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Immune deficiency in chronic rhinosinusitis: screening and treatment

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Abstract

Introduction—Chronic rhinosinusitis (CRS) is a prevalent disease with a high annual cost of treatment. Immune deficiencies are more common in individuals with CRS and should be especially considered in those patients who are refractory to medical and surgical therapy.

Areas covered—We performed a literature search in PubMed of the terms “immunodeficiency” and “sinusitis” or “rhinosinusitis” from 2006 through March 2016. All abstracts were reviewed to determine if they pertained to human disease; relevant articles were evaluated in their entirety and included in this review.

Expert commentary—CRS is a common disease; in those patients with frequent exacerbations or who are refractory to treatment, an immunodeficiency evaluation should be considered. Treatment includes vaccination, antibiotic therapy, immunoglobulin replacement and surgery.

Keywords

Chronic rhinosinusitis; immune deficiency; antibody; immunoglobulin; specific antibody deficiency; common variable immunodeficiency

1. Introduction

Chronic rhinosinusitis (CRS) is a disease characterized by chronic inflammation of the sinonasal tissue. The diagnosis requires 12 weeks or longer of compatible symptoms, such as purulent discharge, nasal congestion, headache, anosmia, and fever. In addition, there should be objective findings on nasal endoscopy and/or sinus computed tomography (CT) scan [1]. Approximately 31 million people in the United States have CRS, which is estimated to result in \$5.8 billion in direct medical costs annually [2]. CRS is a heterogeneous disease and can be classified into two subtypes based upon the presence or absence of nasal polyps. While CRS without nasal polyps (CRSsNP) is more common, CRS with nasal polyps (CRSwNP) comprises approximately 20% of all CRS and has been

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Declaration of interest

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associated with more severe clinical disease [2]. Treatment generally involves corticosteroids, antibiotics, and surgery. In some patients who are refractory to usual medical and surgical therapy, immune deficiency may be playing a role [3].

Immune deficiencies are disorders of the immune system, which result in more frequent infections, more severe infections, and infections with unusual organisms. Primary immune deficiencies (PIDs) are inherited disorders of immune function while secondary immune deficiencies occur as a result of events, such as a viral infection or iatrogenic immunosuppression. Immune deficiency can also be categorized as involving B cells (humoral immunity), T cells (cellular immunity), phagocytes (innate immunity), the complement system (innate immunity) or some combination of factors [4]. The immune deficiency most commonly associated with CRS is humoral immune deficiency, commonly called antibody deficiency. This review will primarily focus on antibody deficiency, but other types of immune deficiency are also included.

Multiple recent studies have confirmed the notion that immune deficiencies are more common in patients with CRS [3,5–7]. For instance, Schwitzguébel et al. [3] performed a meta-analysis, which included 1418 individuals with CRS from 13 studies and found that 23% of patients with difficult-to-treat CRS and 13% of individuals with recurrent CRS had immunoglobulin deficiencies. The authors of this study defined difficult-to-treat CRS as rhinosinusitis that was not controlled despite appropriate medical and surgical management for at least 1 year, and recurrent CRS as rhinosinusitis not controlled by appropriate conservative therapy for 4 months. In addition, they also noted that patients with CRS had a higher prevalence of specific antibody deficiency (SAD) (8–34%). A more recent retrospective study using the new guidelines for sinusitis definition and management found similar trends in humoral immune deficiency among these patients. Interestingly, in the refractory CRS group, there was no significant difference between patients with or without immunoglobulin deficiency based on age, gender, atopy, or polyps [6].

Mahdavinia et al. [8] reviewed the studies that evaluated the frequency and types of immune deficiencies in patients with CRS across different age groups. The authors concluded that given the small nature of most of the studies, it was not possible to determine if there are differences in the prevalence or types of immune deficiencies between adult CRS and pediatric CRS. They do point out that the prevalence of nasal polypsis is lower in pediatric patients. In addition, they underscore differences in the histopathology between age groups: when compared to adults, children had higher lymphocytes, monocyte/macrophages, neutrophils, and NK cells, and fewer submucosal glands, thinner epithelium, and fewer eosinophils in the mucosa. Finally, the authors recommend a thorough immune work-up both in adults and in children with recurrent CRS or other atypical patterns of infections.

2. Screening

The initial work-up for immune deficiencies in patients with CRS should start with a detailed personal and familial history (Table 1). Particular emphasis should be placed on frequency of infections including sinusitis, bronchitis, pneumonia and gastroenteritis. Pre-existing autoimmune disease should be elicited as well as previous therapy with

immunosuppressive drugs such as rituximab. Prior positive cultures, if available, can be useful. For example, antibody deficiency has been associated with encapsulated organisms, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. On the other hand, recurrent or severe *Candida* infections and *Pneumocystis jirovecii* pneumonia are more suggestive of a T-cell deficiency [4].

