Allergy Asthma Immunol Res. 2023 Sep;15(5):562-579
https://doi.org/10.4168/aair.2023.15.5.562
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Review

Current Issues in the Management of IgG Subclass Deficiencies in Adults With Chronic Respiratory Diseases

Jae-Hyuk Jang [1†], **Joo-Hee Kim** [2†], **Hae-Sim Park** [1*]

[1]Department of Allergy and Clinical Immunology, Ajou University Medical Center, Ajou University School of Medicine, Suwon, Korea
[2]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

Received: Mar 28, 2023
Revised: Aug 29, 2023
Accepted: Aug 30, 2023
Published online: Sep 7, 2023

Correspondence to
Hae-Sim Park, MD, PhD
Department of Allergy and Clinical Immunology, Ajou University Medical Center, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 16499, Korea.
Tel: +82-31-219-5196
Fax: +82-31-219-5154
Email: hspark@ajou.ac.kr

†Jae-Hyuk Jang and Joo-Hee Kim contributed equally as first authors.

ORCID iDs
Jae-Hyuk Jang
https://orcid.org/0000-0002-4225-7117
Joo-Hee Kim
https://orcid.org/0000-0002-1572-5149
Hae-Sim Park
https://orcid.org/0000-0003-2614-0303

Disclosure
There are no financial or other issues that might lead to conflict of interest.

ABSTRACT

Primary immunodeficiency diseases (PIDs) are uncommon in adults; however, immunoglobulin G subclass deficiency (IGGSCD) is often found in a subset of adult patients with chronic respiratory diseases. As quantitative laboratory tests are used to diagnose IGGSCD, the clinical significance of IGGSCD remains controversial. However, respiratory infection is a common presenting feature of IGGSCD, and respiratory complications are responsible for subsequent morbidities, such as severe asthma, bronchiectasis, chronic obstructive airway diseases, and mortality. This review summarizes the current epidemiological data for PIDs, focusing on IGGSCD in the adult population. In addition, the investigation, treatment, and management strategies are detailed, including distinct issues faced by patients with chronic airway disease and their physicians in the proper diagnosis and treatment of IGGSCD.

Keywords: Adult; asthma; primary immunodeficiency diseases; IgG; IgG deficiency; infection

INTRODUCTION

Primary immunodeficiency diseases (PIDs) constitute a heterogeneous group of genetic disorders caused by defects in the development or function of the immune system, resulting in increased susceptibility to recurrent infections. Infections in patients with PIDs have unique characteristics, including severity, location, resistance to treatment, and unusual causative microorganisms. Depending on the affected part of the immune system, infection severity may vary from mild to severe life-threatening complications.[1] In addition to predisposing patients to infections, PIDs increase susceptibility to autoimmunity, lymphoproliferation, and malignancies.[2]

Most PIDs usually occur and are diagnosed in childhood. However, it has become more urgent to consider PIDs in adults and even in the elderly population.[3,4] There are specific situations in which PIDs are diagnosed in adulthood. First, certain types of humoral immunodeficiencies can occur initially in adulthood. Second, as advanced molecular diagnostic methods and effective treatments have been introduced into clinical practice, patients with PIDs who initially present in childhood with a mild phenotype can survive

into adulthood. However, diagnosing PIDs in adulthood can be delayed due to either a late onset of PID symptoms or subtle/subclinical immunodeficiency. This delay could result from a lack of physician awareness regarding timely referrals, an unusual presentation of the disease with differing penetrance, or a lack of infrastructural facilities. In the adult age group, predominantly antibody deficiency (PAD), which includes common variable immunodeficiency (CVID), selective immunoglobulin (Ig) A deficiency, specific antibody deficiency (SAD), and IgG subclass deficiency (IGGSCD), is the most common diagnosis.[3]

Chronic respiratory diseases are the most common complications of PAD and a significant source of morbidity and mortality for these patients.[5] Because of the prominent role of antibodies in protection against bacteria, lung disease is a frequent concern for patients with PAD. In addition to bacterial infections, respiratory viruses may lead to pulmonary exacerbations in pre-existing airway diseases.[6] Indeed, structural and functional lung impairment is recognized as an important risk factor for morbidity and mortality in PAD.[7] Compared to diseases with a total deficiency of Igs, such as CVID and X-linked agammaglobulinemia (XLA), IGGSCD and SAD are considered mild forms of PID. However, IGGSCD and decreased IgG levels have recently been suggested as risk factors for acute exacerbation and hospitalization in patients with chronic respiratory diseases.[8,10]

A diagnosis of IGGSCD should be considered for patients with recurrent infections and confirmed by measurement of IgG subclass levels. However, a definitive diagnosis of IGGSCD has been controversial in clinical practice.[2] The measurement of IgG subclass levels is not universally recommended to evaluate antibody-mediated immunity; low IgG subclass levels have been reported in 2% of healthy individuals.[11] However, significant associations have been reported between IGGSCD and chronic respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and refractory chronic rhinosinusitis (CRS), and patients with comorbid IGGSCD present a more severe phenotype, although assessment of the biologic importance (IgG response against exogenous infection) is needed.[5,6]

This review highlights recent epidemiological research on the prevalence of humoral immunodeficiency, especially IGGSCD, in association with chronic respiratory disorders in adults. Furthermore, it discusses the unique clinical and immunological features of patients with IGGSCD that overlap with those of chronic airway disease, which could help physicians achieve better management in clinical practice.

EPIDEMIOLOGY OF PIDs AND IGGSCD IN ADULTS

The burden of PIDs and IGGSCD in adults

PIDs have traditionally been viewed as a group of illnesses that occur in pediatric patients. New advances in diagnosis and treatment have led to an increase in adult PID patients. Studies performed in the past decade have provided evidence that the prevalence of PIDs in adults has been underestimated. Data from the United States Immunodeficiency Network (USIDNET) registry demonstrate that 16.7% of PID patients are enrolled before 18 years of age; however, 83.3% are enrolled after 18, and 14.0% are enrolled after 65.[12] The latest data from the European Society for Immunodeficiencies (ESID) registry demonstrate that 9% of all subjects present with initial manifestations after 40.[13] Global data from the Jeffrey Modell Foundation (JMF) demonstrated that the proportion of the adult population with PIDs increases over time. The increasing survival of children with severe immunodeficiencies also alters the age

https://doi.org/10.4168/aair.2023.15.5.562

distribution of PID patients. Indeed, from 2013 to 2021, there was an 86.1% increase in the global prevalence of PID; adult PID patients comprised 35.8% of the total PID cases.[14]

Most PID cases in adults belong to the category of PAD; however, other immunodeficiencies (*e.g.*, complement deficiency and late-onset combined immunodeficiency) occur in adulthood. The USIDNET registry shows that adults aged > 18 years accounted for 91.1% of patients with antibody deficiencies,[12] and the ESID registry demonstrates that patients over 65 account for 8% of the total patients registered.[4] The first PID survey conducted in Japan in 2011 showed that the median ages of patients with XLA, CVID, and chronic granulomatous disease were 12.8, 25.1, and 14.7 years, respectively.[15] A Korean adult PID cohort revealed that all PID patients except one had antibody deficiencies.[16] Globally, PAD was the most prevalent category, with the following order of subtypes: CVID, selective IgA deficiency, and IGGSCD.[14]

The latest survey using physician reports from the JMF revealed that IGGSCD is the 3rd most common subtype of PID.[14] A historical cohort study over 31 years using the Rochester Epidemiology Project reported that 25% of patients with PAD had IGGSCD, the second most common PID.[17] However, the USIDNET antibody deficiency cohort reported that IGGSCD was found in 1.3% of PAD patients.[18] A national survey in Japan in 2011 reported that 66 (13.2%) patients among 501 patients with PAD (58 pediatric and 8 adult patients) had IGGSCD.[15] The national PID registry from pediatric departments in Korea reported a prevalence of 0.25 per million in 2005 for IGGSCD.[19] In another study, 66.7% (56/84) of an adult PID cohort was diagnosed with IGGSCD.[20]

Association of PIDs with chronic airway diseases in adults

In contrast to children with antibody deficiency who are referred due to recurrent acute infections, adults are usually referred due to chronic airway diseases such as CRS, asthma, or COPD.[6,21] Decreased IgG subclass levels have been reported in patients with refractory CRS, some overlapping with specific antibody deficiencies.[22,23] A meta-analysis of 1,418 individuals with CRS from 13 studies revealed that 13% of patients with recurrent CRS and 23% of patients with difficult-to-treat CRS had Ig deficiency, suggesting that 10% of CRS patients may potentially have CVID.[24] In addition, the prevalence of IGGSCD (5% to 50%) and SAD (8% to 34%) was reported in CRS patients. The CRS cohort study also revealed that 23% of CRS patients with normal IgG levels had SAD. CRS patients with SAD received significantly more antibiotic courses than those without SAD.[22] A subsequent study showed that CRS patients with more severe SAD were more likely to have asthma and require frequent antibiotic courses.[23]

