

Chronic rhinosinusitis

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Chronic rhinosinusitis (CRS) has a substantial effect on the patient's quality of life. It has recently been accepted that CRS has multiple distinct components, e.g. infection and inflammation, which has led to changes in the therapeutic approach. In addition, it is no longer considered practical to manage CRS as a prolonged version of acute rhinosinusitis. A CRS diagnosis is based on the type and duration of symptoms, together with an objective finding of inflammation of the nasal mucosa or paranasal sinuses. Differences in treatment are based on the presence or absence of nasal polyps.

Keywords: chronic rhinosinusitis, nasal polyps, inflammation, nasal mucosa, paranasal sinuses

Introduction

Chronic sinusitis is currently recognised as an inflammatory disease of the upper airways, associated with a multifactorial aetiology.¹ Although chronic rhinosinusitis (CRS), with and without nasal polyposis (NP), falls under the umbrella term of chronic rhinosinusitis, these separate disease entities are likely to have different pathogeneses, and can be distinguished individually by their unique inflammatory characteristics.² In addition to common presenting symptoms, CRS is associated with a reduction in the patient's quality of life, daily productivity and quality of sleep.¹

Definition

CRS can be defined as a complex inflammatory condition which persists for 12 weeks or longer, and can be subdivided into CRS, either with or without NP or allergic fungal rhinosinusitis.¹⁻⁴ It involves the lining of the nasal passages, as well as the paranasal sinuses.³⁻⁵

Diagnosis

Besides documented inflammation of the paranasal sinuses or nasal mucosa, the presence of at least two of the important clinical symptoms listed in Table I (one of the two symptoms must be either obstruction or discharge) lasting for 12 weeks or longer¹⁻⁴ is required in order for a diagnosis of CRS to be made. Other symptoms may include fatigue, headaches, ear pain or fullness, toothache and difficulty sleeping.¹

A diagnosis of CRS must be confirmed by at least one of the following objective findings:

- *Nasal endoscopy*:⁶ The presence of nasal polyps.¹
- *Computed tomography (CT)*:^{5,6} Demonstrating inflammation in the paranasal sinuses.¹
- Purulence or oedema within the middle meatus.¹

Table I: Important clinical features of chronic rhinosinusitis

- Pain and pressure or fullness (facial)^{1,2,4,6}
- Obstruction or blockage (nasal)^{1,2,4,6}
- Anterior or posterior purulent nasal drainage^{1,2,4,6}
- Anosmia or hyposmia⁶ (reduced smell)^{1,2,4}

In general, bacterial culture from patients with CRS is unnecessary.^{3,6} Nasal swabs are not representative of the sinus contents. Thus, they are not useful when making a decision about antibiotic treatment.⁴ However, endoscopic culture of the middle meatus may be recommended in situations of serious complications, e.g. intracranial extension and orbital infection, or for patients with nosocomial sinusitis.^{5,6} Invasive fungal sinusitis should be considered in immunocompromised patients.⁶

Contributing factors to the development of chronic rhinosinusitis

The following factors may contribute to the development of CRS: asthma, allergic and non-allergic rhinitis, immune and ciliary dysfunction, cystic fibrosis, lost ostia patency, defective mucociliary clearance, exacerbated respiratory disease relating to acetylsalicylic acid, and structural abnormalities and/or immunodeficiency.^{4,6}

Indications for referral

Indications for referral include the following:

- The presence of a persistent crust, i.e. in conditions such as Wegener granulomatosis; irregular surfaces; diffuse haemorrhagic areas; and vascular malformations of ectasias and bleeding from minor trauma on physical examination. All of these should raise red flags.⁶
- The presence of "red flag" symptoms, such as unilateral symptoms, blockage, bleeding or bloodstained discharge, proptosis, diplopia, cacosmia, epiphora and neurological symptoms.²

- Patients with refractory CRS or those who did not respond to treatment may be referred for an alternative diagnosis.^{6,7}
- When mucous recirculation syndrome is suspected.⁷
- Patients with allergic fungal rhinosinusitis.⁴

Surgery

Surgery should not be the first intervention⁴ in most cases of CRS, with the possible exception of allergic fungal rhinosinusitis (AFRS). A trial of medical treatment should be provided to patients with large polyps before surgery, except when the nature of the polyps is in doubt.⁷

Pharmacological treatment options

Suggested adult dosages have been included in this article in instances where pharmacological treatment options are provided. Reference should be made to the package inserts for additional prescribing and safety information.

