

## Review Article

# Pulmonary Manifestations of Primary Humoral Deficiencies

Ana Casal <sup>1</sup>, Vanessa Riveiro,<sup>1</sup> Juan Suárez-Antelo,<sup>1</sup> Lucía Ferreiro,<sup>1,2</sup>  
Nuria Rodríguez-Núñez,<sup>1</sup> Adriana Lama,<sup>1</sup> María Elena Toubes,<sup>1</sup> and Luis Valdés<sup>1,2,3</sup>

<sup>1</sup>Pneumology Department, Hospital Clínico Universitario, Santiago de Compostela, Spain

<sup>2</sup>Pneumology Interdisciplinary Research Group, Santiago de Compostela Health Research Institute (IDIS), Santiago de Compostela, Spain

<sup>3</sup>University of Santiago de Compostela, Santiago de Compostela, Spain

Correspondence should be addressed to Ana Casal; [ana.casal.mourino@sergas.es](mailto:ana.casal.mourino@sergas.es)

Received 12 February 2022; Revised 16 March 2022; Accepted 25 March 2022; Published 10 April 2022

Academic Editor: Jack Kastelik

Copyright © 2022 Ana Casal et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Primary immunodeficiencies are a group of conditions characterized by developmental or functional alterations in the immune system caused by hereditary genetic defects. Primary immunodeficiencies may affect either the innate or the adaptive (humoral and cellular) immune system. Pulmonary complications in primary humoral deficiencies are frequent and varied and are associated with high morbidity and mortality rates. The types of complications include bronchiectasis secondary to recurrent respiratory infections and interstitial pulmonary involvement, which can be associated with autoimmune cytopenias, lymphoproliferation, and a range of immunological manifestations. Early detection is key to timely management. Immunoglobulin replacement therapy reduces the severity of disease, the frequency of exacerbations, and hospital admissions in some primary humoral deficiencies. Therefore, the presence of pulmonary disease with concomitant infectious and/or autoimmune complications should raise suspicion of primary humoral deficiencies and warrants a request for immunoglobulin determination in blood. Once diagnosis is confirmed; early immunoglobulin replacement therapy will improve the course of the disease. Further studies are needed to better understand the pathogenesis of pulmonary disease related to primary humoral deficiencies and favor the development of targeted therapies that improve the prognosis of patients.

## 1. Generalities about Primary Immunodeficiencies

Primary immunodeficiencies (PIDs) are caused by a deficient development or function of the immune system secondary to an often hereditary genetic defect. PIDs affect the innate as well as the adaptive (humoral and cellular) immune system. In general terms, PIDs and, above all, primary humoral deficiencies (PHDs), are associated with a higher risk for infections, autoimmune diseases, and neoplasms; therefore, early diagnosis is crucial. PIDs comprise more than 250 syndromes, of which, only a group is clinically relevant. Table 1 details the most frequent PIDs.

Immunoglobulins (Ig) play a key role in protecting the lungs from infections, with predominance of a range of specific isotypes in the different parts of the airways [1]. At the level of the airways, the most frequent Igs are IgA and

IgM, whereas IgG is more commonly found in the alveolar space [2]. IgA prevents bacterial adhesion and neutralizes toxins, whereas IgM activates the complement system, which allows the opsonization of pathogens. In turn, IgG (originated from the systemic circulation) enters the airways through passive diffusion and provides protection against infections, such as pneumonia [3]. In most patients with PHDs, systemic IgG and local IgA are absent or dysfunctional, and serum IgA compensates, at least partially, IgG deficiency in the airways.

*1.1. Physiopathological Mechanisms of Primary Humoral Deficiencies.* The development of PHDs is mediated by a range of physiopathological mechanisms. Some PHDs are caused by developmental defects in memory B cells result in the loss of Igs production [*i.e.*: X-linked agammaglobulinemia

TABLE 1: Most common primary immunodeficiencies and type of associated immune defect.

Primary immunodeficiencies	Type of immunity affected
Selective IgA deficiency	Humoral immunity
Common variable immunodeficiency	Humoral immunity
Immunoglobulin subclass deficiency	Humoral immunity
X-linked agammaglobulinemia	Humoral immunity
Hyper-IgM syndrome.	Humoral immunity
DiGeorge syndrome	Cellular immunity
Severe combined immunodeficiency	Humoral and cellular immunity
Wiskott–Aldrich syndrome	Humoral and cellular immunity
Complement alteration	Innate immunity
Phagocyte dysfunction	Innate immunity
Alteration in pattern recognition receptors	Innate immunity

(XLA)]. Other patients produce Igs but at low trough levels, which compromises protection against infections [*i.e.*: *common variable immunodeficiency (CVID)*]. In some cases, patients produce normal IgM values but are unable to perform class-switch recombination (*i.e.*: *hyper-IgM syndrome*). Other patients do not produce IgG subclasses (*i.e.*: *IgG-subclass deficiency*). Finally, other subjects do not develop Ig specific enough to neutralize a specific pathogen (*i.e.*: *specific antibody deficiency*) [4].

## 2. Pulmonary Complications Associated with Primary Humoral Deficiencies

Lung disease is a frequent complication of PHDs, with high morbidity and mortality rates. The range of clinical manifestations is broad, including acute and chronic infectious processes, structural abnormalities, and malignancies (Table 2). The chronic lung diseases most commonly associated with PHDs are bronchiectasis and interstitial lung disease (ILD). Whereas bronchiectasis result from recurrent respiratory tract infections, susceptibility to ILD is determined by multiple factors and can be induced by processes such as cytopenias, autoimmune diseases, lymphoproliferative syndromes, and/or immune dysregulation.

**2.1. Respiratory Infections.** The main clinical implication of PHDs are recurrent bacterial infections in the upper and lower airways [5]. There is a high risk for recurrent pneumonia, which has been reported in 75–84% of patients with CVID [6]. The most frequent causative agents include encapsulated bacteria (*Haemophilus influenzae* or *Streptococcus pneumoniae*). Recurrence and rare complications such as pneumatoceles and cavitation should raise suspicion of an underlying immunodeficiency. Early diagnosis and management with prophylactic antibiotics and Ig replacement therapy reduce the frequency of infections and their long-term effects (chronic airflow obstruction, atelectasis, and bronchiectasis, to name a few) [7].