Recurrent infections in the lower airways due to PID may result in a chronic inflammatory response leading to airway hyperreactivity, remodeling, and, consequently, fixed obstruction. A study using data from the USIDNET registry showed that a total of 1,937 patients with various PIDs had pulmonary disease comorbidities, including airway (86.8%), parenchymal (18.5%), pleural (4.6%), vascular (4.3%), and other (13.9%) disorders.[7,25] The highest prevalence of airway diseases was noted in patients with CVID, followed by those with isotype or antibody deficiency (10.2%), combined immunodeficiency (9.3%), and agammaglobulinemia (6.4%).[7] Asthmatic patients are more likely to receive a diagnosis of selective IgA deficiency/CVID than nonasthmatic individuals.[26] Another study showed bronchial hyperreactivity during the methacholine challenge test in 42.5% of children affected by various PADs.[27] An earlier study demonstrated that age over 40 years and chronic bronchitis in smokers were risk factors for airway obstruction in adults with IgG deficiency.[28]

https://doi.org/10.4168/aair.2023.15.5.562

Airway wall thickening was the most frequent high-resolution computed tomography (HRCT) abnormality, which was found in 71% of CVID or IGGSCD patients.[29] It has been suggested that there is a significant association between PADs and asthma.[30-32]

The association between asthma and IGGSCD was first described in children: 30% of asthmatic children had IGGSCD (predominantly IgG2), and a higher frequency of IGGSCD was observed in severe asthmatic children and adolescents.[33] Significant reductions in total IgG and IgG subclass levels have been shown in adult patients with brittle asthma and patients with infective exacerbations compared to those with mild asthma.[34] In that study, atopy, cigarette smoking, and oral/inhaled steroid doses were not associated with IgG or IgG subclass levels. Another study showed that Ig levels in mild or severe asthmatic patients were generally within the normal range; however, IgA and IgG levels were significantly lower in severe asthmatic patients than in normal subjects.[35] Lee *et al.*[9] reported that among 2,866 enrolled asthmatic patients, 157 (5.49%) had PAD, of which IGGSCD, particularly IgG3 subclass deficiency (IGG3SCD), was the most prevalent type (58%). The asthmatic patients with PIDs showed a 1.6-fold increased risk for asthma exacerbation. The subsequent study also showed that 23.3% of IGGSCD patients had comorbid SAD, indicating that asthmatic patients with IGGSCD could be subsequently categorized as having SAD, but there are still patients with isolated IGGSCD.[20]

The prevalence of IGGSCD in COPD patients has been reported as 20%.[36] In 2 COPD cohorts, decreased IgG subclass levels were independent risk factors for symptom exacerbations (IgG1 and IgG2) and hospitalizations (IgG2) (adjusted hazard ratios [aHRs] 1.19 and 1.30 for exacerbation and 1.33 and 1.52 for hospitalization, respectively).[36] The latest study showed that the mortality of IGGSCD patients differed according to the affected IgG subclass. The one-year mortality rate was highest in patients with IgG1 deficiency (56%), followed by IgG4 (31%), IgG2 (27%), and IgG3 deficiencies (24%). Patients with 2 or more IgG subclass deficiencies had a higher 1-year mortality rate than those without any single deficiency.[10] Using frozen sera from 2 COPD trials, 24% of COPD patients with at least one exacerbation per year had IgG deficiency, and decreased total IgG levels were significantly associated with an increased risk of exacerbations and hospitalizations (aHRs 1.27 and 1.39 for exacerbation and 1.57 and 1.92 for hospitalization, respectively).[37] A pooled meta-analysis demonstrated that the overall frequency of hypogammaglobulinemia was 28.4%, and a higher risk of COPD hospitalizations was observed among participants with low IgG levels than among those with normal levels (aHR, 1.29; 95% confidence interval [CI], 1.06–1.56; $P = 0.01$).[38] Therefore, considering the epidemiological evidence of the relationship between PIDs, especially IGGSCD or hypogammaglobulinemia, and chronic airway disease, the detection of PIDs is essential to prevent disease progression in specific populations, such as patients with refractory CRS, exacerbation-prone patients, and severe asthma or COPD patients with frequent exacerbations.

CLINICAL AND LABORATORY FEATURES OF ASTHMATIC PATIENTS WITH COMORBID IGGSCD

Respiratory infection

IGGSCD is a comorbidity in patients with adult asthma characterized by frequent upper and lower respiratory infections, even with anti-asthmatic medications.[8,9,34] Seasonal respiratory virus infections are well-recognized causes of asthma exacerbation.[39] IGG3SCD alone or

https://doi.org/10.4168/aair.2023.15.5.562

in combination with other Ig or IgG subclasses, presenting as recurrent upper or lower respiratory tract infections, has been reported to be the most common subtype of IGGSCD in patients with adult asthma.[9,40-42] Specific pathogens that can cause respiratory infections in patients with PIDs include viruses, such as rhinoviruses, enteroviruses, bocaviruses, respiratory syncytial virus, influenza, coronavirus disease 2019 (COVID-19), adenoviruses, human metapneumovirus, and parainfluenza viruses, and bacteria, such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and anaerobes.[43] Data from studies exploring viruses or bacteria in patients with IGGSCD have yet to be reported, and there are few studies of PADs. Pathogen detection rates were increased in patients with PADs compared to controls, and viral detection was associated with worsening respiratory symptom scores compared with baseline scores. Human rhinovirus, parainfluenza, *S. pneumoniae*, and *H. influenzae* are common pathogens.[44] The frequency and severity of infections may fluctuate or wane over time, even if the immunological abnormality persists. On the other hand, infections can persist, but the subclass abnormality may not.[2] Other clinical conditions associated with IGGSCD include atopy and autoimmune disease.[45] A higher incidence of malignancy is generally not associated with IGGSCD.[2]

Asthma exacerbation

A previous study demonstrated that asthmatic patients with IGGSCD are characterized by reduced levels of Ig subclasses, and experience frequent exacerbations (2.46 ± 1.96) every 6 months.[8] Lee *et al.*[9] reported that asthmatic patients with IGGSCD had a 1.7-fold increased risk of asthma exacerbations compared to mild asthmatic patients without IGGSCD (relative risk, 1.696; 95% CI, 1.284–2.239; $P < 0.001$), suggesting that patients with both asthma and IGGSCD exhibit an exacerbation-prone phenotype. Another study explored the phenotypes in patients with asthma with hypogammaglobulinemia compared to those without hypogammaglobulinemia. The asthmatic patients with hypogammaglobulinemia had lower IgG subclass levels and blood eosinophil counts, a lower fraction of exhaled nitric oxide, and a more severe composite score for bronchiectasis, suggesting that a subset of asthma patients with PID may have a T2-low phenotype.[46] However, patients with asthma often have other T2 comorbidities, such as allergic rhinitis (AR), CRS, and nasal polyps (NPs). Abrahamian *et al.*[40] reported that 52.9% of patients with symptomatic IGG3SCD have AR with or without asthma. A systematic review and meta-analysis of CRS patients with comorbid PIDs revealed that 31%–72% had atopy, 15%–68% had asthma, and 13%–60% had NPs.[24] Exacerbation-prone and comorbid CRS are common clinical manifestations of asthma with IGGSCD[8,41,47]; however, endo/phenotyping in this group according to clinical and immunological parameters remains to be determined.

Lung function decline with fixed airflow limitation

Decreased lung function with fixed airflow limitation is commonly observed in parallel with frequent exacerbations due to infections. An earlier study showed that the mean forced expiratory volume in one second (FEV1) was 59.4%–70.9% of the predicted value in asthmatic patients with hypogammaglobulinemia or IGGSCD; subsequent studies also showed moderate airflow limitations of 66.2%–73.4% of the predicted FEV1 in patients with asthma and IGGSCD.[8,41,46] Indeed, the prevalence of severe asthma was higher in patients with asthma and IGGSCD than in those without IGGSCD. Previous studies reported that patients with brittle asthma had significantly lower IgG, IgG1, IgG2, and IgG3 levels than those with mild asthma.[28,34] Balzar *et al.*[35] reported that IgA and IgG levels were decreased in patients with severe asthma compared to normal subjects, while those with mild asthma had intermediate levels and were not significantly different from either group. Lee *et al.*[9] reported

https://doi.org/10.4168/aair.2023.15.5.562

that severe asthma was significantly more prevalent in asthmatic patients with PID than those without PID (32.48% *vs.* 13.00%).

