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Review

# Adult Primary Antibody Deficiencies and the Lung

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Abstract

Primary antibody deficiency diseases result from a genetic defect that causes misfunction of 1 or more of the immune system elements. Due to the increased awareness among physicians and the success of new treatment modalities, the number of pediatric patients reaching adult age and the number of patients diagnosed in adult age is increasing. Adult patients comprise more than half of the total cases. Primary antibody deficiencies are the most common immunodeficiency type in adults, and these may cause recurrent upper and lower respiratory tract infections and result in the development of bronchiectasis. Among non-infectious pulmonary complications, any type of interstitial lung disease may be seen; however, a special type seen in patients with common variable immunodeficiency, namely granulomatous lymphocytic interstitial lung disease, is the one most commonly investigated. Underlying or accompanying immunodeficiency may be present in patients with asthma and chronic obstructive pulmonary disease, especially if the disease requires frequent hospitalizations and/or is severe. Early diagnosis and appropriate management of primary antibody deficiency diseases in patients with respiratory symptoms are crucial to decrease complications and increase survival.

**KEYWORDS:** Bronchiectasis, common variable immunodeficiency, granulomatous lymphocytic interstitial lung disease, primary immunodeficiency

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## INTRODUCTION

There have been more than 400 primary immunodeficiency (PID) diseases described until now.[1] While most of those diseases presents and are diagnosed during childhood, the vast majority of patients are adults.[2] A study that analyzed various national registries in an attempt to estimate the worldwide prevalence and incidence of PIDs reported that those are not only diseases of childhood, but new cases older than 25 years old comprise more than 50% of all PID patients.[3]

Genetic alterations that affect the immune system and cause PID also may cause infectious, autoimmune, and malignant complications. Allergists/Immunologists are primarily involved in the diagnosis and follow-up of those patients; however, because of complications like bronchiectasis, interstitial lung disease, gastrointestinal disease and malignancies, pulmonologists, hematologists, and rheumatologists are also involved during the course of the diseases. Admission of those patients with PID may be complex, and patients may be initially managed by non-allergist/immunologists raising the need for higher awareness from non-immunologists as well. The United Kingdom Primary Immunodeficiency (UKPID) Registry reported that there was a median delay, defined as the time between the onset of symptoms and diagnosis, of 8 years for common variable immunodeficiency (CVID) in adults aged over 30 years.[4] In this registry, the major accompanying disorders were either respiratory (bronchiectasis in nearly 20% of the cohort) or hematological.[4] The most common type of PID in adults is primary antibody deficiencies (PAD). However, improved survival of children with PID may change the prevalence of various types of PIDs in the adult population.[3]

Functional or quantitative insufficiency in the immune system leads to immunodeficiency diseases that may be acquired, such as human immunodeficiency virus infection or primary (PID) in the case of a genetic defect. The most common infection sites in patients with PAD are the airways and the lungs.[5] PADs may lead to recurrent infections, immune dysregulation and autoimmunity, and the development of cancer as well as infectious and non-infectious pulmonary complications. This review will focus on pulmonary complications of PAD when to suspect an underlying PAD in lung diseases and management of those patients with lung disease and PAD.

## CLINICAL AND RESEARCH CONSEQUENCES

### Mucosal Immunity of the Respiratory System

Under normal circumstances, thousands of microorganisms and particles in each breath are efficiently eliminated by the respiratory tract without an apparent inflammatory response.[6] The defense in the upper respiratory tract is mainly mechanical and provided by mucociliary clearance, whereas alveolar surfaces lack ciliated epithelium, and alveolar macrophages mainly mediate defense. All other components of the respiratory system, namely bronchial epithelial cells, neutrophils, lymphocytes, and surfactant products, play roles in defense against pathogens and toxins. Airway mucus that covers the epithelium is constantly produced by goblet cells and the submucosal gland, and due to the rhythmic beat of

