

Chronic rhinosinusitis

Alleviating symptoms and improving quality of life

DAKSHIKA A. GUNARATNE BMed, MS, MPH, FRACS
YURESH S. NAIDOO BE(Hons), MB BS, FRACS, PhD

Sinus complaints are common and can be attributed to a variety of rhinological and nonrhinological disorders. Chronic rhinosinusitis is a disease of persistent sinonasal inflammation for which corticosteroid therapy provides patients with symptomatic relief and an improved quality of life. Functional endoscopic sinus surgery provides a means for long-term management with use of topical therapies alone.

Chronic rhinosinusitis (CRS) is defined by symptomatology in conjunction with endoscopic and/or radiological findings (Box 1). However, in general practice and in epidemiological studies, the definition is often based on symptomatology alone, which may overestimate the prevalence due to overlap with rhinitis conditions.¹

Epidemiology

The true prevalence of CRS is estimated to be less than 5% when using guideline-based diagnostic criteria.² It is more commonly diagnosed in middle-aged and older patients, women, current

*Medicine*Today 2022; 23(10): 26-34

Dr Gunaratne is a Rhinology and Endoscopic Sinus and Skull Base Surgery Fellow in the Department of Otolaryngology, Head and Neck Surgery at Westmead Hospital, Sydney.

Associate Professor Naidoo is a Consultant in the Department of Otolaryngology, Head and Neck Surgery at Concord Hospital, Sydney; and Clinical Associate Professor at Macquarie University, Sydney, NSW.



KEY POINTS

- Chronic rhinosinusitis is a heterogeneous condition of sinonasal inflammation, manifesting with symptoms of nasal obstruction/congestion, nasal discharge, reduction in smell and facial pain/pressure. Endoscopic and radiological assessment shows mucosal oedema with or without nasal polyps.
- Despite overlapping symptomatology, history, examination and imaging can differentiate chronic rhinosinusitis from rhinitis, sinonasal neoplasms and nonsinogenic pathology, such as headache or migraine disorders.
- Management with topical and systemic corticosteroids and nasal saline irrigation is complemented by functional endoscopic sinus surgery to facilitate improved delivery of topical therapy. Doxycycline and macrolide antibiotics can be used for their anti-inflammatory and immunomodulatory effects, however, prolonged courses are required.
- Functional endoscopic sinus surgery entails removal of bony sinonasal partitions to reduce the surface area of the inflammatory burden, and maximise access for nasal sprays and irrigation into the sinuses.
- Biological therapy is available for refractory disease.
- First-line management that can be initiated by GPs includes intranasal corticosteroid sprays and saline nasal irrigations. Noncontrast CT of the paranasal sinuses is the imaging modality of choice and should be performed in patients who have persistent symptoms and before specialist referral.
- Long-term supplementary care by the treating specialists and GP is required to ensure patient compliance with maintenance therapy and management of disease exacerbations or recurrence.

and former cigarette smokers and individuals who consume alcohol on a regular basis.³

CRS imposes a greater impact on social functioning than angina or chronic heart failure.⁴ Total direct costs of CRS with nasal polyps in a Dutch cohort of patients was €1500 per patient per year, primarily due to outpatient department visits and hospitalisation.⁵ The indirect costs are amplified as the disease process predominantly affects people of working age resulting in missed work and study and reduced productivity.

Classification

CRS is heterogeneous and multifactorial in aetiology, but the common outcome is chronic sinonasal inflammation. Previous disease distinctions based on the presence or absence of nasal polyps have been replaced by nuanced systems incorporating disease distribution, underlying immune dysfunction and aetiology. The current classification of CRS is divided into primary and secondary disease and further categorised based on distribution and endotype (Figures 1 and 2).¹ This enables stratification of patients into clinically relevant phenotypes that guide management (Box 2).⁶⁻⁹

Definitive endotype diagnosis is based on histopathological analysis of sinonasal tissue and mucous; examination of cell type (eosinophils, neutrophils, lymphocytes) and quantity (number per high powered field); epithelial, subepithelial and basement membrane alterations; and the presence of fungal elements and cell breakdown products. Standardised reporting has been developed to assist pathologists and clinicians.

Pathophysiology

CRS is due to a complex dysfunctional interaction between environmental factors and the host immune system. Interactions and influences of environmental stimuli vary between individuals, giving rise to differing endotypes and phenotypes of disease. There is mounting evidence for an underlying

genetic basis with polymorphisms in the major histocompatibility complex (MHC) genes involved in antigen-specific adaptive immune responses, innate immunity and specific inflammatory pathways and mediators.¹⁰ Additional areas of active research include the role of allergy, staphylococcal superantigen, bacterial biofilm, fungal colonisation and abnormalities of the eicosanoid pathway. Nevertheless, the final common pathway is a loss of immune tolerance at the mucosal level and beyond, with subsequent chronic inflammation, tissue remodelling and symptom development.

This inflammatory response can propagate from the confines of the sinonasal cavity to affect the lower airway, and vice versa – the united airway disease hypothesis.¹¹ The purported mechanism is that localised airway inflammation leads to a systemic response, with bone marrow involvement, resulting in the release of progenitor cells that are then recruited to distant tissue sites.¹² It has been shown that allergen exposure in one part of the airway (upper or lower) can elicit an inflammatory response in both areas within 24 to 48 hours of the challenge.^{13,14} A neurogenic nasobronchial reflex has also been described.¹⁵ The united airways hypothesis exists for atopic and nonatopic individuals as seen in patients with NSAID-exacerbated respiratory disease (NERD), characterised by the Samter's triad of aspirin sensitivity, nasal polyposis and asthma.

