

Primary Immunodeficiency and Rhinosinusitis



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KEYWORDS

- Immune deficiency • Antibody deficiency • Immunoglobulin replacement
- Chronic sinusitis

KEY POINTS

- Patients with difficult-to-treat or refractory chronic rhinosinusitis should be evaluated for underlying primary immunodeficiency.
- Initial investigations of humoral immunodeficiency include serum immunoglobulins and specific antibody response.
- B-cell disorders, including selective immunoglobulin (Ig) A deficiency, common variable immune deficiency, and selective IgG subclass deficiency, are the most common primary immunodeficiency disorders in the adult population; congenital agammaglobulinemia is common in children.
- Early aggressive therapy, including prophylactic antibiotics and intravenous immunoglobulin, can improve clinical outcomes in this population. The role of endoscopic sinus surgery in improving clinical outcomes is unclear.

INTRODUCTION

Sinusitis is a common condition that affects 1 in 8 adults in the United States.¹ The definition of acute rhinosinusitis entails purulent nasal drainage, nasal obstruction, and facial pain or pressure for up to 4 weeks. Chronic rhinosinusitis (CRS) is diagnosed for symptoms persisting greater than 12 weeks. Recurrent acute rhinosinusitis is 4 or more episodes of acute bacterial sinusitis per year with resolution of symptoms between episodes.² The direct cost of management of both acute rhinosinusitis and CRS totals more than \$11 billion per year with additional indirect costs related to lost workdays, reduced productivity, and reduced quality of life.³ A subset of patients

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with CRS have refractory disease that persists despite medical and surgical intervention. Underlying conditions that contribute to refractory CRS include allergic rhinitis, granulomatosis with polyangiitis, cystic fibrosis, aspirin-exacerbated respiratory disease, and immunodeficiency.

Primary immunodeficiency represents a multitude of genetic mutations that result in impairment of either the adaptive or innate immune response. This condition is in contrast with secondary immunodeficiency, which results from comorbid medical conditions, including primary illness, human immunodeficiency virus (HIV), and malnutrition, or iatrogenic causes, such as chemotherapy and immune-modulating medication.^{4,5} Immunodeficiency manifests in more frequent infections, infections of increased severity, or infections with atypical microorganisms. Defects of immunity can be categorized based on impairment of the humoral, cellular, or innate immune systems. The innate immune system is antigen independent and is involved in pathogen phagocytosis, complement-mediated opsonization, and antigen presentation to activate the adaptive immune system.⁶ The adaptive immune system can be categorized into humoral immunity and cellular immunity. With humoral immunity, an extracellular antibody-mediated response occurs against a specific antigen with the assistance of B and helper T lymphocytes. Antibody isotypes are determined by the constant region of the immunoglobulin heavy chain. Serum immunoglobulin (Ig) M is produced in initial infection before class switching to IgG, which has the highest opsonization and neutralization activity. Serum IgA is monomeric but dimerizes on secretion at mucosal surfaces, where it binds microbes to prevent invasion. IgE plays a role in defense against parasitic infection, although increased levels of IgE are seen in atopic and allergic conditions. With cellular immunity, an intracellular response occurs with release of cytokines and activation of cytotoxic T lymphocytes. The activation and function these two arms of the adaptive immune response are summarized in [Table 1](#).

REVIEW OF PRIMARY IMMUNODEFICIENCIES ASSOCIATED WITH CHRONIC RHINOSINUSITIS

A comprehensive list of primary immunodeficiencies and their clinical manifestations is shown in [Table 2](#). Most primary immunodeficiencies affecting the paranasal sinuses are humoral deficits. Antibodies function in protecting mucosal surfaces, including the

Table 1 Review of adaptive immune system	
Humoral Immunity	Cell-Mediated Immunity
• B cell receptors internalize antigen and present part of antigen on surface via MHC type II receptor; T cell receptor–MHC type II interaction causes activation and release of IL-2 and IL-4, which contribute to B cell activation and maturation to secrete immunoglobulins • T cell–independent antibody pathogen neutralization, antibody-dependent cell-mediated cytotoxicity, complement fixation, and agglutination	• Antigen-presenting cells phagocytize antigen and present a fragment of antigen on surface via MHC type II receptor, and secrete IL-1; helper T cells recognize this and secrete IL-2; IL-2 upregulates other T cells, including killer T cells, macrophages, and natural killer cells • Killer T cells attack the infected cells via MHC type I receptor • Natural killer cells are granular lymphocytes that kill infected cells, activated by IL-2 with resulting nonspecific cytotoxic activity

Abbreviations: IL, interleukin; MHC, major histocompatibility complex.