Before initiating CRS treatment, contributing factors need to be identified and treated.⁶ CRS cannot be “cured” in most people, and the intention of therapy is to reduce the signs and symptoms, and to improve patients’ quality of life.^{4,6,7} Because CRS responds incompletely to treatment, it may be necessary to continue with long-term treatment.⁷ The objectives of treatment are to:

- Reduce complications:⁶ Minimise or control mucosal oedema and inflammation;^{3,4,6} and control infection, if present.^{3,4,6}
- Maintain adequate sinus drainage and ventilation.^{3,4}
- Reduce the number of acute exacerbations.⁴
- Prevent disease progression or recurrence.⁷

Nasal saline

Saline nasal irrigation reduces postnasal drainage, removes secretions, rinses away allergens and irritants, and assists in restoring normal mucociliary clearance.^{1,4} If obvious mucus or crusting is present, a saline spray or irrigation can be used immediately prior to the administration of other intranasal medications.⁴ Although nasal saline is an effective adjunctive treatment for CRS, it was indicated in studies to be less effective than topical glucocorticoids as monotherapy.^{1,4}

Saline irrigation with a high volume (> 100 ml) is more effective than a saline nasal spray.^{1,4} Depending on the severity of symptoms, nasal irrigation may be performed as needed; daily or multiple times per day.^{1,4}

Place in therapy

Nasal saline should be used as adjunctive to intranasal corticosteroids in patients with and without nasal polyps.^{1,4}

Intranasal corticosteroids

Intranasal corticosteroids (INCS) are the cornerstone of maintenance treatment, and are helpful in all types of CRS.^{2,4} INCS suppress inflammation at multiple points in the inflammatory cascade, decrease vascular permeability and

reduce glycoprotein release from the submucosal glands, i.e. thin mucus.^{1,7}

INCS can be administered either as a nasal spray or as a solution for instillation. Treatment is usually initiated using a nasal spray.⁴ Table II contains information on which type of product to use, and Tables III and IV contain a list of INCS products.

Place in therapy

INCS is recommended for:

- Chronic sinusitis, with and without nasal polyposis.¹
- *CRS with nasal polyps (CRSwNP)*: INCS reduces the size of nasal polyps, improves nasal symptoms,^{4,6} and may delay the re-growth of nasal polyps.^{4,7} INCS are the mainstay of maintenance treatment⁴ following the surgical removal of polyps.
- *CRS without nasal polyps (CRSsNP)*: INCS are recommended for their anti-inflammatory properties and because long-term adverse effects have not been reported.⁶

Table II: Choosing an intranasal corticosteroid product

Drops	Initiate treatment with INCS drops ⁷ in patients with nasal polyposis, and in those with severe obstruction
Sprays	Nasal sprays with once-daily dosing are convenient, and can help optimise patient compliance ⁴
Instillation	Instillation is recommended in patients who have persistent symptoms, despite consistent use of INCS ⁴ Can reach the middle meatus, where polyps often form ⁴

INCS: intranasal corticosteroids

Table III: A list of intranasal corticosteroid nasal sprays¹

Intranasal corticosteroid nasal sprays	Dosage per spray	Sprays per nostril	Frequency per day
Mometasone furoate	50 µg	1	Twice
Beclomethasone dipropionate monohydrate	42 µg	1	Twice
Fluticasone propionate	50 µg	2	Once
Fluticasone furoate	50 µg	2	Once
Budesonide	32 µg	1-4	Once
Ciclesonide	50 µg	2	Once
Flunisolide	Not listed	2	Twice
Triamcinolone acetonide	55 µg	2	Once

Table IV: Other intranasal corticosteroid products

Other intranasal corticosteroid products	Strength	Frequency per nostril
Prednisolone nasal drops	1% solution	2-4 drops, once or twice daily
Budesonide nebulising solution	Mix budesonide nebulising solution into a high-volume saline irrigation, using either: <ul style="list-style-type: none"> • 0.5 mg (2.0 ml of 0.25 mg/ml), or • 1.0 mg (2.0 ml of 0.50 mg/ml) 	Rinse the nasal cavities (both), once or twice daily

