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REVIEW

Check for updates

An update on appropriate lung management in patients with primary antibody deficiencies

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ABSTRACT

Introduction: Predominantly antibody deficiencies (PADs) represent the most common inborn errors of immunity (IEIs), constituting over 50% of all IEIs detected globally. Compared to other IEIs, PADs are linked to a more favorable long-term prognosis and are typically diagnosed in adulthood. We analyzed the most recent literature on lung involvement in PAD using PUBMED Central.

Areas covered: PADs are characterized by their impact on the respiratory system, which results in significant morbidity and mortality due to the impairment of both humoral and mucosal immune responses. This impact leads to a broad spectrum of complications that could be infection-related, inflammatory, or neoplastic.

Expert opinion: Defined guidelines are unavailable, but a strict assessment of pulmonary status should be recommended in patients with characteristic immunologic patterns (low IgA serum level, reduced percentage of switched memory B cells, increased IgM serum levels, increased percentage of CD21 low B cells, autoimmune cytopenia, and splenomegaly).

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KEYWORDS
Primary antibody deficiency; lung function; GLILD; bronchiectasis; antibiotic prophylaxis; IgG replacement therapy; long-term management; tailored treatment

1. Introduction

Inborn errors of immunity (IEI) encompass to date more than 500 genetic disorders, all characterized by a compromise in the integrity of the immune system [1]. Previously referred to as primary immunodeficiency disorders (PIDs), the term has been recently updated to reflect the broad spectrum of immune alterations, including immune deficiency and dysregulation. These conditions are associated with a wide range of clinical phenotypes, such as increased susceptibility to infections, autoimmunity, autoinflammation, allergies, bone marrow failure, and/or malignancy. Even if they were traditionally considered rare diseases, thanks to the progression of the research, the actual collective incidence reported is 6 per 10,000 people [2].

In the most recent International Union of Immunological Societies (IUIS) update, 555 IEIs and 17 phenocopies have been classified in 10 groups based on the underlying immune defect [1]. Predominantly antibody deficiencies (PADs) are the most prevalent IEIs, accounting for nearly half of all IEIs diagnosed worldwide [3]; they are usually associated with a better long-term prognosis and can range from a complete impairment of antibody production, such as X-linked agammaglobulinemia (XLA), to a more selective antibody deficiency, such as specific antibody deficiency (SAD) [1]. Common variable immunodeficiency (CVID), the most frequent symptomatic antibody deficiency diagnosed in adulthood, is estimated to affect about 14 in 100,000 individuals [4]. This entity encompasses several clinical and laboratory phenotypes, most lacking a known underlying genetic defect [5].

It is characterized by significant heterogeneity, ranging from increased susceptibility to bacterial infections to immune-mediated manifestations, including autoimmunity, enteropathy, granulomatous diseases, and malignancies, which are overall observed in approximately 68% of CVID patients [6].

A key feature of these disorders is their impact on the respiratory system, which are linked to impairment in both humoral and mucosal immune responses. Infectious and non-infectious lung comorbidities could result, over time, in significant morbidity and mortality [7,8].

Respiratory involvement can be attributed, on the one hand, to a vicious cycle of recurrent infections, inflammation, and tissue damage/remodeling that ultimately results in bronchiectasis and, on the other hand, to immune-mediated interstitial lung diseases (ILD) [9].

These complications should not be considered separately but as a continuum from immune deficiency to immune dysregulation, often co-occurring in the same patient (Figure 1). Of note, the prevalence of these comorbidities varies depending on the type of PAD. For example, patients with XLA are more susceptible to recurrent and severe infections with

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Article highlights

- Infection- and non-infection-related chronic lung diseases are the most frequent complication reported in PAD patients, with a deep impact on burden of disease, QoL, and mortality.
- Focus on the knowledge of the rare and 'atypical' pulmonary manifestations.
- Immunological, genetic, clinical, and radiological markers could be used as early predictors of presence, type, and severity of lung involvement.
- Personalized medicine is probably the future for the management of PAD lung complications, with a more tailored approach to therapy.
- Further studies are needed to develop and validate prognostic scores and management protocols, to achieve follow-up strategies.

a lower likelihood of developing ILD in comparison with CVID patients [10].

Although the relevance of pulmonary involvement in PADs is well established, only a few studies have investigated pulmonary function in these patients.

Chen et al., analyzing longitudinal pulmonary function tests (PFTs) of 37 patients (29 with CVID and 8 with XLA), reported a rate of decline in forced expiratory volume in 1 second (FEV1) approximately twice that of the healthy nonsmoking adult population, with a greater decline observed in the XLA group [11].

In a larger and more recent study by Sperlich et al., lung parameters of 110 CVID patients were analyzed, focusing on the impact of bronchiectasis on lung integrity. The study found that patients with bronchiectasis had worse lung function and a higher rate of decline in lung parameters than those without bronchiectasis [12].

Recently, in a multicenter study involving 185 CVID patients, we found that the baseline lung volumes of our patients were in the lower third of the normal distribution for healthy individuals of the same age, sex, ethnicity, and height. However, possibly due to immunoglobulin replacement therapy, the rate of lung volume decline after diagnosis over a 7 years period was not greater than what is physiologically expected [13].

We used PUBMED Central for consulting the most recent literature, searching for the following MeSH terms: PAD; CVID; LUNG INVOLVEMENT; LUNG DISEASE; BRONCHIECTASIS; GLILD.

2. Lung complications and management in pad patients

2.1. Respiratory tract infections

Patients with PADs often get repeated infections, especially recurrent sinopulmonary infections, because of their immunological defects.

Despite appropriate immunoglobulin replacement therapy (IgRT), a group often remains susceptible to infection, suggesting a persistent immune defect that cannot be rescued by IgRT alone (e.g. IgA deficiency) [14].

Over time, recurrent infections can lead to chronic lung conditions, impacting patients' morbidity and mortality.

The bacterial pathogens most commonly implicated in recurrent pneumonia, chronic bronchitis, sinusitis, and otitis

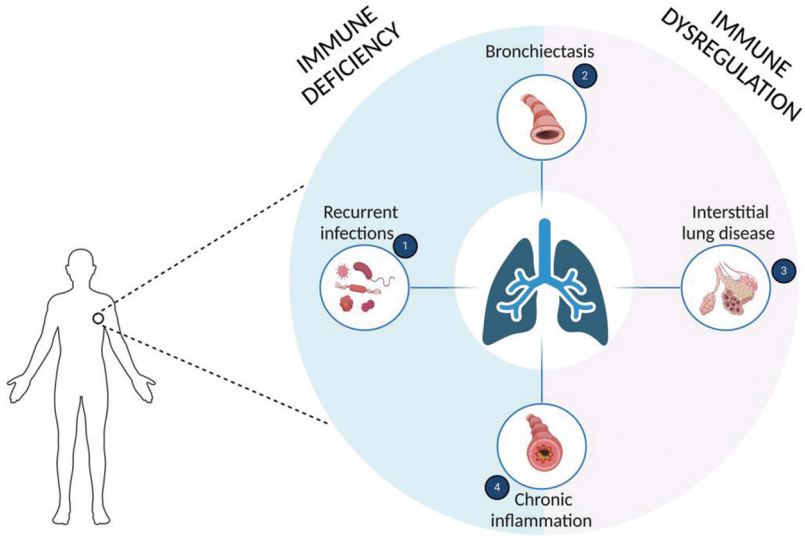


Figure 1. The figure summarizes the main pulmonary complications in patients with PADs, highlighting the continuum from immune deficiency to immune dysregulation. **Recurrent infections**: due to humoral immune impairment, PAD patients are highly susceptible to recurrent and severe respiratory tract infections, particularly those caused by encapsulated bacteria; **Bronchiectasis**: recurring infections and interstitial inflammation can lead to the development of bronchiectasis, a condition characterized by abnormal dilation of the airways. Bronchiectasis increases the risk of chronic bacterial colonization, creating a 'vicious cycle' that results in both structural and functional lung damage; **immune-mediated interstitial lung disease**: due to the underlying immune dysregulation and of the pro-inflammatory microenvironment, which is favored by recurring infections, PAD patients are prone to develop immune-mediated interstitial lung disease (ILD). This condition is characterized by interstitial infiltrates, which can lead to structural damage, bronchiectasis, and the potential progression to pulmonary fibrosis. These inflammatory processes can impair lung function and, if left untreated, may progress to respiratory failure. **Chronic functional obstruction**: chronic inflammation resulting from recurrent respiratory tract infections and immune-mediated interstitial lung disease may lead to the development of functional airway obstruction, presenting a clinical picture that resembles asthma or chronic obstructive pulmonary disease (COPD) without the typical associations with smoking. The underlying functional and structural lung damage may make the patient more susceptible to new infections, thereby sustaining a vicious cycle. Created in BioRender. Buso, H. (2025) https://BioRender.com/hyu48mw.

in PAD patients include *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella Catarrhalis* [15].

