

Updates in the management of chronic rhinosinusitis

Practice points

- Chronic rhinosinusitis (CRS) is one of the most common chronic diseases in the UK, with an estimated prevalence of 10.4%.
- The diagnosis of CRS is made on the basis of the presence of two or more symptoms, persisting at least 12 weeks, one of which should be either nasal obstruction or rhinorrhea, and a second, which may also include facial pain or anosmia.
- It is categorized by two major phenotypes: CRS with or without polyps (CRSwNP or CRSsNP, respectively). The difference in their pathogenesis forms the basis of their distinct management pathways, described in the latest EPOS guidelines.
- The pathogenesis of CRS is multifactorial. It comprises an interacting triad of intrinsic mucosal inflammation, local microbial community and mucociliary dysfunction.
- CRSwNP largely demonstrates eosinophilic (T-helper-2) inflammatory responses, while CRSsNP demonstrates neutrophilic (T-helper-1) responses.
- ENT examination with anterior rhinoscopy (primary care) or endoscopy (specialist care) is recommended.
- CT scans should not be requested in primary care, but may be considered in the specialist setting.
- Endoscopic sinus surgery is recommended for those who have failed maximal medical therapy. It is a safe procedure, which is effective in improving quality of life.
- Balloon sinuplasty allows the treatment of medically refractive CRS in an office-based setting; further evidence is required.
- Improved awareness of diagnostic criteria and evidence-based care will enhance diagnostic accuracy and ensure optimal CRS management by ENT and non-ENT specialists.

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Chronic rhinosinusitis (CRS) is one of the most common chronic diseases in the UK, with an estimated prevalence of 10.4%. CRS has been shown to have a significant impact on quality of life, worse in some domains of the Short Form-36 than COPD or angina. It carries a high socioeconomic burden; with estimated healthcare costs in the USA of \$772/patient/year (2011). Untreated, CRS may also cause exacerbation of co-existing asthma. Given its frequency of presentation to primary care, A&E, respiratory medicine, allergy, neurology and ENT, here, we aim to inform readers about key developments in the diagnosis and management of adult CRS, following the publication of the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS). In particular, improved knowledge of diagnostic criteria and evidence-based care will enhance diagnostic accuracy and ensure optimal CRS management from the onset of disease; both improving symptom control and reducing secondary care referrals.

Keywords: antibiotics • balloon sinuplasty • chronic • functional endoscopic sinus surgery • intranasal corticosteroids • nasal polyps • oral steroids • rhinosinusitis • saline irrigation

What is chronic rhinosinusitis?

Rhinosinusitis is an inflammatory condition of the mucosa of the nose and paranasal sinuses of multifactorial etiology. It is deemed chronic rhinosinusitis (CRS) when persisting for at least 12 weeks without complete resolution. It is diagnosed in patients with a distinct set of symptoms and signs as defined by EPOS (Box 1) [1]. It is categorized by two major phenotypes: CRS with or without polyps (CRSwNP or CRSsNP, respectively).

CRS epidemiology

There is a lack of accurate epidemiological data on CRSsNP and CRSwNP; the reported prevalence ranges widely from 5 to 15% [2]. This is due in part to geographical variation [3], but also differences in diagnostic criteria used in studies and grouping together of the two major phenotypes. In the non-specialist setting, where endoscopic confirmation of disease is not always possible, the prevalence may be overestimated [4].

In a recent multinational study undertaken by the Global Allergy and Asthma European Network, the total prevalence of both CRSsNP and CRSwNP has been estimated at 10.9 and 15.5% in Europe and the USA, respectively [5,6]. CRSsNP is more common in female subjects (6:4) [6], and increases with age, with incidence reaching a plateau after 60 years [7]. The average age of onset of CRSwNP is 42 years, [1] with prevalence ranging from 1 to 4.5% in Europe [8], but only two thirds of patients with CRSwNP seek medical advice for their symptoms [8]. CRSwNP is more common in males (2:1) [9,10], elderly patients (5% at 60 years) and those with asthma (26% of those with CRSwNP had asthma) [8], aspirin intolerance (36–96% have CRSwNP) [11] and cystic fibrosis.

Etiology

The pathogenesis of the persistent inflammation of CRS is complex and multifactorial. Idiopathic or pri-

mary CRS is discussed here, which is distinct from secondary CRS due to either systemic diseases (including Wegener's granulomatosis or sarcoidosis) or genetic disease (such as primary ciliary dyskinesia and cystic fibrosis). Of key importance, the presence or absence of nasal polyps largely correlates with eosinophilic (T-helper-2) or neutrophilic (T-helper-1) inflammation, respectively. This forms the basis of their distinct management pathways (Figures 1 & 2).

CRSwNP is typically characterized by a T-helper-2 dominated cytokine pattern involving IL-5, resulting in increased eosinophilia and mast cell activity. The mucosal inflammatory response is greater in CRSwNP than in CRSsNP. CRSsNP exhibits T-helper-1 cytokine profile of IFN- γ gamma and TNF, triggering a neutrophilia. More recently, high levels of TGF- β have been found in CRSsNP causing fibrosis, while low levels were seen in CRSwNP [12].

Timperley *et al.* describe an interacting triad of: intrinsic mucosal inflammation; local microbial community; and mucociliary dysfunction [13] (Figure 3). Persistent mucosal inflammation is the key feature of CRS, diffuse in CRSwNP and more localized to the osteomeatal complex in CRSsNP leading to its obstruction [14]. The inflammatory damage to the mucosal barrier enhances pathogen binding/invasion, leading to impaired mucociliary function. Environmental factors such as active and passive inhalation of cigarette smoke may cause mucosal damage directly or via immune response. Of note, active and passive smokers have increased prevalence of CRS [15,16] and have poorer outcomes post-surgery [17], due to persistent inflammation and poor mucociliary clearance. Active tobacco smoking is associated with increases in markers of systemic inflammation in patients with CRS [18].

Various microbial etiologies have been postulated. Viral infection may create an initial insult, which predisposes to chronic mucosal inflammation, impairing

Box 1. Definition of chronic rhinosinusitis.