A thorough physical examination is also important and should not be limited to the lungs and sinuses. Lymphadenopathy, splenomegaly, or skin findings, such as granulomas can be helpful in making the correct diagnosis. Laboratory tests should include a complete blood count (CBC) with differential, serum immunoglobulins, and antibody levels to pneumococcal serotypes or antibody levels against other polysaccharide antigens for which vaccines exist. A CT scan of the sinuses should be obtained if one has not already been performed [9]. Based on these results, additional studies may be required to evaluate response to a polysaccharide vaccine. Flow cytometry to enumerate B- and T-cell subtypes might be useful as well as response to a protein antigen, such as tetanus. In rare cases, complement could be ordered as some complement deficiencies have a clinical phenotype similar to antibody deficiency. IgG subclasses are not generally useful in evaluating antibody deficiency (Table 2) [1,4].

There are some subtle laboratory findings that could also indicate the presence of an immune deficiency. Bright et al. recently published a compilation of these clues [10]. The most notable ones include: (i) hypergammaglobulinemia should prompt the consideration of HIV infection, especially if greater than 30 g/L, (ii) low-background optical density on the IgA TTG assay or low-background staining on antiendomysial IgA testing should lead to the suspicion of IgA deficiency, (iii) very low IgE (<2 IU) when testing for allergy should make clinicians check the other immunoglobulins, as approximately 7% of those patients may have an antibody deficiency, (iv) patients with low-globulin gap should undergo a follow-up measurement of IgG concentration as 89% of patient with a globulin gap <18 g/L had an IgG <6 g/L. Prompt use of the globulin gap has been shown to improve early detection of hypogammaglobulinemia [11,12], (v) low monocyte counts have been associated with a recently described PID caused by GATA-2 deficiency, and (iv) idiopathic thrombocytopenic purpura can be the presenting feature of primary or secondary immune deficiencies.

2.1. CRS and common variable immunodeficiency (CVID)

CVID encompasses a group of heterogeneous disorders [13–19]. Recently, there has been some controversy regarding the best parameters to diagnose CVID. In 2015, the International Consensus Document on CVID was published and proposed six diagnostic criteria for this condition: (1) the patient must have at least one characteristic clinical manifestation of CVID (infection, autoimmunity, or lymphoproliferation), (2) low IgG (at least two measurements more than 3 weeks apart), (3) low IgA or low IgM, (4) for those patients whose IgG is more than 100 mg/dL, demonstrate an inadequate response to at least one T-dependent or T-independent antigen, (5) exclude other causes of hypogammaglobulinemia, and (6) genetic studies for monogenic forms of CVID (not required). Of note, the authors of the consensus also mention that the diagnosis of CVID can be made in an asymptomatic patient who fulfills criteria 2–5 [13]. A different set of

diagnostic criteria proposed by Ameratunga et al. [17] included other variables, such as low IgG3, low-memory B cells, autoantibodies, increased CD21, and certain histologic findings (e.g. granulomas).

Most of the cases of CVID are sporadic and polygenic. Monogenic CVID-like immune deficiencies have been associated with mutations in genes, such as *CD19*, *CD20*, *CD21*, *CD27*, *CTLA-4*, and *ICOS*; among others. The pathophysiological hallmark of CVID is loss of B-cell function. Driessen et al. used a combined flow cytometric and molecular analysis of B cells from 37 CVID patients to identify five B-cell defect patterns: (1) B-cell production in 18%, (2) early peripheral B-cell maturation or survival in 11%, (3) B-cell activation and proliferation in 32%, (4) germinal center in 19%, and (5) postgerminal center in 16% [20]. This study provides new insights into the mechanisms involved in the pathogenesis of CVID and opens the door for more a targeted therapeutic approach in the future.

Resnick et al. have reported on the morbidity and mortality in CVID over four decades [21]. They studied 473 patients with CVID over four decades and reported that 94% of patients had at least one significant infection. In most cases, the infection was of the sinopulmonary tract. When known, the predominant organisms included *Streptococcus* species and *Haemophilus influenzae*. The incidence of bacterial infections in CVID has been reduced by the use of immunoglobulin replacement. Of the 411 subjects with known follow-up, 19.6% had died. The median age of death was 44 years for female and 42 years for males. The most common causes of death were respiratory failure from chronic lung disease, lymphoid or other malignancy, or overwhelming infections [21]. Another study in a different cohort of CVID patients showed that 82% had a history of chronic or episodic rhinitis or rhinosinusitis. Interestingly, only 5.6% had a detectable specific IgE to aeroallergens [13].

Angulo-Perez et al. published an evaluation of the prevalence, location, and tomographic severity of CRS in adult patients with CVID. Their study included 21 patients with CVID and all of them underwent a CT scan of the sinuses. According to the Lund-Mackay score, 52% of these patients had CRS. The maxillary sinus was the one, which was primarily affected (33%). The authors suggest that, given the high prevalence of CRS in their cohort, all patients who are diagnosed with CVID should undergo a CT scan of the sinuses [22].

