Global Osteitis Scoring Scale and chronic rhinosinusitis: a marker of revision surgery

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Objectives: Determine the incidence and severity of osteitis in patients with chronic rhinosinusitis (CRS) using a new Global Osteitis Scoring Scale.
Design: Validation and prospective case–control study.
Setting: Academic Tertiary Otolaryngology Department (Academic Medical Centre, Amsterdam).
Participants: A prospective series of 102 patients undergoing a computed tomography (CT) sinuses as part of their evaluation for CRS between January and May 2008 (study group) and an age- and gender-matched control group of 68 non-rhinosinusitis patients. Seventy-eight of the CRS patients completed the nasal subset of the RhinoSinusitis Outcome Measure (RSOM-31) and visual analogue scales. Their CT scans were assessed for osteitis using a newly developed Global Osteitis Scoring Scale. A subsample of 35 scans were additionally scored by a second otolaryngologist and a radiologist.
Main outcome measures: Global Osteitis Scoring Scale.
Results: The interrater variability of Global Osteitis Scoring Scale was low (average intraclass correlation coefficient: 0.94). Forty per cent of the CRS group and none of the control group had evidence of clinically significant osteitis. In the CRS group (102 patients), the severity of osteitis was correlated with Lund–Mackay (L–M) score ($P < 0.001$), duration of symptoms ($P < 0.01$) and previous surgery ($P < 0.001$), rising in incidence with increasing number of previous operations. There was no association between osteitis and age, gender, smoking, co-existing asthma, allergy or Sumpter's triad. Additionally, there was no correlation between osteitis and symptom burden including headache, facial pain and nasal subset score of the RhinoSinusitis Outcome Measure.
Conclusion: In patients with recalcitrant CRS who have undergone multiple surgeries in the past, the incidence of osteitis can be as high as 64%. It does not seem to be associated with more troublesome symptoms; however, it is strongly associated with previous sinus surgery, which may be a manifestation of a shared endpoint (underlying recalcitrant disease).

Although the pathophysiology of chronic rhinosinusitis (CRS) remains unclear, a number of factors have been implicated including, but not limited to, chronic inflammation of the bony framework of the paranasal sinuses. A number of animal studies[1–4] have demonstrated a link between experimentally induced rhinosinusitis and chronic inflammation of the bony middle turbinate as well as the ethmoid and maxillary sinus bony walls. Similarly, radiological studies performed in humans using different criteria to define osteitis showed that the incidence of radiological changes associated with bony inflammation ranged between 4%,[5] 36%,[6] and 60%.[7] However, although these studies paved the way for subsequent research and provided valuable data, they were based on localised measurements and not on a global grading system, concurrently assessing the severity and the extent of bony involvement over the paranasal sinuses. More importantly, although there have been studies correlating the bony changes seen on the computed tomography (CT) scan with a poorer surgical outcome[7] and with recurrent disease,[6] none of these studies used a validated questionnaire to assess the relationship between symptom burden, patient characteristics and osteitis. We performed this prospective case–control study to examine the patient and disease factors associated with the presence and severity of bony involvement in CRS using a newly developed composite global scoring system (Global Osteitis Scoring Scale).

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Materials and methods

Patients

All 102 patients undergoing thin slice CT scanning (axial 1.3-mm slices, coronal and sagittal multiplanar reconstructions, using a Brilliance 64 CT or Mx8000 QUAD; Philips Medical Systems, Best, the Netherlands) as part of their evaluation for CRS between January and May 2008 were included in this study. A subgroup (n = 78) of these patients completed on the day of scanning, the nasal subset of the Rhinosinusitis Outcome Measure 31 (RSOM 31) and a visual analogue scale (VAS), grading their overall sense of well-being, sinus complaints, headache, facial pain, nasal obstruction, sense of smell, rhinorrhea, post-nasal drip and thick nasal discharge.

Controls

A group of 68 non-CRS patients undergoing CT of their sinuses during the same period was included as a control group. The age, gender, smoking habits, duration of symptoms, presence of asthma, ASA triad, previous date, number and type of sinus operations were recorded.