**2.2. Bronchiectasis.** Bronchiectasis is the most frequent chronic airway disease associated with PHDs, and it is reported in 30–60% of patients with CVID [8]. This condition is also common in IgG subclass deficiency, especially when associated with IgA deficiency. PHDs increase the frequency

of pulmonary infections that characterize bronchiectasis. Bronchiectasis derives from long-standing active inflammation resulting from recurrent infections, which causes irreversible dilatation of the bronchial airways and perpetuates respiratory tract infections (Cole's vicious circle) [9]. A similar vicious circle may occur in chronic sinusitis. Immune defects are considered relevant factors in the development of bronchiectasis.

As stated before, milder forms of PHDs (lower levels of IgA or IgM) are also associated with bronchiectasis, which potentially may progress. For this reason, IGRT should be considered to minimize chronic respiratory complications and improve prognosis [10].

Patients usually develop dyspnea, prolonged cough, purulent sputum, and, occasionally, hemoptysis. At functional level, variable airflow obstruction, which can be progressive, is observed [11]. Diagnosis is typically based on computed tomography (CT), as chest radiographs can be inadequate. In this line, a recent study found that cough was more associated with bronchiectasis on CT than airflow spirometry obstruction in PHDs patients [12]. Furthermore, colonization of the airways can worsen the course of disease. Screening for sputum colonization is useful for selecting antibiotic therapy and is of vital importance to limit resistance associated with macrolide therapy [13].

Therefore, early diagnosis and treatment are crucial to prevent the deleterious effects of PHDs on the lungs. A gold-standard therapy for adult non-cystic fibrosis (CF) bronchiectasis is not available and is usually extrapolated from CF trials. Physiotherapy is considered a standard therapy, but there are no guidelines defining the best approach. Azithromycin, apart from its antibacterial power, is known to have immunomodulatory effects in chronic lung disorders. Its use has been suggested for its interesting impact on respiratory exacerbations [14]. Despite all this, some patients, however, will still develop bronchiectasis even after Ig replacement therapy and/or associated antibiotic treatment.

**2.3. Interstitial Lung Disease (ILD).** ILD in patients with PHDs has a distinctive clinical and immunological profile that does not necessarily involve the presence of bronchiectasis. Around 10–20% of patients with CVID develop ILD. ILD appears far less common in other forms of PIDs. The etiology of this disease may be related to infections (human

TABLE 2: Pulmonary complications associated with primary immunodeficiencies.

PIDs group	Frequency	Pulmonary complication	Infectious	Example of PIDs	Other
Humoral immunity	50–60%	Recurrent pneumonia		Airway disease	CVID
		Infections by encapsulated or atypical pathogens		(bronchiectasis or asthma) ILD (LIP, COP, GLILD)	IgA deficiency XLA
Cellular immunity	5–10%	Recurrent pulmonary infections		Airway disease	Wiskott–Aldrich
		( <i>Pseudomonas</i> , <i>Pneumocystis jiroveci</i> , CMV, <i>Aspergillus</i> ...)		(bronchiectasis, BO) Malignancy (lymphoma)	DiGeorge
Combined ID (humoral + cellular)	20%	Opportunistic infections in childhood (CMV, <i>P. jiroveci</i> , <i>Microbacteria</i> ...)		ILD	SCID
				Malignancy (lymphoma, leukemia)	Ataxia telangiectasia
Phagocyte disorders	10–15%	Recurrent pulmonary infections ( <i>S. aureus</i> , <i>Klebsiella</i> , <i>Serratia</i> , <i>Nocardia</i> , <i>Aspergillus</i> ...)		Autoimmune disease	
		Necrotizing pneumonia		Antiphospholipid syndrome	CGD
		Pulmonary abscess Empyema		ILD (granulomatosis)	Chédiak–Higashi
Complement deficiency	2%	Infections by encapsulated pathogens ( <i>S. Pneumoniae</i> , <i>H. Influenzae</i> , <i>N. Meningitidis</i> )		Autoimmune disease (vasculitis, SLE)	Complement deficiency

CGD, chronic granulomatous disease; CMV, cytomegalovirus; COP, Cryptogenic organizing pneumonia; CVID, common variable immunodeficiency; GLILD, granulomatous-lymphocytic interstitial lung disease; ID, immunodeficiency; ILD, diffuse interstitial lung disease; LIP, lymphoid interstitial pneumonia; OB, obliterative bronchiolitis; PIDs, primary immunodeficiency; SCID, severe combined immunodeficiency; SLE, Systemic lupus erythematosus; XLA, X-linked agammaglobulinemia.

herpes virus 8 or Epstein–Barr virus) or to an underlying immune dysregulation. Differentiating ILD from other forms of chronic lung disease on the basis of the clinical history alone can be challenging, as its most common symptoms are nonspecific. Physical examination may be useful, with crackles being more suggestive of ILD and wheezing being more likely to be with a sign of obstructive disease. The most frequent radiological findings include the presence of pulmonary nodules, ground-glass opacities, and hilomediastinal adenopathies [11]. Diagnosis is based on histological results that exclude other causes (primarily a malignancy such as lymphoma). The range of histological forms of interstitial is broad, being the most common organizing pneumonia, lymphoid interstitial pneumonia, follicular bronchiolitis, or granulomatous disease. Histological patterns may overlap and are not correlated with a particular immune deficiency. Moreover, many types of PHDs are associated with an increased risk for systemic autoimmune disorders that may involve respiratory interstitial tissue (as connective tissue diseases or vasculitis) [4].

