Bende, 2004; Bramerson et al., 2004; Oleszkiewicz & Hummel, 2019).

However, in the absence of complete anosmia, self-evaluation of olfactory function has been found to correlate poorly with objective measures of olfaction (Landis et al., 2003; Philpott et al., 2006; Haxel et al., 2012; Delank & Stoll, 1998). Therefore, psychosocial measurements of olfaction are useful outcome measures.

Threshold testing tests peripheral olfactory changes, typical in CRS (Hedner et al., 2010). Identification and discrimination tests are more useful for the cognitive aspects of olfaction (Rimmer, et al., 2019; Hedner et al., 2010).

The most commonly available tests of olfaction include the University of Pennsylvania Smell Identification Test (UPSIT) and the Sniffin' Sticks test. The Sniffin' Sticks test covers identification, threshold and discrimination. It is reliable, has been validated in many countries and normative data for children and adults are available. The UPSIT test is a reliable and validated odour identification test (Hummel et al., 2017). Odour identification is subject to cultural differences and this must be considered when testing olfaction.

In patients with identified olfactory dysfunction and no identifiable cause, an MRI scan may be warranted to evaluate the olfactory apparatus including the neuroepithelium, olfactory bulbs and olfactory pathways. An MRI may also exclude undetected nasal cavity or paranasal sinus neoplasms.

Measures of disease control

Disease control is an important concept for assessing a patient before and after treatment trials are begun. Disease control can be determined using a visual analogue scale approach in a table such as that proposed by EPOS 2020 (see next page). Uncontrolled disease may be defined as CRS symptoms persisting after 12 weeks or more of medical treatment. Symptoms are three or more of the following: nasal blockage, mucopurulent discharge on most days of the week, impaired smell and sleep disturbance or fatigue impairing daily activities, and VAS>5. The impact of the sense of nasal obstruction, the appearance on endoscopy and the use of systemic medications remain the most important disease control measures.

Figure 1.2.3. Assessment of current clinical control of CRS.



EPOS 2020: Assessment of current clinical control of CRS (in the last month)

	Controlled (all of the following)	Partly controlled (at least 1 present)	Uncontrolled (3 or more present)
Nasal blockage¹	Not present or not bothersome ²	Present on most days of the week ³	Present on most days of the week ³
Rhinorrhoea / Postnasal drip¹	Little and mucous ²	Mucopurulent on most days of the week ³	Mucopurulent on most days of the week ³
Facial pain / Pressure¹	Not present or not bothersome ²	Present on most days of the week ³	Present on most days of the week ³
Smell¹	Normal or only slightly impaired ²	Impaired ³	Impaired ³
Sleep disturbance or fatigue¹	Not present ²	Present ³	Present ³
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa ⁴	Diseased mucosa ⁴
Rescue treatment (in last 6 months)	Not needed	Need of 1 course of rescue treatment	Symptoms (as above) persist despite rescue treatment(s)

¹ Symptoms of CRS; ² For research VAS ≤ 5; ³ For research VAS > 5; ⁴ Showing nasal polyps, mucopurulent secretions or inflamed mucosa

CRS, chronic rhinosinusitis; VAS, visual analogue scale.

(reproduced with permission from Fokkens et al., 2020)

SECTION 3 - MEDICAL MANAGEMENT

- Nasal irrigation is a widespread firstline treatment with little consensus regarding the method.
- Intranasal corticosteroids are safe and effective for long term use.
- If short courses of oral corticosteroids are prescribed, both patients and practitioners must remain vigilant to avoid side effects.
- There is insufficient evidence for the use of montelukast medication.
- A short course of antibiotics may have a role to play in non-T2 CRSwNP but patient selection is important and side effects need to be managed.
- The effectiveness of allergen immunotherapy in the treatment of CRSwNP remains unclear.

Standard first-line treatments

Despite CRS's significant incidence and quality of life implications, there are few large and well-conducted studies of current first line therapies.

Saline sprays and irrigation

Nasal irrigation has become a widespread first line and post-surgical treatment in patients with CRS. Potential benefits include removing antigens, biofilms and inflammatory mediators, mechanical removal of mucous and crusts, and increased hydration of the sol layer (Fokkens et al., 2020). Several RCTs have been performed, although there is much heterogeneity and few quality studies. Two Cochrane reviews have been undertaken (Harvey, Hannan, Badia & Scadding, 2007; Chong et al., 2016), and both highlighted issues with study design and short term follow up

There remains little consensus regarding the composition of solutions or methods of irrigation (Casale, 2018). Previous studies have demonstrated a wide range of osmolality and pH of commercial and homemade preparations (Lilic et al., 2014). A recent in vitro study of cultured human nasal epithelia cells found that hypertonic and seawater solutions resulted in cell damage although the clinical significance is unknown (Jiao, 2020). The use of room temperature solutions appears satisfactory. Currently, there is insufficient evidence to recommend adding agents such as xylitol, hyaluronate or xyloglucan, although some studies, mostly in postoperative patients have shown a benefit (Fokkens et al., 2020). Antiseptics, mucolytics and baby shampoo cause additional side effects without clear benefit (Fokkens et al., 2020). High volume approaches may be preferable if tolerated.

In summary, nasal irrigation is considered low risk, easy to perform and economical, especially if homemade solutions are used. Care needs to be taken in the preparation of solutions and cleaning of irrigation devices.

Intranasal corticosteroids

Intranasal corticosteroids (INCS) remain the primary initial therapy for CRS management and have been available since the early 1970s. Used for their potent anti-inflammatory effects, various drugs and delivery systems exist, with availability and cost varying by location. This first-line treatment may be trialled for up to three months. Many are available over the counter (pharmacist only), and none are currently subsidised by the Australian government Pharmaceutical Benefits Scheme (PBS). Aqueous nasal sprays are the most common delivery system. Correct administration technique and regular adherence to treatment are required to obtain maximal benefit.

