

Immunologic Evaluation of Pediatric Chronic and Recurrent Acute Rhinosinusitis

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Abstract

Background: Although pediatric rhinosinusitis is a commonly encountered clinical entity, the diagnostic approach and treatment algorithm are constantly evolving. In addition to anatomic and allergic etiologies, immunologic deficiencies have been implicated in the pathogenesis of rhinosinusitis; however, the prevalence of immunologic disease in pediatric rhinosinusitis is poorly defined.

Objective: To inform the approach to the evaluation of pediatric patients with rhinosinusitis, this retrospective pilot study examined the prevalence of abnormal results detected on immunologic testing in pediatric patients with chronic rhinosinusitis (CRS) and recurrent acute rhinosinusitis (RARS).

Methods: Patients between 2008 and 2018 were identified using International Classification of Diseases 9/10 codes. Imaging, endoscopy findings, and clinical criteria were used to diagnose CRS and RARS (n = 27). We reviewed available results, including quantitative immunoglobulins (Igs), thyroid evaluation, complete blood count, and titers to *Streptococcus*, *Haemophilus influenzae* type B (HiB), Diphtheria, and Tetanus. Statistical analyses were performed with the Mann–Whitney U test and Fisher’s exact test.

Results: Our initial search yielded 140 patients, of which 27 met diagnostic criteria for CRS (17) or RARS (10). Eight patients (29.6%) underwent adenoidectomy and 5 (18.5%) underwent endoscopic sinus surgery. The most common Ig deficiencies were IgM, 13.0%, and IgA, 11.1%. Four (23.5%) of the 17 patients had significantly elevated IgE levels, indicating a possible allergic etiology. Within this cohort, there was an increased incidence of insufficient protective titers to polysaccharide vaccines. HiB titers were not protective in 35% of our cohort. Insufficient pneumococcal protection was more common in patients >10 years, while deficient IgM was more common in those <10 years.

Conclusion: High-yield testing in pediatric rhinosinusitis should include titers to polysaccharide antigens, specifically *Streptococcus pneumoniae* and *H. influenzae*. Low-yield tests that may be deferred during initial testing include thyroid studies and Tetanus and Diphtheria antibodies. Prospective, high-volume studies are required to further elucidate the role of immunologic testing in this population.

Keywords

pediatric rhinosinusitis, recurrent acute rhinosinusitis, chronic rhinosinusitis, immunologic disease, immunoglobulin deficiency

Introduction

Rhinosinusitis is a commonly encountered problem in both pediatric and otolaryngologic practice. On average, children experience 6 to 8 upper respiratory infections per year and 5% to 10% of these are complicated by rhinosinusitis.^{1–4} In a study of children with chronic purulent rhinorrhea and nasal obstruction by history, computed tomography (CT) scans revealed that 64%

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exhibited sinus disease.⁵ In comparison, the incidence of sinus pathology on CT scans in asymptomatic individuals ranges from 4% to 20%.^{6,7} The evaluation and treatment of pediatric rhinosinusitis consumed approximately \$1.8 billion in health-care resources for children younger than 12 years in 1996.⁸ Despite its prevalence, the diagnostic approach and treatment algorithm for pediatric chronic rhinosinusitis (CRS) and recurrent acute rhinosinusitis (RARS) are not well studied and constantly evolving.

Pediatric rhinosinusitis is defined as inflammation of the nose and paranasal sinuses manifesting as 2 or more symptoms, either nasal obstruction/congestion or nasal discharge, with either endoscopic or CT signs of polyps, mucosal edema/obstruction, and mucopurulent discharge. Additional symptoms include facial pain/pressure and cough.⁹ Acute rhinosinusitis is defined by disease duration less than 12 weeks with complete resolution of symptoms. CRS is defined by a disease duration greater than 12 weeks without complete resolution of symptoms. RARS is characterized by recurrent acute infections with relatively symptom-free intervals in between, though some chronic element may be present between the acute infections.^{1,4,9,10}