2.2. CRS and SAD

The diagnosis of SAD should be given to patients older than 2 years with recurrent respiratory tract infections (recurrent sinopulmonary infections with encapsulated organisms and recurrent viral respiratory infections), normal immunoglobulin and IgG subclass levels, and impaired response to pneumococcal capsular polysaccharide. Four different phenotypes of SADs are based on their antibody response: mild, moderate, severe, and memory. The definitions of the mild and moderate phenotypes depend on the age of the patient. If the individual is less than 6 years old, the mild phenotype is defined as a concentration of >1.3 µg/mL for >50% of types with a twofold increase for <50% of the serotypes. If the patient is more than 6 years old, then it is defined as a concentration of >1.3 µg/mL for >70% of types with a twofold increase for <70% of the serotypes. The moderate phenotype for patients less than 6 years of age is defined as a concentration >1.3 µg/mL for <50% of serotypes and for

those more than 6 years of age as a concentration of $>1.3 \mu\text{g/mL}$ for $<70\%$ of serotypes. Across all age groups, a severe phenotype is described as $>1.3 \mu\text{g/mL}$ for two or fewer serotypes. Finally, the memory phenotype involves the loss of immunologic memory within 6 months [4,23].

Carr et al. [24] performed a retrospective study to evaluate the role of SAD in patients with medically refractory CRS. Patients with medically refractory CRS were included if they had IgG, IgA, and serum anti-pneumococcal antibody levels measured. Patients with pre-existing PIDs were excluded from the study. A protective antibody level for each serotype was defined as $1.3 \mu\text{g/mL}$. Of the 129 CRS patients that were included, 72% had low-baseline anti-pneumococcal antibody levels, and 11.6% were diagnosed with SAD based on an inadequate response to the 23-valent unconjugated pneumococcal vaccine. Patients with SAD had also statistically lower levels of IgA. As a whole, these findings demonstrate an impaired humoral immunity that likely contributes to the pathogenesis of CRS in this subgroup of patients.

More recently, Kashani et al. [25] published another retrospective study that evaluated the role of SAD in CRS. In this cohort, the prevalence of SAD in CRS patients was higher (23.4%) than reported in the Carr study. Of note, an adequate response was defined as protective antibody levels ($1.3 \mu\text{g/mL}$) in 7 or more of 14 pneumococcal serotypes. In addition, the authors found that patients with SAD received more antibiotic courses compared to those patients who responded appropriately to the 23-valent unconjugated pneumococcal vaccine. Finally, they observed that the patients with SAD who received immunoglobulin replacement therapy had more episodes of pneumonia and fewer numbers of protective anti-pneumococcal antibody levels compared to those who did not.

2.3. CRS and selective IgA deficiency

Immunoglobulin (Ig)A is the most abundant immunoglobulin in the human body and is considered a first-line defense in the mucosa of the upper airways. Selective IgA deficiency (SIGAD) is characterized by serum IgA level of less than 7 mg/dL , normal serum IgG, and IgM levels, and normal or low polysaccharide vaccine response (in subjects older than 4 years) [4,26]. Many patients with SIGAD are asymptomatic and do not have autoimmunity or frequent sinopulmonary infections. However, in some CRS patient cohorts, SIGAD has been reported [3,6].

There has been significant progress in understanding the role of IgA in disorders, such as CRS. In normal mucosal surfaces, dimers of IgA (d-IgA) are actively transported across the epithelium by the polymeric immunoglobulin receptor (pIgR). In the apical pole, a proteolytic cleavage releases secretory IgA, which consists of d-IgA and the extracellular part of the pIgR known as the secretory component (SC). SC protects IgA from degradation and can have, itself, some anti-microbial properties. Hupin et al. studied this pathway by analyzing nasal and ethmoidal biopsies, as well as nasal secretions, of patients with CRSwNP, CRSsNP, allergic rhinitis, and controls [27]. The authors found decreased levels of pIgR, SC, and IgA antibodies to *Staphylococcus aureus* enterotoxin B in patients with CRSwNP. In addition, pIgR downregulation was associated with increased IgA deposition in

subepithelial areas and eosinophilic inflammation. The authors speculate that defective IgA transport by pIgR might play a role in the pathogenesis of CRSwNP.

2.4. CRS and CD8⁺ T lymphocyte deficiency

There have been reports of a subgroup of difficult-to-treat CRS patients with decreased circulating CD8⁺ T lymphocytes [28,29]. Given the phenotypic similarities between major histocompatibility complex class 1 (MHC1) deficiencies and severe CRS, the authors performed a pooling-based genome-wide association study to screen for polymorphisms within genes classically associated with MHC1 deficiency. For this purpose, they recruited 206 patients with severe CRS (either CRSsNP or CRSwNP) and 196 controls. Severe CRS was defined by the presence of either: (i) persistent signs/symptoms of CRS despite prior endoscopic sinus surgery (ESS); or (ii) a history of more than one ESS for CRS regardless of outcome. Results showed a significant association between CRS and SNPs in the CD8A (SNP rs3810831) and Tapasin-binding protein [TAPBP] (SNP rs2282851) genes. More specifically, homozygosity for the major TT allele in CD8A was associated with higher frequency of affected relatives, increased severity as characterized by younger age at diagnosis, younger age at first surgery, and greater number of surgeries. In addition, TAPBP was associated with increased risk for CRS (OR: 1.53) [28]. The authors speculate that these polymorphisms might affect the numbers or function of CD8⁺ T lymphocytes.