Aetiology

The aetiology of primary CRS is multifactorial, with involvement of environmental, host immune behaviour, allergy, infective and genetic elements. CRS can also be secondary to a wide array of local and systemic disease processes. Common causes of localised disease include dental infection (odontogenic sinusitis), inhaled noninvasive fungal accumulation (mycetoma), neoplasia and anatomic alterations (e.g. uncinate process lateralisation and silent sinus syndrome). Systemic considerations include autoimmune and vasculitic processes (granulomatosis with polyangiitis, Churg-Strauss

1. DEFINITION OF CRS IN ADULTS¹

CRS is diagnosed by the presence of two or more of the following symptoms for 12 weeks or more:

- nasal blockage/obstruction/congestion*
- nasal discharge (anterior/posterior)*
- hyposmia/anosmia
- facial pain/pressure

There also needs to be:

- endoscopic signs of:
 - nasal polyps and/or
 - mucopurulent discharge primarily from the middle meatus and/or
 - oedema/mucosal obstruction primarily in the middle meatus

and/or

- CT findings of mucosal changes within the ostiomeatal complex and/or sinuses

Abbreviation: CRS = chronic rhinosinusitis.

* Must include at least one of these symptoms for a diagnosis of CRS to be made.

syndrome), cystic fibrosis (CF) and primary ciliary dyskinesia (PCD; especially in children with CRS) and immune deficiency. In these circumstances, investigation and management of the underlying aetiology is pivotal to addressing the CRS.

Associations

About 25% of patients with CRS have asthma (compared with 5% in the general population).¹ Onset of asthma may precede or follow the onset of CRS and the type of asthma can mirror the CRS endotype – childhood allergic asthma in central compartment atopic disease (CCAD) and adult-onset eosinophilic asthma in type 2 eosinophilic CRS. Allergic rhinitis has significant symptom overlap with CRS. The prevalence of allergy in CRS varies with phenotype, with stronger associations in CCAD and allergic fungal rhinosinusitis (AFRS). Other relevant CRS associations include gastro-oesophageal reflux disease (GORD), NERD, immunodeficiency, smoking, alcohol consumption and exposure to air pollution.

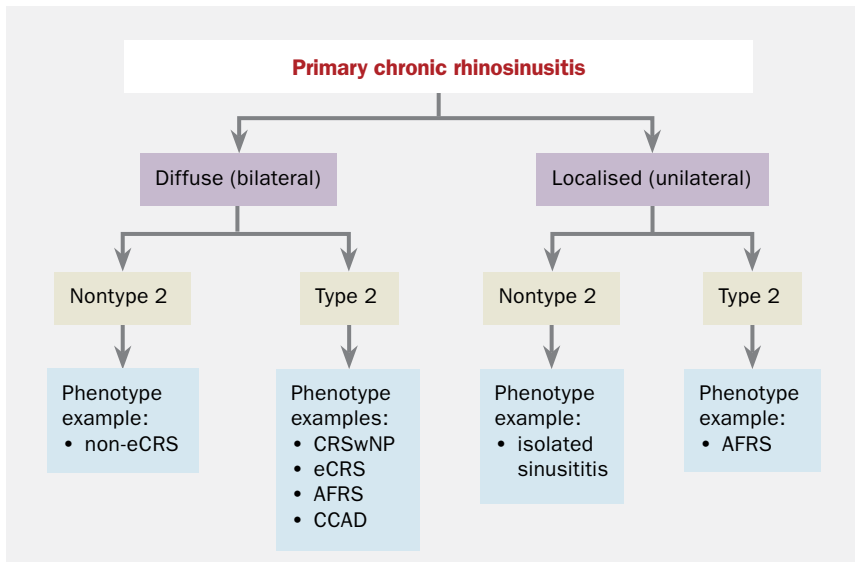


Figure 1. Classification of primary chronic rhinosinusitis.¹

Abbreviations: AFRS = allergic fungal rhinosinusitis; CCAD = central compartment atopic disease; CRSwNP = chronic rhinosinusitis with nasal polyps; eCRS = eosinophilic CRS.

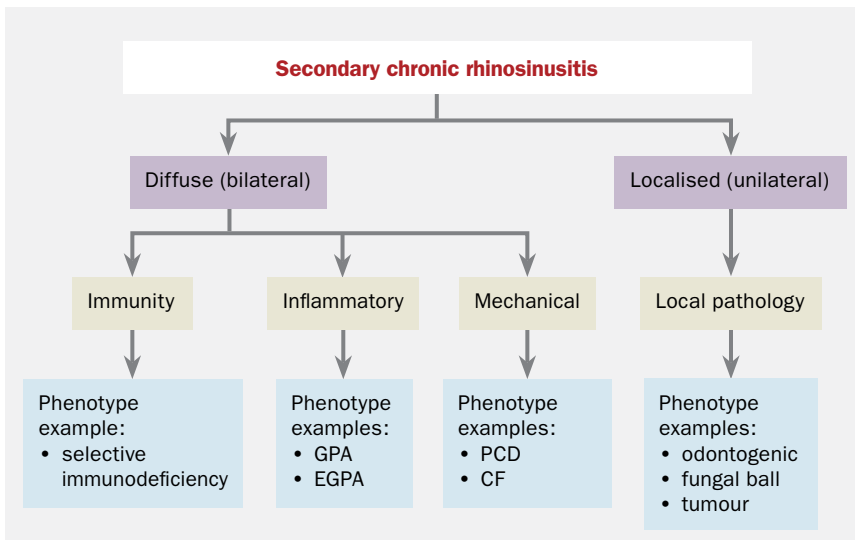


Figure 2. Classification of secondary chronic rhinosinusitis.¹

Abbreviations: CF = cystic fibrosis; EGPA = eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease); GPA = granulomatosis with polyangiitis (Wegener’s disease); PCD = primary ciliary dyskinesia.