Despite these standard definitions, the clinical signs and symptoms indicative of rhinosinusitis can result from multiple etiologic factors, especially in the pediatric population. There can be anatomic abnormalities such as adenoid hypertrophy and ostiomeatal complex obstruction, which necessitate surgical intervention. In addition, underlying medical conditions, such as allergic disease or primary immune deficiency, confers an increased risk for the development of rhinosinusitis. Recent studies have demonstrated a significant prevalence of immunoglobulin (Ig) anomalies in adult and pediatric patients with RARS and CRS, with common abnormalities being low IgG and IgA levels.^{11–17} All young children have a physiologic nadir in Ig levels between the first 3 and 6 months of life. IgA and IgM are low at birth, rise gradually, and reach adult levels by 17 to 18 years of age. Antibody response to vaccines against encapsulated bacteria may not reach adult levels until age 10.¹⁸ Although primary immune disorders are a predisposing factor to rhinosinusitis, existing evidence is limited in the value and role of immunologic evaluations in the pediatric patient population.

The objective of this retrospective study was to examine outcomes and trends arising from the immunologic evaluation of pediatric patients with CRS and RARS.

Material and Methods

This study was approved by the institutional review board of Weill Cornell Medical College (protocol number: 1712018821A002). Pediatric patients with

a diagnosis of recurrent acute or CRS who underwent immunologic testing between 2008 and 2018 were identified utilizing Informatics for Integrating Biology and the Bedside (i2b2) software.¹⁹ This was used to search electronic medical records within Epic between 2000 and August 2018. International Classification of Diseases (ICD)-9 and ICD-10 diagnostic codes were used to identify any patient aged 18 years or younger with sinusitis (Table 1). To identify individuals with immunologic testing results, the presence of complete blood count (CBC) and/or Ig testing was used as an additional inclusion criteria within the i2b2 program.

After this preliminary search, medical records were screened by the authors to identify and include only individuals who met the aforementioned diagnostic criteria for RARS and CRS. Patients with immunologic testing were included when the evaluation occurred after the diagnosis of sinusitis. Results were heterogeneous but included a CBC, quantitative Igs, IgG subclass testing, and pathogen-specific antibody testing (Diphtheria, *Haemophilus*, Tetanus, Pneumococcus, Measles, Mumps, Rubella, and Varicella). Ig levels were compared against age-adjusted reference intervals determined by New York Hospital Laboratories. For Tetanus and Diphtheria titers, an antibody concentration of greater than 0.1 international units per milliliter (IU/mL) was considered protective. For *Haemophilus* and pneumococcal titers, an antibody concentration below 1.0 µg/mL was considered to be nonprotective. A subset of individuals also underwent serum testing for environmental and food allergies.

The Mann–Whitney *U* test was used to analyze associations between age and immunologic abnormalities. The Fisher's exact test was used to analyze associations between immunologic abnormalities and age, sex, type of rhinosinusitis (RARS vs CRS), and interventions used (surgical vs medical). A cutoff of 10 years was used to

Table 1. ICD-9 and ICD-10 Diagnostic Codes in Electronic Medical Record Search.

	ICD-9	ICD-10
Acute maxillary sinusitis	461.0	J01.00
Acute ethmoidal sinusitis	461.2	J01.20
Acute sphenoidal sinusitis	461.3	J01.30
Acute frontal sinusitis	461.1	J01.1
Other acute sinusitis	461.8	J01.80
Acute sinusitis, unspecified	461.9	J01.90
Chronic maxillary sinusitis	473.0	J32.0
Chronic ethmoidal sinusitis	473.2	J32.2
Chronic sphenoidal sinusitis	473.3	J32.3
Chronic frontal sinusitis	473.1	J32.1
Other chronic sinusitis	473.8	J32.8
Chronic sinusitis, unspecified	473.9	J32.9

Abbreviation: ICD, International Classification of Diseases.

Table 2. Clinical Characteristics.

