Premiere Publications from The Triological Society

Read all three of our prestigious publications, each offering high-quality content to keep you informed with the latest developments in the field.

**The Laryngoscope**

*FOUNDED IN 1896*

Editor-in-Chief: Samuel H. Selesnick, MD, FACS

The leading source for information in head and neck disorders.

[Laryngoscope.com](http://Laryngoscope.com)

**Investigative Otolaryngology**

*Open Access*

Editor-in-Chief: D. Bradley Welling, MD, PhD, FACS

Rapid dissemination of the science and practice of otolaryngology-head and neck surgery.

[InvestigativeOto.com](http://InvestigativeOto.com)

**ENTtoday**

A publication of the Triological Society

Editor-in-Chief: Alexander Chiu, MD

Must-have timely information that Otolaryngologist-head and neck surgeons can use in daily practice.

[Enttoday.org](http://Enttoday.org)
Acute Exacerbations in Recurrent Acute Rhinosinusitis: Differences in Quality of Life and Endoscopy

Daniel M. Beswick, MD; Noel F. Ayoub, MD, MBA; Jess C. Mace, MPH, CCRP; Alia Mowery, BS; Peter H. Hwang, MD; Timothy L. Smith, MD, MPH

Objectives/Hypothesis: Research surrounding outcome differences for patients with recurrent acute rhinosinusitis (RARS) is scarce. This investigation explored quality of life (QOL) and sinonasal attributes in patients during acute episodes (AEs) and in-between AEs of RARS.

Study Design: Retrospective outcomes research.

Methods: Data from patients with RARS were collected from two academic institutions between 2009 and 2017 using prospective and retrospective methodology. During clinical presentation, subjects were classified as with or without an AEs using guideline definitions of acute bacterial rhinosinusitis (ABRS). Between-group differences in 22-item Sino-Nasal Outcome Test (SNOT-22) survey and Lund-Kennedy (LK) endoscopy scores were assessed.

Results: Four hundred twenty-three clinical visits from 202 patients were included. Visits during an AE (168/423, 40%) were associated with significantly worse SNOT-22 total scores compared to between AEs (255/423, 60%; median = 53.0 [interquartile range (IQR) = 24.0] vs. 34.0 [IQR = 29.5]) and all SNOT-22 subdomain scores (all P < .001). LK scores were available for 167 visits, with 56 (34%) completed during an AE. Compared to visits without an AE, endoscopy findings associated with an AE were less frequently normal (LK score = 0, 45% vs. 62%, P = .031) with worse median LK scores (2.0 [IQR = 4.0] vs. 0.0 [IQR = 2.0], P = .005).

Conclusions: AEs are associated with significantly worse QOL and mildly worse endoscopic findings. Almost half of visits during AEs had negative endoscopy, identifying a disparity between patient symptoms and objective findings and calling into question alternative or concomitant diagnoses. Diagnostic criteria for ABRS or AEs in RARS do not require objective confirmation of inflammation, presenting a conundrum for clinicians. The potential for overdiagnosis of ABRS and AEs should be considered when determining the risk/benefit ratio of treatments for RARS.

Key Words: Recurrent acute rhinosinusitis, sinusitis, chronic disease, outcome assessment (healthcare), quality of life, patient-reported outcome measures, diagnosis, exacerbation.

Level of Evidence: 2c

INTRODUCTION

Recurrent acute rhinosinusitis (RARS) has been defined as a disease pattern consisting of repeated episodes of acute bacterial rhinosinusitis (ABRS) with disease-free intervals between acute episodes (AEs)1,2 Most countries have high consistency in their recommendations for diagnosing acute rhinosinusitis, and recent guidelines have delineated that four or more annual episodes of ABRS are required to establish a diagnosis.1-3 RARS has been associated with significant direct and indirect costs (e.g., >$1,000 healthcare costs and >4 missed workdays per patient per year), with upward of 100,000 patients affected by this disease in the United States.4 Limited research into the pathogenesis of RARS has been conducted, though many clinicians would agree that alterations and compromise of ostiomeatal complex anatomy or physiology are involved.5-8 Originating from both a paucity of current evidence and related to diagnostic uncertainty, RARS has been identified as a top-two area of research by the American Rhinologic Society.9