Timing treatment for ILD is challenging. It is imperative that immunoglobulin replacement therapy is optimized in patients with ILD. The reason is that ILD may stabilize with this intervention in a subset of patients. A reasonable option in patients with mild to moderate ILD symptoms is inhaled corticosteroids (with or without long-acting beta agonists) and/or prophylactic azithromycin, as these therapies have been shown efficacious in follicular bronchiolitis [15]. Systemic corticosteroid treatment and/or immunomodulators may also be effective.

**2.4. Granulomatosis.** The presence of non-necrotizing granuloma in a lung tissue specimen is nonspecific and may be associated with infections or other types of processes (drugs, interstitial disease, to name a few). Up to 25% of patients with CVID develop non-necrotizing granuloma as a

manifestation of granulomatous-lymphocytic interstitial lung disease (GLILD). This occasionally leads to misdiagnosis of sarcoidosis due to their radiological and histological similarities (Table 3). Therefore, serum Ig determination is recommended in all patients with a recent diagnosis of sarcoidosis. Some authors consider GLILD as a pulmonary manifestation of a systemic syndrome associated with autoimmune cytopenias, splenomegaly, enteritis, and lymphadenopathies [16]. Definitive diagnosis requires histological confirmation by a surgical lung biopsy. Treatment involves high doses of corticosteroids, although the disease may progress despite optimal treatment [17]. There is limited evidence demonstrating that the use of rituximab associated with azathioprine may improve lung function and/or radiological findings in patients with GLILD [18, 19].

**2.5. Obliterative Bronchiolitis.** As previously mentioned, long-standing inflammation resulting from recurrent respiratory tract infections may induce a progressive narrowing of the bronchial lumen, thereby causing obliterative bronchiolitis. This may also occur in rheumatological diseases frequently associated with PHDs. The presence of disproportionate chronic airflow obstruction for the degree of bronchiectasis, reduced DLCO, and/or oxygen desaturation with exertion in a patient with immunodeficiency are suggestive of obliterative bronchiolitis [20].

**2.6. Respiratory Amyloidosis.** Amyloidosis is characterized by extracellular deposition of insoluble misfolded proteins that aggregate in tissues and cause organ dysfunction [21]. There are multiple forms of amyloidosis, and diagnosis requires histological confirmation. Light chain amyloidosis (AL) most frequently affects the lungs, and it may affect any of its structures. Respiratory complications are less frequent

TABLE 3: Differential characteristics of GLILD vs sarcoidosis.

Characteristics:		GLILD - CVID	Sarcoidosis
Laboratory analysis	Immunoglobulin values	IgG + IgA ± IgM	—
	Autoimmune cytopenias	Autoimmune hemolytic anemia Autoimmune thrombocytopenic purpura	—
Clinical signs		Splenomegaly	—
		Recurrent infections	—
Associated ILD		Lymphoid interstitial pneumonia	—
		Follicular bronchiolitis	—
BF	CD4/CD8 ratio	Low	High (CD4/CD8: >3,5)
	Site predominance	Lower	Upper
HRCT	Nodules	>1 cm	<1 cm
	Enlarged hilomediastinal lymph nodes	Random distribution	Perilymphatic
	Bronchiectasis	Frequent	Frequent
Treatment		Frequent	—
		Immunosuppression (corticoids ± azathioprine/mycophenolate/ rituximab)	Immunosuppression (corticoids ± methotrexate vs other immunosuppressants)
Prognosis		Immunoglobulin replacement	—
		Poor prognosis	Good prognosis Possibility of spontaneous remission

BAL, bronchoalveolar lavage; CVID, common variable immunodeficiency; GLILD, granulomatous-lymphocytic interstitial lung disease; HRCT, high-resolution computerized tomography; ILD, interstitial lung diseases.

in other forms of amyloidosis, such as serum amyloidosis (SAA) [22]. Systemic amyloidosis does not only affect the lungs (parenchyma, adenopathies, and pleura), but it may also involve other organs, such as the kidneys and/or the heart. In contrast, localized amyloidosis only affects the respiratory tract (nodules, cysts, and ILD).

Tracheobronchial amyloidosis accounts for 1.1% of cases [23], presents in patients older than 60 years, shows no gender-based differences, and may appear in systemic forms of amyloidosis [24]. Associated chronic airflow obstruction may lead to misdiagnosis of asthma or chronic obstructive pulmonary disease. Findings on chest CT scan include a narrowing of the bronchial lumen, atelectasis, and/or bronchiectasis [25]. Definitive diagnosis requires histological confirmation. Prognosis is poor and depends on the frequency of respiratory tract infections and progressive airflow obstruction.

Nodular and cystic amyloidosis accounts for 44–58% of all respiratory forms and usually appears in patients in their sixties, being more frequent in male subjects (men:women, 3:2) [26]. More than half the patients suffer from a related connective tissue disease (prevalingly Sjögren's disease). Pulmonary nodules may be multiple, have different shapes and sizes, and are associated with cysts in up to 81% of cases [27].

Interstitial amyloidosis is generally secondary to an underlying disease (lymphoproliferative or connective tissue disease) and may be constrained to the lung (rarely) or be associated with systemic amyloidosis (predominant form). Specific radiological findings include irregular linear opacities, thickening of interlobular septae, honeycombing, bronchiectasis, nodules, cysts, and growth of hilomediastinal lymph nodes.

Pulmonary vascular amyloidosis is usually associated with systemic amyloidosis involving the heart. In most cases, patients remain asymptomatic, although cases of

hemoptiysis, hemothorax, and other hemorrhagic diatheses have been reported [28].

Finally, pleural amyloidosis is a rare form of respiratory amyloidosis and accounts for 5–10% of respiratory forms, being exclusive of AL forms. The resulting pleural effusion is a transudate, an exudate or a chylothorax. It has a poor prognosis and has a median survival of 1.6 months, which decreases with heart involvement [29].

