Nasal endoscopy score thresholds to trigger consideration of chronic rhinosinusitis treatment escalation and implications for disease control

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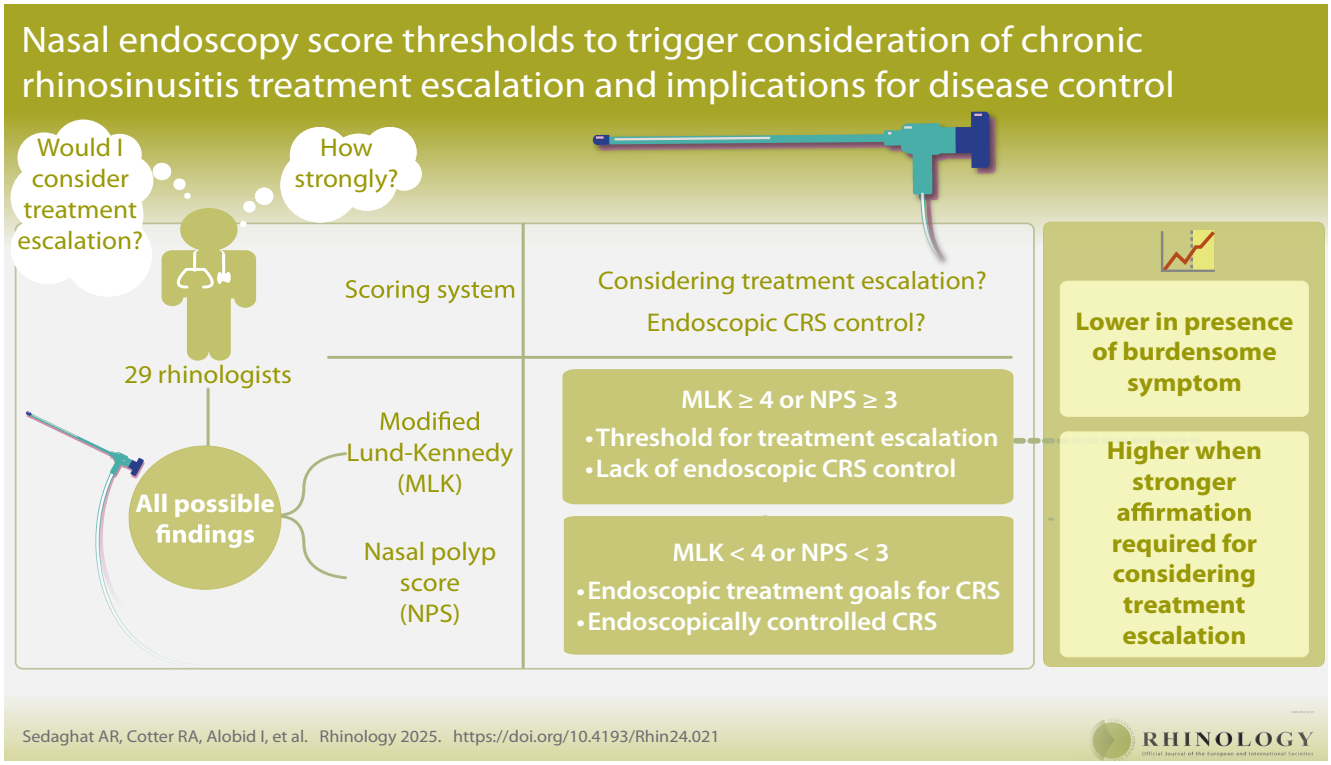

Abstract

Background: In the absence of direct evidence supporting how to use nasal endoscopy findings to judge chronic rhinosinusitis (CRS) disease control, experts' practice patterns could provide guidance. **Methodology**: Participants consisted of a diverse group of twenty-nine rhinologists. Participants were presented with every possible combination of bilateral nasal endoscopy findings represented by the modified Lund-Kennedy (MLK; range: 0–12) endoscopic scoring system and Nasal Polyp Score (NPS; range: 0–8). Reflecting the practical consequence of CRS disease control assessment, participants were asked whether they would consider CRS treatment escalation based on each scenario in the absence of any CRS symptoms, and how strongly they considered escalating therapy. The same scenarios were then presented in the context of 1 burdensome CRS symptom and participants again were asked whether they would consider treatment escalation. **Results**: The median threshold total MLK score for considering treatment escalation was ≥4 and 75.9% of participants' MLK thresholds were within 1 point of 4. The median threshold total NPS for considering treatment escalation was ≥3 and 62.5% of participants' NPS thresholds were within 1 point of 3. Endoscopy score thresholds decreased in the presence of 1 burdensome symptom and generally increased when requiring stronger affirmation for considering CRS treatment escalation. **Conclusion**: Reflecting the practice patterns of a diverse group of rhinologists, MLK score ≥4 or NPS ≥3 may serve as thresholds for considering CRS treatment escalation. Alternatively, MLK score <4 or NPS <3 may serve as endoscopic goals of CRS treatment. These results provide guidance for using nasal endoscopy findings as a criterion of CRS disease control.

Key words: chronic rhinosinusitis, control, nasal endoscopy, Lund-Kennedy score, nasal polyp score, outcome measure

Introduction

Chronic rhinosinusitis (CRS) disease control serves as a goal of treatment for CRS, and treatment of CRS can be escalated specifically to achieve control [1-3]. However, the criteria by which CRS disease control is assessed remains a subject of discussion [4]. A recent international study identified consensus criteria for the assessment of CRS disease control that were broadly agreed upon as well as several criteria that reached near-consensus, around which there is active debate [5]. Among these near-consensus criteria was nasal endoscopy findings.

The use of nasal endoscopy findings to assess CRS disease control - and therefore a focus on reducing nasal endoscopy findings as a goal of treatment - has been historically controversial. Positive nasal endoscopy findings have traditionally been considered an objective measure of disease burden and a reflection of uncontrolled disease that could motivate escalation of a patient's CRS treatment. However, there is presently a lack of direct evidence to support a role for endoscopic disease burden in judging CRS disease control [6,7]. While future investigations may provide this evidence, there is a present need for guidance on how nasal endoscopy findings could be used to assess CRS disease control.

In the absence of scientific evidence, the practice patterns of experts and experienced providers may serve to inform how nasal endoscopy findings are interpreted to indicate CRS disease control. Because decisions regarding treatment escalation are the practical consequences of a provider's perceived lack of CRS disease control, a complete understanding of how nasal endoscopy findings influence providers to consider CRS treatment escalation could offer guidance for how nasal endoscopy findings may be incorporated into assessment of CRS disease control.

The specific objective of our study was to determine a minimum level of nasal endoscopy findings - based on the commonly used, established endoscopy scales reflected by the modified Lund-Kennedy (MLK) endoscopic scoring system [8] and Nasal Polyp Score (NPS) [9] - that would lead to consideration of CRS treatment escalation and by extension, indicate a lack of CRS disease control. We believe that the findings from this study provide important, novel insights reflective of real-world practice for the implementation of a nasal endoscopy criterion in the assessment of CRS disease control by establishing thresholds for MLK score and NPS, above which nasal endoscopy findings may indicate uncontrolled CRS and the possible need for treatment escalation.

Materials and methods

Study participants

This study was approved by the University of Cincinnati Institutional Review Board. Currently practicing rhinologists (Table 1), defined as otorhinolaryngologists whose practices are focused on the subspeciality of rhinology, were recruited and provided informed consent for inclusion into this study. Each rhinologist was anonymized and randomly assigned a participant identification number. Inclusion criterion was a demonstration of expertise in CRS as evidenced by a history as an opinion leader and scholarly activity. Study participants were recruited to represent different career stages and geographic locales.

