Abstract
Chronic rhinosinusitis with nasal polyps is a heterogeneous disease with a variety of medical and surgical options available to the patient and provider. Consensus statements and recent trends in outcomes research advocate that treatment be driven by patient-reported outcome measures. To this end, there has been increasing sophistication and nuance in both the outcome instruments themselves, as well as the method in which they are collected and interpreted. This is reflected in concepts such as the minimally clinically important difference and domain stratification, which have helped clinicians understand patient motivations and response to treatment. Medical management with topical and possibly systemic corticosteroids is considered the initial treatment strategy of choice, with endoscopic sinus surgery (ESS) reserved for patients who fail to improve. While there is strong evidence for surgical intervention over continued medical therapy in recalcitrant patients, a variety of additional targeted medical treatments and refinements to the nature and extent of ESS have been proposed to further maximize outcomes. Here, with the understanding that limitations continue to exist in our ability to fully answer many treatment-related questions, we present the current cumulative evidence for a patient-centered and outcomes-focused approach to manage this uniquely challenging disease.

Introduction
Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a heterogeneous disease defined by the phenotype of chronic sinus inflammation with polyp formation. Navigation of treatment strategies for this condition is challenging for
both patients and providers as a variety of medical and surgical options are available. While there is debate concerning the specific interventions, there is clear consensus that optimization of patient reported outcome measures (PROMs) is the primary goal of treatment \[1, 2\].

Since the introduction of PROMs for chronic rhinosinusitis (CRS) in the 1990s, their collection and analysis has become increasingly sophisticated. These refinements have been a boon to our understanding of how symptoms and quality of life (QOL) are influenced by specific interventions, but require an informed clinician to interpret the data. To this end, this chapter seeks to summarize the latest outcomes research on management of CRSwNP, inclusive of all etiologies of nasal polyps contributing to sinonasal symptomatology, in a way that is memorable for clinicians and easily translatable to patient care.

### Primary Outcome Instruments

The ideal PROM instrument captures all impacts of CRS on a patient’s QOL, achieves good reliability, internal consistency, validity and correlates with overall health with minimal survey burden \[3\] (table 1). Over the past 20 years, a variety of measures have been investigated and refined and most correlate closely \[4\] (table 2). The most recent iteration is the Sinonasal Outcome Test-22 (SNOT-22) and it has been longitudinally validated, translated internationally, and found to correlate with anchor questions of overall change after interventions \[5\]. Furthermore, pre-operative

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**Table 1.** Key criteria of quality for clinical research instruments

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Reliability</td>
<td>stability of data administered at different times to the same group (test-retest reliability) or ability to produce similar results using different items from the same instrument (internal consistency) or equivalence of different observers producing the same assessment using the same instrument (inter-rater reliability)</td>
</tr>
<tr>
<td>Validity</td>
<td>extent to which an instrument measures what it intends</td>
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<tr>
<td>Responsiveness</td>
<td>ability of a measure to detect change over time</td>
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</table>

**Table 2.** Selected disease-specific quality of life measurement in sinonasal disease

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Year</th>
<th>Questions, n</th>
<th>Reliability</th>
<th>Validity</th>
<th>Responsiveness</th>
<th>Ease of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSOM-31</td>
<td>1995</td>
<td>31</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>RSDI</td>
<td>1997</td>
<td>30</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>SNOT-20</td>
<td>1998</td>
<td>20</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>SNOT-22</td>
<td>2000</td>
<td>22</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

RSOM-31 = Rhinosinusitis outcome measure; RSDI = rhinosinusitis disability index; SNOT-20 = sinonasal outcome test-20; SNOT-22 = sinonasal outcome test-22; + = not strongly demonstrated; ++ = strongly demonstrated; +++ = very strongly demonstrated.
(baseline) SNOT-22 scores have been advocated as a useful clinical tool in predicting which patients will achieve symptom improvements following surgery [6]. A limitation of the SNOT-22 is that it does not capture medication use or disease duration. The Chronic Sinusitis Survey (CSS) is a 6-item test and an important complementary tool that incorporates this additional data [4]. The complexity of rhinologic disease may ultimately necessitate the integration of multiple PROM instruments to best capture the true impact on QOL [4, 7].

