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REVIEW

Appropriate lung management in patients with primary antibody deficiencies

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ABSTRACT

Introduction: Human primary immunodeficiency diseases (PIDs) include a broad spectrum of more than 350 disorders, involving different branches of the immune system and classified as 'rare diseases.' Predominantly antibody deficiencies (PADs) represent more than half of the PIDs diagnosed in Europe and are often diagnosed in the adulthood.

Areas covered: Although PAD could first present with autoimmune or neoplastic features, respiratory infections are frequent and respiratory disease represents a relevant cause of morbidity and mortality. Pulmonary complications may be classified as infection-related (acute and chronic), immune-mediated, and neoplastic.

Expert opinion: At present, no consensus guidelines are available on how to monitor and manage lung complications in PAD patients. In this review, we will discuss the available diagnostic, prognostic and therapeutic instruments and we will suggest an appropriate and evidence-based approach to lung diseases in primary antibody deficiencies. We will also highlight the possible role of promising new tools and strategies in the management of pulmonary complications. However, future studies are needed to reduce of diagnostic delay of PAD and to better understand lung diseases mechanisms, with the final aim to ameliorate therapeutic options that will have a strong impact on Quality of Life and long-term prognosis of PAD patients.

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Primary antibody deficiencies; GLILD; CVID; bronchiectasis; lung MRI

1. Introduction

Human primary immunodeficiency diseases (PIDs) include a broad spectrum of disorders (more than 350 according to the International Union of Immunological Societies – IUIS – classification), involving different branches of the immune system [1]. Most of them are defined by a well-known underlying genetic defect [1,2]. PIDs are known as 'rare diseases,' but their global incidence might be much more relevant than what generally thought [3]. It has been estimated that something around 6 million people worldwide might be affected by a PID, no more than 1% of which having been definitely diagnosed [4]. The immunologic defect may be broad or extremely selective/specific, implying a huge heterogeneity in infectious manifestations, both in terms of severity and range of involved pathogens [1]. Moreover, infections might not be the main features of certain PIDs (e.g. hereditary angioedema, IPEX or auto-inflammatory disorders). Indeed, the first clinical presentation of some PIDs may be an autoimmune disease or cancer [5,6]. This variability gives a reason for the high degree of underdiagnosis or diagnostic delay.

Despite representing a small number of the IUIS-recognized diseases, predominantly antibody deficiencies (PADs) represent more than a half of the PIDs diagnosed in Europe, according to the ESID registry, and the percentage increases if we consider adult patients [7]. Either B cell intrinsic or B cell extrinsic defects may lead to the impairment in antibody production, but the genetic and mechanistic etiologies are still unknown for the majority of patients. The most prevalent symptomatic PAD, indeed, Common Variable Immunodeficiency (CVID), is characterized by a variable phenotype whose genetic basis is still under investigation [8].

Compared to cellular or combined immunodeficiencies, defects of the humoral immune response tend to have a better long-term prognosis and are often diagnosed in the adulthood, with a peak around the third decade of life [9]. A recent paper based on ESID registry reported a median age at diagnosis of 31 and a mean of 31.4 years for CVID [10]. Respiratory disease is a relevant cause of morbidity and mortality in PAD patients [11]. Pulmonary complications may be classified as infection-related (acute and chronic), immune-mediated and neoplastic [12]. Respiratory tract infections (RTI) need an immediate and appropriate diagnostic approach. Due to recurrence, underlying immune defects, diagnostic delay, and not always appropriate management, infections may lead to long-term consequences on airways architecture and function, inducing bronchiectasis, COPD and poor asthma control. Immune-mediated complications encompass a range of interstitial lung diseases (ILDs), that might all be part of a specific entity called GLILD (Granulomatous-Lymphocytic Interstitial Lung Disease). Finally, malignancies are a major cause of morbidity and mortality in PAD and may involve the respiratory tract [5,6,11,13].