Available topical corticosteroid preparations used for intranasal administration in Australia

Generic name and dose/spray	Common brand name	Approx cost (2021)	Cost of daily dose
Pharmacy only			
Mometasone 50mcg	Nasonex	2 pack \$32.95 (140 x 2 sprays)	\$0.94 (400mcg)
Fluticasone propionate 50mcg	Flixonase Nasal, Hayfever 24h Nasal spray	\$18 (120 sprays)	\$1.20 (400mcg)
Budesonide 32 mcg and 64mcg available	Rhinocort/Rhinocort extra strength	Twin packs (120 sprays x 2) \$27.55/29.99	\$0.49 (256mcg)
Beclomethasone dipropionate 50mcg	Beconase Allergy & Hayfever 12 hour	\$12.49 (200 sprays)	\$0.50 *generally recommended for short term use (<6 months)
Prescription required (Private)			
Fluticasone fluroate 27.5mcg	Avamys	\$39 – 47 (120 sprays)	\$2.60 to 3.13 (400mcg)
Ciclesonide 50mcg	Omnaris	\$37.00 (120 sprays)	\$2.47 (400mcg)
Fluticasone propionate nasal drops 400mcg	Flixonase Nasule	\$62 x 28	\$2.21
Budesonide 0.5mg/2mL or 1mg/2mL nebulas	Pulmicort respules	\$26.95/35.95 x 30	\$0.89 (500mcg)

Currently, there is insufficient evidence to suggest that a specific drug offers superior efficacy. However, in practice, mometasone and the fluticasone preparations are often preferred for long term use given very low levels (<1%) of systemic bioavailability (Fokkens et al., 2020; Salib & Howarth, 2003; Saleh & Scadding, 2020).

The 2020 European position paper on rhinosinusitis and nasal polyps (Fokkens et al., 2020) comprehensively reviews relevant studies, including meta-analyses of different clinically relevant outcomes. Of the 42 studies reviewed, 40 were placebo-controlled, 26 were studies of nasal sprays, and the minority of studies (14/38) mostly included subjects who had not had previous CRS surgery. Intranasal corticosteroids were found to positively impact disease specific QOL in the six studies using the SNOT-22 questionnaire. However, the effect was small, so the clinical relevance remains unclear (Fokkens et al., 2020). Symptoms also improved compared to those receiving placebo preparations (18 studies, SMD -0.63n95%, CI -0.89 to -0.37) with a greater benefit evident in those with nasal polyps (Fokkens et al., 2020). When data of endoscopy scores and polyps were pooled, nasal corticosteroids were effective at decreasing scores over placebo. Endoscopy score: (SMD -0.49, 95%CI -0.73 to -0.25, p<0.01; 6 RCT's, n = 286), Polyp score: (SME -0.87, 95%CI -1.17 to -0.57, p<0.01; 2 RCT's n = 184) (Fokkens et al., 2020).

Compared with the Cochrane review in 2016, the EPOS 2020 paper found a greater focus on disease specific QOL in more recent studies. However, severity was not directly assessed, and specific symptoms were not reported in the meta-analysis. The 2016 Cochrane review found moderate quality evidence for a moderate benefit in nasal blockage and small benefit for rhinorrhoea, and high-quality evidence INCS increased risk of epistaxis (Chong et al., 2016).

A smaller number of studies have considered nasal corticosteroids delivered via alternate methods other than simple spray. The most recognised topical corticosteroid preparation is a corticosteroid irrigation. These solutions are typically made with budesonide, betamethasone and mometasone. Studies in CRS have shown that these solutions provide greater symptom control and better disease suppression compared to simple INCS (Harvey et al, 2018; Grayson & Harvey, 2019).

Lastly, the EPOS 2020 paper analysis used all of the 42 RCTs to consider safety. INCS are well tolerated and safe with no significant adverse effects. As per the 2016 Cochrane review, increased epistaxis was reported in some cohorts, overall RR 3.49, 95% CI 2.42 to 5/05, 16 RCT, n = 2021 (Fokkens et al., 2020; Chong et al., 2016). Nasal septal ulcers appear rare, and HPA suppression measured by serum cortisol, 24 hour urinary cortisol, or clinical adrenal insufficiency was not found. There is no evidence of increased intraocular pressure or cataract, and no increase in the risk of infection.

Oral corticosteroids

There are relatively few studies of the use of oral corticosteroids in patients with CRS, and most of these are considered low quality (Head, 2016). The EPOS 2020 statement, which included a meta-analysis of relevant studies of patients with CRSwNP and a 2016 Cochrane review (CRS), found a short-term improvement in symptom scores and specific symptoms such as sense of smell and nasal blockage. Various dosing regimens have been used, starting with between 25-50mg equivalent of prednisone which is sometimes reduced over the short treatment course (< two weeks). Unfortunately, the duration of effect is limited and is no longer evident at three months on average (Fokkens et al., 2020). Some patients may achieve benefits for longer.

Side effects are significant and include insomnia, mood change, gastrointestinal upset, with rare reports of avascular necrosis and fatal varicella-zoster (Richards, 2008). Data is often extrapolated from studies of their use in the lower airways, where repeated short courses have been associated with osteoporosis (Hox, 2020).

The use of OCS is variable. In a recent US study of Rhinologists, less than a quarter of members prescribed them to patients with CRSwNP before surgery (Scott, 2017). The EPOS group concluded that “one to two courses of systemic corticosteroids per year can be a useful addition in patients with partially or uncontrolled disease”. Leung et al. (2020) attempted to model the “minimum effectiveness to avoid further intervention” based on published data of impacts and adverse events associated with OCS and endoscopic sinus surgery (ESS). They concluded that the use of OCS may be a lower risk strategy. The recent EAACI position statement recommends against OCS use except in those with severe symptomatology (Hox, 2020).

If short courses of OCS are prescribed, both patients and practitioners must remain vigilant to avoid OCS overuse. A minimum of two short (two to three week) courses to a maximum of 500mg/12months are recommended. This advice may change over time.

In summary, **intranasal corticosteroids, especially via nasal irrigation, are safe and effective for long term use in patients with CRS.** Oral corticosteroids should be minimised due to systemic effects.

Other treatment modalities

Montelukast

Montelukast is the only anti-leukotriene available in Australia. This class of drugs block the actions of cysteinyl leukotrienes (CysLT) synthesised by eosinophils and mast cells via the breakdown of arachidonic acid. Their use in CRS is based on studies of allergic rhinitis, asthma and CRSwNP, which

have demonstrated increased CysLT production and upregulation of its receptor. Only montelukast has been studied in a randomised controlled trial (RCT), and overall the quality of evidence is very low. Currently there is insufficient evidence of benefit over placebo, and studies of their use in patients who have failed nasal corticosteroids have not been performed (Fokkens, et al., 2020).

Montelukast is well tolerated and may be of benefit for children with allergic asthma or adults with exercise induced asthma. Montelukast is generally well tolerated. Reported side effects include headaches and less commonly neuropsychiatric events (Glockler-Lauf et al., 2019). The US Food and Drug Administration (FDA) issued a box warning regarding this in 2020. <https://www.fda.gov/news-events/press-announcements/fda-requires-stronger-warning-about-risk-neuropsychiatric-events-associated-asthma-and-allergy>

Antifungals

The presence of fungus in both normal and diseased sinuses is very common, but its relationship to pathogenesis of CRS is unclear and the host immune response appears to be an important factor. A series of studies have looked at topical and systemic antifungals and meta-analysis shows no evidence of benefit (Head et al., 2018; Kennedy et al., 2005). There is evidence against the use of topical antifungals (Sacks et al., 2018).

