Endoscopic grading systems for nasal polyps: are we comparing apples to oranges?*

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Abstract

Endoscopic grading of nasal polyps (NP) is typically a coprimary endpoint in clinical trials evaluating treatments for chronic rhinosinusitis with nasal polyps (CRSwNP). However, a consensus on the most effective way to grade nasal polyps has not been reached. Different scales have been used, hampering the interpretation of data across trials. This review compares the characteristics of NP grading systems used in registration trials for approved NP treatments. These fundamental differences in grading systems make quantitative comparison of outcomes between trials inaccurate and potentially misleading. In lieu of a universal grading system, reporting the baseline distribution of polyp grades (unilateral and/or summed/total grades), as well as changes from baseline over time by baseline grade may help improve interpretability of outcomes and reduce inaccuracy when attempting cross-trial comparisons and making therapeutic decisions.

Key words: nasal polyps, nasal obstruction, nose diseases, sinusitis

Introduction

Chronic rhinosinusitis (CRS) is a common chronic inflammatory condition affecting approximately 10% of the population worldwide [1-6]. Although EPOS2020 has proposed classification of CRS based on the underlying pathophysiologic mechanism of the disease (i.e. endotype) [1, 7], CRS has historically been phenotypically categorized based on the absence (CRSsNP) or presence (CRSwNP) of nasal polyps (NP) and this phenotypic NP-centered characterization is presently the most practical means of classifying patients with CRS in the clinic. NP can arise from the chronic inflammation of the Schneiderian mucosa, most frequently from the ethmoid cavity and/or middle meatus or, less commonly, from the superior meatus, olfactory cleft, or within the paranasal sinuses. NP have been reported to be present in 1-4% of the population and in approximately 20-30% of patients with CRS [1, 8, 9]. Identification of NP and classification of a patient as having CRSwNP is important for several reasons. First, the presence of NP is often predictive of the presence of asthma or atopy, which may occur concomitantly with CRS specific and general quality of life (QOL)-modifying disease processes [10]. Second, since in many parts of the world, NP are found to contain very prominent Type-2 inflammatory profiles, the presence of NP is often predictive of positive treatment response to Type-2 inflammation-targeting treatments such as corticosteroids or Type-2-specific biologic agents [11]. In fact, the current usage of Type-2-specific biologic agents such dupilumab, omalizumab and mepolizumab have been indicated by national and international regulatory agencies to be used specifically for CRSwNP. Moreover, the presence of NP may directly cause symptomatology for patients—causing nasal airway obstruction, impairment of sinus ventilation and drainage, and hyposmia due to inflammation of the olfactory epithelium and their mass effect. The costs of CRSwNP for society are considerable due to direct costs of the disease but certainly also the impact on productivity [12-14]. In the study of treatments for CRSwNP, it is important to assess the outcome of treatment in a manner that ensures reliable, sensitive evaluation of efficacy and facilitates comparison between different options. The size of NP and severity of symptoms including nasal obstruction and reduction of sense of smell are commonly used as outcome measures for CRSwNP.

Although NP size described by using currently available scoring systems is not well-correlated with symptom burden, the use of endoscopic NP grading scales to assess the extent or bulk of NP tissue has become one of the most common mechanisms for assessing outcomes in CRSwNP clinical research. NP size is, in particular, an outcome that is also used in regulatory assessment of pharmacologic effects in studies of treatments for patients with CRSwNP. In the last decade, numerous advances have been made in the treatment of CRSwNP with the development of enhanced methods for delivery of topical treatments and the use of biologicals [15-19]. Given the rapid proliferation of treatments for CRSwNP and the associated studies that are reporting the efficacies of these treatments, there is an increasing need for understanding of the differences in grading scales and inclusion criteria that are used to assess NP outcomes in these studies. In this review, we summarize and describe the different NP grading scales that have been reported in the past, with a particular focus on scales used in recent clinical trials. We also discuss the strengths and limitations of NP grading scales. We believe that this review will serve as a resource to aid in the interpretation of the results of increasing numbers of clinical trials for treatments of CRSwNP.