No worldwide accepted or European consensus guidelines are currently available on how to monitor and manage lung complications in PID patients. A recent survey, indeed, showed

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Article highlights

- Internationally recognized evidence-based guidelines need to be designed, in order to standardize the approach to diagnosis, monitoring, and treatment of lung diseases in PAD. This will go through technical improvements and new acquisitions in terms of pathogenic mechanisms and will reduce the diagnostic delay of lung complications, improving patients' QoL and survival.
- IgG replacement therapy enhances survival and reduces severe and invasive infections. However, patients might still develop chronic infection-related lung disease (CLD). Adjunct therapies as Azithromycin prophylaxis, pulmonary rehabilitation, and new IgA and IgM enriched Ig preparations that will soon be available need to be included in standardized guidelines, in order to prevent the progression of CLD.
- HRCT scan still represents the gold standard for lung imaging in PADs. Recent evidence supports the possible role of lung magnetic resonance imaging (MRI) in diagnosing and monitoring lung disease in PAD patients. Without exposure to ionizing radiation, recently developed chest MRI techniques might offer both structural and functional information in a single examination. MRI is thus destined to become a routinely used lung imaging approach for PAD patients.
- GLILD, whose diagnosis is currently based on a multi-step process culminating in an invasive open-lung or VATS biopsy, still represents a great challenge. In the next future, the diagnostic process will hopefully move to a more clinical-radiologic-plus-MDT-discussion-based approach, with an increasing importance of BAL. Cryo-biopsy will likely become the first-line approach when a lung tissue biopsy is needed.
- In terms of treatment, we are looking for interesting correlations between GLILD behavior and possible predisposing factors, underlying genetic defects, concomitant conditions, peripheral blood or BALF lymphocytes distribution, histochemical characterization of tissue samples. These correlations will emerge from ongoing observational studies and from case series, allowing clinicians to consider more tailored treatment strategies either on the basis of patients' classification in subgroups, or starting from the immunologic mechanisms highlighted in each single patient.
- Starting from a better understanding of mechanisms and correlations, relatively large multicenter-controlled trial with existing drugs will be designed, hopefully leading to PAD-specific evidence-based treatment guidelines for ILDs.

a great heterogeneity in the frequency of clinical, functional and radiologic evaluation of patients' lung health across Europe [14]. Herein we will discuss the available diagnostic, prognostic and therapeutic instruments and we will suggest an appropriate and evidence-based approach to lung diseases in primary antibody deficiencies. We will focus on those diseases listed between the 'predominantly antibody deficiency' in the IUIS classification, particularly referring to those in which IgG replacement represents the standard of therapy [1].

2. Primary antibody deficiencies

The spectrum of Primary Antibody Deficiencies ranges from conditions with Mendelian inheritance, as X-linked (XLA) or autosomal recessive Agammaglobulinemia, to diseases with predominant polygenic inheritance, such as Common Variable Immunodeficiency (CVID) [9]. Mature B cells may thus be absent, as in XLA, or may present an almost normal development, being selectively impaired only the antibody response to polysaccaridic antigens, as in Specific Antibody Deficiencies (SpAD). Inadequate response to micro-organisms goes together with a poor response to vaccination (e.g. 23-valent anti-pneumococcal vaccine), that is indeed included between the diagnostic criteria for CVID [9].

Due to the lack of protective antibodies, the respiratory tract is the major target for acute infections, requiring immunoglobulin replacement therapy and frequent courses of antibiotics [15,16]. Recent studies underline that IgG replacement therapy enhances survival and reduces risk of pneumonia and other invasive infections [17], but substitutive therapy, even at high dose, cannot block the development of chronic infection-related pulmonary diseases [18,19].

Apart from the infection-related symptoms, PAD may be characterized by an increased incidence of allergic and autoimmune diseases, polyclonal lymphoproliferation and cancer, due to an underlying immune dysregulation usually accompanying the immune defect [20–22].