To higher risk to develop severe respiratory infections, it is also related to a perturbed oropharynx microbiota enriched with potentially pathogenic bacteria and decreased protective species. The connection between viral upper respiratory tract infections and subsequent bacterial infections is not fully understood. *Human rhinovirus (HRV)* infections are more common in PAD patients than in the general healthy population with prolonged viral elimination periods [16]. On the other hand, fungal infections are rare due to the adequate integrity of the cellular immune response [17].

Managing these patients requires identifying and treating even subclinical infections, which may be challenging [13,18,19].

2.1.1. Management

In this scenario, multidisciplinary management is fundamental. The approach to infections in PAD patients involves microbiological examinations (e.g. sputum culture tests), noninvasive methods (e.g. CT imaging and MRI of the airways), and, sometimes, an invasive approach (e.g. bronchoscopy with bronchoalveolar fluid lavage useful for identifying pathogens but also contributes to mechanical removal of mucus). Lung biopsy can also be used when solid or cavitated lesions are detected [20,21]. Identifying the pathogen with either direct culture tests on sputum and/or blood, immunofluorescence staining, PCR testing, and amplicon sequencing is crucial for managing infections. Next-generation sequencing (NGS) and matrix-assisted laser desorption ionization (MALDI-TOF MS) are new promising tools [22]. In addition, antimicrobial susceptibility tests should guide appropriate antibiotic therapy.

However, until results are available, it is helpful to prescribe broad-spectrum antibiotics based on the patient's past infectious, pharmacological history, and comorbidities. After diagnosis of the infectious episode, the antibiotic treatment duration must be longer than standard (Table 1).

Antibiotic therapy may also be used prophylactically, as reported in a trial demonstrating that a low dose of azithromycin (250 mg a day three times a week) was effective in reducing respiratory exacerbations in patients with chronic infection-related pulmonary diseases [23]. Atypical mycobacteriosis should be excluded and the risk of QT interval prolongation should be assessed on electrocardiogram before starting azithromycin prophylaxis. Alternatively, in PAD patients with CD4+ T cell counts <200/µl, trimethoprim/sulfamethoxazole (TMP/SMX) may be prescribed. Rational use of antibiotics is always recommended both in therapy and prophylactically, due to their effects on the microbiota and the risk of developing resistance [21]. In some cases, comprehensive antimicrobial prophylaxis, including fluconazole, or targeted regimens against *Pneumocystis jirovecii*, or for respiratory viruses (e.g. palivizumab for *VRS*), should be implemented [22].

Immunoglobulin substitutive therapy (IgRT) is the gold standard approach to ensure optimal serum Ig levels. Several studies show that appropriate IgG trough levels reduce mortality rate due to severe bacterial pneumonia and the incidence of major infections [18,24].

Current evidence suggests that a target IgG trough level of 7–10 g/L can reduce the risk of severe respiratory infections, especially in patients with chronic lung disease, whereas a meta-analysis by Orange et al. suggested that the incidence of pneumonia decreased by 27% for every 100 mg/dL increase in trough serum IgG levels [25].

The standard dosage of IgRT is 400–600 mg/kg every 3–4-weeks, but sometimes higher dosages (600–800 mg/kg) are required in patients with severe recurrent infections. A subgroup of PAD patients, even with appropriate IgRT, often remain susceptible to infections because of a severe phenotype characterized by extremely low levels of IgA and IgM, underlying chronic lung disease and increased risk of bacterial colonization [26]. A tailored approach based on IgG trough level and the frequency of infections is needed due to the inter-individual variability. Frequent monitoring of serum Ig is also necessary [18,27–29]. Weekly subcutaneous immunoglobulins (SCIG) replacement therapy seems to be advantageous in comparison to intravenous immunoglobulins (IVIG) in increasing higher minimal IgG levels with a linear reduction in infections [18,22,30].

Although CVID patients have an inherently impaired response to vaccinations due to their immunodeficiency, vaccination remains strongly recommended, except for live attenuated vaccines, which are still contraindicated. Indeed, vaccines have been

Table 1. Key points to consider to manage infections in primary antibody deficiency.

STRATEGY FOR INFECTIONS	
BROAD-SPECTRUM ANTIBIOTICS	• Based on the patient's past infectious, pharmacological history and comorbidities. • Duration could be longer than standard.
ANTIBIOTIC PROPHYLAXIS	• Low dose of azithromycin (250 mg/day three times a week) effective in reducing respiratory exacerbations in patients with chronic infection-related pulmonary diseases. • Trimethoprim/Sulfamethoxazole (TMP/SMX) may be prescribed in PAD patients with CD4+ T cell counts <200/µl.
IgRT	• Appropriate IgG trough levels (7–10 g/L) reduce mortality rate due to severe bacterial pneumonia and the incidence of major infections. • Standard dosage of IgRT is 400–600 mg/kg every 3–4 weeks. Higher dosages (600–800 mg/kg) are required in patients with severe recurrent infections. • Subcutaneous immunoglobulin (SCIG) replacement therapy may be superior to intravenous immunoglobulin (IVIG) at boosting IgG levels and reducing infections. • A tailored approach based on IgG trough level and the frequency of infections is needed due to the inter-individual variability.
VACCINATION	• Vaccines, even with a partial response, are beneficial in enhancing protection against severe infections, particularly when administered regularly and in conjunction with IgRT. • Live attenuated vaccines are contraindicated.

shown to be beneficial in enhancing protection against severe infections, particularly when administered regularly and in conjunction with IgRT [31]. In CVID patients, even partial responses to vaccines can provide significant protection, particularly against common pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [31].

2.2. SARS-CoV-2 infection

Increased susceptibility to viral respiratory infections has been reported in patients with PADs. In fact, a recent prospective study demonstrated that, on average, these patients experienced symptomatic respiratory exacerbations every 6 days, compared to every 6 weeks in healthy controls [16].

During the COVID-19 pandemic, CVID patients had an increased risk of prolonged *SARS-CoV-2* infection and re-infection and a higher COVID-19-related morbidity and mortality compared to the general population [32,33]. In particular, CVID patients with noninfectious chronic lung involvement, including GLILD, had the worst outcomes, with a higher risk of hospitalization and mortality [34]. Additionally, CVID patients exhibited a higher prevalence of long COVID-19 in comparison to the general population [35].

2.2.1. Management

In PAD patients who develop *SARS-CoV-2* infection early therapeutic or prophylactic measures are mandatory to prevent severe or fatal course of COVID-19 (Table 2). In particular, during pandemic, patients were treated with antiviral drugs and/or monoclonal antibodies (mabs). Different studies demonstrated that antivirals were effective in reducing the risk of hospitalization, while mabs had a positive effect on hospitalization duration and in mitigating COVID-19 severity [36].

The widespread use of vaccination using novel vaccine technology in a population that is characterized by an impaired response to immunization [31,37] demonstrated a rate of seroconversion of 58.3% in CVID patients after two doses of COVID-19 vaccine that increased to 77.8% after three doses [38]. Vaccination with three doses had an impact on disease duration and significantly reduced the risk of severe disease [39]. PAD patients exhibited a persistent T cell response to *SARS-CoV-2* vaccination compared to healthy controls that further increased in parallel to boosters, accrual number of exposures, and formation of hybrid immunity [38].

In addition, several studies confirmed the safety of COVID-19 vaccine in PAD patients [40,41]. These data on the response to *SARS-CoV-2* vaccination further support the indication for vaccination in PAD.

2.3. Bronchiectasis

Bronchiectasis, characterized by irreversible dilatation and bronchi damage, is a major respiratory complication frequently observed in PAD patients, associated with recurrent pulmonary infections and leading over time to lung damage. A study of 302 patients with PAD found that bronchiectasis prevalence increased from 47.3% to 53.7% over 5 years in patients with CVID [42].