Table 1. Study participants.

Name (alphabetical order)	Institution
Isam Alobid	University of Barcelona
Saad Alsaleh	Kind Saud University
Wilma Anselmo-Lima	University of São Paulo
Manuel Bernal-Sprekelsen	University of Barcelona
Rakesh Chandra	Vanderbilt University
Jannis Constantinidis	Aristotle University
Wytske Fokkens	Amsterdam University Medical Center
Christine Franzese	University of Missouri
Stacey Gray	Harvard Medical School
Ashleigh Halderman	University of Texas Southwestern Medical Center
Eric Holbrook	Harvard Medical School
Claire Hopkins	King's College
Peter Hwang	Stanford University
Basile Landis	University of Geneva
Valerie Lund	University College London
Edward McCoul	Ochsner Clinic Foundation
Verena Niederberger-Leppin	Medical University of Vienna
Erin O'Brien	Mayo Clinic
Carl Philpott	University of East Anglia
Steven Pletcher	University of California San Francisco
Melissa Pynnonen	University of Michigan
Sietze Reitsma	Amsterdam University Medical Center
Joanne Rimmer	Monash University
Sanna Toppila-Salmi	University of Eastern Finland
Eric Wang	University of Pittsburgh
Marilene Wang	University of California Los Angeles
Sarah Wise	Emory University
Bradford Woodworth	University of Alabama Birmingham
William Yao	University of Texas Houston

Study design

The primary objective of this study was to identify discrete, numerical thresholds for nasal endoscopy findings (based on MLK score and NPS) as an independent outcome measure (i.e., in the absence of CRS symptoms) in adults with primary, diffuse CRS that would lead rhinologists (i.e., the study participants) to

consider escalation of CRS treatment. Rhinologists were chosen to study the perspective of the healthcare provider based on their subspecialty expertise. The secondary objectives of this study were to determine 1) how the thresholds for nasal endoscopy findings triggering consideration for treatment escalation would be impacted by the presence of CRS symptoms and the strength of confidence for consideration of treatment escalation and 2) the association between thresholds for nasal endoscopy scores and participants' views on the importance of nasal endoscopy findings in treatment decisions and their overall years in practice.

The study design was implemented using two questionnaires that were completed electronically. At the beginning of the first questionnaire, participants were asked to 1) use a visual analog scale (VAS) with scores ranging from 0 to 100 to rate "how important, on average, are nasal endoscopy findings in your decision to escalate a patient's chronic rhinosinusitis treatment?" and 2) report using integer values the number of years they have been practicing as a rhinologist (not including training). Next, nasal endoscopy scenarios were presented to the participants.

Nasal endoscopy scenarios were presented with MLK [8] and NPS [9] scales (Table 2). The MLK scale assesses three criteria (discharge, edema, and polyps) that are evaluated on each side of the nasal cavity, for a maximum bilateral score of 12 [8]. The NPS scale includes five levels of polyp size/extent [9] that is assessed on each side for a maximum bilateral score of 8. Each of these scales was explicitly explained to participants immediately before scenarios were presented to them. To achieve our primary objective, every possible combination of bilateral nasal endoscopy findings achievable using the MLK endoscopic scale (378 scenarios) and the NPS scale (15 scenarios) were presented to each participant. All nasal endoscopy findings based on MLK and NPS scales were provided in descriptive language and not numerical scores. As an example, one MLK endoscopic score scenario was presented as: "mild edema on one side, polyps confined to the middle meatus on the other side". In the first questionnaire, participants were instructed 1) that all scenarios were in reference to adult patients with primary diffuse CRS and 2) to consider each nasal endoscopy scenario in the absence of any CRS symptoms. No indication was given about prior endoscopic sinus surgery or (for MLK scenarios) polyp status for the hypothetical patients in each scenario to maintain the generality of our study findings. Participants were then asked whether they would consider CRS treatment with response options of "no", "maybe" and "yes". The comparison of response options "maybe" vs. "yes" was interpreted to reflect participants' strength of confidence or affirmation in considering treatment escalation. Twenty-four hours after completion of this questionnaire, the second questionnaire was made accessible to participants with the same nasal endoscopy scenarios as in the first questionnaire, but participants were instructed to consider the scenarios in the setting of 1 burdensome CRS symptom experienced by the patient. Methodologically, "1 burdensome CRS symptom" was chosen as the clinical context for the second questionnaire because previous work has suggested that at least 1 CRS disease manifestation (e.g., burdensome symptom) may be necessary for nasal endoscopy findings to maximally influence rhinologists' assessment of a lack of control [10].

Table 2. Endoscopic scoring scales*.

Modified Lund-Kennedy [8]	Nasal Polyp Score [9]
Polyps	0 = no polyps
0 = no polyps 1 = polyps in middle meatus only 2 = beyond middle meatus	1 = Small nasal polyps in the middle meatus not reaching below the inferior border of the middle turbinate
Edema	2 = Nasal polyps reaching below the lower border of the middle turbinate
0 = absent 1 = mild 2 = severe	3 = Large nasal polyps reaching the lower border of the inferior turbinate or nasal polyps medial to the middle turbinate (which score 2 plus additional nasal polyps medial and beyond the borders of the middle turbinate)
Discharge	
0 = no discharge 1 = thin, clear discharge 2 = thick, purulent discharge	4 = Large nasal polyps causing complete obstruction of the inferior nasal cavity

*For unilateral score; total score is calculated as the sum of both sides (i.e., sum of unilateral scores for left and right).

Participants were given 3 weeks to complete each questionnaire. Participants were also unable to access their responses from the first questionnaire when completing the second questionnaire. For both questionnaires, participants were instructed that neither the hypothetical patient's current treatment regimen nor how treatment would be escalated was being specified. Participants were explicitly asked to acknowledge that they understood these instructions.

Statistical analysis

All analyses were performed using the statistical software package R (www.r-project.org) [11]. Recruitment of participants was performed to 1) have sufficient sample size to identify mean MLK endoscopic score and NPS thresholds within 1 point of the true value with 95% power and 2) have broad representation of experts of different backgrounds, training and geographic locale. Correlations were performed using Spearman's method. For each nasal endoscopy scenario provided, the participant's response was dichotomized as an affirmative to whether they would consider escalation of treatment (response of "maybe" or "yes") or not (response of "no"). Where explicitly specified,

Table 3. Participant-level modified Lund-Kennedy endoscopy score predicting consideration for escalation of CRS treatment.

Participant*	In the absence of CRS symptoms			
	Cut-off	AUC	Sensitivity	Specificity
1	≥4	0.963	91.1%	88.9%
2	≥4	0.968	91.3%	90.0%
3	≥5	0.908	79.8%	94.1%
4	≥6	0.757	76.7%	60.5%
5	≥4	0.989	92.3%	100.0%
6	≥5	0.924	82.6%	87.9%
7	≥3	0.990	96.8%	100.0%
8	≥5	0.952	82.8%	96.7%
9	≥4	0.970	91.8%	91.7%
10	≥7	0.744	55.7%	79.2%
11	≥4	0.968	91.3%	90.0%
12	≥4	0.965	91.1%	88.9%
13	≥3	0.974	97.6%	87.5%
14	≥2	0.999	99.5%	100%
15	≥6	0.823	65.5%	85.7%
16	≥4	0.985	90.8%	100.0%
17	≥3	0.989	96.3%	100.0%
18	≥4	0.967	90.8%	87.5%
19	≥4	0.968	91.3%	90.0%
20	≥4	0.958	90.8%	87.5%
21	≥4	0.976	92.3%	100.0%
22	≥4	0.944	81.5%	92.3%
23	≥6	0.830	88.9%	60.0%
24	≥7	0.828	79.7%	70.2%
25	≥5	0.901	82.5%	82.9%
26	≥6	0.866	66.6%	89.1%
27	≥5	0.862	83.7%	74.5%
28	≥5	0.849	81.8%	71.1%
29	≥5	0.901	82.7%	83.3%

*Participant identification numbers were randomly assigned and do not reflect order of participants shown in Table 1.