- Inflammation of the nose and paranasal sinuses
- Characterized by two or more symptoms:
 - One must be either nasal blockage/obstruction/congestion or nasal discharge (anterior or posterior nasal drip)
 - \pm facial pain/pressure
 - \pm reduction or loss of smell
 - And either endoscopic signs:
 - Polyps and/or
 - Mucopurulent discharge primarily from middle meatus and/or
 - Edema/ mucosal obstruction primarily in middle meatus
 - And/or CT changes:
 - Mucosal changes within the osteomeatal complex and/ or sinuses

Data taken from EPOS guidelines [1].

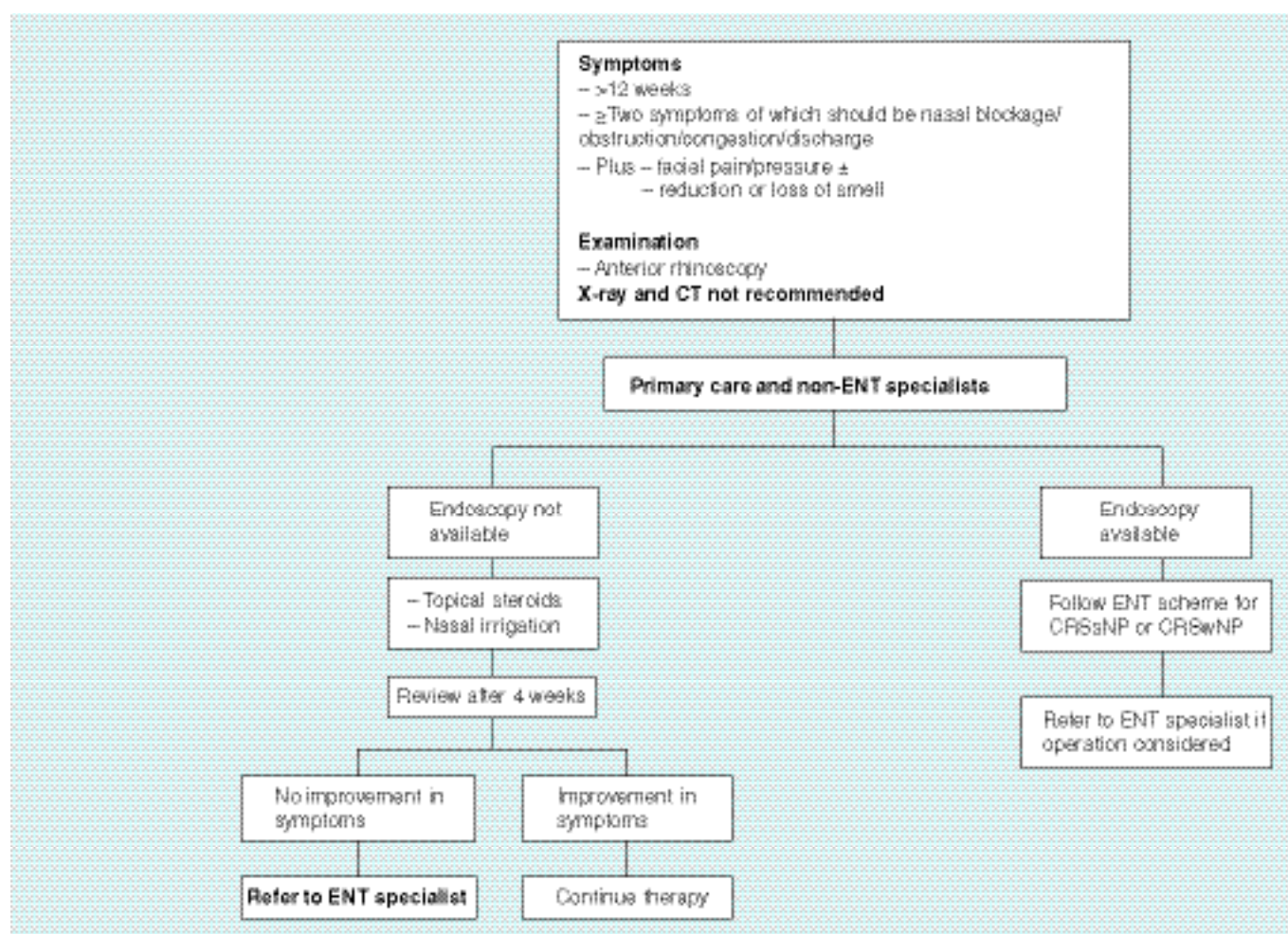


Figure 1. Management scheme for chronic rhinosinusitis in adults for primary care physicians and non-ENT specialists.

CRSsNP: Chronic rhinosinusitis without nasal polyps; CRSwNP: Chronic rhinosinusitis with nasal polyps; VAS: Visual analogue scale. Adapted from EPOS guidelines.

mucociliary transport and facilitating bacterial infection [13]. There is limited evidence supporting this initial insult theory or a significant role for viruses in the stimulation of chronic inflammation, however, it is highly possible they play an etiological role [1]. The ‘staphylococcal superantigen hypothesis’ proposes that colonizing *Staphylococcus aureus* secretes superantigenic toxins that amplify TH2 responses and local eosinophilic inflammation. This is supported by a significantly increased colonization rate of *S. aureus* in patients with CRSwNP (63.6%), not significant in patients with CRSsNP (27.3%) [19]. *S. aureus* has also been identified invading epithelial cells from patients with CRSwNP [20]. Regardless of an intra- or extra-cellular localization in the epithelium, *S. aureus* is capable of inducing a TH2 cytokine pattern in CRSwNP. However, as this is only associated in only 50% of CRSwNP cases, there has been a movement away from the primary pathogen-driven hypothesis towards a disease-modifying role [21,22].

Biofilms are collections of live bacteria (including *S. aureus*, *Haemophilus influenza* and *Pseudomonas aeruginosa*) within an extracellular matrix. They perpetuate the inflammatory response, increase resistance to host defense and antibiotics, and predict poor post-operative outcomes. [23] Further work is required to further understand their pathogenic role.