Table V: Place in therapy and suggested dosages of oral corticosteroids

Place in therapy	CRSsNP	Relieves severe and refractory mucosal oedema ⁴
	CRSwNP	Reduces the size of polyps ^{1,4}
	AFRS	Minimises mucosal inflammation ⁴
Suggested adult dosage	CRSwNP	Oral prednisone, 20 mg twice daily for 5 days, followed by 10 mg twice daily for 5 days, then 10 mg once daily for 5 days ⁴ <i>British guidelines:</i> ⁴ Prednisolone (0.5 mg/kg every morning for 5-10 days), and the instillation of betamethasone nasal drops ⁴
	As part of intensive medical management of CRSsNP	Oral prednisone, 20 mg twice daily for 5 days, followed by 20 mg daily for 5 days ⁴
	Severe polypoid disease, unresponsive to INCS therapy	A two-week course of prednisone may reduce the polyp size or grade, e.g. 30 mg/day for 4 days. Thereafter, reduce the dose by 5 mg every 2 days for 10 days ⁶ INCS is recommended to maintain this improvement ⁶
	After endoscopic sinus surgery	Systemic prednisone, e.g. 30 mg/day, given 5 days before and 9 days after, may provide benefit ⁶

AFRS: allergic fungal rhinosinusitis, INCS: intranasal corticosteroids, CRSsNP: chronic rhinosinusitis without nasal polyps, CRSwNP: chronic rhinosinusitis with nasal polyps

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Special considerations

Special consideration applies in certain circumstances. Some individuals may experience local nasal irritation, sore throat and epistaxis.⁷ Nasal sprays containing benzalkonium chloride may irritate the nose.⁷ If the risk of systemic absorption is high, i.e. with betamethasone and dexamethasone, short-term use only is recommended.⁷

Oral corticosteroids

Currently, there is no consensus regarding the dose and duration of treatment of oral corticosteroids for CRS^{1,4} (Table V). However, the lowest effective dose should always be used to reduce the risk of serious adverse events.⁶ Treatment options include prednisone or prednisolone (5.0-60.0 mg once daily), methylprednisolone (7.5-60.0 mg once daily), or dexamethasone (0.5-4.5 mg twice daily).¹

Place in therapy

Oral corticosteroids should be used as follows:

- As an intermittent short course (1-3 weeks) for symptomatic NP or the treatment of CRSsNP.¹
- Use briefly in combination with, or prior to, the application of INCS.^{2,7}
- Use for severe nasal obstruction,⁷ uncontrolled symptoms following conventional pharmacotherapy (as short-term rescue medication),⁷ and as part of medical polypectomy for nasal polyps.⁷

Medical polypectomy

A brief course of oral corticosteroids may be administered to patients with large polyps, nasal blockage or an impaired sense of smell.⁴

Oral corticosteroid therapy, i.e. prednisolone (0.5 mg/kg each morning for 5-10 days, is accompanied by instillations of betamethasone nasal drops⁴ (2 drops per nostril, 3 times a day for 5 days, then twice daily until the bottle runs out).⁷ Since

polyps tend to recur, fluticasone (drops or spray) or mometasone (spray) is recommended as maintenance therapy owing to their lower bioavailability. However, treatment efficacy varies in different patients.⁴ It should be noted that the initial use of betamethasone nasal drops only may be effective for smaller polyps.⁷

Antimicrobial agents

Oral antimicrobial agents

Compared to acute bacterial rhinosinusitis (ABRS), the bacteriology of CRS is different and not as well understood.^{5,8} The microbiology of rhinosinusitis in some patients with CRS may evolve through several phases.^{3,8} In addition, fungi may colonise the sinuses, and cause allergic fungal rhinosinusitis or invasive fungal sinusitis.³

Currently, there is only limited evidence that antibiotics are effective in the treatment of CRS. In addition, the duration of treatment has not been studied prospectively.³ The use of antibiotics may be considered in secondary care for the treatment of CRS.²

Initial antimicrobial treatment should be effective against the most likely bacterial aetiologies, including aerobic, anaerobic pathogens, methicillin-resistant *Staphylococcus aureus* (in case of risk of infection),³ as well as the most common encapsulated organisms associated with an ABRS, e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.⁵