Table 2
Primary immunodeficiency disorders

Disease	Pathogenesis	Clinical Presentation	Treatment
B-cell Disorders			
Congenital agammaglobulinemia ^a	Sporadic or X linked (Bruton) Low immunoglobulin level (<10%) after maternal immunoglobulin is catabolized Presents 6–9 mo of age	Otitis media, sinusitis Sepsis: encapsulated pyogenic organisms Hypoplastic tonsils and adenoids	Prophylactic antibiotics Immunoglobulin replacement
Selective IgA deficiency ^a	Most common immunodeficiency disorder (1 in 700) Low IgA level (<5 mg/dL)	Atopy Sinusitis, pneumonia, otitis media Associated with anaphylaxis during blood transfusion (anti-IgA antibodies)	Antibiotics as needed
Selective IgG subclass deficiency ^a	Low IgG1, IgG2, IgG3, or IgG4 levels Total IgG normal	Otitis media, sinusitis, pneumonia	Immunoglobulin replacement
Common variable hypogammaglobulinemia ^a	Low IgG, IgA, IgM levels Bimodal: age 5–15 y, age 25–45 y, M = F Normal quantity but defective B cells	Sinopulmonary infections Increased risk of malignancy and autoimmune disease Normal tonsils and adenoids	Immunoglobulin replacement
T-cell Disorders			
DiGeorge syndrome	Third and fourth pharyngeal pouch anomaly Agenesis of thymus and parathyroid glands Deletion in 22q11 in >80% Decreased T cells, normal number of B cells	Hypocalcemia and tetany Hypertelorism, mandibular hypoplasia, bifid uvula, short philtrum Fungal infections (thrush), <i>Pneumocystis jirovecii</i> pneumonia	Fetal thymus transplant is experimental
Chronic mucocutaneous candidiasis	T cells Defect specific to <i>Candida</i>	Thrush Infection of nails and skin	Antifungals

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Table 2
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Disease	Pathogenesis	Clinical Presentation	Treatment
Combined B-cell and T-cell Disorders			
Severe combined immunodeficiency disease ^a	X linked or recessive Severe lack of T and B cells Associated adenosine deaminase deficiency	Otitis, pneumocystis pneumonia, candida, diarrhea Failure to thrive, death by age 2 y Absence of tonsils and adenoids	Hematopoietic stem cell transplant Immunoglobulin replacement
Wiskott-Aldrich syndrome ^a	X linked Associated with IgM deficiency Abnormal humoral response to polysaccharide antigens	Triad: thrombocytopenia, eczema, recurrent severe infections Increased risk of atopic disorders, leukemia/lymphoma	Antibiotics Platelets High-dose immunoglobulin replacement Bone marrow transplant
Ataxia-telangiectasia	Caused by a DNA repair defect (gene responsible on chromosome 11) Low immunoglobulin level, and CD3 and CD4 T cells	Recurrent sinopulmonary infections Oculocutaneous telangiectasia Progressive cerebellar ataxia High incidence of malignancy	Antibiotics as needed
Phagocytic/Neutrophil Disorders			
Chronic granulomatous disease ^a	X linked or recessive Defect in NADPH oxidase	Chronic pulmonary, GI, urinary infections Infections by catalase-positive organisms	Prophylactic antibiotics
Chédiak-Higashi syndrome	Autosomal recessive Defect in lysosomal transport protein	Oculocutaneous albinism, neuropathy, neutropenia Staphylococcus and pseudomonas infections	Hematopoietic stem cell transplant
Complement Disorders			

C1 esterase deficiency	Autosomal dominant	Recurrent angioedema Associated with lupus and collagen vascular diseases	Prophylactic danazol
Terminal complement deficiency (C5–C9)	Inability to form membrane attack complex	Recurrent meningococcal or gonococcal infections	Meningococcal vaccine Antibiotics as needed

Abbreviations: GI, gastrointestinal; NADPH, nicotinamide adenine dinucleotide phosphate

^a Frequently manifest with sinusitis.

upper and lower airways, and affected individuals develop recurrent otitis media, sinusitis, and pneumonia. These patients are also at increased risk of invasive infections, including meningitis, osteomyelitis, and septicemia, because of antibody dysfunction and/or deficiency.⁷ Immunoglobulins in nasal secretions provide antibody-mediated defense against microbes and potential irritants.⁸ Humoral immunodeficiency can result from impaired B cell development, immunoglobulin production, or immunoglobulin efficacy.