**2.7. IgG4-Related Pulmonary Disease.** IgG4-related lung disease (IgG4-RD) is a chronic fibroinflammatory disorder characterized by lymphoplasmacytic infiltrates, tissue fibrosis, and elevated plasma IgG4 levels [30]. IgG4-RD may present as a solitary lesion (20% of cases) or affect multiple organs (with synchronous or metachronous involvement of two or more extrapulmonary organs). Manifestations of the systemic form include a weight loss of 5–10 kg, pancreatitis, sialadenitis, lymphadenopathy, retroperitoneal/periaortic fibrosis, and/or tubulointerstitial nephropathy, among others [31]. Definitive diagnosis requires histological confirmation. Both, symptomatic and asymptomatic forms require treatment to prevent their potentially irreversible effects. Management involves long-term corticosteroid therapy (maintenance treatment for 1 to 3 years) combined or not with immunosuppressive therapy with corticosteroid-sparing drugs (mycophenolate mofetil, azathioprine, methotrexate, and/or rituximab) [32, 33]. IgG4-RD has an uncertain diagnosis, and relapse is associated with elevated levels of IgG4, IgE and eosinophils [34].

**2.8. Malignant Diseases Involving the Lung.** Neoplastic disorders are a major cause of death in patients with PHDs. CVID patients are at an increased risk of gastric carcinoma and lymphoma [35]. PHDs patients may develop different



types of lymphoid lung lesions (B-cell and non-Hodgkin and Hodgkin lymphoma). These should be considered in differential diagnosis of GLILD [36]. Lung metastases or primary carcinoma have also been reported in PHDs [37].

### 3. Types of Primary Humoral Deficiencies

**3.1. Selective IgA Deficiency.** Selective IgA deficiency (SIgAD) is the most frequent PHDs, with an estimated prevalence of 1:600 in North America and Europe [38]. Diagnosis is based on serum levels of IgA <7 mg/dL and normal levels of IgG and IgM. SIgAD is caused by a defect in B-cell maturation. Two out of three patients with SIgAD remain asymptomatic, whereas the remainder will develop recurrent bacterial infections, autoimmune diseases, gastrointestinal problems, and/or atopy [39]. The fact that most patients remain asymptomatic suggests the presence of IgA compensatory mechanisms at the level of the local mucosa. Additionally, it is known that symptomatic patients may also present IgG subclass deficiency (primarily IgG2), which is associated with the presence of bronchiectasis [40]. Likewise, there is evidence of a higher frequency of SIgAD in families with a member suffering from CVID, which suggests a relationship between the two conditions or even a potential progression of SIgAD into CVID [41].

**3.2. Common Variable Immunodeficiency.** The estimated prevalence of CVID ranges from 1:25,000 to 1:50,000, without gender-based differences, and onset generally occurs between the age of 20 and 40 years [42]. CVID is characterized by a reduction in IgG and IgA production, associated or not with IgM, which results in low responsiveness to polysaccharide vaccines. The diagnostic criteria for CVID of the *European Society of Immunodeficiency* are described in Table 4 [43]. Although the molecular etiology of CVID is unclear, 10–25% of cases have an autosomal dominant inheritance pattern. CVID is associated with recurrent infections (prevalingly sinopulmonary infection by encapsulated and atypical bacteria), autoimmune diseases (hemolytic anemia, thrombocytopenic purpura, thyroiditis, and rheumatoid arthritis), GLILD, splenomegaly, gastrointestinal problems, or even malignant diseases (non-Hodgkin lymphoma and gastric cancer). Multiorgan involvement is frequent [44]. Due to the multiple forms of presentation of the disease, delayed diagnosis is frequent.

**3.3. Immunoglobulin Subclass Deficiency.** As mentioned above, IgG is the most abundant antibody in the systemic circulation, with 4 subclasses distinguished by structural and functional differences, known as isotypes. Manifestations of Igs subclass deficiency include reduced levels of some IgG isotype and normal levels of IgA and IgM (in two determinations separated by at least one month, during a period free of symptoms) [5]. IgG2 deficiency is more frequent in childhood, and IgG4 is found in 8% of the Caucasian population. Igs subclass deficiency may co-occur with SIgAD, which explains the appearance of autoimmune diseases or asthma. Patients with IgG1 and IgG2 may have

poor response to polysaccharide vaccines and are more prone to airway infections by encapsulated pathogens (*Streptococcus pneumoniae* and *Haemophilus influenzae*).

**3.4. Hyper-IgM Syndrome.** Hyper-IgM syndrome embraces a group of disorders characterized by normal or elevated levels of IgM and reduced levels of IgG and IgA [45]. The most frequent form of hyper-IgM syndrome (accounting for 70% of all cases) is X-linked hyper-IgM, where T cells lack functional CD40 ligand and cannot signal B cells to switch [46]. This defect predisposes the patient to bacterial respiratory infections and other infections caused by pathogens less frequently associated with humoral immunodeficiencies, such as *Pneumocystis*. This condition is also associated with a higher risk for gastrointestinal infections and autoimmune diseases [47].

**3.5. Other Rare Primary Immunodeficiencies.** Table 5 describes other rare primary immunodeficiencies (humoral and others) and their main characteristics.

### 4. Diagnosis of Primary Humoral Deficiencies

Although the mechanisms of immunodeficiencies are well known, delayed diagnosis is frequent, especially when onset occurs in adulthood. The Immune Deficiency Foundation and the American Academy of Allergy, Asthma and Immunology provide guidelines and establish diagnostic criteria for the appropriate identification of the different syndromes [48, 49]. The first (and most important) step for correct diagnosis is to maintain a high level of suspicion in patients with recurrent infections. In the presence of recurrent infections, respiratory exacerbations, or bronchorrhea, screening, including Ig determination (IgG, IgM and IgA), is recommended. Reduced levels of IgG are suggestive of a primary immunodeficiency. Figure 1 shows a diagnostic algorithm [50]. It is worth mentioning that normal IgG levels in a patient with recurrent infections does not exclude a diagnosis of PHD, and IgG subclasses and responsiveness to immunization should be assessed.