3. Pulmonary complications of PADs and their management

3.1. Infections and infection-related diseases

PAD-associated acute infections (e.g. pneumonia) and chronic infection-related lung diseases (bronchiectasis, COPD) have been accurately described in several reviews and retrospective studies [12,23–25]. The defect in antibody-mediated response explains the susceptibility to bacterial infections and their recurrence. The impaired response also influences the time to complete recovery despite appropriate treatment, the rate of colonization in the presence of bronchiectasis and the degree of resistance following the repeated use of antibiotics [25]. Selective IgA deficiency (sIgAD) may be asymptomatic or mildly symptomatic in terms of infections, that mainly involve the respiratory tract [26]. The co-existence of an IgG subclass deficiency may significantly worsen the infectious phenotype [27]. IgG deficiency is characterized by recurrent sinopulmonary infections, with rates of sinusitis and pneumonia similar to CVID; CVID patients, however, present a significantly higher prevalence of bronchiectasis and of non-infectious complications [28]. Moreover, diseases as congenital agammaglobulinemia and hyper-IgM syndromes (HIgM) (when due to a defective CD40:CD40 ligand interaction), may present a deeper immune defect if compared to other PADs, leading to a more severe infectious phenotype with increased susceptibility, respectively, to certain viral infections or to opportunistic infections like *Pneumocystis Jirovecii* [29,30]. More in general, it has been suggested that in PADs the impairment in immune response might be broader than what commonly thought, involving multiple non-B cell immunological defects, such as T-cell, MBL, TLR, AMP deficiency, and/or impaired neutrophil function [31]. Recent studies, indeed, highlighted the increased frequency of viral infections and viral-plus-bacterial co-infections in PAD patients, particularly during symptomatic respiratory exacerbations [25,32]. This might explain why, in agammaglobulinemic as in some CVID patients, chronic lung disease progression still occurs despite maintaining an appropriate IgG trough level, with a rate of decline in lung function that is approximately twofold in CVID patients compared to the rate of healthy non-smoking adults [24,33,34].

3.1.1. Acute infections

To promptly manage acute pulmonary infections in PAD patients, early imaging (computed tomography [CT] scan) and specific microbiologic sampling represent the optimal approach. The latter may require non-invasive tests (e.g sputum culture), but invasive procedures (e.g. bronchoscopy to reveal bacterial grown in bronchoalveolar lavage fluid, lung biopsies in case of solid/cavitary lesions) are often necessary to obtain a representative sample. Once the microbiologic diagnosis is established, an antimicrobial susceptibility test will determine the drug of choice. Sometimes advanced diagnostic testing including immunohistochemistry and quantitative molecular assays may be performed as additional components in the diagnostic algorithm [35,36].

The importance of early antimicrobial therapy cannot be overemphasized, accordingly broad-spectrum antimicrobial therapy must be started as soon as possible, considering patients' epidemiologic history and any prior microbiologic data or previous courses of antimicrobial agents. A list of the most involved pathogens is reported in Table 1. Once the microbiologic diagnosis is made, empiric therapy can be modified accordingly. The optimal duration of antimicrobial treatment of PAD patients has not been defined, even if is generally accepted the need for longer courses if compared to immunocompetent individuals. Experienced clinicians often prescribe courses of antimicrobials that are at least two times longer than standard recommendations.

Furthermore, to provide adequate Ig replacement therapy is essential in this context. As no specific IgG trough concentration has been defined, target IgG trough level should be the one able to keep the patient infection-free [24]. Therefore, transiently, higher doses of Ig (600–800 mg/kg/month) may help to clear acute bacterial infections and possibly to prevent the evolution towards chronic lung disease [45,46].

