What is the most appropriate treatment for chronic rhinosinusitis?

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Keywords: sinusitis, rhinitis, antibiotics, nasal surgery

Word count: 2558

Contributorship statement:

AW composed the majority of the text. CH provided the literature base for review and composed the text of the introduction. CP devised the idea for the article and edited the article's content.

No funding was sought or allocated to this article.

Conflict of interests: CH and CP are co – chief investigators of the MACRO trial

Acknowledgements: none.

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Abstract

Chronic rhinosinusitis (CRS) is a common, treatable disease that affects approximately 11% of British adults. It places an enormous burden on patients, with significant detriment to their quality of life, and the health service as it consumes vast numbers of both primary and secondary care resources. However, there is considerable variability in treatment strategies and prescribing practices. This review summarises the key recommendations from landmark guidelines in the treatment of CRS and critically appraises the evidence for treatment.

Main messages:

- Chronic rhinosinusitis is a common disease in UK adults and causes significant detriment to life
- The best evidence for effective treatment is for topical intranasal corticosteroids and saline irrigation
- For patients who do not respond to this first line treatment, there are many potential avenues for further treatment but there is controversy about which strategy is the most effective

Chronic rhinosinusitis (CRS) is defined as inflammation of the mucosal lining of the nasal cavity and paranasal sinuses that has been present for more than three months; causing characteristic symptoms such as nasal blockage, discharge, reduction or loss of smell sensation, and facial pressure. It is a broad clinical description that encompasses several phenotypes, most often divided into CRS with polyps and CRS without polyps. CRS may be the end point of several different inflammatory pathways and may be secondary to specific conditions such as cystic fibrosis or fungal aetiology, but most often cannot be attributed to a single pathophysiological trigger.

CRS places an enormous burden upon both physicians and its sufferers. It is common amongst the general population, affecting approximately 11% of UK adults [1], and causes greater detriment to quality of life (QoL) than angina or chronic lower respiratory tract disease [2]. Not only is it a quality of life issue, CRS patients frequently have comorbid asthma, and poorly controlled CRS is associated with more frequent asthma exacerbations and a need for hospitalisation. The socio-economic cost of CRS is significant with 57% of patients reporting absenteeism and 28% experiencing associated anxiety and depression [3] [4]. One percent of all UK adults will visit their GP with CRS symptoms each year and require an average of 4 appointments each year; despite this, one in three patients in primary care have poorly controlled symptoms[5]. CRS that cannot be adequately managed in primary care may require referral to secondary care, and data from Hospital Episode Statistics shows that in a single year there were approximately 120,000 outpatient consultations for CRS and 40,000 sinus operations performed in England and Wales[6]. However, there remains considerable debate regarding optimum management strategies leading to wide variation in practice [7].

Treatment evidence and guidelines

The touchstone for treatment of CRS is The European Position Paper on Rhinosinusitis and Nasal Polyps published in 2012 (EPOS 2012) [8]. EPOS 2012 syntheses the best available evidence and expert opinion into easy to follow treatment flowcharts for both primary care physicians and ENT specialists, but acknowledges the large gaps in high quality trial data upon which to base their guidance. In the intervening 7 years since EPOS was published, the International Consensus Statement on Allergy and Rhinology (ICAR) [9] was agreed by a multinational working group who undertook a comprehensive overview of the literature. The working group graded the available evidence and used it as the basis for recommendations; where no evidence was available no recommendation was made. ICAR is therefore an exhaustive insight into the current state of the science in CRS and an invaluable tool for the

otolaryngology community; for primary care however the EPOS 2012 remains perhaps the more accessible guide. In addition there have also been several Cochrane reviews [10-16] of treatments available for CRS, and these reviews along with the international consensus guidelines have been used to synthesise a NICE clinical knowledge summary, most recently updated in 2018 [17].