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the cilia, clearance is maintained, and almost 90% of inhaled particles and microorganisms are eliminated.[7]

It has been observed that there are defects in epithelial barrier structure and function of asthmatic patients, which may cause increased susceptibility to infection that in turn leads to inflammatory response and exacerbation of the underlying chronic respiratory disease.[8]

Immunoglobulin A (IgA) is the most abundant Ig in adults; in blood 90% exists as monomeric IgA, whereas in airway secretions, 50% is in the form of secretory IgA (sIgA) that is dimeric.[5,9] Through receptor blockage and neutralization, sIgA helps eliminate pathogens and antigens that reach respiratory surfaces. sIgA that is mainly derived from the mucosa-associated lymphoid tissue is the predominant Ig in the upper airways, whereas IgG that is mainly derived from the systemic circulation by passive diffusion, is the predominant Ig in the alveolar spaces, and mucosa-associated lymphoid tissue-derived IgM is predominant at the bronchial surfaces and enhances pathogen opsonization through activation of the complement system.[5,10]

**Pulmonary and Extrapulmonary Manifestations Suggesting PID, and Diagnostic Tests**

Recurrent pulmonary and upper respiratory tract infections are the most important warning signs that should prompt suspicion of PID. A detailed clinical history, including family history and physical examination combined with complete blood count, serum biochemistry, and Ig level measurement, can diagnose most PID patients. To evaluate humoral immunity, serum Igs (IgA, IgG, IgM, and IgE) are measured. Results may show a quantitative deficiency, suggesting selective or partial IgA deficiency, hyper-IgE or hyper-IgM syndrome, or may suggest CVID. Measurement of Ig levels, vaccine or disease-specific antibody titers, B cell counts, and phenotyping are generally sufficient to diagnose or exclude humoral PID.[11] If the diagnosis is not established, but the suspicion is high, functional and molecular studies are needed, which should be conducted at reference centers.[12]

An external panel consisting of 43 experts from all over Spain (19 adult and 15 pediatric immunologists, 5 adult and 4 pediatric pulmonologists), indicated their level of agreement on conclusions and recommendations to document the warning signs of PID in patients with respiratory involvement, the necessary diagnostic tests, and the treatment.[12] Table 1 summarizes the unanimity (100% agreement) and consensus (at least 80% agreement) recommendations/conclusions of the panel.

Figure 1 shows the diagnostic algorithm of patients with recurrent sinopulmonary infections, bronchiectasis, or interstitial lung disease.[12]

**Main Points**

- Primary antibody deficiency diseases may present at adult age with respiratory system symptoms.
- Management of primary immunodeficiency diseases requires teamwork, in which chest physicians play an important role; therefore, awareness of those diseases and the pulmonary complications they cause should be increased.
- Any patient with severe, unusual, or recurrent infections, bronchiectasis, and interstitial lung disease, particularly granulomatous, should be investigated for primary antibody deficiency. The investigation may include patients with asthma, a severe obstructive pulmonary disease with recurrent infections, and a prior diagnosis of sarcoidosis with unusual features.

**Lung Disease in PAD**

X-linked agammaglobulinemia is an X-linked recessive inherited disease. Affected individuals have a severely reduced amount of peripheral B cells and all classes of antibodies with a lack of humoral response. Patients typically present in early childhood with recurrent infections of the respiratory and other systems that may be severe and lead to sepsis and meningitis. Diagnosis is achieved mainly in childhood. However, late diagnosis in adolescence or adult age has been reported. There is a high risk of the development of bronchiectasis and chronic lung disease.[13] A study including 168 male patients with XLA from the Italian Primary Immunodeficiency Network (IPINet) registry reported that respiratory infections were the most frequent manifestation (39.9% pneumonia), and the incidence of chronic lung disease at the time of diagnosis was 13.1%.[13] After a mean follow-up period of 8.5 years, an additional 38.4% developed chronic lung disease despite regular immunoglobulin therapy. The overall survival rate at 43 years was 92.7%, lower when there was chronic lung disease (90.5%).[13]