3.1.2. Chronic infection-related airways diseases

The cumulative incidence of chronic lung diseases has been decribed to reach 80% after a 17-year follow-up in a cohort of XLA patients [47] while in CVID, the incidence of bronchiectasis has been shown to increase over time for almost all age groups, leading to an increased risk of death [24,25,48]. More generally, a recently published study showed radiological evidence of bronchial pathology (bronchiectasis in 61%, bronchial wall thickening in 44% and mucus plugging in 29%) in 80% of chest HRCT scan of a multicenter cohort of CVID patients [49]. Chronic infection-related lung damage (e.g. bronchiectasis) has not been reported as a significant feature of sIgAD [26,50]. The co-existence of an IgG subclass deficiency has been shown to be crucial in terms of chronicity and severity of lung disease [27]. The high incidence of chronic lung diseases is a direct consequence of diagnostic delay, severity of the infectious respiratory phenotype, and difficulty to define appropriate treatment strategies. The recurrence of acute infections over these underlying chronic lung conditions has been proposed to be defined as respiratory exacerbations of PAD patients, using the definition already validated for COPD [25]. Respiratory exacerbations in PAD are mainly caused by encapsulated bacteria. Despite an appropriate IgG replacement therapy, indeed, low IgM and particularly low IgA serum levels have been found to be risk factors for S. pneumoniae and H. influenzae airways colonization [51]. Chronic lung disease (CLD) is a relevant cause of mortality in PAD patients. In a cohort of XLA patients, after 25 years of follow-up, 38% of deaths were due to CLD. In an Italian cohort of CVID patient, death for respiratory failure due to chronic lung disease accounted for 30.4% of all causes of death [6,47].

3.1.2.1. Bronchiectasis. The most prevalent chronic infection-related lung disease diagnosed in PADs is bronchiectasis [10,34]. Other chronic pulmonary complications affecting airways include chronic obstructive pulmonary disease (COPD) and asthma [31,52]. Bronchiectasis present as atypical bronchial and bronchiolar dilatations, resulting from a 'vicious cycle,' in which repeated episodes of infection and inflammation lead to the destruction of the airways and lung parenchyma, with a consequent decline in lung function [31,53–55] (Figure 1). A recent retrospective study on adult patients with primary antibody deficiencies reported 47% suffering from bronchiectasis; history of LRTI was the only factor directly associated with the development of bronchiectasis [19,56]. However, it has also been demonstrated that, once the remodeling process is ongoing, airway inflammation gets worse even in the absence of bacterial infection. This is related to neutrophil accumulation through an increase in pro-inflammatory cytokines expression and adhesion molecule production. Over time, airway inflammation leads to hyper-reactivity, further lung remodeling, and development of new bronchiectasis [57,58]. In PAD patients, defects and dysregulation of the immune system further enhance this vicious cycle [31].

3.1.2.2 Management. The management of bronchiectasis has been extensively studied in cystic fibrosis (CF) patients. On the contrary, there is no standardized treatment for adult non-cystic fibrosis bronchiectasis (NCFB), including those related to PIDs, and therapeutic strategies tend to be simply extrapolated from CF clinical trials [59]. Several clinical trials

Table 1. Infectious pathogens reported in respiratory tract infections (RTI) in PADs.

Type of pathogen	*Isolated pathogen*	Reference
Bacteria	Frequent: *Haemophilus influenzae type B, Streptococcus pneumoniae, Pseudomonas* spp, *Staphylococcus* spp. (incl. Methicillin resistant), Mycoplasma spp, *Neisseria meningitidis, Moraxella* spp. Rare: *Klebsiella* spp, *Bordetella pertussis, Chlamydia trachomatis, Ureaplasma urealyticum, Fusobacterium*spp, *Serratia* spp, *Stenotrophomonas maltophilia, Enterobacter*spp, *Proteus* spp, *Achromobacter xylosoxidans, Citrobacter* spp.	[25,31,32,37–40,92]
Virus	*Rhinovirus, Adenovirus, Coronavirus, Influenza A, Influenza B, enterovirus, RSV, hMPV*	[31,41,42]
Opportunistic pathogens (rare, reported in XLA and HIGM)	*Mycobacterium hominis, Mycobacterium avium, Pneumocystis Jirovecii*	[29,31,40,43,44,92]

