Original Article

Novel Chronic Rhinosinusitis (CRS) Subtypes Based on Clinical Features and Response to Treatment

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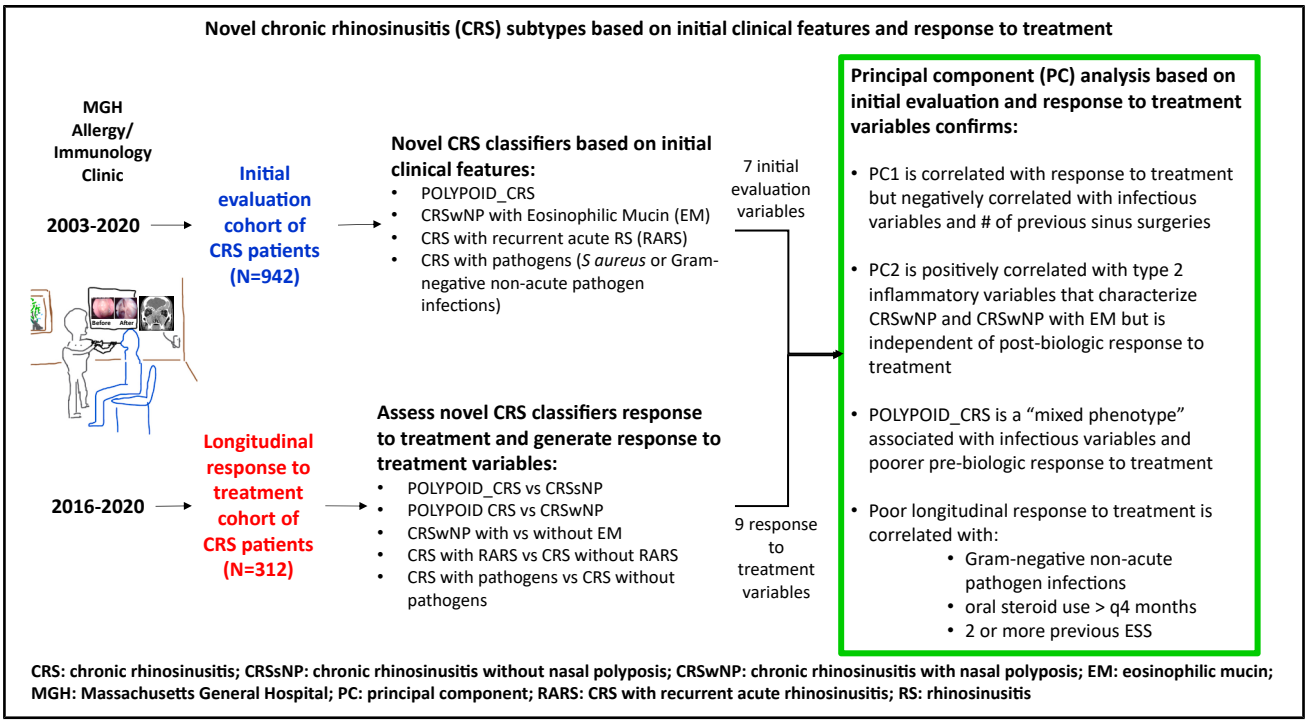
What is already known about this topic? Chronic rhinosinusitis (CRS) is classified into "CRS without polyps," "CRS with polyps," and "allergic fungal rhinosinusitis," but greater clinical and pathologic heterogeneity of CRS has been appreciated for several decades.

What does this article add to our knowledge? This study examines novel CRS subtypes in 942 patients based on initial evaluation and longitudinal responses to treatment, including topical steroid and antimicrobial treatments and biologics. Novel CRS subtypes demonstrate different comorbidities and responses to treatment.

How does this study impact current management guidelines? This study identifies novel subtypes of patients with CRS (beyond the conventional CRS classification) based on comorbidities and burden of illness and identifies which CRS subtypes respond better or poorly to each type of medical treatment.

VISUAL SUMMARY



Abbreviations used

AEC- absolute eosinophil count (in blood)
AFRS- allergic fungal rhinosinusitis
CRS- chronic rhinosinusitis
CRSsNP- CRS without nasal polyposis
CRSwNP- CRS with nasal polyposis
CT- computed tomography
EMR- electronic medical record
EMRS- eosinophilic mucin rhinosinusitis
ENT- ear, nose and throat
GLM- glue-like mucus
GNNASP- Gram-negative nonacute sinusitis pathogen infection
PC- principal-component
PCA- principal-component analysis
PGA- end-of-treatment physician global assessment
POLYPOID_CRS- CRS with intrasinus polypoid tissue but without frank nasal polyposis
RARS- recurrent acute rhinosinusitis
SRBC- sinus instillation with concentrated budesonide
SRB-dilute- sinus rinse with dilute budesonide
SRB-neat- sinus instillation with undiluted budesonide
SR-gent- sinus instillation with gentamicin
SR-itra- sinus instillation with itraconazole
SR-tobra- sinus instillation with tobramycin
TSRS- topical steroid resistance score
Z-SCT- Zinreich modified sinus CT score
Z-SCT-HD- Zinreich modified sinus CT score adjusted for hyperdensities

BACKGROUND: Current classification of chronic rhinosinusitis (CRS) is based primarily on the absence or presence of nasal polyposis.

OBJECTIVE: To (1) examine novel CRS classifiers based on clinical characteristics and (2) examine whether these classifiers predict response to treatment.

METHODS: Between 2004 and 2020, patients seen initially at Massachusetts General Hospital meeting the CRS definition (N = 942 cohort) were analyzed retrospectively for clinical characteristics. Patients seen through 2016 to 2020 (N = 312 cohort) were analyzed longitudinally for their response to treatment, including antibiotics; oral steroids; dilute budesonide rinses; instillation of budesonide, itraconazole, gentamicin, or tobramycin; and biologic treatment. Treatment responses and an "end-of-treatment" physician global assessment were recorded on a 0 to 3 scale. Results were analyzed by CRS subgroups and novel subset classifiers. Principal-component analysis was used to further interrogate CRS classifiers.

RESULTS: Eosinophilic mucin was present in 134 patients, including 40 (4.2%) with allergic fungal rhinosinusitis and 94 (10%) with eosinophilic mucin rhinosinusitis. Relative to patients with CRS with nasal polyps but without eosinophilic mucin rhinosinusitis, patients with eosinophilic mucin rhinosinusitis have a higher burden of illness and a poorer response to topical steroids but comparably good responses to dupilumab. Patients with POLYPOID_CRS, characterized by intrasinus polypoid tissue without frank nasal polyposis, have a mixed infectious and T_H2 inflammatory phenotype with a disproportionately high burden of bacterial infection and a 65.8% prevalence of tissue eosinophils. Patients with CRS with a history of recurrent acute rhinosinusitis or CRS with *Staphylococcus aureus* or Gram-negative nonacute sinusitis pathogen infection ("CRS with pathogens") have a higher burden of illness and poorer response to treatment. Historic features associated with "poor" responders include Gram-negative nonacute sinusitis pathogen infection, oral steroid use more than every 4 months, and 2 or more previous surgeries. Principal-component analysis confirmed a strong inverse relationship between both bacterial infection and number of previous surgeries with response to treatment. Overall, medical treatment reduced the frequency of sinus surgery compared with historic frequencies and was beneficial with end-of-treatment physician global assessment scores of 2 or higher in 78.5% of patients.

CONCLUSIONS: Novel classifiers of CRS can be defined on the basis of clinical characteristics and response to medical treatment. © 2025 American Academy of Allergy, Asthma & Immunology **(J Allergy Clin Immunol Pract 2025;■:■-■)**

Key words: *Chronic rhinosinusitis; Treatment; Subgroups; Subsets; Classifiers; Principal component; Eosinophilic mucin; Polypoid; Bacterial infection; Surgery*

INTRODUCTION

Chronic rhinosinusitis (CRS) is defined as an inflammatory condition of the paranasal sinuses having a duration of at least 3 months despite attempts at medical treatment and characterized by at least 2 of the following 4 symptoms: nasal congestion, facial pain or pressure, anterior or posterior purulent nasal drainage, and disturbance of sense of smell coupled with objective findings.[1] The clinical and pathologic heterogeneity of CRS has been appreciated for several decades. Studies over the past 2 decades have mostly been based on the consensus definitions of CRS published in 2004, which group CRS into 3 main clinical subgroups, namely, CRS without nasal polyposis (CRSsNP), CRS with nasal polyposis (CRSwNP), and allergic fungal rhinosinusitis (AFRS).[1] However, even in 2004, it was acknowledged that other well-defined subtypes of CRSwNP exist, such as "aspirin-exacerbated respiratory disease", and it was acknowledged that subtypes of CRSsNP were yet to be defined.

Since 2004, significant progress has been made toward understanding several key aspects of CRS, including host-microbial

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interactions relevant to disease pathogenesis and clinical presentation (reviewed in Hamilos[2]). For example, some patients with CRS have a genetically defined loss of function of a bitter taste receptor expressed in sinus epithelium that predisposes patients to infection with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and other pathogens.[3,4] Other defects in innate immunity or epithelial barrier function have also been described in small series of patients. Furthermore, inflammatory "endotypes" of CRS have been identified that show overlap between CRSsNP and CRSwNP[5-7] that may ultimately impact decisions about targeted biologic treatment options.[8] However, there has been less progress toward identifying distinct clinical patterns of illness of patients with CRS that impact patients' response to medical treatment.

In this study, we summarize the clinical features of a large number of patients seen at Massachusetts General Hospital (MGH) over 19 years who were evaluated initially for CRS and who were followed longitudinally to assess their response to medical treatment. Each patient in our center received a comprehensive initial evaluation, including evaluations for allergic and immunologic contributing factors to their disease, analysis of sinus computed tomography (CT) scans, analysis of sinus surgical pathology reports, and analysis of comorbidities (such as asthma, aspirin sensitivity, and gastroesophageal reflux). Because many of these patients were followed longitudinally with repeated follow-up visits, we were also able to analyze their response to various treatment strategies. Our aims were to (1) summarize the key clinical characteristics of our large referral population of patients with CRS based on their initial evaluation and (2) to review the longitudinal treatment of a cohort of these patients using a simple scoring system to assess each patient's response to various medical treatments. Because there are only a handful of Food and Drug Administration—approved treatments for CRS (mostly biologics for treatment of CRSwNP), as part of aim (2), we also included analysis of non—Food and Drug Administration—approved but widely used topical steroid and antimicrobial treatments for CRS that we and others have used in real-world clinical practice. In addition, because we have several MGH-affiliated ear, nose and throat (ENT) physicians who comanaged our patients and performed most of their surgeries, we incorporated their contributions to patients' management into the analysis in aim (2).

Our hypothesis was that clinical features present at each patient's initial evaluation or unfolding longitudinally in response to medical treatment would identify important novel subtypes of patients with CRS beyond our conventional CRS classifications and identify features associated with "good" versus "poor" responses to medical treatment. We further hypothesized that our study would identify clinical CRS subtypes in need of improved treatment strategies. We believe that our study results confirm these hypotheses and identify novel CRS subtypes that could prove useful in future treatment trials.

METHODS

This study was approved by the MGH Human Subjects Committee as a noninterventional retrospective case review series. All data were obtained by review of patient medical records in the MGH Epic electronic medical record (EMR) system.

Data acquisition in the initial evaluation CRS cohort (N = 942) with review of previous records

Between 2004 and 2020, patients with CRS seen initially by the investigator (D.L.H.) and who met the CRS definition[1] were identified by reviewing the daily schedule of the investigator's patients or by performing a search of the EMR using multiple search terms, including "chronic sinusitis, chronic rhinosinusitis, chronic pansinusitis, nasal polyposis, nasal polyp, chronic maxillary sinusitis." The Epic EMR was used. Each diagnosis of CRS was confirmed by review of patient's EMR. Outside records accessible through the EMR were also reviewed for CRS-relevant information, including reports of sinus CT scans, sinus surgery and pathology reports, and blood test results.