Table 4. Participant-level Nasal Polyp Score predicting possible consideration for escalation of CRSwNP treatment.

Participant*	In the absence of CRS symptoms			
	Cut-off	AUC	Sensitivity	Specificity
1	≥2	1.00	100.0%	100.0%
2	≥3	0.942	84.6%	100.0%
3	≥2	1.000	100.0%	100.0%
4	≥5	0.990	100.0%	90.0%
5	≥3	0.986	91.7%	100.0%
6	≥4	0.852	100%	54.5%
7	≥1	1.000	100.0%	100.0%
8	≥3	0.986	91.7%	100.0%
9	≥3	0.942	84.6%	100.0%
10	≥5	0.900	80.0%	80.0%
11	≥1	1.000	100.0%	100.0%
12	≥1	1.000	100.0%	100.0%
13	≥1	1.000	100.0%	100.0%
14	≥1	1.000	100.0%	100.0%
15	≥3	1.000	100.0%	100.0%
16	≥1	1.000	100.0%	100.0%
17	≥1	1.000	100.0%	100.0%
18	≥1	1.000	100.0%	100.0%
19	≥1	1.000	100.0%	100.0%
20	≥1	1.000	100.0%	100.0%
21	≥3	1.000	100.0%	100.0%
22	≥3	0.986	91.7%	100.0%
23	≥4	0.954	88.9%	83.3%
24	≥5	0.900	80.0%	80.0%
25	≥3	1.000	100.0%	100.0%
26	≥4	0.955	81.8%	100.0%
27	≥3	0.986	91.7%	100.0%
28	≥5	0.954	83.3%	88.9%
29	≥3	0.986	91.7%	100.0%

*Participant identification numbers were randomly assigned and do not reflect order of participants shown in Table 1.

secondary analyses reflecting participants' stronger confidence in treatment escalation were performed by dichotomizing the participant's response such that an affirmative response was defined only by a response of "yes".

Analyses of scenarios using MLK and NPS scales were performed separately. All analyses were performed in relation to total bilateral MLK score and total bilateral NPS. Associations with consideration for treatment escalation as a dependent variable were sought with logistic regression. Threshold MLK score and NPS for consideration of treatment escalation were determined on a participant-by-participant basis using receiver operator characteristic (ROC) curve analysis. Threshold MLK score and NPS were chosen as those that maximized the sum of sensitivity and specificity for predicting consideration for treatment escalation. In the rare circumstances when two different threshold scores were identified that maximized the sum of sensitivity and specificity, the threshold score that maximized positive predictive value between those two threshold scores was chosen. For every ROC analysis, the area under the ROC curve (AUC) was calculated using the trapezoid rule.

Results

Study participants

A total of 29 rhinologists with different backgrounds (geograp-

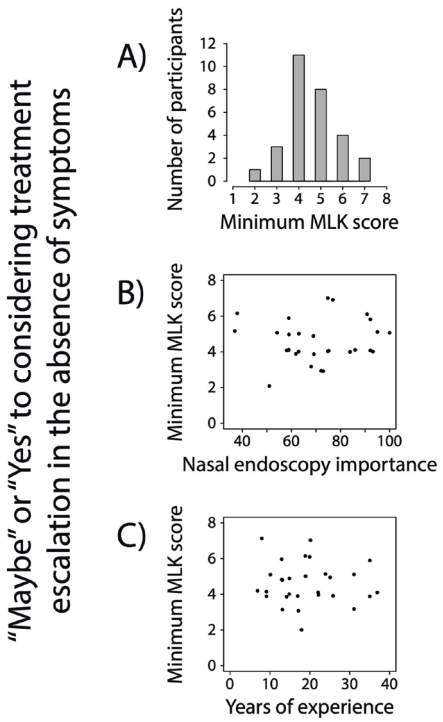

Figure 1. Participants' modified Lund-Kennedy endoscopic score thresholds in the absence of CRS symptoms that best predict consideration for CRS treatment escalation A) shown in a histogram plot and plotted against participants' B) ratings of importance of nasal endoscopy findings in their decision to escalate CRS treatment and C) years of experience.

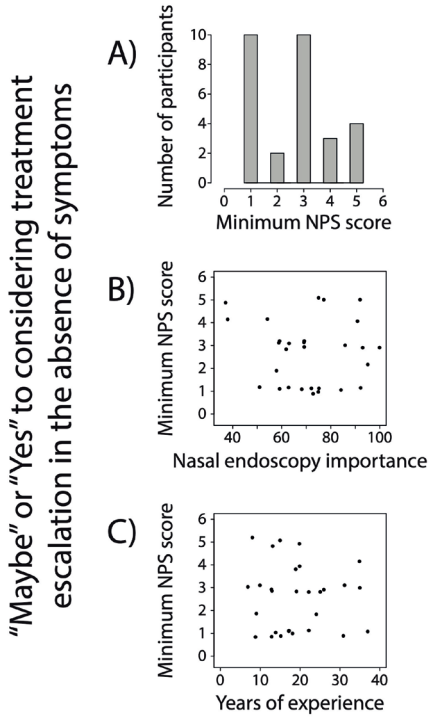

Figure 2. Participants' nasal polyp score thresholds in the absence of CRS symptoms that best predict consideration for CRS treatment escalation A) shown in a histogram plot and plotted against participants' B) ratings of importance of nasal endoscopy findings in their decision to escalate CRS treatment and C) years of experience.

hic areas and experience) were recruited and their identities are summarized in Table 1. These participants consisted of 15 (51.7%) males and 14 (48.3%) females and had a mean of 19.2 years (SD: 8.5; median: 18; range: 7 – 37) of experience in independent practice as a rhinologist. Participants rated the importance of nasal endoscopy findings in their decision to escalate a patient's CRS treatment (on a scale of 0 [not at all important] to 100 [of utmost importance]) with mean score of 71.0 (SD: 16.3, median: 69, range: 37 – 100).

Escalation of chronic rhinosinusitis treatment based on modified Lund-Kennedy scale nasal endoscopy findings in the absence of symptoms

Given a nasal endoscopy finding in the absence of CRS symptoms, participants were asked whether they would consider CRS treatment escalation. Out of 378 different bilateral discharge, edema, and polyp score combinations within the MLK scale, the median number of scenarios for which participants indicated no consideration for treatment escalation was 13 (range: 2 – 299, mean: 46, SD: 73), indicating that for most scenarios, nasal endoscopy findings reflected in the MLK score may motivate consideration for CRS treatment escalation. Consideration of treatment escalation was associated with similar magnitude with each of the MLK components (discharge, edema and polyps) scores (Supplemental materials). The total bilateral MLK score thresholds that best predicted when each participant would consider escalating a patient's CRS treatment are shown in Table 3 and Figure 1A. The median threshold for MLK score that led to consideration for escalation of treatment in the absence of any CRS symptoms was ≥4 (range: 2 – 7, mean: 4.6, SD: 1.2) and 22 out of 29 (75.9%) participants' MLK score thresholds were within 1 point of 4. For no participant was any nasal endoscopy finding (i.e., a threshold MLK score of ≥1) the best predictor for consideration of CRS treatment escalation in the absence of CRS symptoms. Neither the participants' ratings of the importance they placed on nasal endoscopy in treatment escalation (ρ=0.07, p=0.689) nor the participants' years of experience (ρ = -0.02, p=0.904) in practice correlated with their MLK threshold for considering treatment escalation in the absence of symptoms (Figures 1B and 1C).