Outcomes – Global Osteitis Scoring Scale

The scans were reviewed by a radiologist and an otolaryngologist, and each sinus individually assessed for presence, severity and extent of osteitis. A global composite grading system for osteitis (Global Osteitis Score) was developed in collaboration with the radiology department as follows: Osteitis was defined as loss of bone definition/hyperostosis/new bone formation or signal heterogeneity overlying each sinus wall. The area of maximal thickness of each osteitic focus was measured (Fig. 1).

The grading per sinus was as follows:

Grade 1: Less than 50% of the sinus walls involved and osteitis <3 mm wide.

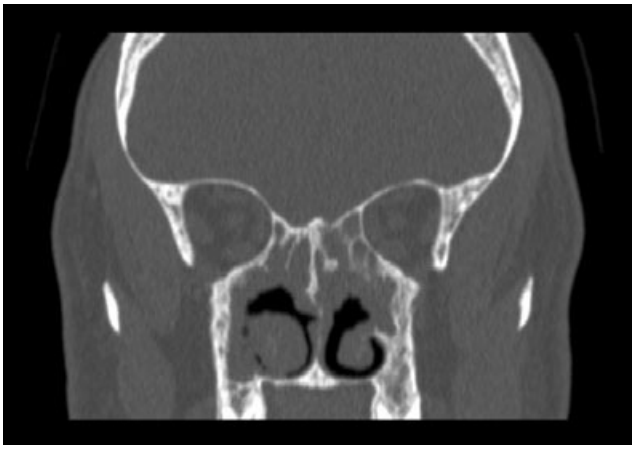
Grade 2: Less than 50% of the sinus was involved and 3–5 mm width.

Grade 3: Less than 50% of the sinus involved and wider than 5 mm or greater than 50% of the sinus wall involved and <3 mm wide osteitic changes.

Grade 4: Greater than 50% of the sinus wall involved and 3–5 mm.

Grade 5: Greater than 50% of the sinus wall and thicker than 5 mm.

In this way, each sinus was given a grading ranging from 0 to 5. The scores of all 10 sinuses (Right and left frontal, anterior ethmoid, posterior ethmoid, maxillary and sphenoid) were added, producing a global osteitis score (range: 0–50). Osteitis was thus classified as not significant (<5), mild (5–20), moderate (20–35) and severe (higher than 35).



LOW RESOLUTION FIG

Fig. 1. Coronal computed tomography slice of patient having undergone three previous endoscopic ethmoidectomies showing evidence of extensive osteitis.

Outcomes – Lund–Mackay Grading Scale

The presence and extent of mucosal disease in the paranasal sinuses was evaluated with the Lund–Mackay radiological grading system.

Chi-square and Fisher's exact test were used for comparing categorical variables, while comparisons between groups were performed using unpaired t-test for normally distributed variables and Wilcoxon rank test for non-parametric variables, as required. The level of significance was set at 0.05 for double-sided comparisons, and Bonferroni correction was used for all multiple comparisons. Linear stepwise regression (0.10 entering, 0.05 removing variable threshold) was performed for assessing the predictor variables of the main outcome (Global Osteitis Score). For the sample of 35 CT scans scored additionally by an independent radiologist and otolaryngologist, average intraclass correlation coefficients were calculated for each sinus assessed and for the total Global Osteitis Score.

Results

Characteristics of the two groups

The characteristics of our patients and of the control group are shown in Table 1. There were no differences in the age and sex distribution between the two groups but, as expected, CRS patients had significantly higher

Table 1. Characteristics of the two groups

	Chronic rhinosinusitis group (n = 102)	Control group (n = 68)	P value
Age (median, range)	44 (8–82)	43 (12–83)	0.771 – Wilcoxon
L–M score (median, range)	10 (3–24)	2 (0–14)	<0.001 – Wilcoxon
Gender (n, %)	55 (54%) Male	31 (46%) Male	0.287 – Chi-square
Smokers (n, %)	10 (12.5%)	8 (17%)	0.481 – Chi-square
Asthma (n, %)	37 (45%)	5 (9%)	<0.001 – Chi-square

Lund–Mackay scores. The indications for the CT in the control group included anosmia, maxillofacial trauma, hypophyseal tumours and idiopathic facial pain (exclusion CT). Thirty-seven (45%) patients in the CRS group suffered from asthma, 39 (51%) had skin prick test proven allergies and 9 (12%) were diagnosed with ASA triad, while 49 (48%) had nasal polyps and 9 (8.8%) had a mucocele. Their median duration of symptoms was 93 months (range 2 to 576), and 75 (73.5%) of the CRS patients had undergone sinus surgery in the past (median number of surgeries 2, range 0 to 7). Fourteen (13.7%) of these surgeries were performed in our department. Their symptom burden, as assessed by RSOM and VAS scales, is displayed in Table 2.