PAD patients with bronchiectasis may be asymptomatic or may present respiratory symptoms including persistent productive cough, dyspnea, and occasionally hemoptysis and/or constitutional symptoms including fatigue and weight loss. Infections often persist for weeks, and diagnostic workup is warranted in patients with protracted bacterial bronchitis and treatment-resistant symptoms. Bronchiectasis is the result of a vicious circle of repeated infections and inflammation destroying lung tissue and leading over time to airway remodeling (Figure 2(a)).

Risk factors for bronchiectasis include advanced age that reduces systemic and respiratory mucosal innate and adaptive immunity contributing to increasing infections and potential lung tissue damage [28,43,44] and a history of sinusitis and pneumonia that impaired airway clearance mechanisms leading to chronic bacterial colonization [45,46]. PAD diagnostic delay and prolonged respiratory symptoms before diagnosis may contribute to disease progression.

2.3.1. Management

In PAD patients, bronchiectasis is suspected based on clinical symptoms including chronic cough and sputum production, and on obstructive patterns at PFTs. High-resolution CT scan (HRCT) remains the gold standard due to its sensitivity in detecting airway dilatation, mucus plugging, and bronchial wall thickening (Figure 3). However, concerns about radiation exposure, particularly in patients with radiosensitivity or increased cancer risk due to immunodeficiency, make MRI an appealing alternative. Actually, MRI techniques provide imaging quality comparable to low-dose CT, enabling its use for monitoring structural abnormalities and early airway changes [27,47–50].

Monitoring and follow-up protocols are essential for optimizing outcomes. Lung function tests play a key role in monitoring these patients and should be prescribed at PAD diagnosis and during follow-up, at least once a year. Several

Table 2. Key points to consider to manage COVID-19 in primary antibody deficiency.

STRATEGY FOR COVID-19	
ANTIVIRAL DRUGS	• Effective in reducing hospitalization risk.
MONOCLONAL ANTIBODIES (mABS)	• Positive effect on hospitalization and in mitigating disease severity.
VACCINATION	• Novel safe vaccine technology • In CVID patients, the rate of seroconversion of 58.3% after two doses increased to 77.8% after three doses. • Three doses had a positive impact on disease duration and significantly reduced the risk of severe disease • In PAD patients, COVID-19 vaccination was safe.

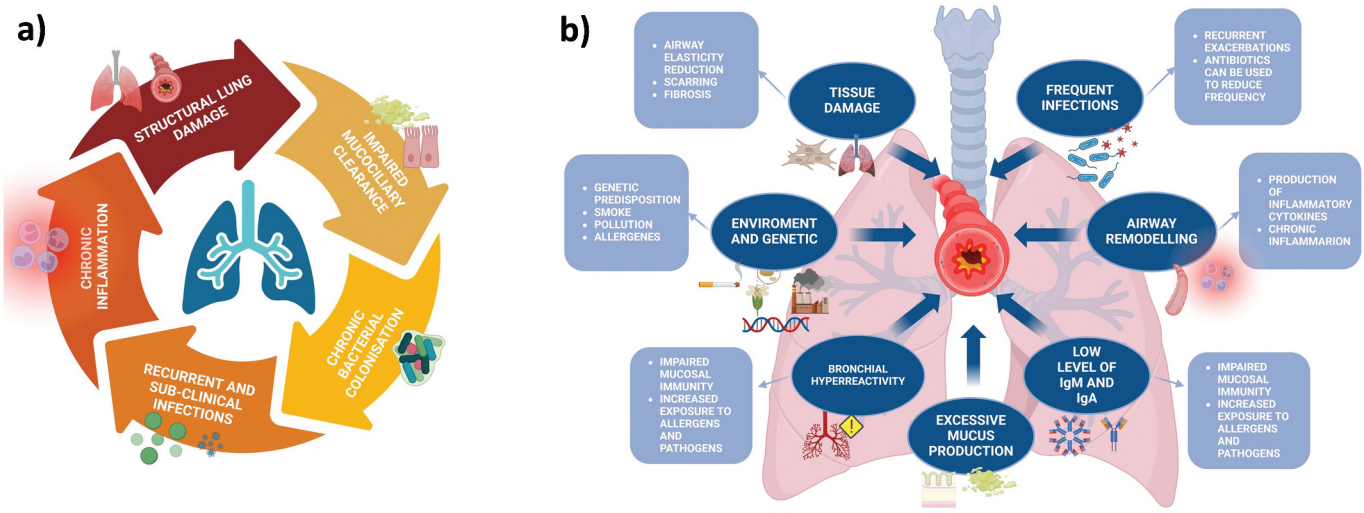


Figure 2. (a) The development of bronchiectasis in the clinical picture of these patients is based on the establishment of a vicious circle of events. (b) Key mechanisms contributing to the development of asthma and COPD in patients with primary immunodeficiencies created in BioRender. Del11, P. (2025) https://BioRender.com/ud0yqk1,created in BioRender. Del11, P. (2025) https://BioRender.com/n65g900.



Figure 3. High-resolution computed tomography images of the lungs of a 24-years-old male patient with XLA, showing bronchiectasis of the left lower lobe (arrows), characterized by an airway lumen larger than the associated pulmonary artery and lack of tapering to the periphery. Mild bronchial wall thickening is also present. (a) Axial projection. (b) Coronal projection. (Unpublished data obtained from patient's medical record. Informed consent was obtained from subject, who gave permission for publication).

studies demonstrate a lower median FEV1 in bronchiectasis patients than in patients without bronchiectasis [13].

As already mentioned, recurrent and prolonged infections, followed by inflammation, can disrupt the normal anatomy of the airways creating an ideal environment for pathogen colonization. Consequently, it is crucial to perform sputum tests to assess potential antibiotic resistance, and in case of a flare-up, it is important to undertake a reexamination [20] (Table 3).

Antibiotic prophylaxis in PAD remains a debated issue due to the lack of clear guidelines, limited available data, and concerns about antibiotic resistance. As a result, its prescription varies widely, often influenced by individual clinical judgment and personal experience.

However, macrolides, and above all azithromycin, have been shown to have immunomodulatory and anti-inflammatory effects and to prevent biofilm formation by bacteria, limiting bronchial damage. In a 3-year, double-blind, placebo-controlled, randomized clinical trial, authors demonstrated that PAD patients may benefit from low doses of azithromycin (250 mg once daily, 3 times a week for 2 years). In particular, azithromycin was effective in reducing exacerbation episodes per patient-year, with a consequent reduction in additional antibiotic courses and risk of hospitalization [23]. Conversely, in prescribing azithromycin long-term prophylaxis, physicians should take into account the possibility of macrolide resistance, together with alterations of intestinal and respiratory microbiomes that need to be restored with the use of probiotics [19].

In addition, in PAD patients with bronchiectasis, azithromycin monotherapy may favor the development of non-tuberculous mycobacterial infection. For this reason before starting long-term azithromycin prophylaxis and during treatment, nontuberculous mycobacterial infection should be ruled out periodically [23].

Therapeutically, IgRT is pivotal in managing PAD-related bronchiectasis. An early initiation of IgRT, compared to no or delayed treatment, is highly cost-effective and significantly improves expectancy and quality of life [51]. The importance

Table 3. Key points to manage bronchiectasis in primary antibody deficiency.