Escalation of chronic rhinosinusitis with nasal polyps treatment based on nasal endoscopy findings reflecting Nasal Polyp Score in the absence of symptoms

We next asked participants to focus on chronic rhinosinusitis with nasal polyps (CRSwNP) and whether they would consider

escalation of treatment based on nasal endoscopy findings reflecting all possible combinations of the NPS scale in the absence of CRS symptoms. Out of 15 different polyp score combinations in NPS, the median number of scenarios for which participants indicated no consideration for treatment escalation was 3 (range: 1 – 11, mean: 4, SD: 3), indicating that many scenarios reflected in the NPS scale may motivate consideration for CRS treatment escalation. The total bilateral NPS thresholds that best identified when each participant would consider escalating treatment of a patient's CRSwNP are shown in Table 4 and Figure 2A. The median NPS threshold that led to consideration for treatment escalation was ≥3 (range: 1 – 5, mean: 2.6, SD: 1.4), and 15 out of 29 (62.5%) participants' NPS thresholds were within 1 point of 3. The distribution of participants' NPS thresholds for consideration of treatment escalation was bimodal. While ten participants indicated that any visualization of nasal polyps (i.e., an NPS ≥1) would trigger consideration of CRSwNP treatment escalation, 10 other participants indicated that a minimum NPS of 3 would be necessary to consider CRSwNP treatment escalation. Neither the participants' ratings of the importance they place on nasal endoscopy in treatment escalation (ρ= -0.03, p=0.868) nor the participants' years of experience in practice (ρ= -0.03, p=0.877) correlated with their NPS threshold for considering treatment escalation in the absence of symptoms (Figures 2B and 2C).

Influence of symptoms and certainty in consideration of treatment escalation on modified Lund-Kennedy score and Nasal Polyp Score thresholds

We also evaluated how the impact of CRS symptoms and certainty in rhinologists' consideration of treatment escalation would influence the MLK score and NPS thresholds that we identified. To study the impact of CRS symptomatology, all nasal endoscopy scenarios were presented to rhinologists in the context of a CRS patient also having 1 burdensome CRS symptom. For both MLK score and NPS, this led to generally lower thresholds at which rhinologists would consider treatment escalation, i.e., in the presence of a burdensome CRS symptom, less endoscopic burden of disease was required for rhinologists to consider treatment escalation (Supplemental materials).

To study the impact of rhinologists' strength of confidence in consideration of treatment escalation on MLK score and NPS thresholds, we repeated our analyses by defining affirmation for considering treatment escalation as only a response of "yes" (i.e., not including the "maybe" response option). We found that for MLK score, this led to higher thresholds, indicating that greater endoscopic disease burden was required for participants to more strongly consider treatment escalation. For example, in the absence of CRS symptoms, stronger confidence in consideration for CRS treatment escalation required a median MLK score ≥6 (Supplemental materials). For NPS, however, the median threshold for considering treatment escalation—for both an asymptomatic patient and a patient with 1 burdensome CRSwNP symptom—stayed stable at NPS ≥3 (Supplemental materials).

Discussion

Use of nasal endoscopy findings as a criterion for judging CRS disease control is controversial with a paucity of supportive evidence [5,12]. However, guidance may be derived from the practice patterns of those with expertise in the management of CRS—specifically, what level of nasal endoscopy findings would trigger their consideration of CRS treatment escalation as the real-world reflection of CRS disease control assessment. Among our rhinologist study participants, we found that consideration for CRS treatment escalation was triggered by a median MLK score ≥4 or a median NPS ≥3, with overall low variability between participants. These values of MLK score and NPS may therefore serve as thresholds for nasal endoscopy findings—as reflections of CRS that is not controlled—to trigger consideration of CRS treatment escalation. As a corollary, MLK score <4 or NPS <3 may therefore serve as nasal endoscopy goals in the treatment of CRS.

The first criteria for CRS disease control were proposed by the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) and included a nasal endoscopy criterion that considered any nasal endoscopy finding reflecting "diseased mucosa" (e.g., edema, nasal polyps, or discharge) as a reflection of lost CRS disease control [13]. However, subsequent studies have shown that this nasal endoscopy criterion may be inessential, rarely changing the EPOS classification of CRS control [14,15]. The significance of nasal endoscopy findings as a CRS treatment target has also been called into question by weak - or no - correlation with patients' CRS symptom burden or quality of life [7,8,16-18]. Nevertheless, the reality is that nasal endoscopy findings play an important role in rhinologists' assessment of CRS disease control. Nasal endoscopy findings are among the CRS disease characteristics that most greatly associate with how rhinologists assess a patient's CRS disease control, playing an especially important role by providing tangible evidence of active disease to which to attribute symptoms [10]. However, it remains unclear how exactly the magnitude of disease burden observed in nasal endoscopy is used by rhinologists to judge disease control in CRS and by extension, to direct treatment of CRS.

In this study, by synthesizing the treatment decisions of 29 rhinologists, we found that consideration for CRS treatment escalation occurred at a median total bilateral MLK score ≥4 or a median total bilateral NPS ≥3 in the absence of CRS symptoms. With low variation around these median values in the broad and diverse group of rhinologists who participated in this study, MLK score ≥4 or NPS ≥3 could therefore serve as thresholds to trigger consideration for escalation of CRS treatment. These results also imply that an MLK score <4 or an NPS <3 may be indicative of

acceptable endoscopic CRS disease burden and therefore specifically represent outcomes that could serve as endoscopic goals for treatment of CRS. As expected, the presence of burdensome CRS symptomatology reduced these thresholds while requiring a stronger affirmation for consideration of treatment escalation could increase these thresholds. Unexpectedly, the degree of importance that participants explicitly placed on nasal endoscopy findings to impact CRS treatment decisions did not correlate with the threshold MLK score or NPS at which they would consider treatment escalation. Similarly, participants' years of experience in clinical practice as a rhinologist did not correlate with the threshold MLK score or NPS at which they would consider treatment escalation. Our analysis of nasal endoscopy findings reflecting NPS for CRSwNP patients also indicated a greater predilection to consider treatment escalation for lesser findings compared to MLK score. For example, even in the absence of CRSwNP symptoms, a sizeable group of rhinologists considered treatment escalation for any nasal polyps (NPS ≥1). In fact, the threshold NPS for consideration of treatment escalation in the absence of CRSwNP symptoms was bimodal with one modal group representing the rhinologists who considered treatment escalation due to any nasal polyps while the other larger modal group of rhinologists required higher NPS (≥3) to consider CRSwNP treatment escalation. Moreover, while the median MLK score threshold for consideration of treatment escalation was sensitive to various factors (for example increasing to ≥6 when requiring a stronger affirmation for consideration of treatment escalation), the median NPS threshold remained stable at NPS ≥3 regardless of how strongly we required study participants to affirm consideration of treatment escalation and regardless of whether the scenario involved an asymptomatic patient or a patient with a burdensome CRSwNP symptom.