Helicobacter pylori and acid reflux have been linked with CRSsNP [24], but EPOS concluded there was not enough causal evidence to warrant treating it at present. A fungal causative role has not been established in primary CRS with or without nasal polyps. There has been no convincing immunological data and no evidence of clinical improvement following topical or systemic antifungal therapy versus placebo in a Cochrane meta-analysis [25,26]. However, due to an intrinsic or induced change in immunity of CRS patients, fungi might have a disease-modifying role [27,28].

Mucociliary debris clearance is impaired in CRS [29]. Cilial impairment may occur primarily (primary

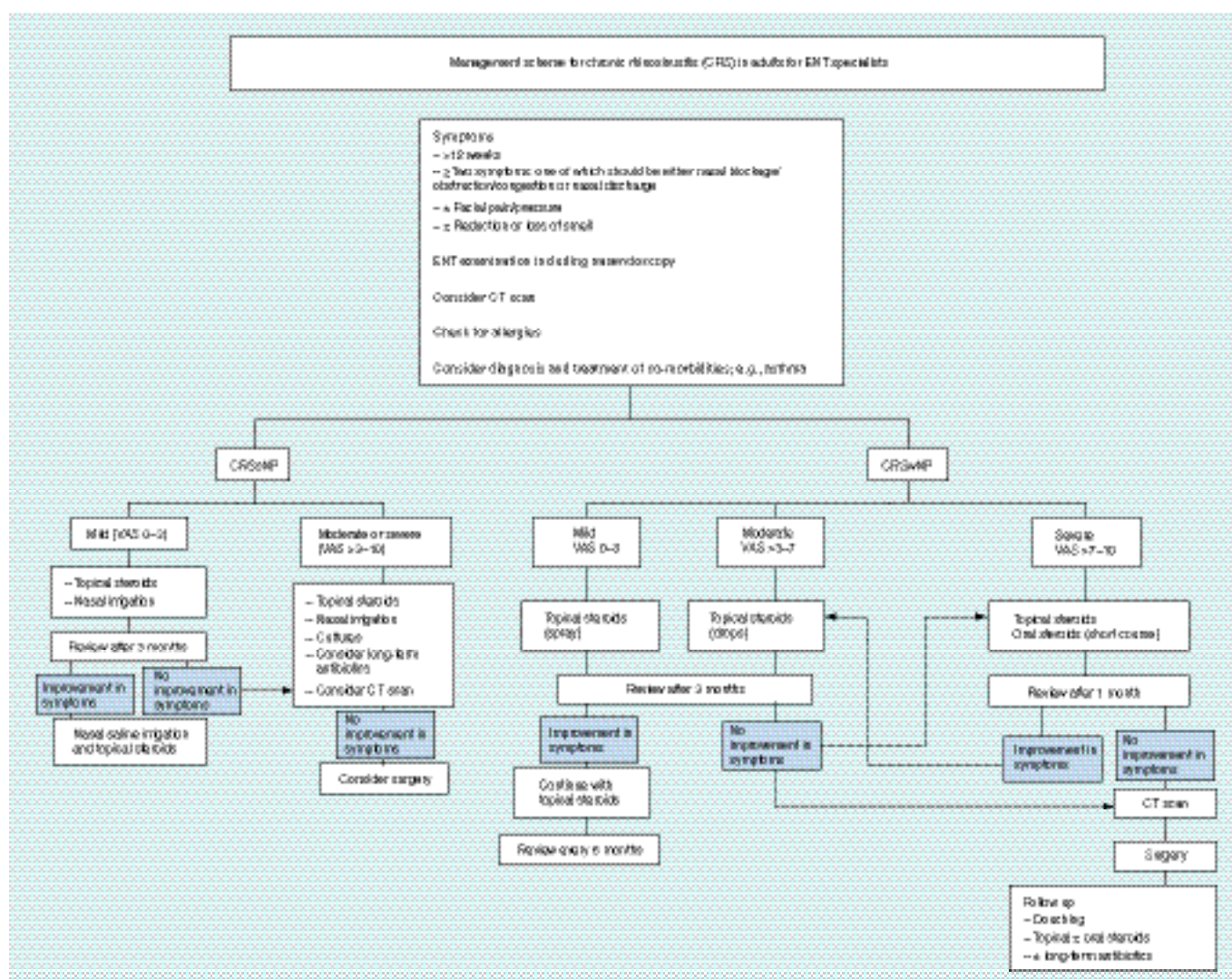


Figure 2. Management scheme for chronic rhinosinusitis in adults for ENT specialists.

CRSsNP: Chronic rhinosinusitis without nasal polyps; CRSwNP: Chronic rhinosinusitis with nasal polyps; VAS: Visual analogue scale. Adapted from EPOS guidelines.

ciliary dyskinesia), but more commonly are secondary to inflammation or infection. Mucociliary clearance is impeded by sinus ostial obstruction and recirculation. This delayed mucociliary flow prolongs contact time with microbes, antigens and inflammatory substances, promoting further microbial colonization and inflammation.

Allergic rhinitis can occur alongside CRS, but are likely to be independent entities [30]. In support of this, not all patients with CRS have proven allergy on skin prick testing or raised total/specific IgE levels. EPOS recommends taking an allergy history and to perform relevant allergy tests where positive, to appropriately direct treatment and surgical expectations (see diagnosis).

No genetic links have been found in primary CRS with or without nasal polyps [31,32]. Given the relation-

ship of CRS to other airway disorders with well-characterized genetic components, such as asthma, the study of CRS genetics requires further investigation through large collaborative studies, to advance knowledge of the mechanisms that underlie this disorder.

Diagnosis

Clinical history

The diagnosis of CRS is made on the basis of the presence of two or more symptoms, one of which should be either nasal obstruction or rhinorrhea, and a second, which may include facial pain or anosmia (Box 1). The most common symptoms reported by patients with CRS were blocked nose (83.7%), nasal discharge (63.6%), pain/pressure (64.7%), and reduced sense of smell (48.5%) [5]. Hyposmia was significantly worse with polyps (90.3%) than without (75.5%),

as was sleep disturbance at night (61.2%) [33]. There is a higher prevalence and severity of facial pain in patients without polyps than with (69.7 and 44.9%, respectively) [34].