Antibiotics in CRSwNP

Short course antibiotic treatment:

Short courses (≤ 4 weeks) antibiotics (including amoxicillin clavulanate, quinolones, cephalosporins, doxycycline macrolides) have shown minimal improvement in acute symptom exacerbations eCRSwNP but the evidence is very limited (Van Zele et al., 2010).

Long term antibiotic treatment

Long term (> 4 weeks) antibiotic treatment is confined to the use of macrolides and is discussed below.

Macrolide antibiotics have been used at low doses for their anti-inflammatory properties in both upper (Gibson et al., 2017) and lower airway inflammatory disease. There is very little specific data examining the use of macrolides solely in CRSwNP. There are two double blind placebo controlled studies which included a total of 124 subjects with eCRSwNP and eCRSsNP using roxithromycin 150mg daily (Wallwork et al., 2006) and azithromycin 500mg weekly (Videler, Badia & Harvey, 2011) for 12 weeks. The former showed improvement at 12 weeks especially in the low IgE group while the latter demonstrated a trend to improvement. However, the anti-IL8 effects of macrolides are not suited to T2 eosinophilic inflammation and benefit has been mainly demonstrated in specific non-T2 CRS phenotypes (Oakley, Harvey & Lund, 2017; Oakley, Christensen et al., 2018)

Clarithromycin particularly and less so erythromycin and azithromycin are CYP3A4 inhibitors. Over 50% of prescribed drugs are metabolised via the hepatic CYP3A4 enzyme and inhibition of this enzyme can lead to reduced drug metabolism and increased drug levels with potential drug toxicity e.g. statins, inhaled steroids, amiodarone (Horn, 2015). Therefore when prescribing a macrolide, a drug history to exclude this possibility must be undertaken.

Macrolides prolong the QT interval, potentially increasing the risk of arrhythmia, however there are differences between randomised controlled trial data and observational data which make it difficult to be completely sure about the relevance of this. An appropriate cardiac history and ideally an electrocardiogram (ECG) to exclude QT prolongation should be undertaken.

In addition, there are concerns regarding the development of antibiotic resistance while taking long term antibiotics which was demonstrated in the (AMAZES) asthma trial taking azithromycin 500mg 3 times a week described by Gibson et al., 2017. Also, gastrointestinal side effects such as diarrhoea occur more commonly on macrolide therapy compared to placebo (Gibson et al., 2017).

In summary, macrolides may have a role to play in non-T2 CRSwNP. Patient selection is essential and adverse outcomes need to be considered (Oakley, Harvey & Lund, 2017; Oakley, Christensen et al., 2018).

Aspirin desensitisation and treatment

There is no evidence for aspirin treatment in patients without aspirin sensitivity although the condition is commonly underdiagnosed (Kowalski, 2019).

Various protocols and preparations have been described mostly using aspirin. A recent analysis found insufficient evidence for any benefit of nasal lysine-aspirin, which is less widely available (Fokkens et al., 2020). Traditional aspirin desensitisation protocols up dose patients every two-three hours using protocols which take two-three clinic visits to complete (Kowalski., 2019). Recent studies have reported successful up dosing during a single visit, which would improve the availability and significantly reduce the short-term cost of this treatment (Stevens et al., 2020). Given the nature of the condition most patients develop symptoms affecting the upper and lower respiratory tract during desensitisation, however anaphylaxis is rare. Recent opinion suggests that most protocols can safely be undertaken in an outpatient setting as long as patients have well controlled asthma (forced expiratory volume FEV1 >70%). Symptoms typically occur between 50-100mg of aspirin. These may be reduced by pre-treatment with montelukast (Steven et al., 2020).

Assessing the effectiveness of long-term aspirin therapy in these patients using high quality evidence such as a double blind placebo challenge has been difficult. A recent meta-analysis by Chu et al., 2019 (cited in Stevens et al., 2019) found a reduction in symptoms and improved quality of life but higher adverse event rates. Pooled analysis of three double blind placebo controlled studies published in the EPOS 2020 paper favoured treatment over placebo at six months with improvement in symptom and SNOT-22 scores. However the change in SNOT-22 scores did not reach a clinically important mean difference (Fokkens et al., 2020). Two studies showed a significant reduction in FEV1 compared to placebo (Mortazavi et al., 2017; Esmaeilzadeh et al., 2015). Exact dosing depends on regional aspirin preparations, with most studies using daily doses of approximately 600 – 1200mg. Up to 34% of patients experience side effects, mostly gastrointestinal, and it is important to remember that the desensitisation effect is short lived with a refractory period of around 48 hours (Kowalski, 2019) hence continuing adherence is essential. There is very little data to guide long term management of aspirin treatment.

Allergen Immunotherapy

The relationship between allergy and CRS remains unclear. Most studies of allergen immunotherapy (AIT) are retrospective and there are currently no RCT's. It has been suggested that some subpopulations, such as the 5-10% of individuals with CRS with allergic fungal rhinosinusitis (AFRS), a subset of polypoid CRS characterised by Type 1 hypersensitivity to fungi, may be better candidates, although this diagnosis itself remains somewhat controversial (Fokkens et al., 2020). The assessment of outcomes is potentially confounded by coexistent allergic rhinitis and asthma.

A 2014 systematic review of AIT for CRS found short term evidence of improvement on endoscopic examination, reduced intranasal and oral steroid use and less revision surgery, with some improvement in symptom scores, concluding that there is weak evidence to support the use of AIT as adjunctive treatment in this condition (DeYoung et al., 2014). If both CRS and allergic rhinitis (AR) co-exist, then AIT can be expected to provide benefits for AR-related symptoms. Information regarding practical aspects of allergen immunotherapy for health professionals in Australia and New Zealand can be found on the ASCIA website <https://www.allergy.org.au/hp/papers/ascia-aeroallergen-immunology-guide> (ASCIA, 2019).

SECTION 4 - THE ERA OF BIOLOGIC THERAPY

- **A number of T2 targeted biologics have been trialled in patients with CRSwNP with positive outcomes.**
- **T2 biologics for CRSwNP have an acceptable safety profile.**
- **These treatments are high cost and need to be used in a cost-effective manner.**
- **The challenge is to identify patients who will most likely benefit from them.**

Dupilumab

Dupilumab (Dupixent) is the first biological therapy to be approved for the treatment of adults with inadequately controlled CRSwNP in the European Union and the United States of America. It is a fully human IgG4 monoclonal antibody against the interleukin -4 receptor α (IL-4R α) subunit, which is shared by the Type 1 IL-4 and the T2 IL-4/IL-13 receptor complexes. By binding to and blocking this subunit, dupilumab inhibits IL-4 and IL-13, which are the major drivers of human T2 inflammatory disease such as asthma, atopic dermatitis and CRSwNP.