### 5. Treatment of Primary Humoral Deficiencies

The management of PHDs requires a multidimensional approach. Thus, management includes general measures such as immunization (influenza and pneumococcus), appropriate treatment of infectious complications (appropriate antimicrobial dosage and antibiotic prophylaxis), or immunosuppression (in GLILD), bronchodilators (in case of airway involvement), or hematopoietic stem cell transplantation, where indicated (in combined immunodeficiencies) [5].

The timing of initiation of Ig replacement therapy is controversial. In general terms, the initiation of treatment should be considered in patients with  $\geq 2$  hospital admissions in one year or  $\geq 3$  recurrent infections managed in ambulatory care. A laboratory analysis should be requested including a hemogram and biochemistry with markers of

TABLE 4: Diagnostic criteria for common variable immunodeficiency (modified from Seidel et al.)[32].

Required criterion	Values < 2DS of IgG + IgA ± IgM (in 2 tests)
≥ 1 of subsequent tests	Increased susceptibility to infections
	Autoimmune manifestations
	Granulomatous disease
≥ 1 of subsequent tests	Unexplained polyclonal lymphoproliferation
	A member of the family suffers from humoral immunodeficiency
	Poor response to immunization (and/or absence of isoheamagglutinins)
Required criteria (all)	Low levels of memory B cells (<70% of the reference value for the age of the patient)
	Exclusion of secondary causes of hypogammaglobulinemia
	Minimum age ≥4 year to establish diagnosis
	Absence of notable T-lymphocytes deficiency

TABLE 5: Rare primary immunodeficiencies and their characteristics.

PIDs	Type of immunity affected	Characteristics
X-linked agammaglobulinemia	Humoral	85% of congenital agammaglobulinemias
		Caused by mutations in Bruton’s tyrosine kinase (BTK) located in the X chromosome
		Absence of BTK protein: Absence of B-cell differentiation and reduction of all Ig isotypes
Severe combined immunodeficiency	Humoral and cellular	Susceptibility to bacterial infections from 6 months of age
		Susceptibility to encapsulated bacteria and viruses
		Heterogeneous group of life-threatening PIDs with dramatic reduction of T and B lymphocytes ± NK cells
Wiskott-Aldrich syndrome	Humoral and cellular	Caused by a variety of genetic alterations (IL2RG, ADA, IL7R, RAG1, RAG2, JAK3. . .)
		Susceptibility to recurrent severe infections, chronic diarrhea, and failure to thrive
		Treatment includes prophylaxis/management of infections, Ig replacement, and hematopoietic stem cell transplantation
DiGeorge syndrome	Cellular	Hereditary X-linked disorder caused by WAS protein mutations
		Susceptibility to thrombocytopenia, bacterial/fungal/viral infections, eczema, autoimmune diseases and malignancy (lymphoma)
		Treatment includes prophylactic antibiotics, platelet transfusions, ig replacement, immunosuppressants, and hematopoietic stem cell transplantation
Complement alteration	Innate	Most frequent cause: 22q11.2 chromosome deletion
		Classic triad: Congenital heart disease, thymic hypoplasia and hypocalcemia
		Susceptibility to recurrent infections, autoimmunity, developmental delay, cleft palate and chronic inflammatory diseases
Alteration in pattern recognition receptors	Innate	Diagnosis: Low T-lymphocyte values CD3+ associated with typical manifestations and/or chromosome 22q11.2 deletion
		High number of complement alterations that may affect the classic (CH50) or alternative pathway (AH50)
		Susceptibility to infections by encapsulated pathogens

ADA, adenosine deaminase; BTK, Bruton’s tyrosine kinase; CLEC, C-type lectin; Ig, immunoglobulins; JAK3, Janus Kinase 3; NK, natural killer; NOD, nucleotide oligomerization domain; PIDs, primary immunodeficiency; RAG, recombination activating gene; RIG1, retinoic acid-inducible gene I; SLE, Systemic lupus erythematosus.

kidney and liver function, serologies for HIV, HBV, and HCV, and IgA determination (risk for anaphylaxis in the presence of IgA deficiency due to the potential presence of anti-IgA Ab) [11]. Treatment is generally intravenous

(monthly) or subcutaneous (weekly), and blood pressure should be monitored during first infusion. The starting dose is an intravenous dose of Ig (400–600 mg/kg/month) to maintain IgG values within the 500–800 mg/dL range. In

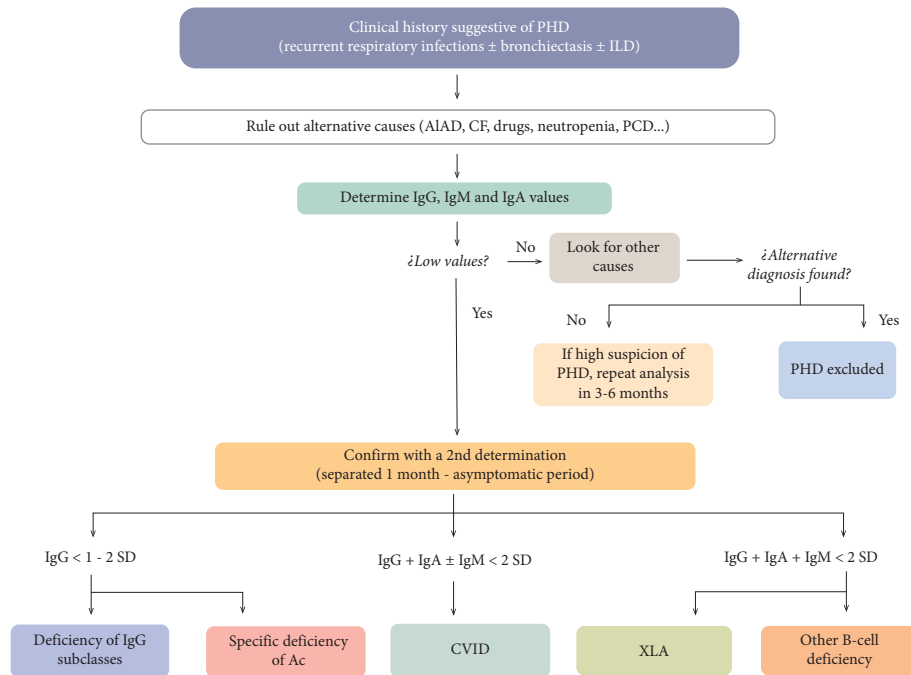


FIGURE 1: Diagnostic approach to primary humoral deficiencies in patients with respiratory symptoms (modified from Berger et al.) [50]. ALAD, alpha-1-antitrypsin deficiency; Ac, antibodies; CF, cystic fibrosis; CVID, common variable immunodeficiency; ILD, interstitial lung diseases; PCD, primary ciliary dyskinesia; PHD, primary humoral deficiency; SD, standard deviation; XLA, X-linked agammaglobulinemia.