Intranasal treatment

The foundation of CRS treatment is regular use of intranasal saline irrigation and corticosteroids and this strategy finds unanimous favour amongst the guidelines mentioned above. The evidence is weak but consistent: a Cochrane systematic review studied the effects of saline irrigation in people with chronic sinusitis [12]. This identified only two studies that could robustly be included - one which compared the effect of high volume hypertonic saline irrigation to placebo in CRS patients both with and without polyps, and another which studied only patients with polyps and compared the use of nasal saline irrigation. This Cochrane review concluded that there was weak evidence from these trials to support the use of nasal saline irrigation. In addition, it is a low-cost treatment which with low risk of adverse events. For this reason, it is recommended for virtually all patients with CRS although in practice is usually used in combination with other therapies.

Intranasal corticosteroids are similarly favoured by all expert guidelines. There is a greater number of trials upon which to base this opinion. A Cochrane systematic review [11] identified (search date August 2015) 18 randomised controlled trials (RCTs) which studied the use of intranasal steroids versus placebo in CRS. The majority of these studies included patients with nasal polyps. Regular intranasal corticosteroid use was reported to be superior to placebo in all reported symptoms, although there was no evidence to support an overall improvement in quality of life. A further Cochrane review of the different formulations of intranasal corticosteroids and methods of delivery [13] did not identify any single agent with convincing evidence of superiority, however there is an advantage offered by the second generation agents (e.g. mometasone furoate, fluticasone propionate, fluticasone furoate) which have

favourable pharmacokinetic characteristics that minimise systemic bioavailability (< 1%) compared with older intranasal corticosteroids (e.g. beclomethasone diproprionate, betamethasone).

Oral corticosteroids

Oral corticosteroids are commonly prescribed in the treatment of CRS although there is a distinct lack of evidence for their efficacy. The NICE CKS makes no reference to their use. A Cochrane review in 2016 [16] identified no studies of their use in CRS without polyps, a fact which is also reflected in the ICAR guideline [9]. Their use in patients with polyps is better established, with several studies demonstrating short term efficacy of oral corticosteroids in improving CRS related quality of life scores. Treatment courses are short – a typical regime might be 30mg per day of prednisolone for two to three weeks – and thus the risk of side effects such as adrenal suppression and loss of bone mass are minimal. However, there is a risk of side effects such as gastrointestinal disturbance and insomnia even with these short courses. Patients should also be warned of the risk of osteonecrosis – a risk which may occur at doses of steroid previously thought to be safe (lowest reported associated total dose 105mg, median associated dose 981mg) [18]. The benefit of oral corticosteroids typically last three to six months, and so are a reasonable choice for patients who have not improved on the first line of saline irrigation and topical corticosteroids. However, an evidence-based risk analysis of oral corticosteroid use in CRS with polyps performed by Leung et al [19] demonstrated that risk exceeded benefit if used more frequently than once every two years. Oral corticosteroid use is therefore restricted to short, infrequent courses, and with full disclosure of the potential serious associated side effects for patients.

Antibiotics

Where there is consensus recommending the use of nasal douches and corticosteroids, there is controversy regarding the use of antibiotics. Antibiotics are one of the most commonly prescribed medicines for CRS: of the 1% of UK adults with CRS who visit their GP each year,

91% of them will receive an antibiotic prescription [20]. They will often receive not just one but repeated courses of antibiotics [21]. There is pressure upon GPs to use antibiotics as a first line treatment, as recently some Clinical Commissioning Groups (CCGs) have insisted on a 3 month trial of macrolide antibiotics prior to secondary care referral [22].

With the exception of acute infective exacerbations, routine use of antibiotics is controversial for three main reasons: firstly; the lack of high-quality evidence to support their efficacy; secondly, the emerging threat of antibiotic resistance; and thirdly, the side effects which may accompany some of the most commonly used agents.

In 2016, the ICAR guideline noted a paucity of evidence for antibiotic use [9]; however, on balance it recommended that patients with polyps should not be prescribed short courses of non-macrolide antibiotics, unless in the particular circumstances of suffering an acute exacerbation. No conclusions could be drawn on longer courses, or for patients without polyps. This echoes the findings of a Cochrane review of the use of antibiotics in CRS, which found very little evidence that non-macrolide antibiotics are effective in patients with chronic rhinosinusitis although only two studies were fit for inclusion in analysis[15]. These recommendations guided the NICE Clinical Knowledge Summary [17] to make the recommendation to seek specialist advice before initiating long-term antibiotics in primary care.