Bronchiectasis

Bronchiectasis has been occasionally observed in patients with asthma or PADs, including IGGSCD.[48,49] ESID registry data showed that 80% of CVID patients had radiological evidence of bronchial pathology, including bronchiectasis in 61%, bronchial wall thickening in 44%, and mucus plugging in 29%.[50] A single-center study to compare CVID and other PADs (11 patients had IGGSCD and 3 had selective IgA deficiencies) showed that the HRCT pattern was similar between the 2 groups. Airway wall thickening and bronchiectasis were the most frequent HRCT abnormalities observed in both the CVID and IGGSCD groups; however, linear and irregular opacities (indicating parenchymal-interstitial abnormalities) were more prevalent in the CVID group than in the IGGSCD group.[29] An isolated IgG2 deficiency is an independent risk factor for bronchiectasis exacerbation. In this study, the participants with bronchiectasis had comorbid asthma (34.7%), COPD (11.2%), and CRS (4.0%).[51] In this population, bronchiectasis is linked to repeated episodes of infection and inflammation that destroy the airways and lung parenchyma—a vicious cycle—leading to a decline in lung function and obstructive airway diseases. Therefore, correction of IGGSCD using intravenous or subcutaneous Ig replacement therapy (IGRT) may result in a clinically meaningful reduction in respiratory infections and prevent lung function decline.

IMMUNOPATHOGENIC MECHANISM OF IGGSCD

There is increasing evidence that IgG subclasses play a crucial role in preventing viral or bacterial infections.[52] IgG1 is the most prevalent subclass, comprising up to 70% of the total IgG level; therefore, a lack of IgG1 in patients with various primary and secondary antibody deficiencies can decrease total IgG levels (hypogammaglobulinemia). IgG1 deficiencies, sometimes in combination with other IGGSCDs, are associated with recurrent infections. IgG2 subclass deficiency predisposes patients to infections due to an inability to generate measurable titers of antibodies to bacterial capsular polysaccharides (*S. pneumoniae* and *H. influenzae* type B). IgG3 is particularly relevant in the primary antibody response to respiratory viral agents, as it is the most functional subclass, closely followed by IgG1, due to its superior affinity to FcεR. IgG4 is the least common subclass, accounting for only 2%–6% of the total IgG level. The relevance of IgG4 deficiency is uncertain; however, a few studies have claimed that selective IgG4 deficiency may play a pathogenic role in patients with severe infections or bronchiectasis.[53] In addition, there is growing evidence that PADs involve multiple non-B-cell immunological defects, such as T cells, mannose-binding lectin, Toll-like receptors, antimicrobial peptides, and/or neutrophils.[54,55] In line with these findings, recent studies have shown that viral infections in this population are associated with clinical deterioration.[44,56] Bacterial and viral coinfections were detected in 25% of CVID patients with exacerbations of the underlying respiratory diseases.[57]

A pathogenic mechanism of IGGSCD has been proposed: heterozygous gamma gene deletions are reported to reduce serum levels of the corresponding subclasses, and rare homozygous gene deletions have also been described.[58] However, regulatory dysfunction of B lymphocytes has been suggested to be a primary mechanism in PADs.[59] Immunophenotyping of the B-cell compartment has been utilized to improve the diagnosis of PADs in recent years, and patients with PADs showed reduced Ig-switched memory B cells, T helper 17 cells, and naïve T cells.

https://doi.org/10.4168/aair.2023.15.5.562

Blanco *et al.*[60] revealed that patients with IGGSCD or CVID showed defects in memory B-cell subsets and plasma cells. Sohn *et al.*[61] reported that the ability to proliferate and activate B lymphocytes was significantly decreased in asthmatic patients with IGGSCD compared to those without IGGSCD, and this decrease was more profound in severe asthmatic patients, indicating that functional defects in B lymphocytes exist in asthmatic patients with IGGSCD.

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH IGGSCD

Clinical diagnosis of IGGSCD

The diagnosis of IGGSCD can be difficult because it relies on the combination of clinical suspicion and laboratory confirmation.[2] Certain factors may raise clinical suspicions, such as a patient's family history and the presence of associated symptoms or conditions. Patients with IGGSCD present with recurrent episodes of rhinosinusitis, bronchitis, and pneumonia as well as a high prevalence of asthma with frequent exacerbations. It is also essential to consider a patient's family history, as there may be a hereditary component to the condition; however, the specific gene has not yet been identified.[62]

The 10 warning signs, including the type, location, and severity of infections, are a commonly used for screening patients based on their history and were first developed by the JMF.[2] Patients with 2 or more positive findings for warning signs should be evaluated for PIDs. This method has been widely used for decades; however, these warning signs do not consider different spectra of PIDs, such as autoimmunity or malignancy, which has low sensitivity for diagnosing PIDs.[63] Diagnostic delay is more significant in adults than children, leading to increased morbidity and mortality.[64] Thus, there has been an attempt to modify the warning signs and tailor them to different targets to improve physicians' identification of possible PIDs. A concise set of specialty-specific warning signs may help diagnose PIDs in clinical practice.[65] For allergy specialists, clinical suspicion of PIDs should be considered in patients with difficult-to-treat or severe asthma, recurrent CRS, and otitis. In particular, 4 or more viral or bacterial respiratory infections per year in patients with asthma or CRS could be the major manifestations for diagnosing IGGSCD. It is suggested that physicians receive education on tailored screening tools for PIDs and that the warning signs be expanded to increase the rate of early diagnosis and improve the prognosis of the disease.

It is possible to diagnose IGGSCD when a patient with recurrent infections, especially respiratory complications, has a deficiency in one or more IgG subclasses (> 2 standard deviations [SDs] below age-matched reference values) with normal total IgG concentrations. Confirming a diagnosis of IGGSCD in the laboratory involves measuring a patient's serum Ig and IgG subclass levels; nephelometry and turbidimetry are widely applied with sufficient sensitivity.[2] The concentration of IgG subclasses is age, sex, and race-dependent and the reference ranges of IgG subclasses are not fully standardized but manufacturer-based.[66] The 4 IgG subclass levels should be checked simultaneously and confirmed by additional measurements taken at least one month after the initial visit. It is also important to check patient medications, as certain drugs can cause secondary immunodeficiencies. Medications that can affect the IgG level include B-cell targeted therapy (such as rituximab and anti-CD20 therapy), immunosuppressive drugs (such as methotrexate, mycophenolate, sulfasalazine, cyclophosphamide, and azathioprine), antipsychotic drugs (such as clozapine and chlorpromazine), and antiepileptic drugs (such as phenytoin, carbamazepine, and valproate).[67]

https://doi.org/10.4168/aair.2023.15.5.562

Short courses of oral corticosteroids have been associated with a transient decrease in serum IgG levels, which can last for several weeks beyond the cessation of the corticosteroid burst.[68,69] Long-term oral corticosteroid therapy has been associated with significantly decreased IgG levels.[70] However, high-dose inhaled corticosteroids (ICSs) have not been shown to have a demonstrable effect on serum IgG levels. Therefore, the diagnosis of IGGSCD should be based not only on deficiencies of the IgG subclass levels but also on clinical characteristics of patients with recurrent infections including medications and medical histories.

IGGSCD can be accompanied by other PADs. Low IgA levels are often detected in patients with IGGSCD. Selective IgA deficiency is a common immunologic abnormality affecting approximately 1/300 to 700 white patients, and most cases of selective IgA deficiency are asymptomatic. However, approximately 30% of patients present with recurrent infections.[2] In the pediatric age group, patients with IGGSCD with low IgA levels presented more frequent and severe infections than those with normal IgA levels.[71,72] In adults, an earlier study showed that IgA deficiency in combination with IgG2 or IgG3 deficiency was associated with impaired lung function.[73] In later studies, 30% of patients in the US with recurrent infections and subnormal IgG2 levels (≤ 2 SDs below the mean) had lower levels of IgA, and only 0.64% of adult PAD patients had lower IgA levels and IGGSCD in the Korea cohort study.[9,74] Neither study reported any association between the presence of IgA deficiency and infection severity in adult patients with IGGSCD. To assess the clinical significance of IgA deficiency in patients with IGGSCD, longitudinal registry data should be collected and analyzed in adult populations covering different ethnic and age groups.

Current guidelines recommend that before diagnosing IGGSCD, the antibody response to polysaccharide antigens should be estimated in patients with recurrent infections, irrespective of their IgG subclass or IgA levels.[75] Some patients with IGGSCD or selective IgA exhibit SAD.[16,40,76] The World Health Organization ELISA test (WHO ELISA) or multiplex fluorescent bead assay (Luminex) is currently used to diagnose SADs worldwide.[75] However, neither of these tests is commercially available in Korea; therefore, the accurate diagnosis and proper management of SAD with or without IGGSCD is limited in clinical practice in Korea.

