



Medical therapy, refractory chronic rhinosinusitis, and productivity costs

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Purpose of review

The purpose of this review is to address the most recent advances in the medical therapy for chronic rhinosinusitis (CRS), define recalcitrant and refractory CRS, and discuss the productivity costs associated with CRS.

Recent findings

Recent studies evaluating anti-IL-4 receptor α antibodies and calcium channel blockers have demonstrated promising early results during management of CRS. Recent appropriateness criteria have been developed to assist clinicians with defining which patients have 'refractory' CRS and may be considered candidates for endoscopic sinus surgery. Productivity costs appear to be associated with disease severity and can be reduced with appropriate interventions.

Summary

Topical corticosteroid therapy and high volume saline irrigation continue to be the cornerstone to medical therapy, whereas use of systemic corticosteroids and antibiotics depends on CRS phenotype and presence of acute exacerbation. More research is needed before routine use of novel immunomodulatory therapies such as anti-IL5, anti-IgE, anti-IL4, and calcium channel blockers. Clinicians should apply an appropriate definition for refractory CRS when discussing role of sinus surgery. Assessing the degree of work productivity impairment can assist in treatment decision-making and may help predict treatment outcomes.

Keywords

chronic rhinosinusitis, costs, medical therapy, productivity, refractory

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disease of the paranasal sinuses characterized by persistent symptoms for at least 12 weeks [1–3]. One important end result of CRS is reduced quality of life (QoL), which is primarily driven by living with daily symptoms of nasal obstruction, purulent nasal discharge, reduced sense of smell, and facial discomfort [4]. Living with reduced QoL results in substantial effects on individual patients, the healthcare system, and even impacts society in the form of reduced work productivity [5]. Although the estimated annual direct healthcare costs of \$10 billion do not rival other common chronic conditions such as diabetes and cardiovascular disease [6], the indirect costs from lost productivity related to CRS are estimated to exceed \$13 billion per annum in the United States [7]. These indirect economic losses are comparable with other chronic diseases such as asthma, migraine, and low back pain [5].

Fortunately, with appropriate medical therapy and, when indicated, endoscopic sinus surgery

(ESS), CRS symptoms can be improved and QoL can return back to US population norms [8]. The objectives of this study are to review the role of medical therapy in the management of CRS while focusing on the most up-to-date evidence and innovative treatments. Furthermore, the article will discuss refractory CRS and the negative impact on work productivity. The purpose is to improve the use of evidence-based medical therapy options for CRS along with improving the understanding of how CRS and subsequent treatment impact work productivity.

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KEY POINTS

- Topical intranasal corticosteroids and high volume saline irrigations are recommended as maintenance medical therapy for CRS.
- Refractory CRS refers to patients with persistent symptoms despite appropriate medical therapy.
- Recalcitrant CRS refers to patients with persistent symptoms despite appropriate medical therapy and surgical therapy.
- Productivity costs related to CRS exceed \$13 billion USD annually and are associated with the severity of QoL impairment.
- Patients with mild work impairment from CRS are often stable with continued medical therapy alone, whereas patients with severe work impairment often require ESS to receive clinical improvement.

MEDICAL THERAPY

As CRS is a chronic inflammatory disease, appropriate prolonged medical therapy is a fundamental component to control of disease and successful patient outcomes [9^{¶¶}]. The primary goals of medical therapy are to reduce sinonasal mucosal inflammation and restore sinus function back to normal. Successful medical therapy has been shown to significantly improve patient QoL and in certain CRS patients it can obviate the need for ESS [10–13]. Given the importance of medical therapy for CRS, healthcare providers managing this condition should have a thorough understanding of the evidence surrounding the various options. Treatment goals should be to use appropriate medical therapies in the correct patient at the correct time to optimize patient outcomes and health system performance [14].

There is increasing evidence to suggest that different endotypes and phenotypes of CRS exist and that these may influence which therapies are effective [15,16^{¶¶}]. Currently, CRS is divided into two main phenotypically divided groups: CRS with nasal polyposis (CRSwNP) and without nasal polyposis (CRSSNP). Although there is a great deal of overlap in the management of these two groups, strategies do diverge in some areas and not all therapies are equally effective between or within these two groups [9^{¶¶}]. Some patients respond well to one therapy, whereas others do not. As the pathogenesis of CRS becomes more defined, medications are being developed that target specific disease processes in hopes of providing more effective, precision medicine options [17].