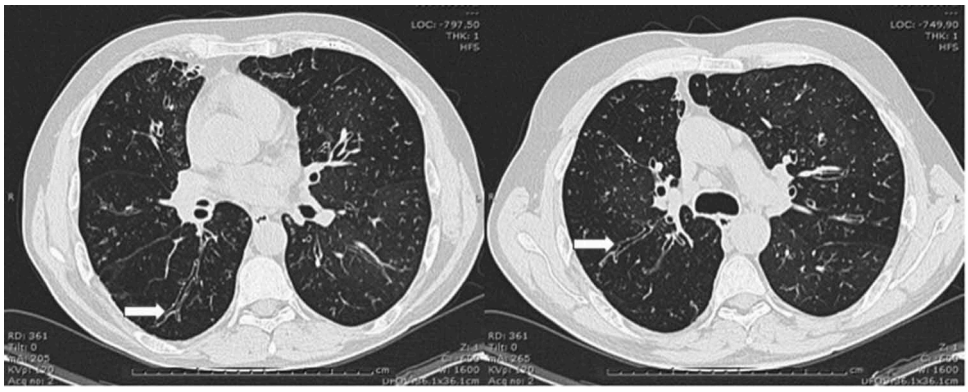

Figure 1. Bronchiectasis in a CVID patient. Panels show bronchiectasis (arrows) in a CVID patient in two different slices of a chest high-resolution CT scan.

have proven that macrolide antibiotics are effective to successfully manage cystic fibrosis (CF), non-CF associated bronchiectasis (NCFB), COPD, and asthma [60–64] all conditions with a lower rate of respiratory exacerbations in comparison to severe PAD. Macrolides, especially azithromycin, have antimicrobial, immunomodulatory and anti-inflammatory properties, and prevent the development of the biofilm produced by bacteria, acting on the vicious circle infection-inflammation that leads to airway hyper-reactivity and remodeling [57]. Differently from these respiratory diseases, no guidelines to manage respiratory diseases in PAD patients are available. Despite lacking specific evidence, physiotherapy programs and antibiotic prophylaxis have been routinely used in PAD patients with bronchiectasis [65–67]. Only few reviews have been written on the use of antimicrobial prophylaxis in PAD. According to these papers, the efficacy of antimicrobial prophylaxis in PADs patients remains uncertain and the risk of bacterial resistance makes this practice poorly widespread. However, PAD patients might take advantage of antibiotics prophylaxis [8]. Up to now the use of antibiotic prophylaxis in CVID has been heterogeneous and mainly based on single-institution-specific experience [68]. There has been no consensus on which antibiotic agent to use, at what dose (half of a therapeutic dose, full doses) and on how to schedule the prophylactic regimen (intermittent single agent, rotational antibiotics, periodically changing antibiotics monthly to every 6 months). Moreover, the available reports were neither based on randomized clinical trial, nor associated with controlled measurements of patients safety and quality health outcomes [69]. Recently, new data on antibiotic prophylaxis in PAD patients became available from a 36-month, Phase II, randomized, double-blind, placebo-controlled, multi-center clinical trial on long-term prophylactic treatment with azithromycin in adult PAD patients [70]. In that trial, 89 PAD patients with bronchiectasis and/or COPD were enrolled. Patients received for 24 months either azithromycin, 250 mg once daily for three consecutive days per week, or an identical-appearing placebo. The study showed that long-term oral azithromycin prophylaxis in patients affected by primary antibody deficiencies and chronic infection-related pulmonary diseases significantly reduced the episodes of respiratory exacerbations per patient-year. Moreover, in the group of patients receiving azithromycin, the number of additional courses of antibiotics for treating respiratory exacerbations was lower than in the placebo group, as well as the number of hospitalizations. In addition, after starting azithromycin, decreased counts of absolute number of WBC and neutrophils were observed. The administration of azithromycin was proven to be safe as no serious adverse events or drug-related cardiovascular mortality were reported. It had been previously demonstrated that daily intake of low dose of azithromycin resulted in development of azithromycin-resistant pathogens, whereas the same dose given 3 times a week did not increase bacterial resistance [71]. During the study time, indeed, an increased rate of macrolide-resistant organisms was not observed in the azithromycin compared to the placebo group [70]. These results were comparable with those already provided by other similar randomized studies done in COPD, in CF patients and in non-CF patients with bronchiectasis, although a lower azithromycin dosage has been used [60–64]. The efficacy of a low-dose macrolide prophylaxis on PAD respiratory exacerbations could be related both to antimicrobial and anti-inflammatory action of the macrolides and is confirmed by the decrease of neutrophils count [70].