Our results provide novel insights and have important implications for the use of nasal endoscopy findings in CRS disease control assessment and treatment decisions. The present study is the first to explicitly show the full breadth and variability in how endoscopic burden of CRS influences treatment decisions in a diverse group of rhinologists by identifying specific, quantitative thresholds for nasal endoscopy findings in terms of MLK score and NPS that would lead these rhinologists to consider treatment escalation. Our results also illustrate that the variability in nasal endoscopy score thresholds was overall not large, reflecting the large degree of commonality between rhinologists. Moreover, the lack of correlation between participants' rating of importance they placed on nasal endoscopy findings and their threshold values of MLK score and NPS may also reflect commonality between rhinologists despite differences in their conscious and outwardly stated opinions regarding the role of nasal endoscopy. Perhaps the most important implications of our results are that any positive (i.e., non-zero) nasal endoscopy may be insufficient to indicate loss of CRS control (i.e., unacceptability of nasal endoscopy findings) in the opinion of most rhinologists, as reflected by our findings that MLK score ≥4 and NPS ≥3 are required by the majority of rhinologists to trigger consideration for CRS treatment escalation. In fact, some positive nasal endoscopy findings may be acceptable. For example, achieving an MLK score <4 and NPS <3 could be viewed as an alternative treatment goal to the complete absence of any nasal endoscopy finding (i.e., nasal endoscopy scores of zero).

Our results should be interpreted in the context of our study limitations. Although we have identified MLK score ≥4 and NPS ≥3 as possible thresholds for endoscopic burden of disease to indicate loss of disease control and trigger consideration of treatment escalation in a manner globally reflective of our study participants, variability existed on a participant-by-participant level. This variability could be related to participants' individual interpretations of the descriptive endoscopic findings based on the MLK and NPS scales. Moreover, we acknowledge the presence of confounding factors, such as concomitant CRS symptomatology, that could impact how endoscopic disease burden influences consideration for treatment escalation. For these reasons, we have sought to transparently report all results—from participant-level results to results accounting for the presence of burdensome CRS symptomatology and accounting for strength in confidence/affirmation of consideration for treatment escalation. Finally, although study participants were instructed to consider nasal endoscopy findings independent of the patient's current treatment regimen or how treatment would be escalated, these factors may very well influence consideration for treatment escalation. Therefore, treatment-specific approaches may be developed in the future while our current results may presently provide a general framework for using endoscopic burden of disease to motivate treatment decisions.

Conclusion

Endoscopic burden of CRS reflected by MLK score ≥4 or NPS ≥3 may be used as thresholds to indicate loss of CRS disease control. Alternatively, MLK score <4 or NPS <3 may serve as endoscopic goals of CRS treatment. However, factors such as the presence of concomitant burdensome CRS symptomatology influence the thresholds of endoscopic disease burden that motivate CRS treatment decisions. Nevertheless, our results, reflecting diverse expert rhinologists' practice patterns, may provide guidance for how endoscopic burden of disease could inform treatment decisions as a criterion of CRS disease control.

Authorship contribution

ARS: concept of study, study design, collection of data, statistical analysis, interpretation of results, write up of manuscript, critical review of all contents. RAC, IA, SA, WTAL, MBS, RKC, JC, WJF, CF, STG, AAH, EHH, CH, PHH, ECK, BNL, VJL, EDM, VNL, EKO, CMP, SDP, MAP, SR, JR, STS, EWW, MBW, SKW, BAW, WCY: collection of

data, interpretation of results, write up of manuscript, critical review of all contents. KMP: study design, interpretation of results, write up of manuscript, critical review of all contents.

Conflict of interest

The authors declare that they have no conflicts of interests related to the contents of this study.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Association of modified Lund-Kennedy scale components with consideration for treatment escalation

For the MLK scenarios presented in the context of no CRS symptoms, we also checked for association between consideration for treatment escalation (as the dependent variable) and the individual MLK scale component scores for discharge, edema and polyps (as independent variables all considered simultaneously in a multivariable regression). We found that consideration for treatment escalation was significantly associated with all component scores: discharge (OR=1.95, 95%CI: 1.84 – 2.07, p<0.001), edema (OR=1.30, 95%CI: 1.23 – 1.37, p<0.001) and polyp (OR = 1.77, 95%CI: 1.68 – 1.87, p<0.001) scores. In line with these findings, consideration for treatment escalation was associated with the presence of at least a score of 2 on either side of the patient for discharge—(OR = 2.86, 95%CI: 2.65 – 3.09, p<0.001)—i.e., "thick, purulent mucus", edema (OR=1.45, 95%CI: 1.37 – 1.55, p<0.001)—i.e., "severe edema", and polyps (OR=1.81, 95%CI: 1.70 – 1.93, p<0.001)—i.e., polyps extending beyond/outside of the middle meatus, while controlling for the MLK component (discharge, edema, and polyp) score in the other categories respectively.

For the MLK scenarios presented in the context of 1 burdensome CRS symptom, we similarly sought association between consideration for treatment escalation (as the dependent variable) and the individual discharge, edema and polyp score components of the MLK scale (as independent variables) using a multivariable regression model. We found that consideration for treatment escalation was similarly associated with all MLK component scores: discharge (OR=2.26, 95%CI: 1.96 – 2.61, p<0.001), edema (OR=2.20, 95%CI: 1.91 – 2.54, p<0.001) and polyp (OR = 6.33, 95%CI: 5.08 – 7.89, p<0.001) scores. Consideration for treatment escalation was associated with the presence of at least a score of 2 on either side for discharge—(OR = 4.03, 95%CI: 3.16 – 5.14, p<0.001)—i.e., "thick, purulent mucus", edema (OR=2.62, 95%CI: 2.18 – 3.16, p<0.001)—i.e., "severe edema", and polyps (OR=7.54, 95%CI: 4.83 – 11.76, p<0.001)—i.e., polyps extending beyond/outside of the middle meatus, while controlling for the MLK component (discharge, edema, and polyps) score in the other categories respectively.

Influence of 1 burdensome CRS symptom on consideration of treatment escalation based on modified Lund-Kennedy score

We presented the 378 different possible discharge, edema and polyp score combinations in the MLK endoscopy scale and for each, asked participants whether they would consider CRS treatment escalation if the patient had 1 burdensome symptom. Affirmative consideration for treatment escalation was defined as response of "maybe" or "yes". Out of 378 different scenarios, the median number for which participants indicated no consideration for escalation of treatment was 3 (range: 0 – 87, mean: 7, SD: 16), indicating that almost all positive nasal endoscopy findings reflected in MLK scale—in the setting of a burdensome CRS symptom experienced by the patient—may motivate consideration for escalation of CRS treatment. The MLK scores that best identified when each participant would consider escalating treatment of a patient's CRS are shown in Supplemental Table 1 and Supplemental Figure 1A. The median MLK score prompting consideration for CRS treatment escalation was ≥3 (range: 0 – 6, mean: 2.6, SD: 1.8). For 6 participants, any nasal endoscopy finding (i.e., a threshold MLK score of ≥1) prompted CRS treatment escalation. For 5 participants, treatment escalation would be considered for all scenarios (even with no nasal endoscopy findings) in the setting of 1 burdensome symptom. The MLK threshold for considering treatment escalation in the presence of 1 burdensome CRS symptom was weakly correlated with participants' ratings of the importance they place on nasal endoscopy in treatment escalation ($\rho = 0.37$, $p = 0.049$) but not participants' years of experience ($\rho = 0.10$, $p = 0.602$) (Supplemental Figures 1B and C).