In IgG subclass deficiency (IgGSD), serum concentrations of 1 or more subclasses of IgG are significantly reduced with normal total IgG levels. Quantitative deficiency may not lead to clinical disorder, and to establish the diagnosis, documentation of antibody dysfunction is required. Most individuals with 1 or more IgGSD are asymptomatic, and recurrent sinopulmonary infections are the most common presentation in symptomatic ones. In a retrospective study including 300 adult patients with IgGSD, the mean age at diagnosis was 50 ± 12 years, 82.3% of them were female, and age at infection onset was ≥18 years in 95.7%.[14] Selective IgA deficiency is the most common immunologic defect (prevalence of 0.1-1%), which is defined as low levels of serum IgA (<7 mg/dL) with normal levels of other immunoglobulins and otherwise normal immune system.[15] Majority of patients are asymptomatic (85-90%), in the remaining recurrent respiratory tract infections are the most common presentation type.

CVID is the best-described PAD in adults. It is defined as common because it is one of the most frequent types of immunodeficiency and as a variable because the clinical presentation is heterogeneous.[16] The CVID term was recently changed to "CVID disorders" to draw attention to the heterogeneous nature of the disease.[17] Patients may present at any age either with recurrent infections, autoimmunity, or systemic granulomatous disease. The disorder is mainly diagnosed between the ages of 20 and 40 years with an average delay from 6 to 8 years.[18] Serum levels of IgG, IgA, and/or IgM are reduced, and specific antibody production is either absent or low and other disorders that may cause antibody deficiency should be excluded. Figure 2 reviews the European Society of Immunodeficiencies (ESID) criteria for the diagnosis of CVID.[19]

**Table 1.** The Recommendations/Conclusions of the Spanish Expert Panel on Warning Signs, Diagnosis and Management of Primary Immunodeficiency Diseases in Lung Disease (Adapted From Reference 12)

| | |
|---|---|
| Respiratory manifestations with suspicion of PID (adult and pediatric patients) | Recurrent bronchial infections (≥2/year), with cough and purulent suputum<br>Idiopathic bronchiectasis<br>Recurrent pneumonias*<br>Chronic bronchial infection<br>Prolonged antibiotic treatment needed for respiratory infections<br>Pulmonary abscess and pneumatocele<br>Infections caused by rare or opportunistic microorganisms<br>GLILD<br>Lymphoproliferative syndrome<br>Alveolar proteinosis<br>Thymoma (adults), tymic aplasia (infant) |
| Most common extrapulmonary manifestations of PID | Recurrent or complicated sinusitis<br>Recurrent or complicated otitis<br>Extrapulmonary infections requiring admission<br>Chronic diarrhea or malabsorbtion<br>Difficult-to-treat giardiasis<br>Autoimmune cytopenias or other autoimmunity<br>Lymphadenopathies and hepatosplenomegaly<br>Related cancers, especially associated with viruses<br>Family history of PID or consistent manifestations |
| Minimum tests to be performed in follow-up of patients with PID and respiratory symptoms | Patient visit every 6-12 months<br>CBC, biochemistry with LDH and Igs every 6-12 months<br>More frequent, at least at dose adjustment IgG trough level measurement (in patients under Ig replacement therapy)<br>Annual lung function tests<br>Spirometry every 4-6 months in the absence of lung disease<br>Sputum culture must be performed at each visit if the patient is expectorating and in case of exacerbation<br>Lung CT every 2-3 years if the patient has lung involvement and every 5 years otherwise. Radiation must be minimized in the case of radiosensitive PID.<br>Extrapulmonary tests are performed according to patient's symptoms |

Unanimity (100% agreement) and consensus (at least 80% agreement) recommendations/conclusions are given. *One pneumonia per year for more than 1 year.
GLILD, granulomatous lymphocytic interstitial lung disease; PID, primary immunodeficiency; CBC, complete blood count; LDH, lactate dehydrogenase.