Another challenging issue for clinicians when diagnosing IGGSCD is whether the presented clinical symptoms result from an underlying progressive immunodeficiency. When pediatric patients with IGGSCD (n = 24) were followed up for 40 months, 4 children were reported to have a progression of different diagnoses of CVID.[77] Another study showed that 2% of patients with selective IgA deficiency progressed to CVID in an Italian pediatric cohort.[78] In adults, patients with symptomatic IgA deficiency with IGGSCD subsequently developed CVID after 2-15 years, and mutations of the gene TNFRSF13B encoding TACI have been found in some patients.[79] The International Consensus Document guideline recommends that milder laboratory phenotypes such as IgA deficiency or IGGSCD may evolve over time until laboratory criteria are met, and a diagnosis of CVID is appropriate.[80]

MANAGEMENT OF IGGSCD IN PATIENTS

General considerations for IGGSCD

The main principles of managing patients with IGGSCD comprise treatment for acute infections, management for respiratory comorbidities, prevention of infections, and cautious use of Ig in selected patients (**Figure**).[2,81]

https://doi.org/10.4168/aair.2023.15.5.562

Recurrent and potentially fatal respiratory infections are common in patients with PIDs[43]; however, infectious complications in patients with IGGSCD are usually milder than those in subjects with severe PADs, such as CVID or XLA. Patients with humoral defects, including IGGSCD, are particularly susceptible to sinopulmonary infections caused by viral and encapsulated bacterial infections.[43] Broad-spectrum antibiotics are generally used for respiratory tract infections caused by bacterial pathogens. The coverage of antibiotics should be balanced between the need for a broad range to cover the expected pathogen and the risk of the development of antibiotic resistance, which can be speculated based on a personal history of allergy and previous evidence of microbiological resistance.[6] Sputum examination or bronchoalveolar lavage can allow microbiological diagnosis and indicate a more precise resistance profile of the true pathogens.[6] Additional management, including tympanocentesis with or without tympanostomy, is helpful for patients with recurrent acute otitis media or sinusitis despite conventional therapy.[43]

IGRT is a potential treatment option for selected patients with persistent IGGSCD and recurrent viral/bacterial respiratory infections even with antibiotic therapies.[82] Current guidelines recommend that the principles of managing IGGSCD should follow those provided for SAD. IGRT can prevent respiratory infections, not by replenishing the deficient IgG subclass but by providing effective IgGs against respiratory pathogens.[40] The recommended

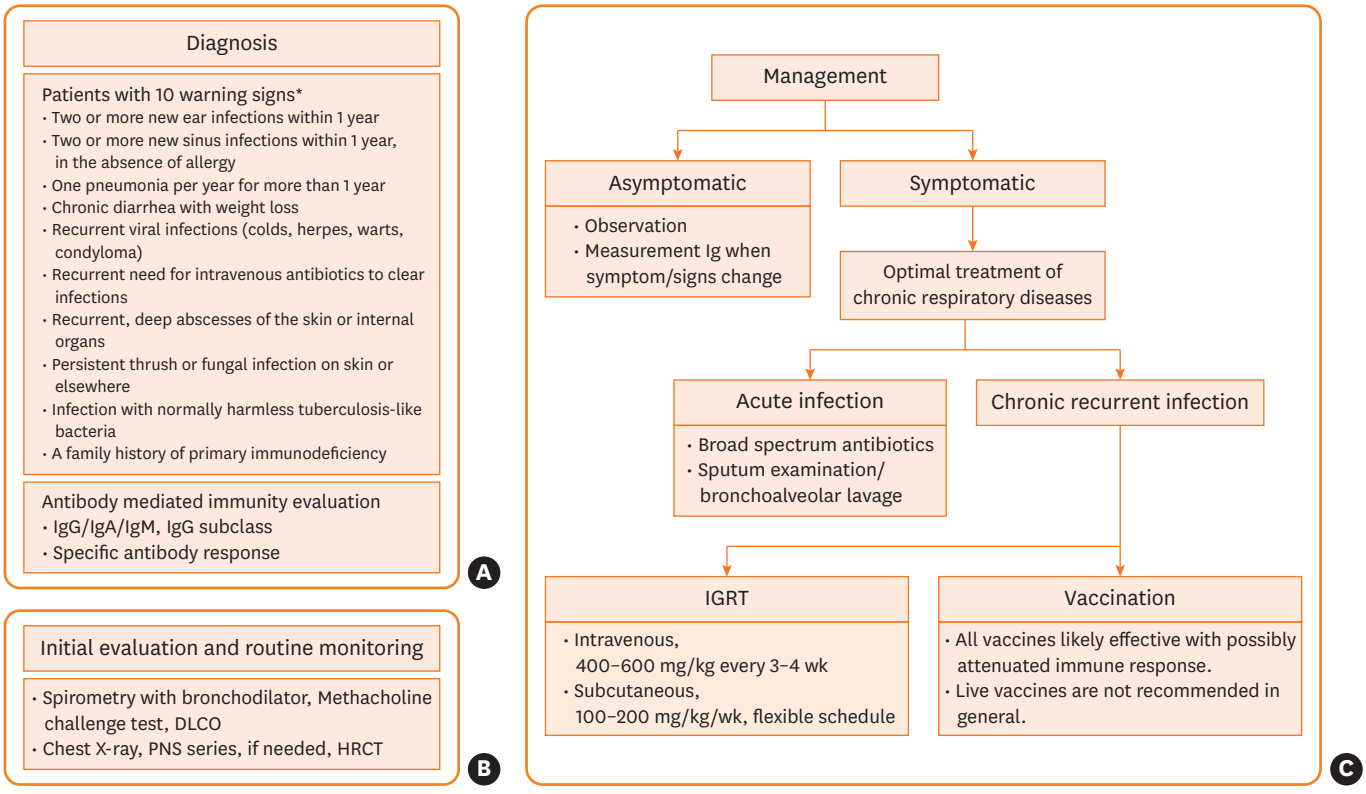

Figure. The diagnosis and management algorithm in adult patients with PIDs including IGGSCD. (A) Clinical suspicion and laboratory confirmation are essential to diagnose PIDs. (B) The respiratory functional and radiological examination is involved in the initial evaluation and routine monitoring. (C) The management of patients with IGGSCD is a combination of acute infection control using broad-spectrum antibiotics and prevention of chronic recurrent infection using IGRT and vaccination. Patients with ≥ 2 positive signs are suspected to have primary immunodeficiency.
Ig, immunoglobulin; DLCO, diffusing capacity of carbon monoxide; PNS, paranasal sinus x-ray; HRCT, high resolution computed tomography; IGRT, immunoglobulin replacement treatment; BCG, Bacille Calmette-Guérin; IGGSCD, IgG subclass deficiency; PID, primary immunodeficiency disease.
*Source From Jeffrey Modell Foundation.[81]

https://doi.org/10.4168/aair.2023.15.5.562

starting dose is 400–600 mg/kg every 3–4 weeks for intravenous Ig (IVIG) and 100–200 mg/kg/week for subcutaneous IgG replacement, which is more flexible.[82] It is important to provide all initial IVIG infusions under physician supervision in a facility equipped to handle the most severe acute medical complications. Immunological and clinical severity is a determining factor for IGRT continuation. Among those who respond to IGRT, selected patients deemed stable and unlikely to have severe symptom recurrence can discontinue treatment after 1 to 2 years for 4 to 6 months and then be re-evaluated.[2] There are limitations when administering IGRT, and consensus regarding the selection of appropriate patients; the timing of initiation; and the appropriate dose, interval, and duration of IGRT is needed.