Following up on these findings, this same group did another study to determine the clinical characteristics of 67 patients with low CD8⁺ T lymphocyte levels (CRS/low CD8⁺) and compare them to those of 480 individuals with conventional CRSwNP. There was no difference between the two groups in terms of gender, history of asthma, aspirin intolerance, eczema, or smoking. Both groups have similar bacteriology, and there was no significant difference in the prevalence of *S. aureus*. CRS/Low CD8⁺ patients required surgery less frequently and time to first surgery was longer, suggesting a milder disease. However, the rate of antibiotic use was higher in the CRS/low CD8⁺ group. This finding remained true regardless of the presence of nasal polypsis. Finally, when compared to healthy controls, CRS/low CD8⁺ patients had similar levels of MHC1 expression and no major abnormality in CD8 T lymphocyte subsets [29]. The authors speculate that abnormal CD8A or TAPBP gene function may contribute to the development of refractory CRS via altered MHC1 function of circulating CD8⁺ T lymphocytes. These abnormalities would then lead to suboptimal clearance of infected cells and an impaired adaptive immune response. Finally, they propose that identification of markers in the CD8A or TAPBP genes via sequencing may offer a basis for genetic testing in CRS [28,29]. Overall, these results are promising, but need to be confirmed by other investigators before such genetic testing becomes standard-of-care for CRS.

2.5. CRS and IgG subclass deficiency

The most recent practice parameters on PID state that the diagnosis of IgG subclass deficiency is controversial. This diagnosis should be considered in a subject with recurrent infections, one or more IgG subclass levels less than the fifth percentile, and normal total concentrations of IgG, IgM, and IgA [4]. At our institution, we do not measure IgG subclasses routinely.

2.6. CRS and secondary immune deficiencies

Historically, secondary immune deficiencies had been less studied compared to PID, but its prevalence is rising due to the increased use of immunosuppressive agents. Duraisingham et al. recently published a cohort study comparing patients with primary and secondary immune deficiencies [30]. The most common causes of secondary immune deficiencies in this cohort were chemotherapy for B-cell lymphoma and the use of rituximab, corticosteroids, or other immunosuppressive medications. Individuals with secondary antibody deficiencies had similar levels of serum IgG, but higher levels of IgM and IgA and a higher frequency of switched B cells. In addition, the authors found that patients with secondary immune deficiencies responded as well as PID patients to immunoglobulin replacement and highlighted the need for early diagnosis [30].

Rituximab is a monoclonal antibody that causes anti-CD20-mediated B-cell depletion. The indications for rituximab are growing and, with them, the incidence of rituximab-induced hypogammaglobulinemia as well. In the past few years, several cohorts of these patients have been published [31–35]. Robert et al. recently reported a study in patients who received rituximab for management of systemic autoimmune disorders. Moderate-to-severe hypogammaglobulinemia was seen in 26% of patients, but approximately 50% of these cases improved and resolved spontaneously. They found that spontaneous resolution was more common in patients who developed hypogammaglobulinemia within 6 months of starting rituximab. In addition, immunoglobulin replacement was initiated in 4.2% of patient due to recurrent infections [31]. In another cohort, 38.5% of patients with lymphoma and normal immunoglobulin levels at baseline developed hypogammaglobulinemia after rituximab therapy.

Rituximab-induced hypogammaglobulinemia is also becoming a more frequent cause of consultation in the immunology service [33]. It is important that oncologist or rheumatologist check baseline immunoglobulin levels before starting rituximab therapy in order to be able to differentiate between a pre-existing immune deficiency and rituximab-induced hypogammaglobulinemia.

Gujadhur et al. reported a case of cytomegalovirus (CMV) sinusitis after solid organ transplant in an HIV-negative patient who was successfully treated with a combination of surgery, antiviral therapy, and a reduction in immunosuppression [36].

Recent literature on CRS in HIV patients emphasizes the importance of atypical clinical manifestations and opportunistic infections in these individuals. For instance, Sridhar et al. reported a case of CMV pansinusitis, bilateral otitis media, and encephalitis with circulating CMV infected cytomegalic cells in a patient with AIDS. The severe CMV infection was controlled with foscarnet and with the initiation of antiretroviral therapy [37]. Another report described the case of a patient with HIV presenting with allergic fungal rhinosinusitis. The authors stress the importance of ruling out invasive fungal disease in HIV patients and of sending sinus samples for cultures of all possible pathogens, including viruses, anaerobic bacteria, anaerobic bacteria, fungus, and mycobacteria [38].

Recent reviews on the HIV-associated manifestations in otolaryngology underscore the high prevalence of CRS in HIV patients due to altered immunity and impaired clearance. These authors also mention that physicians and other healthcare providers need to have a high level of suspicion for atypical pathogens such as *Alternaria alternata*, *Aspergillus*, *Pseudallescheria boydii*, *Cryptococcus*, *Candida albicans*, *Acanthamoeba castellanii*, *Microsporidium*, and *Legionella pneumophila* [39,40].

Finally, it is important to mention that not all symptoms of CRS are due to an infectious agent; one report describes the case of a patient with AIDS presenting with what appeared to be CRS. Further endoscopic and radiological evaluation discovered a sinonasal Burkitt lymphoma. Complete remission was achieved with a combination of chemotherapy and anti-retroviral therapy [41].