Traditional medical therapies for chronic rhinosinusitis

Currently, best available evidence supports a maintenance medical therapy strategy of daily topical intranasal corticosteroids combined with high-volume saline irrigations [9^{¶¶}]. A recent meta-analysis by Chong *et al.* [18[¶]] demonstrated that intranasal corticosteroid therapy significantly improved sinonasal symptoms; however, the evidence supporting improvements in QoL was of low quality, making it difficult to provide strong conclusions on this patient outcome. Although the positive role of saline irrigations as an adjunct to topical corticosteroids is well accepted [11], a recent meta-analysis confirmed these findings and emphasized the lack of benefit from low-volume saline sprays (i.e. <5 ml) while supporting the importance of using a daily high-volume irrigation strategy (>150 ml) [19[¶]].

The use of short courses (<3 weeks) of systemic corticosteroids and antibiotics often depends on the CRS phenotype after failed topical corticosteroid therapy or as rescue medications for acute exacerbations. A recent meta-analysis continues to support the beneficial impact of using a prolonged course (12 weeks) of a systemic anti-inflammatory antibiotic in certain patients with CRSsNP [20[¶]]. Antibiotics with anti-inflammatory properties include macrolides (i.e. clarithromycin, azithromycin, and roxithromycin), trimethoprim–sulfamethoxazole, and doxycycline. The use of prolonged anti-inflammatory antibiotics needs to be balanced with the potential serious adverse effects of rhabdomyolysis and prolonged QT.

Although the appropriateness and timing of a short-course systemic corticosteroid treatment remain controversial during management of CRS, best available evidence supports that it improves symptom severity and QoL in patients with CRSwNP [21[¶]]. However, without the use of adjuvant topical corticosteroid therapy, the beneficial effects from systemic corticosteroids alone are lost 3–6 months after completing the therapy [22]. Given potential adverse effects, it is important to emphasize the need for clinicians to involve patients in a shared decision-making process when considering systemic antibiotics and corticosteroids.

Novel therapies for chronic rhinosinusitis

As our understanding of the pathogenesis of CRS improves [23], novel immunomodulatory therapies are being developed to target and interrupt specific pathologic processes [24,25]. This section will discuss four promising treatments that include anti-IL-5, anti-IgE, anti-IL-4R α , and calcium channel blockers.

Anti-IL-5 therapy

Over 80% of CRSwNP is associated with eosinophilia, especially patients with a history of aspirin sensitivity and asthma [26,27]. IL-5 is thought to play a significant role in the pathophysiology of CRSwNP, as it mediates eosinophil growth, recruitment, and activation [26]. Anti-IL-5 therapy involves humanized IgG mAbs that bind free IL-5 and impair eosinophil-mediated inflammation [9[■]]. In polyp tissue studies, anti-IL-5 mAbs have been shown to induce eosinophil apoptosis and reduce tissue eosinophilia [28].

There have been two randomized control trials (RCTs) examining the impact of anti-IL-5 therapy on CRSwNP [27,29]. Although both studies were small and lacked long-term follow-up, anti-IL-5 therapy produced mild improvements in blood eosinophil levels and polyp scores. However, there were no improvements in symptoms scores or QoL. Given the importance of improving patient-reported outcomes during management of CRS, further studies investigating the clinical impact of anti-IL-5 therapies are needed before it can be recommended as a routine therapeutic option for CRS.

Anti-IgE therapy

IgE is a potent inflammatory mediator responsible for mast cell activation; however, the role of IgE-mediated inflammation in the pathophysiology of CRS remains unclear [9[■],30]. Similarly to IL-5, high levels of serum IgE are also associated with the presence of asthma and a history of asthma [26,30,31]. Monoclonal anti-IgE antibodies function by binding free serum IgE as well as decreasing availability of IgE receptors located on mast cells, basophils, and dendritic cells. This results in a degree of antigen 'insensitivity' [30,31]. Omalizumab is an anti-IgE mAb approved for use in patients more than 6 years of age with moderate-to-severe uncontrolled allergic asthma [26].

There have been two RCTs examining the efficacy of omalizumab in CRSwNP, as well as a recent systematic review [30,32,33]. Again, similarly to anti-IL-5 evidence, both trials were limited by small sample sizes, short follow-up duration, and cohort heterogeneity [30,32,33]. Overall, clinical benefit was only demonstrated in one of the trials and was limited to mild improvements in objective measures (radiologic imaging and polyp size) and patient-reported outcomes (total symptoms and QoL). Despite the low quality of evidence to support anti-IgE therapy, it remains a promising potential medical therapy when used in the correct subgroup of patients with CRS.