Common adverse effects of IGRT include headache, myalgia, back pain, arthralgia, chills, malaise, fatigue, fever, and flushing. These flu-like symptoms account for more than 80% of Ig-induced adverse effects. These symptoms occur within the first hour of infusion, and some adverse effects (such as fever or fatigue) may develop within 24 hours. These symptoms are associated with rapid infusion and develop during the initial infusion period. Hence, it is recommended that infusion should start at a slow rate for the first 30 minutes.[83] There are uncommon but serious adverse effects of IGRT, including renal impairment, arrhythmia, aseptic meningitis, thromboembolic reactions, hemolytic reactions, and anaphylaxis. These adverse effects are associated with specific Ig preparations and individual differences. Assessing individual risk factors, such as preexisting atherosclerosis, old age, diabetes mellitus, hypertension, and dyslipidemia, and subsequent infusion at a slow rate or premedication can minimize these adverse effects. Anaphylaxis due to IgE or IgG antibodies to IgA in the Ig product is a rare complication of IGRT in patients with IGGSCD.[82]

Specific considerations for IGGSCD and asthma

Patients with IGGSCD may have a more severe form of asthma, requiring more aggressive treatment.[6,8] Treating underlying chronic airway diseases can help prevent recurrent viral infections. An epidemic study of pediatric asthma demonstrated the potential beneficial effects of ICSs in preventing viral asthma exacerbations.[84] In addition, the remarkable success of the current T2-targeting biologics in preventing asthma exacerbations has provided overwhelming evidence of the central role of this pathway in virus-induced asthma exacerbations.[85] Therefore, it is critical for asthmatic patients with IGGSCD to closely monitor their asthma control status to ensure proper treatment and management.

By preventing pulmonary infections, IGRT may reduce associated complications, such as bronchiectasis and acute exacerbations of chronic airway diseases.[82] Several studies have revealed the beneficial effects of IGRT for IGGSCD, demonstrating that IGRT significantly improves quality of life, decreases infection incidence, and reduces asthma exacerbations and the need for antibiotics (**Table**).[8,40,82,86-90] It has also been reported that IGRT is effective in PAD patients with comorbidities such as asthma and CRS.[8,91] A retrospective study showed that IGRT significantly decreased the rate of acute sinus infections in adults with CRS and PID.[91] Open-label trials examining the effects of medium- to high-dose IGRT in corticosteroid-dependent or severe asthma patients with antibody deficiencies such as SAD or IGGSCD demonstrated reductions in the corticosteroid dose as well as improvements in the peak flows, symptom scores, and hospitalization rate.[8,92-94] For patients with severe asthma without antibody deficiencies, IGRT showed beneficial effects in reducing exacerbation and steroid requirements in a previous study[95]; however, double-blind placebo-controlled asthma studies did not show that IGRT provided significant clinical benefits.[96-98] In addition, the cost and potential adverse effects associated with IGRT should be considered.

https://doi.org/10.4168/aair.2023.15.5.562

Table. Efficacy of immunoglobulin replacement treatment

Group	Year	Patients	Design	No.	Immunoglobulin replacement dose, frequency/duration, route	Results
Söderström *et al.*[88]	1991	Adults, IGGSCD	Prospective blind crossover	43	25 mg/kg/wk, 1 yr, IM	· Significantly fewer days with infection during prophylaxis · Fewer attacks of acute bronchitis during treatment
Barlan *et al.*[89]	1993	Adults, children; IGG3SCD	Prospective cohort	12	400 mg/kg every 3 wks–600 mg/kg every 2 wks, IV	· Reduction in the frequency of infections
Olinder-Nielsen *et al.*[87]	2007	Adults, selective or combined IGGSCD	Retrospective	132	100 mg/kg/wk, IV/IM	· Reduction in antibiotic-demanding respiratory tract infections during Ig prophylaxis
Abrahamian *et al.*[40]	2009	Adults, IGG3SCD	Retrospective	17	300–400 mg/kg every 2 wks, IV	· Six of the 13 patients had dramatic relief from their recurrent infections. · Five patients experienced moderate clinical improvement and two patients had no response.
Abdou *et al.*[86]	2009	Adults, IGGSCD ± SAD	Open-label	10	400 mg/kg/mon, 12 mon, IV	· Decreased the number of infections and the need for antibiotics and hospitalization · Improved quality of life
Kim *et al.*[8]	2017	Adults, IGGSCD	Open-label	30	400 mg/kg/mon, 6 mon, IV	· Reduced asthma exacerbation · Improved asthma control status and quality of life
Vivarelli *et al.*[90]	2021	Adults, IGGSCD or UAD	Retrospective	143	0.14 ± 0.06 g/kg/mon, 1 yr, IV	· Reduced respiratory infections and hospitalizations

IGGSCD, immunoglobulin G subclass deficiency; IGG3SCD, immunoglobulin G subclass 3 deficiency; SAD, specific antibody deficiency; UAD, unclassified antibody deficiency.

MONITORING OF PATIENTS WITH IGGSCD

Pulmonary diseases, including bronchiectasis, are prevalent complications of recurrent chronic infections in patients with PADs. In patients with IGGSCD, respiratory complications from recurrent viral and encapsulated bacterial infections are generally expected.[43] Other chronic respiratory complications include COPD and asthma. Early diagnosis with proper management can prevent permanent organ damage caused by recurrent infections. The currently used diagnostic methods include radiological and functional tests to evaluate respiratory status and lung disease in patients with PADs.[6]

Several functional tests evaluate respiratory status in patients with IGGSCD, including spirometry, airway reversibility tests with bronchodilators, methacholine challenge tests, and the diffusing capacity of the lung for carbon monoxide. These pulmonary tests aim to identify respiratory comorbidities and evaluate a patient's initial status. Recently, a study showed that the lung function of patients with chronic airway diseases and IGGSCD declined significantly despite the treatment of underlying respiratory conditions.[41] Therefore, initial evaluation and monitoring of pulmonary function are essential to managing patients with IGGSCD. Spirometry before and after bronchodilator administration should be performed at the first visit and annually thereafter. The methacholine challenge test can be further considered if needed. The diffusing capacity of the lung for carbon monoxide can be evaluated if interstitial lung disease is suspected.[6]

HRCT is used to evaluate a patient's initial status and monitor disease progression. HRCT is the gold standard for diagnosing bronchiectasis and interstitial lung diseases.[6] Early diagnosis and aggressive management can lead to good outcomes, considering that bronchiectasis at diagnosis predicts a poor prognosis.[49] However, performing routine surveillance using HRCT is not recommended due to the irradiation hazard. Instead, it is suggested that patients with humoral deficiencies, despite receiving adequate treatment, be evaluated for new or worsening lung complications every 5 to 10 years.[43]

https://doi.org/10.4168/aair.2023.15.5.562

VACCINATION IN PATIENTS WITH IGGSCD

Most vaccines are considered effective and safe in adult patients with IGGSCD. Even though the antibody response to vaccines may be decreased in these patients, they can still develop some level of protective antibodies and can be vaccinated safely. However, live attenuated vaccines (except Bacille-Calmette-Guérin), such as oral polio, adenovirus, typhoid, and yellow fever vaccines, are not recommended.[99] Inactivated or recombinant influenza, human papillomavirus, and all other vaccines, especially the pneumococcal and *H. influenzae* type B vaccines, are recommended in patients with B-cell defects. Pneumococcal vaccination should be administered based on a patient's risk. In patients with minor antibody deficiencies, conjugate vaccines should be administered for better immunogenicity after vaccination.[99] Additional immunization is reported to help enhance immunity in patients with associated IgG2 deficiency who require 2 doses of the conjugated vaccine.[2]

Patients who receive IGRT do not generally need additional immunizations, as therapeutic IgG can provide most of the immunization efficacy in childhood. However, it is suggested that nonviable vaccines, such as inactivated influenza and papilloma vaccines, may be given for additional cellular immunity. It is recommended that live vaccines, such as the measles, rubella, and varicella vaccines, which may be affected by IGRT, not be given to patients between 3 and 11 months after IGRT, depending on the indication and dose.[99] IGRT does not affect live vaccines such as oral polio and yellow fever vaccines.

There is no doubt about the effectiveness of COVID-19 vaccination in healthy patients with immunity. COVID-19 vaccination has also been shown to produce adequate antibody responses in approximately 73% of patients with PIDs and spike-directed T-cell immunity in most patients after vaccination.[100] Additionally, a recent study revealed no difference in response to COVID-19 vaccination in patients with PIDs receiving IGRT compared to those not receiving IGRT.[101] COVID-19 vaccines have shown an excellent safety profile in patients with PIDs. Multiple international cohort studies have reported that COVID-19 vaccines are safe for patients with PIDs, although reactogenicity to mRNA vaccines is more frequent in these patients than in the general population.[100] Common adverse reactions include fever, myalgia, and fatigue, but the severity does not seem to be increased in patients with PIDs. There is no existing evidence that patients with PIDs are at higher risk for adverse events after COVID-19 vaccination. Given the type of vaccination, the mRNA vaccine should be strongly recommended to most patients with inborn errors of immunity. The mRNA vaccine showed more potent immunogenicity than adenovirus-based vaccines, which can cause serious complications such as vaccine-induced immune thrombotic thrombocytopenia. Ideal vaccine regimens and booster timings are necessary for patients with PIDs.