Osteitis by group

Radiological evidence of sinus wall hyperostosis and heterogeneity was present in 65 (63.7%) of the CRS patients and 10 (14%) of the controls. ($P < 0.001$), while clinically significant osteitis (arbitrary defined by Global Osteitis Score < 5) was present in 41(40%) of the CRS patients and none of the controls ($P < 0.001$). Mean Global Osteitis Score was 9.2 (SD 14.2, range 0–50) in CRS patients and 0.2 (SD 0.7, range 0–3.5) in the controls ($P < 0.001$).

Osteitis and CRS: patient characteristics, symptoms and co-morbidity

In the subgroup of patients (n = 78) who completed the nasal subset of the RSOM 31 questionnaire, there was no correlation between any of the VAS or the RSOM scales and osteitis, and, conversely in ANOVA, VAS and RSOM scores did not differ between patients with no, mild, moderate or severe osteitis (Table 2). In CRS patients, gender, asthma, ASA triad, smoking or allergy was not correlated with the presence or extent of osteitis. However, the presence of nasal polyps was associated with a

Table 2. Quality of life and symptoms of chronic rhinosinusitis (CRS) patients with and without osteitis

	CRS patients (n = 78) Mean (SD)	CRS with osteitis group (n = 34) Mean (SD)	CRS without osteitis group (n = 43) Mean (SD)	P value
Rhinosinusitis outcome measure (RSOM)-1 (blocked nose)	2.49 (1.61)	2.74 (1.61)	2.36 (1.63)	0.328
RSOM-2 (runny nose)	1.84 (1.50)	1.96 (1.52)	1.78 (1.42)	0.614
RSOM-3 (sneezing)	1.75 (1.49)	1.74 (1.43)	1.76 (1.55)	0.957
RSOM-4 (reduced smell)	2.49 (2.88)	2.11 (1.82)	2.70 (1.88)	0.194
RSOM-5 (post-nasal drip)	2.14 (1.64)	2.00 (1.64)	2.22 (1.65)	0.584
RSOM-6 (thick nasal discharge)	2.26 (1.74)	2.44 (1.74)	2.16 (1.77)	0.493
General sinus problems	51.8 (31.8)	63.88 (29.51)	55.93 (33.04)	0.312
Headache	36.8 (33.9)	36.04 (30.15)	37.20 (36.05)	0.887
Facial pain	47.3 (34.2)	45.48 (31.75)	48.28 (35.74)	0.734
Nasal obstruction	50.7 (33.0)	55.63 (31.61)	48.10 (33.76)	0.341
Rhinorrhea	34.3 (31.6)	33.04 (31.80)	35.06 (31.79)	0.791
Post-nasal drip	38.7 (33.0)	38.08 (32.26)	39.06 (33.71)	0.903
Anosmia	51.8 (37.7)	47.44 (40.71)	54.28 (36.26)	0.452
Sinus pressure	49.3 (36.5)	55.80 (34.98)	46.10 (37.21)	0.336
Overall health	40.1 (30.4)	40.89 (29.48)	39.71 (31.26)	0.873

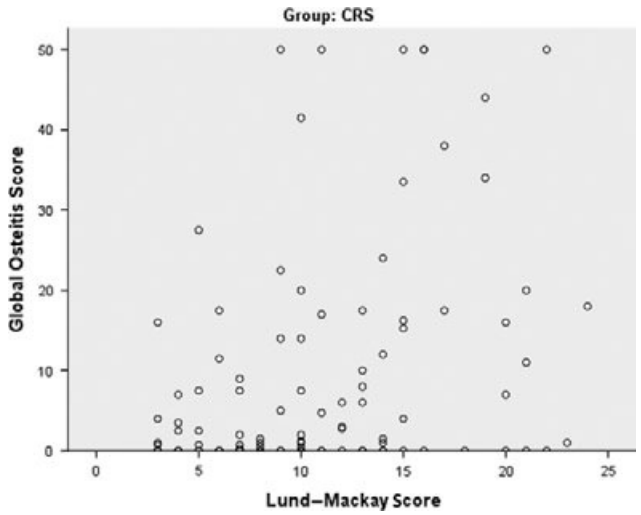


Fig. 2. Correlation between Lund–Mackay scores and Global Osteitis Scoring Scale.