The Minimal Clinically Important Difference
Longitudinal comparisons of baseline and interval PROM scores have served as the basis for evaluating interventions for CRSwNP. The minimal clinically important difference (MCID) is the smallest difference in score perceived as beneficial by a patient [8]. This concept links PROM score change with practical patient benefit, thereby increasing the clinical interpretability and allowing researchers to use this numerical threshold in describing frequencies of achieving clinically meaningful treatment success. Hopkins et al. [5] integrated this intuitive approach into the SNOT-22 instrument and found the MCID to be 9.

Domain Stratification and Utility Scores
Aggregate reporting of PROM scores is useful in large cohorts of patients, but may be oversimplified for a patient or clinician seeking the potential impact of a given intervention on symptoms. Factor analysis of the SNOT-22 has revealed 5 correlated but discrete measured health domains in CRS [9]. Reporting of domains allows for a refined understanding of how interventions impact each domain, and how symptoms influence treatment selection. For instance, DeConde et al. [10] found that patients electing surgery over continued medical therapy have comparable sinonasal symptomatology but carry greater burdens of psychological and sleep symptomatology. Utility scores, or a quantification of value for a patient’s health state, also correlate most strongly with these domains [11]. Thus, domain stratification and utility valuation are important symptom-based methods of enhancing clinical precision in determining which patients will benefit from which interventions.

Secondary Outcome Instruments
A variety of secondary outcome measures, or outcomes that do not directly address QOL, have been described to provide additional information to the treating practitioner. These include nasal breathing, radiographic (Lund–Mackay) [12], endoscopic (Lund–Kennedy) [13] and olfactory scores [14]. The secondary outcome measures provide important information that guides treatment for the practitioner as well as validates treatment outcomes in research. Although secondary outcome measures do not correlate perfectly with PROMs, endoscopy accounts for 33% of the variance seen in PROMs [DeConde, in press].

Medical Outcomes
CRSwNP can have a significant impact on QOL due to nasal obstruction, congestion, discharge and loss of sense of smell [15]. The goals of treatment are to improve QOL, as reported in PROMs, eliminate or reduce the size and number of polyps, restore nasal airflow and improve olfaction [16]. Medical treatment is the initial strategy in these patients, with surgery considered for recalcitrant patients.

Topical Corticosteroids
Corticosteroids disrupt the inflammatory pathway at many levels and are implicated in the infiltration and activation of eosinophils and chemoattractant cytokines [17]. In 2012, a Cochrane Review based on 40 studies and 3,624 patients showed that topical corticosteroids consistently demonstrate significant benefit in PROMs, polyp size
and nasal airflow. However, no significant improvement in sense of smell was shown [16]. In general, topical nasal corticosteroids are well tolerated, with limited systemic absorption and adverse events limited to nasal irritation and epistaxis. Level 1 evidence supports usage of topical corticosteroids for CRSwNP and should be a part of first-line therapy [1] (table 3).

**Oral Corticosteroids**

Systemic corticosteroids are used in cases of symptomatic CRSwNP that have failed nasal topical treatment, but there is heterogeneity concerning the specific indication, dosage and duration. In 2010, a Cochrane Review showed improvement in PROMs, polyp size, nasal airflow, as well as sense of smell, which was not demonstrated in topical corticosteroid treatment. Furthermore, when compared to topical corticosteroids alone, the use of oral corticosteroids preceding topical treatment showed more durable improvements in polyp size and sense of smell [18]. Despite the benefit, using systemic corticosteroids must be weighed against the adverse effects, which include gastrointestinal complications, growth suppression, diabetes mellitus, hypertension, psychiatric effects, osteopenia, osteoporosis and avascular necrosis [19]. In a non-randomized study where patients were treated with repeated 7–10 day courses of 1 mg/kg/day on average about 7 times per year 5 years, significant (>40%) rates of osteopenia and osteoporosis and adrenal insufficiency (48.4%) on laboratory testing were observed [20]. Another RCT evaluating the use of 50 mg daily of prednisone for 2 weeks showed that about half of the adverse events were psychiatric (insomnia and mood disturbance) with insomnia as significantly more common in the treatment group [21]. Level 1 evidence supports short-course of systemic corticosteroids with dosage between 30 and 50 mg with or without taper for up to 2 weeks followed by topical corticosteroid treatment (table 3).