Congenital agammaglobulinemia is a primary humoral immunodeficiency wherein a de novo or X-linked mutation in a tyrosine kinase impairs cell signaling, resulting in impaired B-cell survival. The incidence of X-linked agammaglobulinemia is 1 in 190,000 male births.⁹ Clinical manifestations can appear within the first year of life, commonly with infections of encapsulated organisms including *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*.⁹ Although maternally transmitted IgG protect infants in the first few months of life, mucosal membrane infections, particularly sinusitis and otitis media, can be seen with a lack of secreted IgA.⁹ Intravenous immunoglobulin (IVIG) is the mainstay of treatment of agammaglobulinemia and has been shown to reduce serious infections and pulmonary disability.¹⁰ Gastrointestinal and sinopulmonary infections can persist in individuals receiving IVIG, in which case chronic antibiotic therapy is indicated.

Severe combined immunodeficiency (SCID) is a combined B cell and T cell deficiency causing marked immunologic impairment. Current estimates of incidence are approximately 1 in 54,000.¹¹ SCID is characterized by severe, recurrent bacterial, viral, and fungal infections; chronic diarrhea; and failure to thrive. Most patients present in the first year of life and, without intervention, severe infection and mortality occur by age 2 years. Immune reconstitution with hematopoietic stem cell transplant is curative in 90% of cases.¹²

Common variable immune deficiency (CVID) is a common primary immunodeficiency in adults, affecting about 1 in 25,000 individuals.¹³ Patients experience variable hypogammaglobulinemia with reductions in IgG and IgA or IgM levels. Presentation of CVID is highly variable, frequently delaying diagnosis.^{14,15} Recurrent infections of the upper and lower airway are common and, over time, bronchiectasis may develop. In a study by Oksenhendler and colleagues,¹⁵ sinusitis was present in 63% of patients before study enrollment. Gastrointestinal infections and chronic diarrhea are also common, as is splenomegaly and associated liver disease and portal hypertension.¹⁵ Bondioni and colleagues¹⁶ showed a high prevalence of sinusitis and pulmonary changes in individuals with CVID, although the two did not correlate in severity. In addition, about 25% of patients with CVID develop autoimmune conditions, including thrombocytopenia, hemolytic anemia, and pernicious anemia. Patients with CVID are at increased risk of malignancy, with 6% to 8% developing B cell lymphoma and showing shorter survival than age-matched and sex-matched controls.^{15,17} Immunoglobulin replacement is the primary treatment of CVID. It has been shown to reduce the incidence of pneumonia and significantly decrease associated hospitalizations.¹⁸

Selective IgA deficiency reflects reduced levels of serum IgA with normal levels of IgG and IgM. It is the most common primary immunodeficiency, with an incidence of 1 in 223 to 1 in 1000 in the general population, although the true incidence is unknown because most individuals are asymptomatic.¹⁹ Clinical manifestations of IgA deficiency include recurrent sinopulmonary infections, gastrointestinal infections and inflammatory disorders, and a predisposition to asthma and atopy.^{20–22} In addition, anaphylaxis can be seen in the presence of anti-IgA antibodies. A study by Carr and colleagues²³ showed low serum immunoglobulin levels in patients with refractory CRS and inadequate antipneumococcal titers following vaccination. Similarly, Odat and Alqudah²⁴ showed low serum IgA levels in individuals with refractory CRS

compared with age-matched and sex-matched controls. Treatment of IgA deficiency involves treating associated conditions, with consideration of prophylactic antibiotics in the case of recurrent infections. IVIG is not used because these individuals synthesize normal IgG antibodies.