STRATEGY FOR BRONCHIECTASIS	
ANTIBIOTIC PROPHYLAXIS	• Macrolides, e.g. azithromycin, are effective against bronchial damage by reducing inflammation and preventing bacterial biofilms. • Low dose of azithromycin (250 mg once daily, for 2 years) reduces exacerbation episodes, need for further antibiotics and risk of hospitalization. • Consider the risk of macrolide resistance and any changes to the intestinal and respiratory microbiomes, which can be treated with probiotics. • Before starting long-term azithromycin prophylaxis and during treatment, nontuberculous mycobacterial infection should be ruled out periodically.
IgRT	• An early initiation is highly cost-effective and significantly improves expectancy and quality of life. • A higher dose of IVIG is inversely associated with lung function decline, and a higher IgG trough level is associated with a slower decline in lung volumes. • Some patients often require higher IgRT doses (1000 mg/dl) and the time required to achieve the target IgG level is longer and significantly associated with the infection frequency.
NEBULIZED IgA/INCREASING IgRT FREQUENCY	• Serum levels of IgA/IgM may be lower in patients with bronchiectasis compared to those without the condition. • The implementation of IgRT with nebulized IgA could be a promising strategy for the future.
NEUTROPHIL ELASTASE (NE) INHIBITORS	• The drug was safe even if not associated with significant changes of the pulmonary function parameters. • Further studies are necessary to evaluate the clinical efficacy in PAD patients.
PULMONARY REHABILITATION AND AIRWAY CLEARANCE TECHNIQUES	• Enhancing sputum elimination and lung function.

of IgRT is further supported by its beneficial role in pulmonary function. Indeed, a higher dose of IVIG was inversely associated with lung function decline [11], and a higher IgG trough level was associated with a slower decline in lung volumes. In line with these results, Buso et al. demonstrated that patients with normal FEV1 showed higher IgG serum trough levels [13]. Accordingly, Hwangpo et al. found an improvement in forced expiratory flow at 25–75% (FEF25–75%) in patients receiving an additional IgG dose compared to those who did not [52].

CVID patients with bronchiectasis often require higher IgRT doses (approximately 1000 mg/dl) than CVID without lung comorbidities, as IgG improves mucus clearance and airway inflammation but, in bronchiectasis patients, the time required to achieve the target IgG level was longer and significantly associated with the infection frequency. In addition, earlier studies suggest that patients with a very low memory B cell count and abnormal lung function might benefit from higher IgRT doses that could improve small airway function [13,27–29,47,53].

Associated IgA and IgM deficiencies, common in PAD, complicate the disease course by impairing mucosal immunity and contribute to bronchiectasis development. In fact, in patients with bronchiectasis, serum IgA was significantly lower compared with patients without bronchiectasis [45]. Moreover, patients at risk for bronchiectasis often exhibit low serum IgM that may play a role in its pathogenesis [12]. To overcome these absences, recent evidence suggests supplementation with nebulized IgA or increasing the frequency of IgG replacement [13,28,29,53]. Genetic predispositions, such as mutations in LRBA, CTLA-4, and PI3KCD, also contribute to bronchiectasis by exacerbating immune dysregulation and pulmonary inflammation [53,54].

A recent study found an association between increased neutrophil elastase (NE) activity and a higher chance of bronchiectasis exacerbation. On this basis, in a study conducted in 2019, the use of neutrophil elastase inhibitors was evaluated as a therapeutic option for non-cystic fibrosis bronchiectasis in immunocompetent individuals. The study revealed that the drug was safe even if it was not associated with significant changes of the pulmonary function parameters from baseline to end of treatment. Further studies are needed with a focus on PAD patients [55–57].

Finally, despite no specific evidence in PAD patients, long-term bronchiectasis management also includes pulmonary rehabilitation and airway clearance techniques, with hypertonic saline and positive expiratory pressure devices enhancing sputum elimination and lung function [27,29].

2.4. Chronic obstructive and infection-related pulmonary disease (asthma and COPD)

Asthma and COPD are common forms of chronic obstructive pulmonary disease that may occur in PAD patients. Notably, it has been shown that PAD patients may fulfill the functional diagnostic criteria for COPD (according to GOLD guidelines https://goldcopd.org/2024-gold-report), even in the absence of a smoking or exposure history. Obstructive lung disease or bronchial hyperresponsiveness has been reported in about a third of CVID and, at least, in 5% of XLA patients (Figure 2(b)). The onset age of symptoms could not be linked to PAD diagnosis; in fact, asthma and COPD could be initial symptoms of PAD or develop later during follow-up. Also, IgA deficiency increases the risk of asthma, as well as asthma is a comorbidity associated with IgG subclass deficiency or unclassified antibody deficiency [58] (Figure 2(b)).

Of note, in a recent study on lung function trajectories in CVID, patients with COPD had a significantly lower level of serum IgA, IgM, and peripheral blood marginal zone B cells percentage, all findings that suggest a mucosal defect and an impairment in T-independent immune response likely contributing to the increased frequency of exacerbations and/or progression of COPD [13]. Moreover, among all lung comorbidities, COPD was associated with a greater decline in lung

volume, which was significantly higher than the physiologically predicted decline for age.

In 2020, Berber analyzed bacteria in patients' throats with XLA and CVID, revealing higher bacterial load in patients, even after IgRT and antibiotics. This was associated with the severity of lung disease, suggesting a role for IgA in regulating bacterial proliferation. Higher bacterial levels are a hallmark of this condition and respiratory disease. The *Prevotellaceae* family was found to be overrepresented in CVID and XLA patients with low IgA, possibly linked to a compromised airway barrier [46,59,60].

In addition, it has been shown that CVID patients with COPD exhibit a microbiome ecosystem enriched with *Streptococcus* and *Haemophilus* that represents a source of infection and inflammation [19].

Moreover, COPD and asthma have been found more frequent among CVID patients with bronchiectasis, reflecting the cumulative effect of recurrent respiratory infections over time. In particular, the co-occurrence of COPD and bronchiectasis is associated with poorer outcomes and increased mortality [13,45].

In COPD, the underlying mechanism is related to airway constriction and chronic inflammation, whereas the role of immune defects in asthma pathogenesis is still unclear. PAD patients often lack IgE but, despite this they could have airway bronchoconstriction and asthma. Moreover, the exact role of immune defect in asthma pathogenesis is still under investigation but disruption in mucosal barriers and altered lung microbiota have been clearly implicated in asthma pathogenesis in immunocompetent individuals, suggesting a similar mechanism in immunodeficient patients [28,29,61].

2.4.1. Management

Asthma and COPD in patients with PAD are framed and treated as standard, according to GINA and GOLD guidelines (GINA guidelines: https://ginasthma.org/2024-report/; GOLD guidelines: https://goldcopd.org/2024-gold-report/). The focus of managing asthma and COPD in patients with PAD is on symptoms, exacerbations, and lung function [20,28,29] (Table 4).

An appropriate and personalized IgG replacement strategy may be effective in reducing asthma and COPD progression by reducing the severity and rate of exacerbations, sparing corticosteroids, and improving airway obstruction [45,62].

As for bronchiectasis, antibiotic prophylaxis has been shown to be a powerful add-on strategy and azithromycin, in particular, has been shown to significantly reduce the risk of asthma or COPD exacerbations also in CVID patients [23]. Bronchodilators administered by inhalation (short-acting beta 2 and muscarinic agonists) treat activity-related breathlessness and mild symptoms as monotherapy or combined, as required. Beta 2 agonists and LABA/LAMA could be useful for patients with a high symptom burden, impaired lung function (FEV1 <60% predicted) and high risk of exacerbation [20,29,63]. Roflumilast significantly reduces exacerbations in patients with severe obstruction, frequent exacerbations, and chronic bronchitis and in patients who still experience exacerbations despite triple therapy [64]. As for non-pharmacological treatments, pulmonary rehabilitation is superior to drug therapy for patients with functional impairment, helping with dyspnea, exercise tolerance, and quality of life. Early pulmonary rehabilitation also improves outcomes. In cases of purulent sputum, a microbiological culture examination can be performed to determine targeted antibiotic therapy [20] in patients with repeated exacerbations or suspected bacterial resistance. Patients unresponsive to prior treatment require hospitalization. Lung transplants are for patients under 70 years with severe impairments [29].

In future, the possibility of manipulating respiratory microbiota through pharmacological interventions may hopefully contribute to restoring the microbiota composition and reduce inflammation and damage progression [19]. As for bronchiectasis, future availability of locally deliverable IgA preparations might be of help in this direction.

2.5. Immune-mediated interstitial lung disease

The actual incidence of interstitial lung disease in PAD remains ambiguous and fluctuates according to the specific immune deficiency. ILD manifests in an estimated 10–20% of people with CVID. The incidence may be underestimated, as CT findings indicative of ILD (ground glass opacity and/or multiple lung nodules) were observed in 64% CVID patients exhibiting

Table 4. Key points of management of asthma and COPD in primary antibody deficiency.