Influence of 1 burdensome CRS symptom on consideration of treatment escalation based on Nasal Polyp Score

We provided all 15 different possible combinations of the NPS scale and asked participants whether they would consider CRSwNP treatment escalation given each of those endoscopic findings if the patient was also experiencing 1 burdensome CRSwNP symptom. Consideration for treatment escalation was again defined by responses of "maybe" or "yes". Out of 15 different NPS scenarios, the median number of scenarios for which participants indicated no consideration for escalation of treatment was 1 (range: 0 – 5, mean: 1, SD: 1), indicating that the majority of polyp findings on nasal endoscopy reflected in the NPS scale motivated consideration for escalation of CRS treatment. The NPS that best identified when each participant would consider escalating treatment of a patient's CRSwNP is shown in Supplemental Table 2 and Supplemental Figure 2A. The median threshold for NPS that led to consideration for escalation of treatment was ≥1 (range: 0 – 4, mean: 1.6, SD: 1.0). Six participants indicated that they would consider treatment escalation for a CRSwNP patient even without any nasal polyp findings on endoscopy (NPS = 0). Fifteen participants indicated that any visualization of nasal polyps (i.e., an NPS ≥1) would trigger consideration of CRSwNP treatment escalation. However, a second peak of participants indicated that the minimum NPS that would trigger consideration of treatment escalation was 3 (Supplemental Figure 2A). Neither the participants' ratings of the importance they place on nasal endoscopy in treatment

escalation ($\rho = 0.010$, p=0.616) nor the participants' years of experience in practice ($\rho = 0.082$, p=0.672) correlated with their NPS threshold for considering treatment escalation in the presence of 1 burdensome CRSwNP symptom (Supplemental Figures 2B and 2C).

Influence of confidence in consideration of treatment escalation on modified Lund-Kennedy score threshold

From when we presented the 378 different discharge, edema and polyp score combinations in the MLK endoscopy scale to our rhinologist study participants and asked whether they would consider CRS treatment escalation in the absence of CRS symptoms, we next used only a response of "yes" (out of possible choices "no", "maybe" and "yes") to indicate greater confidence in considering treatment escalation for the nasal endoscopy scenarios. In this case, out of the 378 different combinations in the MLK scale, the median number of scenarios for which participants indicated no consideration for escalation of treatment was 85 (range: 9 – 378, mean: 141, SD: 129), still indicating that the majority of scenarios of positive nasal endoscopy findings would motivate consideration for escalation of CRS treatment. However, it should be noted that four participants did not affirmatively respond to any scenario with "yes"—they only provided "maybe" responses. Excluding those four participants, with this alternative and stricter definition for consideration of treatment escalation (Supplemental Table 3 [left] and Supplemental Figure 3), the median threshold for MLK score that led to consideration for escalation of treatment was ≥6 (range: 4 – 8, mean ≥5.8, SD: 1.1).

Next, we re-analyzed the MLK scenarios that were presented to participants in the context of a patient experiencing 1 burdensome CRS symptom and again used only a response of "yes" to indicate greater confidence in affirmation to the question of considering CRS treatment escalation. Out of the 378 different combinations in the MLK scale, the median number of scenarios for which participants indicated no consideration for escalation of treatment was 23 (range: 1 – 378, mean: 57, SD: 81), still indicating that the majority of scenarios of positive nasal endoscopy findings in the setting of a burdensome CRS symptom motivated consideration for escalation of CRS treatment. However, one participant did not affirmatively respond to any scenario with "yes"—instead only providing "maybe" responses. Excluding that one participant, the median threshold MLK score that led to consideration for escalation of treatment (Supplemental Table 3, right and Supplemental Figure 4) was ≥5 (range: 1 – 7, mean: 4.8, SD: 1.2).

Influence of confidence in consideration of treatment escalation on Nasal Polyp Score threshold

In the context of a patient with no CRSwNP symptoms, we presented the 15 different possible combinations in the NPS scale to our rhinologist study participants and asked whether they would consider CRSwNP treatment escalation. We again performed our analyses by only using a response of "yes" to indicate greater confidence in affirmation to the question of considering CRS treatment escalation in response to the NPS scenarios. In this case, out of the 15 different combinations in the NPS scale, the median number of scenarios for which participants indicated no consideration for treatment escalation was 6 (range: 1 – 15, mean: 7, SD: 5), still indicating that the majority of scenarios of positive NPS scale findings may motivate consideration for escalation of CRSwNP treatment. However, six participants did not affirmatively respond to any scenario with "yes"—they only provided "maybe" responses. Excluding those six participants, the median threshold for NPS (Supplemental Table 4, left and Supplemental Figure 5) that led to consideration for escalation of treatment was ≥3 (range: 1 – 8, mean: 3.5, SD: 1.5).

Next, we presented the NPS scenarios to participating rhinologists in the context of patient experiencing 1 burdensome CRSwNP symptom and asked whether they would consider CRSwNP treatment escalation but again performed our analyses by only using a response of "yes" to indicate greater confidence in affirmation to the question of considering treatment escalation. Out of the 15 different combinations in the NPS scale, the median number of scenarios for which participants indicated no consideration for escalation of treatment was 3 (range: 1 – 15, mean: 4, SD: 3), still indicating that the majority of scenarios of positive NPS scale findings may motivate consideration for escalation of CRSwNP treatment. However, it should be noted that one participant did not affirmatively respond to any scenario with "yes"—only "maybe" responses. Excluding that 1 participant, the median threshold for NPS (Supplemental Table 4, right and Supplemental Figure 6) that led to consideration for escalation of treatment was ≥3 (range: 1 – 5, mean: 2.7, SD: 1.2).

Supplemental Table 1. Participant-level modified Lund-Kennedy endoscopy score predicting possible consideration for escalation of CRS treatment in the presence of 1 burdensome CRS symptom.

Participant*	In the presence of 1 burdensome CRS symptom			
	Cut-off	AUC	Sensitivity	Specificity
1	≥3	0.992	96.5%	100.0%
2	≥0	—	—	—
3	≥3	0.992	96.5%	100.0%
4	≥1	1.000	100.0%	100.0%
5	≥4	0.978	90.1%	100.0%
6	≥4	0.965	91.8%	91.7%
7	≥3	0.992	96.5%	100.0%
8	≥4	0.968	91.3%	90.0%
9	≥4	0.958	90.8%	87.5%
10	≥0	—	—	—
11	≥2	0.999	99.5%	100.0%
12	≥3	0.992	96.5%	100.0%
13	≥0	—	—	—
14	≥1	1.000	100.0%	100.0%
15	≥1	1.000	100.0%	100.0%
16	≥1	1.000	100.0%	100.0%
17	≥1	1.000	100.0%	100.0%
18	≥5	0.961	77.9%	100.0%
19	≥4	0.986	91.1%	100.0%
20	≥3	0.992	96.5%	100.0%
21	≥4	0.984	92.6%	100.0%
22	≥5	0.945	80.4%	95.0%
23	≥6	0.890	74.2%	88.5%
24	≥4	0.968	91.3%	90.0%
25	≥3	0.993	97.1%	100.0%
26	≥0	—	—	—
27	≥4	0.965	90.8%	87.5%
28	≥1	1.000	100.0%	100.0%
29	≥0	—	—	—

*Participant identification numbers were randomly assigned and do not reflect order of participants shown in Table 1.

Supplemental Table 2. Participant-level Nasal Polyp Score predicting possible consideration for escalation of CRSwNP treatment in the presence of 1 burdensome CRSwNP symptom.