Clinical features

The cardinal symptoms of CRS are nasal blockage, obstruction or congestion; anterior or posterior nasal discharge; facial pain or pressure; and hyposmia or anosmia. Hyposmia is more common in patients with the type 2 endotype of CRS and is believed to be caused by both mechanical

obstruction of the olfactory cleft from mucous and polyps, as well as the effect of inflammatory changes on olfactory neuron function. These patients often respond favourably to courses of systemic corticosteroids and report a return of their smell while on the medication. Facial pain is a common presenting symptom and often

suspected to be ‘sinus’ in origin but, in isolation, is rarely due to CRS.¹⁶

In all patients with a sinonasal presentation, red flag symptoms and signs that may indicate a disease complication or an alternative diagnosis (e.g. sinonasal malignancy) must be elicited (Box 3). Furthermore, certain occupational exposures have been associated with the development of sinonasal squamous cell carcinoma (nickel, softwood dust) and adenocarcinoma (hardwood dust).

Investigations

Quality of life (QoL) measures

The sinonasal outcome test (SNOT-22) is a multi-language validated self-administered CRS-specific questionnaire of 22 items rated from 0 (no problem at all) to 5 (worst possible symptom) to help measure disease severity in patients with CRS. Total scores greater than 50 reflect a severe impact of CRS and a cut-off score of 40 or more is incorporated into the criteria for biological therapy.¹⁷ Other QoL measures include the nasal obstruction and symptom evaluation (NOSE) scale, the 36-item short form survey (SF-36) and visual analogue scales (VAS).

Imaging

Noncontrast CT of the paranasal sinuses is the primary imaging modality and provides sufficient information regarding disease extent and anatomical factors relevant for surgery in most patients. The presence of a double density on the soft tissue sequences is a hallmark of fungal disease. However, there are limitations in differentiating opacification due to the presence of polyps, mucous and neoplasms, as well as delineating extent of disease beyond the paranasal sinuses. The Lund-Mackay score was developed to stratify the severity of disease based on CT, with higher scores predicting greater risk of disease recurrence.¹⁸ Contrast enhanced CTs are rarely performed for CRS, as MRI provides greater detail without the added radiation exposure. MRI with gadolinium enhancement provides the greatest detail regarding the nature and extent of sinonasal disease. Mucous, polyps

2. EXAMPLES OF CLINICAL PHENOTYPES OF CHRONIC RHINOSINUSITIS (CRS)

Central compartment atopic disease

Central compartment atopic disease (CCAD) is a severe form of an inhalant allergy. Disease extends beyond inferior turbinate congestion, typical of allergic rhinitis, to affect the middle turbinate and middle meatus, resulting in oedema, polypoid changes and secondary obstruction of the frontal, ethmoid and maxillary sinuses. It is a similarly IgE-mediated process and often presents in younger patients (teens to 30 years of age) with rhinitis symptoms (e.g. congestion, pruritis, rhinorrhoea, sneezing), preservation of smell and other associated atopic disease (e.g. conjunctivitis, childhood asthma, eczema). Middle turbinate head oedema and polypoid changes are highly specific for the diagnosis of CCAD.⁶ Radiologically and intraoperatively, the sinus mucosa is relatively normal with only secondary mucous trapping due to obstruction of the sinus outflow tracts. A 'halo' of normal sinus aeration can be seen surrounding the affected central nasal compartment (Figure 3). Histopathology can show elevated tissue eosinophilia without activation (no eosinophil aggregates or Charcot-Leyden crystals). Serum eosinophils levels are within normal range, but total and specific IgE levels are elevated. Allergy testing shows strong sensitisation, often to a single aeroallergen.⁷

Eosinophilic CRS and NSAID-exacerbated respiratory disease

Eosinophilic CRS (eCRS) often develops in adults (30 to 50 years of age), occasionally following a viral upper respiratory tract infection, before which they were completely well. Smell loss, which is corticosteroid responsive, is prominent along with food- and alcohol-induced exacerbations and the development of asthma. Nasal polyposis and thick eosinophilic mucin are prevalent, and radiological and intraoperative findings show pansinus involvement (Figure 4). Serum eosinophilia is present, and histopathology can show tissue eosinophilia with evidence of activation. Patients may not be IgE-sensitised or exhibit multi-allergen sensitisation.⁷

In cases of NSAID-exacerbated respiratory disease (NERD) (also known as aspirin exacerbated respiratory disease [AERD]), Samter's triad (nasal polyposis, adult-onset asthma and aspirin insensitivity) may be evident. This is a non-IgE (nonallergic) hypersensitivity reaction to NSAIDs due to COX-1 inhibition in patients with abnormal arachidonic acid metabolism and elevated levels of cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄). NERD is the most severe phenotype of primary eCRS and typically advances from the upper airway (rhinitis, CRS and nasal polyps) to the lower airway (asthma) and NSAID-insensitivity over a period of two to five years. Acute asthma attacks usually occur within three hours after taking NSAIDs, along with severe rhinorrhoea, conjunctival injection, facial flushing, periorbital oedema and abdominal pain.^{1,8}

Noneosinophilic CRS

Disease onset is often later in life (50 years of age and onwards) with a predilection for women and those with obesity. Both CRS and bronchial disease is poorly responsive to corticosteroids and nasal polyps are less prominent. Radiologically, pansinusitis is present and indistinguishable from eCRS. Neutrophils, not eosinophils, may be the dominant tissue cell type and there is no evidence of allergen sensitisation on serum or skin prick testing.⁷ Patients may respond well to long-term (>12 weeks) courses of macrolide therapy.