3. Treatment

3.1. Vaccination

Some patients who initially have low levels of specific antibodies against pneumococcal serotypes will develop an immune response against the polysaccharide vaccine that places them in the normal range. Many of those patients will then develop fewer sinus infections requiring antibiotics. Some patients who do not respond normally to the polysaccharide vaccine will achieve a normal response, that is, protection against 50–70% of the serotypes, if given a conjugated pneumococcal antigen vaccine. Their need for antibiotics to treat sinus infections will often be reduced in frequency [25].

3.2. Antibiotics

In patients with antibody deficiencies, early treatment of acute exacerbations of CRS is indicated. As organisms may be atypical, culture-based treatment may be useful. Longer courses of antibiotics are often required given the difficulty to eradicate pathogens present in sinus cavities. Occasionally, prophylactic antibiotics can be useful to reduce the frequency of CRS exacerbations [1,7].

The microbiology of CRS can be affected by multiple factors, including the presence of an underlying immune deficiency. *S. aureus* and anaerobic gram-negative bacteria are the predominant organisms isolated in CRS [1,42]. There is no significant difference in the bacteriology between patients with CRSsNP and CRSwNP. *Pseudomonas aeruginosa* and other aerobic and facultative gram-negative rods are commonly cultured from the secretions of individuals with nosocomial sinusitis, a condition that is usually seen after prolonged endotracheal or nasogastric intubation. Similar bacteria can be seen in cystic fibrosis and in patients with an underlying immune deficiency [1]. Invasive fungal sinusitis (most commonly caused by *Aspergillus fumigatus*) can be seen in patients with uncontrolled diabetes, HIV infection, and in those who receive prolonged immunosuppressive therapy, such as transplant recipients. It is important to consider these differences in microbiology as the clinician will have to adjust the antimicrobial therapy accordingly.

3.3. Immunoglobulin replacement

If a CRS patient with antibody deficiency continues to have infections despite appropriate vaccination and a prophylactic antibiotic regimen, immunoglobulin replacement should be considered. Immunoglobulin replacement has been shown to decrease the rate of sinopulmonary infections in patients with CVID [21,43]. Immunoglobulin replacement should be considered on an individual basis in patients with SAD and is not indicated in patients with isolated SIGAD [4].

Recent studies show that between 4.2% and 6.6% of patients with rituximab-induced hypogammaglobulinemia are started on immunoglobulin replacement due to recurrent infection. A 17 patient cohort by Barmettler et al. reported two subsets of patients with hypogammaglobulinemia post-rituximab: one of which recovers and one with persistent hypogammaglobulinemia with long-lasting low or absent memory B cells [32]. The authors recommend following the B-cell subset by flow cytometry, IgA, and IgM in order to determine the length of immunoglobulin replacement.

3.4. Surgery

Surgery should be considered for those patients with CRS who respond poorly to maximal medical therapy and is mainly targeted toward removing mucosal disease and the involved bone within the sinuses and restoring functional sinus drainage [1]. Endoscopic approaches, such as the functional endoscopic sinus surgery (FESS), are currently the standard of care. The effects of an underlying immune deficiency on sinus surgery outcomes are unclear, but some recent studies have begun to address this question. Khalid et al. performed a nested case-control study to compare the improvement after sinus surgery between patients with immune dysfunction and those without it [44]. They found that preoperative disease severity, as assessed by CT scan and endoscopic findings, was similar between both groups. Importantly, both groups had significant improvements in endoscopic scores and quality of life measures after FESS. Of note, the immune dysfunction group was composed of patients with an immune deficiency (mostly secondary causes) or an autoimmune disorder (mostly sarcoidosis). The authors state that both of these subgroups had similar improvement when compared to their matched controls.

Similarly, a retrospective cohort study by Dao et al. found that the addition of sinus surgery to standard antibiotic therapy significantly improved sinus disease resolution in patients with immune dysfunction. The study sample consisted of 132 patients with noninvasive rhinosinusitis and secondary immune deficiencies (diabetics, transplant recipients, cancer patients, and individuals with immune suppression due to acute illness in the intensive care unit). Most of the patients had CRS (90.9%) and only a small proportion had ABRS (9.1%). The authors suggested having a lower threshold for surgery in these patients given their diminished capabilities for clearing infections and the increased risk of severe life-threatening invasive disease [45].

Finally, it is important to note that, given the lack of guidelines for surgical management of CRS patients with immune deficiencies, practice patterns vary widely across the United States. When members of the American Rhinologic Society were asked how they would

treat immunocompromised patients with CRS ‘impacting their health status’, 28.1% responded they would use intravenous antibiotics without surgery, 36% intravenous antibiotics with surgery, 21.3% oral antibiotics without surgery, and 14.6% oral antibiotics with surgery. Of note, only 89 out of the 871 members completed the survey and the majority of responders were sinus and skull base surgeons [46]. These results point to the fact that there is no standardized treatment strategy for this patient population and that there is an urgent need for further research in the area.