Repeated ABRS episodes, which form the foundation of the diagnosis of RARS, may be purely symptom based, defined by new onset of sinonasal symptoms in accordance with a duration or disease course that implicates a bacterial etiology.2 Although purulent nasal drainage is often present in ABRS, it is not required to make the diagnosis according to clinical practice guidelines.2 Corresponding
detriments in disease-specific quality of life (QOL) or changes in sinonasal attributes, as evidence through endoscopic exam, that occur during AEs have not been rigorously studied. A recent investigation identified that computed tomography (CT) imaging performed during AEs in patients referred for RARS only rarely identified true sinus inflammation and more often suggested nonsinus etiologies for patients’ symptoms.10 One interpretation of their data is that symptom-based definitions of AEs may not provide enough diagnostic specificity to accurately identify episodes of ABRS. In light of this, we investigated disease-specific QOL impairment reported by patients during AEs and explored differences in endoscopic findings between patients presenting with AEs and in between AEs of RARS.

MATERIALS AND METHODS

Study Population and Inclusion Criteria

Data collection was conducted as part of an investigator-monitored, observational research study of adult human subjects funded by the National Institute on Deafness and Other Communication Disorders (Bethesda, Maryland; federal grant #R01 DC005805) at Oregon Health and Science University (OHSU; Portland, Oregon) combined with an additional adult patient outcomes data repository at Stanford University (Palo Alto, California) collected per routine clinical practice. Study data were prospectively and retrospectively collected from heterogeneous patient populations referred to these two academic, rhinology clinics for symptoms associated with RARS. Symptomatic, adult patients (>18 years of age) with a confirmed diagnosis of RARS from a fellowship-trained rhinologist were included, with all patients having at least four annual episodes of ABRS according to published guideline criteria.11 Diagnostic criteria have been established by current clinical practice guidelines for adult sinusitis from the American Academy of Otolaryngology–Head and Neck Surgery. Patients were treated in accordance with clinical standard of care (SOC) for RARS, including medical and surgical management when indicated. The institutional review board (IRB) at both OHSU (IRB #7198) and Stanford University (IRB #36074) provided ethical oversight, review of research protocols, and data safety. Data collection methods were determined minimal risk and did not deviate from the SOC for the treatment of RARS.

Exclusion Criteria

Patients were excluded from final statistical analysis if they presented with any variant of comorbid primary ciliary dyskinesia due to differential disease pathology and treatment considerations, as well as increased likelihood of exacerbated symptoms associated with sinusitis. Patient-reported outcome measures (PROMs) and endoscopy scores collected in the 6-month period following endoscopic sinus surgery (ESS) were excluded due to potential confounding effects in symptom severity during postoperative healing. Additional exclusions included patients unable or unwilling to complete PROMs during routine clinical appointments.

Patient-Reported Outcome Measures

Each study participant provided a comprehensive medical and social history during baseline enrollment meetings or during initial clinical presentation per the SOC. Patients were also instructed to provide complete responses to the 22-item Sino-Nasal Outcome Test (SNOT-22) survey, the primary outcome of interest, to quantify current sinonasal symptom severity at the time of presentation. The SNOT-22 is a widely used, validated, survey instrument designed to quantify the severity of symptoms associated with sinonasal disorders using Likert scale (item score range = 0–5) response options (Washington University, St. Louis, MO).12 Validated factor analysis of SNOT-22 item scores in a patient population with chronic rhinosinusitis (CRS) has previously identified five symptom domains that can be categorized and summarized into rhinologic (score range = 0–30), extranasal rhinologic (score range = 0–15), ear and/or facial (score range = 0–25), psychological dysfunction (score range = 0–35), and sleep dysfunction (score range = 0–25).13 Higher summarized SNOT-22 total score (range = 0–110) and domain scores reflect overall worse sinonasal symptom severity.