Allergic fungal rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is the result of an IgE-mediated hypersensitivity reaction to extramucosal (noninvasive) fungus. It is most common in younger (20 to 40 years of age), immunocompetent, atopic patients (>50% have allergic rhinitis or asthma). Fungi are typically of the Dematiaceae family (e.g. *Alternaria*, *Bipolaris*, *Curvularia*) but *Aspergillus* may also be causative. Disease may be unilateral or bilateral, with gradual progression and extension to extra-sinonasal compartments (e.g. intracranial, infratemporal fossa, orbit). The disease process is expansive rather than infiltrative and, as such, soft tissue barriers, such as the dura mater and periorbita, are usually preserved. Facial asymmetry (e.g. proptosis, telecanthus) may be present. Serum total IgE and fungal-specific IgE and IgG levels are grossly elevated. CT shows bony erosion, thinning and expansive disease with double density opacification (Figure 5). MRI reveals signal void within the sinuses corresponding to the regions of fungus.⁹

Abbreviations: COX-1 = cyclo-oxygenase; CRS = chronic rhinosinusitis; Ig = immunoglobulin.



Figure 3. Relative maxillary and ethmoid sinus sparing with aeration (black) in a patient with central compartment atopic disease.

Abbreviations: B = brain; E = ethmoid sinus; M = maxillary sinus; O = orbit.

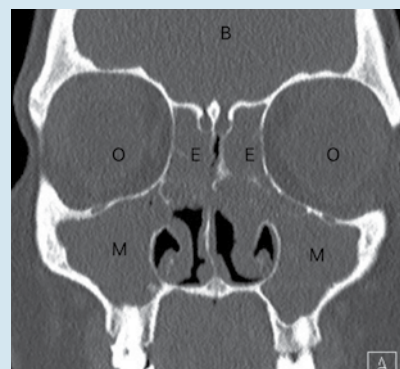


Figure 4. Pan-sinusitis (grey opacification) of maxillary and anterior ethmoid sinuses in a patient with eosinophilic CRS who has had previous surgery.

Abbreviations: B = brain; E = ethmoid sinus; M = maxillary sinus; O = orbit.

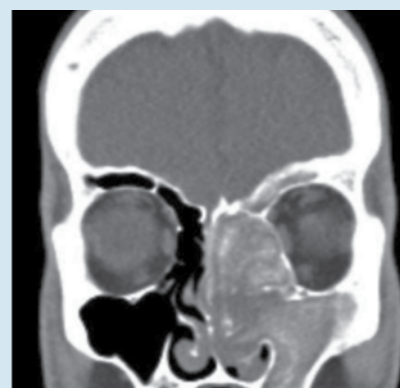


Figure 5. Unilateral (left) allergic fungal rhinosinusitis with double density (white amongst grey opacification) throughout the sinuses and expansion into the left orbit.

(T2-hyperintense), neoplasms (T1 with contrast enhancement) and fungus (T1 and T2 signal void) can be clearly distinguished, and disease extension into surrounding regions (e.g. intracranial, intraorbital, infratemporal fossa) mapped. The principal limitations of MRI are availability, cost and lack of clear bony anatomy for surgical planning. For both CT and MRI, current imaging technology permits submillimetre image slicing that can be merged with real-time patient landmarks to allow use of intraoperative navigation systems that assist with localisation for difficult cases. This has been demonstrated to reduce major and total complications.¹⁹

Sinus x-rays no longer have a primary role in sinonasal disease, as multidetector and cone beam CT reduce radiation exposure by shortening scan time and using postprocessing techniques to preserve image quality and anatomical accuracy.

Nasal function assessment

Peak nasal inspiratory flow and rhinomanometry can be used to quantitatively assess nasal obstruction (pre- and post-treatment). The University of Pennsylvania Smell Identification Test (UPSIT) and European Sniffin' Sticks can be used for assessment of hyposmia/anosmia.

Other tests

Routine preoperative haematology and biochemistry are often performed to exclude undiagnosed thrombocytopenia, coagulopathy or other abnormalities that may impact on general anaesthesia or surgery. Serum total and specific IgE can help elicit an underlying allergic process, but skin prick testing is preferred. Further serological testing (e.g. autoimmune and vasculitic screen, genetic testing for CF) is directed by clinical suspicion of a possible underlying aetiology for CRS.

Differential diagnosis

The clinical presentation of CRS can overlap with a variety of other sinonasal and neurological disorders. Facial pain as a primary presentation in the absence of

other rhinological symptoms is rarely due to CRS. In a prospective study where CT scans were performed acutely in patients presenting with suspected recurrent acute rhinosinusitis, only one patient (of 48) had findings consistent with sinusitis whereas the remainder had rhinitis (47%), headache/migraine (37%) or facial pain otherwise undefined (12.5%).¹² A careful history of symptoms and symptom duration, the presence of red flag features, findings on nasendoscopy and imaging can assist in differentiating CRS from other conditions such as rhinitis (viral, postviral, bacterial, allergic) sinonasal neoplasms, migraine, headache, trigeminal neuralgia, temporomandibular joint disorder dysfunction and midsegment facial pain.