4. Expert commentary

In summary, the prevalence of immune deficiencies is higher in CRS patients. CRS that is refractory to medical and surgical management should prompt suspicion for an underlying immune defect. In individuals with CRS, the most common immune deficiencies are humoral and include CVID, SAD, SIGAD, and some secondary immune deficiencies. Others include the newly identified CD8+ T lymphocyte deficiency and defects in the Toll-like receptor pathways. Initial work-up should include a detailed history and physical exam, followed by laboratory tests. These should start with a CBC with differential, serum immunoglobulins, and antibody levels against polysaccharide antigens such as *Streptococcus pneumoniae*. Depending upon the results, additional tests may be required. Treatment will depend on the frequency of infections and laboratory findings. Management options include close observation, vaccination, antibiotic therapy (for a few weeks, culture-based therapy or long-term prophylaxis), immunoglobulin replacement, and surgery.

5. Five-year view

Some of the new advances in this field will be focused on developing personalized diagnostic and therapeutic strategies for patients with CRS. In that respect, obtaining a more specific immune cell phenotype for these individuals could become standard of care. This will not only allow for the identification of new clinically relevant immune deficiencies, but will also help clinicians tailor their treatment strategy. As an example, in the recently identified subgroup of CRS/low CD8+ patients, greater emphasis should be placed on adequate antibiotic therapy (including the possibility of long-term prophylaxis) rather than on vaccination or immunoglobulin replacement.

Epigenetics is another area of research, which is already providing new insights into the role of immune deficiencies in CRS. As emphasized by a recent review article [47], primary antibody deficiencies are only partly explained by genetic abnormalities. Epigenetic mechanisms can modulate multiple B-cell processes that are affected in antibody deficiencies, including B-cell differentiation and maturation, antibody affinity maturation, and plasma cell differentiation. For instance, B-cell differentiation can be altered by specific DNA demethylation patterns of gene segments that have been associated with the binding sites of B-cell-specific transcription factors, such as early B-cell factor 1, paired box 5, and E2F [48]. A recent article by Cahill et al. [49] highlights the importance of epigenetic modifications in the pathogenesis of a subphenotype of aspirin exacerbated respiratory disease (AERD). The authors show that nasal polyp fibroblasts from patients with AERD are resistant to the anti-proliferative effects of prostaglandin E₂ (PGE₂). This resistance is due to

the decreased expression of E prostanoid (EP)₂, the receptor of PGE₂. Interestingly, they also demonstrate that histone acetylation of the EP₂ receptor promoter (PTGER₂) correlates with mRNA levels of the receptor itself. This leads them to speculate that the refractory nasal polyposis seen in subjects with AERD might be due epigenetic modifications of PTGER₂.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

1. Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol.* 2014; 113:347–385. [PubMed: 25256029]
2. Hamilos DL. Chronic rhinosinusitis: epidemiology and medical management. *J Allergy Clin Immunol.* 2011; 128:693–707. [PubMed: 21890184]
- 3••. Schwitzguébel AJ, Jandus P, Lacroix JS, et al. Immunoglobulin deficiency in patients with chronic rhinosinusitis: systematic review of the literature and meta-analysis. *J Allergy Clin Immunol.* 2015; 136:1523–1531. This meta-analysis describes the current literature on the prevalence of antibody deficiency in CRS. [PubMed: 26329513]
4. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol.* 2015; 136:1186–1205. [PubMed: 26371839]
5. Alqudah M, Graham SM, Ballas ZK. High prevalence of humoral immunodeficiency patients with refractory chronic rhinosinusitis. *Am J Rhinol Allergy.* 2010; 24:409–412. [PubMed: 21144219]
6. Odat H, Alqudah M. Prevalence and pattern of humoral immunodeficiency in chronic refractory sinusitis. *Eur Arch Otorhinolaryngol.* 2016; Epub ahead of print. doi: 10.1007/s00405-016-3981-x
7. Ryan MW, Brooks EG. Rhinosinusitis and comorbidities. *Curr Allergy Asthma Rep.* 2010; 10:188–193. [PubMed: 20424995]
8. Mahdavinia M, Grammer LC III. Chronic rhinosinusitis and age: is the pathogenesis different? *Expert Rev Anti Infect Ther.* 2013; 11:1029–1040. [PubMed: 24073878]
9. Nayan S, Alizadehfard R, Desrosiers M. Humoral primary immunodeficiencies in chronic rhinosinusitis. *Curr Allergy Asthma Rep.* 2015; 15:46. [PubMed: 26149586]
- 10•. Bright PD, Rooney N, Virgo PF, et al. Laboratory clues to immunodeficiency; missed chances for early diagnosis? *J Clin Pathol.* 2015; 68:1–5. This is a review of laboratory findings that may lead to the diagnosis of immune deficiency. [PubMed: 25352642]
11. Holding S, Jolles S. Current screening approaches for antibody deficiency. *Curr Opin Allergy Clin Immunol.* 2015; 15:547–555. [PubMed: 26513714]
12. Holding S, Khan S, Sewell WA, et al. Using calculated globulin fraction to reduce diagnostic delay in primary and secondary hypogammaglobulinaemias: results of a demonstration project. *Ann Clin Biochem.* 2015; 52:319–326. [PubMed: 25024432]
13. Bonilla FA, Barlan I, Chapel H, et al. International Consensus Document (ICON): common variable immunodeficiency disorders. *J Allergy Clin Immunol Pract.* 2016; 4:38–59. [PubMed: 26563668]
14. Agondi RC, Barros MT, Kokron CM, et al. Can patients with common variable immunodeficiency have allergic rhinitis? *Am J Rhinol Allergy.* 2013; 27:79–83. [PubMed: 23562193]
15. Ozcan C, Metin A, Erkocoglu M, et al. Allergic diseases in children with primary immunodeficiencies. *Turk J Pediatr.* 2014; 56:41–47. [PubMed: 24827946]