IgG subclass deficiency is characterized by a reduction in the level of one of the 4 IgG isotypes with a normal level of total IgG. Often, IgG subclass deficiency is a laboratory diagnosis, although clinically significant antibody dysfunction can result in recurrent sinopulmonary infections, atopy, associated IgA deficiency, and an inadequate response to vaccination.²⁵ In 1 study, IgG subclass deficiency was noted in 21% of patients presenting with prolonged or severe infections.²⁶ IgG subtypes are designated based on the heavy-chain antigenic epitope, with IgG1 and IgG3 active against toxins and viral protein antigens, whereas IgG2 and IgG4 target bacterial capsular polysaccharides.²⁷ IgG subclass deficiency has been shown in individuals with refractory rhinosinusitis, although the clinical significance is unknown because 2% to 20% of healthy individuals show reduced levels of 1 or more IgG subclasses.^{4,28} The normal levels of IgG subclasses vary with age: IgG1 reaches normal adult levels at 5 years of age, whereas IgG2, IgG3, and IgG4 reach adult levels only by adolescence.²⁹ Because IgG1 comprises about 60% of total serum IgG, low levels of IgG1 are often associated with low total serum IgG. IgG2 subclass deficiency is more prevalent in children than in adults and can be associated with frequent infections given the role of IgG2 in the polysaccharide capsule antigen response.³⁰ IgG2 subclass deficiency can occur in isolation or also with IgG4 or IgA deficiency. IgG3 subclass deficiency occurs more commonly in adults than in children.³¹ Symptomatic patients have recurrent sinopulmonary infections similar to other subclass deficiencies. In addition, IgG4 deficiency is common in the general population and most individuals are asymptomatic. Deficiency of this subclass has been associated with lung infections, bronchiectasis, and autoimmune conditions.³² Although IgG subclass deficiency can contribute to chronic sinusitis, Seppänen and colleagues³³ showed IgG4 with low IgG1 or IgG2 level to be associated with chronic or recurrent sinusitis. Treatment of IgG subclass deficiency includes vaccination with the conjugated pneumococcal vaccine in the event of a poor response to the unconjugated polysaccharide vaccine. Antibiotic therapy is indicated for sinopulmonary infections, with recurrent infections warranting prophylactic administration. Despite normal levels of total IgG, IVIG can also be considered for individuals with infections persistent despite antibiotics, although this is controversial because not all patients show improvement.^{34,35}

Specific antibody deficiency (SAD) is a humoral immune deficiency characterized by normal serum concentrations of IgG, IgM, and IgA with an inadequate response to polysaccharide antigens as with *S pneumoniae* or *H influenzae* vaccination. A diagnosis of SAD can be difficult to establish because an abnormal vaccine response can indicate a more extensive immunologic defect warranting further evaluation. In addition, consensus has not been established as to the number of serotypes and degree of deficiency needed for diagnosis. As determined by Boyle and colleagues,³⁶ the incidence of SAD in children with recurrent infections is 14.9%, although the prevalence in the general population is not known. SAD has been associated with allergic rhinitis and recurrent infections, including otitis media, sinusitis, and bronchitis.^{23,36,37} Carr and colleagues²³ showed the incidence of SAD to be 11.6% of patients with refractory CRS. These patients also had lower levels of serum IgA and preimmunization antipneumococcal titers, suggestive of impaired sinonasal mucosal immunity. Vaccination with the PCV13 (pneumococcal conjugate vaccine 13) is recommended for individuals with SAD. In children with inadequate response to the pneumococcal polysaccharide vaccine, 80% to 90% responded to the conjugate vaccine.³⁸ Similar

to other humoral immunodeficiencies, antibiotics are indicated for active infections with prophylactic administration for recurrent infections. In small studies and a case report, IVIG was shown to decrease the frequency of infections in patients with SAD, although its use remains controversial given the normal levels of total immunoglobulins and monitoring for response because IgG trough levels are not helpful.^{39,40}

Wiskott-Aldrich syndrome (WAS) is a rare cause of immunodeficiency, occurring in 1 in 100,000 live births.⁴¹ Classic WAS is associated with innate and adaptive immunodeficiency, thrombocytopenia, and eczema. However, in its less severe form, X-linked thrombocytopenia, the disease can present with thrombocytopenia with or without infections or eczema.⁴² Frequent infections in patients with WAS include otitis media, sinusitis, skin abscess, pneumonia, gastrointestinal and genitourinary infections, and meningitis.^{43,44} Treatment of WAS includes prophylactic antibiotics to prevent *Pneumocystis jirovecii* pneumonia, prophylactic acyclovir to treat recurrent herpes simplex infections, and platelet transfusions to treat major bleeding episodes.⁴² IVIG is indicated for individuals with significant antibody deficiency. Immunosuppression with medication, such as rituximab, can be used to treat autoimmune manifestations such as autoimmune cytopenia. Elective splenectomy can also be performed to address the thrombocytopenia, although this increases the incidence of sepsis and is not routinely recommended. WAS can be cured with hematopoietic cell transplant from human leukocyte antigen–matched donors.⁴²