some cases, it is necessary to increase the therapeutic target to 800–1000 mg/dL to achieve the intended effects [51]. During follow-up, the number of episodes of infection will determine the most appropriate dose [52].

Immunoglobulin replacement therapy reduces the progression of chronic airflow obstruction in patients with recurrent respiratory infections [51]. Immunoglobulin replacement therapy also improves pulmonary function (FEV<sub>1</sub> and FVC) in patients with respiratory disease, when the levels of serum IgG achieved exceed 500 mg/dL [53].

## 6. Monitoring Primary Humoral Deficiencies

Survival of patients with PHDs has improved in past few decades as a result of prompt diagnosis and adequate treatment [54]. Nevertheless, reducing the number of exacerbations is not always achieved [55]. There are no international guidelines that describe the appropriate monitoring approach for patients with lung involvement secondary to PHDs. It has been suggested that they should be evaluated (lung function, imaging studies, and laboratory tests) at least once every 6–12 months [55]. It has also been recommended to perform a thorax CT scan in treated patients with respiratory symptoms to monitor the potential progression of lung complications [56].

## 7. Conclusions

The range of respiratory manifestations of PHDs is broad, including infections and immunological disorders, which initially are reversible, but may ultimately cause chronic airflow obstruction. Therefore, early detection and management of an

underlying PHD in a patient with lung disease is crucial. IGRT reduces the severity and frequency of exacerbations and decreases hospital admissions and their associated costs, especially in some humoral immunodeficiencies. The presence of lung disease with associated infectious and/or autoimmune complications is strongly suggestive of PHD [57]. In this context, it is necessary to determine plasma Ig levels and, where appropriate, provide early Ig replacement therapy to improve patient prognosis [58].

## Abbreviations

AL:	Light chain (AL) amyloidosis
CF:	Cystic fibrosis
CT:	Computed tomography
CVID:	Common variable immunodeficiency
GLILD:	Granulomatous-lymphocytic interstitial lung disease
Ig:	Immunoglobulins
IgG4-RD:	IgG4-related disease
ILD:	Interstitial lung disease
PHDs:	Primary humoral deficiencies
PIDs:	Primary immunodeficiencies
SAA:	Serum amyloidosis
SIgAD:	Selective IgA deficiency.

## Conflicts of Interest

The authors declare no conflicts of interest associated with this publication. This project did not receive financial support that could have influenced its outcome.

## Authors' Contributions

Ana Casal contributed to conception and design, drafted the submitted article, and approved the final version. Vansessa Riveiro drafted the submitted article and approved the final version. Juan Suárez-Antelo revised the article critically and approved the final version. Lucía Ferreiro revised the article critically and approved of the final version. Nuria Rodríguez-Núñez revised the article critically and approved the final version. Adriana Lama revised the article critically and approved the final version. Malena Toubes revised the article critically and approved of the final version. Luis Valdés contributed to conception and design, drafted the submitted article, and approved of the final version.