Although facial pain is reported by two-thirds of patients with CRS, it is rarely severe, and facial pain alone in the absence of other symptoms of CRS is unlikely to be sinogenic [35]. A structured history of the pain and its associated symptoms is essential, alongside targeted investigations [36]. Over 90% of self- and doctor-diagnosed sinus headaches meet the International Headache Society criteria for migraines, yet 60% are given antibiotic treatment [1].

The differential diagnosis includes rhinitis (including allergic and non-allergic), structural abnormalities including hypertrophied turbinates and septal deviations, inflammatory conditions of the nose including vasculitic disease and tumors. Unilateral symptoms, blood-stained rhinorrhea and neurological or visual signs warrant urgent referral (**Box 2**).

Clinical examination

Anterior rhinoscopy should be performed in the primary care setting looking for nasal discharge or large

nasal polyps, which are often associated with significant anosmia. It is often possible to get a view of the middle meatus and middle turbinate using a simple otoscope in the nostril. This area should be inspected for edema, purulence and nasal polyps. Hypertrophied inferior turbinates may be mistaken for nasal polyps. However, the latter are often pale and multiple, while turbinates are usually bilaterally enlarged, symmetrical and the mucosa is similar to that over the nasal septum.

Nasal endoscopy, with or without local anesthetic/decongestant, allows better visualization of the middle and superior meati and nasopharynx and can facilitate the diagnosis of CRS, reducing the need for additional imaging [37,38]. Endoscopy aims to provide an objective measure in the evaluation of CRS, and findings can be quantified in terms of polyposis, edema, discharge, crusting and scarring (post-surgery) [39,40].

The diagnosis of CRSwNP is made by visualization of nasal polyps in the nasal cavity. If no polyps are seen endoscopically, CRSsNP is diagnosed and treated accordingly (**Figures 4 & 5**). Of note, normal endoscopic findings in those with isolated facial pain suggest the pain is unlikely to be due to CRS.

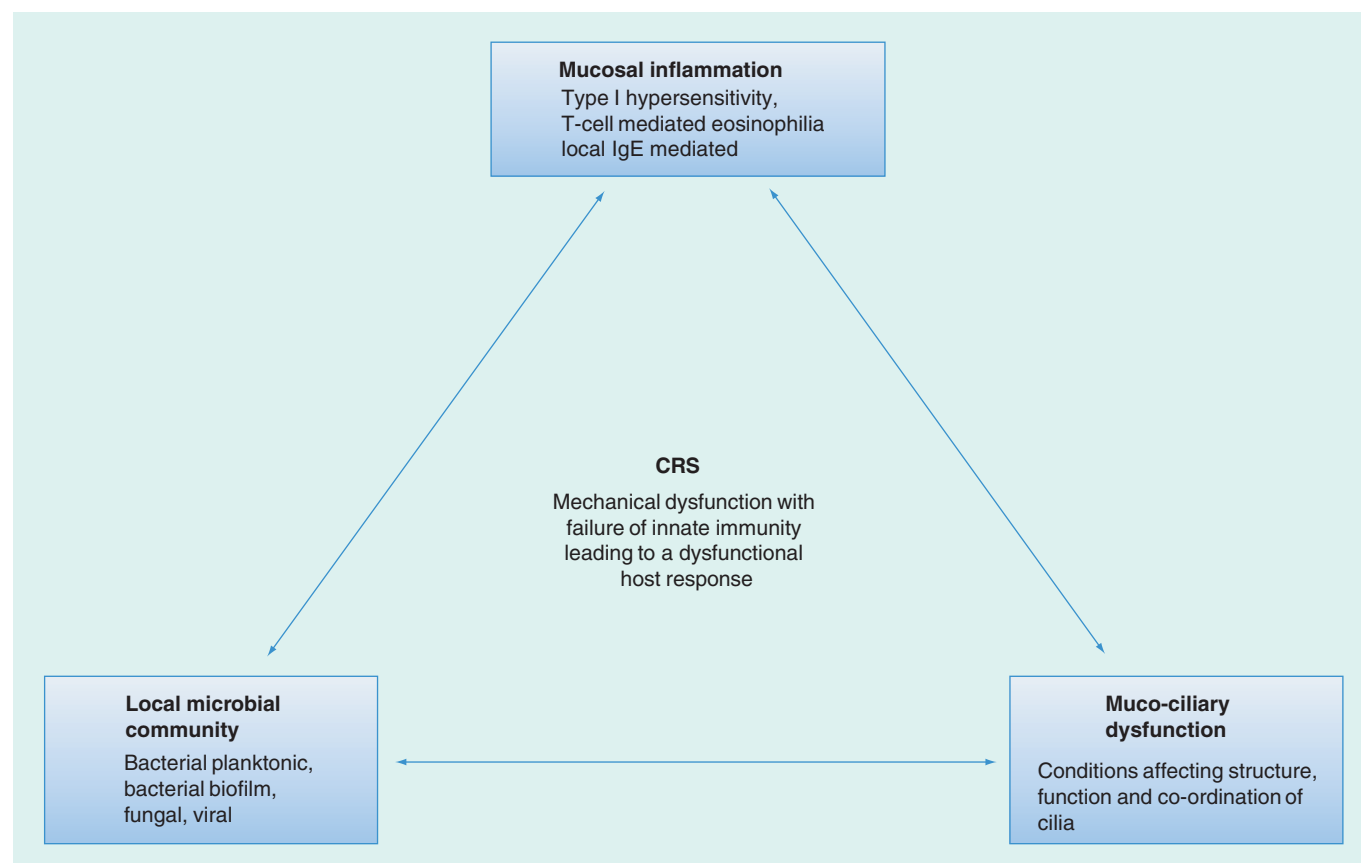


Figure 3. Etiology of CRS as interaction between infection, inflammation and mucociliary dysfunction, as described by Timperley *et al.* [13].