Data collection from this cohort included patient demographics, date of initial CRS consultation, CRS-pertinent past records, presence or absence of comorbidities, smoking history, CRS symptoms, medication use, sinus CT reports, sinus pathology reports within or outside of MGH, results of allergic and immunologic testing, and past history of sinus infections (based on clinic notes, endoscopic reports, and record of antibiotic prescriptions). A detailed listing of all data collected from the initial evaluation is available in this article's Online Repository at www.jaci-inpractice.org. A "historic rate of sinus surgery/y" was calculated for each patient as the number of sinus surgeries at the initial visit/duration of CRS in years.

Sinus CT scan scoring

A modification of the Zinreich method of sinus CT scoring system was used to quantify mucosal disease in the sinuses,[9,10] denoted as the Zinreich modified sinus CT (Z-SCT) score. The Z-SCT score consisted of a sinus cavity score (range, 0-50) plus a sinus ostial score (range, 0-8) as summarized in this article's Online Repository at www.jaci-inpractice.org. A further modification, denoted as the "Z-SCT-HD score," consisted of the Z-SCT score supplemented with a "hyperdensity score" of 0 or 5 depending on the absence or presence of hyperdensities in 1 or more opacified sinuses. The range of Z-SCT-HD score was from 0 to 63.

CRS classification nomenclature

The terms "CRS without nasal polyposis" (CRSsNP), "CRS with nasal polyposis" (CRSwNP), and "allergic fungal rhinosinusitis" (AFRS) were used as previously defined to denote the 3 recognized subgroups of CRS.[1] Once a patient was identified as having CRSwNP, the patient remained classified as having CRSwNP thereafter even if nasal polyps were surgically removed. We adopted the term "POLYPOID_CRS" to define patients who were noted either by nasal endoscopy or by sinus surgery to have areas within 1 or more sinuses on at least 2 separate occasions of focal elevated edematous mucosa (more than trace amounts) above the background level without pedunculated growth from the base attachment, which does not have the appearance of a mucous retention cyst with no previous history of nasal polyps and no subsequent development of nasal polyposis. Patients with POLYPOID_CRS who later developed nasal polyposis (which rarely occurred in this study) were classified as having CRSwNP. "Eosinophilic mucin rhinosinusitis" (EMRS) was defined as the subtype of patients with CRSwNP who have "eosinophilic mucin" with a negative stain for fungal hyphae identified in a pathology report from a sinus surgery specimen.[11,12] Glue-like mucus (GLM) cases were defined as cases in which an ENT surgeon noted the presence of "eosinophilic mucin," "allergic mucin," or GLM at sinus surgery or on nasal endoscopy without pathologic confirmation of eosinophilic mucin. Patients with CRS who reported a history of recurrent acute rhinosinusitis (RARS) episodes occurring every 4 months or more often were subclassified as having "CRS with RARS."[13] Patients

with CRS who had a history of sinus infection with *S aureus* (including methicillin-resistant *S aureus*) or a Gram-negative non-acute sinusitis pathogen (denoted as "GNNASP infection"), such as infections with *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Klebsiella oxytoca*, or other Gram-negative pathogen, were subclassified as "CRS with pathogens."

Additional data acquisition in the longitudinal response-to-treatment cohort

All patients seen between 2016 and 2020 (N = 312) were analyzed longitudinally for their response to treatment (RTT), including antibiotics; oral steroids; dilute budesonide rinses; instillation of budesonide, itraconazole, gentamicin, or tobramycin; and biologic treatment. All information available in the EMR from the time of the initial evaluation until the final clinic visit was recorded, including information from physicians outside of MGH. RTT cohort data included the total duration of follow-up and number of clinic visits with the investigator; number of antibiotic courses used for sinusitis; number of prednisone or systemic steroid courses used for sinusitis; immunologic or allergic test results; results of bacterial and fungal sinus cultures; type(s) of sinus rinses, sinus instillations, and biologics used and patients' ratings of the effectiveness of each over time; and findings from nasal endoscopy performed by the investigator or ENT colleagues, including presence or absence of nasal polyps, polypoid changes within sinus cavities, purulent mucus, adherent mucus, and "GLM."

Use of intranasal steroids, dilute budesonide rinses, and medicated sinus instillations in the RTT cohort

Patients used intranasal steroids at standard doses, either 1 or 2 sprays/nostril once or twice daily. Dilute budesonide sinus rinses were used at concentrations of 0.5 to 1.0 mg/240 mL (0.0048 or 0.0097 mM/L), typically delivered as 120 mL per nostril once or twice daily. Concentrated budesonide instillations were used at 0.5 to 1.0 mg in a 7-mL volume (0.166-0.332 mM/L) once per nostril daily with head-tilting maneuvers (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Undiluted budesonide instillations were used at 0.125 to 0.50 mg in 2- mL volume (0.145-0.58 mM/L) once per nostril daily. Itraconazole, gentamicin, and tobramycin sinus instillations were performed similarly at a concentration of 100 MCG/mL in 7- or 7.5-mL volume. Each patient using a medicated sinus instillation was instructed to perform the instillation in the head-down forward position first for 1 minute followed by the lateral supine position next for 1 minute once per nostril daily, with the left and right nostrils instilled sequentially.

Evaluation of response to treatment for sinus rinses, sinus instillations, and use of biologics for CRS and end-of-treatment physician global assessment in the RTT cohort

Each patient in the RTT cohort was treated by the investigator (D.L.H.) for a minimum of 6 months (range, 6-199 months). Most patients were also simultaneously receiving treatment by an ENT physician, a primary physician, and often other specialists. All medications used for CRS or "sinus infection" were recorded from the EMR by reviewing doctor's notes and EMR prescription records. The choice of which medicated rinse or instillation was used by each patient was determined by the investigator or patient preference. Not all patients received each type of medicated sinus rinse. Patients who failed to improve on dilute budesonide rinses (SRB-dilute) were usually advised to try the concentrated budesonide instillation (SRBC), and their treatment response to each was scored separately. Similarly, some patients who failed to improve on SRBC were tried on undiluted budesonide instillation (SRB-neat), and their response to each of these was recorded separately. Patients who were satisfied to remain on dilute budesonide rinses were not advanced to concentrated or undiluted budesonide instillations. Similarly, patients were prescribed itraconazole, gentamicin, or tobramycin instillations on the basis of investigator's judgment and sinus culture results, and the response to each was recorded separately. For patients who were placed on biologic treatment, treatment response scores for dilute budesonide rinse and each medicated sinus instillation were recorded just before starting the biologic. Likewise, if a patient responded poorly to one biologic and was switched to another biologic, treatment response to the first biologic was recorded just before starting the second biologic.

An RTT scoring system was devised to assess each patient's response to treatment with dilute budesonide rinses, each type of medicated sinus instillation, and biologic treatment as presented in Table I and described in detail in this article's Online Repository at www.jaci-inpractice.org. This same scoring system was used to assign a "prebiologic" physician global assessment (PGA) score just before starting the biologic and an "end-of-treatment" PGA score for each patient at their last clinic visit. In 6% of PGA scorings, uncertainty in the scoring resulted in assigning a half-point tiebreaker score (eg, 0.5, 1.5, or 2.5).

Because most patients were treated with topical budesonide rinses or sinus instillations at 1 or more concentrations ranging from "dilute" to "fully concentrated," a "topical steroid resistance score" (TSRS) was devised (range, 0-9) based on each patient's response to these or conventional intranasal steroids as outlined in Table E1 in this article's Online Repository at www.jaci-inpractice.org. Patients who remained symptomatic but who were not using a topical steroid treatment (16 of 312 patients) were arbitrarily assigned a midrange score of 4.5 to minimize their impact on the data analysis.

Data analysis

Descriptive statistics. For each patient in the initial evaluation cohort (N = 942) and the RTT cohort (N = 312), data were collected and summary statistics were generated for the CRS subgroups (CRSsNP, CRSwNP, POLYPOID_CRS, and AFRS) as well as the CRS subtypes "non-EMRS versus EMRS" (both defined within the subgroup of patients with CRSwNP), "CRS without RARS versus CRS with RARS," and "CRS without pathogens versus CRS with pathogens." Continuous variables are presented as medians and interquartile ranges (first to third quartile) and analyzed by nonparametric statistical tests, including Mann-Whitney *U* test for independent samples and Wilcoxon sign-rank test for paired samples. Categorical variables were analyzed as either nominal (eg, race/ethnicity) or dichotomous (eg, presence or absence of allergy to dust mites), summarized as the number of patients or percentage of patients in each subgroup and analyzed using χ^2 test or Fisher exact test, as appropriate. For χ^2 comparisons of the 3 CRS subgroups in Table II, adjustments were made for multiple comparison testing (see this article's Online Repository at www.jaci-inpractice.org).[14]

Principal-component analysis

We performed an unsupervised principal-component analysis (PCA) to identify key component variables and investigate whether novel subtypes of CRS could be identified from this analysis.[15] The

TABLE I. RTT scoring system used to assess responses to medical treatment and to assign PGA scores pre- and postbiologic in the RTT cohort

		Objective response to treatment (nasal endoscopy, sinus CT, and/or improvement in sense of smell)			
		Worse (0)	No change or slightly improved (1)	Moderately improved (2)	Dramatically improved (3)
Patient reported symptom response to treatment	Not improved or worse (0)	0	0	1	1
	Mildly improved w/sustained use (1)	0	1	2	2
	Moderately improved with sustained use (2)	1	2	2	3
	Dramatically improved with sustained use (3)	1	2	3	3

PCA incorporated 7 variables derived from each patient's initial CRS evaluation, including duration of CRS in years, number of previous sinus surgeries, anosmia score, previous antibiotic use/response score, infection score, skin testing score, Z-SCT+HD score, and 9 variables derived from the RTT study, including number of antibiotic courses/y, number of prednisone courses/y, TSRS, total number of sinus pathogens cultured, number of asthma exacerbations/y, number of sinus surgeries/y, endo-inflammation score, endo-infection score, and end-of-treatment PGA score. The definitions of each PCA variable are outlined in this article's Online Repository at www.jaci-inpractice.org. PCAs were carried out using the Analyze-It software for Excel (Windows 10/Microsoft 365) (Analyse-it Software, Ltd, Leeds, UK).

RESULTS

Figure 1 summarizes the flow diagram of the initial evaluation cohort of patients with CRS (N = 942) seen by the investigator between 2003 and 2020 and the longitudinal evaluation of medical treatment in the RTT cohort of patients (N = 312) seen between 2016 and 2020. Under the diagnosis of CRS, 3 subgroups are identified— CRSsNP, CRSwNP, and POLYPOID_CRS—with the sum of these equal to 100%. AFRS is a subset of these, mostly encompassed within the CRSwNP subgroup (as shown in the initial evaluation cohort summary table, Table II). Additional subtypes of CRS are identified and analyzed in the initial evaluation cohort and the longitudinal RTT cohort.

Distribution of cases over 3 time intervals (N = 942 patients)

The distribution of new CRSsNP, CRSwNP, and POLYPOID_CRS cases seen in the periods 2003 to 2008, 2009 to 2014, and 2015 to 2020 is shown in Figure E2, *A*, in this article's Online Repository at www.jaci-inpractice.org. We observed a rise in the percentage of CRSwNP cases relative to CRSsNP cases over the 17-year period, with the percentage of POLYPOID_CRS cases remaining relatively stable. Within the CRSwNP subgroup, we also observed an increase in the percentage of EMRS cases over time (Figure E2, *B*), which is only partly explained by the increased percentage of CRSwNP cases, because the ratio of EMRS/CRSwNP cases also increased during the 3 time intervals from 18.7% to 22.9% to 30.8%.

Demographic and clinical characteristics of CRSsNP, CRSwNP, and POLYPOID_CRS subgroups of patients within the initial evaluation cohort (N = 942 patients)

Table II summarizes the demographic and clinical characteristics of patients with CRS classified by CRS subgroups (CRSsNP, CRSwNP, and POLYPOID_CRS) as well as by alternative CRS subtypes, including non-EMRS versus EMRS, CRS without RARS versus CRS with RARS, and CRS without pathogens versus CRS with pathogens. Figure 2, *A-F*, illustrates some of the distinguishing features of CRSsNP, CRSwNP, and POLYPOID_CRS.