CRSsNP is often associated with a bacterial infection.⁶ Whenever possible, the endoscopic culture of purulent mucus obtained from the middle meatus or another accessible sinus ostium should guide the choice of antibiotic treatment.⁴ However, if this is not possible, the choice of antimicrobial agent is made empirically.^{3,4} Empiric antibiotic treatment is not recommended in patients:

- Who have recently failed antibiotic treatment with a similar regimen.⁴

Table VI: Available antibiotic therapies¹

	Antibiotic therapy	Dosage (mg)	Daily frequency	Duration
Non-macrolide antibiotics	Amoxicillin or clavulanate	875	Twice	10-14 days
	Cefuroxime	250	Twice	10-14 days
	Cefaclor	250-500	Three	10-14 days
	Cefprozil	250-500	Twice	10-14 days
	Cefpodoxime	200	Twice	10-14 days
	Trimethoprim-sulphamethoxazole	160/800	Twice	10-14 days
	Levofloxacin	500	Once	10-14 days
	Moxifloxacin	400	Once	10 days
Macrolides	Clarithromycin	500	Short-course: Twice daily	14 days
			Long-term course: ^{**} Once daily	12 weeks
	Azithromycin	500	Once	3 days
	Erythromycin	250-800	Four times	10 days
	Roxithromycin	150	Short-course: Once daily	10 days
Long-term course: ^{**} Once daily			12 weeks	

* Long-term macrolide therapy is not recommended in patients with nasal polyps¹

** Potential adverse effects, as well as possible interactions with other medication, should be considered with prolonged macrolide therapy¹

Table VII: The duration of treatment of oral antibiotics

Short-term	Two weeks' treatment may be used for the acute exacerbation of rhinosinusitis ⁷ Non-macrolide treatment for < 3 weeks may be considered for CRSsNP when purulence is present ¹ Doxycycline may be considered for nasal polyposis ¹ Doxycycline 200 mg once, then 100 mg daily for 20 days, may be considered for CRSwNP ^{1,2,4}
Long-term (≥ 12 weeks)	Macrolides may be considered ^{1,2} for CRSsNP

CRSsNP: chronic rhinosinusitis without nasal polyps, CRSwNP: chronic rhinosinusitis with nasal polyps

- With a history of infection with Gram-negative or methicillin-resistant *S. aureus* or other highly drug-resistant bacteria.⁴
- Who are highly immunosuppressed, and therefore at risk of invasive fungal rhinosinusitis.⁴

If a patient was given an antibiotic in the past three months, a different class of antibiotic should be used.³

A second course of empiric intensive treatment may be initiated in patients for whom intensive medical treatment appeared to have helped, but did not result in a sufficient improvement in symptoms or the resolution of the CT findings. The second course may be initiated provided that there is no clear indication of surgical intervention, there are no signs or symptoms suggesting another condition, the patient does not appear to be severely ill, or prefers to continue with medical treatment in order to avoid surgery.⁴

Table VI contains a list of available antibiotic therapies, and Table VII information on short- and long-term antibiotic treatment.

Systemic and topical antifungal therapy does not appear to be effective in the treatment of CRS. Therefore, it should not be used as an empirical treatment.³

Topical antimicrobial agents

The routine use of topical antimicrobial agents is not recommended during the management of CRSsNP.¹ Depending on antimicrobial susceptibility, topical antimicrobial agents, such

as mupirocin, gentamicin or tobramycin, once or twice daily for four weeks, may be useful in patients who have undergone prior surgery.⁴

Topical aminoglycosides should be used for a defined treatment period and with caution. Owing to the potential risk of ototoxicity, the use of topical aminoglycosides is contraindicated in the sphenoidal region.⁴