Assessment of symptom severity

It is useful to quantify the severity of symptoms reported by patients, as it allows more effective monitoring of response to treatment. The simplest way is to use a 10 cm visual analog scale (VAS), asking the patient to mark on the line 'how troublesome are your symptoms of rhinosinusitis, which allows categorization into mild (VAS 0–3), moderate (>3–7) and severe (>7–10) (Box 3). There are also a number of disease specific patient-rated outcome measures (PROMs) that record the severity of a number of individual symptoms important to patients with CRS. Most widely used in the medical literature are the 31 item Rhinosinusitis Outcome Test (RSOM-31), the 22 item Sinonasal Outcome Test (SNOT-22), and the Chronic Sinusitis Survey (CSS). These add to the clinical record, demonstrate the presence of defining symptoms hence enhancing diagnostic accuracy, and are sensitive to changes over time when used in repeated measures [34,41].

Imaging

Plain sinus x-rays are not recommended in any circumstance – they lack both the sensitivity and specificity required. CT is the preferred imaging modality, offering optimal air bone and soft tissue discrimination. It should not be a primary step in the diagnosis of CRS unless symptoms are unilateral or sinister. Guidelines state CT scans should be requested only in the specialist setting after a failed trial of medical treatment. This reduces radiation exposure, costs, incidental findings (present in a fifth of the population, where CRS symptoms were absent) [1] and improved detection of differential diagnoses (which may otherwise be missed in a nonspecialist setting) [42]. CT ordering by otolaryngologists has not increased over the past 6 years [43] (see coronal and axial CT scans).

There is a strong correlation between number of symptoms and presence of CRS on CT [44], however, only 50% patients meeting a symptomatic definition of

CRS will have supporting evidence of disease on same day endoscopy and CT. A symptom-based diagnosis alone has a sensitivity and specificity of 89% and 12%, respectively, compared with CT. CT findings can be staged according to the Lund-Mackay system [45].

Other tests

A history of allergy, asthma and aspirin-sensitivity should be sought and when positive, allergy tests performed. An *in vivo* skin prick test is the gold standard as it is efficient, safe and cost-effective. *In vitro* biological assays for total or allergen-specific IgE (e.g., CAP-RAST test) can be performed as a second line approach, which is also efficient but more costly [46]. Skin prick testing is more sensitive and has a higher positive predictive value than RAST testing but carries a very small risk of anaphylaxis, and therefore must be done in a setting with resuscitation equipment available. It also requires the patient to discontinue antihistamine medication 1 week prior to testing. Peak expiratory flow rate measurement should be considered in those with nasal polyps, as up to 60% of patients have co-existing lower airway disease [47].

Of interest, a recently published trial demonstrated vitamin D3 insufficiency was found in 55% of all CRSwNP patients, and in 80% of those of African-American race. Lower levels of vitamin D3 were associated with worse Lund-Mackay Scores on CT. Thus its role in CRSwNP warrants further investigation as an additional prognostic marker [48]. In order to rule out secondary causes of CRSsNP, other blood tests may be performed such as an ESR, angiotensin converting enzyme (may be raised in sarcoidosis and TB) and C-ANCA (may be raised in Wegener's granulomatosis) [49]. More specific tests of nasal function, usually performed in the research setting include measurement of olfactory function, nasal airflow using a peak nasal inspiratory flow rate and nasal cavity volume using rhinomanometry or acoustic rhinometry.

Management

The aim of CRS management is to restore the functional integrity of the inflamed mucosal lining with relief of patient symptoms. Patient-reported outcome measures often help guide response to treatment more than objective clinical measurements [1,50].

The management of CRSsNP and CRSwNP are distinct in the current EPOS guidelines, based on the differences in their underlying etiology and pathophysiology. Medical therapy is the primary treatment modality for both pathways. A 1-month trial of nasal irrigation and topical steroids is recommended in primary care, followed by referral to ENT if symptoms do not improve. The recommended treatment is modified

Box 2. Red flag symptoms.

- Unilateral symptoms
- Bleeding
- Crusting
- Cacosmia
- Orbital symptoms
- Periorbital edema
- Displaced globe
- Reduced or double vision
- Ophthalmoplegia
- Severe unilateral or bilateral frontal headache
- Frontal swelling
- Signs of meningitis or focal neurological signs

according to the severity of symptoms measured on a VAS. In general, in mild disease, topical steroids and saline irrigation form the basis of treatment. In more severe cases, under specialist care, low dose antibiotics may be considered, and in CRSwNP systemic steroids also play an important role. If maximal medical treatment fails, a CT scan of the sinuses is performed to confirm the correct diagnosis and surgical intervention may be considered [1]. Pathways for primary care and ENT specialist care are shown in [Figures 1 & 2](#). Some key areas of CRS evidence-based management are discussed below ([Table 1](#)).

Intranasal corticosteroid

EPOS meta-analysis demonstrates Level Ia evidence supporting the use of intranasal corticosteroid (INCS) for CRSsNP and CRSwNP [1]. Corticosteroids reduce inflammation, neutrophilic and eosinophilic infiltration and function. INCS reduces turbinate reactivity and nasal symptoms preoperatively [13].

Numerous factors contribute to INCS successfully reaching the sinuses, such as surgical state of the sinus cavity, delivery device and technique. The nasal airway and sinus ostia must be unobstructed. CRS associated mucosal edema means <2% of total irrigation volume reaches the unoperated sinuses [51]. Surgery improves the delivery of medications to sino-nasal mucosa [52,53]. The choice of device affects distribution, high volume positive pressure irrigation, such as squeeze bottles or 'neti pots', offer best delivery to the sinus cavities, and is ideal for use in postoperative patients [54–56]. Low volume sprays, drops and nebulizers have poorer distribution and are best for nasal cavity treatment, especially prior to surgery, with less than 50% reaching the middle meatus [56,57]. Increased ease of use and patient education enhances patient compliance. It is imperative to ensure optimal use of each method – for example, correct head positioning is essential for the application of steroid nasal drops, through lying with the head extended or flexed forwards onto the lap. In summary, while high volume irrigation is superior in terms of sinus penetration in a postoperative state, a balance should be found between symptomatic control and patient compliance, which may be higher with a spray.