Chronic granulomatous disease (CGD) is an uncommon primary immunodeficiency that occurs in 1 in 200,000 live births. CGD is attributable to a defect in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which prevents the generation of oxygen radicals to kill pathogens after phagocytosis. Catalase-positive organisms such as *S aureus*, *Burkholderia cepacia*, and *Aspergillus* are phagocytosed, leading to the generation of granulomas and a chronic inflammatory response. Patients present with recurrent pneumonias, suppurative adenitis, hepatic abscesses, and osteomyelitis. Sinusitis affects 15% of patients with CGD, with frequent fungal sinus infections.⁴⁵ Treatment entails lifelong antibacterial and antifungal prophylaxis with aggressive management of infectious complications, whereas curative therapy entails hematopoietic cell transplant.⁴⁶

Individuals with primary immunodeficiency and CRS with nasal polyps (CRSwNP) also warrant special consideration. In a study investigating immunoglobulin levels and genotyping the complement C4 allele, Seppänen and colleagues³³ found that low complement level and IgG subclass and IgA deficiency were more common in those with chronic sinusitis rather than acute sinusitis. In analysis of patients with SAD and chronic sinusitis, the presence of nasal polyposis was not differentially associated with pneumococcal antibody response.²³ Similarly, in a retrospective review of immunodeficiencies associated with refractory CRS, Alqudah and colleagues⁴⁷ found that nasal polyposis was present in 28% of the study population and this group tended to show an impaired response to the unconjugated pneumococcal polysaccharide vaccine, although this was not significant. There are limited data on treatment response in individuals with CRSwNP and primary immunodeficiency. In Khalid and colleagues⁴⁸ review of functional endoscopic sinus surgery outcomes in this group, 2 individuals had nasal polyposis, although their clinical courses and outcomes were not specifically delineated.

DIAGNOSTIC WORK-UP FOR PRIMARY IMMUNODEFICIENCY

Current guidelines dictate that immune function should be evaluated in individuals with CRS or recurrent acute rhinosinusitis in the event of failed management or

sinusitis associated with otitis media, bronchiectasis, or pneumonia.² The European Society for Immunodeficiencies recommends testing for primary immunodeficiency in adults with 4 or more infections requiring antibiotics within 1 year, recurrent or persistent infections necessitating prolonged antibiotics, 2 or more severe bacterial infections (sepsis, osteomyelitis, and so forth), multiple radiographically confirmed pneumonia in 3 years, infections of atypical pathogens or unusual locations, or a family history of primary immunodeficiency.⁴⁹ In addition to recurrent infections, pediatric immunodeficiency may present with impaired growth or failure to thrive. Although CRS is a chronic condition with recurring exacerbations and bacterial infections, Sethi and colleagues⁵⁰ advocate screening for primary immunodeficiency on meeting the following criteria: persistence of sinus infection after sinus surgery, inadequate response to antibiotic therapy, unusual pathogens on sinonasal culture, recurrent acute sinusitis, or a history of infections at other sites.

Initial laboratory evaluation includes a complete blood count with differential to quantify lymphocytes; quantitative serum immunoglobulins (IgM, IgG, IgA, and IgE); and the specific antibody response to polysaccharide vaccine antigens, including *H influenzae* type b and *S pneumoniae* (Fig. 1).⁴ IgG subclasses can be quantified with initial testing or after inadequate vaccine response has been documented. A summary of laboratory findings in individuals with antibody deficiencies is seen in Table 3. Similar to humoral immunodeficiency, those with complement pathway defects can present with recurrent infections of encapsulated organisms such as *Neisseria* despite normal blood counts