Antileukotrienes

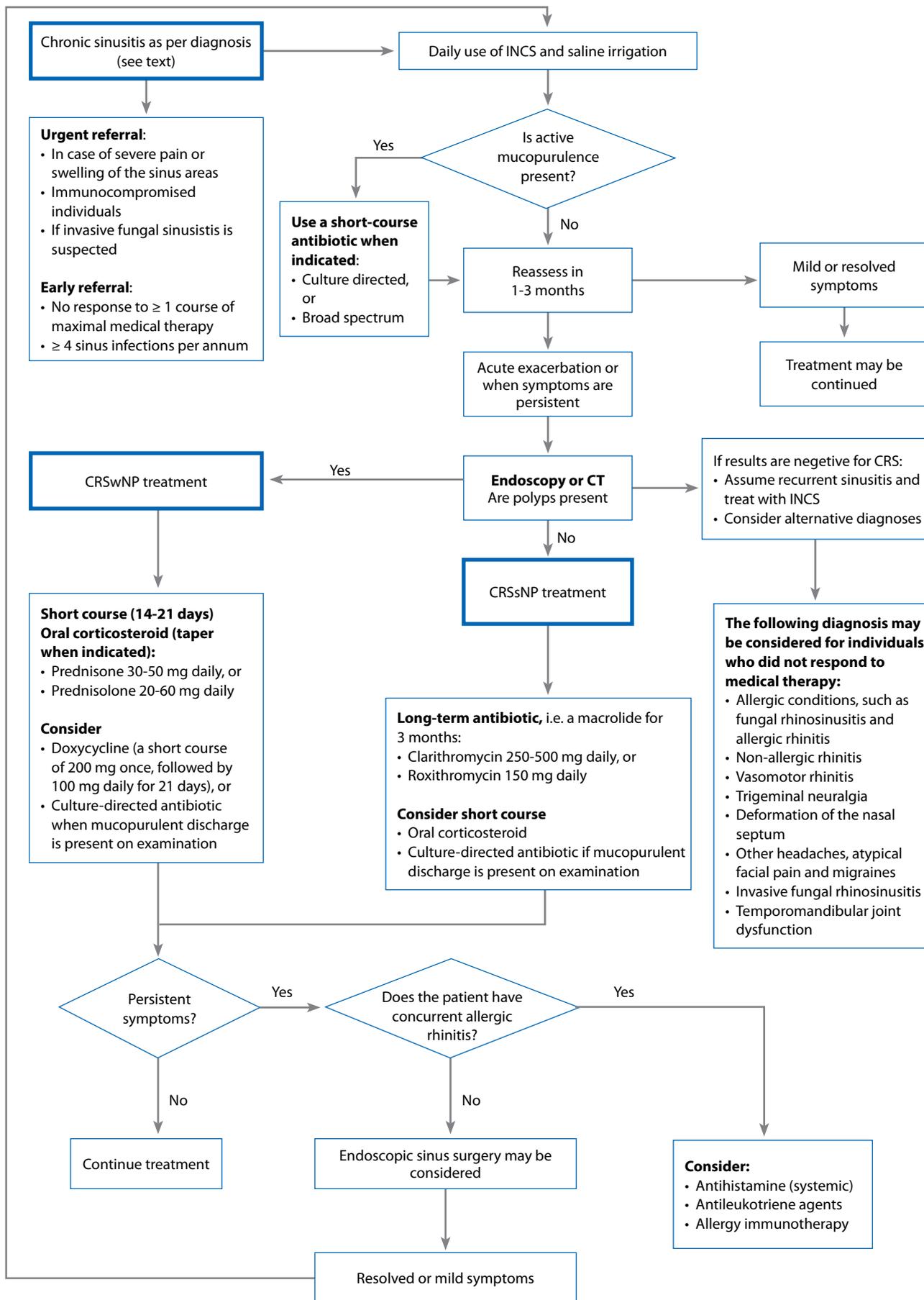
Antileukotrienes are generally less effective than the INCS, but some studies have reported additive effects.⁴ Treatment with antileukotrienes (Table VIII) may be more effective in those with concomitant asthma and aspirin intolerance.⁴

Table VIII: Treatment with antileukotrienes

Product	Dosage and treatment frequency
Montelukast	10 mg, once daily ¹
Zafirlukast	20 mg, twice daily ¹
Zileuton	600 mg, four times daily ¹

Place in therapy

Antileukotrienes may be considered in patients with aspirin-sensitive rhinosinusitis⁷ (acetylsalicylic acid sensitivity),⁶ asthma⁷ and nasal polyposis.^{1,7} They may be useful in patients with refractory postnasal drainage and nasal congestion.⁴