Although an increased rate of macrolide-resistant organisms was not observed, physicians need to take into consideration the evidence that macrolides resistance is increasing [72,73]. However, the risk of driving a bacterial resistance because of long-term macrolide prophylaxis could be balanced by benefits on the overall bacterial resistance due to the reduction of number of antibiotic courses. In the trial, no sputum sample positive for non-tuberculous mycobacterial infection was identified. Despite that, clinicians have to take into account that azithromycin could also select resistant non-tuberculous mycobacteria if mycobacterial infection is present, especially in presence of bronchiectasis, thus predisposing to non-tuberculous mycobacterial infection, in the same way as in CF [74]. As a consequence, pulmonary nontuberculous mycobacterial infection should be ruled out before starting long-term azithromycin prophylaxis [74]. On the basis of the above-mentioned evidence, however, adding azithromycin to the treatment regimen of PAD patients with chronic infection-related pulmonary diseases may be considered a good choice.

Apart from antibiotic prophylaxis, physiotherapy represents another standard adjunct to therapy in NCFB that is used in PAD patients with bronchiectasis and chronic lung disease,

despite lacking consensus guidelines stating a precise indication and the best approach [75,76]. A supervised Pulmonary Rehabilitation and Exercise Training programs might be recommended to certain patients, even though a short-term improvement in exercise capacity and Heath-Related QoL, does not necessarily predict to a long-term benefit [77].

3.1.2.3. Asthma and COPD. Chronic airways inflammation due to recurrent infections may lead to airway hyper-reactivity and remodeling, with reversible or fixed obstruction. Indeed, an impaired antibody response has been suggested as a possible cause of COPD in those patients without smoking history and/or alpha-1 proteinase inhibitor deficiency [78]. An association between bronchial hyper-reactivity after methacholine challenge test and PADs has also been highlighted, particularly when an IgA deficiency is present [79]. PAD patients also present an increased frequency of allergic diseases. Thus, frequently exacerbating asthmatic and COPD patients are more likely to receive a diagnosis of PAD, particularly sIgAD, SpAD, IgG subclass deficiency, and CVID [80,81]. This association may account for the increased frequency of bacterial infections driving acute exacerbations of the underlying respiratory disease and for the inadequate control despite optimal medical therapy [81,82]. All these considered, PADs should be ruled out in frequently exacerbating COPD and severe uncontrolled asthmatic patients, even if sometimes the distinction between primary and secondary antibody deficiency might be complicated [78,83].

3.1.2.4 Management. The presence of bronchial hyper-reactivity and fixed obstruction must be ruled out in PAD patients, performing a complete plethysmography and, when appropriate, a methacholine challenge. The standard medical therapy for asthma and COPD may be applied to PAD patients. Moreover, there is evidence of a positive impact of Ig replacement therapy on chronic obstructive lung diseases, leading to amelioration of airway obstruction and reduction in the frequency of exacerbations, particularly in asthmatic and COPD patients with previously undiagnosed PAD [84–86]. Azithromycin prophylaxis and pulmonary rehabilitation programs may also be helpful. The consequent reduction in courses and cumulative annual dose of oral corticosteroids, potentially further lowering the gamma-globulin serum levels, rescue antibiotic use, and hospitalizations for acute respiratory exacerbations of asthma and COPD may have a significant impact on QoL, development of antibiotic resistance and healthcare costs.