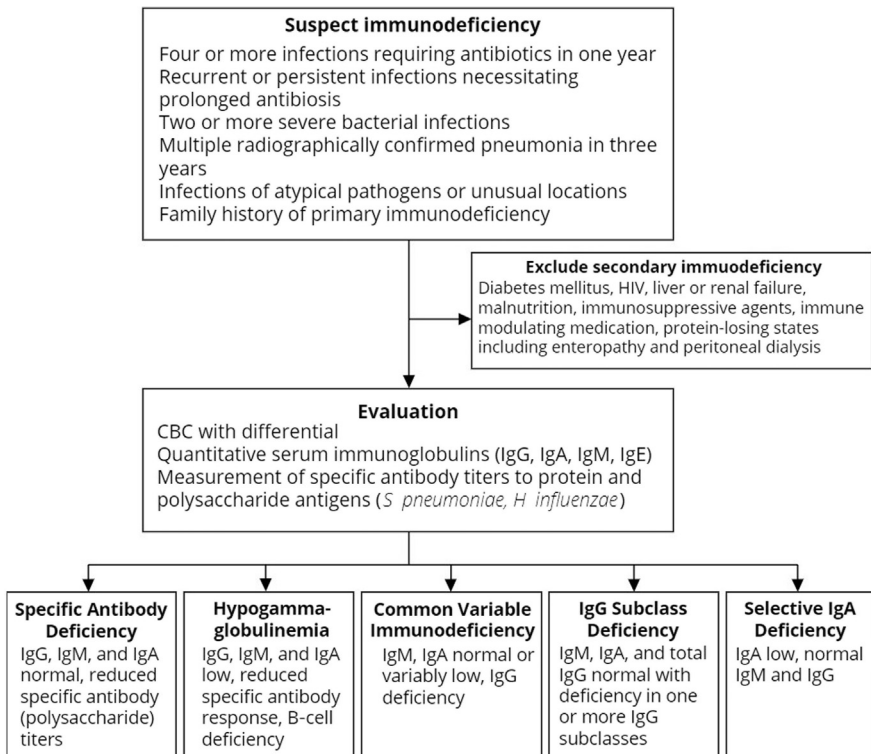


Fig. 1. Flowchart with proposed work-up of patients with CRS and suspected immunodeficiency. CBC, complete blood count.

Table 3
Laboratory values in various humoral immune disorders

Diagnosis	IgG	IgA	IgM	Vaccine Response	B Cells
SAD	Normal	Normal	Normal	Specific antibody titers <1.3 µg/mL	Normal
Hypogammaglobulinemia	Usually <200 mg/dL	Usually <20 mg/dL	Usually <20 mg/dL	Normal	<2% of lymphocytes
Common variable immunodeficiency	Usually the IgG level is <400 mg/dL	Low	Low	Low	Normal or low
IgG subclass deficiency	IgG subclass levels 2 SDs less than the mean for age- matched controls	Can be low	Can be low	Low	Normal
Selective IgA deficiency	Normal	IgA <7 mg/dL	Normal	Normal or low	Normal
Secondary immunodeficiency	Low	Normal	Normal	Normal or low	Normal or low

Abbreviation: SAD, Specific Antibody Deficiency; SD, standard deviation.

Adapted from Chiarella SE, Grammer LC. Immune deficiency in chronic rhinosinusitis: screening and treatment. *Expert Rev Clin Immunol* 2017;13(2):117-123; with permission.

and immunoglobulin levels and function. In these cases, a total hemolytic complement (CH50) assay is warranted.⁵¹ Individuals infected with usually benign viruses such as cytomegalovirus or Epstein-Barr virus, fungi, or opportunistic infections should be evaluated for T-cell defects because these indicate cellular immune deficiency.⁵²

PREVALENCE OF PRIMARY IMMUNODEFICIENCY IN REFRACTORY CHRONIC RHINOSINUSITIS

Primary immunodeficiency is a risk factor in the development of CRS. In a meta-analysis performed by Schwitzguébel and colleagues,⁵³ the pooled prevalence of CVID, IgA deficiency, and IgG deficiency was 9.4% for recurrent CRS and 18.6% for difficult-to-treat CRS (defined as noncontrolled rhinosinusitis despite sinus surgery and medical management for at least 1 year). A similar incidence of humoral immunodeficiency was observed by Vanlerberghe and colleagues²⁸ in which 21.8% of patients with refractory sinusitis showed humoral immune disorders. The prevalence of specific humoral immunodeficiencies has been evaluated in several studies. In a retrospective review of 78 patients with refractory sinusitis, Chee and colleagues⁵⁴ showed low serum IgG levels in 17.9%, low IgA levels in 16.7%, and low IgM levels in 5.1%. This study also evaluated the role of cellular immunity in CRS and found the *in vitro* T-cell response was reduced in 26.3% of patients and 54.8% had abnormal proliferation rates. Similarly, delayed-type hypersensitivity skin testing showed reduced response or anergy in 40% of 55 patients tested. Although the contribution of this finding to the pathogenesis of refractory chronic sinusitis is unknown, aberrant T-cell function could impair normal humoral immunity and the response to viral and fungal pathogens.