CRS: chronic rhinosinusitis, CRSsNP: chronic rhinosinusitis without nasal polyps, CRSwNP: chronic rhinosinusitis with nasal polyps, CT computed tomography, INCS: intranasal corticosteroids

Figure 1: Medical therapy for chronic rhinosinusitis

Antihistamines

Antihistamine treatment may be helpful in patients with CRS and concomitant allergic rhinitis.^{1,4} It is uncertain whether or not antihistamines provide any additional benefit in patients who are already using topical glucocorticoids. However, it may be worthwhile in patients who have persistent nasal symptoms despite the use of INCS.⁴

Decongestants

Currently, there is no evidence to support the use of decongestants for CRSwNP or CRSsNP.² The chronic use of oral decongestants, such as pseudoephedrine, is generally avoided for the maintenance treatment of CRSsNP.⁴

Nasal drops or sprays containing sympathomimetic agents, i.e. ephedrine or xylometazoline, can increase nasal vasoconstriction.⁷ Short-term intranasal decongestants, in combination with topical corticosteroids, may be helpful in exacerbations of rhinosinusitis with nasal blockage.⁷

Aspirin desensitisation and therapy

Anti-IgE monoclonal antibody treatment with omalizumab may be considered in patients with the combination of CRSwNP, asthma and aspirin intolerance.⁴

Anti-IgE monoclonal antibody treatment

Anti-IgE monoclonal antibody treatment (omalizumab) can be considered in patients with chronic sinusitis with polyposis and asthma.^{1,4}

Summary of the recommendations for the treatment of chronic rhinosinusitis

Figure 1 contains a summary of the approach to medical therapies for CRS.^{1,5,6} Depending on the response to treatment, a patient's chronic sinusitis-specific symptoms may be classified as persistent, mild or resolved. Persistent symptoms have a negative effect, while mild symptoms do not have a negative effect on daily productivity, functioning or quality of life.¹

Chronic rhinosinusitis without nasal polyps

CRSsNP accounts for approximately two thirds of CRS cases.⁴ Initial treatment involves the use of INCS, in conjunction with saline irrigation.¹ Intensive medical management of patients with CRSsNP who have not received treatment in the immediate past includes either long-term macrolide treatment, or a short course of oral glucocorticoids combined with a prolonged course of oral antibiotics for 3-4 weeks, which may be extended for up to six weeks (or for an additional seven days after the symptoms have cleared),⁴ with one or more adjunctive therapies, i.e. intranasal saline or INCS.⁴

Patients without polyps may benefit from a prolonged course of macrolide therapy.^{1,2} There is no consistent evidence supporting the routine use of short-course systemic corticosteroids in

CRSsNP.¹ A short course of oral steroids may be considered in patients with persistent or severe symptoms.^{1,6} Short-course antibiotics are generally considered when the symptoms indicate infection, i.e. pain or purulence.^{1,6}

Chronic rhinosinusitis with nasal polyps

In the absence of facial pain, pressure or purulent drainage, and when bacterial infection is unlikely, the initial treatment of CRSwNP focuses on establishing a regimen which reduces or controls the mucosal inflammation, and reduces the size and/or extent of nasal polyps.⁴

Initial therapy includes INCS, in conjunction with saline irrigation.¹ Short-course oral corticosteroids⁶ are followed by maintenance INCS.¹ Antileukotriene agents may be considered in patients with acetylsalicylic acid sensitivity.^{1,6} A short or long course of doxycycline may also be considered.^{1,2} Systemic antibiotics are generally not indicated in the absence of infection when managing CRSwNP.¹ A broad-spectrum or a culture-directed oral antibiotic may be necessary during periods of acute exacerbation with superimposed infection.¹

Allergic fungal rhinosinusitis

Surgery is usually required for patients with AFRS in order to maximise sinus ventilation and drainage via the removal of inspissated mucus, which should be cultured for fungus.⁴ Treatment after surgery usually involves the use of oral and topical corticosteroids. The use of oral and topical antifungal agents is not recommended.⁴

Conclusion

The aim of medical therapies is not only to minimise the risk of acute inflammatory exacerbation, but also to optimise patients' quality of life and daily functioning.¹ The development of appropriate treatment strategies, as well as advances in the understanding of the pathophysiology of CRS, have improved outcomes for patients with CRS.⁵

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