3.2. Immune-mediated lung diseases

Apart from infection-related complication, a great challenge in PAD patients' management is currently represented by the Interstitial Lung Diseases (ILDs). Despite a possible role of infectious agents as triggers having been hypothesized, the hallmark of ILDs is represented by immune dysregulation; the whole pathogenic mechanisms, however, are still far from being understood [87–90].

3.2.1. Interstitial lung diseases

As for immunocompetent patients, ILDs consist of a group of diseases relying on a chronic inflammatory and often pro-fibrotic process clinically characterized by the insidious onset of dry cough and dyspnoea on effort. Commonly, symptoms do not occur in the initial stages, and an unrecognized or lately recognized disease progression may lead to pulmonary fibrosis, possibly complicated by pulmonary hypertension, cor pulmonale, and progressive respiratory failure. In terms of lung function, a decrease in carbon monoxide diffusion capacity could precede the onset of a restrictive pattern at PFTs. Thus, a DLCO reduction should be investigated by additional dynamic functional testing, as 6-min walking test (6MWT) or Cardiopulmonary Exercise Test (CPET). Chest imaging (HRCT) modifications may also anticipate clinical and functional manifestations [91].

ILDs, rather than recurrent infections and bronchiectasis, have been suggested as the main cause of a decline in lung function in patients with CVID [11]. Moreover, the prevalence of ILDs in PAD patients with recurrent respiratory infections has been reported as much higher than expected in the general population [11,92,93]. A prevalence of at least 10–20% has been reported in CVID, but it is likely underestimated [94,95]. ILDs have also been reported in other PADs. Occasionally, they may be found in selective IgA deficiency, particularly when associated with IgG subclass deficiency and to a clinical phenotype dominated by autoimmune features [16]. More commonly, they have been described as a feature of CTLA-4 haploinsufficiency and STAT3 gain-of-funtion mutations [96,97]. Granulomatous or Lymphocytic ILDs have also been described in patients with a CVID phenotype and an underlying defect in recombination-activating gene 1 (RAG1), and in lipopolysaccharide responsive beige-like anchor protein (LRBA) deficiency [98–101]. Finally, Granulomatous-lymphocytic ILD (GLILD) has been reported in at least two patients with 22q11.2 deletion syndrome [102]. On the other hand, there is no evidence of ILDs in different cohorts of HIGM syndrome and congenital agammaglobulinemia patients [16]. Thus, the diagnostic process of a primary antibody deficiency with ILD features should be completed with a genetic analysis, aimed at identifying defects as LRBA or CTLA-4 deficiencies that, for instance, belong to the group of 'diseases of immune dysregulation' of the IUIS classification of primary immunodeficiencies. In terms of severity, there are no data showing specific associations between ILD severity and the type of PAD.

Different ILD patterns have been described in PADs, including follicular bronchiolitis (FB), nodular lymphoid hyperplasia, sarcoid-like granulomatous disease, organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), non-specific interstitial pneumonia (NSIP) and hypersensitivity pneumonitis (HP), with possible radiologic and histologic overlapping features [100,103–105]. There is no consistent correlation between specific ILD patterns and a particular immune deficiency [11]. Systemic immune-mediated disorders potentially affecting the lung interstitium may also be present in patients with primary antibody defects (e.g. vasculitis and connective tissue diseases) [92].