Patients classified as CRSsNP, CRSwNP, or POLYPOID_CRS did not differ significantly in terms of age or age of onset of CRS, but compared with patients with CRSsNP and patients with POLYPOID_CRS, patients with CRSwNP were more frequently male and had a longer duration of illness. The number of previous sinus surgeries was significantly greater in patients with CRSwNP and patients with POLYPOID_CRS compared with patients with CRSsNP ($P < .001$ for both). Most patients with CRSsNP and patients with POLYPOID_CRS were female, whereas most patients with CRSwNP were male (53.9%, $P < .001$). Dust mite, cat, or dog allergy was statistically more common in patients with CRSwNP, whereas pollen or mold allergy was not different between subgroups. However, the number of positive mold allergy skin test results (out of 6 species tested) was higher in patients with CRSwNP compared with patients with CRSsNP ($P < .001$). Antibiotic use more than every 4 months and "dramatic response to antibiotics" were significantly associated with CRSsNP, whereas oral steroid use was significantly associated with CRSwNP and POLYPOID_CRS ($P < .001$ for both compared with CRSsNP).

Asthma was much more prevalent in CRSwNP and POLYPOID_CRS compared with CRSsNP. Aspirin/nonsteroidal anti-inflammatory drug intolerance was much more prevalent in CRSwNP compared with either CRSsNP or POLYPOID_CRS. The prevalence of gastroesophageal reflux disease in the 3 subgroups was not statistically different. Crohn disease was present in only a very small percentage of patients and was not statistically different between groups. AFRS was diagnosed almost exclusively in CRSwNP.

A comparison of symptoms revealed that anterior/posterior nasal drainage, facial pain, facial pressure, and headache were more common in patients with CRSsNP ($P \leq .008$ for each, data not shown), whereas anosmia was strongly associated with CRSwNP relative to both CRSsNP and POLYPOID_CRS ($P < .001$). Aguesia was only more common in CRSwNP.

The Z-SCT score was significantly greater in patients with CRSwNP than in patients with CRSsNP and patients with POLYPOID_CRS ($P < .001$ for both). The Z-SCT score was also greater in patients with POLYPOID_CRS than in patients with CRSsNP ($P < .001$). Hyperdensities in opacified sinuses

TABLE II. Summary of demographic and clinical characteristics of the initial evaluation cohort of patients with CRS classified by CRS subgroups (CRSsNP, CRSwNP, and POLYPOID_CRS) and by alternative CRS subset classifiers (non-EMRS vs EMRS, CRS without RARS vs CRS with RARS, CRS without pathogens vs CRS with pathogens)*

	CRS subgroups			CRS subsets					
Clinical feature	**CRSsNP (n = 383) (A)**	**CRSwNP (N = 475) (B)**	**POLYPOID_CRS (N = 84) (C)**	**Non-EMRS† (n = 258) (D)**	**EMRS† (N = 92) (E) *P* values denote (D) vs (E)**	**CRS without RARS (n = 786) (F)**	**CRS with RARS (N = 156) (G) *P* values denote (F) vs (G)**	**CRS without pathogens (n = 806) (H)**	**CRS with pathogens (n = 135) (I) *P* values denote (H) vs (I)**
Age (y), median (IQR)	48 (38.5-57)	49 (38.5-59) A vs B, $P = .13$	51 (42.5-60) B vs C, $P = .93$ A vs C, $P = .45$	48 (38-59)	49.5 (40-58) $P = .95$	49 (40-59)	45 (35-56) $P = .002$	48 (38-58)	52 (42-62) $P = .008$
Sex: male, %	38.4	53.9 $P < .001$	44.0	55.8	43.5 $P = .04$	48.7	36.5 $P = .005$	47.8	40.4 $P = .09$
Duration of illness (y)	4.0 (1.5-11)	6 (2-15) A vs B, $P < .001$	5 (2-10) A vs C, $P = .60$ B vs C, $P = .03$	7.5 (3-16)	7.0 (3-15) $P = .25$	5 (2-12)	7 (2-15) $P = .009$	5.0 (2-12)	6.0 (2-15) $P = .58$
Age of onset of CRS (y)	39 (27-50)	39 (27-50) A vs B, $P = .91$	43 (32-53) A vs C, $P = .06$ B vs C, $P = .06$	37 (24-49)	40 (27-49.75) $P = .34$	41 (28-51)	33 (24-45) $P < .001$	39.7 (27-50)	41.0 (28-54.5) $P = .08$
No. of previous sinus surgeries	0 (0-1)	1 (0-2) A vs B, $P < .001$	1 (0-2) A vs C, $P < .001$ B vs C, $P = .32$	1 (1-2)	2.54 (1-3) $P = .02$	1 (0-1)	1 (0-2) $P = .01$	1 (0-1)	2 (1-3) $P < .001$
Dust mite allergy, %	37.5	49.2 $P = .005$	43.0	48.8	46.7 $P = .63$	43.7	46.1 $P = .60$	45.2	37.5 $P = .12$
Mold allergy, %	31.1	35.6 $P = .13$	37.5	37.9	37.4 $P = .49$	35.8	37.6 $P = .48$	36.3	35.0 $P = .98$
No. of positive mold skin test results	0 (0-1)	0 (0-1) A vs B, $P < .001$	0 (0-1) A vs C, $P = .33$ B vs C, $P = .85$	0 (0-0)	0 (0-0) $P = .83$	0 (0-1)	0 (0-1) $P = .91$	0 (0-1)	0 (0-1) $P = .79$
Cat allergy, %	16.1	32.5 A vs B, $P < .001$	29.5	30.6	32.2 $P = .91$	25.2	26.8 $P = .68$	25.4	25.8 $P = .94$
Dog allergy, %	14.8	29.2 $P < .001$	23.4	28.0	30.8 $P = .62$	22.3	24.8 $P = .50$	23.0	21.1 $P = .62$
Antibiotic > every 4 mo, %	39.9	22.5 $P < .001$	35.7	28.3	20.6 $P = .14$	25.4	58.3 $P < .001$	28.0	47.4 $P < .001$
Dramatic response to Ab Rx, %	9.4	1.9 $P < .001$	4.8	2.3	2.2 $P = .93$	2.8	17.3 $P < .001$	5.4	3.7 $P = .38$
Oral steroid > every 4 mo, %	8.1	21.9 A vs B, $P < .001$	21.4 A vs C, $P < .001$	25.6	30.4 $P = .37$	14.7	24.4 $P = .004$	13.9	30.4 $P < .001$
Asthma, %	33.4	65.3 $P < .001$	53.6	64.2	85.9 $P < .001$	51.6	49.4 $P = .60$	49.9	59.2 $P = .04$
ASA or NSAID intolerance, %	1.0	15.6 $P < .001$	2.4	16.6	26.0 $P = .04$	9.0	5.8 $P = .16$	8.4	8.9 $P = .86$
AFRS, %	0.52	7.2 $P < .001$	0	8.1	13.0 $P = .18$	4.1	2.6 $P = .34$	2.8	9.6 $P < .001$

Eosinophilic mucin (% of cases per group)	1.8	12.2 $P < .001$	8.3	0 (by subset definition)	100	6.7	7.7 $P = .52$	4.1	23.7 $P < .001$
Anosmia, severe, %	3.6	38.9 $P < .001$	10.7 A vs C, $P = .02$	37.7	54.3 $P = .005$	23.2	16.7 $P = .07$	21.9	23.0 $P = .91$
Ageusia, severe, %	2.1	8.4 $P < .001$	6.0	8.9	7.6 $P = .70$	6.1	3.2 $P = .12$	5.4	6.7 $P = .74$
GERD, %	13.8	11.2 $P = .22$	19.0	11.6	8.7 $P = .43$	13.2	14.1 $P = .30$	18.6	28.1 $P = .01$
Zinreich sinus CT score	7 (2-17)	34 (21-47) A vs B, $P < .001$	19.5 (12-31.25) A vs C, $P < .001$ B vs C, $P < .001$	29 (18-46)	45 (35-53) $P < .001$	21 (9-37)	13 (3-28) $P < .001$	18 (6-34)	26.5 (15-42) $P < .001$
Sinus CT hyperdensities, %	2.6	28.4 A vs B, $P < .001$	15.5 A vs C, $P < .001$ B vs C, $P = .001$	30.1	67.1 $P < .001$	21.6	20.3 $P = .74$	19.7	30.6 $P = .001$
Total serum IgE‡, median (IQR)	73 (13-173)	110 (37-279) A vs B, $P = .007$	89 (36-271) A vs C, $P = .21$ B vs C, $P = .64$	96 (36-262)	129.5 (60-290) $P = .36$	97.5 (34-246)	76.0 (17-231) $P = .23$	96.5 (30-268)	88 (17-208) $P = .11$
AEC (per μL)	190 (100-330)	360 (198-661) A vs B, $P < .001$	320 (130-470) A vs C, $P = .006$ B vs C, $P = .025$	300 (169-588)	540 (315-781) $P < .001$	280 (140-520)	290 (153-495) $P = .83$	270 (140-489)	20 (150-560) $P = .19$
Staphylococcus aureus infection, %	2.4	11.4 A vs B, $P < .001$	15.5 A vs C, $P = .001$ B vs C, $P = .30$	10.1	27.2 $P < .001$	7.4	14.1 $P = .006$	0 (by subset definition)	59.2
Gram-negative nonacute sinusitis pathogen infection, %	5.2	10.5 A vs B, $P = .003$	20.2 A vs C, $P < .001$ B vs C, $P = .02$	12.4	15.2 $P = .50$	8.2	15.4 $P = .005$	0 (by subset definition)	65.2

Ab, Antibody; *ASA*, aspirin; *GERD*, gastroesophageal reflux disease; *NSAID*, nonsteroidal anti-inflammatory drug; *Rx*, treatment.

*Dichotomous variables were analyzed by χ^2 analysis. Continuous variables are expressed as median (first to third quartile) and analyzed by Mann-Whitney *U* test. For χ^2 comparisons of the 3 CRS subgroups (columns A, B, and C only), to minimize type I error for multiple comparison testing, we adjusted the statistically significant level from $P = .05$ to $P = .01$.

†Non-EMRS and EMRS are defined here as subsets of the CRSwNP subgroup who had had previous sinus surgery, because the diagnosis of EMRS was made on surgically collected specimens in all cases.

‡Total serum IgE is presented as the median (IQR).