Management

Management of CRS entails complementary medical and surgical interventions to suppress the sinonasal inflammatory burden, minimise symptoms and maximise quality of life. Corticosteroids are fundamental to achieving these goals, and surgery offers a means for topical administration to achieve disease control and avoid systemic exposure. Nasal saline irrigations, antibiotics and management of comorbidities (e.g. allergy, GORD, autoimmune/vasculitis) supplement overall care.

Intranasal corticosteroids

High-quality evidence supports the long-term efficacy and safety of intranasal corticosteroids (INCS).¹ Superiority of one type over another (e.g. mometasone, budesonide, fluticasone, beclomethasone) has not been demonstrated; however, higher doses may be associated with an increased risk of epistaxis.²⁰ Symptom reduction is greatest in patients with nasal polyps by reducing polyp size and preventing recurrence. Delivery of INCS through a nasal irrigation medium has been shown to improve sinonasal penetration and symptom and disease control in postoperative patients compared with simple spray devices.²¹ High-volume, high-pressure delivery achieves the desired anti-inflammatory effects with almost

3. RED FLAG SYMPTOMS

Red flag symptoms and signs that may indicate a disease complication or an alternative diagnosis must be elicited in all patients with a sinonasal presentation. These include:

- unilateral symptoms (particularly if progressive)
- epistaxis and blood-stained secretions or phlegm
- ocular symptoms and signs (e.g. visual disturbance, ophthalmoplegia, orbital oedema, globe displacement/proptosis, epiphora)
- facial and dental/gingival paraesthesia or anaesthesia
- facial asymmetry
- frontal swelling
- neurological signs
- signs of meningitis
- cervical lymphadenopathy

negligible systemic absorption.

Concerns about the impact of prolonged INCS use have been quashed, with no significant effects on the hypothalamic-pituitary axis, cortisol levels, childhood growth rate, bone mineral density, intraocular pressures, lens opacification or local mucosal atrophy demonstrated in multiple studies.²²⁻²⁴ Common local adverse effects occur in 5 to 10% of patients and include epistaxis, throat irritation, nasal dryness, and burning and stinging sensations. Except for epistaxis, the incidence of such side effects is similar to placebo, and they are mild in severity, usually resolving without discontinuation of treatment.²⁵

Systemic corticosteroids

Systemic corticosteroids, with or without local corticosteroid treatment, significantly reduce symptoms and nasal polyps.¹ Dosage and duration have not been standardised but most studies report courses of two to three weeks, with or without tapering regimens.^{26,27} One to two courses of systemic corticosteroids per year can be a useful adjunct to regular INCS treatment; however, if more frequent courses are required,

surgery should be considered. Adverse effects include hypothalamic–pituitary–adrenal axis inhibition, hyperglycaemia and diabetes, osteoporosis, avascular necrosis of the femoral head, gastrointestinal disturbance and peptic ulceration, cataract formation, glaucoma, infection, hypertension, acute myocardial infection, neuropsychiatric effects and cushingoid features. Fortunately, besides minor sleep disturbance and gastrointestinal upset, most of these side effects are extremely rare and have not been demonstrated with infrequent, short courses. Nonetheless, all patients prescribed systemic corticosteroids must be counselled about the possible adverse effects, especially those with vulnerable comorbidities (e.g. diabetes, psychiatric disorders, peptic ulcer disease).²⁶

Antibiotics

The role of antibiotics in CRS is unclear and, when used, it is chiefly for their immunomodulatory, not antimicrobial, activity. The most commonly used antibiotics for CRS are doxycycline and macrolides (e.g. clarithromycin, roxithromycin, azithromycin).

Doxycycline is a tetracycline antibiotic most effective in CRS with a type 2 inflammatory endotype. Anti-inflammatory effects are exerted by inhibiting the activity of matrix metalloproteinases, suppressing proinflammatory cytokines (e.g. tumor necrosis factor [TNF]- α , interleukin [IL]-1b, and IL-6) and decreasing eosinophil and neutrophil activity in CRS with nasal polyposis.²⁸ Benefit has been shown with short (<3 weeks) and long (12 weeks) courses of doxycycline, typically administered at a 100 mg daily dose. Common side effects include gastrointestinal upset (e.g. nausea, vomiting, abdominal pain, diarrhoea) and skin reactions (e.g. rash, pruritis, photosensitivity), particularly the increased susceptibility to sunburn.²⁸ Enamel hypoplasia and teeth discolouration has been a historic concern; however, due to the reduced calcium binding of doxycycline compared with other tetracyclines, this risk is extremely low, and up to a 21-day course of doxycycline in children of any age is

supported by the American Academy of Paediatrics.²⁹

Macrolides have antineutrophilic and anti-inflammatory (TNF- α , IL-8) properties, with greatest benefit demonstrated in Th1-mediated noneosinophilic CRS (nontype 2 CRS).^{1,30} Dose appears to be less significant than duration of treatment, and a minimum 12-week course is recommended to determine response.²⁸ Before initiation, a thorough cardiac history and baseline ECG are recommended as macrolides can cause a prolonged QT interval and lead to the torsades de pointes arrhythmia.

Nasal saline irrigation

Nasal irrigation with isotonic saline or Ringer's lactate is effective in patients with CRS. Irrigation can provide symptomatic relief and serve as a medium for delivery of INCS. The addition of baby shampoo, honey or dexpanthenol, as well as high temperatures and high salt concentrations, have not been shown to confer an additional benefit.¹ Head position during irrigation can impact on saline distribution, with head positioned down providing improved penetration of the frontal sinuses.³¹

Other medical therapies

Immunotherapy is a primary treatment for patients with CCAD and can be initiated pre- or postoperatively to achieve durable symptom relief. Postoperative aspirin desensitisation can be considered in cases of NERD to reduce symptoms in those who need revision functional endoscopic sinus surgery (FESS), in those who require systemic corticosteroids and to improve asthma and respiratory control. For CRS alone, antihistamines, decongestants, antifungals and proton pump inhibitors have not been shown to have significant benefit and are not recommended.¹ However, benefit may be seen on a case-by-case basis depending on comorbidities.