STRATEGY FOR ASTHMA AND COPD	
CORTICOSTEROIDS AND BRONCHODILATORS (BETA 2 AGONISTS AND LABA/LAMA)	• Treatment according to GINA and GOLD disease-specific guidelines, focused on symptoms, exacerbations, and lung function. • For patients with a high symptom burden, impaired lung function (FEV1 < 60% predicted) and high risk of exacerbation.
ROFLUMILAST	• In patients with severe obstruction, frequent exacerbations despite triple asthma therapy, and chronic bronchitis, significantly reduce exacerbations.
IgRT	• A personalized treatment strategy reduces exacerbations and helps in sparing steroids. It can also reduce disease progression, improving airway obstruction.
PULMONARY REHABILITATION	• For patients with functional impairment, it is superior to drug therapy improving dyspnea, exercise tolerance, and quality of life. Early rehabilitation improves outcomes.
ANTIBIOTIC PROPHYLAXIS	• Powerful add-on strategy. Azithromycin significantly reduces the risk of exacerbations also in CVID patients.
PHARMACOLOGICAL INTERVENTIONS ON RESPIRATORY MICROBIOTA	• Future possibilities, like locally deliverable IgA preparations, aimed at restoring the microbiota composition, reduce inflammation and damage progression.
LUNG TRANSPLANTS	• For patients under 70 years with severe respiratory impairments.

respiratory symptoms at a tertiary referral hospital [65]. The interpretation of these CT results is hampered by the fact that PFTs are not consistently reduced and may not signify clinically relevant interstitial lung disease (ILD). ILD seems significantly less prevalent in other types of PAD. Interstitial lung disease was either missing or exceedingly infrequent in many extensive investigations of X-linked and autosomal recessive hyper IgM syndrome. Interstitial lung disease is exceedingly uncommon in individuals with congenital agammaglobulinemia, especially X-linked agammaglobulinemia (XLA) [65,66].

Due to its generic symptoms, interstitial lung disease (ILD) can be challenging to differentiate from other chronic lung diseases. Physical examination can help identify crackles, wheezing, and ronchi. PFT can differentiate obstructive chronic lung diseases from restrictive lung diseases. High-resolution CT is essential for assessing chronic lung illness in PAD, often highlighting an overlap between ILD and infection-related lung damage. A lung biopsy confirms the diagnosis of ILD, excludes lymphoma or other malignancies, and may guide treatment.

2.5.1. Granulomatous lymphocytic interstitial lung disease (GLILD)

According to the British Lung Foundation/United Kingdom Primary Immunodeficiency Network consensus statement, GLILD is defined as 'a distinct clinical-radio-pathological interstitial lung disease (ILD) occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded [67].

It is important to note that GLILD should be considered an 'umbrella' term encompassing different dysregulatory complications, all of which share the common feature of pulmonary interstitial involvement. Indeed, rather than a complication limited to the lung (often reported in literature as CVID-ILD), GLILD should be considered as a part of a multisystemic immune-disorder.

The typical associated clinical manifestations include hepatosplenomegaly, observed in nearly half of the patients, autoimmune cytopenia (e.g. idiopathic thrombocytopenic purpura or autoimmune hemolytic anemia), reported in almost two-thirds of patients, and lymphadenopathy with polyclonal lymphoproliferation, reported in almost all patients [68].

The two distinctive features of GLILD are non-necrotizing sarcoid-like granulomas and lymphoid hyperplasia, characterized by the development of germinal centers during tertiary lymphoid organogenesis, both reflecting an aberrant immune response to chronic antigenic stimulation [69].

The exact trigger of this dysregulated immune response remains unknown; however, a possible role of *Human Herpesvirus type 8 (HHV8)* has been hypothesized [70].

As reported in CVID patients with only infections, also in GLILD patients a significant microbiome alteration in the respiratory tract was identified, suggesting a possible link to both local and systemic immune dysregulation. In particular, Conchiformibius spp. has been proposed as a potential pathobiont and a possible relevant microbiological marker for GLILD [71].

Several studies have highlighted a distinct immunological profile in GLILD patients with a key role in B cells. Indeed, in GLILD, a peculiar distribution of B cells subtype has been described, with an expansion of CD21 low B cells both in the peripheral blood and in the Bronchoalveolar Lavage Fluid (BALF), which reflects ongoing immune activation and exhaustion [6,72,73].

This subset of B cells has been previously linked to other autoimmune disorders, such as Sjögren's syndrome and systemic lupus erythematosus, further emphasizing its relevance in autoimmune diseases [74,75].

Maglione et al. further demonstrated the critical role of B cells in GLILD development, showing that BAFF-driven B cell hyperplasia, indicated by elevated serum IgM levels, is correlated with the progression ILD [76].

Moving to the T-cell compartment, GLILD is characterized by a predominance of CD4+ T cells, in particular T follicular helper-like, and a significant reduction in regulatory T cells (FoxP3+CD25+ T-regs) in BALF. This reflects an impairment in immune response regulation and a loss of immune tolerance [6,77]. The decrease in T-regs, which are crucial for maintaining immune homeostasis and suppressing autoreactive immune responses, likely contributes to the pathogenesis of the disease. Indeed, in CVID patients with autoimmunity, reduced expression of CTLA-4 and LRBA, essential for a proper Treg function, has been observed, even without identifiable genetic mutations [78].

In line with this dysregulated environment, elevated levels of serum markers associated with T cell activation and exhaustion, such as TNF-α, IFN-γ, soluble IL-2 receptor (sIL-2 R), and soluble TIM-3 (sTIM-3), have been reported in GLILD patients [79].

Indeed, a recent study by Abyazi et al. has shown that in general CVID patients with non-infection complications such as GLILD have a distinct plasma proteomic profile characterized by cytokine dysregulation with T-cell activation and infiltration in tissues [80].

According to the previously mentioned British consensus, a definitive diagnosis of GLILD requires evidence of granuloma and/or lymphoid hyperplasia obtained by surgical lung biopsy [67].

However, due to the associated risks, the use of this technique is still under discussion. Video-assisted thoracoscopic surgery (VATS), transbronchial biopsy (TBB), and even extra-pulmonary biopsy have been employed to confirm the diagnosis [81]. Also, bronchoalveolar lavage fluid also plays an important role in the differential diagnosis of infections (including bacterial, mycobacterial, and fungal cultures) and typically shows lymphocytosis, with possible CD21low expansion.

With a clearer understanding of the overall clinical picture, immunological alterations, and the identification of potential biomarkers, the overall role of biopsy in clinical practice might now be limited to selected cases, primarily for the purpose of excluding underlying malignancies. Indeed, according to a recent clinical survey the majority of experienced clinicians consider HRCT a sufficient alternative to biopsy for diagnosing GLILD in most patients [81].

In this scenario, the definition of peculiar radiological pulmonary alteration on HRCT is essential. According to a recent study by Scarpa et al., GLILD usually affects the lower fields of

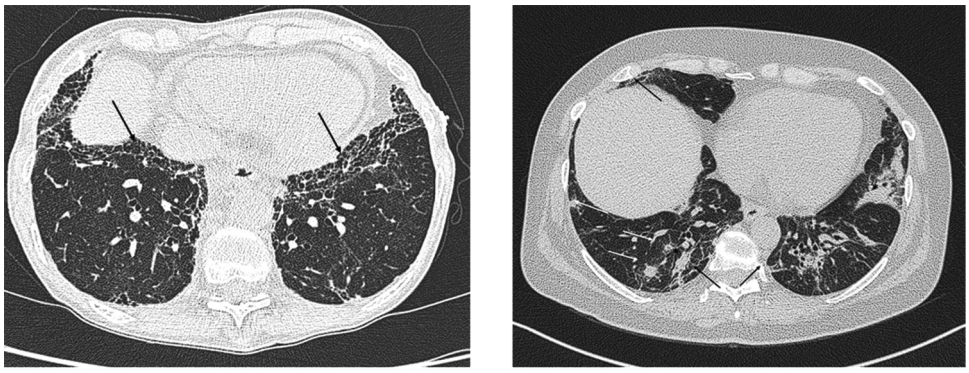


Figure 4. (a) High-resolution computed tomography images of the lungs of a 72-years-old female patient, showing fibrotic GL-ILD at lung bases substeined by reticulations with inner traction bronchiectasis (arrows). Axial projection shown. (b) High-resolution computed tomography images of the lungs of a 59-years-old female patient. GL-ILD-related consolidations (asterisks), nodules (white arrows), and reticulations (black arrows) are appreciable at lung bases. Axial projection shown. (unpublished data obtained from patient's medical record. Informed consent was obtained from subject, who gave permission for publication).

the lungs with the typical development of multiple non-perilymphatic small nodules (<10 mm), parenchymal scars/bands, consolidations, Ground Glass Opacities (GGO), bronchiectasis, and mediastinal enlarged lymph nodes [82] (Figure 4).