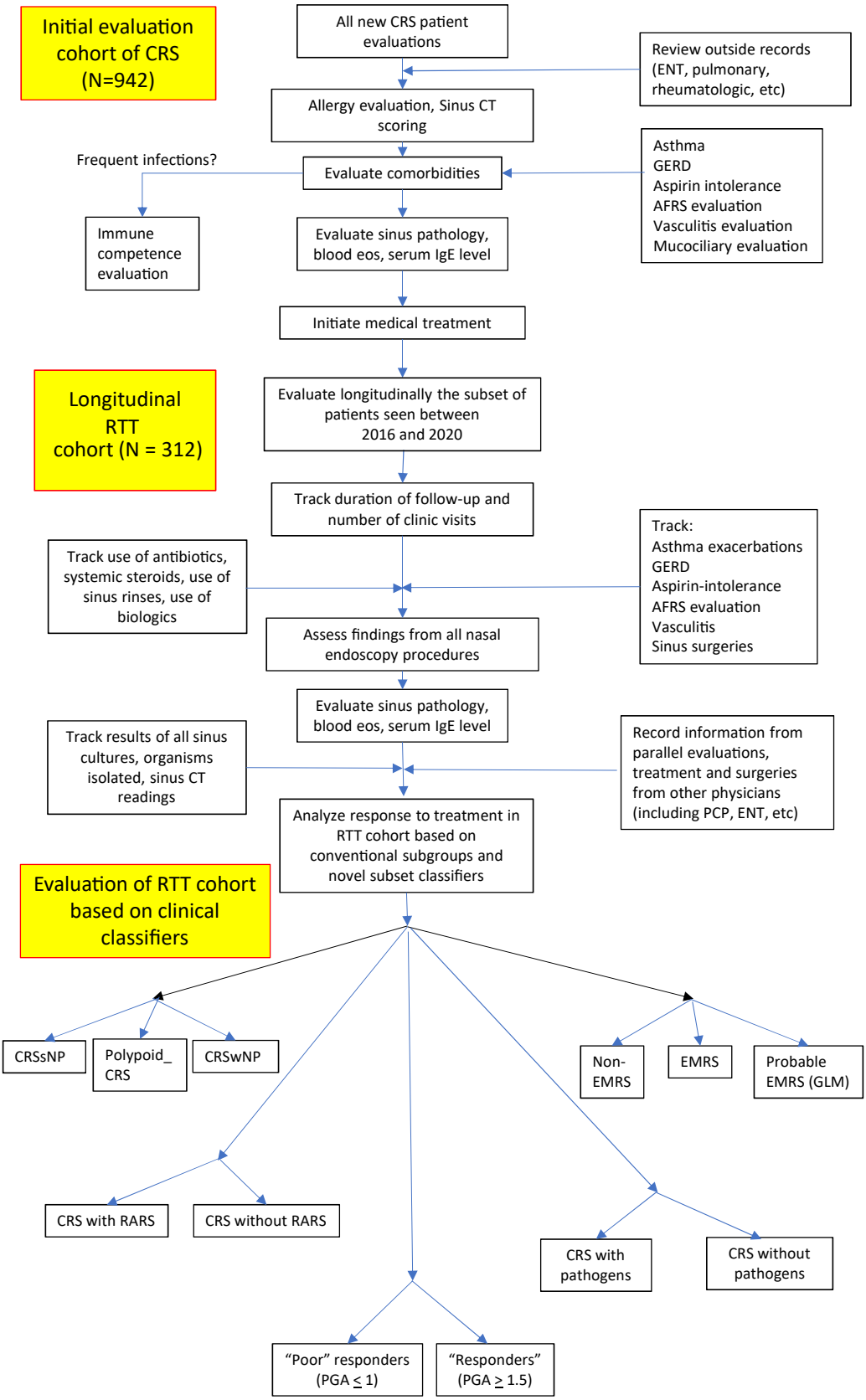

FIGURE 1. Flow diagram for the initial evaluation of patients with CRS in the "initial evaluation cohort (N = 942)" and the longitudinal "RTT" cohort. Because this was a retrospective study, we collected as much information as possible from our institution's EMR for each patient. Not all evaluations were performed on each patient. *Eos*, Eosinophils; *GERD*, gastroesophageal reflux disease.

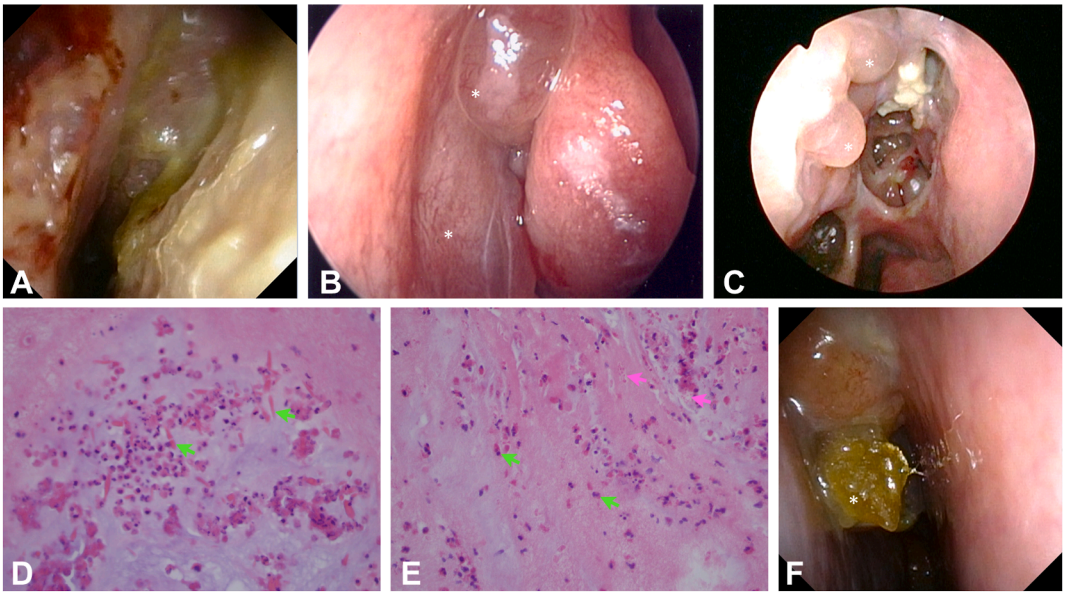

FIGURE 2. (**A**) Image of the right maxillary sinus through a maxillary antrostomy of a patient with CRSsNP illustrating erythematous, edematous mucosa with thick, adherent greenish mucus on the medial wall of the maxillary sinus. (**B**) Typical appearance of nasal polyps (denoted by white asterisk) filling the right middle meatus of a patient with CRSwNP. (**C**) Image of a surgically opened right anterior ethmoid sinus of a patient with POLYPOID_CRS illustrating prominent polypoid mucosal changes (denoted by white asterisks) within the ethmoid cavity with associated adherent purulent mucus. (**D**) High power view of eosinophilic mucin from a patient with EMRS demonstrating numerous eosinophils and extracellular Charcot-Leyden crystals (green arrows), hallmark features of eosinophilic inflammation. Photo taken at 40× magnification. (**E**) High power view of eosinophilic mucin from the patient with EMRS in Figure 2, *D*, demonstrating numerous eosinophils (green arrows) and eosinophil degranulation (pink arrows), hallmark features of eosinophilic inflammation. Photo taken at 40× magnification. (**F**) Typical appearance of adherent GLM (denoted by the white asterisk) beneath a nasal polyp in the right nasal cavity of a patient with CRSwNP.

were noted in patients with CRSsNP (2.6%), patients with CRSwNP (28.4%), and patients with POLYPOID_CRS (15.5%). These differences are highly significant. A history of sinus infection with *S aureus* was found more commonly in CRSwNP or POLYPOID_CRS than in CRSsNP ($P < .001$ and $P = .001$, respectively) without significant difference between CRSwNP and POLYPOID_CRS ($P = .30$). A history of Gram-negative nonacute sinusitis pathogen was found more commonly in patients with CRSwNP and patients with POLYPOID_CRS than in patients with CRSsNP ($P = .003$ and $P < .001$, respectively) and more commonly in patients with POLYPOID_CRS than in patients with CRSwNP ($P = .02$). Total serum IgE levels were available from 24.5% of patients with CRSsNP, 36.6% of patients with CRSwNP, and 40.5% of patients with POLYPOID_CRS and were higher in patients with CRSwNP relative to patients with CRSsNP ($P = .007$) but not patients with POLYPOID_CRS ($P = .64$). Blood absolute eosinophil counts (AECs) were available from 47.2% of patients with CRSsNP, 55.4% of patients with CRSwNP, and 66.7% of patients with POLYPOID_CRS and were higher in CRSwNP than in CRSsNP ($P < .001$) or POLYPOID_CRS ($P = .025$).

Tissue pathology reports from sinus surgery were available for 328 patients (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Tissue eosinophils were reported in 31.0% of patients with CRSsNP, 81.5% of patients with CRSwNP, and 65.8% of patients with POLYPOID_CRS ($P < .001$). As expected, polypoid tissue was also reported with a much higher frequency in CRSwNP and POLYPOID_CRS ($P < .001$) (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Overall, POLYPOID_CRS shared some features with CRSsNP (eg, antibiotic use > every 4 months), but many other features with CRSwNP (eg, oral steroid use > every 4 months, higher Zinreich sinus CT scores, CT hyperdensities, increased likelihood of *S aureus* or Gram-negative pathogen infection, eosinophilic mucin, and elevated blood AEC), suggesting that POLYPOID_CRS is a mixed phenotype.

AFRS and EMRS are distinct forms ("subtypes") of "eosinophilic mucin rhinosinusitis"

Within the CRS cohort (N = 942), 134 patients were diagnosed with "CRS with eosinophilic mucin." Of these, 40 were diagnosed with AFRS and 94 with EMRS. Compared with AFRS, patients with EMRS had less mold allergy and lower total serum IgE but more asthma, aspirin or nonsteroidal anti-inflammatory drug intolerance, anosmia, higher Zinreich sinus CT scores, and higher blood AECs (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). Similar differences were previously reported.[11] The breakdown of cases confirmed that 92.5% of AFRS and 97.9% of EMRS cases were in either the CRSwNP subgroup or the POLYPOID_CRS subgroup.

Within the CRSwNP subgroup, patients with eosinophilic mucin (EM-positive) have more T_H2 inflammation and a greater burden of illness relative to EM-negative patients

Patients with CRSwNP were further subclassified as being either EM-positive, if their sinus tissue pathology demonstrated eosinophilic mucin (N = 94), or EM-negative (N = 381).

Compared with EM-negative patients with CRSwNP (which included some patients later classified as having "GLM"), EM-positive patients had a greater number of previous sinus surgeries, a greater prevalence of asthma, aspirin intolerance, and anosmia, and a higher blood AEC (Table II). EM-positive patients also had a greater prevalence of *S aureus* sinus infections compared with EM-negative patients. Zinreich sinus CT scores were also higher and sinus CT hyperdensities much more frequently reported in EM-positive patients (67.1%) compared with EM-negative patients with CRSwNP (30.1%) ($P < .001$). Considering only patients with CRSwNP with previous surgery, the sensitivity of hyperdensities in opacified sinus cavities for EM was 57.8%, with specificity of 80.6% (data not shown). Overall, these features indicate that EM-positive patients have a higher burden of illness.

Very similar differences were found between patients with and without GLM among the patients with CRSwNP after excluding confirmed EM-positive cases (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). These included higher blood AECs, higher Zinreich sinus CT scores, and a higher prevalence of asthma, CT hyperdensities, and anosmia compared with patients without GLM with CRSwNP, demonstrating that in the absence of pathologically confirmed eosinophilic mucin, GLM is highly suggestive of the presence of EM.

Patients with CRS "with RARS" have distinctive features compared with patients with CRS "without RARS" (N = 942 cohort)

A history of RARS exacerbations was reported more frequently in patients with CRSsNP (21.7%) than in patients with CRSwNP (12.2%) and patients with POLYPOID_CRS (17.9%) ($P = .001$). Compared with patients with CRS without RARS, patients with CRS with RARS were younger at their first clinic visit, younger at their age of onset of CRS, more often female, had more sinus surgeries, more often used antibiotics more than every 4 months, more often reported a dramatic response to antibiotics (17.3% of cases), and more often used oral steroids more than every 4 months (Table II). In contrast, only 2.8% of patients with CRS without RARS reported a dramatic response to antibiotics (4.7%, 1.2%, and 4.3%, for CRSsNP, CRSwNP, and POLYPOID_CRS, respectively, $P < .001$). In addition, patients with CRS with RARS had lower total Zinreich sinus CT scores and more frequent *S aureus* and GNNASP infections. Patients with CRS with RARS also had more selective IgA deficiency, IgG or IgG subclass deficiency (excluding isolated IgG4 subclass deficiency), specific antibody deficiency, and selective IgM deficiency than did patients with CRS without RARS (see Table E6 in this article's Online Repository at www.jaci-inpractice.org). The prevalence of "any antibody deficiency" was nearly 4-fold higher in patients with CRS with RARS than in patients with CRS without RARS but still accounted for only a small percent of these patients (12.2% compared with 3.3%, $P < .001$). These results confirm a higher burden of illness and higher prevalence of humoral immune deficiency in patients with CRS with RARS.