Age (years)	8.0 ± 4.1 (1.5–17)
Sex (male/female)	16/11
Recurrent acute rhinosinusitis	10 (37.0%)
Chronic rhinosinusitis	17 (63.0%)
Medical intervention only	15 (55.6%)
Surgery	12 (44.4%)
Adenoidectomy	3 (11.1%)
Tonsillectomy and adenoidectomy	5 (18.5%)
Functional endoscopic sinus surgery	5 (18.5%)

separate the patients into 2 age groups. All statistical analyses were conducted using Stata version 13 (StataCorp, College Station, TX, USA). A *P* level of less than .05 was considered statistically significant.

Results

The initial electronic medical record search for pediatric sinusitis patients who also underwent immunologic testing yielded 140 patients. Patient records were screened to exclude individuals who did not meet diagnostic criteria for either RARS or CRS. Twenty-seven patients in total were included in the final study, 10 with RARS, and 17 with CRS (Table 2). The mean age was 8.0 ± 4.1 years (range 1.5–17 years). Fourteen (55.6%) patients were treated with medical interventions only. Three (11.1%) patients underwent adenoidectomy alone, 5 (18.5%) patients underwent tonsillectomy and adenoidectomy, 5 (18.5%) patients underwent functional endoscopic sinus surgery (FESS), and 2 (7.4%) patients underwent both adenoidectomy and FESS. Nine (33.3%) patients underwent CT of the sinuses with an average Lund–MacKay score of 14.44 ± 4.7 (range 10–23).

Results from 27 individuals who underwent a heterogeneous array of immunologic testing are shown in Table 3. For total Ig levels, 13 (50.0%) of the 26 patients demonstrated an abnormal value outside of reference range. The most prevalent total Ig abnormalities, including values above and below reference range, were elevated IgE (23.5%) and decreased IgM (21.7%). There were no statistically significant differences in proportions of Ig abnormality between individuals with RARS versus CRS (*P* = .420). There were also no significant differences in proportions of Ig abnormality among different age, sex, and types of intervention (*P* = .395, .691, and .431, respectively). There was a trend toward increasing proportion of IgM abnormality in patients younger than 10 years (45.5% vs 0%, *P* = .095). Of the 4 individuals with high IgE levels, 3 (75.0%) tested positive for environmental allergens (*P* = .011). The most common Ig deficiencies were low IgM and/or IgA levels at 13.0% and 11.1%, respectively (Figure 1).

All patients underwent age-appropriate immunizations by clinical history. Eleven (55.0%) of the 20 patients demonstrated *Streptococcus pneumococcal* titers were not protective in 11 of the 20 patients (55.0%). Three (30.0%) of the 10 patients demonstrated deficient *Haemophilus influenzae* B (HiB) titers (Figure 2). There was no difference in proportions of protective *S. pneumococcal* IgG or HiB IgG between individuals with RARS and CRS (*P* = .714) or between individuals receiving medical versus surgical therapy (*P* = .391) (Figure 2). There was a trend toward insufficient pneumococcal IgG protection in patients 10 years and older (42.9% vs 83.3%, *P* = .095).

Seven patients underwent IgG subclass testing with one (14.3%) found to have low IgG1 and one (14.3%) with low IgG2. No patients were found to have deficient levels of Diphtheria (*n* = 14) or Tetanus antibodies (*n* = 13). One of the 5 patients was nonimmune to Measles. One of the 4 patients was nonimmune to Varicella Zoster.

Thyroid function was also assessed in 9 individuals. No patients were found to have abnormal thyroid function tests.

Four (18.2%) of the 22 patients demonstrated hyper-eosinophilia on CBC. One of these individuals was diagnosed with hypereosinophilic syndrome and was also found to have significant polyposis on CT and endoscopic exam. The presence of eosinophilia was significantly associated with the use of medical over surgical therapy (33% of medically treated patients had eosinophilia versus 0% of surgically treated patients, *P* = .044). Positive allergy testing was also associated with eosinophilia (7.1% of nonallergic patients had eosinophilia versus 50% of allergic patients, *P* = .043).

Overall, the prevalence of abnormal testing in this population was 81.4%. There were no significant associations between abnormal immunologic test results and demographic factors, diagnosis, and type of intervention.