The safety of INCS are well demonstrated, particularly for second generation agents such as mometasone furoate, fluticasone propionate, ciclesonide, fluticasone furoate, even in higher than recommended doses, long-term treatment and pregnancy. Systemic bioavailability of second generation agents are minimal (<1%) compared with first generation INCS, such as triamcinolone, flunisolid, beclomethasone and dexamethasone. First generation INCS should not be used long-term [58–60]. Common side effects of INCS include epistaxis



Figure 4. Patient demonstrating extensive CRSwNP, causing expansion of the ethmoid cavities and resulting hypertelorism.

(due to trauma to the septal mucosa), itching, sneezing and dry nose. INCS may need to be continued long-term, particularly in patients with CRSwNP, asthma and atopic predisposition. In a 5-year prospective study of patients undergoing endoscopic sinus surgery, significantly lower use of rescue medication and lower rates of disease recurrence were seen in patients using ongoing topical fluticasone compared with placebo [61].

Oral corticosteroids

CRSwNP

Cochrane systematic review of CRSwNP demonstrated Level Ia evidence for oral steroid use versus placebo [62]. The short-lived benefits (2–4 weeks) should be weighed against systemic side effects, such as reduced glucose tolerance, osteoporosis and weight gain. A maximum of two or three courses should be prescribed within 1 year – failure to control symptoms despite three systemic courses would suggest the need for surgical intervention. A dose of 0.5 mg/kg for 5–10 days is recommended [63].

CRSsNP

EPOS does not advise oral corticosteroids for CRSsNP. A systematic review performed in 2011 found only



Figure 5. Endoscopic view of grade III nasal polyps extending into the right nasal cavity, but not below the inferior turbinate.

level 4 data supporting efficacy (one prospective trial) [64]. No randomized control trials (RCT) were identified and no trials employed systemic corticosteroids alone in treating CRSsNP. Future RCTs are required in this area.

Antibiotics CRSsNP

Macrolides reduce inflammation through reducing IL-8 production (antineutrophilic) [65], altering bacterial biofilm formation [66] and increasing inflammatory cell apoptosis [67]. They have been shown to be effective in the management of chronic airway inflammation cystic fibrosis and asthma.

The evidence supporting the use of macrolides is conflicting, hence the level of recommendation for use in CRSsNP from EPOS is Grade C. The strength of

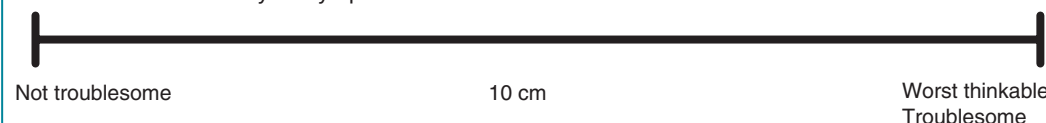
recommendation may change with future research; this is an area where new RCTs are needed. Many open non-RCT trials have demonstrated a 60–80% response rate to long-term macrolides. They are most often given at half the daily dose compared with treating acute infections, for example clarithromycin at 250 mg twice a day [1]. Only two RCTs of long-term macrolides were identified by EPOS. One investigated low dose daily roxithromycin for 3 months versus placebo in patients with CRSsNP, showing significantly improved symptom scores and endoscopic appearances, seen greatest in those with normal levels of IgE (contrasting with patients with CRSwNP who typically have elevated IgE) [68]. A more recent RCT of azithromycin found no benefit in a mixed group of CRSwNP and CRSsNP patients recalcitrant to standard treatment, possibly due to case-mix (i.e., the inclusion of CRSwNP patients), disease severity, under-dosage and under-powering of the study [69]. European guidelines thus recommend low dose macrolides for 12 weeks for moderate/ severe CRSsNP in those with normal IgE levels, when INCS and saline irrigation has failed.

Of significant importance, a recent study demonstrated an increased risk of cardiovascular events and acute coronary syndromes in patients receiving clarithromycin for acute exacerbations of chronic obstructive pulmonary disease [70]. A second study found no increased risk in patients with no underlying cardiovascular disease [71]. Macrolides should thus be avoided in patients with known cardiovascular disease, particularly with prolongation of the QT interval on ECG. There are also drug interactions with commonly prescribed drugs, such as statins and citalopram. Given the risk of side effects and increasing resistance, long-term macrolides for CRS should be withheld until endoscopic or radiological investigations have confirmed the diagnosis [72].

Of note, short term antibiotics for CRSsNP is recommended only for acute exacerbations with positive cultures [1]. No placebo-controlled trials exist.

Box 3. The visual analog scale for severity grading of chronic rhinosinusitis.

- Symptom severity in adult chronic rhinosinusitis is quantified using the visual analog scale (VAS) score. The total severity VAS guides chronic rhinosinusitis treatment:
- How troublesome are your symptoms of rhinosinusitis?



- Mild = VAS 0–3
- Moderate = VAS >3–7
- Severe = VAS >7–10

Table 1. Key EPOS treatment recommendations and supporting evidence.

Therapy	Recommended therapy for CRSwNP	Recommended therapy for CRSsNP
Topical steroids	Yes (Ia)	Yes (Ia)
Oral steroids	Yes (Ia)	Unclear (IV)
Oral antibiotics short term (<4 weeks)	Yes, small effect (III) for doxycycline	During exacerbations (II)
Oral antibiotic therapy long term ≥ 12 weeks	Not currently recommended	Yes, macrolides to be considered, especially if IgE is not elevated (Ib)
Nasal saline irrigation	Yes (Ib, no data on single use)	Yes (Ia)
Decongestant (topical/ oral)	No (No data on single use)	No (no data on single use)
Mucolytics	No (No data)	No (III)
Oral antihistamine in allergic patients	No (No data)	No (no data)
Allergen avoidance in allergic patients	–	Yes (IV)

CRSsNP: Chronic rhinosinusitis without polyps; CRSwNP: Chronic rhinosinusitis with polyps; Level Ia: evidence from systematic review or meta-analysis of randomized controlled trials; Level Ib: evidence from at least one randomized controlled trial; Level Iia: evidence from at least one well designed controlled trial that is not randomized; Level Iib: evidence from at least one well designed quasi-experimental study, for example, cohort study; Level III: evidence from well-designed non-experimental descriptive studies, for example, case series, correlation and comparative studies; Level IV: evidence from expert committee reports, opinions or clinical experience from a panel of experts.