Patients with CRS with a history of infection with *S aureus* or a GNNASP ("CRS with pathogens") also have distinctive features

We classified patients with CRS who had a history of sinus infection with either *S aureus* (including methicillin-resistant *S aureus*) or a GNNASP (excluding infections with acute Gram-negative pathogens *Haemophilus influenzae* or *Moraxella catarrhalis*) as "CRS with pathogens." These comprised 6.5% of patients with CRSsNP, 18.1% of patients with CRSwNP, and 28.6% of patients with POLYPOID_CRS ($P < .001$) (data not shown) As presented in Table II, patients with CRS with pathogens were older, had more previous sinus surgeries, more use of antibiotics more than every 4 months, more use of oral steroids more than every 4 months, more asthma, more AFRS, more eosinophilic mucin, more gastroesophageal reflux disease, higher Z-SCT scores, and had a higher prevalence of hyperdensities compared with patients with CRS without pathogens, indicating a high burden of illness. Patients with CRS with pathogens did not have a higher prevalence of humoral immune deficiency (data not shown).

Less common and rare subtypes of CRS in the N = 942 cohort

Less common and rare subtypes of CRS observed in the N = 942 cohort (summarized in Table E7 in this article's Online Repository at www.jaci-inpractice.org) included rare infectious and noninfectious inflammatory presentations, mucociliary defects (cystic fibrosis and primary ciliary dyskinesia), eosinophilic granulomatous polyangiitis, granulomatous polyangiitis, sarcoidosis, and IgG4-related systemic disease.

Response to medical treatment in the longitudinal RTT cohort

Patients with CRS seen initially or who had follow-up visits between November 2019 and December 2020 constituted the RTT cohort (N = 313). The distribution of cases in this cohort was 86 CRSsNP (27.5%), 200 (CRSwNP 63.9%), and 27 POLYPOID_CRS (8.6%) consistent with the greater percentage of new patients with CRSwNP seen in the period 2015 to 2019. EMRS and GLM cases accounted for 18.8% and 10.9%, respectively, in this cohort.

Table III summarizes the key clinical variables and medical treatments analyzed in this cohort comparing patients with CRS based on conventional subgroups (CRSsNP, CRSwNP, and POLYPOID_CRS) as well as novel classifiers. As previously indicated, not all patients received each type of treatment.

Comparison of response to treatment in patients with CRSsNP, patients with CRSwNP, and patients with POLYPOID_CRS

Consistent with the N = 942 study, patients with CRSwNP continued to experience a higher rate of sinus surgery and oral steroid use compared with patients with CRSsNP and patients with POLYPOID_CRS, whereas patients with CRSsNP and patients with POLYPOID_CRS continued to have greater antibiotic use in the RTT cohort (Table III). Responses to dilute budesonide rinses and concentrated budesonide instillations were not significantly different between groups. Itraconazole

TABLE III. Key clinical variables and response to treatment in CRS subgroups and the CRS subsets (non-EMRS vs EMRS, CRS without RARS vs CRS with RARS, CRS without pathogens vs CRS with pathogens, and "poor" vs "good" responders to treatment) in the longitudinal RTT study*

	CRS subgroups			CRS subsets							
Clinical feature	**CRSsNP (N = 85) (A)**	**CRSwNP (N = 200) (B)**	**POLYPOID_CRS (N = 27) (C)**	**RTT score non-EMRS (N = 143) (D)**	**RTT score EMRS (N = 57) (E)**	**CRS without RARS (N = 228) (F)**	**CRS with RARS (N = 84) (G)**	**CRS without pathogens (N = 214) (H)**	**CRS with pathogens (N = 89) (I)**	**End-of-treatment PGA ≥ 1.5 ("good responders") (N = 255) (J)**	**End-of-treatment PGA ≤ 1.0 ("poor responders") (N = 48) (K)**
No. of sinus surgeries/y	0 (0-0)	0 (0-0.079) A vs B, $P = .05$	0 (0-0.05) A vs C, $P = .23$ B vs C, $P = .99$	0 (0-0.079)	0.071 (0-0.159) D vs E, $P < .001$	0 (0-0.07)	0 (0-0) F vs G, $P = .80$	0 (0-0)	0 (0-0.165) H vs I, $P < .001$	0 (0-0)	0.087 (0-0.18) J vs K, $P < .001$
Antibiotic courses/y	0.66 (0.13-1.41)	0.3 (0-0.98) A vs B, $P = .04$	0.92 (0.39-1.58) A vs C, $P = .32$ B vs C, $P = .01$	0.30 (0-0.94)	0.58 (0-1.09) D vs E, $P = .28$	0.39 (0-0.94)	0.98 (0.30-1.81) F vs G, $P < .001$	0.53 (0-1.11)	0.94 (0.53-1.56) H vs I, $P < .001$	0.40 (0-1)	0.98 (0.29-2.44) J vs K, $P < .001$
Oral steroid courses/y	0.139 (0-0.72)	0.33 (0-1.15) A vs B, $P = .03$	0.270 (0-0.96) A vs C, $P = .82$ B vs C, $P = .26$	0.183 (0-0.947)	0.632 (0.30-1.48) D vs E, $P = .001$	0.31 (0-0.97)	0.09 (0-1) F vs G, $P = .12$	0.18 (0-0.73)	0.64 (0-1.68) H vs I, $P < .001$	0.24 (0-0.92)	0.63 (0-1.69) J vs K, $P = .008$
Asthma exacerbations/y	0 (0-0)	0 (0-0) A vs B, $P = .15$	0 (0-0) A vs C, $P = .66$ B vs C, $P = .71$	0 (0-0)	0 (0-.147) D vs E, $P = .03$	0 (0-0)	0 (0-0) F vs G, $P = .30$	0 (0-0)	0 (0-0.15) H vs I, $P = .006$	0 (0-0)	0 (0-0) J vs K, $P = .55$
RTT scores for each treatment											
SRB-dilute irrigation, RTT score†	2 (1-3)	1 (0-3) A vs B, $P = .43$	1 (0-3) A vs C, $P = .37$ B vs C, $P = .61$	2 (0.5-3)	1 (0-1.75) D vs E, $P = .26$	1 (0-3)	2 (0-3) F vs G, $P = .67$	2 (0-3)	1 (0-2) H vs I, $P = .18$	2 (0-3)	1 (0-1) J vs K, $P = .013$
% use by CRS subset	36.5	26.0	33.0	25.9	24.6	28.9	25.0	32.2	23.6	30.6	25.0
SRBC instillation RTT score‡	2 (1-3)	2 (1-3) A vs B, $P = .60$	1.75 (1-2) A vs C, $P = .48$ B vs C, $P = .68$	2 (1-3)	1 (0-2) D vs E, $P = .002$	2 (1-3)	1.5 (0-2) F vs G, $P = .035$	2 (1-3)	1 (0-2) H vs I, $P < .001$	2 (1-3)	1 (0-1) J vs K, $P < .001$
% use by CRS subset	37.6	77.0	74.1	72.7	82.4	67.5	61.9	60.7	79.8	66.3	66.7
SRB-neat, RTT score§	2 (2-2)	2 (1-3) A vs B, $P = .90$	2 (1.5-2.5) A vs C, $P = .67$ B vs C, $P = .91$	2 (1.62-3)	1.5 (.75-2.0) D vs E, $P = .03$	2 (1-3)	2 (1.25-2) F vs G, $P = .66$	2 (1-3)	2 (1.5-2) H vs I, $P = .76$	2 (1.5-3)	0 (0-1) J vs K, $P = .0071$
% use by CRS subset	1.2	15	7.4	12.6	21.0	11.4	6.7	9.3	12.4	11.0	6.2
SR-itra instillation RTT score‖	2 (1.5-2)	0 (0-1) A vs B, $P = .004$	0 (0-1) A vs C, $P = .03$ B vs C, $P = .94$	0 (0-1)	0 (0-1) D vs E, $P = .89$	1 (0-2)	0 (0-1) F vs G, $P = .31$	1 (0-1.75)	1 (0-2) H vs I, $P = .99$	1 (0-2)	0 (0-1) J vs K, $P = .31$
% use by CRS subset	12.9	8.5	18.5	7.0	12.3	8.8	14.3	7.9	16.8	10.6	10.4

(continued)

TABLE III. *(Continued)*

	CRS subgroups			CRS subsets							
Clinical feature	**CRSsNP (N = 85) (A)**	**CRSwNP (N = 200) (B)**	**POLYPOID_CRS (N = 27) (C)**	**RTT score non-EMRS (N = 143) (D)**	**RTT score EMRS (N = 57) (E)**	**CRS without RARS (N = 228) (F)**	**CRS with RARS (N = 84) (G)**	**CRS without pathogens (N = 214) (H)**	**CRS with pathogens (N = 89) (I)**	**End-of-treatment PGA ≥ 1.5 ("good responders") (N = 255) (J)**	**End-of-treatment PGA ≤ 1.0 ("poor responders") (N = 48) (K)**
SR-gent or SR-tobra instillation RTT score¶	2 (0-2.75)	2 (1-2) A vs B, $P = .87$	2 (1-2.5) A vs C, $P = .65$ B vs C, $P = .55$	1.5 (0.75-2)	2 (1-3) D vs E, $P = .58$	2 (1-2)	1.75 (0-2.75) F vs G, $P = .53$	1.5 (1-2.5)	2 (0.5-2) H vs I, $P = .99$	2 (1-3)	0 (0-1.25) J vs K, $P = .002$
% use by CRS subset	14.1	10.5	48.1	9.8	12.3	11.4	26.7	4.2	41.6	16.0	20.8
Dupilumab RTT score#	3 (1.5-3)	3 (2-3) A vs B, $P = .89$	2.25 (1.5-2.62) A vs C, $P = .63$ B vs C, $P = .34$	3 (1.5-3)	3 (2-3) D vs E, $P = .36$	3 (2-3)	2.5 (2-3) F vs G, $P = .40$	3 (2-3)	2.75 (2-3) H vs I, $P = .33$	3 (2-3)	0.5 (0-1) J vs K, $P = .017$
% use by CRS subset	3.5	16	14.8	12.6	24.6	12.3	13.3	8.4	22.5	14.1	4.2
Prebiologic and postbiologic PGA scores											
Prebiologic PGA score	2 (2-3)	2 (1-3) A vs B, $P = .25$	2 (1.25-2) A vs C, $P = .04$ B vs C, $P = .22$	2 (1.5-3)	2 (1-3) D vs E, $P = .016$	2 (1.5-3)	2 (1-3) F vs G, $P = .062$	2.5 (2-3)	1.5 (1-2) H vs I, $P < .001$	2 (2-3)	0 (0-1) J vs K, $P < .001$
Postbiologic PGA score	3 (2-3)	3 (2-3) A vs B, $P = .86$	2 (1.75-2.75) A vs C, $P = .10$ B vs C, $P = .06$	3 (2-3)	2 (1.5-3) D vs E, $P = .13$	3 (2-3)	2 (1.5-3) F vs G, $P = .024$	3 (2-3)	2 (1.5-3) H vs I, $P = .003$	3 (2-3)	0 (0-1) J vs K, $P < .001$

*Dichotomous variables were analyzed by χ^2 analysis. Continuous variables are expressed as median (first to third quartile) and analyzed by Mann-Whitney *U* test.
†SRB-dilute is dilute budesonide irrigation using either 0.5 mg or 1.0 mg in 240 mL saline.
‡SRBC is concentrated budesonide instillation using either 0.5 mg or 1.0 mg in 7 mL saline.
§SRB-neat is undiluted budesonide instillation using either 0.5 mg or 1.0 mg in 2 mL saline.
‖SR-itra is itraconazole instillation, at a concentration of 100 mg/L.
¶SR-gent or SR-tobra is gentamicin or tobramycin instillation, at a concentration of 100 mg/L.
#Dupilumab dosage is 300 mg subcutaneous every 14 d.

sinus instillations (SR-itra) were prescribed in a small percentage of patients, mostly in those who had used antibiotics repeatedly. Although the sample size is small, patients with CRSsNP responded significantly better to SR-itra than did either patients with CRSwNP or patients with POLYPOID_CRS ($P = .004$ and .03, respectively). Gentamicin (SR-gent) or tobramycin (SR-tobra) instillations were used more frequently in POLYPOID_CRS (48.1%) versus 14.1% and 10.4% in CRSsNP and CRSwNP, respectively, consistent with the greater burden of sinus infections in the POLYPOID_CRS subgroup; however, treatment responses to these were not significantly different in the 3 subgroups. Dupilumab was used mostly in patients with CRSwNP and patients with POLYPOID_CRS. The response to dupilumab was superior to responses to each of the sinus instillations and not statistically different in the 3 subgroups.