Available nasal culture data were examined for prevalence of common pathogens and their association to immunologic deficiencies. The most common pathogen detected was *H. influenzae* with a prevalence of 72.7%, followed by *Streptococcus pneumoniae* (45.5%) and *Moraxella catarrhalis* (18.2%) (Figure 3). The presence of a *Haemophilus* or *S. pneumoniae* on culture was not significantly associated with a corresponding specific antibody deficiency (SAD; *P* = .495 and .764, respectively).

Discussion

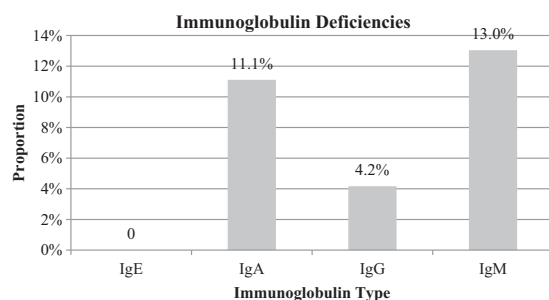
Standards in the treatment of pediatric patients with RARS and CRS include imaging and/or nasal endoscopy, saline lavage, decongestants, steroids, antibiotics, removal of the adenoid pad as a bacterial reservoir,

Table 3. Immunologic Testing Results.

Pt	Age (years)	Sex	Diagnosis	Surgery	Lund–MacKay	CBC	IgE	IgA	IgG	IgM	Pneumococcal IgG	HiB IgG
1	11	M	CRS	A	14	Normal	High (1269.25)	136	1180	107	Normal	12.3
2	5	M	CRS	–	11	Normal	30	134	749	94	Low	Low
3	5	M	CRS	A	–	Normal	–	153	–	–	–	–
4	6	F	CRS	–	–	–	High (227.41)	123	1130	–	–	–
5	4	M	CRS	–	–	Normal	7.26	68	540	84	Low	19.8
6	1.5	F	CRS	–	–	High EOS	16.1	41	757	104	Normal	95.5
7	3	M	CRS	T&A	–	Normal	–	109	1170	65	Normal	–
8	7	F	CRS	–	–	–	–	100	870	High (208)	Normal	–
9	15	M	CRS	ESS	10	Normal	–	102	–	–	Low	–
10	4	M	CRS	–	–	Normal	22.9	66	809	96	–	–
11	9	M	CRS	T&A, ESS	13	Normal	10.19	143	1010	170	Normal	12.3
12	11	F	CRS	A, ESS	12	Normal	–	Low (68)	Low (744)	107	Low	2.2
13	11	F	CRS	ESS	13	Normal	–	155	917	142	Low	Low
14	12	M	CRS	–	22	High EOS	–	–	–	–	–	–
15	9	M	CRS	–	12	High EOS	35	166	1055	Low (37)	–	–
16	8	M	CRS	T&A	–	–	–	Low (34)	726	Low (49)	Low	–
21	11	M	CRS	ESS	23	Normal	17.98	High (368)	1000	68	Low	2.3
17	16	F	RARS	–	–	–	21.78	180	1090	133	–	–
18	9	M	RARS	–	–	Normal	13	117	781	High (212)	Low	Low
19	6	F	RARS	T&A	–	Normal	–	107	832	95	Normal	–
20	3	M	RARS	–	–	Normal	55.8	High (184)	796	63	Low	–
22	6	F	RARS	–	–	Normal	<2	206	887	119	Normal	>9
23	10	F	RARS	A	–	Normal	High (227)	203	1040	132	Low	–
24	5	F	RARS	–	–	Normal	High (231)	88	927	Low (46)	Normal	–
25	4	M	RARS	T&A	–	–	70.4	36	567	50	Low	–
26	7	M	RARS	–	–	High EOS	–	163	High (1320)	124	Normal	–
27	17	F	RARS	–	–	Normal	114	Low (27)	946	139	–	–

Abbreviations: A, adenoidectomy; CBC, complete blood count; CRS, chronic rhinosinusitis; EOS, eosinophils; ESS, endoscopic sinus surgery; F, female; HiB, *Haemophilus influenzae* B; Ig, immunoglobulin; M, male; RARS, recurrent acute rhinosinusitis; T&A, tonsillectomy and adenoidectomy; –, information is unknown.