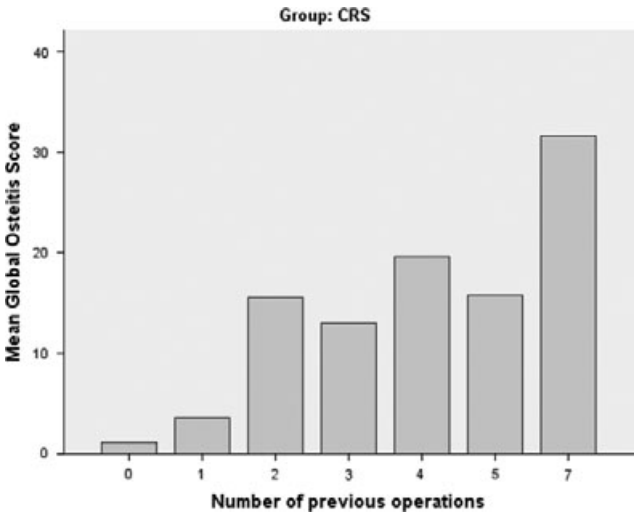


Fig. 3. Correlation between Global Osteitis Scoring Scale and previous surgeries.

higher incidence of osteitis (73 *versus* 55%, $P = 0.04$), while osteitis had a small but significant correlation with age and symptom duration, increasing with rising age ($r = 0.368$, $P = 0.02$) and longer duration of symptoms ($r = 0.358$, $P = 0.01$).

Osteitis and CRS: LM score

Lund–Mackay scoring of mucosal disease correlated with Global Osteitis Scoring Scale ($r = 0.349$, $P < 0.001$) (Fig. 2). The majority of patients with osteitis had evidence of concurrent mucosal disease on the CT scan, and conversely, most patients with low Lund–Mackay (L–M) scores were free of significant osteitis.

Osteitis and CRS: surgery

There was a strong correlation between previous surgery and osteitis. The incidence of osteitis was 33% (9/27) in the non-operated group rising to 75% (56/75) in the operated group ($P < 0.001$). Interestingly, there was an almost linear relation between the mean Global Osteitis Score and the number of previous surgeries, rising from 1.6 in patients with no previous surgeries to 3.6 to those who had undergone one sinus procedure to 15.5 to those with two previous operations to 31.5 in patients with more than six previous sinus surgeries ($P < 0.001$) (Fig. 3).

In patients with CRS, osteitic changes were most commonly observed in the maxillary sinuses, followed by the anterior ethmoids, posterior ethmoids, sphenoids and finally the frontal sinuses (Table 3). This distribution mirrored the locations where surgery has previously been performed (data not shown) (Fig. 4).

Osteitis and CRS: linear regression

On linear stepwise regression, a model was build predicting Global Osteitis Score (adjusted R-Square 0.507, $P < 0.001$). This model included the number of previous surgeries ($P < 0.001$), the presence of nasal polyps ($P = 0.02$) and age ($P = 0.04$).

Characteristics of Global Osteitis Scale

The assessments between the independent radiologist and otolaryngologist and the original grading were very close. The average intraclass correlation coefficient between all three assessors was 0.94 (95% confidence interval: 0.91–0.97). In terms of individual sinuses, the closest interrater agreement was found for maxillary sinuses (0.91, 0.93), followed by the sphenoids (0.89, 0.79) and the frontal sinuses (0.89, 0.77) with the lowest agreement found in the assessment of the ethmoids (posterior: 0.78, 0.54 and anterior 0.59, 0.49).