Dupilumab was shown to benefit patients with CRSwNP in trials of its efficacy in asthma. The potential of subcutaneous dupilumab as add-on therapy to intranasal corticosteroid treatment in adults with CRSwNP was also demonstrated in a multinational, phase II, proof-of-concept study (Bachert et al., 2016).

Two randomised, double-blind, placebo- controlled, multinational, phase III studies of 24 weeks' duration (LIBERTY NP SINUS-24- SINUS-24) and 52 weeks' duration (LIBERTY NP SINUS-52 - SINUS-52) have been published (Bachert et al., 2019).

Each study consisted of a 4-week run-in period followed by a 24-week (SINUS-24) or 52-week (SINUS-52) treatment period and enrolled patients with symptomatic CRSwNP despite prior intranasal corticosteroid therapy who had previously undergone sino-nasal surgery or had received oral corticosteroid treatment in the previous 2 years.

Enrolled patients had to have:

- Combined nasal polyp score (NPS) of 5-8 with a minimum of ≥ 2 in each nostril.
- At least two of the following symptoms: nasal congestion or obstruction (defined as a patient-assessed moderate (score = 2) or severe (score = 3) symptom severity score (scores range: 0 to 3), along with a weekly average symptom severity score of ≥ 1 at randomisation), and either a loss of smell or nasal discharge.

SINUS-24 patients received either placebo or dupilumab 300mg every two weeks for 24 weeks whereas SINUS-52 patients received one of three regimens: placebo q 2 weekly; dupilumab q 2 weekly or dupilumab q 2 weekly for 24 weeks then q 4 weekly for 24 weeks. In addition, all patients sprayed 100 μ g of mometasone furoate in each nostril twice daily. Primary outcome measures were NPS and nasal congestion score. Other measures performed included Lund Mackay score, University of Pennsylvania smell identification test (UPSIT) and SNOT-22.

A treatment effect was seen as early as weeks 4-8 for the co-primary endpoints and weeks 2-4 for the key secondary endpoints in both studies. The beneficial effects of dupilumab on both co-primary endpoints was sustained to week 52 in SINUS-52, least-squares mean (LSM) between-group difference in the LSM change from baseline of -2.40 for the NPS and -0.98 for the nasal congestion score; both $p < 0.0001$ vs placebo (Hoy, 2020).

The most common adverse reactions reported in CRSwNP clinical studies with dupilumab were injection-site reaction and injection-site swelling (incidence $\geq 1/100$ to $< 1/10$) Other commonly observed adverse reactions were conjunctivitis and eosinophilia (<https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent>).

In the pooled analysis, the incidences of the treatment emergent adverse events that occurred most frequently (in $\geq 5\%$ of patients) at 24 weeks were all numerically lower in the dupilumab group than in

the placebo group: (nasopharyngitis (13% vs 15%), headache (7% vs 9%), injection-site erythema (6% vs 8%), epistaxis (6% vs 7%), a worsening of nasal polyps requiring systemic corticosteroid use or nasal polyp surgery (3% vs 12%) and a worsening of asthma (2% vs 7%). Conjunctivitis occurred in seven (1.6%) dupilumab recipients and one (0.4%) placebo recipient. None of the cases were serious, severe or associated with treatment discontinuation (Bachert, et al., 2019).

Dupilumab, like other therapeutic proteins, has immunogenic potential (Sanofi-Aventis, 2019). However, this potential appears to be low.

Dupilumab use was not significantly associated with a higher risk of experiencing systemic hypersensitivity reactions relative to placebo in patients with CRSwNP. Very rare cases of serum sickness/serum sickness-like reactions and anaphylactic reaction have been reported following administration of dupilumab in asthma trials (European Medicines Agency report, 2019).

In the pooled analysis, treatment-emergent anti-drug antibodies (ADAs) most of which were low titre (< 1000) were reported in 4.3% of dupilumab recipients (n = 438) and 2.1% of placebo recipients (n = 281) over 24 weeks, persisting in 1.6% and 0.7% of patients (European Medicines Agency report, 2019).

The presence of ADAs does not appear to impact the exposure, efficacy or safety of dupilumab (Sanofi-Aventis Groupe, 2020).

Omalizumab

Omalizumab is a humanised anti-IgE monoclonal antibody that binds to serum free IgE reducing blood levels and blocking IgE binding to receptors on cells leading to down-regulation of the high affinity receptors on basophils and dendritic cells. It also inhibits mast cell degranulation after challenge, reduces early and late phase responses to allergens. It was the first monoclonal antibody approved for treatment of severe asthma and has shown beneficial effects in patients with nasal polyposis and concomitant asthma, irrespective of their atopic status. It has generally been well tolerated although rare cases of anaphylaxis have been reported. It is dosed by body mass and total IgE level.

CRSwNP appears to occur with similar frequency in atopic and nonatopic individuals so the role of IgE in CRSwNP is not completely clear. IgE is often strongly elevated in the sinus mucosa and nasal polyps compared with controls and IgE concentrations in CRSwNP tissue are strongly correlated with eosinophil markers (Bachert et al., 2021).

A number of small clinical trials suggesting efficacy of omalizumab in CRS were performed before a proof-of-concept study was conducted. Gevaert et al. (2013) have published results of a randomised, double-blind, placebo-controlled study of allergic and nonallergic patients with nasal polyps.

Blood eosinophil counts were clearly elevated, with counts above 300/mL, whereas total serum IgE only ranged from 50 to 150 kU/L. Twenty-four subjects received 4 to 8 subcutaneous doses of omalizumab and the primary end point was the reduction in total nasal endoscopic polyp scores after 16 weeks. This was achieved in the treated group compared to placebo (P < .001). There was improvement in upper and lower airway symptoms, including the sense of smell, sinus opacification on CT scan evaluations, and an improvement in Asthma Quality of Life Questionnaire (AQLQ) scores. The drug was well tolerated.

Following this study, two replicate, randomised, phase 3 trials were undertaken by Gevaert et al. (2020). Enrolled patients included 18-75 year olds weighing between 30-150 Kg, with IgE levels between 30-1500IU/mL. They had persistent bilateral NP, nasal congestions scores ≥ 2 , NPS ≥ 5 , SNOT 22 > 20 and impaired health-related QOL. Dosing was for 24 weeks with omalizumab or placebo subcutaneous injections, either 2-4 weekly depending on dose required for weight and IgE level.