The Hartmann and Baumann scoring methods have been proposed to assess the degree of lung injury and thus identify different stages of the disease [83].

In addition to radiological images, spirometry – a noninvasive test that allows for the monitoring of pulmonary function over time – plays an important role in assessing lung health. Patients with GLILD typically develop a restrictive lung phenotype due to interstitial impairment, leading to a reduction in total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLCO). Our recent findings indicate that patients with GLILD at the time of diagnosis were at the 16th percentile for TLC and the 11th percentile for DLCO compared to healthy individuals. Furthermore, during follow-up, we observed a continued decline in these parameters, placing them below the lower limit of normal (below the 5th percentile) [13].

Moving to extra-thoracic involvement, fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is gaining importance as a tool for providing details about organ involvement, disease activity and for monitoring treatment response [84].

Both HRCT and PET/CT should be used with caution because of the radiation risk, especially considering the underlying higher risk of malignancies in these patients. In this regard, to limit the radiation exposure, the use of thoracic magnetic resonance imaging (MRI) might be a valuable alternative to HRCT allowing a good definition of lung and airways structural changes [85,86].

Further studies on this technique are needed.

During the last years, several diagnostic models integrating clinical-laboratory and radiologic features were proposed but still not validated: (a) Mannina et al.: hypersplenism, polyarthritis, and FVC less than 80% with an area under curve (AUC) of 0,9267 [73]; (b) Hartono et al.: splenomegaly, autoimmune cytopenia (AITP or AIHA), low serum IgA (<13 mg/dl) and CD21low >5% [87]; (c) Cinetto et al.: splenomegaly, autoimmune cytopenia (AITP or AIHA), CD21low percentage and DLCO with an AUC of 0,9861 (72); (d) Cabañero-Navalon et al.: splenomegaly, lymphadenopathy, low CD8+ cells in peripheral blood and high Baumann's CVID-ILD score with an AUC of 0,98568 [88]. All these support the importance of extrapulmonary manifestations in raising the suspicion of this rare ILD.

Furthermore, a recent diagnostic algorithm was proposed, integrating clinical, humoral, radiological, and pathological details and highlighting the role of a multidisciplinary approach [89]).

Finally, it is important to emphasize the increasing role of genetics, with the potential to identify a specific underlying genetic defect in one-third of patients with CVID and pulmonary involvement, thereby guiding subsequent therapy. The most frequent gene defects associated with GLILD are BACH2, CTLA4, KMT2D, LRBA, PIK3R1, STAT3, TACI, TCF3, or WAS [90].

2.5.2. Management

Due to the lack of validated guidelines, the optimal management of ILD in CVID patients remains controversial.

Considering the severity of this condition, prompt recognition is crucial to ensure a personalized management. Warning signs include persistent dry cough and shortness of breath; however, many patients may remain asymptomatic for an extended period, even in the presence of underlying GLILD. For this reason, CVID patients should undergo annual PFTs and, at a minimum, a HRCT at CVID diagnosis and then every 5 years [20].

A closer follow-up is recommended in the subgroup of patients with clinical and immunological signs of undergoing immune dysregulation such as autoimmune cytopenia, splenomegaly, lymphadenopathies, hepatopathy, elevated CD21low B cells, and increasing serum IgM. Thanks to spirometry, pulmonary function parameters can be monitored over time. If evidence of pathological lung decline is observed, particularly in DLCO, an HRCT should be performed to enable prompt identification of an underlying ILD.

Given that these disorders are mediated by immune dysregulation, treatment strategies are based on immunosuppression,

ranging from steroids to various types of target therapies. Although there are no clear criteria for initiating treatment, similar to other forms of ILD outside the context of PADs, the presence of progressive symptoms, evidence of lung function impairment on spirometry, and radiological progression are generally considered indications for starting therapy [91].

We will now focus on different treatment strategies for GLILD as a model for another kind of ILD in the context of PADs (Table 5).

In 2017, glucocorticoids were identified as the first-line treatment for GLILD by the BLF/UKPIN. Still, in the last few years, several studies have questioned the efficacy of corticosteroid monotherapy in maintaining long-lasting remission [92].

Indeed, a multicentre retrospective study showed that a course of high-dose corticosteroids (considered as ≥0.3 mg/kg of prednisone equivalent) improved FVC and HRCT scores in GLILD patients. However, long-term remission was achieved in less than half of the 18 patients included, without any benefits from low dose long maintenance therapy [93].

Another study showed similar results, suggesting mycophenolate as a maintenance therapy to prevent recurrence [94]. Other disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), cyclophosphamide, mycophenolate (MMF), azathioprine, cyclosporin, sirolimus, and hydroxychloroquine, have been used anecdotally with no clear outcome [92].

Considering the central role of B cells in GLILD pathogenesis, rituximab alone or in combination therapy (i.e. azathioprine or MMF) is one of the most promising therapies for GLILD. The efficacy of rituximab monotherapy (administered at 375 mg/m^2 monthly for six infusions, followed by maintenance every 3 months) was recently evaluated in a retrospective study involving six GLILD patients. After treatment, patients improved lung function parameters (particularly DLCO), chest CT imaging, symptom burden, and quality of life [95]. Other administration schedules include the standard hematologic dosage of 375 mg/m^2, on a weekly basis, for 4 consecutive weeks or the administration of 1 g for two times, 2 weeks apart, according to the classical rheumatologic schedule [92].

Given the underlying degree of immune dysregulation, a combination therapy of rituximab and azathioprine or MMF has been proposed to target both B and T cells simultaneously.

This approach has been shown to be effective, leading to improvements in both lung function and radiographic findings, however a possible higher risk of severe infections must be considered [96].

As discussed above, identifying underlying gene defects in CVID patients may also support a tailored approach for GLILD. For example, abatacept was successfully used in patients with CTLA-4 haploinsufficiency and with LRBA mutation with granulomatous manifestations [92]. Belimumab, an anti-BAFF monoclonal antibody, might also be a promising alternative treatment approach, considering the above-mentioned role of BAFF in the pathogenesis of both diseases.

Finally, among all treatment strategies, hematopoietic stem cell transplantation is the only potential curative alternative for GLILD, correcting the underlying immune defect. To date, there are only a few cases of GLILD patients treated with HSCT with variable outcome [92].

However, it is interesting to note that a recent multicenter study of IEWP, which retrospectively analyzed data from adolescent and adult patients with IEI who underwent HSCT, found that overall survival and event-free survival were lower in patients with primary antibody deficiency. This is probably a consequence of the high degree of comorbidity and lung impairment (e.g. GLILD and bronchiectasis) and hepatopathy in patients with PADs selected for HSCT [97]. For this reason, it is crucial to identify potential prognostic markers to select patients in which transplantation is the best treatment choice before the onset of complications and organ damage. Further studies on this topic are needed.

3. Conclusion

PADs are the most prevalent IEIs, accounting for more than 50% of all IEIs identified worldwide. Compared to other IEIs, PADs are associated with a more favorable long-term prognosis and are generally identified in adulthood. PADs have

Table 5. Key points to consider for treatment of GLILD in primary antibody deficiency.

TREATMENT STRATEGY FOR GLILD*	
CORTICOSTEROIDS	• According to BLF/UKPIN (2017) corticosteroids are suggested as first-line treatment. • Corticosteroid monotherapy has limited efficacy in maintaining long-term remission, with high-dose treatment improving FVC and HRCT scores but achieving sustained remission in less than half of cases and low dose maintenance therapy provided no benefit.
DMARDs	• Methotrexate (MTX), mycophenolate (MMF), azathioprine, and hydroxychloroquine use has been reported, either in monotherapy or in combination with rituximab. No clear outcome.
RITUXIMAB	• Monotherapy with different reported schedules for induction and maintenance. • Combination therapy (i.e. azathioprine or MMF) to target both B and T cells simultaneously. Possible higher risk of infections must be considered. • Case series describe a successful use in improving lung function parameters (particularly DLCO), chest CT imaging, symptom burden, and quality of life.
ABATACEPT	• Successfully used in patients with CTLA-4 haploinsufficiency and with LRBA mutation with granulomatous manifestations.
BELIMUMAB	• Anti-BAFF monoclonal antibody, a theoretical promising alternative treatment approach, based on the pathogenetic role of BAFF.
HSCT	• The only potential curative alternative, correcting the underlying immune defect. To date, there are only a few cases of GLILD patients treated with HSCT with variable outcomes. • Lower survival in patients with primary antibody deficiency, due to their high comorbidity rate and lung impairment. • It is crucial to identify potential prognostic markers to select patients in which transplantation is the best treatment choice before the onset of complications and organ damage.