Discussion

Histological correlates of osteitis in chronic rhinosinusitis

Although a variety of endogenous and exogenous factors have been implicated in recalcitrant CRS, the importance of chronic low grade inflammation of the underlying

Fig. 4. Coronal computed tomography slice of a patient with a 30-year history of frontal chronic rhinosinusitis who has undergone two external frontal drainage procedures (right), two endoscopic frontal sinusotomies and an endoscopic Lothrop.

bone has been recognised relatively recently. Different groups use various terms to describe the same process of bone involvement in patients with recalcitrant CRS such as osteitis, osteomyelitis, hyperostosis, bone hyperplasia, bone remodelling and neo-osteogenesis. As there is no marrow space in the flat bones around the sinus, the term 'osteitis' is recommended to describe the process of involvement of bone surrounding the paranasal sinus in patients with CRS. The histological definition of osteitis in CRS as developed in four human histological studies includes the presence of new bone formation, fibrosis, inflammatory cells,[8] periosteal thickening and a varying degree of increased osteoblastic–osteoclastic activity, as shown by the disruption of organised lamellar bone and formation of immature woven bone.[6,9,10] This chronic low grade inflammation does not seem to be associated with direct bacterial invasion, as no group until now been able to demonstrate bacteria in the bone. Rather, it seems to both be stimulated by and act as a 'depot' of inflammatory cytokines, which ensure the persistence of disease, even when the mucosa is either treated medically or removed.[3] These histological changes correspond to a specific radiological appearance on CT, namely, thickened, irregular, heterogeneous lining of the sinus walls, which may be localised or global.[6,7]

Radiological assessment of osteitis: introducing a new grading system

The incidence of radiologically shown osteitis has been examined in four previous studies: Lee *et al.*[6] using a criterion of >3 mm thickness of the ethmoid partitions and maxillary and sphenoid sinus borders in 121 CRS patients undergoing ESS found radiological evidence of osteitis in 82% of the ethmoid, 64% of the sphenoid and 45% of the maxillary sinuses, while the frontal sinus was not evaluated. Kim *et al.*[7] evaluated the bony thickness of the maxillary, ethmoid and middle turbinate of 81 patients with CRS, at specified reference points defining osteitis as bony thickness >3 standard deviations beyond the range of normal reference values. He did not assess the frontal or the sphenoid sinuses, and he found evidence of hyperostosis in 60% of patients. Finally, Biedlingmaier[11] studied the CT appearance of middle turbinate in patients undergoing FESS with resection of the middle turbinate, and using a grading of no/indeterminate/certain osteitis found radiological evidence of osteitis in 14 of 110 middle turbinates. However, none of these studies attempted to produce a comprehensive global osteitis grading, incorporating quantitative measures of the severity as well the extent of osteitis. We propose, in analogy to the Lund–Mackay (L–M) score, a Global Osteitis Scoring Scale, ranging from 0 to 50, that incorporates both the severity of osteitis in each sinus as well as the number of sinuses involved. We have shown that the grading using this scale is easy to perform (usually 2–3 min per patient) and gives reproducible results. We found that interrater variability was low, and the agreement between different assessors, using intraclass correlation coefficient, was excellent (0.947). The best agreement was found for the maxillary sinuses and the lowest for the ethmoids.

Table 3. Incidence of osteitis and surgery per sinus subgroup: our results and comparison with previous studies

	Frontal sinus		Anterior ethmoid		Post-ethmoid		Maxillary		Sphenoid	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
Osteitis presence (score > 1) (%)	17	14	33	30	26	24	35	34	23	22
Mean osteitis score	1.2	1.4	2.1	1.8	1.9	1.7	2.5	2.3	1.9	1.7
Lee *et al.*[6]	N/A	N/A	82%				45%		62%	

Symptom burden and osteitis

Although it has been implicitly assumed that paranasal sinus osteitis would be associated with increased disease severity and more pronounced symptoms including facial pain, this has never before been rigorously assessed. In our study, we did not find evidence of an association between facial pain and osteitis. We found that patients with osteitis tend to have higher Lund–Mackay scores, longer standing disease and to have undergone more surgeries but not more severe symptoms than patients without osteitis. In contrast with acute osteomyelitis of long bones, typically associated with excruciating acute pain, the osteitis of CRS seems to have a more indolent course. The search for a global scale of osteitis may lead us to a better understanding of disease pathophysiology and progress, but, not unlike Lund–Mackay grading of CRS, a direct link between objective radiological measurements of severity and symptom burden remains elusive. However, although this study does not support the blanket association between osteitis and facial pain, it does not rule out its role in occasional patients, with nerve entrapment and localised neuropathic (rather than inflammatory) pain – and indeed, we have (occasionally) seen such patients.