Humoral immunodeficiency was further characterized by Vanlerberghe and colleagues²⁸ in 2006 after patients with refractory sinusitis were subject to humoral immune testing: an incidence of IgA deficiency was detected in 2.2% of individuals, and, in the IgG subclasses evaluated, IgG2 deficiency was noted in 2% and IgG3 deficiency in 17.9% of patients. No patients were found to have CVID, and the distribution of humoral immunodeficiency was not significantly different between adult and child participants. Based on their findings, the investigators recommend screening individuals with refractory CRS for quantitative immunoglobulins as well as IgG subclass deficiency. In addition to evaluation of immunoglobulin isotypes and IgG subclasses, Alqudah and colleagues⁴⁷ assessed the humoral response following unconjugated pneumococcal polysaccharide vaccination: inadequate vaccine response was noted if the increase in postvaccination titers was less than 4-fold for at least 7 of the 14 serotypes; this was found in 67% of patients and was not correlated to deficiency in any 1 immunoglobulin isotype or subclass. In addition, although poor responders tended to have more sinus surgeries and sinopulmonary infections, this was not statistically significant from the study population. Given these findings, the investigators recommended quantitative assessment of humoral immunity in addition to functional assessment in patients with refractory CRS and normal immunoglobulin levels. Further study on the humoral response to vaccination was performed by Carr and colleagues,²³ who assessed individuals with CRS for SAD. In their study of 129 individuals, 72% had low baseline antipneumococcal titers and 11.6% were diagnosed with SAD based on antibody titers less than 1.3 $\mu\text{g/mL}$ for at least 7 of the 14 serotypes.²³ These patients had lower serum IgA levels and lower levels of prevaccination pneumococcal titers, suggestive of deficiency in both humoral and innate immune systems.

Bacterial pathogens in acute sinusitis consist of mostly aerobic bacteria, including *S pneumoniae*, *H influenzae*, and *Moraxella catarrhalis*, whereas isolates of chronic

sinusitis include anaerobes such as *Prevotella*, *Porphoryomonas*, *Peptostreptococcus*, and *Fusobacterium* subspecies.⁵⁵ In studies of patients with primary immunodeficiency and CRS, bacterial isolates are similar: *M catarrhalis*, *S pneumoniae*, *S aureus*, *H influenzae*.^{48,56,57}

TREATMENT

CRS can be difficult to treat in refractory cases and presents lifelong management considerations for patients. Treatment goals include improving quality of life and symptom management through the reduction of mucosal inflammation, maintenance of patent sinus drainage pathways, treating microbial pathogens, and limiting the severity and frequency of acute exacerbations. Initial treatment is designed to minimize symptoms before patients are started on maintenance therapy. Saline irrigation and intranasal glucocorticoids are mainstays of treatment, with antibiotics reserved for initial therapy or acute exacerbations.² Recognition of primary immunodeficiency in individuals with CRS allows early and aggressive treatment of acute exacerbations, prophylactic antibiotics, vaccination with the conjugated pneumococcal antigen vaccine, and initiation of IVIG if indicated.

Before a diagnosis of primary immunodeficiency, most patients have already received multiple courses of antibiotics for treatment of sinusitis or even prophylaxis.⁵⁰ Early culture-directed therapy is warranted because microbial pathogens may be atypical in this population and a longer duration of antibiotics is often required. Prophylactic antibiotics can reduce the frequency of acute exacerbations and, given the high prevalence of sinus inflammation and colonization reported by Kainulainen and colleagues,⁵⁸ they recommend consideration of antibiotic prophylaxis in asymptomatic individuals.^{50,59} Ocampo and Peters⁶⁰ recommend using β -lactams, trimethoprim-sulfamethoxazole, and azithromycin for prophylaxis in this patient population.

Multiple studies have investigated the role of IVIG in patients with primary immunodeficiency and CRS. Initiation of IVIG can be considered for individuals with recurrent sinonasal infections despite prophylactic antibiotics.⁶⁰ In 2006 the US Food and Drug Administration approved subcutaneous immunoglobulin to treat patients with primary immunodeficiency. Subcutaneous administration has been shown to be safe and efficacious with improved tolerance and ease of administration.^{61,62} In a study of patients with CVID or SAD, Walsh and colleagues⁶³ showed a reduction in sinonasal infections from 5 per year to 0.7 per year and discontinuation of prophylactic antibiotic use in 56% of individuals. Improved inflammation as quantified by Lund-Mackay scores was also noted but this was not significant after controlling for prior sinus surgery. Similarly, Roifman and colleagues³¹ showed a reduction in sinopulmonary infections necessitating hospitalization and improved inflammation radiographically after administration of IVIG in patients with hypogammaglobulinemia. These data are contested by the findings of Quinti and colleagues,¹⁴ who showed that IVIG therapy in patients with CVID slowed progression of chronic lung disease but its efficacy in treating sinusitis is less clear. Quinti and colleagues¹⁴ showed an increasing prevalence of sinusitis in patients with CVID even after initiation of IVIG.