Sinonasal Endoscopy Scoring

The paranasal sinuses were evaluated bilaterally using rigid endoscopes (Karl Storz, Tuttlingen, Germany) during routine clinical appointments according to the SOC. Endoscopic findings were quantified by each enrolling physician using the Lund-Kennedy (LK) scoring system (total score range = 0–20), which quantifies visualized pathologic attributes within the paranasal sinuses including the presence and severity of nasal polypsis, discharge, edema, scarring, and crusting.14 Higher summarized LK total scores indicate worse overall disease severity. Although endoscopy was performed on all patients, full LK scores were only available for a subset of patients.

Acute Exacerbation of RARS

As the primary predictor of interest to this investigation, study participants were classified as either presenting with or without an AE of rhinosinusitis concurrent with completion of the SNOT-22 instrument. Acute exacerbations were defined according to established criteria as worsening symptoms such as facial pain or pressure, nasal obstruction, and nasal discharge according to clinical guidelines.2 Patients who met criteria for an acute exacerbation were designated as “with” or “during” an exacerbation, whereas patients who did not meet criteria and presented for routine, scheduled follow-up were designated as “without” or “between” exacerbations. The dichotomous designations of RARS exacerbation were made through retrospective chart review. Endoscopic findings were not factored into designation of group status, as they are not part of the guideline definition of an ABRS episode.2

Statistical Analysis

Investigational data were secured through the assignment of unique study identification numbers for study participants and removal of all protected health information prior to transfer into a centralized database in a closed environment at OHSU (Access [Microsoft, Redmond, WA]) in compliance with the Health Insurance Portability and Accountability Act of 1996. All descriptive and statistical comparisons were completed using SPSS software (version 24.0; IBM, Armonk, NY). Statistical analyses were directed after all scaled measures were evaluated for assumptions of normality and linearity using graphical analysis and Shapiro-Wilk testing. Comparisons of independent observations of patients with and without acute exacerbations of RARS were evaluated using Mann-Whitney U test statistics, which compares rank differences in median score. Interquartile range (IQR), determined by calculating the difference between the 1st and 3rd quartiles, is reported when appropriate. Differences in score frequency between patients with and without AE of RARS were also compared using $\chi^2$ testing where appropriate.
RESULTS

Final Study Population

A total of 229 patients diagnosed with RARS presented to either enrollment center between June 2009 and February 2017, providing clinical histories and a total of 627 survey responses to the SNOT-22 during the observational period. One patient was excluded due to presentation with primary ciliary dyskinesia, and an additional 26 patients were removed from final analyses due to providing SNOT-22 scores only within the 6-month period following ESS. Additional eliminations included 57 incomplete SNOT-22 surveys due to inadequate or missing data. A total of 202 patients providing a total of 423 complete survey responses to the SNOT-22 were considered for final analysis, including 168/423 (40%) clinical visits during acute symptomatic episodes, with 167 completed endoscopic examinations with corresponding LK staging for the total cohort. Descriptors and comorbid conditions for all final study patients are described in Table I.

Comparisons of Symptom and Endoscopic Severity Between Acute Symptomatic Episodes of RARS

The total number of SNOT-22 survey responses (n = 423) provided by all patients were evaluated for median differences between patients presenting to clinic during AEs (n = 168) and patients presenting between AEs (n = 255). Patients presenting during AEs reported significantly worse SNOT-22 total scores as well as across all symptom domains (Table II). Additionally, a total of 56/167 (34%) patients had nasal endoscopy during an AE with median LK endoscopy scores that were significantly worse than patients between AEs (n = 111). A total of 25/56 (45%) patients with an AE were found to have bilateral total LK endoscopy scores of 0, signifying no evidence of nasal inflammation, compared to 69/111 (62%) of patients between exacerbations ($\chi^2 = 4.64, P = .031$).