## References

- [1] C. Pilette, Y. Ouadrhiri, V. Godding, J.-P. Vaerman, and Y. Sibille, "Lung mucosal immunity: immunoglobulin-A revisited," *European Respiratory Journal*, vol. 18, no. 3, pp. 571–588, 2001.
- [2] U. Baumann, K. Göcke, B. Gewecke, J. Freihost, and B. U. von Specht, "Assessment of pulmonary antibodies with induced sputum and bronchoalveolar lavage induced by nasal vaccination against *Pseudomonas aeruginosa*: a clinical phase I/II study," *Respiratory Research*, vol. 8, no. 1, p. 57, 2007.
- [3] H. L. Twigg, "Humoral immune defense (antibodies): recent advances," *Proceedings of the American Thoracic Society*, vol. 2, no. 5, pp. 417–421, 2005.
- [4] N. Verma, B. Grimbacher, and J. R. Hurst, "Lung disease in primary antibody deficiency," *The Lancet Respiratory Medicine*, vol. 3, pp. 651–660, 2015.
- [5] F. A. Bonilla, D. A. Khan, Z. K. Ballas et al., "Practice parameter for the diagnosis and management of primary immunodeficiency," *Journal of Allergy and Clinical Immunology*, vol. 136, no. 5, pp. 1186–1205, 2015.
- [6] J. S. Orange, W. J. Grossman, R. J. Navickis, and M. M. Wilkes, "Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies," *Clinical Immunology*, vol. 137, no. 1, pp. 21–30, 2010.
- [7] P. J. Busse, S. Razvi, and C. Cunningham-Rundles, "Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency," *Journal of Allergy and Clinical Immunology*, vol. 109, no. 6, pp. 1001–1004, 2002.
- [8] R. G. Obregon, D. A. Lynch, T. Kaske, J. D. Newell Jr., and C. H. Kirkpatrick, "Radiologic findings of adult primary immunodeficiency disorders," *Chest*, vol. 106, no. 2, pp. 490–495, 1994.
- [9] P. J. Cole, "Inflammation: a two-edged sword--the model of bronchiectasis," *European Journal of Respiratory Diseases. Supplement*, vol. 147, pp. 6–15, 1986.
- [10] D. A. van Kessel, H. van Velzen-Blad, J. M. van den Bosch, and G. T. Rijkers, "Impaired pneumococcal antibody response in bronchiectasis of unknown aetiology," *European Respiratory Journal*, vol. 25, no. 3, pp. 482–489, 2005.
- [11] P. J. Maglione, "Chronic lung disease in primary antibody deficiency," *Immunology and Allergy Clinics of North America*, vol. 40, no. 3, pp. 437–459, 2020.
- [12] K. Schütz, D. Alecsandru, D. Alecsandru et al., "Imaging of bronchial pathology in antibody deficiency: data from the European chest CT group," *Journal of Clinical Immunology*, vol. 39, no. 1, pp. 45–54, 2019.
- [13] M. Kipourou, K. Manika, A. Papavasileiou et al., "Immunomodulatory effect of macrolides: at what cost?" *Respiratory Medicine Case Reports*, vol. 17, pp. 44–46, 2016.
- [14] M. J. Parnham, V. E. Haber, E. J. Giamarellos-Bourboulis, G. Perletti, G. M. Verleden, and R. Vos, "Azithromycin: mechanisms of action and their relevance for clinical applications," *Pharmacology and Therapeutics*, vol. 143, no. 2, pp. 225–245, 2014.
- [15] M. R. Aerni, R. Vassallo, J. L. Myers, R. M. Lindell, and J. H. Ryu, "Follicular bronchiolitis in surgical lung biopsies: clinical implications in 12 patients," *Respiratory Medicine*, vol. 102, no. 2, pp. 307–312, 2008.
- [16] U. Baumann, J. M. Routes, P. Soler-Palacín, and S. Jolles, "The lung in primary immunodeficiencies: new concepts in infection and inflammation," *Frontiers in Immunology*, vol. 9, Article ID 1837, 2018.
- [17] J.-N. Boursiquot, L. Gerard, L. Gérard et al., "Granulomatous disease in COVID: retrospective analysis of clinical characteristics and treatment efficacy in a cohort of 59 patients," *Journal of Clinical Immunology*, vol. 33, no. 1, pp. 84–95, 2013.
- [18] P. J. Maglione, H. M. Ko, M. B. Beasley, J. A. Strauchen, and C. Cunningham-Rundles, "Tertiary lymphoid neogenesis is a component of pulmonary lymphoid hyperplasia in patients with common variable immunodeficiency," *Journal of Allergy and Clinical Immunology*, vol. 133, no. 2, pp. 535–542, 2014.
- [19] N. M. Chase, J. W. Verbsky, M. K. Hintermeyer et al., "Use of combination chemotherapy for treatment of granulomatous and lymphocytic interstitial lung disease (GLILD) in patients with common variable immunodeficiency (COVID)," *Journal of Clinical Immunology*, vol. 33, no. 1, pp. 30–39, 2013.
- [20] J. Kaufman and R. Komorowski, "Bronchiolitis obliterans organizing pneumonia in common variable immunodeficiency syndrome," *Chest*, vol. 100, no. 2, pp. 552–553, 1991.
- [21] G. Merlini and V. Bellotti, "Molecular mechanisms of amyloidosis," *New England Journal of Medicine*, vol. 349, no. 6, pp. 583–596, 2003.
- [22] C. Planes, D. Kleinknecht, M. Brauner, J. P. Battesti, J. L. Kemeny, and D. Valeyre, "Diffuse interstitial lung disease due to AA amyloidosis," *Thorax*, vol. 47, no. 4, pp. 323–324, 1992.
- [23] A. O'Regan, H. M. Fenlon, J. F. Beamis, M. P. Steele, M. Skinner, and J. L. Berk, "Tracheobronchial amyloidosis. The Boston University experience from 1984 to 1999," *Medicine (Baltimore)*, vol. 79, pp. 69–79, 2000.
- [24] B. Crestani, A. Monnier, M. Kambouchner, J. P. Battesti, P. Reynaud, and D. Valeyre, "Tracheobronchial amyloidosis with hilar lymphadenopathy associated with a serum monoclonal immunoglobulin," *European Respiratory Journal*, vol. 6, pp. 1569–1571, 1993.
- [25] L. Ding, W. Li, K. Wang et al., "Primary tracheobronchial amyloidosis in China: analysis of 64 cases and a review of literature," *Journal of Huazhong University of Science and Technology-Medical sciences*, vol. 30, no. 5, pp. 599–603, 2010.
- [26] A. Khor, J. L. Myers, H. D. Tazelaar, and P. J. Kurtin, "Amyloid-like pulmonary nodules, including localized light-chain deposition," *American Journal of Clinical Pathology*, vol. 121, no. 2, pp. 200–204, 2004.
- [27] R. A. Kyle and P. R. Greipp, "Amyloidosis (AL). Clinical and laboratory features in 229 cases," *Mayo Clinic Proceedings*, vol. 58, pp. 665–683, 1983.
- [28] S. Morgenthal, R. Bayer, E. Schneider et al., "Nodular pulmonary amyloidosis with spontaneous fatal blood aspiration," *Forensic Science International*, vol. 262, pp. e1–e4, 2016.