IgE results are listed in international units per milliliter (IU/mL). Quantitative IgA, IgG, and IgM results are listed in milligrams per deciliter (mg/dL). Pneumococcal and HiB IgG results are listed in micrograms per milliliter (μg/mL).

**Figure 1.** Prevalence of Ig deficiencies in all patients with CRS or RARS. Ig, immunoglobulin.

and endoscopic sinus surgery. Primary immunodeficiency can lead to multiple recurrent infections including rhinosinusitis, and there are existing guidelines for when to screen for immunodeficiency (<http://www.jmfworld.com/library/educational-materials/10-warning-signs>).²⁰ The

recommended evaluation indicates a wide range of studies, including CBC, quantitative Ig levels, specific antibody responses, candida and tetanus skin tests, and lymphocyte surface markers. While a number of studies report on the frequency of immune deficiency in adults with rhinosinusitis, there are few published reports on the prevalence of immunologic abnormalities in the pediatric population with RARS or CRS as their primary complaint.

The European position paper on rhinosinusitis and nasal polyps (EPOS 2012) states that interdisciplinary consultations, such as those in the realm of allergy–immunology, may be useful in the evaluation of pediatric patients with medically refractory disease.⁹ In this study, we retrospectively evaluated 27 RARS/CRS patients who underwent immunologic evaluation.

Fifty percent of the study population exhibited an abnormality in quantitative Ig levels. Twenty-eight

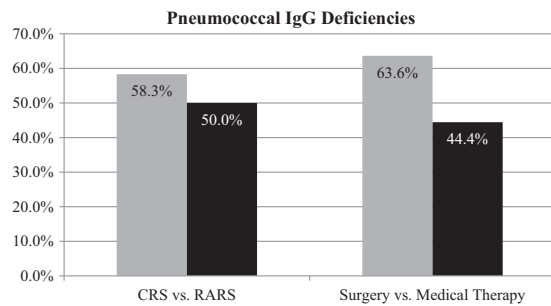


Figure 2. Prevalence of pneumococcal IgG deficiencies in patients with CRS versus RARS ($P=.714$) and patients who underwent surgery versus medical therapy only ($P=.391$). CRS, chronic rhinosinusitis; Ig, immunoglobulin; RARS, recurrent acute rhinosinusitis.

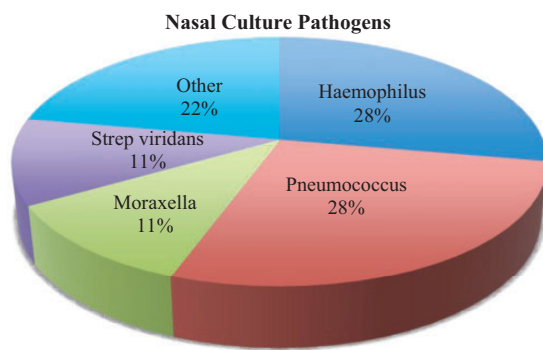


Figure 3. Distribution of nasal culture pathogens in patients with chronic rhinosinusitis and recurrent acute rhinosinusitis.

percent of patients had low levels of IgA, IgG, or IgM, which is higher than the range of 2% to 23% reported in adults with CRS.^{11,13,18,21} The rate of low IgA in this study, 11.1%, is high compared to the rate of selective IgA deficiency, 1.5 to 6.8%, in adults with CRS. In comparison, the prevalence of IgA deficiency in the general population is 0.2% for Caucasians and far more uncommon in the Asian population.²² Up to 90% of individuals with IgA deficiency are asymptomatic.⁹ IgA predominantly functions on mucosal surfaces and deficiencies may play a role in the pathogenesis of sinusitis. The rate of low IgG in this study, 4.2%, falls within the reported range of 0.6% to 16% in the adult CRS population.^{11,21,23,24} The frequency of isolated IgG deficiency is questionable and can be as low as 1 in 10 000 cases; however, IgG subclass deficiency can be as high as 20% in the general population.²⁵ Past studies have found deficiencies more commonly in IgG subclasses 1 through 3, rarely IgG4.^{14,26,27} In the subset of patients who underwent IgG subclass testing, deficiencies IgG1 and IgG2 were noted in 2 patients. The prevalence of low IgM in this study population is high, 13%, compared to the reported range of selective IgM deficiency, 0.9% to