CRSwNP

At present long-term macrolide antibiotics are not recommended for CRSwNP (EPOS Grade C). Long-term treatment (3 weeks at 100 mg once daily) with doxycycline has been shown in a RCT trial to moderately reduce polyp size and symptoms. The effect was longer lasting compared with oral steroids alone, 12 weeks for doxycycline versus 8 weeks for methylprednisolone [73]. Further RCTs investigating long-term treatment with doxycycline or trimethoprim-sulfamethoxazole are required to estimate the clinical benefit of these promising alternatives to macrolides.

Only three placebo-controlled trials have been performed on topical antibiotics in CRSsNP or CRSwNP; all were negative, thus are not recommended by EPOS [74–76]. Side effects such as bacterial resistance, GI upset and liver enzyme elevation should be considered. Bacterial resistance has not been demonstrated in CRS, [69] but has been shown in other areas such as in tonsillitis treatment.

Nasal saline douching

Saline is thought to improve CRS symptoms, through mucus clearance, enhancing ciliary beat activity, removal of allergen, biofilm or inflammatory mediators, and protecting sino-nasal mucosa.

The EPOS guideline recommends saline irrigation for CRSsNP without and following sinus surgery, based on level Ia evidence from a Cochrane review and 2 RCTs [1]. The Cochrane review showed benefits of saline irrigation when used as the sole treatment, but included a mixed group of children and patients with

CRSwNP [77]. Nasal douching should be used, as this has been shown to be more effective over sprays [78]. Evidence is lacking for nasal saline irrigation in CRSwNP and is thus only recommended for symptomatic relief.

Other additions to saline irrigations have been trialed. EPOS supports the use of Xylitol irrigation, as evidence suggests it is well tolerated, reduces nasal bacterial carriage *in vivo* and improves symptoms of CRS compared with saline irrigation alone (level Ib evidence) [79]. EPOS supports the use of 0.05% sodium hypochlorite in saline to a lesser degree than xylitol. Sodium hypochlorite is a bleaching agent against *S. aureus* and *P. aeruginosa*, which was significantly more effective than saline alone in the treatment of *S. aureus* positive CRS patients (level of evidence Iib) [80]. However, these solutions are not commonly used.

Surfactant, contained in baby shampoo, aims to dissolve biofilms by reducing water surface tension [81]. No RCT of surfactants in the treatment of CRSsNP has been identified, but a nonrandomized, open-label trial in 15 CRS patients for 4 weeks showed subjective improvement in 46% of patients (level III evidence) [82]. EPOS thus does not support the use of surfactants based on current evidence.

Other medical treatment

No RCTs have been performed for the use of antihistamines, mucolytics or nasal decongestants in CRSsNP; these treatments are not recommended. In CRSwNP, single studies and anecdotal reports have been performed on nasal decongestants [83], mucolytics [84] and

manuka honey [85]. EPOS does not recommend these due to lack of high quality evidence.

Bacterial lysates have been shown to improve major symptoms, objective x-ray findings and re-infection rates in one RCT of oral OM-85 BV treatment (lyophilised fractions of several common respiratory tract bacterial pathogens), in 284 adults with CRSsNP. EPOS thus states it may be used as an adjunct to standard medical treatment in adults with CRSsNP, but again use is not widespread.

CRSwNP is associated with eosinophilia. Numerous therapies targeting this pathogenic pathway, such as leukotriene antagonists, anti-IgE monoclonal antibodies, anti-IL5 monoclonal antibodies (eosinophil inhibitor) and aspirin desensitization may be of benefit, although at the time of EPOS publication there was insufficient evidence from high quality RCTs to make a strong recommendation for use. A recent RCT of omalizumab (anti-IgE) in patients with allergic and non-allergic CRSwNP and comorbid asthma demonstrated significant improvements in scoring of total nasal endoscopic polyps, CT sinus scans, symptoms and quality-of-life, irrespective of the presence of allergy [86]. IL-5 and its receptor are both elevated in Caucasian (eosinophilic) nasal polyps [87]. A RCT of anti-IL-5 antibodies (two vaccines of mepolizumab) demonstrated evidence for reduced polyp eosinophilia, size and CT scores, with no significant change in symptom scores. Larger trials are required to establish efficacy, while no data on patients without previous sinus surgery are available.

One RCT demonstrated antihistamines were not effective in the treatment of CRSwNP post-surgery [88], although may be used in those with concomitant nasal allergies. Meta-analysis of placebo controlled trials of both topical and intranasal antifungals do not demonstrate any benefit in unselected CRS, further research is required to determine if they are beneficial in selected patients with allergic fungal sinusitis, a subset of CRSwNP [25].

Endoscopic sinus surgery

Endoscopic sinus surgery (ESS) is recommended when optimal medical treatment has failed; persistent symptoms despite either a three month trial of nasal irrigation, topical steroids \pm long-term antibiotics in CRSsNP, or a 3-month course of nasal steroid spray or drops in mild or moderate CRSwNP, or 1 month of medical treatment including systemic and topical steroids with doxycycline in severe CRSwNP.

ESS has been shown to be most effective for nasal obstruction, with moderate improvement in facial pain and post-nasal drip. Hyposmia and headache improve the least [89]. ESS, pioneered by Stammberger and Kennedy in 1985, describes a minimally invasive mucosal

sparing endoscopic approach to the sinuses; preserving mucosa while enlarging natural drainage pathways and removing bony partitions in the ethmoid sinuses, with the aim of improving sinus ventilation, mucociliary function and improving topical access to sinus mucosa. RCT evidence is limited, as randomization and blinding are difficult, surgical approaches vary and studies often combine patients with CRSwNP and CRSsNP.

CRSwNP

A large systematic review found ESS to be a safe and effective treatment, although highlighted the need for high quality RCTs [90]. RCTs of ESS versus medical therapy for CRSwNP have demonstrated improved quality of life scores, with no significant difference in treatment arms at 12 months. [91,92] Thus, chronic rhinosinusitis should be targeted with maximal medical therapy in the first instance, with surgical treatment being reserved for cases refractory to medical therapy.