Participant*	In the presence of 1 burdensome CRSwNP symptom			
	Cut-off	AUC	Sensitivity	Specificity
1	≥1	1.000	100.0%	100.0%
2	≥0	—	—	—
3	≥1	1.000	100.0%	100.0%
4	≥1	1.000	100.0%	100.0%
5	≥3	0.986	91.7%	100.0%
6	≥4	0.990	90.0%	100.0%
7	≥1	1.000	100.0%	100.0%
8	≥3	0.986	91.7%	100.0%
9	≥3	0.942	84.6%	100.0%
10	≥0	—	—	—
11	≥1	1.000	100.0%	100.0%
12	≥1	1.000	100.0%	100.0%
13	≥0	—	—	—
14	≥1	1.000	100.0%	100.0%
15	≥0	—	—	—
16	≥1	1.000	100.0%	100.0%
17	≥1	1.000	100.0%	100.0%
18	≥1	1.000	100.0%	100.0%
19	≥1	1.000	100.0%	100.0%
20	≥1	1.000	100.0%	100.0%
21	≥3	1.000	100.0%	100.0%
22	≥3	0.986	91.7%	100.0%
23	≥4	0.990	90.0%	100.0%
24	≥3	0.986	91.7%	100.0%
25	≥1	1.000	100.0%	100.0%
26	≥1	1.000	100.0%	100.0%
27	≥1	1.000	100.0%	100.0%
28	≥0	—	—	—
29	≥0	—	—	—

*Participant identification numbers were randomly assigned and do not reflect order of participants shown in Table 1.

Supplemental Table 3. Participant-level modified Lund-Kennedy endoscopy score predicting a response of "yes" to consideration for escalation of CRS treatment.

Participant*	In the absence of CRS symptoms				With 1 burdensome CRS symptom			
	Cut-off	AUC	Sensitivity	Specificity	Cut-off	AUC	Sensitivity	Specificity
1	≥5	0.913	79.7%	88.9%	≥4	0.963	91.3%	90.0%
2	≥6	0.847	72.6%	79.6%	≥4	0.973	92.3%	92.9%
3	≥7	0.738	52.0%	82.3%	≥5	0.949	79.8%	100.0%
4	**	—	—	—	≥5	0.900	80.6%	87.0%
5	≥5	0.962	83.0%	96.8%	≥5	0.903	79.7%	88.9%
6	≥6	0.910	74.5%	91.7%	≥6	0.860	71.9%	81.4%
7	≥4	0.968	91.3%	90.0%	≥4	0.968	91.3%	90.0%
8	≥6	0.894	84.8%	76.6%	≥5	0.944	83.9%	91.9%
9	≥5	0.880	84.2%	75.5%	≥5	0.914	81.5%	88.9%
10	**	—	—	—	≥5	0.935	83.8%	89.5%
11	≥4	0.968	91.3%	90.0%	≥3	0.992	97.3%	100.0%
12	≥4	0.965	91.1%	88.9%	≥3	0.992	96.5%	100.0%
13	≥6	0.913	71.6%	94.1%	≥5	0.961	77.9%	100.0%
14	≥6	0.755	76.3%	60.2%	≥1	1.000	100.0%	100.0%
15	≥8	0.792	68.2%	79.2%	≥6	0.838	70.3%	80.8%
16	≥5	0.823	82.7%	65.3%	≥5	0.902	80.1%	85.7%
17	≥6	0.868	70.1%	85.7%	≥4	0.938	93.3%	81.0%
18	≥6	0.867	64.2%	93.1%	≥4	0.968	92.1%	92.3%
19	≥6	0.843	71.7%	81.2%	≥5	0.967	81.9%	100.0%
20	≥6	0.845	70.8%	81.2%	≥6	0.835	70.4%	79.0%
21	≥4	0.982	92.8%	100.0%	≥4	0.984	92.6%	100.0%
22	≥7	0.846	68.2%	84.9%	≥6	0.834	76.0%	75.0%
23	≥7	0.813	82.2%	65.5%	≥7	0.883	81.8%	82.1%
24	**	—	—	—	≥6	0.870	72.7%	84.7%
25	**	—	—	—	**	—	—	—
26	≥7	0.795	54.6%	88.2%	≥6	0.849	73.4%	82.6%
27	≥6	0.760	76.4%	60.6%	≥6	0.785	74.6%	68.5%
28	≥6	0.752	74.8%	61.5%	≥5	0.832	84.7%	70.2%
29	≥6	0.849	71.0%	83.3%	≥4	0.963	91.1%	88.9%

*Participant identification numbers were randomly assigned and do not reflect order of participants shown in Table 1.

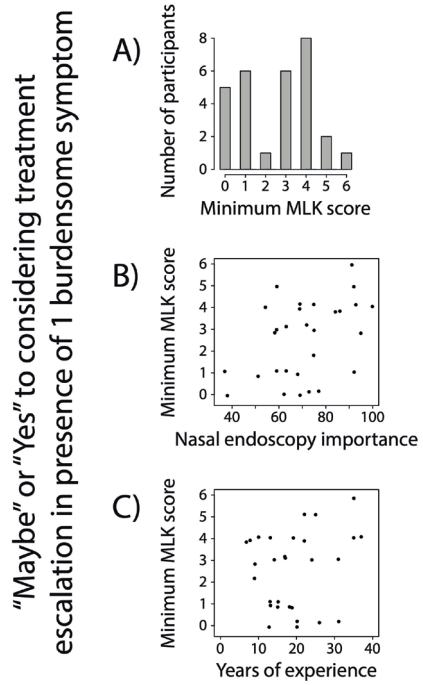
**Participant did not respond with "yes" to consideration for treatment escalation for any scenario.

Supplemental Table 4. Participant-level Nasal Polyp Scores predicting a response of "yes" to consideration for escalation of CRSwNP treatment.

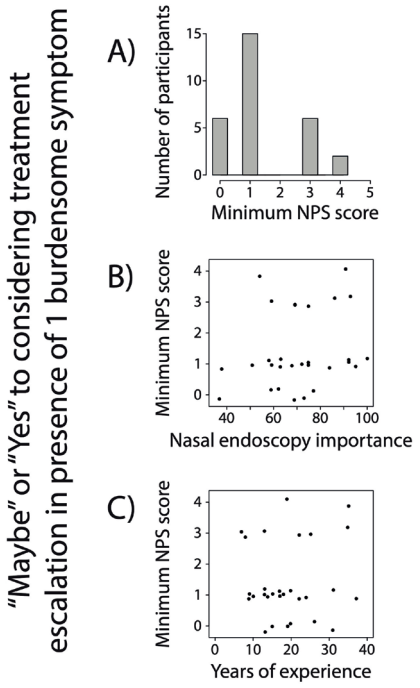
Partici-pant*	In the absence of CRSwNP symptoms				With 1 burdensome CRSwNP symptom			
	Cut-off	AUC	Sensitivity	Specificity	Cut-off	AUC	Sensitivity	Specificity
1	≥3	0.986	91.7%	100.0%	≥2	1.000	100.0%	100.0%
2	≥4	0.954	88.9%	83.3%	≥2	1.000	100.0%	100.0%
3	≥3	1.00	100.0%	100.0%	≥2	1.000	100.0%	100.0%
4	**	—	—	—	≥3	0.986	91.7%	100.0%
5	≥4	0.990	90.0%	100.0%	≥3	0.986	91.7%	100.0%
6	**	—	—	—	≥5	0.900	80.0%	80.0%
7	≥3	0.986	91.7%	100.0%	≥1	1.000	100.0%	100.0%
8	≥4	0.954	88.9%	83.3%	≥4	0.990	90.0%	100.0%
9	≥3	0.986	91.7%	100.0%	≥4	0.955	81.8%	100.0%
10	≥5	0.900	80.0%	80.0%	≥3	0.986	91.7%	100.0%
11	≥1	1.000	100.0%	100.0%	≥1	1.000	100.0%	100.0%
12	≥1	1.000	100.0%	100.0%	≥1	1.000	100.0%	100.0%
13	≥3	0.986	91.7%	100.0%	≥2	1.000	100.0%	100.0%
14	**	—	—	—	≥1	1.000	100.0%	100.0%
15	**	—	—	—	≥4	0.954	88.9%	83.3%
16	≥3	0.986	91.7%	100.0%	≥3	0.986	91.7%	100.0%
17	≥3	0.986	91.7%	100.0%	≥2	1.000	100.0%	100.0%
18	≥1	1.000	100.0%	100.0%	≥1	1.000	100.0%	100.0%
19	≥3	0.986	91.7%	100.0%	≥2	1.000	100.0%	100.0%
20	≥3	0.986	91.7%	100.0%	≥3	0.986	91.7%	100.0%
21	≥3	1.000	100.0%	100.0%	≥3	1.000	100.0%	100.0%
22	≥4	0.954	88.9%	83.3%	≥4	0.954	88.9%	83.3%
23	≥5	0.900	80.0%	80.0%	≥5	0.982	85.7%	100.0%
24	**	—	—	—	≥4	0.954	88.9%	83.3%
25	**	—	—	—	**	—	—	—
26	≥5	0.732	57.1%	75.0%	≥3	1.000	100.0%	100.0%
27	≥4	0.954	88.9%	83.3%	≥4	0.954	88.9%	83.3%
28	≥8	1.000	100.0%	100.0%	≥3	1.000	100.0%	100.0%
29	≥4	0.954	88.9%	83.3%	≥1	1.000	100.0%	100.0%