Respiratory tract infections are the main feature in most patients. Half of the patients had at least 1 episode of pneumonia, while others may have recurrent bronchitis, sinusitis, or otitis.[18] Recurrent respiratory tract infections are often due to common respiratory pathogens; *Haemophilus influenza, Streptococcus pneumoniae, and Mycoplasma pneumonia* and can lead to bronchiectasis.[17] Opportunistic infections with *Pneumocystis jirovecii*, viruses, and nontuberculous mycobacteria may be seen.[17]

The standard of care in CVID is either subcutaneous or intravenous Ig (IVIG) replacement. Optimized Ig therapy substantially reduces episodes of bacterial infections and enhances survival; however, it seems to have no effect on inflammatory

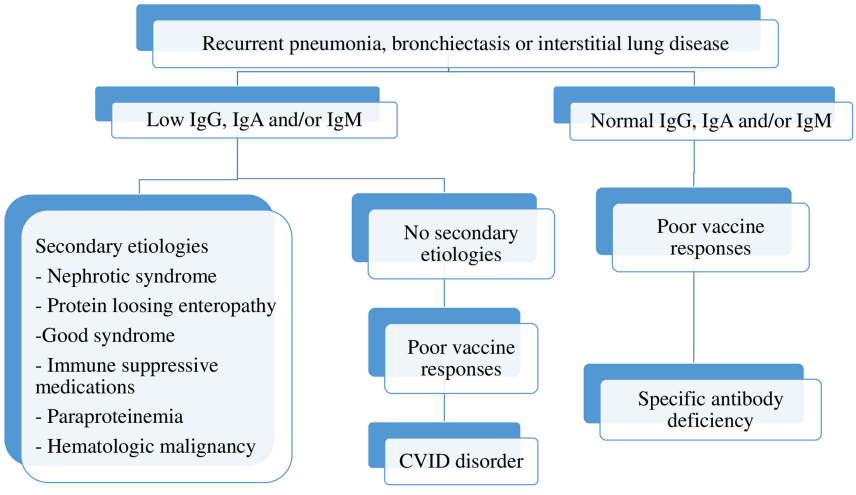


**Figure 1.** The diagnostic algorithm of patients with recurrent sinopulmonary infections, bronchiectasis, or interstitial lung disease. Immunoglobulin replacement therapy should be considered in all cases if there are poor vaccine responses and/or recurrent infections (adapted from reference 17).