**Leukotriene Antagonists**

Leukotrienes (LT) are produced by eosinophils and bind to receptors triggering inflammation. LTs and their receptors are seen at increased levels in nasal polyps and can therefore serve as ther-
Two RCTs have been performed studying treatment of LT antagonists (montelukast) in patients with CRSwNP. Collectively, these studies showed improvement of PROMs, polyp size, nasal airflow and immunologic parameters when compared to placebo [22, 23]. However, in a non-placebo controlled RCT, there was no overall difference in these parameters between the LT group and nasal corticosteroids [24]. The greatest benefit of LT antagonists over nasal corticosteroids was headache, facial pain, sneezing, nasal pruritus, post-nasal drip and smell disturbance [25, 26]. LT antagonists can be considered as adjunctive treatment in patients with predominantly allergic-type nasal symptoms.

**Aspirin Desensitization**

Aspirin exacerbated respiratory disease (AERD) is a condition characterized by nasal polyps, asthma and aspirin (ASA) intolerance [27]. Patients with this condition have been shown to have higher polyp burden and rates of recurrence [28]. To improve outcomes, adjuncts to corticosteroid and LT antagonist treatment, such as ASA desensitization, have been studied. In general, this treatment involves the administration of increasing doses of ASA under clinical supervision until a maintenance dose can be taken. RCTs comparing ASA desensitization therapy to placebo are lacking, due to the inability to adequately blind patients to treatment. As such, literature is limited to cohort and case-control studies. In a long-term review of 65 patients who underwent ASA desensitization, Stevenson et al. [29] demonstrated significant reductions in sinonasal symptoms, olfactory dysfunction, use of systemic corticosteroids and number of endoscopic sinus surgery (ESS) procedures. In a more recent study of post-ESS patients, significant improvement in PROMs, endoscopic scores with desensitization treatment was shown [30]. Based on these limited (level II) data, ASA desensitization may be helpful in the treatment of CRSwNP in AERD especially after ESS (table 3).

**Antibiotics**

This treatment has been thought to benefit patients through both antimicrobial and potentially intrinsic anti-inflammatory effects. In a RCT, Van Zele et al. [31] showed improvement in polyp size only and reduced levels of inflammatory markers after a 20-day course of doxycycline compared to placebo. However, another RCT evaluating long-term macrolide treatment in patients with CRS (52% with nasal polyps) failed to show improvement in PROMs, polyp size, nasal airflow or sense of smell [32]. There is additional data demonstrating potential benefit in PROMs and endoscopic scores in long-term (3 months) macrolide antibiotic treatment in patients with low IgE (<200 μg/l), but this study excluded patients with nasal polyps [33]. Overall, there is data to support the use of oral doxycycline in CRSwNP and potentially long-term oral macrolides in patients with low IgE levels.

**Antimycotics**

Targeting fungi with antifungal therapy holds the possibility of decreasing sinonasal inflammation based on the hypothesis that ubiquitous airborne fungi trigger the pathogenesis of CRSwNP [34]. Unfortunately, the literature shows mixed results, and risk of systemic side effects. For systemic therapy, a double-blind placebo controlled RCT evaluating the use of terbinafine in 53 patients over 6 weeks demonstrated no improvement in PROMs, CT scores [35]. In a subsequent retrospective case-series study of patients with allergic fungal sinusitis (AFS) treated with at least 3 months of itraconazole, Chan et al. [36] found that most patients demonstrated no change in endoscopic scores and little or no change in PROMs, in addition, 19% had elevated liver function tests requiring one patient to stop therapy. A recent RCT demonstrated that patients given itraconazole pre-operatively for 4 weeks prior to surgery experienced significant improvements in SNOT-20 with itraconazole therapy alone (31.28 ± 13.79 to 15.72 ± 9.34, p = <0.001). Un-
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Fortunately, at the 2-month postoperative time point, there were no clinically significant differences between the 2 groups. This study does keep the question open as to what role itraconazole plays ‘maximizing’ medical therapy prior to proceeding to ESS for AFS. Two of the 27 patients that received itraconazole essentially had complete resolution of symptomatic disease and cancelled surgery [37].