History of grading systems

Since at least 1990, various clinical groups have proposed objective, standardized endoscopic scoring (grading) systems to assess the extent of NP in clinical practice and to measure the effect of pharmacological and surgical treatments in clinical trials. These grading scales have most often quantified the extent of NP tissue based on how far it is observed to extend downwards in the vertical plane of the nasal cavity, typically using the middle and inferior turbinate bones as key anatomical landmarks. In 1990, Levine et al. proposed a 6-point (0-5) scale (revised in 1993 by May et al.) for long-term evaluation of patients undergoing endoscopic sinus surgery [20, 21]. Additionally, in 1993, Lund and Mackay proposed a simple 3-step (0-2) scale to use with computed tomography (CT)-scans and endoscopic assessment in patients with CRSwNP [22]. While the Lund-Mackay system became the standard in assessment of CT scans, a range of NP scores from 0 to 2 has been considered to be too crude for assessment of NP to capture meaningful gradations in NP burden. The 0-3 grading system developed by Johansen in 1993 assigns a grade to NPs based on their extension relative to the inferior turbinate (above/at upper edge vs. between upper and lower edges vs. below the lower edge); in addition, the magnitude of obstruction (none/slight vs. troublesome vs. near total/total) is also considered in this grading system [23]. The Lildholdt scale, introduced in 1995, uses the same 0-3 scale as Johansen, but the degree of nasal obstruction was omitted [24]. The original Johansen grading scale and the similar but simplified Lildholdt system were used in many early clinical trials that were performed in Europe and the United States to evaluate topical steroids for CRSwNP, such as budesonide spray and powder, fluticasone drops, and mometasone spray [24-28]. Next, Small et al. expanded the definition of grade 3 in the Lildholdt scale to include '*polyps medial to the middle turbinate*,' with no distinction on how far down those polyps reach into the nasal cavity [29]. Maintaining this expanded definition of grade 3, Gevaert et al. in 2006, expanded the scale by splitting the grade 3 step as introduced by Small et al. in 2005 [29] and by adding grade 4 for completely or almost completely obstructing polyps [30]. In 2006, the Rhinosinusitis Initiative proposed a different system (0-4 scale), splitting grade 1 of the Lildholdt system into grades 1 and 2 depending on the presence of one or multiple polyps in the middle meatus [31]. This system redefined grades 1, 2, and 3 and added a grade 4 ('*polyps completely obstructing the nasal cavity*').

To score disease in a manner that better reflects the polyp mass/volume burden, some researchers attempted to describe polyps in multiple planes. One system, evaluating NP in 3 dimensions, showed less inter-examiner agreement—a major limitation—compared to the simpler one-dimensional systems, possibly due to variation introduced by limitations of endoscopic assessment or the mobility of polyp tissues [32]. Johansson et al. described a grading scale for measuring NP burden in the craniocaudal and anteroposterior dimensions that they referred to as the 'lateral imaging' technique in which the extent of observed polyposis is expressed on a schematic picture of the lateral nasal wall by the examiner [33]. Although Johansson et al. found high inter-examiner reliability for this 2-dimensional scoring system, conducting lateral imaging by hand is time consuming, and the facilitating software program offered by the authors is no longer available [33]. Ultimately, it has been a challenge to develop an endoscopic system that accurately assesses the bulk of NP while maintaining intra and inter-examiner reliability [34]. For these reasons, uni-dimensional grading scales that assess NP burden by quantifying the extension of NP in the craniocaudal dimension are most frequently used.

"Grouping" of grading systems

Although many different uni-dimensional NP grading scales have been developed over time, no consensus has been reached to identify a standard scale and consequently different scales are used in different studies. To discuss NP grading scales that have been used in clinical trials for treatments of CRSwNP, we have categorized NP grading scales into one of four groups (Table 1). All grading scales use the same grade 0 and grade 1 (if we consider the lower edge of the middle turbinate to be equivalent to the superior edge of the inferior turbinate). However, beyond grade 2, these scales diverge in how NP burden is quantified. While almost all grading scales (Groups I-III scales) consider Grade 2 NP to be indicative of polyps reaching below the inferior border of the middle turbinate, this is not the case for the scale proposed