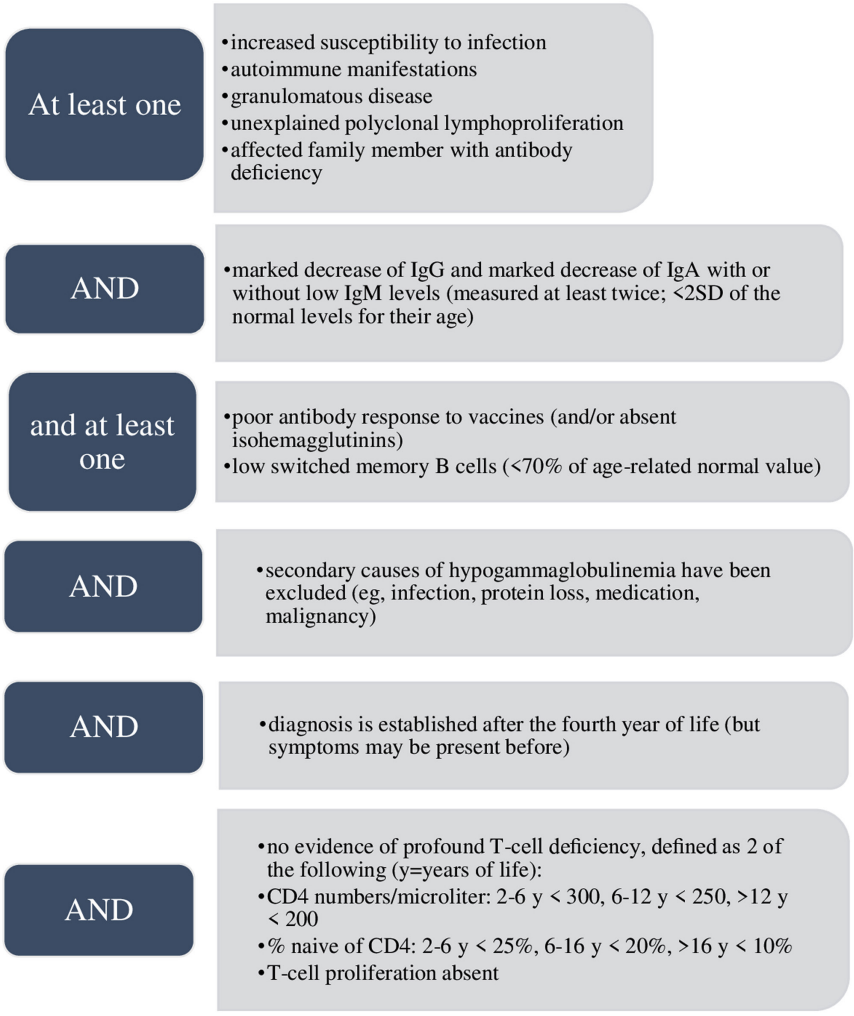


**Figure 2.** ESID registry-working definition for clinical diagnosis of CVID (adapted from reference 19).

complications like progressive lung disease; therefore, more aggressive treatment to prevent progressive scarring and permanent lung damage is usually required.[18,20]

To estimate and follow the degree of pulmonary impairment, pulmonary function tests and diffusion capacity for carbon monoxide are measured. To limit radiation exposure, frequent computed tomography (CT) examinations are not recommended. A biopsy is frequently required to understand the pathology. In CVID, the pathology distribution in the lungs is patchy transbronchial lung biopsy may be inadequate. To avoid sampling errors, video-assisted thoracoscopic surgery or open lung biopsy should be considered.[20] To characterize predominate cellular infiltrate and lung damage, staining for CD3+ T cells and CD19+/CD20+ B cells is required, and additional stains for malignancy and microorganisms should be performed.[20]

**Bronchiectasis**

Bronchiectasis is an abnormal and irreversible dilatation of the bronchi that occurs as an outcome of airway injury. Repeated infections, bacterial colonization, and inflammation occur as a result of poor mucus clearance. Etiology may be cystic fibrosis, post-infectious, chronic obstructive pulmonary disease (COPD), asthma in the case of allergic bronchopulmonary aspergillosis, congenital, autoimmune, secondary to tumors, or various other undetermined conditions and immunodeficiency.[21] A retrospective study from a university hospital in France reported that of 245 adult patients with non-cystic fibrosis bronchiectasis, the underlying reason for bronchiectasis was immunodeficiency in 6%.[21]

A study from the European Chest CT Group, from 15 centers in 9 countries, included 282 patients with PAD.[22] Diagnosis was CVID in 232 (82%) patients of whom 80% had a radiological abnormality in the respiratory system. Bronchiectasis was the most common abnormality (61%), followed by bronchial wall thickening (44%), atelectasis (33%), and mucus plugging (29%). Both the frequency and intensity of bronchiectasis increased with age, with a prevalence of 79% at over 60 years of age.[22] Presence of bronchial wall pathology and bronchiectasis were associated with decreased pulmonary functions; however, normal pulmonary functions, measured as FEV1 > 80% predicted, could not exclude the diagnosis of bronchiectasis; therefore, spirometry was not a good predictor for presence (48.9 % sensitivity) or absence of bronchiectasis (68.8% specificity).[22]

A prospective study including 302 patients with PAD reported that over a 5-year follow-up period, despite IVIG therapy, there was an increase in the prevalence of bronchiectasis from 47.3% to 53.7% in CVID patients.[23]