The end-of-treatment prebiologic PGA was indicative of a "good response" to treatment with a median of 2.0 for each subgroup, although the prebiologic PGA for patients with POLYPOID_CRS was poorer compared with patients with CRSsNP ($P = .04$). However, the postbiologic PGA scores were not significantly different between the subgroups. A significant reduction in the number of sinus surgeries/y was observed in all 3 subgroups relative to each subgroup's historic rate, with a 2-fold reduction in CRSsNP (from mean 0.11 to 0.05 surgeries/y, $P = .03$), a 3-fold reduction in CRSwNP (from mean 0.32 to 0.10 surgeries/y, $P < .001$), and a 4-fold reduction in POLYPOID_CRS (from mean 0.54 to 0.12 surgeries/y, $P = .003$, by Wilcoxon).

CRS subtype classifier 1: EM-negative versus EM-positive patients in the CRSwNP subgroup

Compared with EM-negative patients, EM-positive patients continued to experience a higher frequency of sinus surgeries and asthma exacerbations in the RTT cohort, and EM-positive patients also experienced greater oral steroid use and poorer responses to SRBC and SRB-neat compared with EM-negative patients. SR-itra was used infrequently in EM-negative and EM-positive patients, and the responses to SR-itra were poor in both subgroups. Gentamicin or tobramycin instillations were used infrequently but with some benefit in EM-negative and EM-positive patients. Dupilumab (prescribed in conjunction with an intranasal steroid or budesonide sinus instillation) was used in 12.6% and 24.6% of EM-negative and EM-positive patients, respectively. Responses to dupilumab were superior to responses to SRBC in both EM-negative and EM-positive patients with no statistical difference in responses. A paired *t*-test analysis was performed on the 15 EM-negative and EM-positive patients who used SRBC before and following addition of dupilumab. In both EM-negative and EM-positive patients, the response to dupilumab was dramatically better than that to SRBC (EM-negative: SRBC 0.83 ± 0.79 vs dupilumab 2.47 ± 0.72, $P < .001$; EM-positive: SRBC 0.83 ± 0.75 vs dupilumab 2.62 ± 0.48, $P < .001$).

The prebiologic PGA was significantly lower in EM-positive than in EM-negative patients ($P = .016$), whereas the postbiologic (end-of-treatment) PGA was indicative of a "good response" to treatment (mean RTT score > 2.0) in both groups and not significantly different ($P = .13$). A significant reduction in the number of sinus surgeries/y was observed in both EM-negative and EM-positive patients compared with their historic rates (from 0.28 ± 0.40 to 0.092 ± 0.39 and from 0.40 ± 0.58 to 0.12 ± 0.41, $P < .001$ for both).

CRS subtype classifier 2: Patients with CRS with RARS versus patients with CRS without RARS

Compared with patients with CRS without RARS, patients with CRS with RARS had a higher frequency of sinus infections triggered by a viral upper respiratory tract infection or exposure to young children (14.7% vs 5.3%, $P = .008$) (data not shown). Sinus infections with an acute rhinosinusitis bacterial pathogen (*Streptococcus pneumoniae*, *Haemophilus influenzae,* or *Moraxella catarrhalis*) were also more frequent in patients who reported being triggered by exposure to a viral upper respiratory tract infection or young children (21.2% vs 5.9%, $P = .002$) (data not shown).

Compared with patients with CRS without RARS, patients with CRS with RARS continued to have more frequent antibiotic use and also had more use of SR-gent or SR-tobra in the RTT cohort. Responses to dilute budesonide sinus rinses or instillations of SRBC, SR-neat, SR-itra, SR-gent, or SR-tobra were not significantly different in these subtypes. The pre- and postbiologic PGA scores were lower in patients with CRS with RARS. Compared with historic rates, a significant reduction in the number of sinus surgeries/y was observed in the RTT cohort in both patients with CRS without RARS (from 0.28/y to 0.09/y, $P < .001$) and patients with CRS with RARS (from 0.30/y to 0.08/y, $P = .002$). Patients with POLYPOID_CRS were disproportionately represented in the CRS with RARS subtype (16.0% vs 6.6% in the CRS without RARS subset, $P = .04$).

CRS subtype classifier 3: Patients with CRS with a history of either *S aureus* or GNNASP infection ("CRS with pathogens") versus patients with "CRS without pathogens"

One or more culture-proven infections with *S aureus* or a GNNASP was documented in 100 of the 312 RTT cohort patients. Compared with patients with CRS without pathogens, patients with CRS with pathogens experienced more frequent sinus surgery, antibiotic use, oral steroid use, and asthma exacerbations (Table III). The responses to SRBC instillation were lower in patients with CRS with pathogens ($P < .001$), whereas the responses to dilute budesonide sinus rinses, instillations of SRB-neat, SR-itra, and SR-gent/tobra, and treatment with dupilumab were not significantly different. Both the pre- and postbiologic PGA scores were lower in patients with CRS with pathogens ($P < .001$ and $P = .003$, respectively).

Compared with historic rates, a significant reduction in the number of sinus surgeries/y was observed during the RTT study in both patients with CRS without pathogens (from 0.18 ± 0.53/y to 0.074 ± 0.57/y, $P = .004$) and patients with CRS with pathogens (from 0.48 ± 0.78/y to 0.11 ± 0.45/y, $P < .001$). Patients with POLYPOID_CRS were disproportionately represented in the CRS with pathogens subtype (16.8%) versus 5.6% in the CRS without pathogens subtype ($P = .001$).

CRS subtype classifier 4: "Poor" versus "good responders" to medical treatment

We compared "poor responders" to medical treatment (arbitrarily defined as those having an end-of-treatment PGA ≤ 1.0, $N = 48$) to "good responders" (PGA ≥ 1.5, $N = 255$).

Coefficients

PC

	Component															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Duration of CRS	−0.161	−0.030	0.421	−0.016	0.175	−0.289	0.497	−0.449	0.242	−0.176	0.308	−0.172	0.067	−0.025	0.120	0.015
#Prev. Sinus Surgeries	−0.347	0.056	0.272	−0.277	−0.100	−0.279	0.160	0.128	−0.520	0.133	−0.120	0.159	0.147	−0.119	−0.471	−0.101
RTT_#SinusSurgery/y	−0.036	0.133	−0.310	0.431	−0.349	−0.169	0.370	−0.296	0.149	0.360	−0.289	0.246	−0.018	0.022	−0.053	−0.157
PGA_End of treatment	0.293	0.012	−0.366	−0.422	−0.166	0.093	0.370	0.051	−0.039	−0.125	−0.013	−0.206	0.309	−0.453	0.141	−0.217
Z-SCT+HD	0.026	0.503	0.047	−0.185	−0.180	0.019	0.151	0.133	0.041	0.330	0.043	−0.200	−0.022	0.052	0.093	0.687
Anosmia	0.115	0.446	0.068	0.056	−0.002	−0.017	0.081	0.066	−0.057	−0.578	−0.223	0.359	0.353	0.332	0.132	0.017
Endo-Inflammation	0.031	0.517	0.087	−0.177	0.013	0.055	0.032	0.080	−0.053	0.131	0.240	−0.010	−0.471	0.144	0.163	−0.575
RTT_#Prednisone/y	−0.237	0.265	−0.348	0.373	0.034	0.014	−0.005	0.022	−0.131	−0.277	0.205	−0.563	0.065	0.058	−0.387	−0.042
TSRS	−0.253	0.343	0.237	0.239	0.183	0.073	−0.318	0.012	0.163	0.160	−0.157	−0.030	0.324	−0.567	0.206	−0.139
RTT_#Asthma/y	−0.033	0.127	−0.395	−0.156	0.521	0.061	−0.091	−0.472	−0.318	0.217	0.203	0.250	0.160	0.064	0.055	0.107
Skin test score	0.025	−0.027	0.304	0.081	−0.089	0.766	0.182	−0.335	−0.279	−0.005	−0.233	−0.136	−0.057	0.031	−0.063	−0.001
Ab use/response score	−0.200	−0.082	−0.067	0.024	0.469	0.300	0.440	0.486	0.293	0.200	−0.033	0.097	0.142	0.175	−0.121	−0.073
Infection score	−0.360	0.012	−0.168	−0.375	0.159	−0.121	−0.077	−0.174	0.171	−0.112	−0.650	−0.287	−0.213	0.149	0.104	−0.021
RTT_#Antibiotics/y	−0.407	−0.166	−0.132	0.222	−0.058	−0.018	0.205	0.221	−0.436	−0.120	0.054	0.041	−0.181	−0.094	0.618	0.113
Total#Pathogens	−0.389	0.084	−0.169	−0.184	−0.200	0.270	−0.017	−0.087	0.307	−0.312	0.221	0.419	−0.271	−0.305	−0.224	0.160
Endo-Infection	−0.378	−0.114	−0.025	−0.197	−0.417	0.153	−0.198	−0.065	0.130	0.177	0.247	−0.074	0.471	0.402	0.181	−0.181

FIGURE 3. Heat map of variable loadings for each variable in the PCA. TH2-type inflammation–associated variables are arbitrarily displayed in the upper half of rows, and infection-related variables are arbitrarily displayed in the lower half of rows. *Ab,* Antibiotic.

"Poor responders" had more frequent sinus surgery, more use of antibiotics and oral steroids, and poorer responses to SRB-dilute, SRBC and SRB-neat, SRB-gent/SRB-tobra, and dupilumab (Table III). No disproportionality of cases by CRS subgroup was seen in "poor" versus "good responders." Similarly, no disproportionality of cases by CRS subgroup was seen when "poor responders" were defined by an end-of-treatment PGA of 1.5 or less. However, certain "pre-RTT" clinical features were significantly associated with "poor responders," including historical GNNASP sinus infection (25.0% vs 12.8%, $P = .01$), oral steroid use more than every 4 months (35.5% vs 21.6%, $P = .03$), and a history of 2 or more previous sinus surgeries (44.2% vs 18.9%, $P = .004$).

Patient tolerance of and intraocular pressure in patients with CRS using budesonide instillations in the RTT study

Budesonide instillations (SRBC or SRB-neat) were well tolerated by most patients. Among the 206 patients who had sustained use of SRBC or SRB-neat, 10 reported an elevation in intraocular pressure. However, 3 of these 10 patients also received daily oral systemic steroids. It is unclear in these 10 patients whether the elevated intraocular pressure antedated use of SRBC or SRB-neat. Among the 206 patients, 84 reduced their budesonide instillation concentration or frequency over time. SRBC or SRB-neat was discontinued in 39 patients because of patient preference (13), subjective lack of efficacy (7), improvement in CRS (6), poor insurance coverage (3), throat irritation or postnasal drainage (3), cataracts (2), intolerance (2), concern for glaucoma (1), or epistaxis (1). One patient discontinued SRBC after microinvasive fungal sinusitis was discovered at sinus surgery. No other systemic side effects were noted from these treatments.

PCA of CRS subtypes based on data derived from the initial evaluation and the longitudinal RTT

We performed an unsupervised PCA to further examine whether subtypes of CRS could be defined in our CRS database and to identify the most important variables relating to response to medical treatment. This analysis incorporated 7 variables derived from each patient's initial evaluation and 9 variables derived from the longitudinal RTT cohort study (see Methods).

A summary of the principal components (PCs) and the amount of variance accounted for by each component is shown in Figure 3 and the corresponding scree plot (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). Figure 3 is organized with T_H2-type inflammation variables in the upper half and infectious variables in the lower half to allow for easier recognition of variable relationships. PC1 through PC3 account for only 32.1% of the variance, indicating significant heterogeneity of the patients with CRS. Twelve components are needed to explain 90.5% of the variance of the data. Herein, we highlight insights learned from the first 2 PCs.