Table 1. Publications describing grading systems for nasal polyps.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Group 0 [23]	No polyps	Small polyps not reaching the upper edge of the inferior turbinate and causing only slight obstruction	Medium-sized polyps reaching between the upper and the lower edge of the inferior turbinate and causing troublesome obstruction	Large polyps reaching below the lower edge of the inferior turbinate **and** causing **total or almost total obstruction**	N/A
Group I [18, 24, 27, 35, 45]	No polyps	Small polyps not reaching the upper edge of the inferior turbinate	Medium-sized polyps reaching between the upper and the lower edge of the inferior turbinate	Large polyps reaching below the lower edge of the inferior turbinate	N/A
Group II [29]	No polyps	Polyp in middle meatus, not reaching below the inferior border of the middle turbinate	Polyp reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate	Large polyp reaching to or below the lower border of the inferior turbinate **or polyps medial to the middle turbinate**	N/A
Group III [30, 36-41, 46]	No polyps	Small polyps in the middle meatus not reaching below the inferior border of the middle concha	Polyps reaching below the lower border of the middle turbinate	Large polyps reaching the lower border of the inferior turbinate **or polyps medial to the middle concha**	**Large polyps causing complete (or almost complete) obstruction of the inferior meatus**
Group IV [19, 31, 42-44]	No visible nasal polyps	**Small amount of polypoid** disease confined within middle meatus	**Multiple polyps** occupying the middle meatus	Polyps extending beyond the middle meatus, **within the sphenoethmoid recess but not totally obstructing, or both**	**Polyps completely obstructing the nasal cavity**

by the Rhinosinusitis Initiative [31] (Group IV scales) that considers grade 2 to be multiple polyps filling—but entirely within—the middle meatus. There is a high degree of variability across scales for NP burden that is considered grade 3, ranging from large polyps extending below the inferior turbinate (Group I scales) vs. large polyps reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate (Group II or III scales) vs. polyps extending beyond the middle meatus or within the spheno-ethmoid recess (Group IV scales). Finally in the Group III and IV scales, grade 4 is introduced that includes complete or almost complete obstruction of the inferior meatus (Group III) or complete obstruction of the nasal cavity (Group IV) (Table 1 and extended Table in Supplemental material).

Use of nasal polyp scales in clinical studies of CRSwNP

Perhaps not surprisingly, studies evaluating common treatments of CRSwNP, performed by several clinical trial sponsors and investigators, have used similar NP grading scales (Table 1). In registration trials for fluticasone propionate nasal drops [25, 26], mometasone furoate nasal spray (one of the two) [27], and the exhalation delivery system with fluticasone [18, 35], polyp grades were assessed using the Lildholdt system (Group I). One other registration trial for mometasone furoate applied the Group II scale, expanding the grade 3 definition to polyps extending to the inferior margin of the inferior turbinate and/or present medial to the middle turbinate [29]. Studies assessing the effects of parenteral monoclonal antibodies and oral steroids have applied Group III NP scales maintaining the expanded grade 3 polyp of Group II and adding a new grade 4 category defined as polyps "that reaches below the inferior margin of the inferior turbinate resulting in complete obstruction of the inferior meatus" [30, 36-41]. Studies assessing the effect of drug eluting stents inserted into the middle meatus [19, 42-44] for CRSwNP all use the Rhinosinusitis Initiative grading (Group IV) [31] (Table 1).

The use of the same grading system for evaluation of a particular class of medications allows for comparison within that treatment group. On the contrary, use of different grading systems in the evaluation of diverse treatments can make comparison of these treatments more complicated. In particular, grade 3 polyps (depending on the grading system) may or may not indicate polyps medial to the middle turbinate. The presence or absence of grade 4 polyps in a grading system, complicate comparisons across NP grading with different systems.