CONCLUSIONS

IGGSCD may result in acute rhinosinusitis and lung infection, contributing to continuous inflammatory responses in the airway, such as CRS and asthma. Therefore, the detection and appropriate management of PIDs, including IGGSCD, may reduce acute exacerbations and cumulative morbidity in this population, prevent progression to severe asthma or bronchiectasis, improve quality of life, and decrease healthcare costs for the public. Significant steps toward achieving these goals include the development of a high index of suspicion; correct application of screening tests, such as tests evaluating quantitative Ig,

https://doi.org/10.4168/aair.2023.15.5.562

IgA, IgM, and IgG subclass levels and vaccine responses; and prompt provision of IGRT and immunization. In addition, future investigations are needed to identify the pathogenetic mechanism of IGGSCD and other PADs; establish clinically applicable laboratory methods for the quantitative and qualitative evaluation of Ig and IgG subclasses; and standardize IGRT, especially the dose, interval, and cessation period for patients with IGGSCD.

Given the heterogeneity of the underlying conditions and clinical course of IGGSCD, future studies with clearly defined patient populations need to be designed. A national registry and collaboration with international PID registries would help gather clinical information and understand the natural course of this disease. In addition, well-designed RCTs should be conducted to consider the efficacy and effectiveness of IGRT in these populations.

ACKNOWLEDGMENTS

This work was supported by the Korea Health Technology R&D Project (grant No. HR16C0001).

REFERENCES

1. Thalhammer J, Kindle G, Nieters A, Rusch S, Seppänen MRJ, Fischer A, et al. Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. J Allergy Clin Immunol 2021;148:1332-1341.e5.
PUBMED | CROSSREF
2. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015;136:1186-1205.e1-78.
PUBMED | CROSSREF
3. Rosenberg E, Dent PB, Denburg JA. Primary immune deficiencies in the adult: a previously underrecognized common condition. J Allergy Clin Immunol Pract 2016;4:1101-7.
PUBMED | CROSSREF
4. Verma N, Thaventhiran A, Gathmann B, Thaventhiran J, Grimbacher B; ESID Registry Working Party. Therapeutic management of primary immunodeficiency in older patients. Drugs Aging 2013;30:503-12.
PUBMED | CROSSREF
5. Verma N, Grimbacher B, Hurst JR. Lung disease in primary antibody deficiency. Lancet Respir Med 2015;3:651-60.
PUBMED | CROSSREF
6. Cinetto F, Scarpa R, Rattazzi M, Agostini C. The broad spectrum of lung diseases in primary antibody deficiencies. Eur Respir Rev 2018;27:180019.
PUBMED | CROSSREF
7. Patrawala M, Cui Y, Peng L, Fuleihan RL, Garabedian EK, Patel K, et al. Pulmonary disease burden in primary immune deficiency disorders: data from USIDNET registry. J Clin Immunol 2020;40:340-9.
PUBMED | CROSSREF
8. Kim JH, Ye YM, Ban GY, Shin YS, Lee HY, Nam YH, et al. Effects of immunoglobulin replacement on asthma exacerbation in adult asthmatics with IgG subclass deficiency. Allergy Asthma Immunol Res 2017;9:526-33.
PUBMED | CROSSREF
9. Lee SH, Ban GY, Kim SC, Chung CG, Lee HY, Lee JH, et al. Association between primary immunodeficiency and asthma exacerbation in adult asthmatics. Korean J Intern Med 2020;35:449-56.
PUBMED | CROSSREF
10. Lee H, Kovacs C, Mattman A, Hollander Z, Chen V, Ng R, et al. The impact of IgG subclass deficiency on the risk of mortality in hospitalized patients with COPD. Respir Res 2022;23:141.
PUBMED | CROSSREF
11. Fried AJ, Bonilla FA. Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections. Clin Microbiol Rev 2009;22:396-414.
PUBMED | CROSSREF

12. The United States Immunodeficiency Network (USIDNET). USIDNET Registry [Internet]. Towson (MD): USIDNET; 2022 [cited 2023 Aug 30]. Available from: https://usidnet.org/.
13. European Society for Immunodeficiencies (ESID). Registry Working Party ESID Registry [Internet]. Amsterdam: ESID; 2022 [cited 2023 Aug 30]. Available from: https://esid.org/Working-Parties/Registry-Working-Party/ESID-Registry.
14. Quinn J, Modell V, Orange JS, Modell F. Growth in diagnosis and treatment of primary immunodeficiency within the global Jeffrey Modell Centers Network. Allergy Asthma Clin Immunol 2022;18:19.
PUBMED | CROSSREF
15. Ishimura M, Takada H, Doi T, Imai K, Sasahara Y, Kanegane H, et al. Nationwide survey of patients with primary immunodeficiency diseases in Japan. J Clin Immunol 2011;31:968-76.
PUBMED | CROSSREF
16. Kim JH, Jang JH, Lee SH, Yang EM, Jang SH, Jung KS, et al. Specific antibody deficiency in adult patients with IgG or IgG subclass deficiency. Allergy Asthma Immunol Res 2021;13:271-83.
PUBMED | CROSSREF
17. Joshi AY, Iyer VN, Hagan JB, St. Sauver JL, Boyce TG. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. Mayo Clin Proc 2009;84:16-22.
PUBMED | CROSSREF
18. Pickett G, Motazedi T, Kutac C, Cahill G, Cunnigham-Rundles C, Fuleihan RL, et al. Infection phenotypes among patients with primary antibody deficiency mined from a US patient registry. J Clin Immunol 2021;41:374-81.
PUBMED | CROSSREF
19. Rhim JW, Kim KH, Kim DS, Kim BS, Kim JS, Kim CH, et al. Prevalence of primary immunodeficiency in Korea. J Korean Med Sci 2012;27:788-93.
PUBMED | CROSSREF
20. Kim JH, Ye YM, Lee SH, Ban GY, Nam YH, Choi JH, et al. Distribution and quality of life in patients with primary immunodeficiency diseases in a cohort of Korean adults. Allergy Asthma Immunol Res 2021;13:164-6.
PUBMED | CROSSREF
21. Schussler E, Beasley MB, Maglione PJ. Lung disease in primary antibody deficiencies. J Allergy Clin Immunol Pract 2016;4:1039-52.
PUBMED | CROSSREF
22. Kashani S, Carr TF, Grammer LC, Schleimer RP, Hulse KE, Kato A, et al. Clinical characteristics of adults with chronic rhinosinusitis and specific antibody deficiency. J Allergy Clin Immunol Pract 2015;3:236-42.
PUBMED | CROSSREF
23. Keswani A, Dunn NM, Manzur A, Kashani S, Bossuyt X, Grammer LC, et al. The clinical significance of specific antibody deficiency (SAD) severity in chronic rhinosinusitis (CRS). J Allergy Clin Immunol Pract 2017;5:1105-11.
PUBMED | CROSSREF
24. Schwitzguébel AJ, Jandus P, Lacroix JS, Seebach JD, Harr T. Immunoglobulin deficiency in patients with chronic rhinosinusitis: systematic review of the literature and meta-analysis. J Allergy Clin Immunol 2015;136:1523-31.
PUBMED | CROSSREF
25. Weinberger T, Fuleihan R, Cunningham-Rundles C, Maglione PJ. Factors beyond lack of antibody govern pulmonary complications in primary antibody deficiency. J Clin Immunol 2019;39:440-7.
PUBMED | CROSSREF
26. Urm SH, Yun HD, Fenta YA, Yoo KH, Abraham RS, Hagan J, et al. Asthma and risk of selective IgA deficiency or common variable immunodeficiency: a population-based case-control study. Mayo Clin Proc 2013;88:813-21.
PUBMED | CROSSREF
27. Özcan C, Metin A, Erkoçoğlu M, Kocabas CN. Bronchial hyperreactivity in children with antibody deficiencies. Allergol Immunopathol (Madr) 2015;43:57-61.
PUBMED | CROSSREF
28. Popa V. Airway obstruction in adults with recurrent respiratory infections and IgG deficiency. Chest 1994;105:1066-72.
PUBMED | CROSSREF
29. Cereser L, De Carli M, d'Angelo P, Zanelli E, Zuiani C, Girometti R. High-resolution computed tomography findings in humoral primary immunodeficiencies and correlation with pulmonary function tests. World J Radiol 2018;10:172-83.
PUBMED | CROSSREF
30. Berger M, Geng B, Cameron DW, Murphy LM, Schulman ES. Primary immune deficiency diseases as unrecognized causes of chronic respiratory disease. Respir Med 2017;132:181-8.
PUBMED | CROSSREF

31. Peltola V, Waris M, Kainulainen L, Kero J, Ruuskanen O. Virus shedding after human rhinovirus infection in children, adults and patients with hypogammaglobulinaemia. Clin Microbiol Infect 2013;19:E322-7.
PUBMED | CROSSREF