Endoscopic sinus surgery (ESS) can be considered in individuals with CRS to establish patent sinus drainage pathways and improve ventilation on failure of medical treatment. Few studies have been done to assess the efficacy of sinus surgery on those with primary immunodeficiency. Main outcomes in this population include symptom improvement, antibiotic use, and quality-of-life metrics. An early study of 20 patients with primary immunodeficiency, including IgG subclass deficiency, by Sethi and colleagues⁵⁰ examined the various surgical procedures performed to treat

CRS. The most common procedure performed was ethmoidectomy, followed by revision sphenoidectomy. In 7 patients on antibiotic prophylaxis, 5 were downgraded to intermittent antibiotics and only 1 was continued on regular antibiotics after 6 months. Khalid and colleagues⁴⁸ evaluated ESS in patients with immune deficiency, both primary and secondary, and autoimmune conditions. Compared with case-matched controls, quality-of-life scores and symptom improvement were similar; on 18-month follow-up, computed tomography and endoscopic examinations were similar as well.

CONSIDERATIONS FOR PEDIATRIC PATIENTS

Children with immunodeficiency constitute a unique subset of patients with CRS. Shapiro and colleagues⁶⁴ reviewed the cases of 61 children aged 2 to 13 years with CRS. Thirty-four patients were found to have primary immunodeficiency. Eleven patients had low serum immunoglobulin levels, most commonly IgG3, and 23 had a poor response to vaccination with pneumococcal and *H influenzae* antigens. Patients were managed with antibiotics and few were enrolled in trials of IVIG. Patients were followed over a 1-year period, so long-term improvement and clinical course are unclear.⁶⁴ A large cohort of pediatric patients with CRS and primary immunodeficiency were retrospectively reviewed by Bernatowska and colleagues.⁶⁵ Ramesh and colleagues⁶⁶ published a trial of IVIG in children with CRS without primary immunodeficiency. Quantitative immunoglobulins were assessed and 2 patients had IgG2 subclass deficiency, 1 had decreased total serum IgG level, and another had reduced total IgG and IgG1 levels. IVIG treatment was initiated after patients failed prophylactic antibiotics. Five of 6 patients showed a significant reduction in daily antibiotic use and a mean reduction in sinusitis exacerbations from 9 to 4 per year. Comorbid asthma also improved in 4 of 5 patients with reduced oral steroid use and frequency of exacerbations. The role of sinus surgery in pediatric patients with primary immunodeficiency was evaluated by Lusk and colleagues,⁶⁷ with 5 of 9 patients reporting significant symptom improvement on 2-year follow-up, and prophylactic antibiotics were discontinued in 3 patients.

SUMMARY AND FUTURE CONSIDERATIONS

In patients with refractory CRS, comorbid conditions such as immunodeficiency should be considered. A preliminary work-up, including a complete blood count with differential and quantitative serum immunoglobulins, can aid in diagnosis of commonly occurring primary immunodeficiencies. Treatment with culture-directed or prophylactic antibiotics, IVIG, and ESS if warranted can improve sinopulmonary outcomes and avoid long-term pulmonary complications.

Future research of CRS in the primary immunodeficient population could better define the relationship between the severity of immunodeficiency and CRS symptoms. Research to date has established the prevalence of various primary immunodeficiencies in individuals with recalcitrant CRS, but understanding the degree to which CRS symptoms and quality-of-life impairment are affected by the severity of hypogammaglobinemia could help identify treatment parameters in this population. Additional investigation could aim to optimize medical and surgical treatment. Immune supplementation has been shown to be beneficial in the progression of pulmonary disease in primary immunodeficient patients, but optimizing medical treatment of sinusitis beyond antibiotics is critical. In addition, because immune-modulating medications are becoming increasingly prevalent, secondary immunodeficiency and CRS may become more common. In addition, although quality of life and

symptoms improve with sinus surgery for CRS in patients with immunodeficiency, the timing of and indications for surgery are variable, and best practices remain to be elucidated.

DISCLOSURE

Potential conflicts of interest: none.

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