Impact of non-linearity in grading scales

None of the NP grading systems are a direct measure of polyp mass or bulk and they all use non-linear scaling which is not always ordinal. The non-linearity of the grading results in unequal reduction in polyp volume depending on the grade. For example, in a patient experiencing a 1-grade improvement in NP grade, comparatively minor changes in polyp volume may reduce grade 4 polyps to grade 3 polyps compared to reducing grade 3 polyps to grade 2 polyps or grade 2 polyps to grade

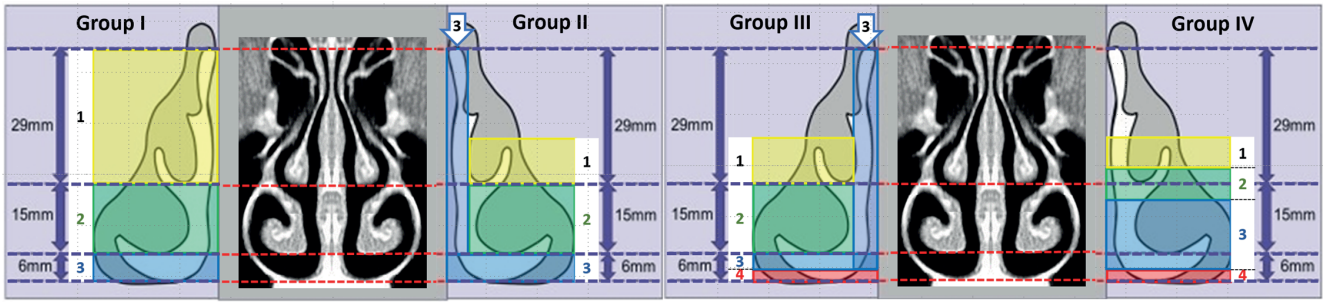


Figure 1. Disparities among nasal polyp grading systems. **Group I** is a non-linear, one-dimensional, 0 to 3 grading system. **Group II** is a non-linear, two-dimensional, 0 to 3 grading system. **Group III** is a non-linear, two-dimensional, 0 to 4 grading system. **Group IV** is a non-linear, one-dimensional, 0 to 4 grading system. Each grade is color coded (grade 1, yellow; grade 2, green; grade 3, blue; grade 4, red).

1 polyps (Figure 1). Another consideration, which introduces non-linearity, is how polyps are defined in the medial to lateral dimension in relation to the middle turbinate. In the Group I scales, grade 3 polyps are defined as large polyps reaching below the inferior turbinate, while in Group II and Group III scales NP medial to the middle turbinate are also considered to be grade 3 polyps, independent of polyp size in the craniocaudal dimension. As a result, in Group II and III scales, a small polyp medial to the middle turbinate would be classified as a higher grade than a larger polyp extending from the middle meatus to just above the inferior edge of the inferior turbinate (Figure 1).