16. Ameratunga R, Storey P, Barker R, et al. Application of diagnostic and treatment criteria for common variable immunodeficiency disorder. *Expert Rev Clin Immunol*. 2016; 12:257–266. [PubMed: 26623716]
17. Ameratunga R, Brewerton M, Slade C, et al. Comparison of diagnostic criteria for common variable immunodeficiency disorder. *Front Immunol*. 2014; 5:415. [PubMed: 25309532]
18. Seppänen M, Aghamohammadi A, Rezaei N. Is there a need to redefine the diagnostic criteria for common variable immunodeficiency? *Clin Exp Immunol*. 2014; 10:1–5.
19. Gathmann B, Mahlaoui N, Gerard L, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol*. 2014; 134:116–126. [PubMed: 24582312]
20. Driessen GJ, Van Zelm MC, Van Hagen PM, et al. B-cell replication history and somatic hypermutation status identify distinct pathophysiologic backgrounds in common variable immunodeficiency. *Blood*. 2011; 118:6814–6823. [PubMed: 22042693]
- 21•. Resnick ES, Moshier EL, Godbold JH, et al. Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood*. 2012; 119:1650–1657. This is a review of the natural history of CVID treated with immunoglobulin replacement; most CVID patients have CRS. [PubMed: 22180439]
22. Angulo-Pérez G, Vivar-Acevedo E, Vargas-Aguayo A, et al. Prevalence, location and tomographic severity of chronic rhinosinusitis in adult patients with common variable immunodeficiency. *Rev Alerg Mex*. 2015; 62:15–21. [PubMed: 25758109]
- 23••. Orange JS, Ballou M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2012; 130:S1–S24. This is a compilation of expert opinion on the utility of diagnostic vaccination with the 23-valent unconjugated pneumococcal vaccine in the evaluation of antibody deficiency. [PubMed: 22935624]
24. Carr TF, Koterba AP, Chandra R, et al. Characterization of specific antibody deficiency in adults with medically refractory chronic rhinosinusitis. *Am J Rhinol Allergy*. 2011; 25:241–244. [PubMed: 21819760]
25. Kashani S, Carr TF, Grammer LC, et al. Clinical characteristics of adults with chronic rhinosinusitis and specific antibody deficiency. *J Allergy Clin Immunol*. 2015; 3:236–242.
26. Ocampo CJ, Peters AT. Antibody deficiency in chronic rhinosinusitis: epidemiology and burden of illness. *Am J Rhinol Allergy*. 2013; 27:34–38. [PubMed: 23406598]
27. Hupin C, Rombaux P, Bowen H, et al. Downregulation of polymeric immunoglobulin receptor and secretory IgA antibodies in eosinophilic airway diseases. *Allergy*. 2013; 68:1589–1597. [PubMed: 24117840]
28. Alromaih S, Mfuna-Endam L, Bosse Y, et al. CD8A gene polymorphisms predict severity factors in chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2013; 3:605–611. [PubMed: 23640800]
29. Gabra N, Alromaih S, Endam LM, et al. Clinical features of cytotoxic CD8+ T-lymphocyte deficiency in chronic rhinosinusitis patients: a demographic and functional study. *Int Forum Allergy Rhinol*. 2014; 4:495–501. [PubMed: 24639246]
30. Duraisingham SS, Buckland M, Dempster J, et al. Primary vs secondary antibody deficiency: clinical feature and infection outcomes of immunoglobulin replacement. *PLoS One*. 2014; 9:e100324. [PubMed: 24971644]
- 31•. Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypo-gammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun*. 2015; 57:60–65. This is a current review of the diagnosis and management of hypogammaglobulinemia induced by rituximab, a biologic that is frequently used in oncology and rheumatology. [PubMed: 25556904]
32. Barmettler S, Price C. Continuing IgG replacement therapy for hypogammaglobulinemia after rituximab—for how long? *J Allergy Clin Immunol*. 2015; 136:1407–1409. [PubMed: 26277594]
33. Fernandez Romero DS, Torre MG, Larrauri BJ, et al. Rituximab and hypogammaglobulinemia. *Medicina (B Aires)*. 2015; 75:319–323. [PubMed: 26502469]