In both studies, the primary end point was met in the omalizumab group with a reduction of about 0.9 to 1.1 points at week 24. In the second of the two studies, the placebo group also showed some, although not significant, change from baseline. NPS improvements of 1 or more and 2 or more points were observed in 56% and 31% of the patients, respectively. Nasal symptoms including loss of smell, postnasal drip, and runny nose were significantly reduced, with nasal congestion as a coprimary end

point. The SNOT-22 score was significantly increased in both studies. Asthma-related QOL was also significantly improved in patients with concomitant asthma based on the percentage of patients achieving greater than or equal to 0.5 improvement in the Asthma Quality of Life Questionnaire score.

Treatment emergent adverse events (AEs) were fewer in active vs placebo groups; no omalizumab-treated subjects withdrew because of these. Most common AEs (>3% subjects) were mild to moderate in severity and included injection site reaction, headaches, nasopharyngitis, abdominal pain, dizziness, and arthralgia. There were no reports of eosinophilic granulomatous polyangiitis or anaphylaxis.

Omalizumab for treatment of CRSwNP has been registered in Australia by the Therapeutic Goods Authority (TGA).

Mepolizumab

Nasal polyps affect up to 4% of the total population (Newton & Ah-See, 2008). In European patients 80% to 90% of nasal polyps are characterised by prominent eosinophilia (Fokkens, Lund & Mullol, 2007; Stoop et al., 1993).

It is assumed that through release of toxic products, eosinophils lead to tissue damage and growth of polyps (Bachert et al., 2000). The accumulation and activation of eosinophils is favoured by low concentrations of TGF- β 1 and by overproduction of IL-5 and eotaxin in NP tissue. High amounts of IL-5 were detected in patients with NP, both at the mRNA and protein levels (Hamilos et al., 1998; Simon et al., 1997). IL-5 would appear to be an ideal target for novel therapies in the management of this complex condition.

Mepolizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody directed against interleukin-5 (IL-5). Upon administration, mepolizumab selectively binds to IL-5, preventing it from associating with interleukin-5 receptor subunit alpha (IL-5RA) on the surface of eosinophils and their progenitors.

Mepolizumab (Nucala) is approved for use in patients with severe eosinophilic asthma following demonstrable benefit in phase II (Dream) and phase III (Mensa) studies (Ortega et al., 2014).

Analyses of the severe asthma studies indicated that mepolizumab may be of benefit in treatment of CRSwNP (Laidlaw et al., 2019; GlaxoSmithKline, 2014; GlaxoSmithKline, 2016). The efficacy of IV mepolizumab versus placebo in the treatment of CRSwNP has been demonstrated in two phase II clinical trials (Gevaert et al., 2011; Bachert et al., 2017)

Gevaert et al. (2011) reported on a phase II DBRCT enrolling thirty patients with severe nasal polyposis (grade 3 or 4 or recurrent after surgery) refractory to corticosteroid therapy. They were randomised to receive either two single intravenous injections (28 days apart) of 750 mg of mepolizumab (n = 520) or placebo (n = 510). Change from baseline in NP score was assessed monthly until one month after the last dose (week 8). Computed tomographic scans were also performed at week 8. Twelve of 20 patients receiving mepolizumab had a significantly improved NP score and computed tomographic scan score, compared with one out of ten patients receiving placebo at week 8 versus baseline. The authors concluded that mepolizumab achieved a statistically significant reduction in NP size for at least one month after dosing in 12 of 20 patients.

A second randomised, double-blind, placebo-controlled trial (Bachert et al., 2017) used mepolizumab 750 mg IV every 4 weeks versus placebo. Patients aged 18 to 70 years with recurrent nasal polyposis requiring surgery were recruited.

Patients received mepolizumab or placebo every four weeks for a total of six doses in addition to daily topical corticosteroid treatment. The primary end point was the number of patients no longer requiring surgery at Week 25 based on a composite end point of endoscopic nasal polyp score and nasal polyposis severity visual analog scale (VAS) score. Secondary end points included change in nasal polyposis severity VAS score, endoscopic nasal polyp score, improvement in individual VAS symptoms (rhinorrhoea, mucus in throat, nasal blockage, and sense of smell), patient-reported outcomes, and safety.

One hundred and five patients received mepolizumab (n = 54) or placebo (n = 51). A significantly greater proportion of patients in the mepolizumab group compared with the placebo group no longer required surgery at Week 25 (16 [30%] vs 5 [10%], respectively; P = .006). There was a significant improvement in nasal polyposis severity VAS score, endoscopic nasal polyp score, all individual VAS symptom scores, and sino-nasal outcome test patient-reported outcome score in the mepolizumab compared with placebo groups. Mepolizumab's safety profile was comparable with that of placebo. The authors concluded that in patients with recurrent nasal polyposis receiving topical corticosteroids who required surgery, mepolizumab treatment led to a greater reduction in the need for surgery and a greater improvement in symptoms than placebo.

A phase III clinical trial (SYNAPSE, NCT03085797) for the treatment of CRSwNP has been completed (Effect of Mepolizumab in Severe Bilateral Nasal Polyps)
<https://clinicaltrials.gov/ct2/show/NCT03085797>

Participants received a total of thirteen doses of 100mg of mepolizumab via subcutaneous injection every four weeks for 52 weeks in addition to standard care that included daily nasal spray of 400µg mometasone furoate. The results from SYNAPSE, reported as an abstract, met both co-primary endpoints, with mepolizumab, in addition to standard of care, demonstrating statistically significant improvements in both the size of nasal polyps at week 52 and in nasal obstruction during weeks 49-52, compared to placebo added to standard of care (Han et al., 2021).

Benralizumab

Benralizumab is an antibody against the IL-5 receptor and is approved for treatment of severe eosinophilic asthma. Its efficacy in asthma with improvement in asthma symptoms and lung function, as well as reduction in annual asthma exacerbations, was demonstrated in two double blind placebo-controlled phase III studies, the SIROCCO (Bleeker et al., 2016) and CALIMA (FitzGerald et al., 2016) studies.

A subset of patients in the asthma trials had NP and demonstrated as good a response as those without.

No proof of concept or phase II studies have been published for the use of benralizumab in CRSwNP, however, there are currently two phase III studies ongoing in severe CRSwNP, the OSTRO and the ORCHID studies (Bachert et al., 2020).

OSTRO is a randomised, double-blinded, multi-centre, parallel-group, 56-week phase III trial involving 413 patients in Europe and North America, to evaluate the efficacy and safety of benralizumab compared to placebo in patients with nasal polyposis. Benralizumab was evaluated in patients, regardless of blood eosinophil count with or without asthma, who were symptomatic despite standard of care therapy, including current use of INCS and prior surgery and/or use of systemic corticosteroids. Patients were randomised to receive either benralizumab 30mg or placebo subcutaneously every four weeks for the first three doses and then every eight weeks.