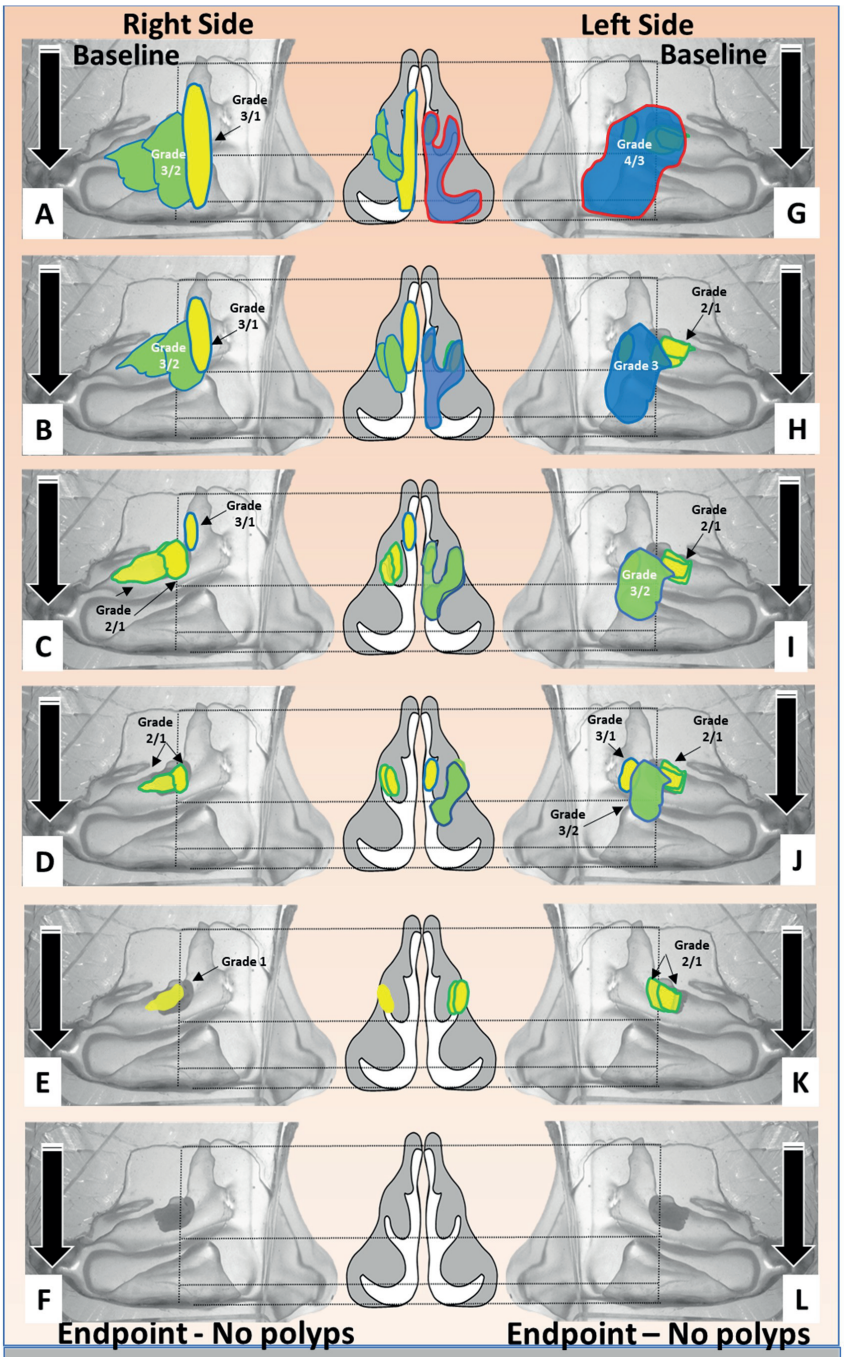
Dynamic range of grading scales

One limitation of polyp grading scales in general is the dynamic range of the quantitative scoring since these scales assess polyps on a scale of 0 to 3 or 0 to 4. First of all, the limited range of possible polyp scores limits investigators' abilities to quantify changes in vertical polyp extension. For example, a polyp that starts at just above the inferior edge of the inferior turbinate and shrinks with treatment to just below the top of the inferior turbinate would be assessed as having had no change in size according to all polyp grading scales (Group I-IV). Moreover, the small dynamic range of possible polyp scores also introduces the greater possibility of "floor" and "ceiling" effects, since patients included in clinical trials may be more easily skewed towards lower or higher total polyp scores.

Ceiling effects are most likely to be seen in trials that recruit patients with the highest-grade polyp burden. While the highest-grade polyps in any grading scale may continue to increase in volume over time through a trial (e.g., patients receiving placebo and non-responders), they can no longer increase in grade. The largest grade polyps can only decrease in grade or remain unchanged. Effectively, these polyps have reached a "ceiling." The impact of this "ceiling" effect is that differences between treatment and control arms may be underestimated since the control arm is more likely to have enlargement of polyps without any corresponding quantitative "worsening" based on the grading scale. Grading scales can also be impacted by a "floor effect." Improvement in polyp scale is constrained to be no larger than the starting polyp burden. For example, grade 1 polyps can only improve by 1 grade even with complete elimination of all polyps by a treatment. The impact of floor effects will be felt most by studies including patients with low polyp grade where even a very effective treatment can quantitatively make, at best, only small improvements in polyp score.