32. Verduyn M, Botto G, Jaubert J, Lier C, Flament T, Guilleminault L. Serum IgG concentrations in adult patients experiencing virus-induced severe asthma exacerbations. J Allergy Clin Immunol Pract 2019;7:1507-1513.e1.
PUBMED | CROSSREF

33. Loftus BG, Price JF, Lobo-Yeo A, Vergani D. IgG subclass deficiency in asthma. Arch Dis Child 1988;63:1434-7.
PUBMED | CROSSREF

34. Ayres JG, Thompson RA. Low IgG subclass levels in brittle asthma and in patients with exacerbations of asthma associated with respiratory infection. Respir Med 1997;91:464-9.
PUBMED | CROSSREF

35. Balzar S, Strand M, Nakano T, Wenzel SE. Subtle immunodeficiency in severe asthma: IgA and IgG2 correlate with lung function and symptoms. Int Arch Allergy Immunol 2006;140:96-102.
PUBMED | CROSSREF

36. Leitao Filho FS, Ra SW, Mattman A, Schellenberg RS, Criner GJ, Woodruff PG, et al. Serum IgG subclass levels and risk of exacerbations and hospitalizations in patients with COPD. Respir Res 2018;19:30.
PUBMED | CROSSREF

37. Leitao Filho FS, Won Ra S, Mattman A, Schellenberg RS, Fishbane N, Criner GJ, et al. Serum IgG and risk of exacerbations and hospitalizations in chronic obstructive pulmonary disease. J Allergy Clin Immunol 2017;140:1164-1167.e6.
PUBMED | CROSSREF

38. Leitao Filho FS, Mattman A, Schellenberg R, Criner GJ, Woodruff P, Lazarus SC, et al. Serum IgG levels and risk of COPD hospitalization: a pooled meta-analysis. Chest 2020;158:1420-30.
PUBMED | CROSSREF

39. Iikura M, Hojo M, Koketsu R, Watanabe S, Sato A, Chino H, et al. The importance of bacterial and viral infections associated with adult asthma exacerbations in clinical practice. PLoS One 2015;10:e0123584.
PUBMED | CROSSREF

40. Abrahamian F, Agrawal S, Gupta S. Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. Clin Exp Immunol 2010;159:344-50.
PUBMED | CROSSREF

41. Kim JH, Park S, Hwang YI, Jang SH, Jung KS, Sim YS, et al. Immunoglobulin G subclass deficiencies in adult patients with chronic airway diseases. J Korean Med Sci 2016;31:1560-5.
PUBMED | CROSSREF

42. Barton J, Barton C, Bertoli L. Duration of frequent or severe respiratory tract infection in adults before diagnosis of IgG subclass deficiency. PLoS One 2019;14:e0216940.
PUBMED | CROSSREF

43. Lehman HK, Yu KOA, Towe CT, Risma KA. Respiratory infections in patients with primary immunodeficiency. J Allergy Clin Immunol Pract 2022;10:683-691.e1.
PUBMED | CROSSREF

44. Ponsford MJ, Price C, Farewell D, Greene G, Moore C, Perry M, et al. Increased respiratory viral detection and symptom burden among patients with primary antibody deficiency: results from the BIPAD study. J Allergy Clin Immunol Pract 2021;9:735-744.e6.
PUBMED | CROSSREF

45. Barton JC, Bertoli LF, Barton JC. Comparisons of CVID and IgGSD: referring physicians, autoimmune conditions, pneumovax reactivity, immunoglobulin levels, blood lymphocyte subsets, and HLA-A and -B typing in 432 adult index patients. J Immunol Res 2014;2014:542706.
PUBMED | CROSSREF

46. Dupin C, Marchand-Adam S, Favelle O, Costes R, Gatault P, Diot P, et al. Asthma and hypogammaglobulinemia: an asthma phenotype with low type 2 inflammation. J Clin Immunol 2016;36:810-7.
PUBMED | CROSSREF

47. Tran Khai Hoan N, Karmochkine M, Laccourreye O, Bonfils P. Nasal polyposis and immunoglobulin-G subclass deficiency. Eur Ann Otorhinolaryngol Head Neck Dis 2014;131:171-5.
PUBMED | CROSSREF

48. De Gracia J, Rodrigo MJ, Morell F, Vendrell M, Miravitlles M, Cruz MJ, et al. IgG subclass deficiencies associated with bronchiectasis. Am J Respir Crit Care Med 1996;153:650-5.
PUBMED | CROSSREF

49. Aliberti S, Amati F, Gramegna A, Vigone B, Oriano M, Sotgiu G, et al. Comparison of different sets of immunological tests to identify treatable immunodeficiencies in adult bronchiectasis patients. ERJ Open Res 2022;8:00388-2021.
PUBMED | CROSSREF

50. Schütz K, Alecsandru D, Grimbacher B, Haddock J, Bruining A, Driessen G, et al. Imaging of bronchial pathology in antibody deficiency: data from the European Chest CT Group. J Clin Immunol 2019;39:45-54.
PUBMED | CROSSREF

51. Zhang Y, Clarke A, Regan KH, Campbell K, Donaldson S, Crowe J, et al. Isolated IgG2 deficiency is an independent risk factor for exacerbations in bronchiectasis. QJM 2022;115:292-7.
PUBMED | CROSSREF

52. Damelang T, Rogerson SJ, Kent SJ, Chung AW. Role of IgG3 in infectious diseases. Trends Immunol 2019;40:197-211.
PUBMED | CROSSREF

53. Rawat A, Suri D, Gupta A, Saikia B, Minz RW, Singh S. Isolated immunoglobulin G4 subclass deficiency in a child with bronchiectasis. Indian J Pediatr 2014;81:932-3.
PUBMED | CROSSREF

54. Mooney D, Edgar D, Einarsson G, Downey D, Elborn S, Tunney M. Chronic lung disease in common variable immune deficiency (CVID): a pathophysiological role for microbial and non-B cell immune factors. Crit Rev Microbiol 2017;43:508-19.
PUBMED | CROSSREF

55. Fevang B, Mollnes TE, Holm AM, Ueland T, Heggelund L, Damås JK, et al. Common variable immunodeficiency and the complement system; low mannose-binding lectin levels are associated with bronchiectasis. Clin Exp Immunol 2005;142:576-84.
PUBMED | CROSSREF

56. Duraisingham SS, Manson A, Grigoriadou S, Buckland M, Tong CY, Longhurst HJ. Immune deficiency: changing spectrum of pathogens. Clin Exp Immunol 2015;181:267-74.
PUBMED | CROSSREF

57. Sperlich JM, Grimbacher B, Workman S, Haque T, Seneviratne SL, Burns SO, et al. Respiratory infections and antibiotic usage in common variable immunodeficiency. J Allergy Clin Immunol Pract 2018;6:159-168.e3.
PUBMED | CROSSREF

58. Pan Q, Hammarström L. Molecular basis of IgG subclass deficiency. Immunol Rev 2000;178:99-110.
PUBMED | CROSSREF

59. Durandy A, Kracker S, Fischer A. Primary antibody deficiencies. Nat Rev Immunol 2013;13:519-33.
PUBMED | CROSSREF

60. Blanco E, Pérez-Andrés M, Arriba-Méndez S, Serrano C, Criado I, Del Pino-Molina L, et al. Defects in memory B-cell and plasma cell subsets expressing different immunoglobulin-subclasses in patients with CVID and immunoglobulin subclass deficiencies. J Allergy Clin Immunol 2019;144:809-24.
PUBMED | CROSSREF

61. Sohn H, Kim JH, Jang JH, Kim SH, Park HS. Functional defects in B lymphocytes in asthmatic patients with IgG subclass deficiency. Allergy Asthma Immunol Res 2023;15:536-8.
PUBMED | CROSSREF

62. Lee JH, Kim SH, Jung CG, Choi Y, Park HS. Familial IgG3 subclass deficiency: a report of two cases. Allergy Asthma Respir Dis 2018;6:184.
CROSSREF

63. Lankisch P, Schiffner J, Ghosh S, Babor F, Borkhardt A, Laws HJ. The Duesseldorf warning signs for primary immunodeficiency: is it time to change the rules? J Clin Immunol 2015;35:273-9.
PUBMED | CROSSREF

64. Holding S, Jolles S. Current screening approaches for antibody deficiency. Curr Opin Allergy Clin Immunol 2015;15:547-55.
PUBMED | CROSSREF

65. Costa-Carvalho BT, Grumach AS, Franco JL, Espinosa-Rosales FJ, Leiva LE, King A, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol 2014;34:10-22.
PUBMED | CROSSREF