Topical treatment has also been investigated as a safer alternative given theoretically decreased systemic absorption [35, 38]. However, in a RCT of 60 patients with CRS, 8-weeks of topical amphotericin B treatment demonstrated worsening of PROMs (non-validated instruments) in the treatment group and no difference in endoscopy scores [39]. Use of both systemic and topical antimycotics is not supported by the literature and may be harmful to patients [2].

Immune Modulators

Inflammatory mediators IL-5 and IgE have been shown to be present at high levels in polyp homogenates, nasal secretions and blood serum in patients with nasal polyps [40]. Recently, antibodies-mediated therapies directed at these targets have been studied. A RCT by Gevaert et al. [41] showed that PROMs (non-validated instruments), polyp size and nasal airflow failed to improve with anti-IL-5 therapy compared to controls; however, patients with elevated nasal IL-5 levels (>40 pg/ml) were more likely to have reduction in polyp size. These findings have been confirmed in another small RCT with 24 patients that demonstrated improvement in PROMs, polyp size and radiographic (CT scores) [42]. Level II evidence does indicate benefit for the use of immune modulators for patients, but larger studies will be required to clarify their role in treatment of CRSwNP (table 3).

The outcomes for medical treatment in nasal polyps, including level of evidence and recommendations, is summarized in table 3.

Surgical Outcomes

When medical management fails to adequately control symptoms, surgical intervention should be considered in patients with CRSwNP [1]. The growth in the quality of data supporting surgical intervention for CRS has evolved dramatically over the past 20 years. Early studies from single-institutions found relatively high rates of improvement (73–98.4%) but lacked standardized and validated outcome measures [43, 44]. Use of validated outcome measures in multi-institutional cohorts demonstrated that patients do achieve an MCID after ESS approximately 75% of the time [45, 46]. Analysis of the data found that presence of polyps either made no difference [46] or were predictive of greater improvement in QOL [44]. When compared to patients electing continued medical therapy, patients electing surgery patients with CRS are more likely to achieve an MCID on the RSDI physical subscale (OR 3.36, 95% CI 1.15–9.87; p = 0.027) and CSS symptom subscale (OR 2.65, 95% CI 1.06–6.66; p = 0.038) [47]. In evaluation of medical versus surgical therapy in a North American cohort of patients with CRSwNP, surgical patients are more likely to improve cardinal symptoms [48].

It is important to note that a handful of RCT’s have not found a difference between patients receiving medical or surgical management [49–52]. The fundamental shortcoming of these studies lies in the fact that patients had not failed preliminary medical therapy as is standard of care in the US. This data reaffirms that all patients should undergo a trial of failed medical therapy prior to surgical therapy.

Extent of Sinus Surgery

Although data support the use of surgery with continued medical therapy in medically recalcitrant CRSwNP, there remains room for improvement in this intervention. Long-term data reflects the potentially relentless nature of this dis-
ease with the mean time to revision surgery approximately 5 years [53]. Further analysis revealed that resection of the middle turbinates’ prolonged the meantime to revision surgery by 6 months. The question remains as to what is the ideal surgical extent for patients undergoing ESS for CRSwNP.

The least invasive method of addressing mechanical obstruction is simple polypectomy and offers an in-office alternative to ESS for patients that cannot tolerate or would like to avoid general anesthesia. A recent analysis by Rudmik et al. [54] demonstrates cost-effectiveness of simple polypectomy in the office for a select group of patients with isolated symptoms of nasal obstruction. This method involves the removal of polyps alone, without disruption of the mucosa or bone from nearby ostia or sinuses. The concern with this procedure does not address the underlying source of inflammation, as demonstrated by a 75% recurrence rate on endoscopy in an 8-year follow-up study [55].