Comparisons of Endoscopically Confirmed Acute Symptomatic Episodes

Additional outcome comparisons were conducted among study participants by dividing the cohort into three groups: 1) patients with an AE with endoscopic evidence of inflammation (LK total score > 0), 2) patients with an AE without endoscopic evidence of inflammation (LK score = 0), and 3) patients without a symptomatic AE (Table III). When evaluating patients with AEs, outcome measure scores between patients with endoscopi-positive AE and endoscopic-negative AE were not found to be statistically different (all $P \geq .151$) except for LK endoscopy scores by definition ($P < .001$). Following adjustments for pairwise comparisons, patients between AEs reported significantly better

---

**TABLE I.**

Patient Descriptors for the Final Study Population With Recurrent Acute Rhinosinusitis (N = 202).

<table>
<thead>
<tr>
<th>Patient Descriptors</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean ± SD (range)</td>
<td>43.1 ± 13.7 (18–77)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80 (40%)</td>
</tr>
<tr>
<td>Female</td>
<td>122 (60%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>153 (76%)</td>
</tr>
<tr>
<td>African American</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Pacific Islander/Native Hawaiian</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>34 (17%)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Previous sinus surgery, n (%)</td>
<td>31 (15%)</td>
</tr>
<tr>
<td>Septal deviation, n (%)</td>
<td>146 (72%)</td>
</tr>
<tr>
<td>Turbinate hypertrophy, n (%)</td>
<td>109 (54%)</td>
</tr>
<tr>
<td>Asthma, n (%)</td>
<td>55 (27%)</td>
</tr>
<tr>
<td>Allergy + mRAST/skin prick, n (%)</td>
<td>99 (49%)</td>
</tr>
<tr>
<td>Depression, history, n (%)</td>
<td>60 (30%)</td>
</tr>
<tr>
<td>Fibromyalgia, n (%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>Alcohol use, n (%)</td>
<td>115 (57%)</td>
</tr>
<tr>
<td>Autoimmune disease, n (%)</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Corticosteroid dependence, n (%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Diabetes mellitus (type I/II), n (%)</td>
<td>13 (6%)</td>
</tr>
</tbody>
</table>

mRAST = modified radioallergosorbent testing; N = sample size; SD = standard deviation.

---

**TABLE II.**

Comparison of SNOT-22 and Endoscopy Scores Both During and Between Acute Exacerbations of Recurrent Acute Rhinosinusitis.

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>During Acute Exacerbation, Median (IQR)</th>
<th>Between Acute Exacerbation, Median (IQR)</th>
<th>Mann-Whitney U Test Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNOT-22 total score</td>
<td>53.0 (24.0)</td>
<td>34.0 (29.5)</td>
<td>8.96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rhinologic domain</td>
<td>14.0 (8.8)</td>
<td>10.0 (9.0)</td>
<td>7.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Extranasal rhinologic domain</td>
<td>9.0 (4.0)</td>
<td>6.0 (5.0)</td>
<td>7.40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ear and/or facial domain</td>
<td>10.0 (6.0)</td>
<td>7.0 (7.0)</td>
<td>6.39</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Psychological dysfunction domain</td>
<td>18.0 (11.8)</td>
<td>9.0 (14.0)</td>
<td>8.28</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sleep dysfunction domain</td>
<td>15.0 (9.0)</td>
<td>9.0 (11.0)</td>
<td>7.24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lund-Kennedy endoscopy score</td>
<td>2.0 (4.0)</td>
<td>0.0 (2.0)</td>
<td>2.81</td>
<td>.005</td>
</tr>
</tbody>
</table>

Test statistics are standardized. IQR = interquartile range; SNOT-22 = 22-item Sino-Nasal Outcome Test.
SNOT-22 total scores compared to both endoscopic-positive (P < .001) and endoscopic-negative (P < .001) acute episodes of RARS. Similar trends were found in rhinologic domain scores (both P < .050), extranasal rhinologic domain scores (both P < .050), psychological domain scores (both P < .050), and sleep dysfunction domain scores (both P < .050). Ear and/or facial domain scores were significantly different between patients with endoscopic negative AEs and those between AEs after pairwise adjustment (P = .001).