The National Comparative Audit of Surgery for CRSwNP and CRSsNP in England and Wales, a large prospective cohort study, described significant improvement in SNOT-22 quality of life scores in both CRSwNP and CRSsNP patients, with benefits maintained over a 5-year period of follow-up. Greater symptomatic improvement was found in patients with CRSwNP, due in part to the greater severity of nasal obstruction [61,93–94]. Other case studies have also demonstrated superior improvement post-surgery in quality of life and symptoms for CRSwNP patients versus CRSsNP [93], such as facial pain and headache [95].

CRSsNP

A cochrane review of surgery versus medical treatment in CRSsNP identified three RCTs meeting their criteria. It concluded that ESS had no additional benefit to medical treatment [96]. However, as for CRSwNP, the studies did not analyze ESS results of patients failing medical therapy. ESS for CRSsNP has been demonstrated to be safe, improve symptom scores and generic and disease specific quality of life in numerous level II/III studies [89,93,97].

Complication rates

Although the sinuses are within close proximity to the orbit and anterior skull base, major complications of ESS are rare. The national audit demonstrated low rates of major complications (0.4%), which may include major hemorrhage and orbital and intracranial complications. In total, 6.6% had minor complications, most frequently perioperative hemorrhage (5.0%) and minor postoperative hemorrhage (0.8%) [98]. CRSsNP patients tend to report postoperative pain more often than polyp patients [93].

A systematic review of safety and efficacy of ESS for CRSwNP demonstrated major complications of 0–1.5% and minor complications of 1.1–20.8%. The most serious complications were cerebrospinal fluid leaks, injury to the internal carotid artery, dural exposure, meningitis, bleeding requiring transfusion, periorbital/orbital fat exposure and orbital penetration [99]. Complications were more likely to occur in those with larger and more extensive nasal polyps and asthma [100].

Revision rates

The relapse rate after surgery for CRSwNP is higher than for CRSsNP [95], with these patients often requiring multiple surgeries. The risk is higher for those with severe CRSwNP, previous surgery and asthma [101]. The national audit demonstrated 20.6% with polyps underwent revision surgery at 5 years, compared with 15.5% of patients without [93]. Prognosis is influenced by the extent of the disease, a history of asthma, aspirin sensitivity, cystic fibrosis, biofilm formation, smoking and allergy.

There is little published evidence upon which to base recommendations for ongoing medical therapy post-surgery. Instead, the same treatments are used in response to symptomatic recurrence and endoscopic appearances. Treating patients postoperatively with fluticasone propionate showed significantly less polyp recurrence 5 years post-ESS [61]. EPOS recommends the use of nasal irrigation postsinus surgery for CRSsNP. A single blind low-powered trial of post-bilateral ESS nasal irrigation in one nostril and none in the other demonstrated a significant improvement in edema at 3 weeks post-surgery ($p = 0.046$), but no significant improvement in edema, adhesions or crusting at 3 weeks and 3 months [102]. There is no evidence for use of nasal saline spray post-surgery [103]. A recent study showed douching with lactated Ringer's solution after ESS results in a significant improvement in sinonasal symptoms, compared with normal saline or hypertonic saline solutions.

Balloon sinuplasty

Approved by NICE in 2008, sinuplasty dilates the drainage pathways of the sinuses by the inflation of a high-pressure balloon in the sinus opening. It is simply a novel instrument with which to perform ESS, and does not change the indication for surgery. However, as it may be performed in selected patients under topical anesthesia, it allows the treatment of medically refractive CRS in an office-based setting.

At present there are limited comparative studies for balloon sinuplasty alone versus conventional ESS; hybrid procedures often take place, for example where nasal polyps are removed endoscopically followed by

balloon sinuplasty. A Cochrane review identified one study meeting their criteria investigating balloon frontal sinuplasty versus conventional ESS (2011), but symptomatic outcomes were not reported [104]. EPOS states its use remains unclear at present (evidence level IV) [1].

Conclusion

CRS is a common condition with significant impact on the quality of life of the patient. Improved diagnostic definitions and a growing understanding of the need to define different phenotype has improved our ability to manage CRS. There is a growing evidence base to support primary medical management. International guidelines such as EPOS will help to disseminate best practice. However, surgery for refractory CRS remains a common procedure, and following surgery recurrence of disease is also prevalent. Therefore, further research is urgently required to improve both medical and surgical treatment strategies.

Future perspective

Current research work in CRS is focusing on endotyping; it is likely that in 10 years time several distinct endotypes will be clearly defined by a set of biological markers, each with separate specific treatment pathways. Medical treatment will evolve, for example, using monoclonal antibodies directly targeting the pathophysiological pathway, such that non-specific immunomodulation with corticosteroids will no longer be required. The anti-inflammatory actions of low dose antibiotics will be achieved in more specific forms, avoiding the risks of antibiotic resistance and cardiovascular side effects. Topical delivery methods are likely to include drug-eluting stents and devices, which may be sited in an office-based setting, building on novel instrumentation such as sinuplasty.

The result of such advances in medical treatment will result in surgical intervention being undertaken much less frequently. Where surgery is required, early intervention will hopefully prevent the acquisition of adverse prognostic factors such as osteitis. Surgery may make use of technological advances such as 3D endoscopy, robotics and image guidance, and will be tailored to the demands of the underlying phenotype. A 'one size fits all' approach to both medical and surgical treatment for CRS is likely to be redundant.

The Holy Grail – the identification of a single causative agent – is likely to remain elusive; in reality it is likely that many etiological agents interact causing inflammation within the sinus. Further work is required to clarify the pathogenic roles of the follow-

ing: genetics through genome wide association studies; biofilms; gastro-esophageal reflux; smoking and environmental irritants; bacterial and fungal colonization, staphylococcal superantigens and the immunological mechanisms of CRSwNP and CRSsNP.

Further iterations of evidence-based guidelines will remain essential to keep apace with the rapidly accumulating medical literature on CRS. This will increase awareness and subsequently improve referrals [105], diagnostic accuracy and treatment of CRS by both non-ENT and ENT specialists, optimizing patient outcomes and reducing practice variation. However, it is likely that CRS will continue to remain a significant

burden, both to individual patients and society, and ongoing research in this area is vital.

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