The primary outcome measures include the effect of benralizumab on nasal polyp burden, assessed by change from baseline in endoscopic total NPS, at week 40 compared to placebo; the effect of benralizumab on patient-reported nasal blockage, assessed by change from baseline in mean NBS, at week 40 compared to placebo. Publication of results is expected in the near future.

Emerging Treatments

A number of compounds are under investigation for the treatment of CRSwNP based on what is known of the pathophysiology of the condition.

Tezepelumab

Tezepelumab is a human anti-TSLP antibody targeting thymic stromal lymphopoietin(TSLP) which is an innate cytokine of importance in triggering T2 inflammatory diseases including asthma and CRSwNP. TSLP enhances T2 cytokine production by mast cells and together with other cytokines, IL-33 and IL-25, activates ILC2 cells. There is increased expression and activity of TSLP in nasal polyp tissue in

CRSwNP patients compared to controls and, in particular, in those with AERD. There is evidence that it may drive PGD2 production from mast cells in this condition (Nagarker et al., 2013).

In a phase II study in asthma Tezepelumab was shown to reduce exacerbations and cause some improvement in lung function (Buchheit et al., 2016).

IL-33 Blockade

AMG 282, which is an anti-ST2 monoclonal antibody, inhibiting the binding of IL-33 to the ST2 receptor. IL-33 is expressed by basal epithelial and endothelial cells, functioning as an alarmin to alert the immune system, particularly innate immune cells (ILC-2) and Th2 cells, to damage or stress. A phase I study assessing the safety and tolerability of AMG 282 in healthy volunteers and in subjects with CRSwNP has been recently completed (Agarwal et al., 2020).

Another monoclonal antibody targeting IL-33, etokimab, will be evaluated for use in adults with chronic rhinosinusitis with nasal polyposis in an upcoming phase II double-blind, placebo-controlled trial (Agarwal et al., 2020).

Anti-Siglec-8 Abs

Sialic acid-binding immunoglobulin-like lectin (Siglec)-8 is a receptor found on mature eosinophils and when activated induces apoptotic cell death in eosinophils. 93 Anti-Siglec-8 antibodies are currently under preclinical investigations (Fajt & Wenzel, 2014).

Chapter 6 of the EPOS 2020 document summarises existing data on a range of lesser known and experimental approaches (Fokkens et al., 2020).

Concluding comments

For CRSwNP management, the advent of effective, targeted biologic therapies with very acceptable safety profiles is a welcome addition to management options and will likely be steroid-sparing and reduce the number of surgical procedures for this group of patients. A number of challenges exist for the treating doctor. The high cost of these medications requires responsible and considered use in the appropriate patients. As there will be a number of biologics available, how to choose between the Mabs and match the optimal treatment to a particular patient is still unknown. When to switch from one biologic to another if there is sub-optimal response is another clinical question for which there is no guidance as yet.

SECTION 5 – SURGICAL MANAGEMENT

- **Endoscopic sinus surgery (ESS) plays a significant role in the management of CRSwNP.**
- **Surgery is safe, reduces symptom burden and improves quality of life.**
- **Outcomes are assessed using scoring systems.**
- **New advances in surgical practice show promise.**

Aims

Endoscopic sinus surgery to reshape the sinus cavity into a single neo-sinus cavity should be performed by a qualified Ear Nose and Throat (ENT) specialist. It plays a significant role in the management of CRSwNP and has demonstrated efficacy and safety (Chester, Antisdell & Sindwani, 2009; Soler et al., 2018).

The aims of surgery are to:

- Reduce symptom burden and improve quality of life.
- Reduce mucosal disease burden.
- Provide an anatomic modification to facilitate effective access for topical therapies which provide higher local drug concentration and reduced systemic exposure (Harvey et al., 2008; Snidvongs et al., 2013; Zhao et al., 2016; Grayson & Harvey, 2019; Kohanski, Toskala & Kennedy, 2018).
- Prevent complications of untreated/inadequately treated CRSwNP.
- Avoid surgical complications.

Whom to refer?

When considering surgery, the impact of CRSwNP on the patient's quality of life and the potential for improvement should be considered. When a patient with CRSwNP is refractory to medical therapy, has a complication of their disease, or when their CRSwNP is contributing to exacerbations of comorbid conditions such as pulmonary disease, they should be referred for consideration of surgery. To achieve a clinically significant improvement in a patient's quality of life, it is recommended that endoscopic sinus surgery be offered to a patient who meets the following criteria (Rudmik et al., 2016; Beswick et al., 2018):

- Evidence of sinus disease on a CT scan.
- Failure of a trial of a minimum of 8 weeks of topical intranasal corticosteroid treatment and a short course of systemic corticosteroid treatment.
- Post-treatment SNOT-22 score of ≥ 20 .

These recommendations are not universal or mandatory. It has been noted that patients with the worst pre-operative CT scan findings and higher SNOT-22 scores achieve the greatest improvement from surgery (Hopkins et al., 2006; Brooks et al., 2018; Le et al., 2018). Further, patients who undergo early surgery, in relation to the onset of their symptoms, have a greater improvement in their symptoms post-operatively. This improvement was better maintained over five years compared to those who underwent surgery beyond 12 months from the onset of their symptoms (Hopkins et al., 2006; Sahlstrand-Johnson et al., 2017; Yip, Hao, Eskander & Lee, 2019). These patients also require less healthcare interventions than those undergoing later surgery (Benninger et al., 2015). Early ESS is also associated with a reduction in the incidence of new asthma diagnoses and less detrimental outcomes (Benninger et al., 2016).

Pre-operative assessments

A CT scan is mandatory prior to any surgery for CRSwNP to confirm the presence of disease, identify unique anatomy and also to identify any particular features that may predispose a patient to complications. As detailed earlier (see Investigations), an MRI scan may be required if there is concern for complications of CRSwNP or for differential diagnoses (e.g. inverting papilloma) where more soft tissue detail is required. The surgeon may liaise with other physicians in order to optimise their patient

pre-operatively, especially with regard to the management of any anticoagulant medications they may be taking. The surgeon may also institute pre-operative oral or topical corticosteroids for to improve the surgical field and reduce bleeding intra-operatively (Pundir et al., 2016; Hwang, Seo, Joo & Kang, 2016; Fokkens et al., 2020). However, prolonged topical corticosteroid use (> 3 months) may increase intra-operative bleeding and pre-operative corticosteroids may impact the accuracy of any intra-operative biopsy results (Tirelli et al., 2019; Akiyama et al., 2019).