A 3-year, double-blind, placebo-controlled randomized trial of prophylaxis with low-dose azithromycin 250 mg once a day, 3 times a week for 2 years, reported a reduction in annual respiratory exacerbations, decrease in the use of antibiotics, reduced risk of hospitalization, and improved quality of life.[24] The authors conclude that adding low-dose azithromycin to manage patients with respiratory exacerbations should be considered a valuable option in PADs.[24] However, a possible beneficial effect on the development and/or progression of bronchiectasis is unknown.

**Interstitial Lung Disease in CVID**

Although any type of interstitial lung disease (ILD) might be seen in CVID, granulomatous lymphocytic interstitial lung disease (GLILD) is the most commonly seen, the most investigated, and the one with the poorest clinical outcome.[16] British Lung Foundation/UKPID Network defined GLILD as; "a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded."[25] GLILD is a systemic disease with adenopathies, splenomegaly, and granulomatous involvement of the liver, lymph nodes, and bone marrow.[5]

There are still many questions regarding the pathogenesis, diagnosis, and management of GLILD. The available evidence is based on case reports and small case series.[26] A European Respiratory Society Clinical Research Collaboration named eGLILDnet was recently announced to address CVID-ILD/GLILD. They plan to organize a professional network to establish a virtual multidisciplinary team for expert discussion of individual cases.[26]

Patients may be asymptomatic; therefore, diagnosis requires a high index of suspicion. Thin slice (<2 mm) CT of the thorax is essential in the diagnostic workup. Coexistence of different histopathological entities, such as lymphocytic interstitial pneumonitis, follicular bronchiolitis, non-necrotizing granuloma, organizing pneumonia, and interstitial fibrosis, account for the heterogeneous appearance of GLILD on CT.[27] Generalized diffuse reticular pattern predominantly involving the lower lung zone was reported in 80%, and large ill-defined bronchocentric nodules or small randomly distributed nodules were found in 50% of the patients with GLILD.[28] Figure 3 shows the CT of a patient with CVID and GLILD.

Patients with CVID have an increased risk of developing lymphoma; therefore, the presence of lymphadenopathy makes diagnosis more complicated and warrants lymph node biopsy even in histologically confirmed cases of GLILD. Flexible bronchoscopy with bronchoalveolar lavage (BAL) is performed to exclude infection, and the specimens should be investigated for microscopy, and bacterial, mycobacterial, and fungal cultures should be performed.[25] Pulmonary function test results show a restrictive defect with reduced diffusion capacity for carbon monoxide. A biopsy is essential to identify pathology for the diagnosis and treatment decisions. The typical finding on histopathology is granulomatous inflammation, peribronchiolar and interstitial lymphoid proliferation, and predominance of CD4 cells.[25] Differential diagnosis includes infection, lymphocytic interstitial pneumonia of any cause, organizing pneumonia, and sarcoidosis. It is important to differentiate between sarcoidosis and CVID. In sarcoidosis, recurrent infections are rare, and hepatosplenomegaly is rare and usually asymptomatic. In sarcoidosis, immunoglobulin levels are elevated, and there is polyclonal hyperglobulinemia and upper lung zone involvement. In contrast, in GLILD the nodules are larger, there is lower lung zone dominance, and prominent hilar adenopathy is not typical, hepatosplenomegaly is common, which may progress to cirrhosis and hypersplenism.[17] In 1 paper, 2 of 16 patients were diagnosed and