ESS in addition to polypectomy both removes the nasal polyposis and marsupializes the sinus cavity with the sinonasal cavity. Browne et al. [56] compared outcomes of patients undergoing polypectomy alone to polypectomy and additional surgery. Additional surgery was defined as surgery to at least one of following regions: middle meatus/uncinate process, anterior or posterior ethmoid, sphenoid or frontal sinuses. While the authors found that there were no significant improvements in PROMs, slight improvement in recurrence rates were observed in the additional surgery group. However, the limit of the additional surgery group was the ethmoid sinus in 85% of patients, suggesting that the true effects of more extensive surgery, including frontal or sphenoid surgery, may not have been captured by this study. A multi-institutional observational study demonstrated a trend of improvement in postoperative PROMs including olfactory measures in complete surgery (defined by bilateral maxillary antrostomies, bilateral total ethmoidectomies, bilateral sphenoidotomies and bilateral frontal sinusotomies (Draf IIa, IIb, or III)) as compared to a targeted approach in CRS [57].

The role of middle turbinate resection has also been investigated as a possible important surgical target in CRSwNP. In a 2006 study by Jankowski et al. [58], ESS with removal of the middle turbinate was compared to endoscopic ethmoidectomy and improvements in PROMs, CT score and polyp recurrence were noted in the group with more extensive surgery. Additional evidence for resection of the middle turbinate in addition to standard ESS has been demonstrated by a retrospective cohort study where patients with CRSwNP who underwent this procedure had a delay in time to revision surgery [53]. Concerns about the clinical detriment of middle turbinate resection can be assuaged by multicenter data showing no diminished QOL is associated with middle turbinate resection [59].

Finally, extended sinusotomies, particularly in the frontal sinus, may play an important role in long-term control of CRSwNP. The frontal recess is a common site of early failure in CRSwNP due to the inherent anatomic bottleneck created by the orbits, frontal beak and septum. In a retrospective review of 339 patients, Naidoo et al. [60] found that patients with nasal polyps were among the highest risk groups for endoscopic failure of standard frontal sinusotomy. Even after complete sphenoidotomies, maxillary antrostomies and Draf 2a frontal sinusotomies, there is a 19.8% endoscopic recurrence rate of polyps at 6 months [61]. However, in the same retrospective review, the revision rate after ESS with Draf 2a was 37% compared to 7% for patients that underwent Draf 3s (p < 0.001) [61]. These data suggest that while ESS and current medical therapies may be inadequate at controlling mucosal inflammation in one-fifth of patients, extended sinusotomies, particularly the Draf III, may be an important adjunct in a subset of patients with CRSwNP.
Conclusion

Improvement in QOL is the primary end point that all clinicians seek to optimize in patients with CRSwNP. Balancing a variety of medical and surgical interventions with a patchwork quilt of evidence requires an educated clinician and an informed patient. Consensus statements emphasize patient education and PROMs as evidence for treatment success, accentuating the shift toward patient-centered results in research and clinical care [1, 2]. Specific attention to patient’s disease within a greater context is especially important in CRSwNP, as it is a benign condition with a high rate of recurrence that can be detrimental to QOL.

Medical therapies remain the first-line therapy in CRSwNP, and surgery remains an important option for recalcitrant cases. Topical corticosteroids are a well-established initial treatment of choice, with systemic treatment as an important adjunct. In medically recalcitrant cases, surgery is the most effective way to improve QOL. Controversy remains as to what is the appropriate extent of surgery in terms of efficacy and cost effectiveness. In order to answer the question of the appropriate surgical extent, randomized study designs, with long-term follow-up (5-years) would preferably be undertaken. Unfortunately, definitive study designs can be cost prohibitive, leaving clinicians and patients gleaning ideal interventions through synthesis of diverse studies and data.

Conflict of Interest

Adam S. DeConde is a consultant for IntersectENT, Inc. (Menlo Park, Calif., USA) which is not affiliated with this work.

References

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