### DISCUSSION

This study was conducted to investigate clinical changes that impact patients with RARS both during and between AEs of symptomatic disease. Results from this study demonstrate that patients experience and report meaningful QOL deficits during an AE compared to patients between disease exacerbations. This is not unexpected, given that AEs are defined by patient symptomatology according to current diagnostic guidelines that were employed in this study. Data from this investigation also found worse LK total scores in patients during AEs compared to patients without an exacerbation. Although the difference in endoscopy scores between AE groups was statistically significant, the clinical relevance of the modest difference is unknown. Somewhat surprisingly, among patients with AEs, the presence of endoscopic inflammation was not associated with worse QOL compared to patients with an AE but with normal endoscopy.

Patients included in this study met current guideline criteria for a diagnosis of RARS with four or more reported episodes of ABRS annually. Each ABRS diagnosis centers on patient symptomatology and a time course indicative of a bacterial etiology. Purulent drainage is often present, but objective confirmation of sinonasal inflammation is not required according to published guidelines for a diagnosis of ABRS or RARS, in contrast to CRS. This may reflect the fact that ABRS is commonly managed in the primary care realm, where endoscopy is not performed, and an aim of limiting overutilization of CT imaging.

Of patients in this study who met criteria for an AE of RARS, endoscopic inflammation was present in only approximately half. It is not clear if these patients had inflammation that was not identifiable on endoscopy but otherwise present, or truly had an absence of sinonasal inflammation, as a substantial discrepancy between endoscopy and CT is known to exist in patients with rhinosinusitis. Among patients with symptoms of CRS who had negative endoscopy and then underwent point-of-care CT imaging, two-thirds had radiologic findings of sinonasal inflammation. This raises the question of whether endoscopy has adequate sensitivity and specificity to confirm an episode of ABRS. Moreover, CT imaging during RARS AEs also has limited correlation with patient symptoms; prior research evaluated the utility of acute radiology in patients with RARS exacerbations and only rarely showed radiologic evidence of sinus disease during AEs. Overall, establishing objective diagnostic criteria for RARS has proven challenging.

Certain groups of patients in this study merit special consideration. Approximately 50% of patients who have symptoms of an AE had negative endoscopy. These patients, who may have had alternative diagnoses besides an AE, had similar total SNOT-22 deficits to patients in an AE with endoscopic inflammation (Table III). These patients may be suffering from other conditions that require management such as allergic rhinitis, viral rhinosinusitis, or neurologic disorders. Relatedly, of subjects who presented in between AEs, over one-third had evidence of endoscopic inflammation, as evidenced by nonzero LK scores. Nasal inflammation would not be expected in patients with exclusively RARS between episodes and calls into question alternative or concomitant diagnoses such as chronic rhinosinusitis, allergic rhinitis, or iatrogenic sinusitis. In this study, a notable percentage of subjects had asthma and allergy (Table I), which may predispose to upper airway inflammation.

Interesting results emerged from the QOL findings in this study. The median SNOT-22 total score in patients between AEs was 34.0, higher than expected compared to mean SNOT-22 total scores in healthy controls (16.4 ± 15.2) and lower than patients with medically refractory CRS. Among patients with an AE, median SNOT-22 total scores were similar between those with endoscopic-positive disease and those with endoscopic-negative disease. However, those with positive endoscopy may have had a higher symptom burden in the rhinologic
and extranasal rhinologic domains, whereas those with negative endoscopy may have had worse symptoms in the ear/facial, sleep dysfunction, and psychological dysfunction domains (Table III). Although these values were not significant in this study, a larger sample size may have identified statistically and clinically relevant differences.