Scenarios of polyp reduction

Simulating reduction of polyp size best illustrates the discussed concepts regarding disparities and differences in polyp grading systems and their impact on interpreting the therapeutic landscape. Figures 2A-F and 2G-L represent polyps graded in a theoretical clinical trial with a gradual reduction in polyp mass for each step from 2A→F and 2G→L. Differences in polyp grade definitions in the scales may change the scoring of the same side of the nose by as much as 2 points in some extreme situations. After grading the two scenarios shown in Figure 2, it is apparent that the same NP can be assigned a different grade at almost every step depending on the system used. In addition, the respective changes in polyp scores are also very disparate. For example, depending on the Group of scoring system applied, the polyp(s) in Figure 2G could initially be scored as grade 3 (Groups I & II) or 4 (Groups III & IV). Once treated and reduced to the polyp in Figure 2I, the polyp masses could be scored as either 2 (Groups I-III) or 3 (Group IV), representing decreases of either 1-point (Groups I, II & IV) or 2-points (Group III) in grade. Polyp grade may even change/increase from grade 2 to grade 3 (Groups II&III) if a polyp medial to the middle turbinate is revealed when a large grade 2 polyp shrinks (Figure 2I→J). In another example (Figure 2A→B→C), a polyp originating medial to the middle turbinate and initially extending to the bottom edge of the inferior turbinate (yellow polyp with blue border) shrinks to above the inferior edge of the middle turbinate, which then reveals a previously hidden small polyp medial to the middle turbinate (spheno-ethmoid recess). The score in the Group



Score and Change from Baseline in Different Grading Systems

	Group I		Group II		Group III		Group IV			Group I		Group II		Group III		Group IV	
	Grade	Change	Grade	Change	Grade	Change	Grade	Change		Grade	Change	Grade	Change	Grade	Change	Grade	Change
A	3	-	3	-	3	-	3	-	G	3	-	3	-	4	-	4	-
B	2	-1	3	0	3	0	3	-1	H	3	0	3	0	3	-1	3	-1
C	1	-2	3	0	3	0	2	-1	I	2	-1	2	-1	2	-2	3	-1
D	1	-2	1	-2	1	-2	2	-1	J	2	-1	3	0	3	-1	3	-1
E	1	-2	1	-2	1	-2	1	-2	K	1	-2	1	-2	1	-3	2	-2
F	0	-3	0	-3	0	-3	0	-3	L	0	-3	0	-3	0	-4	0	-4

Figure 2. Two scenarios of polyps shrinking and subsequent change (reduction/increase) in polyp score over time. Figure 2A→F and Figure 2G→L, are indicated by black arrows and rated based on the criteria of the 4 grading groups. (Group I, 0 to 3; Group II, 0 to 3; Group III, 0 to 4; Group IV, 0 to 4). Polyps are color coded (outline and filling): grade 1, yellow; grade 2, green; grade 3, blue; grade 4, red. Polyp outlines are colored based on the highest assigned grade among the 4 groups, and the polyp fillings are colored based on the lowest assigned grade among the 4 groups. A and G: Polyps graded separately in two nostrils at the beginning of a theoretical clinical trial with large polyps at baseline.

I scale is incrementally reduced by 1 point for Figure 2A→B and 2 points for Figure 2A→C; in contrast, the scores in Groups II & III remain grade 3 (unchanged) throughout this dramatic reduction in polyp bulk. The Group IV scale shows no change for Figure 2A→B and a reduction of 1 point for Figure 2B→C. As the small polyp in the spheno-ethmoid recess in Figure 2C disappears, a 2-point reduction in score is observed in Groups II & III though no additional reduction is observed in Groups I & IV (Figure 2C→D).

Consensus among clinicians and researchers is needed

Polyp grading scales in current use can detect treatment effects but are only loosely reflective of polyp bulk/mass and, because of features such as nonlinearity and non-ordinal grades, are subject to substantial changes in performance with seemingly small changes to methodology or study populations. Although "reduction of bilateral nasal polyp score" has been a primary outcome for most of the pivotal trials for agents approved to treat nasal polyps, the inconsistency in grading systems and polyp grade definitions used has been given surprisingly little attention.