*Genetic screening is highly recommended to potentially guide target therapy.

a systemic involvement with a particular tropism for the respiratory system, leading to considerable morbidity and mortality due to the disruption of both humoral and mucosal immune responses.

Our update underlies the need for a strict assessment and follow-up of the pulmonary involvement in PAD patients, both in patients with infection-related lung complications or in those with dysregulatory complications. The two groups display distinct immunologic patterns including low IgA serum level and reduced frequencies of memory B cells in the first group, often associated to laboratory (e.g. elevated IgM serum levels, increased baseline proportion of CD21 low B cells) and clinical (autoimmune cytopenia, splenomegaly, enteropathy, and liver disease) signs of immune dysregulation in the second one.

Conversely, in patients with autoimmune diseases and extrapulmonary involvement, detecting bronchiectasis and ILD at radiological imaging should raise the suspicion of an underlying immunodeficiency. In fact, if it could be easy to suspect a PAD in patients with recurrent bacterial infections or with infection-related lung disease, it could be more difficult for those who are not familiar with IEI to recognize a PAD in patients with noninfectious lung comorbidities, including ILD and GLILD.

Spreading the knowledge regarding these rare and 'atypical' pulmonary manifestations might hopefully lead to prompt PAD diagnosis, thus allowing to reduce the diagnostic delay, which is often associated with the development of chronic comorbidities that reduce quality (QoL) and expectancy of life.

Nevertheless, we recommend the evidence-based role of antibiotic prophylaxis, IgRT, and the use of immunosuppressant drugs in GLID patients. Once a diagnosis has been made, a personalized follow-up strategy, the evidence-based use of IgRT and antibiotic prophylaxis, and the use of immunosuppressant drugs in GLID patients might then lead to symptoms and QoL improvement, as well as prevent long-term complications.

4. Expert opinion

Due to the rarity of these conditions, currently, there are no validated guidelines on the proper screening and management of lung comorbidities in PAD patients.

According to good clinical practice borrowed from Italian Clinical Referral Centers for IEIs, we here suggest how to manage PAD patients at diagnosis and during follow-up (Figure 5).

At PAD diagnosis, the initial workup should include a high-resolution chest CT scan, PFTs encompassing global spirometry (with eventual post-bronchodilator test or methacholine challenge) and DLCO measurement and blood gas analysis; in case of significant impairment, a 6 min walking test and eventually cardiopulmonary exercise test (CPET) should also be considered [20]. In addition to CT, radiological imaging could include MRI, a radiation-free alternative to HRCT. MRI can indeed be considered as non-inferior to HRCT in the capacity to identify bronchial and parenchymal abnormalities; thus, it may represent a reliable technique to detect lung alterations in PAD patients, despite deserving further investigations [98].

About 50% of all PAD patients display abnormal radiological and functional tests that allow clinicians to identify lung complications including both chronic obstructive and infection-related patterns or restrictive patterns. Obstructive patterns are seen in cases of bronchiectasis, COPD, and asthma. Conversely, restrictive patterns are associated with interstitial lung disease such as GLILD [99].

In case of lung abnormalities at the HRCT scan, bronchoscopy with broncho-alveolar lavage (BAL) has an important diagnostic role in PAD patients. First of all, BAL can be useful for microbiological assessment in patients prone to recurrent infections or who do not respond to treatment, and, at the same time, it has a mechanical role in removing bronchial secretions. Conversely, BAL may play an important role in GLILD diagnosis. Indeed, the cytologic and flow-cytometric evaluation of the bronchoalveolar lavage fluid (BAL-F) contributes to differential diagnosis of GLILD. In GLILD, BAL-F is lymphocyte-enriched (>20%), with reports of decreased, increased (sarcoidosis-like) or normal CD4/CD8 ratio and with an expansion of B lymphocytes, dominated by CD21low B cells. Altogether, BAL-F findings might provide data on different underlying pathogenetic mechanisms and, in combination with HRCT scan, may in our opinion represent an alternative diagnostic tool to lung biopsy. In fact, surgical lung biopsy is still considered the gold standard for GLILD diagnosis [72], but the risk of performing a biopsy in PAD patients is clinically relevant. For this reason, in patients with clinical, radiological, and functional suspicion, we suggest a routine and widespread use of BAL-F, possibly in combination with a less-invasive transbronchial or extrapulmonary histology, to support a diagnosis of GLILD without the need for surgical lung biopsy, as it happens in sarcoidosis. Moreover, similar to sarcoidosis, PET/CT scan is also gaining relevance in the differential diagnostic process of GLILD, providing a whole-body disease assessment and driving the bioptic approach when needed. In addition, to support a noninvasive diagnosis, different algorithms have been proposed; hopefully, their validation will allow early identification of CVID patients with interstitial lung disease, particularly if based on the combination of clinical, immunological, radiological, and functional parameters routinely available in clinical practice (72).

After initial pulmonary assessment, radiological and functional data of PAD patients should be integrated with the type of immunological background. In addition to dosage of serum levels of IgG, IgA, and IgM, percentage of memory and CD21 low B cells, assessing the response to pneumococcal polysaccharide vaccinations is one of the diagnostic criteria for common variable immune deficiencies to test the ability of a T-independent response. In addition, the immune response to an antigen, analyzing specific and neutralizing antibodies, spike-specific memory B cells, and functional T cells, allows stratification of patients in different functional groups a less or more severe clinical phenotype underlying the possibility to use immunization also as a prognostic too. In addition, the results of the genetic screening (strongly recommended in all GLILD patients) help to design a 'tailored' management and treatment strategy [72]. This can be achieved by: optimizing the route and the dose of IgRT, evaluating the need for antibiotic prophylaxis, treating the obstructive disease or ILD (if present) with pharmacological and non-pharmacological approaches, and defining the proper timing of follow-up.