Revision surgery and osteitis

Our study showed also that revision surgery is strongly associated with the extent of osteitis: This association remains strong, even after adjusting for disease duration. However, it is not clear from this study whether this is a cause and effect relationship. Animal experiments have suggested that bone reaction may occur as a response to mucosal trauma, and indeed, it seems intuitive to try and preserve mucosa in any sinus procedure; however, the long-term significance of these experiments remains unknown, as their follow-up period was <3 months, while in our patients, the time since the last surgery did not seem to reduce its effect of surgery. However, other characteristics of CRS, including its resistance to surgical treatment, may be associated with osteitis – not dissimilar to biofilms, chronic inflammation can persist underneath the surface, explaining the persistence of symptoms and the failure of surgery.

Conclusion

In patients with recalcitrant CRS who have undergone multiple surgeries in the past, the incidence of osteitis can be as high as 64%. Using a novel Global Osteitis Grading 0–50 scale, we found the average osteitis grade in CRS patients to be 9.2. Despite anecdotal evidence to the contrary, it does not seem to be associated, in most cases, with more troublesome symptoms, such as headache and facial pain. It is, however, strongly associated with previous sinus surgery, which may be a manifestation of a shared endpoint (underlying recalcitrant disease) rather than a cause and effect relationship. At present, there are more questions than answers regarding the role of osteitis in recalcitrant CRS. Further studies are planned in our department, including histopathological and immunochemistry investigations, at the interface of clinical and basic science, with the aim of understanding further this complex relationship.

Keypoints

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The study was approved by the Academic Medical Center ethics research committee. All patients gave informed consent to participate in the study.

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Conflict of interest

The authors have no conflict of interest to declare.

References

1 Westrin K.M., Norlander T., Stierna P. *et al.* (1992) Experimental maxillary sinusitis induced by Bacteroides fragilis. A bacteriological and histological study in rabbits. *Acta Otolaryngol.* **112,** 107–114

2 Norlander T., Forsgren K., Kumlien J. *et al.* (1992) Cellular regeneration and recovery of the maxillary sinus mucosa. An experimental study in rabbits. *Acta Otolaryngol. Suppl.* **492,** 33–37

3 Bolger W.E., Leonard D., Dick E.J. Jr *et al.* (1997) Gram negative sinusitis: a bacteriologic and histologic study in rabbits. *Am. J. Rhinol.* **11,** 15–25

4 Antunes M.B., Feldman M.D., Cohen N.A. *et al.* (2007) Dose-dependent effects of topical tobramycin in an animal model of Pseudomonas sinusitis. *Am. J. Rhinol.* **21,** 423–427

5 Richtsmeier W.J. (2001) Top 10 reasons for endoscopic maxillary sinus surgery failure. *Laryngoscope* **111** (11 Pt 1), 1952–1956
6 Lee J.T., Kennedy D.W., Palmer J.N. *et al.* (2006) The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. *Am. J. Rhinol.* **20,** 278–282
7 Kim H.Y., Dhong H.J., Lee H.J. *et al.* (2006) Hyperostosis may affect prognosis after primary endoscopic sinus surgery for chronic rhinosinusitis. *Otolaryngol. Head Neck Surg.* **135,** 94–99
8 Kennedy D.W., Senior B.A., Gannon F.H. *et al.* (1998) Histology and histomorphometry of ethmoid bone in chronic rhinosinusitis. *Laryngoscope* **108** (4 Pt 1), 502–507
9 Giacchi R.J., Lebowitz R.A., Yee H.T. *et al.* (2001) Histopathologic evaluation of the ethmoid bone in chronic sinusitis. *Am. J. Rhinol.* **15,** 193–197
10 Cho S.H., Min H.J., Han H.X. *et al.* (2006) CT analysis and histopathology of bone remodeling in patients with chronic rhinosinusitis. *Otolaryngol. Head Neck Surg.* **135,** 404–408

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