While all grading systems have limitations, only the uni-dimensional grading scales, quantifying NP burden in the craniocaudal direction have been validated to have substantial reliability and responsiveness, but three of the four studies validating 0-1 or 0-2 scales have now largely been abandoned because they are insensitive to change [47-49]. Of the scales used in registration trials for CRSwNP, the one-dimensional Lildholdt 0-3 system (Group I) is the only one that has been validated, with acceptable reproducibility and agreement among investigators [33]. The many subsequent modifications to the definition of grade 3 and in particular, the grading of polyps medial to the middle turbinate, complicates reliable cross-trial comparisons. These modifications to the Lildholdt system, for which intra- and inter-examiner reliability have not been established, have progressed to a point where the grade 4 definition is indistinguishable from the original definition of grade 3 polyps by Johannsen et al. in 1993 [33] (Table 1 and Table S1). Consensus among clinicians and researchers on the grading scale to be used in future trials investigating treatments for nasal polyps is needed if comparison between trials is to be performed.

We propose several actions for future clinical trials to help improve transparency and the ease of interpretation of results. Reporting of unilateral and summed/total polyp grade distribution at study baseline and endpoints in clinical investigations would improve interpretability across trials and enhance the quality of research in this area by providing greater insight into the extent to which floor or ceiling effects may be impacting the reported results. Moreover, one could argue that reporting percent change from baseline instead of the mean reduction in NP score may be better, especially when comparing trials with different baseline scoring. Nevertheless, the fundamental limitations of the non-linear scale and different scales and grade definitions remain.

Conclusions

Given the rapid proliferation of treatments for CRSwNP and the associated studies that are reporting the efficacies of these treatments, there is an increasing need for the understanding of NP grading scales that are used to report outcomes with respect to NP burden. However, we would highlight that prior studies have shown that objective measures (e.g. endoscopic grading) of CRS disease burden correlate poorly with patient-reported outcome measures (PROMs). For a disease that profoundly reduces quality of life, the primary endpoints of any treatment for CRS—independent of NP—should be improvements observed using a high-quality patient reported outcome measure. It is also important to note that many regulatory agencies mandate demonstration of effectiveness of a CRSwNP treatment using an NP grading scale. NP grade therefore remains an important outcome measure for studies of CRSwNP treatments.

With the increasing number of clinical trials being completed for treatments of CRSwNP, there is also increasing opportunity and need to use published data to perform systematic reviews, meta-analyses and comparative effectiveness studies. NP outcomes remain difficult to compare across studies because of the variety of endoscopic grading scales that are used across studies. At present, there is no one widely accepted manner or grading scale for the assessment of NP. All nasal polyp grading systems are likely suitable for reporting change within a trial with similar baseline polyp scores and distribution, but inconsistencies make appropriate numerical comparisons of magnitudes of change between studies difficult, and the results of such comparisons potentially misleading.

In the absence of a universal grading system, reporting baseline distribution of polyps unilaterally as well as summed/total grades and changes from baseline over time by baseline grade may help improve interpretability of outcomes and reduce inaccuracy when attempting cross-trial comparisons and making therapeutic decisions based on NP score. Cross-study comparisons of change in polyp grade should consider differences in grading scales, patient populations, polyp score inclusion/exclusion criteria and polyp distribution. Methodology and features specific to nasal polyp trials need to be considered to avoid comparing "apples to oranges".

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Authorship contribution

All invited authors accepted the invitation and contributed

actively to the submitted manuscript. ICMJE criteria for authorship have been met by all authors and conflicts of interest have been declared. All authors had final approval of the manuscript submitted

Conflict of interest

PGD has reported being an employee and shareholder of Optinose during the conduct of the study. SR reports grants and consulting fees from Sanofi, GSK and Novartis. CH has received advisory board fees from Sanofi, GSK and Astra Zeneca, and speaker honoraria from Sanofi, GSK, Mylan, Intersect and Olympus. ARS declares no conflicts of interest. AP has received advisory board fees from Sanofi Regeneron, Astra Zeneca, GSK, and Optinose. WJF reports grants from Sanofi, GSK and Novartis, and consulting fees and speaker honoraria from Sanofi and GSK.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Table S1. Publications describing grading systems for nasal polyps. Key differences in definitions are bolded.

			Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	Johansen 1993	Budesonide (200µg bid) versus placebo/ Spray pump	No polyps	Small polyps not reaching the upper edge of the inferior turbinate and causing only slight obstruction	Medium-sized polyps reaching between the upper and the lower edge of the inferior turbinate and causing troublesome obstruction	Large polyps reaching below the lower edge of the inferior turbinate **and** causing **total or almost total obstruction**	N/A
Group I (18, 24, 27, 35, 45)	Lildholdt 1995	Budesonide (400µg bid, 200µg bid) versus placebo/ Dry powder nasal inhaler	No polyps	Small polyps not reaching the upper edge of the inferior turbinate	Medium-sized polyps reaching between the upper and the lower edge of the inferior turbinate	Large polyps reaching below the lower edge of the inferior turbinate	N/A
	Leopold 2019 (also used by Vlckova 2009 and Sindwani 2019	fluticasone propionate (372µg bid, 186 µg bid) versus placebo/ Exhalation Delivery System	No polyps	Polyps in middle meatus, not reaching below the inferior border of the middle turbinate	Polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate	Large polyps reaching below the lower inferior border of the inferior turbinate	N/A
	Stjarne 2006	Mometasone furoate (200µg bid, 200µg qd) versus placebo / Spray pump	No polyps	Polyps in the middle meatus, not reaching below the inferior border of the middle turbinate	Polyps reaching below the inferior border of the middle concha, but not the inferior border of the inferior turbinate	Large polyps reaching below the lower inferior border of the inferior turbinate	
Group II (29)	Small 2005	Mometasone furoate (200µg bid, 200µg qd) versus placebo/ Spray pump	No polyps	Polyp in middle meatus, not reaching below the inferior border of the middle turbinate	Polyp reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate	Large polyp reaching to or below the lower border of the inferior turbinate **or polyps medial to the middle turbinate**	N/A

			Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Group III (30, 36-41, 46)	Gevaert 2006	Reslizumab (1mg/kg, 3mg/kg) versus placebo/ IV infusion	No polyps	Small polyps in the middle meatus not reaching below the inferior border of the middle concha	Polyps reaching below the lower border of the middle turbinate	Large polyps reaching the lower border of the inferior turbinate **or polyps medial to the middle concha**	**Large polyps causing complete obstruction of the inferior meatus**
	VanZele 2010	Methylprednisolone versus doxycycline versus placebo/ Oral	No polyps	Small polyps in the middle meatus not reaching below the inferior border of the middle concha	Polyps reaching below the lower border of the middle turbinate	Large polyps reaching the lower border of the inferior turbinate **or polyps medial to the middle concha**	**Large polyps causing almost complete congestion/obstruction of the inferior meatus**
	Bachert 2019	Dupilumab (300mg) + mometasone spray (400µg) versus placebo + mometasone spray (400µg)/ Subcutaneous injection	No polyps	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate	Polyps reaching below the lower border of the middle turbinate	Large polyps reaching the lower border of the inferior turbinate **or polyps medial to the middle turbinate**	**Large polyps causing complete obstruction of the inferior nasal cavity**
	Gevaert 2020	Omalizumab (75-600mg every 2 or 4 weeks based on body weight and serum total IgE) + mometasone spray (200µg bid or qd if unable to tolerate bid) versus placebo + mometasone spray (200µg bid or qd if unable to tolerate bid)/ Subcutaneous injection	No nasal polyps	Small nasal polyps in the middle meatus not reaching below the inferior border of the middle turbinate	Nasal polyps reaching below the lower border of the middle turbinate	Large nasal polyps reaching the lower border of the inferior turbinate or **polyps medial to the middle turbinate**	**Large nasal polyps causing complete obstruction of the inferior nasal cavity**
Group IV (19, 31, 42-44)	Meltzer 2006	Grading scale recommended by the Rhinosinusitus Initiative/ N/A	No visible nasal polyps	**Small amount of polypoid** disease confined within middle meatus	**Multiple polyps** occupying the middle meatus	Polyps extending beyond the middle meatus, **within the sphenoethmoid recess but not totally obstructing, or both**	**Polyps completely obstructing the nasal cavity**