PC1, which accounts for 16.7% of the data variance, is strongly negatively correlated with the number of previous sinus surgeries, infection score, number of antibiotics used/y, total number of pathogens score, endo-infection score, and to a lesser extent TSRS, number of prednisone courses/y, previous antibiotic use/response score, and duration of CRS. PC1 is most positively correlated with PGA and therefore highlights patients with CRS who responded well to medical treatment, that is, those with fewer previous sinus surgeries, fewer sinus infections, and better sensitivity to topical steroids.

PC2, which accounts for 15.4% of the data variance, is positively correlated with endo-inflammation score, Z-SCT-HD score, and anosmia and to a lesser extent TSRS and number of prednisone courses/y. PC2 is most negatively correlated with number of antibiotics/y, previous antibiotic use/response score, and endo-infection score. PC2 highlights patients with CRSwNP with a greater burden of polyposis, anosmia, and Z-SCT-HD scores who have fewer infections and less use of antibiotics. EM-positive patients with aspirin-exacerbated respiratory disease typify these patients. It is noteworthy that PC2 shows no correlation with end-of-treatment PGA, consistent with our analysis showing that even though EM-positive patients had higher TSRSs and poorer responses to SRBC and SRB-neat, they had comparably good responses to biologics, such as dupilumab, relative to EM-negative patients with CRSwNP.

Figure 4 is the PCA monoplot of PC1 (x-axis) and PC2 (y-axis) demonstrating the variable loadings displayed as vectors and correlations between variables (explained in the Figure 4 legend). The monoplot demonstrates that Z-SCT-HD score, endo-inflammation score, and anosmia score are highly correlated consistent with the strong relationship of these variables to CRSwNP, including both EM-negative and EM-positive patients. Notably, these variables do not correlate with PGA score (ie, vector angles nearly 90 degrees with PGA) consistent with the observation that the PGA scores (postbiologic) of EM-negative and EM-positive patients were not statistically

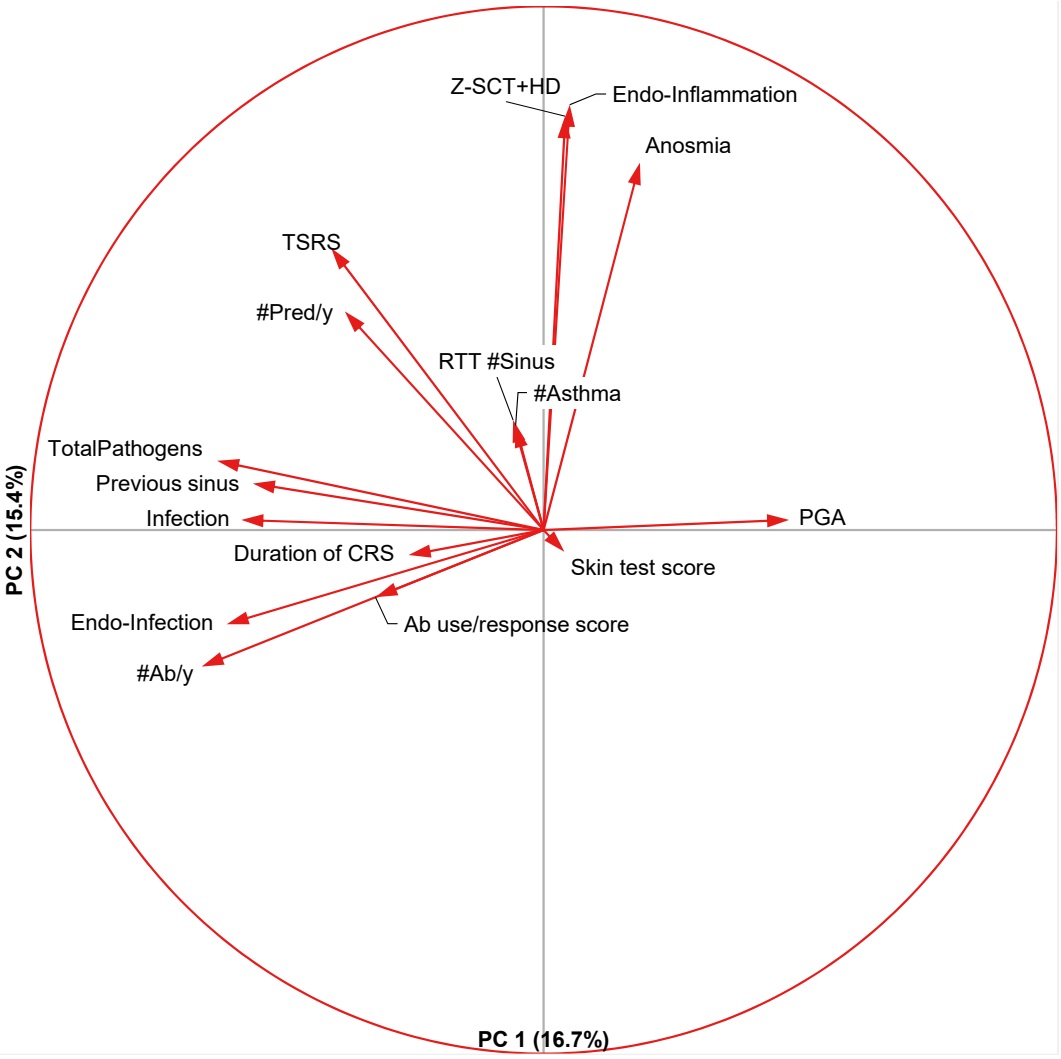

FIGURE 4. PCA monoplot of PC1 (x-axis) and PC2 (y-axis) demonstrating the variable loadings and correlations between variables displayed as vectors. The length and direction of each vector indicates the variable loading with the first and second PC. Correlations are represented by the angle between 2 variables. A small angle indicates that the variables are positively correlated. An angle near 90 degrees indicates that the variables are not correlated. An angle near 180 degrees indicates that the variables are negatively correlated. *Ab,* Antibiotic.

different. The variables of TSRS and number of prednisone courses/y correlate strongly, consistent with TSRS being an indicator of steroid resistance or steroid dependency in patients with CRS. The number of previous sinus surgeries is highly correlated with the previous infection score and the total pathogen score. Furthermore, these factors, as well as the number of antibiotics/y, endo-infection score, and the antibiotic use/response score, demonstrate moderately strong negative correlations with the PGA score, reinforcing the importance of bacterial infections in the responses to medical treatment observed in the RTT cohort. Finally, the skin testing score shows low factor weighting and no correlation with the PGA score, suggesting that allergy to dust mites or fungi contributed little to response to the medical treatment.

Figure 5 shows a biplot of PC1 (x-axis) and PC2 (y-axis), which illustrates with distribution of CRSsNP, CRSwNP, and POLYPOID_CRS cases by color coding and also includes the variable loadings for each variable in the PCA. The 3 variables with the highest loadings, Z-SCT-HD score, endo-inflammation score, and anosmia, relate to CRSwNP. The number of antibiotics used/y has the fourth highest loading and correlates most strongly with the endo-infection score and the antibiotic use/response score. The other infectious variables (total pathogen score and infection score) show intermediate loadings but strong negative correlations with PGA.

In Figure 5, the color coding shows a moderate segregation of patients with CRSwNP and patients with CRSsNP mostly along PC2 (y-axis), which shows the strongest positive correlation with T_H2-type variables and CRSwNP. There is significant overlap of patients with CRSwNP and patients with CRSsNP as has been reported in studies of CRS endotypes.[5] Patients with POLYPOID_CRS cluster mostly in the lower left quadrant

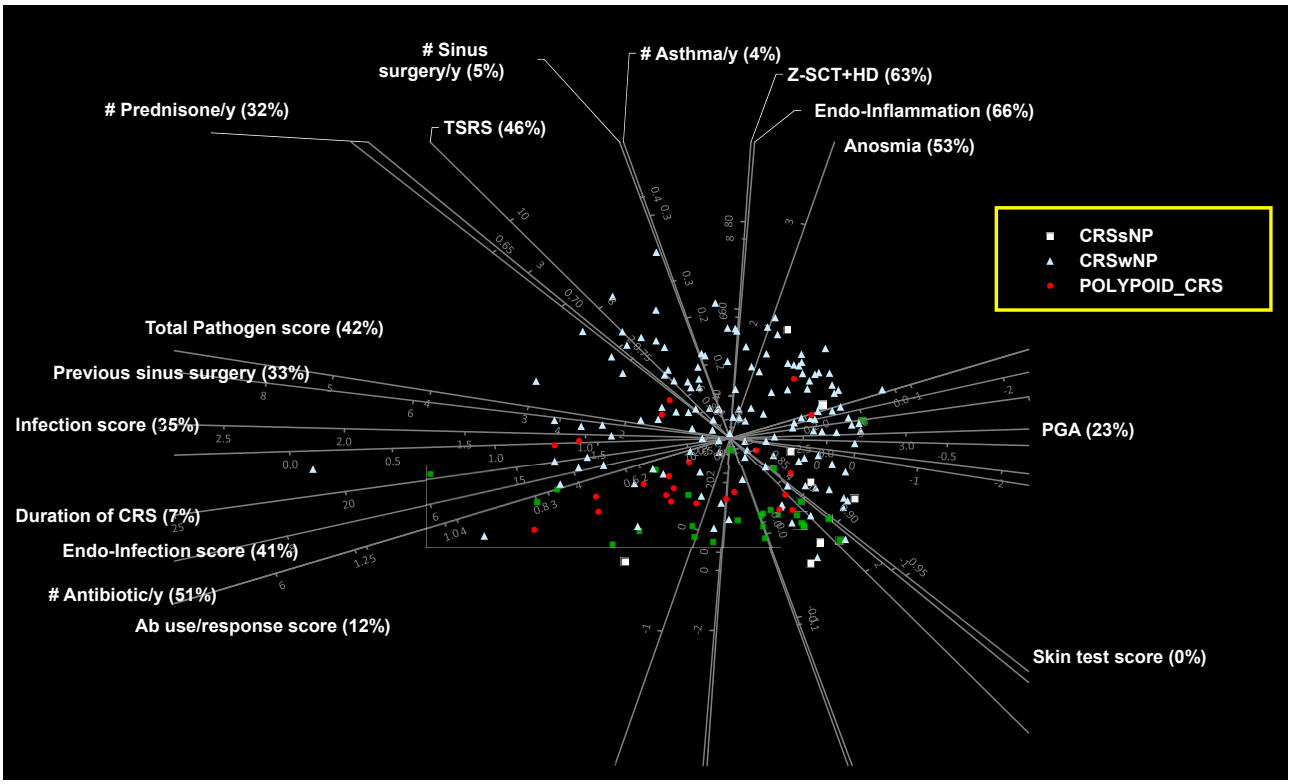

FIGURE 5. PCA biplot of PC1 vs PC2 color coded to show individual patients by CRS subgroups. The color coding shows a moderate segregation of patients with CRSwNP and patients with CRSsNP mostly along PC2 (y-axis) (which shows the strongest association with CRSwNP variables) with some overlap of patients with CRSwNP and patients with CRSsNP as has been reported in other studies. Patients with POLYPOID_CRS cluster mostly in the lower left quadrant where they show positive correlations with antibiotic use history, number of antibiotics used/y and endo-infection score. *Ab,* Antibody.

where they are mostly distinct from patients with CRSwNP and show positive correlations with number of antibiotics used/y, endo-infection score, and antibiotic use/response score. POLYPOID_CRS is the only one of the 3 CRS subgroups to show a positive correlation with infectious variables. Furthermore, patients with POLYPOID_CRS have a relatively poor response to medical treatment, with 15 of the 23 (65.2%) patients with POLYPOID_CRS having a PGA 2.0 or lower.