We believe that findings from this study highlight that diagnoses of ABRS and RARS AEs are made in a milieu of necessary ambiguity. This may result in the overdiagnosis of ABRS and RARS AEs. Patients who do not meet criteria for ABRS episodes do not have RARS, and their symptom exacerbations may be explained by other etiologies such as viral rhinosinusitis, allergic rhinitis, migraine, or other neurologic disorders. Prior work has demonstrated that patients with sinus symptoms and primary headache disorders, but not rhinosinusitis (negative endoscopy and imaging), have elevated SNOT-22 total and rhinologic domain scores, similar to the population in the current study. Clinical practice guidelines define the diagnosis of ABRS and RARS without requiring confirmation of objective inflammation, which suggests that some degree of uncertainty is acceptable for diagnostic purposes and, by extension, consideration of certain treatments such antibiotic therapy. However, when surgical intervention for RARS is considered, multidisciplinary appropriateness criteria are more demanding and necessitate the confirmation of objective (endoscopic or radiologic) sinonasal inflammation to consider ESS.

This study is one of the first to quantify the disease-specific QOL impairment experienced by patients with RARS during an AE and explore associations between changes in endoscopic inflammation and patient symptom severity that accompany an AE of RARS. The modest median increase in total LK score from 0.0 (IQR ±2.0) to 2.0 (IQR ±4.0) identified in this study shows that some patients have endoscopic inflammation consistent with ABRS. A larger increase in LK total score would not be expected in patients with RARS, as polyps, scarring, and crusting are not common in this population. However, the results also show that 45% of patients with an AE have no evidence of inflammation on endoscopic exam (LK total score = 0). This lack of consistently present endoscopic inflammation is aligned with Barham et al., and these findings suggest that many patient-perceived AEs do not have associated endoscopic inflammation. Based on these findings, caution should be exercised when considering treatment options for RARS such as antibiotics or endoscopic sinus surgery.

ESS leads to improved outcomes for patients with RARS in selected patient cohorts. Current appropriateness criteria, intended to help guide surgical candidacy for RARS, have also included the need to confirm at least one true episode of ABRS prior to recommending ESS as a treatment option. Findings from this current study highlight the importance of verifying an ABR episode, as many patients with symptom-based AEs did not have substantial intranasal inflammation consistent with an ABR episode.

This study is subject to several limitations and caveats that should be considered during interpretation. Data utilized for this study were sourced from prospective cohort studies and supplemented by retrospective review, and as such the data are partially subject to biases associated with retrospective research and secondary data analysis. Within-subject comparisons of patients may have provided additional insight into average QOL and endoscopic exam differences both during and between AEs over time. However, despite identifying patients diagnosed with RARS from two academic institutions over a 9-year observational period, we were limited to unpaired, nonparametric rank testing due to limitations in sample size derived from observational data collection and the rarity of patients presenting with a diagnosis of RARS. Additionally, the SNOT-22 survey instrument has been validated for sinonasal disease and used extensively in patients with CRS, as well as in the limited research on RARS, but the instrument has not been specifically validated for use in patients with RARS. In this study, widely employed clinical practice guidelines were used to classify patients with ABRS, and different categorizations and potentially findings may have resulted if European guidelines were employed, which include the diagnosis of postviral rhinosinusitis and require endoscopic or radiologic confirmation of inflammation to diagnose rhinosinusitis.

Lastly, patients included in this study were referred to academic, tertiary referral care centers, and these findings may not be externally valid or more broadly generalizable to other patient populations.

**CONCLUSION**

Symptom-based RARS AEs are associated with meaningfully worse QOL and mildly worse endoscopy scores compared to patients at baseline. Almost half of visits during guideline-defined, symptom-based AEs had normal endoscopy, identifying a disparity between patient-reported symptoms and objective findings of disease and calling into question alternative or concomitant diagnoses for patients with negative endoscopy. Current diagnostic criteria for RARS do not require objective confirmation of sinonasal inflammation for ABRS or AEs and present a conundrum for clinicians. The potential for overdiagnosis of ABRS and AEs should be considered when determining the risk/benefit ratio of treatments for RARS.

**BIBLIOGRAPHY**