Anti-IL-4R α therapy

IL-4 plays a role in Th2 cell-mediated inflammation, which is associated with CRSwNP [34]. IL-4 also appears to potentiate the immune response of fibroblasts in CRS [35–37]. Dupilumab is a monoclonal anti-IL-4 antibody that targets the α subunit of the IL-4 receptor (R α), which inhibits signaling of IL-4 and IL-13 [38]. Clinical trials in other Th2 cell-mediated diseases, such as asthma and atopic dermatitis, have demonstrated significant clinical improvement with the use of dupilumab [39,40].

A recent RCT has investigated the impact of subcutaneous dupilumab (600 mg loading dose followed by 300 mg/week for 15 weeks) in patients with CRSwNP who continued to have symptoms despite topical intranasal corticosteroids [38]. Results demonstrated significant improvements in radiographic imaging and polyp size compared with the placebo group. Additionally, patients received significant improvements in QoL using the sinonasal outcome test 22 metric. These effects were even greater in patients with concurrent asthma [38]. Although dupilumab represents a promising medical therapy, larger trials with longer duration of follow-up are required before routine use in management of CRS.

Calcium channel blockers

A single study has investigated the potential role of calcium channel blockers (CCB) for treatment of CRSwNP. Recent research has suggested that verapamil, an L-type CCB classically used in cardiac disease, may also have an immunomodulatory function [41[■]]. Studies [42,43] have shown that verapamil reduces Th2 cell-associated inflammation in asthma and inhibits P-glycoprotein in sinonasal epithelial cells. Given these pharmacologic features, a recent study by Bleier *et al.* [41[■]] examined the effect of verapamil on human sinonasal polyp explants compared with dexamethasone. Results demonstrated that verapamil inhibited the secretion of IL-5, IL-6, and thymic stromal lymphopoietin with similar efficacy to dexamethasone [41[■]]. Although the mechanism of these effects is unclear, further study into CCB as a potential alternative therapy to modulation of sinonasal inflammation is warranted.

REFRACTORY AND RECALCITRANT CHRONIC RHINOSINUSITIS

The terms refractory and recalcitrant CRS are often used to describe a cohort of patients with CRS who continue to suffer from symptoms despite treatment. However, to improve communication and research standardization, it will be important to

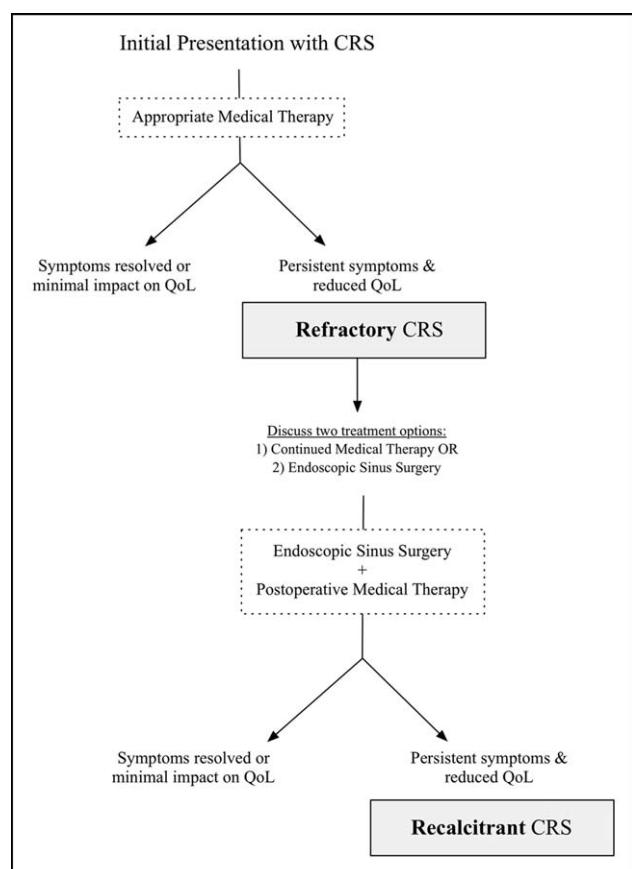


FIGURE 1. Temporal relationship of refractory CRS versus recalcitrant CRS. CRS, chronic rhinosinusitis; QoL, quality of life.

provide more objective definitions. Based on the evidence, it appears that these two terms represent patients with CRS who have persistent symptoms at different time points along the management spectrum (Fig. 1).