It is, however recognised that there does remain a role for appropriate use of macrolide antibiotics in specific circumstances. In particular there is growing interest in immune-modulating and anti-inflammatory effects of macrolides in chronic airway inflammatory disease, with low-dose long term macrolides being prescribed for its effects on the immune response and not primarily as an anti-bacterial agent [23]. The Cochrane review of 2016 noted that there was a moderate quality of evidence of a modest improvement in disease-specific quality of life in patients with chronic rhinosinusitis without nasal polyps receiving three months

of a macrolide [15]. However, this improvement was short lived, as three months following the cessation of the antibiotics there was no measurable effect of treatment.

Resistance

Antibiotic resistance is considered one of the most significant threats to patients' safety in Europe [24]. Evaluating effectiveness of antibiotics and promoting appropriate usage is integral to the UK 5-year antimicrobial resistance strategy [25] . Given the high prevalence of CRS and the variability in prescribing, overuse of inappropriate antibiotics may represent a public health danger through selective pressure on bacteria and resistance. In particular, macrolide resistance has been noted to have implications in infections secondary to *Streptococcus pneumoniae* (upper and lower respiratory tract infections) and *Mycoplasma genitalium* (sexually transmitted infections), leading to longer duration of illness and requirement for multiple antibiotic courses [26].

Side effects

Antibiotics are commonly associate with wide range of side effects ranging from the mild (rash, nausea, diarrhoea) to the life threatening (anaphylaxis). Specific to the use of macrolides are concerns about potential cardiovascular side-effects [27]. There have been a number of publications raising concerns about cardiac toxicity with erythromycin in patients with a prolonged QT interval [28, 29]. A 2016 study which looked at adverse outcomes associated with clarithromycin use found a significant association was found between clarithromycin use and cardiovascular mortality, where longer durations of clarithromycin use were associated with more cardiovascular events [29]. By contrast, this association was not found with use of β-lactam antibiotics leading the authors to hypothesise that it was an effect specific to clarithromycin. This hypothesis was unintentionally tested by the lead investigators of the CLARICOR trial who had planned to measure the efficacy of a two-week course of 500mg clarithromycin twice daily to improve the clinical manifestations of stable coronary heart disease [30]. The study was halted prematurely due to the finding of excess deaths in the

intervention group: all-cause mortality was significantly higher in the group had taken clarithromycin, an effect which persisted for 10 years post intervention. The use of clarithromycin in patients with known cardiovascular disease is therefore only undertaken with a significant degree of caution.

Surgery

Patients who are referred to secondary care who are considered to have tried and failed appropriate medical therapy – which is to say, a sufficient trial of nasal douching and topical steroids - are considered candidates for endoscopic sinus surgery (ESS) [31, 32]. ESS is a loosely defined procedure and can range from very simple balloon expansion of the sinus openings, to extensive procedures that open every bony partition within the sinuses. The risks of surgery include epistaxis, breach of the skull base with resultant CSF leak or meningitis, and injury to the intraorbital structures which may result in impaired vision. Insufficient evidence to define the role and extent of surgery contributes to a 5-fold variation in UK intervention rates [33], with wide variation in surgical practice and very high rates of revision surgery [34] [35]. Such uncertainty resulted in inclusion of ESS in the NICE Database of Treatment Uncertainties (DUETS)[36].

However, there can be no doubt that in appropriately selected patients, surgery offers significant and durable relief from symptoms. The largest UK study of CRS and its outcomes demonstrated that not only was there a significant improvement in patient reported symptoms following ESS, but that patients who had surgery earlier in their disease course had a greater degree of improvement that lasted longer versus those who underwent delayed surgery [37]. In addition to improving nasal symptoms, a systematic review demonstrated that ESS is associated with improved asthma control with significantly fewer attacks, hospitalisations, and a reduced requirement for medication use following sinus surgery in patients with comorbid CRS and asthma [38]. Each of the international consensus guidelines referenced above

recommends that patients who have tried a course of appropriate medical therapy but do not have control of their symptoms should be considered as a candidate for surgery[8, 9].