Surgery

The endoscope has revolutionised modern surgical management of acute and chronic, benign and malignant sinonasal disease.

Straight and angled endoscopes and instruments permit reach into previously difficult-to-access regions, with clear delineation of anatomy and disease, and minimal intra- and postoperative morbidity. Intraoperative surgical navigation has further improved safety and fostered surgical innovation to address intracranial and intraorbital disease via an endonasal endoscopic approach.

The term functional endoscopic sinus surgery was coined to reflect operative objectives of disease eradication and creation of a functional sinonasal cavity that incorporated the natural sinus ostia, allowed adequate sinus ventilation, facilitated mucociliary clearance and enabled instillation of topical therapies. In this regard, FESS involves removal of the bony sinus partitions that obscure the natural, narrow (<2 to 3 mm) sinus drainage pathways, to create wide openings to achieve the aforementioned objectives. The extent of surgery is tailored to the patient's anatomy and distribution and severity of disease. Complications include postoperative bleeding, infection, scarring and disease recurrence that may necessitate revision surgery. Major complications are extremely rare (<1%) but include skull base breach and cerebrospinal fluid leak, nasolacrimal and orbital injury, anosmia and major vessel bleeding (carotid artery).

Underlying septal deformities and turbinate hypertrophy are often addressed concurrently with FESS to provide an unobstructed nasal passage for breathing and delivery of topical medications.

Biological therapy

Since 2019, biological therapy has entered the CRS management paradigm for select patients with refractory disease despite maximal medical and surgical therapy (Box 4). Biological therapy has shown efficacy in reducing nasal symptoms (congestion, rhinorrhoea, hyposmia, post-nasal drip) and polyp scores. Predicated on our understanding of the united airway and their established role in severe asthma, the following monoclonal antibodies target

factors driving the type 2 inflammatory pathway:

- dupilumab (IL-4/IL-13)
- mepolizumab (IL-5)
- reslizumab (IL-5)
- benralizumab (IL-5 receptor)
- omalizumab (IgE).

However, cost effectiveness remains a concern. Although dupilumab, mepolizumab and omalizumab are TGA approved for CRS, they are not PBS listed and, as such, patients can expect to incur costs exceeding \$1500 per month for treatment.

Refractory CRS

Despite optimal medical and surgical management, some patients may continue to experience significant symptoms of CRS and demonstrate nasal polyp recurrence. In such cases, factors to consider include:

- patient compliance with postoperative and maintenance management
- smoking and recreational drug use
- occupational chemical exposure
- alternative diagnoses (e.g. odontogenic sinusitis, AFRS, granulomatous and autoimmune conditions, CF, PCD, NERD, Samter's triad)
- exacerbating comorbidities (e.g. allergic rhinitis, asthma, laryngopharyngeal reflux)
- surgical factors, such as unaddressed sinuses, missed natural sinus ostia (predisposing to a recirculation phenomenon), scarring and cicatrization, middle turbinate lateralisation, and sumping and mucostasis.

Repeat CT imaging and a more exhaustive panel of investigations, including skin prick allergy testing, an autoimmune and vasculitic screen and histopathological assessment for CRS endotype, ciliary abnormalities and granulomatous conditions, can be considered. Systemic corticosteroids and a prolonged course of doxycycline or macrolide antibiotics can be trialled as a means of medical salvage. Multidisciplinary input from an immunologist and/or a respiratory physician for immunotherapy, aspirin or fungal desensitisation, biological

agents and management of lower airway disease if present may be required. If unsuccessful, revision surgery with more extensive FESS, including medial maxillectomy and modified endoscopic Lothrop procedures, could be considered.

Paediatric CRS

The definition of paediatric CRS differs slightly from adults in that cough replaces hyposmia or anosmia as a cardinal symptom.¹ Prevalence is estimated to be 2% and is reported to have a greater impact on QoL than asthma and juvenile arthritis.³² The aetiology is multifactorial and includes immune function immaturity; viral, bacterial and fungal infection; allergy; adenoiditis; environmental factors (e.g. cigarette smoke exposure, daycare attendance); and systemic disorders (e.g. CF, PCD).

Clinical features include nasal obstruction or congestion, anterior and posterior rhinorrhoea, cough, facial pain or pressure, hyposmia or anosmia, fever, irritability, headaches, halitosis, fatigue, dental pain, ear pain/pressure/fullness and nasal polyps. Paediatric-specific differential diagnoses include adenoiditis, intranasal foreign body, choanal atresia or stenosis, CF and PCD. Initial investigations include allergy testing and swabs of nasal discharge for culture-directed antibiotic therapy. Plain x-rays have a limited role; however, lateral views can assess adenoid size. CT (or MRI) is reserved for patients who do not respond to treatment or if surgery is considered. Additional investigations include genetic and sweat testing for CF and haematology for immunodeficiency. Given the rarity of nasal polyps in children, all presenting with such should undergo investigation for CF. The diagnosis of PCD requires mucosal biopsy.