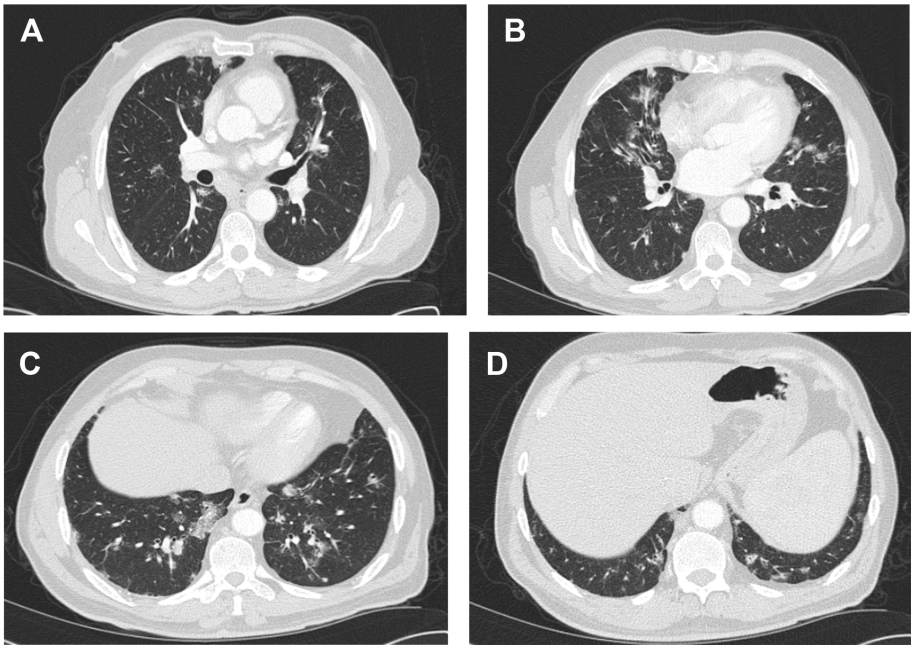


**Figure 3.** A 55-year-old male patient has experienced recurrent sinopulmonary infections for 5 years. CT revealed peribronchovascular ground-glass opacities and dilatation of the bronchi in these opacities on both lung fields, and opacities are predominantly on lower lung zones. The patient was diagnosed with CVID, and CT findings were consistent with GLILD.

**Table 2.** British Lung Foundation/United Kingdom Primary Immunodeficiency Network consensus statement on the Definition, Diagnosis, and Management of GLILD (Adapted from Reference 25)

| | **Consensus** |
|---|---|
| Essential tests in the workup of suspected GLILD | CT thorax<br>Spirometry<br>Lung volumes<br>Gas transfer<br>Flexible bronchoscopy to exclude infection (with BAL)<br>Surgical lung biopsy |
| Diagnostic testing of BAL fluid from suspected GLILD | Microscopy and culture<br>Mycobacterial culture<br>Fungal culture |
| Differential diagnosis on radiology | Infection<br>Organizing pneumonia<br>Lymphoid interstitial pneumonia<br>Sarcoidosis<br>Lymphoma |
| Differential diagnosis on histopathology | Infection<br>Organizing pneumonia<br>Lymphoid interstitial pneumonia<br>Sarcoidosis |
| Treatment decision | Symptomatic with abnormal and deteriorating lung function<br>Asymptomatic with abnormal and deteriorating lung function<br>Symptomatic with normal but deteriorating lung function<br>Not treat if asymptomatic with normal and stable lung function |
| First-line therapy for GLILD | Corticosteroids |
| Second-line therapy | Azathioprine<br>Rituximab<br>Mycophenolate |

GLILD, granulomatous lymphocytic interstitial lung disease; BAL, bronchoalveolar lavage.

treated for sarcoidosis before the demonstration of hypogammaglobulinemia and CVID.[28] To avoid missing the diagnosis of PID and adverse consequences of immunosuppressive treatment, the measurement of serum immunoglobulins in suspected sarcoidosis cases is recommended.[26,28]

Of the 29 sporadic CVID patients identified in Oxford Primary Immune Deficiencies Database, ILD was identified in 19 (65%); however, almost 1 in every 4 patients do not have any symptoms of ILD, emphasizing the importance of performing a thin slice CT or high-resolution computed tomography at the time of diagnosis.[29] There were no well-formed granulomas on lung biopsy (most were in other anatomical sites), and the authors concluded that there was more than 1 pathological process suggesting different possible etiologies, and based on CT findings performing a biopsy is essential.[29]