The path forwards

In the last two decades the majority of new treatments that have become available for CRS have in the main been refinements rather than revolutions – for examples new formulations of intranasal steroids or third generation antihistamines. However, there are some genuinely new and exciting innovations which are on the cusp of integration to clinical practice. Monoclonal antibodies that bind to targets such as IgE, IL4, and IL5 were developed primarily as treatments for asthma, but clinical trials have demonstrated that several of these agents may also be effective in CRS with polyps [39]. At present they remain expensive and are limited to subsets of patients with difficult to treat asthma, but as prices fall in future and evidence for their efficacy accumulates then in future they may become available for the treatment of CRS. There have also been several promising avenues of research that may unlock further therapeutic targets, such as the role of the microbiome in sinus disease. However, as alluded to in the many international guidelines, there is a paucity of evidence for many of the treatments that are currently used in CRS before even considering new innovations. This has led to a redoubling of efforts in CRS research to produce high quality evidence for commonly available treatments. Key to these efforts are the need to accurately define the endotypes of disease which will be studied in trials, as broad clinical phenotypes such as “polyps” may encompass a wide range of underlying pathophysiology. Tightly defining the endotypes of disease for trial inclusion will permit robust examination of the response to treatment in each subgroup. Meta-analyses of CRS outcomes have been hampered by the broad clinical phenotypes, and using precise endotypes will enhance our ability to pool data from multiple trials; this will also be enabled by international consensus statements that define key criteria such appropriateness for ESS [40] and standardised sets of outcome measures [41]; and funding has been secured for one of the largest ever trials of interventions in CRS which will

specifically examine the question of the efficacy of both macrolides and ESS (the MACRO trial [42]) in subgroups of patients defined by precise clinical and pathological parameters. At present, treatment of CRS exists in a time of genuine clinical equipoise where treatment is empirical and even international guidelines depend more heavily on expert opinion than robust scientific statements. Ongoing research endeavours aim to transform the treatment of CRS and usher in the era of precise, personalised medicine for these patients.

Self Test Questions

1) Which of the following are typical symptoms of chronic rhinosinusitis?
   a) Bleeding and crusting
   b) Unilateral blood tinged discharge
   c) Blockage, discharge, loss of sense of smell, facial pressure
   d) Visual disturbance

Answer: c) these are typical CRS symptoms. Bleeding and crusting should raise the possibility of vasculitis, septal perforations, or recreational cocaine use. Unilateral blood tinged discharge is a red flag sign that should prompt concerns of malignancy. Visual disturbance may be caused by rare complications of CRS, but is not at all typical.

2) The first line treatment for CRS is oral steroids and antibiotics. True or false?
   Answer: false. The first line treatment for CRS should be topical steroids and saline irrigation.

3) A prolonged course of antibiotics (e.g. up to 3 months) may occasionally be used in specific circumstances. What group of antibiotics has the best evidence to support their use for prolonged courses in CRS?
   a) Penicillins
   b) Macrolides
   c) Aminoglycosides
   d) Fluoroquinolones

Answer: Macrolides.

4) And what adverse effects should the patient be advised of with these long term antibiotics?
   a) Cardiac comorbidity
   b) Osteonecrosis of the femoral head
   c) Epistaxis
   d) Infertility

Answer: Cardiac comorbidity, particularly in patients with known heart disease. Osteonecrosis of the femoral head is a complication of oral steroids, while topical steroids may cause epistaxis. Macrolides are not recognised to cause infertility but their use should be restricted during pregnancy. The Food and Drug Administration of USA recommend that if a macrolide must be used in pregnancy then azithromycin is category B (i.e. safe in animal studies) while clarithromycin is category C (i.e. shown to cause harm in animal studies).

5) There is good evidence to support the superiority of surgical treatment of CRS compared to medical treatment. True or false?
   Answer: false. There are very few high quality trials that compare medical treatment to surgery, and meta-analysis is made difficult by wide variability in study protocols.

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3 Research questions

- Is it possible to identify specific endotypes of CRS to replace the broad clinical phenotypes that we currently base our treatment plans on?
- Are macrolide antibiotics an effective treatment in CRS?
- Is best medical treatment superior to surgery in the treatment of CRS?

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