‘Refractory CRS’ describes patients with persistent symptoms despite receiving appropriate medical therapy and thus are considered candidates for ESS as a treatment option [44²²,45²²]. In contrast, ‘recalcitrant CRS’ appears to describe a cohort of patients with persistent symptoms of CRS despite receiving both appropriate medical therapies and appropriately performed ESS [46].

Although 75–80% of patients with refractory CRS will receive significant benefit from ESS [47], there will be a proportion of patients who continue to suffer despite continued postoperative medical therapies and are thus classified as ‘recalcitrant.’ Recalcitrant CRS often includes difficult to treat subgroups of patients with aspirin-exacerbated respiratory disease, osteitis, severe combined upper airway disease, immunodeficiencies, bacterial biofilms, and systemic inflammatory diseases such as granulomatosis with polyangiitis and sarcoidosis [48]. As a result, recalcitrant CRS typically applies

to a more severe cohort of patients and clinicians often need to consider less utilized medical therapies such as topical antibiotics and immunomodulators, depending on clinical scenario [48].

With the purpose to standardize the definition of refractory CRS and help improve the value of ESS, a recent RAND appropriateness study by Rudmik *et al.* [44²²,45²²] has provided clinical criteria for refractory CRS, thus providing indications for appropriate ESS. The study involved a modified Delphi methodology using an international, multidisciplinary panel of 10 experts in the management of CRS. The results provided defined criteria for refractory CRS (i.e. patient considered to be a candidate for ESS), which involved the following: must have a minimum impairment in QoL of sinonasal outcome test 22 score at least 20, radiologic evidence of sinus inflammation using a minimum CT Lund–MacKay score at least 1, and minimum trial of appropriate medical therapies specific to either CRSwNP and CRSsNP (Table 1).

Using the RAND appropriateness criteria for ESS, it is possible to define refractory CRS and may consider ESS as a treatment option. Although there remains to be a consensus definition for recalcitrant CRS, current evidence supports that it pertains to patients with persistent symptoms despite providing appropriate medical and surgical treatment for CRS.

PRODUCTIVITY COSTS

As healthcare expenditures continue to grow at an unsustainable rate, it is important for clinicians to understand the economics behind healthcare delivery and collaborate with other stakeholders to improve the value of care [49,50]. Direct costs are defined as the monetary value of the specific healthcare resources that were consumed during the management of a patient (i.e. physician visits, diagnostic testing, treatment) [51]. Although precise estimates of overall direct cost depend on the stakeholder perspective, the annual direct cost of CRS in the United States from the perspective of third-party payers is estimated to be \$10 billion [6].

Indirect costs are the monetized value of the time lost from work by way of ‘presenteeism’ (reduced productivity while at work) and ‘absenteeism’ (missed time from work). Developing an efficient and high-performing healthcare system to deliver high-quality care and reduce productivity costs is essential to a well functioning society [52].

There have been several studies [5,53,54²², 55²²,56–58] evaluating the impact of CRS on productivity costs. Overall these studies have demonstrated that CRS impacts work productivity and the

Table 1. Appropriateness criteria for refractory chronic rhinosinusitis

CRS with nasal polyps	CT paranasal sinuses Lund–Mackay score ≥ 1 Posttreatment SNOT-22 score ≥ 20 Received appropriate medical therapy consisting of: Topical intranasal corticosteroid therapy for ≥ 8 -week duration and, Short course of systemic corticosteroid for 1 to 3-week duration
CRS without nasal polyps	CT paranasal sinuses Lund–Mackay score ≥ 1 Posttreatment SNOT-22 score ≥ 20 Received appropriate medical therapy consisting of: Topical intranasal corticosteroid therapy for ≥ 8 -week duration and either, Short course of broad-spectrum/culture-directed systemic antibiotic for 2 to 3-week duration OR Prolonged course of systemic low-dose anti-inflammatory antibiotic for ≥ 12 -week duration

CRS, chronic rhinosinusitis; CT, computed tomography; SNOT, sinonasal outcome test.

degree of work impairment is related to the severity of CRS. Specifically, when productivity costs were evaluated on a population level, which likely included more patients with milder phenotypes, the annual mean days missed from work was only 6 days [57]. This is in contrast to patients missing over 20 days/year in a cohort with refractory CRS who had larger baseline reductions in their QoL [5]. Overall CRS-specific productivity costs from the

perspective of the US society are estimated to be in excess of \$13 billion per year [5,7].