First-line management with nasal saline irrigation and INCS is recommended. In the absence of acute bacterial suprainfection, there is no robust evidence to support the use of short- or long-term topical, oral or intravenous antibiotics. However, small retrospective series have reported success with long-term (four weeks or greater) culture-directed intravenous antibiotics

4. INDICATIONS FOR BIOLOGICAL THERAPY IN CRS WITH NASAL POLYPS¹

Presence of bilateral polyps in a patient who has had functional endoscopic sinus surgery* plus the presence of three of the following criteria:

- evidence of type 2 inflammation (tissue eosinophil ≥ 10 /hpf or blood eosinophil ≥ 250 mc/L or total IgE ≥ 100 IU/mL)
- need for systemic corticosteroids (two or more courses per year or long term [>3 months] low-dose steroids) or contraindication to systemic steroids
- significantly impaired quality of life (SNOT-22 total score ≥ 40)
- significant loss of smell (anosmic on smell test)
- diagnosis of comorbid asthma requiring regular inhaled corticosteroids

Abbreviations: CRS = chronic rhinosinusitis; hpf = high power field (x400); Ig = immunoglobulin; SNOT-22 = sino-nasal outcome test-22.

* Exceptional circumstances excluded (e.g. not fit for surgery).

following surgery.¹ Treatment with systemic corticosteroids tapered over 30 days and combined with amoxicillin and clavulanate was shown to be beneficial in improving symptoms, CT scores and relapse rates compared with amoxicillin and clavulanate treatment alone.³³ Antihistamines, decongestants and antileukotrienes are not recommended.³⁴

Adenoidectomy is typically the first surgical intervention and provides symptom resolution in about 50% of cases.¹ Research has shown adenoids (of any size) to harbour pathogenic bacteria, with biofilm formation present in over 80% of paediatric patients with CRS. Maxillary sinus (antral) lavage can be performed concurrently to obtain specimens to guide antibiotics and is recommended in children with comorbid asthma who have more severe disease on preoperative CT.¹ There is a high-rate concordance of cultures obtained from the adenoids, middle meati and maxillary sinus. FESS can be performed as the primary surgical intervention, or after adenoidectomy, with symptom reduction, minimal

5. PRACTICE POINTS FOR GPs FOR MANAGING CHRONIC RHINOSINUSITIS

- Chronic rhinosinusitis (CRS) is characterised by symptoms of nasal obstruction or congestion, anterior and posterior nasal discharge, facial pain or pressure, and hyposmia or anosmia for 12 weeks or more. Endoscopy may demonstrate nasal polyps, mucopurulent discharge or mucosal oedema with equivalent changes identified on CT. The presence of any red flag features warrants immediate specialist referral.
- CRS is classified as primary or secondary, and further categorised based on the underlying inflammatory endotype (type 2 or nontype 2 inflammation). This delineates different phenotypes of disease that have differing presentations, histopathological findings, treatment strategies and prognoses.
- There is significant symptom overlap with rhinitis disorders. Facial pain in isolation is rarely of sinus origin and a headache or migraine disorder should be considered. Allergy should be investigated with measurement of serum specific IgE levels or skin prick testing and a noncontrast CT of the paranasal sinuses obtained as the first imaging modality and before specialist referral.
- Inhaled nasal corticosteroids and nasal saline irrigation are appropriate first-line treatment that can be initiated by the GP. Short courses (2 to 3 weeks) of oral corticosteroids can be used if nonresponsive or during exacerbations. Directed by clinical findings, investigation and management of contributory comorbidities and underlying systemic disorders should be performed on a case-by-case basis.
- Functional endoscopic sinus surgery aims to create a sinonasal cavity in which the mucosal inflammatory load can be controlled with topical corticosteroids alone, minimising a patient's exposure to systemic corticosteroids.
- Biological therapy is available to assist patients with severe eosinophilic (type 2) CRS refractory to conventional medical and surgical intervention.
- All children with CRS and nasal polyps should be investigated for cystic fibrosis and primary ciliary dyskinesia. Adenoidectomy, antral lavage and balloon sinuplasty are alternative surgical interventions to endoscopic sinus surgery in children.

morbidity and no clinically significant impact on facial growth seen in almost 90% of patients.³⁵ Balloon sinuplasty may have a role in paediatric CRS treatment, by providing greater intraoperative access than antral lavage with less postoperative care required than FESS due to increased tissue preservation.³⁶

Role of the GP

GPs have an important role in the management of adult and paediatric patients with CRS (Box 5). Through history taking, examination and appropriate investigations, an accurate provisional diagnosis can be made and CRS differentiated from conditions with overlapping symptoms. Medical management in the form of saline irrigation, INCS and short courses of oral corticosteroids can be initiated, and education provided on the natural history of CRS and compliance with therapy. Low (or ultra low) dose, noncontrast CT of the paranasal

sinuses is a noninvasive investigation with minimal radiation exposure that can assist with diagnosis and should be performed before referral. Specialist referral is recommended if symptoms persist or recur, or red flag features are evident on presentation, so that a correct diagnosis can be established and a treatment plan formulated.

Conclusion

CRS is a heterogeneous disorder that can develop in patients of all ages. Endotyping and phenotyping enables appropriate patient counselling regarding their disease and implementation of tailored, stepwise, medical and surgical interventions to alleviate symptoms and improve QoL. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: None.