DISCUSSION

The results of this study demonstrate that certain clinical features present at initial evaluation of each patient with CRS plus other features emerging in response to medical treatment help define novel clinical subtypes beyond the conventional CRS classification. This study also identifies clinical variables most strongly associated with "good" versus "poor" responses to medical treatment.

The analysis of key differences between patients with CRSsNP and patients with CRSwNP in the initial evaluation cohort (N = 942) both confirm and expand on previous reports.[16] Patients with CRSsNP are more likely female, have greater antibiotic use, are more likely to report a dramatic response to antibiotic treatment, and more likely have symptoms of facial pain/pressure/headaches and anterior/posterior nasal drainage. In contrast, patients with CRSwNP have a higher prevalence of sinus surgery, dust mite, mold, cat, and dog allergy, oral steroid use, hyposmia, anosmia, asthma, aspirin intolerance, AFRS, tissue eosinophilia, eosinophilic mucin, sinus CT hyperdensities, elevated total serum IgE, and elevated blood AECs. We also found that patients with CRSwNP have an increased prevalence of *S aureus* and GNNASP infections.

We identified a novel POLYPOID_CRS subgroup as a mixed phenotype between CRSsNP and CRSwNP. We found that patients with POLYPOID_CRS had tissue eosinophilia in 65% of cases but were also disproportionately represented in the "CRS with pathogens" subtype, suggesting that infection plays a role in creating this phenotype. In the RTT cohort, patients with POLYPOID_CRS were again overrepresented in the CRS with pathogens subtype, with 66.7% of patients with POLYPOID_CRS falling in this subtype. Furthermore, the Figure 5 PCA biplot illustrated that patients with POLYPOID_CRS cluster mostly in the lower left quadrant where they, unlike patients with CRSwNP, show positive correlations with antibiotic use history, number of antibiotics used/y, and endo-infection score. It is known that a subset of patients with CRS possess defective innate immunity, such as the nonfunctional TAS2R38 genotype,[3] which predisposes them to infection with GNNASP and *S aureus* infections and which correlates with poor surgical outcomes in patients with CRS without nasal polyps.[17] Because patients with POLYPOID_CRS do not have nasal polyps, a defect in innate immunity such as a

nonfunctional TAS2R38 genotype is one potential explanation for their increased prevalence of *S aureus* and GNNASP infections. This subtype deserves further attention, especially considering that patients with POLYPOID_CRS do not qualify for biologic treatments or clinical trials targeting patients with nasal polyps, but 65.8% of them had moderate or abundant tissue eosinophils confirming type 2 inflammation (endotype), and some of them met other criteria for use of a biologic for CRS, such as need for systemic corticosteroids and comorbid asthma.[18]

We found that patients with CRS with RARS were younger at their initial visit, had a younger age of CRS onset, more often reported a dramatic response to antibiotics, more often had humoral immune deficiency, and had lower total Zinreich sinus CT scores. These results are mostly consistent with the findings of Kwah et al.[19] The mean end-of-treatment PGA in patients with CRS with RARS was poor compared with that in patients with CRS without RARS, consistent with sinus infection having a negative effect on response to treatment. In contrast, patients with "CRS with pathogens" had more chronic infections and were not more likely to have humoral immune deficiency, and we hypothesize that their infectious predisposition is likely a result of 1 or more defects in innate immunity as mentioned above. Both the CRS with RARS and CRS with pathogens subtypes highlight the importance of infection in contributing to the burden of illness of CRS and poor response to medical treatment. Patients with POLYPOID_CRS were highly disproportionately represented in the CRS with pathogens subtype, with 66.7% of patients with POLYPOID_CRS falling in this category. Finally, the analysis of "poor" versus "good" responders to medical treatment in the RTT cohort identified clinical features present at the initial CRS evaluation as significantly associated with poor response, including history of GNNASP infection, oral steroid use more than every 4 months, and a history of 2 or more previous sinus surgeries. During the RTT period, a history of 2 or more previous sinus surgeries remained highly significantly associated with poor responders.

EMRS is an important subtype of CRSwNP comprising 19.8% of patients with CRSwNP in the initial evaluation cohort and 29.5% of patients in the longitudinal RTT cohort. The proportion of EMRS cases among the new patients with CRSwNP in our clinic increased steadily from 2004 to 2020 from 18.7% to 22.9% to 30.8%. Although this increase could simply reflect an increased appreciation by pathologists of the importance of EM recognition and reporting in our institution or a change in referral patterns to our clinic, the possibility that EMRS prevalence is increasing is worth considering, especially since the prevalence of other eosinophilic diseases, such as eosinophilic esophagitis, is increasing.[20] We further identified that patients with GLM share clinical features with patients with EMRS and respond similarly to medical treatment. We suspect that most of our patients with GLM had EMRS merely lacking pathologic confirmation. The importance of EMRS in the management of CRSwNP is borne out by the increased burden of illness (sinus surgery, asthma, anosmia, and aspirin intolerance) and the poorer response to SRBC and SRB-neat (reflected in higher TSRSs) consistent with EMRS being "steroid resistant" relative to patients without EMRS. An important finding in this study, however, is that patients with EMRS who failed to improve on SRBC or SRB-neat improved greatly on dupilumab treatment consistent with other reports.[21]

Only 31.9% of our patients with EMRS were diagnosed clinically with aspirin intolerance. It is known that the prevalence of aspirin intolerance in patients with CRSwNP is underreported by patient history and is 15% higher when patients undergo aspirin challenge.[22,23] Because we did not routinely perform aspirin challenges in patients with EMRS, the true prevalence of aspirin intolerance in these patients is likely closer to the 54% reported by Ferguson.[11] We also confirmed a much higher prevalence of sinus CT hyperdensities in patients with EMRS and GLM and found that the presence of CT hyperdensities in patients with CRSwNP had a sensitivity of 57.8% and a specificity of 80.6% for the presence of EM. CT hyperdensities in an opacified sinus are therefore highly suggestive of the presence of either EMRS or AFRS in patients with CRSwNP.

Dilute budesonide sinus rinses were used in a small fraction of patients, most commonly in patients with CRSsNP, with moderate benefit (median RTT score of 2). Our ENT colleagues often initiate topical dilute budesonide rinses and reserve more concentrated budesonide instillations for patients who fail to respond adequately to these rinses. Concentrated low-volume budesonide instillations (SRBC) were used more frequently in patients with CRSwNP and patients with POLYPOID-CRS, with overall moderately good benefit (median RTT score 2 with interquartile range 1-3). A small fraction of patients were "stepped up" to undiluted budesonide instillations (SRB-neat) due to lack of response to SRBC. Because various strengths of budesonide topical treatments were used by most patients in either a "step-up" or "step-down" manner, we devised a *post hoc* TSRS on the basis of responses to these treatments. In the PCA, the TSRS showed predictivity comparable to other markers of T_H2 inflammation and a strong correlation with the number of prednisone courses/y, suggesting that a systematically determined TSRS based on response to varying concentrations of topical budesonide could be a useful clinical tool. Because of the potential of systemic side effects of SRBC and SRB-neat, our patients were routinely advised to have yearly ophthalmologic evaluations to monitor intraocular pressure and development of cataracts, and treatment was stepped down when clinically warranted.

Itraconazole sinus instillations were used in a small percentage of patients with CRS, with the best responses in patients with CRSsNP (median RTT score 2 with interquartile range 1.5-2) but poor responses in patients with CRSwNP and patients with POLYPOID_CRS (median RTT scores of 0 for both). We have found SR-itra to be without side effects and most beneficial in patients with CRS who have used antibiotics repeatedly even though we have not found sinus fungal cultures useful in predicting who might benefit from them. Gentamicin or tobramycin instillations (SR-gent or SR-tobra) were used most frequently in patients with POLYPOID_CRS (48.1%) with moderate benefit (median RTT score of 2 with interquartile range 1-2.5), consistent with the greater burden of *S aureus* and GNNASP infections in this CRS subgroup. SR-gent and SR-tobra were well tolerated and sometimes helped patients eradicate sinus infections even after oral antibiotics had failed. They are most beneficial in postsurgical patients with culture-proven

infection who can effectively deliver the instillation to their infected sinuses. We avoid using instillations for sphenoid sinus infections and instead recommend using gentamicin or tobramycin via a nasal nebulizer, because our instillation technique does not effectively deliver medication to the sphenoid sinuses (a precaution to avoid instilling aminoglycoside antibiotics into the Eustacian tubes).

Dupilumab and other biologics were used more often in patients with CRSwNP and patients with POLYPOID_CRS, consistent with Food and Drug Administration—approved indications for these for nasal polyposis or comorbid asthma. Dupilumab was used most commonly, and responses to dupilumab were superior to those to topical budesonide regardless of the budesonide concentration used in both patients with and without EMRS. Dupilumab also produced a highly significant incremental improvement in patients with and without EMRS who had used SRBC prebiologic and who continued using SRBC following introduction of dupilumab. These observations demonstrate that dupilumab overcomes steroid resistance, which is particularly impressive in patients with EMRS who manifest greater baseline steroid resistance.

In the RTT cohort, the median end-of-treatment PGA was indicative of a "good" response to treatment, with a median of 3 for patients with CRSsNP and patients with CRSwNP and 2 for patients with POLYPOID_CRS, although this difference did not reach statistical significance. The median end-of-treatment PGA was lower in CRS with RARS versus CRS without RARS ($P = .024$) and in CRS with pathogens versus CRS without pathogens ($P = .003$), highlighting the importance of infection in treatment outcomes.

The PCA demonstrated significant heterogeneity in our patients, consistent with the multiplicity of factors known to affect the clinical presentation and response to treatment in patients with CRS. Twelve PCs were needed to explain 90.5% of the variance of the data. PC1 highlighted patients with CRS who had fewer previous sinus surgeries, fewer sinus infections, and who showed the strongest correlation with good response to medical treatment. PC2 highlighted patients with CRSwNP with a greater burden of polyposis, anosmia, and Z-SCT-HD scores who have had fewer infections and less use of antibiotics. These include both patients with and without EMRS and patients with aspirin-exacerbated respiratory disease. It is noteworthy that PC2 showed no correlation with PGA, consistent with our observation that patients with and without EMRS have comparably good responses to dupilumab. Each additional PC from the analysis accounted for 8.8% of the data variance or less and was not discussed further.

The predictivity weightings from the first 2 components of the PCA confirm that variables relating to T_H2 inflammation (endo-inflammation, Z-SCT-HD score, anosmia, and TSRS) and variables relating to infection (number of antibiotics/y, total pathogen score, endo-infection score, and infection score) account for most of the variance in these components. Infectious variables (total pathogen score, endo-infection score, and infection score) are the most negatively correlated with PGA, highlighting their relevance to patients' outcomes. In addition, the number of previous sinus surgeries was highly correlated with the total pathogen score and previous infection score and negatively correlated with PGA. Although this could be partially explained by more culturing of these patients or alteration of the sinus mucosal microbiome following surgery,[24] we found no correlation between the number of sinus surgeries/y in the RTT study and infectious parameters or PGA. Our ENT colleagues are excellent at performing intraoperative sinus cultures and treating sinus infections in the immediate postoperative period, thereby minimizing the long-term impact of sinus infections on our patients' treatment outcomes.

Limitations of the study include that the study design was retrospective, patients who failed to follow-up for at least 6 months were not included in the RTT cohort, certain variables were dependent on patient's recall, not all patients received the same treatments, and the TSRS was derived *post hoc* from patients' responses to different types and variable concentrations of topical steroids. We acknowledge that the TSRS is a crude estimate of topical steroid resistance, but we believe there is a solid rationale for hypothesizing that a more systematically derived TSRS, based on assessing each patient's response to graded concentrations of topical steroids, could help predict which patients with CRSwNP are most likely to have nasal polyp recurrence, need for revision sinus surgery, or need for biologic treatment. Finally, the scoring systems derived for the RTT study were not validated but were based on the physician's best estimate of responses to each treatment. This lack of validation of RTT scores is offset somewhat by the fact that most patients had multiple clinic visits with the investigator over an extended period of time. The overall positive responses to treatment in this study highlight the importance of novel treatment strategies to optimize the management of patients with CRS.

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