Two recent studies [53,54[■]] evaluated how the productivity costs, in patients with refractory CRS, are impacted when they elect to continue with medical therapy alone or chose to receive ESS. The results from these studies identified two important findings. First, patient treatment selection appears to be associated with the severity of their

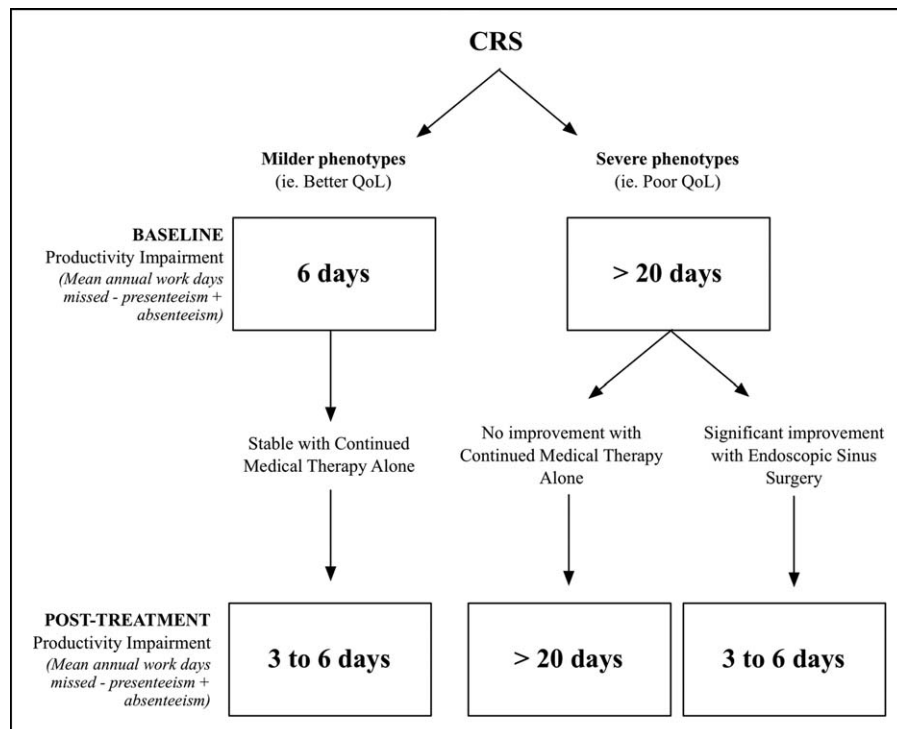


FIGURE 2. Relationship between productivity impairment and treatment outcomes. CRS, chronic rhinosinusitis; QoL, quality of life.

baseline productivity impairment. Specifically, patients with lower productivity costs (i.e. better functioning at work) tended to select continued medical therapy alone as opposed to patients who had larger baseline productivity costs (i.e. poor functioning at work) tended to select sinus surgery. This is important because assessing the severity of baseline productivity impairment may assist clinicians in providing care that is focused on patient preferences for treatment. Incorporating patient preferences into treatment decisions is important for improving patient-centered care [59].

A second important finding was that the severity of baseline productivity impairment helped to predict treatment success from either continued medical therapy alone or ESS. Specifically, patients who had better baseline productivity were effectively managed with continued medical therapy alone, meaning their productivity level was maintained at their baseline level. Meanwhile, patients with larger baseline productivity impairment got worse with continued medical therapy alone and received significant improvements in productivity by receiving ESS (Fig. 2). The relationship between baseline level of productivity impairment and degree of treatment success from either continued medical therapy or ESS was confirmed by two recent prospective studies [55[■],56] and a recent cluster analysis study [16[■]]. Again, these data support the concept that clinicians may benefit from assessing baseline productivity impairment to help inform patients to their expected outcomes when discussing various treatment options for CRS.

In summary, CRS often reduces a patient's ability to function at work and this creates productivity costs to society. As the degree of productivity costs can vary between patients and may help predict treatment outcomes, assessing the severity of productivity impairment may assist in providing appropriate patient-centered care for CRS.

CONCLUSION

Topical corticosteroid therapy and high-volume saline irrigation continue to be the cornerstone of medical therapy, whereas use of systemic corticosteroids and antibiotics depends on CRS phenotype and presence of acute exacerbation. More research is needed before routine use of novel immunomodulatory therapies such as anti-IL5, anti-IgE, anti-IL4, and CCBs. Clinicians should apply an appropriate definition for refractory CRS when discussing role of sinus surgery. Assessing the degree of work productivity impairment can assist in treatment decision-making and may help predict treatment outcomes.

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Conflicts of interest

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- of outstanding interest

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