Chronic rhinosinusitis

Alleviating symptoms and improving quality of life

DAKSHIKA A. GUNARATNE BMed, MS, MPH, FRACS; **YURESH S. NAIDOO** BE(Hons), MB BS, FRACS, PhD

References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020; 58(Suppl S29): 1-464.
2. Sedaghat AR, Kuan EC, Scadding GK. Epidemiology of chronic rhinosinusitis: prevalence and risk factors. *J Allergy Clin Immunol Pract* 2022; S2213-2198(22)00032-0.
3. Habib AR, Campbell R, Kalish L, et al. The burden of chronic upper airway disorders in Australia: a population-based cross-sectional study. *Aust J Otolaryngol* 2019; 2: 28.
4. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg* 1995; 113: 104-109.
5. Lourijesen ES, Fokkens WJ, Reitsma S. Direct and indirect costs of adult patients with chronic rhinosinusitis with nasal polyps. *Rhinology* 2020; 58: 213-217.
6. Hamizan AW, Loftus PA, Alvarado R, et al. Allergic phenotype of chronic rhinosinusitis based on radiologic pattern of disease. *Laryngoscope* 2018; 128: 2015-2021.
7. Grayson JW, Cavada M, Harvey RJ. Clinically relevant phenotypes in chronic rhinosinusitis. *J Otolaryngol Head Neck Surg* 2019; 48: 23.
8. Kim SD, Cho KS. Samter's triad: state of the art. *Clin Exp Otorhinolaryngol* 2018; 11: 71-80.
9. Ryan MW. Allergic fungal rhinosinusitis. *Otolaryngol Clin N Am* 2011; 44: 697-710.
10. Hsu J, Avila PC, Kern RC, et al. Genetics of chronic rhinosinusitis: state of the field and directions forward. *J Allergy Clin Immunol* 2013; 131: 977-993. e1-993.
11. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003; 111: 1171-1183.
12. Denburg JA, Sehmi R, Saito H, et al. Systemic aspects of allergic disease: bone marrow responses. *J Allergy Clin Immunol* 2000; 106 (5 Suppl): S242-S246.
13. Braunstahl GJ, Kleinjan A, Overbeek SE, et al. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000; 161: 2051-2057.
14. Braunstahl GJ, Overbeek SE, Fokkens WJ, et al. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med* 2001; 164: 858-865.
15. Udem BJ, McAlexander M, Hunter DD. Neurobiology of the upper and lower airways. *Allergy* 1999; 54 Suppl 57: 81-93.
16. Barham HP, Zhang AS, Christensen JM, Sacks R, Harvey RJ. Acute radiology rarely confirms sinus disease in suspected recurrent acute rhinosinusitis. *Int Forum Allergy Rhinol* 2017; 7: 726-733.
17. Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. *Rhinology* 2016; 54: 129-133.
18. Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology* 1993; 31:183-184.
19. Dalgorf DM, Sacks R, Wormald PJ, et al. Image-guided surgery influences perioperative morbidity from endoscopic sinus surgery: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2013; 149: 17-29.
20. Choong LY, Head K, Hopkins C, et al. Different types of intranasal steroids for chronic rhinosinusitis. *Cochrane Database Syst Rev* 2016; 4(4): CD011993.
21. Harvey RJ, Snidvongs K, Kalish LH, Oakley GM, Sacks R. Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery. *Int Forum Allergy Rhinol* 2018; 8: 461-470.
22. Oakley GM, Harvey RJ. Topical steroids. In BA Woodworth, DM Poetker, DD Reh (Eds): *Rhinosinusitis with nasal polyposis*. *Adv Otorhinolaryngol*. Basel, Karger, 2016, vol 79, pp 121-130.
23. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012; 50: 1-12.
24. Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. *J Investig Allergol Clin Immunol* 2012; 22: 1-12.
25. Verkerk MM, Bhatia D, Rimmer J, et al. Intranasal steroids and the myth of mucosal atrophy: a systematic review of original histological assessments. *Am J Rhinol Allergy* 2015; 29: 3-18.
26. Hox V, Lourijesen E, Jordens A, et al. Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. *Clin Transl Allergy* 2020; 10: 1.
27. Mansi A, Bui R, Chaaban MR. Oral Corticosteroid regimens in the management of chronic rhinosinusitis. *Ear Nose Throat J* 2022; 101: 123-130.
28. Lees KA, Oriandi RR, Oakley G, Alt JA. The role of macrolides and doxycycline in chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2017; 157: 1048-1052.
29. Stultz JS, Eiland LS. Doxycycline and tooth discoloration in children: changing of recommendations based on evidence of safety. *Ann Pharmacother* 2019; 53: 11621166.
30. Oakley GM, Harvey RJ, Lund VJ. The role of macrolides in chronic rhinosinusitis (CRSsNP and CRSwNP). *Curr Allergy Asthma Rep* 2017; 17: 30.
31. Barham HP, Ramakrishnan VR, Knisely A, et al. Frontal sinus surgery and sinus distribution of nasal irrigation. *Int Forum Allergy Rhinol* 2016; 6: 238-242.
32. Gilani S, Shin JJ. The Burden and visit prevalence of pediatric chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2017; 157: 1048-1052.
33. Ozturk F, Bakirtas A, Ileri F, Turktaş I. Efficacy and tolerability of systemic methylprednisolone in children and adolescents with chronic rhinosinusitis: a double-blind, placebo-controlled randomized trial. *J Allergy Clin Immunol* 2011; 128: 348-352.
34. Shaikh N, Wald ER, Pi M. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. *Cochrane Database Syst Rev* 2012; (9): CD007909.
35. Hebert RL, 2nd, Bent JP, 3rd. Meta-analysis of outcomes of pediatric functional endoscopic sinus surgery. *Laryngoscope* 1998; 108: 796-799.
36. Ramadan HH, Terrell AM. Balloon catheter sinuplasty and adenoidectomy in children with chronic rhinosinusitis. *Ann Otol Rhinol Laryngol* 2010; 119: 578-582.