There is currently no evidence to support the use of pre-operative antibiotics in CRSwNP (Orlandi et al., 2021).

Surgical procedures

Surgery for CRSwNP has been shown to be effective and involves endoscopic sinus surgery by a qualified ENT specialist. Surgery may also include open procedures and adjunct procedures such as septoplasty and/or inferior turbinate reductions (Blomqvist et al., 2009; Soler et al., 2018). Endoscopic sinus surgery has also been shown to be more cost-effective than ongoing medical management in the management of patients with refractory CRS (Rudmik, Soler et al., 2015; Scangas et al., 2017).

The extent of surgery is a matter of debate, however, more complete surgery with larger ostia has been shown to achieve better outcomes and improved penetration with topical therapies than targeted surgery (DeConde et al., 2015; Grobler et al., 2008; Grayson et al., 2019). Less extensive surgery is appropriate for patients with non-polypoid CRS conditions with minimal disease involving the maxillary sinus or osteomeatal complex only (Orlandi et al., 2021).

Balloon sinuplasty is expensive, has been associated with an increased risk of operative complications and has yet to demonstrate superiority over ESS (Alam et al., 2018; Ference, Graber & Conley, 2015). Therefore, balloon dilatation is recommended only in limited cases of CRSsNP patients with mild disease without complications (Bikhazi et al., 2014; Jenks et al., 2017; Fokkens et al., 2020; Orlandi et al., 2021). These devices are not currently available in Australia.

Complications

Overall complications rates from ESS vary from 0.36% to 6.6%. (Hopkins et al., 2006; Orlandi et al., 2021; Hosemann & Draf, 2013). The rate of minor complications is approximately 5% and include infection, epistaxis, mucosal adhesions and consequences of minor violations of the lamina papyracea (Orlandi et al., 2021; Hosemann & Draf, 2013). Major complications range from 0.38-1% and include significant haemorrhage requiring intervention, violation of the skull base, cerebrospinal fluid (CSF) leak and significant orbital or optic nerve injury (Hopkins et al., 2006; Orlandi et al., 2021).

Outcomes and their measurement

Outcomes of ESS can be measured using many outcome metrics. These include patient-reported and objective measures. Endoscopic sinus surgery has been shown to improve both classes of metrics including endoscopy scores, CRS-specific quality of life measures, cardinal and non-cardinal symptoms and overall healthy utility scores (Orlandi et al., 2021). The following tools are most commonly utilised:

- The SNOT-22 test or nasal obstruction symptom evaluation (NOSE) scale. These tests are more responsive to clinical changes post-operatively than general health measures (Lidder et al., 2017). A minimally clinically important difference of 8.9 has been defined for the SNOT-22 test (Hopkins et al., 2009).
- Endoscopic scoring systems such as the Lund-Kennedy score or the modified-Lund Kennedy/Mackay score (Snidvongs et al., 2014).
- Complications.
- Corticosteroid requirements post-operatively.
- Surgical revision rates.
- Olfaction (see Investigations).
- Respiratory function tests (in patients with asthma, cystic fibrosis etc).

Recurrence

Rate of recurrence is difficult to quantify due to the heterogeneity of disease, surgical techniques and post-operative management. Whilst recurrence does not equate with revision surgery, surgical revision rates of up to 14-24% have been reported (Govindaraj, Agbetoba, & Becker, 2012; Grayson, Li et al., 2020; Loftus et al., 2020). Recurrence is more likely in patients with more severe disease (e.g. aspirin exacerbated respiratory disease), incomplete or inadequate surgery, poor post-operative compliance, a history of previous surgery, and in smokers (Hopkins, Slack et al., 2009; Krzeski et al., 2011; Georgalas et al., 2014; Loftus et al., 2020).

New procedures

Categorising CRS using anatomic distribution of disease and endotyping to enable subtyping patients will allow a more targeted and personalised approach to the management of CRS. Further, genetic, immunologic or molecular profiling will permit the development of precision medicine in the management of CRSwNP (Hellings et al., 2017; Fokkens, 2020).

Biodegradable drug-eluting stents have been designed to function as mechanical spacers that deliver a precise and sustained release of medication over a period of time (Orlandi et al., 2021). Currently available stents release corticosteroid over 30 days (such as Intersect ENT <https://www.intersectent.com/products/propel>). These stents do not result in any significant systemic absorption or ocular complications and they have been shown to reduce the need for further interventions, corticosteroid use, polyposis and adhesions post-operatively (Forwith et al., 2011; Murr et al., 2011; Marple et al., 2012; Han et al., 2012). Other stents are in development that release a corticosteroid over a longer period (24 weeks), that release an antibiotic, or release a combination of an antibiotic and cystic fibrosis transmembrane conductance regulator potentiator, ivacaftor. (Cho et al., 2018; Douglas et al., 2019; Cho et al., 2019). However, there is some concern that material composing the stent itself may induce inflammation and many studies demonstrating efficacy were industry sponsored and/or lack a non-stented arm (Orlandi et al., 2007; Huang et al., 2015).

Robotic sinus surgery is not currently in practice due to the limitations of instrument size (Campbell & Harvey, 2021; Campbell, 2019). However, robotics certainly shows promise for ESS, particularly with robotic endoscope holders (Mattheis et al., 2019).

In-office procedures such as polypectomy, balloon dilatation and insertion of drug-eluting stents have increased in popularity due to the perceived reduction in costs associated with a procedure performed in an ambulatory setting. Many of these devices (such as drug-eluting stents and sinus balloons) are not currently available in Australia.