*Participant identification numbers were randomly assigned and do not reflect order of participants shown in Table 1.

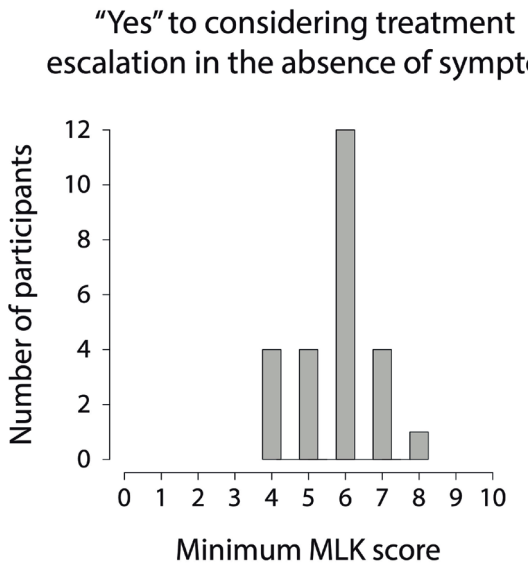
**Participant did not respond with "yes" to consideration for treatment escalation for any scenario.



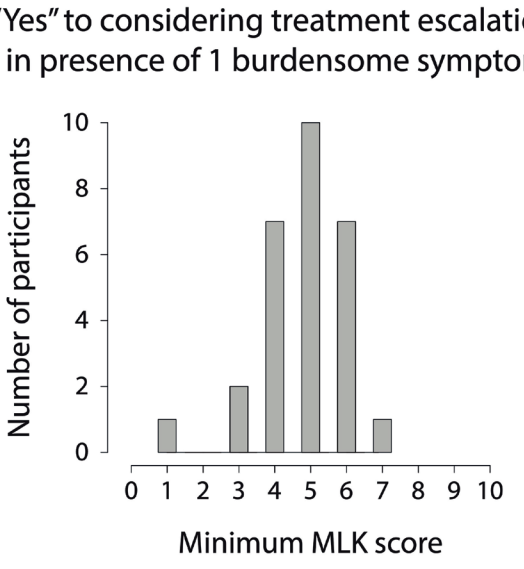
Supplemental Figure S1. Participants' modified Lund-Kennedy score thresholds in the presence of 1 burdensome CRS symptom that best predict a response of "maybe" or "yes" to consideration for CRS treatment escalation A) shown in a histogram plot and plotted against participants' B) ratings for importance of nasal endoscopy findings to their decision to escalate CRS treatment and C) years of experience.



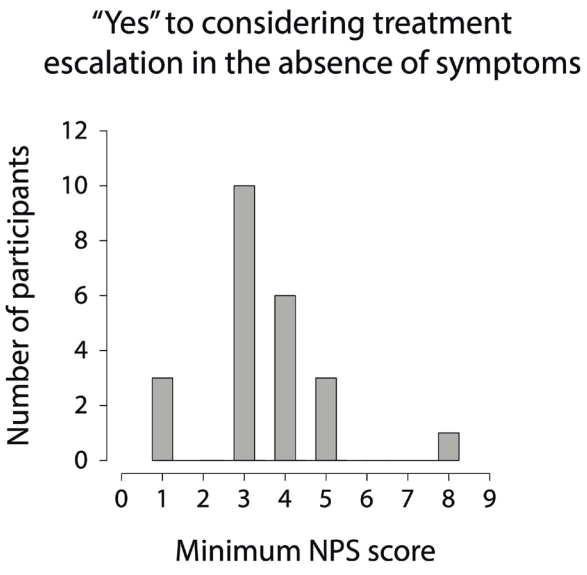
Supplemental Figure S2. Participants' nasal polyp score thresholds in the presence of 1 burdensome CRSwNP symptom that best predict a response of "maybe" or "yes" to consideration for CRSwNP treatment escalation A) shown in a histogram plot and plotted against participants' B) ratings for importance of nasal endoscopy findings to their decision to escalate CRSwNP treatment and C) years of experience.



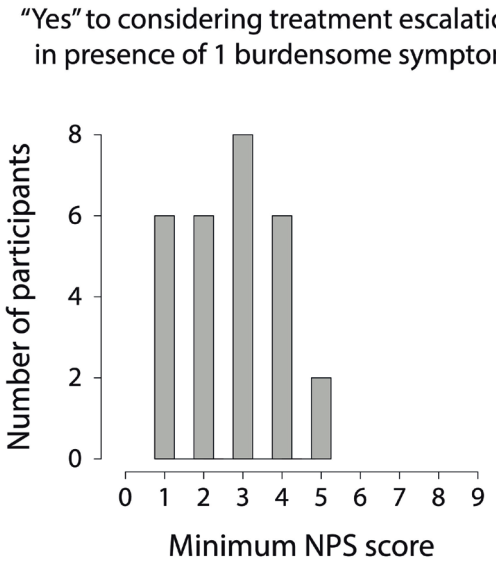
Supplemental Figure S3. Histogram plot of participants' modified Lund-Kennedy score thresholds in the absence of CRS symptoms that best predict a response of "yes" to consideration for CRS treatment escalation.



Supplemental Figure S4. Histogram plot of participants' modified Lund-Kennedy score thresholds in the presence of 1 burdensome CRS symptom that best predict a response of "yes" to consideration for CRS treatment escalation.



Supplemental Figure S5. Histogram plot of participants' Nasal Polyp Score thresholds in the absence of CRSwNP symptoms that best predict a response of "yes" to consideration for CRSwNP treatment escalation.



Supplemental Figure S6. Histogram plot of participants' Nasal Polyp Score thresholds in the presence of 1 burdensome CRSwNP symptom that best predict a response of "yes" to consideration for CRSwNP treatment escalation.