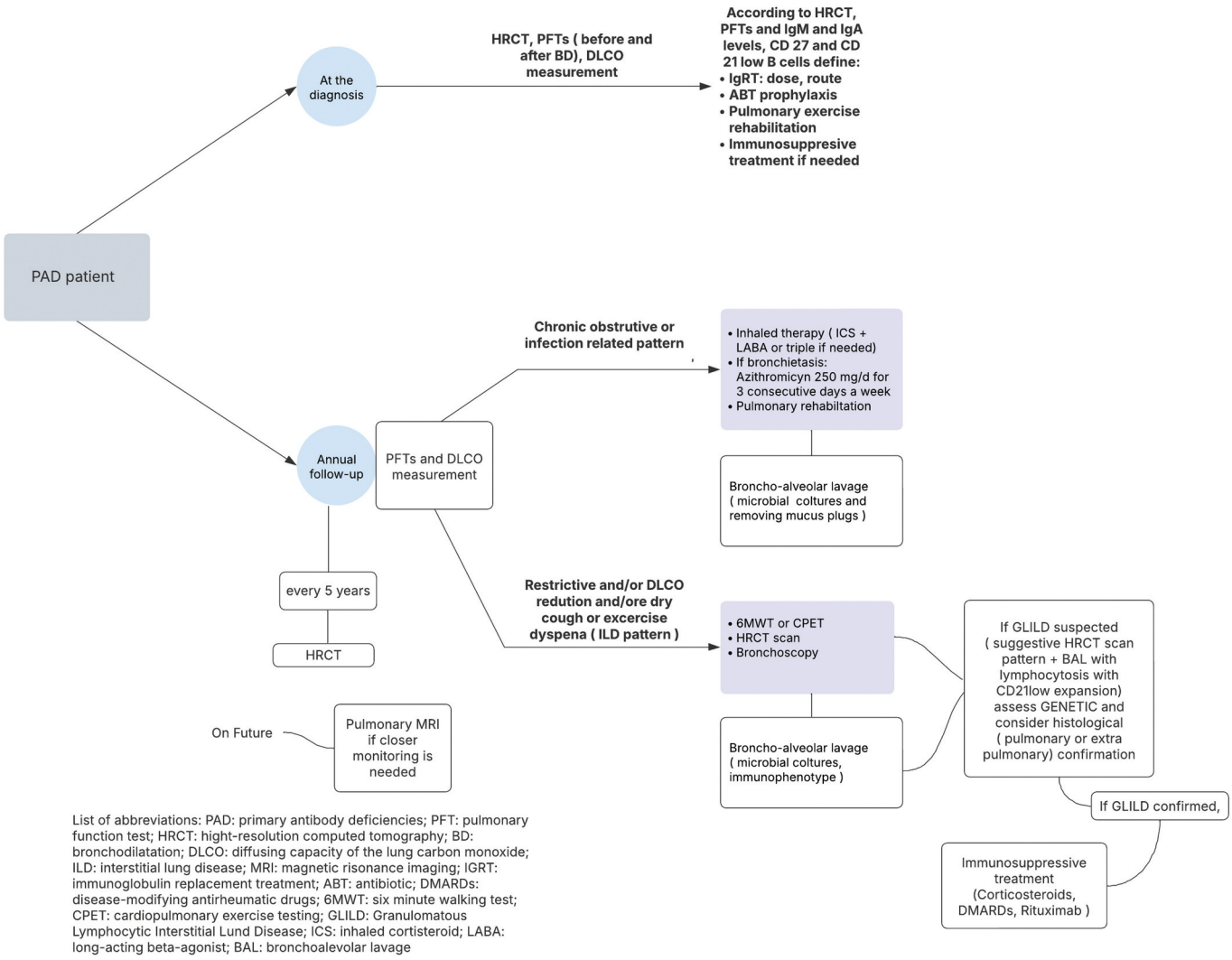


Figure 5. Algorithm approach to lung involvement in PADs.

In patients with bronchiectasis, COPD and asthma, higher doses of IgRT are useful to achieve higher IgG TL and to better control the vicious circle infection-inflammation otherwise leading, over time, to lung damage and functional decline. In line with this, we found that a severe reduction in switched memory B cells (<2%) and lower IgG TL appear to be associated with worse pulmonary function (13). Conversely, GLILD patients require a higher dose of IgRT to reach IgG trough levels similar to patients without ILD, due to a sort of 'peripheral consumption' [100].

In addition, patients with infection-related lung comorbidities, particularly if lacking IgA and frequently exacerbating, may benefit from antibiotic prophylaxis with azithromycin also for its anti-inflammatory and immunomodulatory effect [23].

Moreover, in all PAD patients, vaccinations against bacterial and respiratory viruses, including annual *Influenza* and *SARS-CoV-2*, should be encouraged, even if a subgroup of patients develops a suboptimal response to immunization. Several studies demonstrate that vaccinations are well tolerated and safe and need to be scheduled regularly [31,101].

Additionally, patients with asthma or COPD should be treated with inhaled corticosteroids and bronchodilators according to disease-specific guidelines.

On the other hand, no treatment guidelines are available for GLILD; different therapeutic schedules have been proposed, but the optimal management remains controversial. Indeed, there is still no consensus on when to initiate treatment, in lack of studies clearly demonstrating an advantage from early treatment in comparison to watchful waiting. Nonetheless, considering the high burden of multifactorial chronic lung disease in PAD patients, in our opinion early signs of clinical, radiological and/or functional ILD progression should support an interventional strategy. In this scenario, we proposed a not yet validated model combining immunological markers (marginal zone B cells percentage and IgA serum levels) and radiologic findings (presence of lung lower field consolidations and lymph nodes enlargement) as a possible predictor of the need for a GLILD-specific pharmacologic therapy [82].

Several papers suggested using corticosteroids as the first line of treatment with ambivalent results in maintaining long-

lasting remission as well as reported for mycophenolate to prevent recurrence [92–94].

Promising results are related to the use of rituximab because of the central role of B cells in the pathogenesis of the disease. Rituximab, alone or in combination with immunosuppressive drugs, demonstrated efficacy in improving lung function parameters, chest CT imaging, symptom burden, and quality of life [65,95].

In consideration of its safety profile (also compared to glucocorticoids), rituximab monotherapy has been gaining consideration over the last few years as the first choice for immunosuppression in GLILD patients. After the first course, data on maintenance therapy (rituximab *versus* conventional DMARDS) are extremely limited; however, rituximab has been successfully used also as a long-term monotherapy, with different proposed administration schedules.

In this scenario of lack of evidence-based data, it is important to highlight that GLILD patients deserve genetic screening. Indeed, while no specific treatment is recommended for unmutated patients and rituximab has been shown to be effective in TACI mutated CVID patients [76], in specific monogenic forms of antibody deficiencies, a more tailored approach might be available, as in CTLA4 haploinsufficiency where abatacept is the treatment of choice. For this reason, genetic screening is strongly recommended in PAD patients with ILD and, more in general, with noninfectious complications. In the next future we expect to achieve, by a combination of genetic, immunologic, and functional information (including evaluation of pathways-specific mediators in BALF and serum), a better understanding of the underlying pathogenic mechanisms might vary between different individuals. This could pave the way for new targeted therapeutic interventions: anti-BAFF in patients with elevated IgM levels, abatacept in those with typical features of CTLA-4/LRBA impairment, JAK inhibitors in the presence of altered interferon signatures, mTOR-inhibitors like sirolimus in patients with ALPS-like lymphoproliferation and early HSCT in patients with a high risk of developing severe forms of the disease.

In addition, all PAD patients with chronic lung disease may take advantage of cycles of respiratory rehabilitation that are not a PAD-specific treatment but might have a significant impact on symptoms and QoL [27,29].

Regarding follow-up, lung disease screening and monitoring in PAD patients should include annual PFTs with DLCO and on-demand imaging and microbiological assessments in case of respiratory infections. Moreover, we suggest performing high-resolution chest CT scans at least once every 5 years in asymptomatic patients. It is still unclear if early detection of ILD should lead to treatment initiation in asymptomatic patients and no validated prognostic scores are currently available, but radiological signs may anticipate symptoms onset and functional impairment and awareness of ILD may be in turn at least helpful in designing a personalized follow-up schedule. In presence of clinical conditions suggesting an infectious episode and worsening of respiratory symptoms or functional test indicative of interstitial lung disease, clinicians should consider anticipating the HRCT scan to ensure a prompt diagnosis. Being aware of the concerns of radiation exposure of an already 'at risk' population, we expect that MRI will become standardized and routinely used in ILDs allowing to clinicians to be more confident in prescribing more frequent lung imaging, in particular in patients that need a close follow-up due to increased risk of developing GLILD or to an already diagnosed GLILD without immediate indication to treatment [98]. Finally, concerning GLILD re-assessment after treatment initiation, we generally suggest to wait at least 3 months before PFTs and DLCO reevaluation and to reschedule a high-resolution CT scan between 3 and 6 months, in order to drive the choice on maintenance therapy that, in case of rituximab, generally begins after 3 or 6 months since the first administration. If a PET/CT scan has been performed before treatment, showing extrapulmonary involvement of granulomatous or non-clonal lymphoproliferative disease, we also recommend PET/CT repetition at least 3 months after the rituximab induction course, or at the end of the glucocorticoid tapering in case GC had been the treatment of choice. After the first post-treatment functional and radiologic evaluation, further follow-up assessments should be scheduled on a personalized basis, with PFTs and DLCO to be initially performed every 6 months.

In conclusion, despite different treatment approaches including Ig replacement therapy, antibiotic prophylaxis, and immunosuppressive drugs, infection- and non-infection-related chronic lung diseases are the most frequent complication reported in PAD patients, with a profound impact on burden of disease, QoL, and mortality. For this reason and given the heterogeneity of PAD, it is mandatory to identify immunological, genetic, clinical, and radiological markers that could be used as early predictors of presence, type, and severity of lung involvement. Further studies are needed to develop and validate prognostic scores and management protocols, to achieve personalized interventional and follow-up strategies.

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