66. Harkness T, Fu X, Zhang Y, Choi HK, Stone JH, Blumenthal KG, et al. Immunoglobulin G and immunoglobulin G subclass concentrations differ according to sex and race. Ann Allergy Asthma Immunol 2020;125:190-195.e2.
PUBMED | CROSSREF

67. Otani IM, Lehman HK, Jongco AM, Tsao LR, Azar AE, Tarrant TK, et al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: a work group report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees. J Allergy Clin Immunol 2022;149:1525-60.
PUBMED | CROSSREF

68. Posey WC, Nelson HS, Branch B, Pearlman DS. The effects of acute corticosteroid therapy for asthma on serum immunoglobulin levels. J Allergy Clin Immunol 1978;62:340-8.
PUBMED | CROSSREF

69. Butler WT, Rossen RD. Effects of corticosteroids on immunity in man. I. Decreased serum IgG concentration caused by 3 or 5 days of high doses of methylprednisolone. J Clin Invest 1973;52:2629-40.
PUBMED | CROSSREF

70. Wirsum C, Glaser C, Gutenberger S, Keller B, Unger S, Voll RE, et al. Secondary antibody deficiency in glucocorticoid therapy clearly differs from primary antibody deficiency. J Clin Immunol 2016;36:406-12.
PUBMED | CROSSREF

71. Beard LJ, Ferrante A, Oxelius VA, Maxwell GM. IgG subclass deficiency in children with IgA deficiency presenting with recurrent or severe respiratory infections. Pediatr Res 1986;20:937-42.
PUBMED | CROSSREF

72. Morell A, Muehlheim E, Schaad U, Skvaril F, Rossi E. Susceptibility to infections in children with selective IgA- and IgA-IgG subclass deficiency. Eur J Pediatr 1986;145:199-203.
PUBMED | CROSSREF

73. Björkander J, Bake B, Oxelius VA, Hanson LA. Impaired lung function in patients with IgA deficiency and low levels of IgG2 or IgG3. N Engl J Med 1985;313:720-4.
PUBMED | CROSSREF

74. Barton JC, Barton JC, Bertoli LF, Acton RT. Characterization of adult patients with IgG subclass deficiency and subnormal IgG2. PLoS One 2020;15:e0240522.
PUBMED | CROSSREF

75. Sorensen RU, Edgar D. Specific antibody deficiencies in clinical practice. J Allergy Clin Immunol Pract 2019;7:801-8.
PUBMED | CROSSREF

76. Edwards E, Razvi S, Cunningham-Rundles C. IgA deficiency: clinical correlates and responses to pneumococcal vaccine. Clin Immunol 2004;111:93-7.
PUBMED | CROSSREF

77. Schatorjé EJ, de Jong E, van Hout RW, García Vivas Y, de Vries E. The challenge of immunoglobulin-G subclass deficiency and specific polysaccharide antibody deficiency--a Dutch Pediatric Cohort Study. J Clin Immunol 2016;36:141-8.
PUBMED | CROSSREF

78. Lougaris V, Sorlini A, Monfredini C, Ingrasciotta G, Caravaggio A, Lorenzini T, et al. Clinical and laboratory features of 184 Italian pediatric patients affected with selective IgA deficiency (SIgAD): a longitudinal single-center study. J Clin Immunol 2019;39:470-5.
PUBMED | CROSSREF

79. Aghamohammadi A, Mohammadi J, Parvaneh N, Rezaei N, Moin M, Espanol T, et al. Progression of selective IgA deficiency to common variable immunodeficiency. Int Arch Allergy Immunol 2008;147:87-92.
PUBMED | CROSSREF

80. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International consensus document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract 2016;4:38-59.
PUBMED | CROSSREF

81. Jeffrey Modell Foundation. Primary immunodeficiency resource centre [Internet]. New York (NY): Jeffrey Modell Foundation; 2021 [cited 2023 Aug 6]. Available from: http://www.info4pi.org/library/educational-materials/.

82. Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol 2017;139:S1-46.
PUBMED | CROSSREF

83. Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. Front Immunol 2018;9:1299.
PUBMED | CROSSREF

84. Jackson DJ, Gern JE. Rhinovirus Infections and their roles in asthma: etiology and exacerbations. J Allergy Clin Immunol Pract 2022;10:673-81.
PUBMED | CROSSREF

85. Park SY, Kang SY, Song WJ, Kim JH. Evolving concept of severe asthma: transition from diagnosis to treatable traits. Allergy Asthma Immunol Res 2022;14:447-64.
PUBMED | CROSSREF

86. Abdou NI, Greenwell CA, Mehta R, Narra M, Hester JD, Halsey JF. Efficacy of intravenous gammaglobulin for immunoglobulin G subclass and/or antibody deficiency in adults. Int Arch Allergy Immunol 2009;149:267-74.
PUBMED | CROSSREF

87. Olinder-Nielsen AM, Granert C, Forsberg P, Friman V, Vietorisz A, Björkander J. Immunoglobulin prophylaxis in 350 adults with IgG subclass deficiency and recurrent respiratory tract infections: a long-term follow-up. Scand J Infect Dis 2007;39:44-50.
PUBMED | CROSSREF

88. Söderström T, Söderström R, Enskog A. Immunoglobulin subclasses and prophylactic use of immunoglobulin in immunoglobulin G subclass deficiency. Cancer 1991;68:1426-9.
PUBMED | CROSSREF

89. Barlan IB, Geha RS, Schneider LC. Therapy for patients with recurrent infections and low serum IgG3 levels. J Allergy Clin Immunol 1993;92:353-5.
PUBMED | CROSSREF

90. Vivarelli E, Matucci A, Bormioli S, Parronchi P, Liotta F, Cosmi L, et al. Effectiveness of low-dose intravenous immunoglobulin therapy in minor primary antibody deficiencies: a 2-year real-life experience. Clin Exp Immunol 2021;205:346-53.
PUBMED | CROSSREF

91. Makary CA, Behnke J, Peppers B, Ramadan HH. Outcome of immunoglobulin replacement therapy in adults with rhinosinusitis. Laryngoscope 2022;132:732-6.
PUBMED | CROSSREF

92. Schwartz HJ, Hostoffer RW, McFadden ER Jr, Berger M. The response to intravenous immunoglobulin replacement therapy in patients with asthma with specific antibody deficiency. Allergy Asthma Proc 2006;27:53-8.
PUBMED

93. Tiotiu A, Salvator H, Jaussaud R, Jankowski R, Couderc LJ, Catherinot E, et al. Efficacy of immunoglobulin replacement therapy and azithromycin in severe asthma with antibody deficiency. Allergol Int 2020;69:215-22.
PUBMED | CROSSREF

94. Landwehr LP, Jeppson JD, Katlan MG, Esterl B, McCormick D, Hamilos DL, et al. Benefits of high-dose i.v. immunoglobulin in patients with severe steroid-dependent asthma. Chest 1998;114:1349-56.
PUBMED | CROSSREF

95. Haque S, Boyce N, Thien FC, O'Hehir RE, Douglass J. Role of intravenous immunoglobulin in severe steroid-dependent asthma. Intern Med J 2003;33:341-4.
PUBMED | CROSSREF

96. Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. Clin Immunol 1999;91:126-33.
PUBMED | CROSSREF

97. Salmun LM, Barlan I, Wolf HM, Eibl M, Twarog FJ, Geha RS, et al. Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: a double-blind, placebo-controlled, randomized trial. J Allergy Clin Immunol 1999;103:810-5.
PUBMED | CROSSREF

98. Niggemann B, Leupold W, Schuster A, Schuster R, v Berg A, Grübl A, et al. Prospective, double-blind, placebo-controlled, multicentre study on the effect of high-dose, intravenous immunoglobulin in children and adolescents with severe bronchial asthma. Clin Exp Allergy 1998;28:205-10.
PUBMED | CROSSREF

99. Sobh A, Bonilla FA. Vaccination in primary immunodeficiency disorders. J Allergy Clin Immunol Pract 2016;4:1066-75.
PUBMED | CROSSREF

100. Durkee-Shock JR, Keller MD. Immunizing the imperfect immune system: Coronavirus disease 2019 vaccination in patients with inborn errors of immunity. Ann Allergy Asthma Immunol 2022;129:562-571.e1.
PUBMED | CROSSREF

101. Delmonte OM, Bergerson JRE, Burbelo PD, Durkee-Shock JR, Dobbs K, Bosticardo M, et al. Antibody responses to the SARS-CoV-2 vaccine in individuals with various inborn errors of immunity. J Allergy Clin Immunol 2021;148:1192-7.
PUBMED | CROSSREF