Management of GLILD should be multidisciplinary and include immunologists, chest physicians, radiologists, and pathologists. Immunoglobulin therapy, either subcutaneous or intravenous, should be optimized; however, there is no consensus on the routine use of antibiotic prophylaxis.[25] A summary of the British Lung Foundation/UKPID Network consensus statement on the definition, diagnosis, and management of GLILD is given in Table 2.

**Immunodeficiency in Asthma and COPD**

Asthma is a heterogeneous disease that has many different endotypes. Defects in epithelial barrier function, in the interferon and toll-like receptor response as well as CVID, sIgA deficiency, and hyper-IgE syndrome have all been reported to be associated with asthma; however, it is still not clear if the reported immune defects are involved in the pathogenesis of asthma, or if asthma develops as a consequence of the PID and repeated respiratory tract infections.[30]

Among US patients with CVID, asthma (33-47%), not bronchiectasis (15%) was the most common respiratory complication, and eventually irreversible obstructive disease as COPD or asthma COPD overlap may develop.[31] Of the 2866 Korean adult asthmatic patients, 157 (5.49%) was reported to have PID presenting with recurrent respiratory tract infections and had lower levels of IgG, A, M, and/or IgG subclass.[32] In this study, there was a 1.7 times higher relative risk of asthma exacerbation, and the prevalence of severe asthma was higher in the PID group (32.48% vs. 13%). To prevent asthma exacerbations, 25 patients received immunoglobulin replacement therapy.[32] The authors conclude that early diagnosis and management of PID, including immunoglobulin replacement is critical for adult patients with recurrent asthma exacerbations and severe asthma symptoms.[32]

A population-based case–control study in 2013 included 39 patients, 26 with sIgA deficiency and 13 with CVID.[33] Each patient was compared with 4 age and sex-matched controls to analyze if there was an association between history of asthma and diagnosis of sIgA deficiency or CVID.[33] Authors concluded that a current history of asthma or a history of ever having asthma was associated with an increased risk of sIgA

deficiency, or CVID compared with those without such histories (OR: 2.46-4.98).[33]

A study that investigated the relationship between risk of COPD exacerbations and hospitalizations, and serum total IgG levels, analyzed the data of 2 large cohorts (MACRO and STATCOPE). The derivation cohort was selected from MACRO, and the validation cohort was sampled from STATCOPE.[34] Results of the study showed that total IgG deficiency was relatively common among patients with COPD (a quarter of patients with moderate to severe COPD) and that reduced total IgG levels were found to be associated with increased risk of exacerbations and hospitalizations with the greatest risk when levels were below 7.0 g/L.[34] In another study, the same authors investigated the prevalence of IgG subclass deficiency and its association with exacerbations and hospitalizations in COPD, using subjects from MACRO and STATCOPE cohorts.[35] One or more IgG subclass deficiencies were found in 17.7% of MACRO and 20.4% of STATCOPE cohorts related to increased risk of exacerbations and hospitalizations.[35] Further studies are needed that investigate the possible role of immunoglobulin replacement therapy in high-risk COPD patients.

## CONCLUSION

There are both infectious and non-infectious pulmonary complications of PIDs. It is important to prevent complications related to repeated infections, and when present, to prevent progression. Awareness, timely diagnosis, and management of non-infectious pulmonary complications are vital because those complications are related to mortality and considerable morbidity. There may be underlying immunodeficiency in common diseases, such as COPD and asthma; especially if the disease is more severe and with recurrent exacerbations and/or hospitalizations. Physicians who are treating patients with lung disease should always keep in mind that any patient with severe, unusual, or recurrent infections, bronchiectasis, ILD, particularly granulomatous, should be investigated for primary immunodeficiency.

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