- [29] J. L. Berk, J. Keane, D. C. Seldin et al., "Persistent pleural effusions in primary systemic amyloidosis," *Chest*, vol. 124, no. 3, pp. 969–977, 2003.
- [30] F. Martínez-Valle, A. Fernández-Codina, I. Pinal-Fernández, O. Orozco-Gálvez, and M. Vilardell-Tarrés, "IgG4-related disease: evidence from six recent cohorts," *Autoimmunity Reviews*, vol. 16, pp. 168–172, 2017.
- [31] T. Kamisawa, Y. Zen, S. Pillai, and J. H. Stone, "IgG4-related disease," *The Lancet*, vol. 385, no. 9976, pp. 1460–1471, 2015.
- [32] J. C. Keenan, E. Miller, J. Jessurun, T. Allen, and H. J. Kim, "IgG4-related lung disease: a case series of 6 patients and review of the literature," *Sarcoidosis Vasculitis and Diffuse Lung Diseases: Official Journal of WASOG*, vol. 32, pp. 360–367, 2016.
- [33] M. N. Carruthers, M. D. Topazian, A. Khosroshahi et al., "Rituximab for IgG4-related disease: a prospective, open-label trial," *Annals of the Rheumatic Diseases*, vol. 74, no. 6, pp. 1171–1177, 2015.
- [34] Z. S. Wallace, V. Deshpande, H. Mattoo et al., "IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients," *Arthritis and Rheumatology*, vol. 67, no. 9, pp. 2466–2475, 2015.
- [35] I. Quinti, C. Agostini, S. Tabolli et al., "Malignancies are the major cause of death in patients with adult onset common variable immunodeficiency," *Blood*, vol. 120, no. 9, pp. 1953–1954, 2012.
- [36] A. Sirajuddin, K. Raparia, V. A. Lewis et al., "Primary pulmonary lymphoid lesions: radiologic and pathologic findings," *RadioGraphics*, vol. 36, no. 1, pp. 53–70, 2016.
- [37] R. Yazdani, H. Abolhassani, M. Asgardoost et al., "Infectious and noninfectious pulmonary complications in patients with primary immunodeficiency disorders," *Journal of Investigational Allergology and Clinical Immunology*, vol. 27, no. 4, pp. 213–224, 2017.
- [38] N. Wang and L. Hammarström, "IgA deficiency," *Current Opinion in Allergy and Clinical Immunology*, vol. 12, no. 6, pp. 602–608, 2012.
- [39] L. Yel, "Selective IgA deficiency," *Journal of Clinical Immunology*, vol. 30, no. 1, pp. 10–16, 2010.
- [40] C. Cunningham-Rundles, "Physiology of IgA and IgA deficiency," *Journal of Clinical Immunology*, vol. 21, pp. 303–309, 2001.
- [41] Q. Pan-Hammarström, U. Salzer, L. Du et al., "Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency," *Nature Genetics*, vol. 39, no. 4, pp. 429–430, 2007.
- [42] W. Al-Herz and L. D. Notarangelo, "Classification of primary immunodeficiency disorders: one-fits-all does not help anymore," *Clinical Immunology*, vol. 144, no. 1, pp. 24–25, 2012.
- [43] M. G. Seidel, G. Kindle, B. Gathmann et al., "The European Society for Immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity," *The Journal of Allergy and Clinical Immunology: In Practice*, vol. 7, pp. 1763–1770, 2019.
- [44] C. Cunningham-Rundles, "The many faces of common variable immunodeficiency," *Hematology*, vol. 2012, no. 1, pp. 301–305, 2012.
- [45] B. K. Al-Saud, Z. Al-Sum, H. Alassiri et al., "Clinical, immunological, and molecular characterization of hyper-IgM syndrome due to CD40 deficiency in eleven patients," *Journal of Clinical Immunology*, vol. 33, no. 8, pp. 1325–1335, 2013.
- [46] E. Schussler, M. B. Beasley, and P. J. Maglione, "Lung disease in primary antibody deficiencies," *Journal of Allergy and Clinical Immunology: In Practice*, vol. 4, no. 6, pp. 1039–1052, 2016.
- [47] C. Duarte-Rey, D. P. Bogdanos, P. S. C. Leung, J.-M. Anaya, and M. E. Gershwin, "IgM predominance in autoimmune disease: genetics and gender," *Autoimmunity Reviews*, vol. 11, no. 6-7, pp. A404–A412, 2012.
- [48] R. H. Buckley, *Diagnostic and Clinical Care Guidelines for Primary Immunodeficiency Diseases*, Immune deficiency foundation (IDF), Towson, MD, USA, 3rd edition, 2015.
- [49] L. D. Notarangelo, A. Fischer, R. S. Geha et al., "Primary immunodeficiencies: 2009 update," *Journal of Allergy and Clinical Immunology*, vol. 124, no. 6, pp. 1161–1178, 2009.
- [50] M. Berger, B. Geng, D. W. Cameron, L. M. Murphy, and E. S. Schulman, "Primary immune deficiency diseases as unrecognized causes of chronic respiratory disease," *Respiratory Medicine*, vol. 132, pp. 181–188, 2017.
- [51] P. Soler-Palacín, J. de García, L. I. González-Grando et al., "Primary immunodeficiency diseases in lung disease: warning signs, diagnosis and management," *Respiratory Research*, vol. 19, p. 219, 2018.
- [52] H. Chapel and C. Cunningham-Rundles, "Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions," *British Journal of Haematology*, vol. 145, no. 6, pp. 709–727, 2009.
- [53] C. Roifman, H. Levison, and E. Gelfand, "High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease," *The Lancet*, vol. 329, no. 8541, pp. 1075–1077, 1987.
- [54] J. Chinen, D. Anmuth, A. R. K. Franklin, and W. T. Shearer, "Long-term follow-up of patients with primary immunodeficiencies," *Journal of Allergy and Clinical Immunology*, vol. 120, no. 4, pp. 795–797, 2007.
- [55] P. Roxo Júnior, "Imunodeficiências primárias: aspectos relevantes para o pneumologista," *Jornal Brasileiro de Pneumologia*, vol. 35, no. 10, pp. 1008–1017, 2009.
- [56] F. A. Bonilla, I. L. Bernstein, D. A. Khan et al., "Practice parameter for the diagnosis and management of primary immunodeficiency," *Annals of Allergy, Asthma, and Immunology*, vol. 94, no. 5, pp. S1–S63, 2005.
- [57] F. Cinetto, R. Scarpa, M. Rattazzi, and C. Agostini, "The broad spectrum of lung diseases in primary antibody deficiencies," *European Respiratory Review*, vol. 27, no. 149, Article ID 180019, 2018.
- [58] H. J. Schwartz, R. W. Hostoffer, E. R. McFadden Jr., and M. Berger, "The response to intravenous immunoglobulin replacement therapy in patients with asthma with specific antibody deficiency," *Allergy and Asthma Proceedings*, vol. 27, pp. 53–58, 2006.