6.9%, in adults with CRS.^{11,24} In the general population, the prevalence of primary selective IgM deficiency is reported to range from 0.03% to 3.8%.²⁸ In this study, patients with low IgA and IgM do not meet diagnostic criteria for selective IgA or IgM deficiency. Indeed, immunologic laboratory results should be interpreted cautiously in the pediatric age-group, as they may reflect normal antibody variations. This may account for the higher rates of subclinical abnormalities in comparison to reported values for selective Ig deficiencies. We hypothesize that those with subclinical deficiencies may still be at higher risk for infection.

Despite high percentages of normal total Ig levels, a significant proportion of patients in this study population exhibited low pneumococcal titers, which is consistent with the reported results in the adult CRS population.^{11,15} One limitation of this study is that post-booster vaccine titers were not available for comparison to prevaccine levels. Therefore, it was not possible to confirm a diagnosis of specific polysaccharide antigen deficiency. Interestingly, this study also revealed a high prevalence of nonprotective HiB IgG, leading to repeat vaccination in these individuals. This is consistent with the past reports that patients with recurrent infections may lack the ability to make pathogen-specific Igs when exposed, despite normal overall levels.²⁹ Indeed, SAD, in which there is an inadequate response to polysaccharide antigens in the setting of normal IgG concentrations, has a prevalence of 5% to 10% in children over 2 years and as high as 40% in adults with CRS.^{30,31} In this study, the presence of low pneumococcal titers was significantly associated with age 10 years or greater. We hypothesize that this population of children with RARS and CRS may have had waning immunity and consequently an increased risk for infection. These patients may benefit from booster vaccination.

The results of this study highlight several known causes of CRS and RARS in the pediatric population. A large portion of patients underwent surgical interventions, including adenoidectomy and endoscopic sinus surgery, to correct anatomic anomalies. A significant portion of individuals also exhibited elevated IgE levels and evidence for allergic disease. Specific analysis of immunologic testing in this disease population identified a significant rate of Ig anomalies. There were derangements in total Ig levels for IgG, M, and A. Although these abnormalities did not meet diagnostic criteria for selective Ig deficiency, it is possible that low antibody levels may still confer a higher risk for infection. Current recommendations from EPOS 2012 direct physicians treating individuals with CRS to evaluate immune function with Ig quantification and titers to tetanus, diphtheria, and pneumococcus. Interestingly, in our patient population, no individuals displayed abnormalities to tetanus and diphtheria, while a high prevalence of

patients was deficient in pneumococcus and HiB titers. The study is limited by the lack of data regarding post-booster vaccination titers.

Because of the retrospective design, only CRS and RARS patients who also underwent immunologic evaluation could be examined, which created a significant selection bias and potentially exaggerated the prevalence of abnormal results (81.5%) due to high pretest probability. This high proportion may also be due to the inclusion of all testing abnormalities, including Ig values falling both below and above reference ranges. Furthermore, not everyone underwent the same number of tests. This study included a small number of patients and may be underpowered to explore certain associations between rarer immunologic dysfunction and rhinosinusitis.

Conclusion

This study examines the immunologic evaluation of pediatric patients with CRS and RARS. The results highlight several major contributors to rhinosinusitis, including allergic disease and immunodeficiency disorders. These findings introduce the question of how best to utilize immunologic testing in pediatric CRS/RARS. Based on this study population, high-yield testing should include specific antibodies to polysaccharide antigens, particularly those found on *S. pneumoniae* and *H. influenzae*. Future prospective, high-volume studies are required to further elucidate the impact of immunologic disorders in the development of pediatric CRS and RARS.

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Declaration of Conflicting Interests

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