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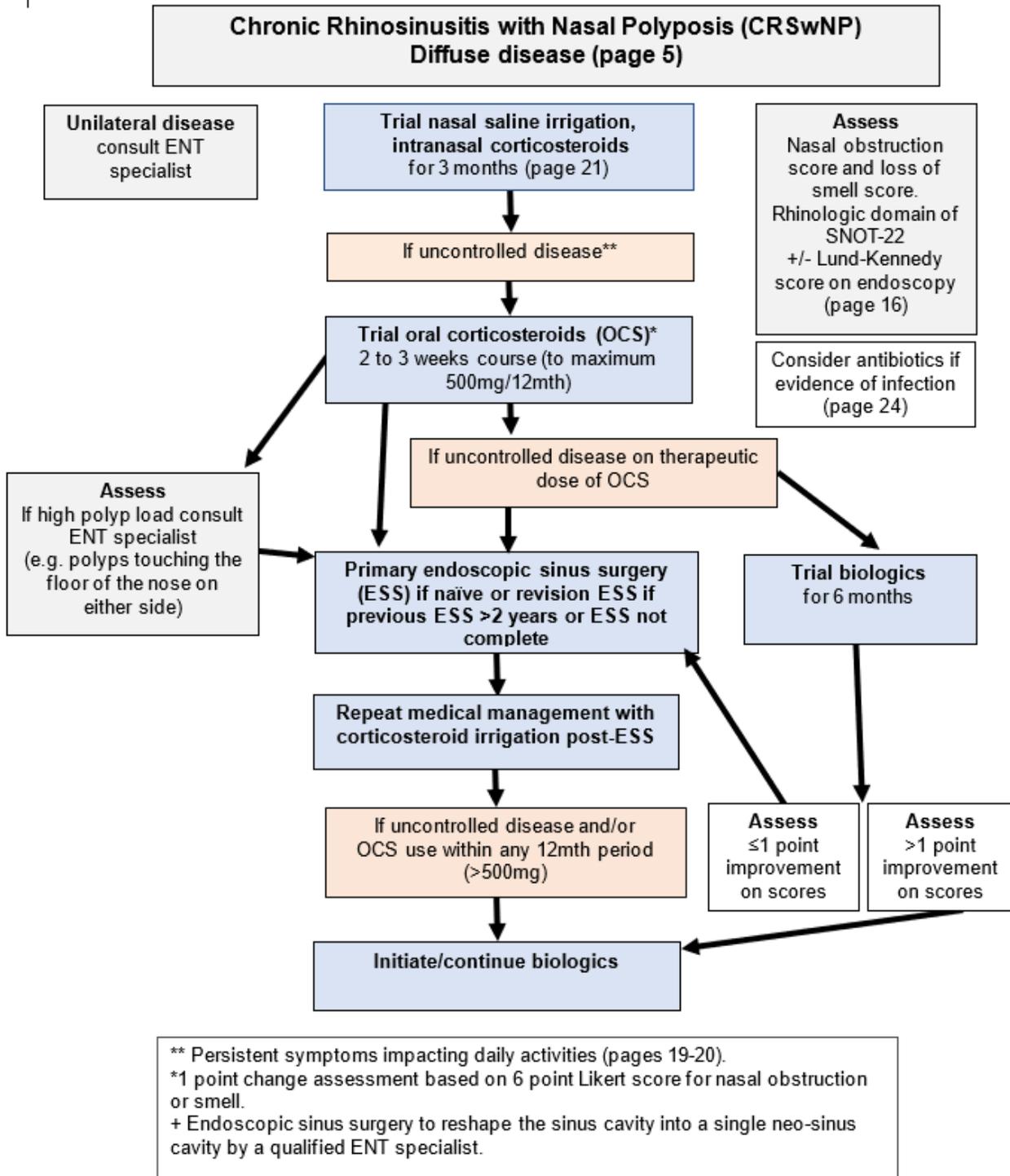
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SECTION 6 – TREATMENT ALGORITHM



SECTION 7 – ABBREVIATIONS

ACQ-7	asthma control questionnaire-7
ADA	anti-drug antibody
AD	aspirin desensitisation
AE	adverse event
AERD	aspirin exacerbated respiratory disease (Samter's Triad)
AFRS	allergic fungal rhinosinusitis
AIT	allergen immunotherapy
AFRS	allergic fungal rhinosinusitis
Anti-IgE	anti-immunoglobulin E
AQLQ	asthma quality of life questionnaire
AR	allergic rhinitis
AR	acoustic rhinometry
ASCIA	Australasian Society of Clinical Immunology and Allergy
ASOHNS	Australian Society of Otolaryngology Head & Neck Surgery
CCAD	central compartment atopic disease
CF	cystic fibrosis
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
COPD	chronic inflammatory lung disease
CRS	chronic rhinosinusitis
CRSwNP	chronic rhinosinusitis with nasal polyps
CRSsNP	chronic rhinosinusitis sine (without) nasal polyps
cysLTs	cysteinyl leukotrienes
DBPCT	double blind, placebo-controlled trial
ECG	electrocardiogram
eCRS	eosinophilic rhinosinusitis
ENT	ear, nose and throat
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
EQ-5D	Euro QOL five-dimensional questionnaire
ESS	endoscopic sinonasal surgery
FDA	Food and Drug Administration (US)
FESS	functional endoscopic sinus surgery
FEV1	forced expiratory volume
GINA	Global Initiative for Asthma
HPF	high powered field
HR	heart rate
HRQL	health-related quality of life
IFN	interferon
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG1	immunoglobulin G1
IL	interleukin
IL-5RA	interleukin-5 receptor alpha
INCS	intranasal corticosteroids
LK	Lund-Kennedy
LKES	Lund-Kennedy endoscopy scoring
LMS	Lund-Mackay score
LR	likelihood ratio
LSM	least-squares mean
LTA4	leukotriene A4 hydrolase
LTB4	leukotriene B4
LTC4	leukotriene C4

LTD4	leukotriene D4
LTE4	leukotriene E4
MCID	mean clinically important difference
MLK	modified Lund Kennedy score
MRI	magnetic resonance imaging
NERD	NSAID-exacerbated respiratory disease
NOSE	nasal obstruction symptom evaluation
NP	nasal polyps
NPS	nasal polyp score
NSAIDs	non-steroidal anti-inflammatory drugs
OMC	ostiomeatal complex occlusion
OR	odds ratio
PBS	Pharmaceutical Benefits scheme (Australia)
PNIF	peak nasal inspiratory flow
PROMs	patient-rated outcome measurement
PCRS	paediatric chronic rhinosinusitis
PG	prostaglandin
PGE2	prostaglandin E2, also known as dinoprostone
PGG2	postaglandin G2
PGH2	prostaglandin H2
PND	postnasal drip
PNIF	peak nasal inspiratory flow
POSE	perioperative sinus endoscopy score
PROMS	patient reported outcome measures
QOD	questionnaire of olfactory disorders
QOL	quality of life
RCT	randomised controlled trial
RS	rhinosinusitis
RM	rhinomanometry
SF-12	short form (12) health survey
SF-36	short form (36) health survey
SCT	sinus control test
SNAQ	sino-nasal questionnaire
SNOT-22	sino-nasal outcome test
SPT	skin prick test
T2	Type 2
TGA	Therapeutic Goods Authority (Australia)
Th	T helper
TSLP	Thymic stromal lymphopietin
UPSIT	University of Pennsylvania Smell Identification Test
VAS	visual analogue scale

SECTION 8 - REFERENCES

References are listed on the ASCIA website:

<https://www.allergy.org.au/hp/papers/references-crswnp-a-l>
<https://www.allergy.org.au/hp/papers/references-crswnp-m-z>