34. Kaplan B, Kopyltsova Y, Khokhar A, et al. Rituximab and immune deficiency: case series and review of the literature. *J Allergy Clin Immunol Pract*. 2014; 2:594–600. [PubMed: 25213054]
35. Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. *Clin Lymphoma Myeloma Leuk*. 2013; 13:106–111.
36. Gujadhur A, Thomson N, Aung AK, et al. CMV sinusitis in a HIV-negative renal transplant recipient. *Transplantation*. 2014; 97:e55–7. [PubMed: 24827770]
37. Sridhar S, Li IW, Wong SC, et al. Circulating cytomegalic cells in a patient with advanced HIV presenting with cytomegalovirus rhinosinusitis. *J Clin Virol*. 2015; 65:87–89. [PubMed: 25766996]
38. Myles IA, Gada S. Allergen immunotherapy in an HIV+ patient with allergic fungal rhinosinusitis. *Case Reports Immunol*. 2015; 2015:875260. [PubMed: 25954557]
39. Iacovou E, Vlastarakos PV, Papacharalampous G, et al. Diagnosis and treatment of HIV-associated manifestations in otolaryngology. *Infect Dis Rep*. 2012; 4:e9. [PubMed: 24470939]
40. Sanjar FA, Queiroz BE, Miziara ID. Otolaryngologic manifestations in HIV disease – clinical aspects and treatment. *Braz J Otorhinolaryngol*. 2011; 77:391–400. [PubMed: 21739017]
41. Werutsky G, De Carvalho GP, Da Silva VD, et al. AIDS-related sinonasal Burkitt lymphoma successfully treated with intensive chemotherapy regimen and high active antiretroviral therapy. *Hematol Oncol Stem Cell Ther*. 2011; 4:41–44. [PubMed: 21460606]
42. Stevens WW, Peters AT. Immunodeficiency in chronic sinusitis: recognition and treatment. *Am J Rhinol Allergy*. 2015; 29:115–118. [PubMed: 25785751]
43. Resnick ES, Cunningham-Rundles C. The many faces of the clinical picture of common variable immunodeficiency. *Curr Opin Allergy Clin Immunol*. 2012; 12:595–601. [PubMed: 23026770]
44. Khalid AN, Mace JC, Smith TL. Outcomes of sinus surgery in ambulatory patients with immune dysfunction. *Am J Rhinol Allergy*. 2010; 24:230–233. [PubMed: 20537292]
45. Dao AM, Rereddy SK, Wise SK, et al. Management of non-invasive rhinosinusitis in the immunosuppressed patient population. *Laryngoscope*. 2015; 125:1767–1771. [PubMed: 25946593]
46. Patel ZM. Practice patterns regarding noninvasive rhinosinusitis in the immunosuppressed patient population. *Allergy Rhinol (Providence)*. 2013; 4:e151–4. [PubMed: 24498520]
47. Rodriguez-Cortez VC, Del Pino-Molina L, Rodriguez-Ubreva J, et al. Dissecting epigenetic dysregulation of primary antibody deficiencies. *J Clin Immunol*. 2016; 36:48–56. [PubMed: 26984849]
48. Lee ST, Xiao Y, Muench MO, et al. A global DNA methylation and gene expression analysis of early human B-cell development reveals a demethylation signature and transcription factor network. *Nucleic Acids Res*. 2012; 40:11339–11351. [PubMed: 23074194]
49. Cahill KN, Raby BA, Zhou X, et al. Impaired E Prostanoid2 expression and resistance to prostaglandin E2 in nasal polyp fibroblasts from subjects with aspirin-exacerbated respiratory disease. *A J Respir Cell Mol Biol*. 2016; 54:34–4.

Key issues

- Chronic rhinosinusitis (CRS) is a prevalent disease with a high burden in medical costs.
- In some patients, immune deficiency contributes to the pathophysiology of CRS.
- The most common immune deficiencies associated with CRS are humoral deficiencies such as specific antibody deficiency (SAD) and common variable immune deficiency (CVID).
- New immune defects are being identified in patients with CRS such as CD8+ T cell deficiency and multiple defects in the Toll-like receptor (TLR) pathways.
- Current treatments for these immune deficiencies include vaccination, antibiotics, immunoglobulin replacement, and surgery.
- As we recognize the diversity of immune defects that contribute to the pathophysiology of CRS, new targeted therapies will emerge.

Table 1

Immune deficiency work-up considerations in a patient with refractory chronic rhinosinusitis.

Evaluation components	Comment
Personal and familial clinical history	Evaluate for recurrent sinopulmonary infections, recurrent diarrhea. Prior positive cultures are also helpful
Physical examination	Evaluate evidence of current sinus or lung infection or sequel of infections. Also evaluate for skin findings, such as granulomas, lymphadenopathy and/or splenomegaly
Laboratory tests	CBC with differential, serum immunoglobulins (IgG, IgM, and IgA), response to protein and polysaccharide vaccines, flow cytometry to quantify B- and T-cell subsets, and HIV testing

Table 2

Laboratory findings in primary and secondary antibody deficiencies.

Diagnosis	IgG	IgA	IgM	Vaccine response	B cells
Normal	Normal	Normal	Normal	Normal	Normal
SAD	Normal	Normal	Normal	Low	Normal
SIGAD	Normal	Undetectable	Normal	Normal or low	Normal
CVID ^a	Low	Low	Normal or low	Low	Normal or low
Secondary immune deficiencies	Low	Normal	Normal	Normal or low	Normal or low

^aThe European Society of Immunodeficiencies (ESID), the International Consensus Document (ICON), and the Joint Council of Allergy, Asthma and Immunology (JCAAI) have slightly different CVID definitions [4,13].