3.2.1.1. GLILD. More recently, the 'umbrella' definition of 'granulomatous lymphocytic interstitial lung disease' (GLILD) has been adopted, encompassing granulomatous disease and all forms of pulmonary lymphoid hyperplasia (PLH) found in PAD

[95,106]. The exact borders of this definition may appear still not clear but, due to its broad spectrum of histologic and radiological patterns, it has been described as the most common ILD in PADs (Table 2). Thus, we will subsequently refer to GLILD as a spectrum of diseases rather than to a single, univocal disease.

According to the British Lung Foundation/UK-PID Network consensus statement, GLILD represents 'a distinct clinico-radio -pathological 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' [108]. GLILD has been associated with poor clinical outcomes. Its pathogenesis and appropriate management are currently under investigation [11,18,105]. Infectious agents may act as triggers, as hypothesized for other granulomatous diseases [90,109]. GLILD is usually described as part of a multisystem granulomatous/inflammatory disease, potentially involving lymph-nodes, spleen, liver, GI tract and/or other organs [108,110]. The presence of splenomegaly, past or present immune cytopenias (ITP or AIHA), low serum IgA levels, higher IgM levels, and percentage expansion of CD21low B cells have been suggested as highly sensitive predictors, allowing the identification of a subset of PAD patients with higher risk for developing GLILD [111,112].

The main histopathological features are represented by peri-bronchiolar and/or interstitial lymphocytic infiltration and sarcoid-like non-caseating granulomas. Features of organizing pneumonia and interstitial fibrosis may also be seen in a significant proportion of patients. The ectopic B cell follicles express markers of germinal centers and proliferation despite the underlying B cell maturation defects [95]. T cells (particularly CD4+) have been described as the predominant lymphocyte population in most patients; B cell tissue predominance is less frequent. Regulatory T cells (Treg) have been reported as almost absent [100,105].

Despite prognosis having been described as poor, no specific data are available regarding ILD-related mortality in PAD patients. It is likely that mortality due to chronic lung disease in PAD cohorts includes also ILD-related mortality, at least in those PADs known to be potentially complicated by ILDs [113]. What we know is mainly derived from CVID-based studies. In a single-center CVID cohort from Colorado, U.S., a significantly worse survival was found between GLILD and all other non-infectious lung complications [105]. Poorer survival in CVID has been associated with the prevalence of GLILD (and cancer) in a recent retrospective analysis of the European Society for Immunodeficiency (ESID) registry data, while the presence of granulomatous disease (including extrapulmonary location) has not been related to a significantly reduced survival in a U.S.-based cohort [10,113].

3.2.1.2 Management. As for other ILDs, patients complaining dry cough or dyspnea, or showing signatures of ILD during the routine lung monitoring for PAD, should undergo pulmonary function tests to rule out the presence of a possible restrictive pattern, an impairment in gas transfer, hypoxia at rest or on exercise (during 6MWT or cardio-pulmonary exercise test (CPET)).

High-resolution computed tomography (HRCT), the gold standard imaging technique for ILDs, may show parenchymal consolidation, bronchial wall thickening, reticular and/or nodular changes and/or fibrosis, with or without ground-glass opacities, predominantly affecting the lower lobes (Figure 2(a–d)). Bronchiectasis, air trapping, emphysema may also be present, since GLILD does not necessarily occur as single lung signature of PAD [114,115]. No validated radiologic scores are currently available for GLILD. The differential diagnosis includes infections, other well-defined ILDs (particularly sarcoidosis) and monoclonal lymphoproliferative diseases. FDG-positron emission tomography-CT (PET-CT) may thus be performed when the initial suspicion is lymphoma, potentially unmasking a clinically hidden extra-pulmonary involvement. A recent study underlined the role of FDG-PET-CT scan also in assessing and monitoring the response to treatment in CVID patients with GLILD [116] (Figure 2(e)).

Definitive diagnosis, in PAD patients, relies on a high index of suspicion, on the basis of clinical, radiological and microbiological picture, and on histopathologic confirmation [100]. An open lung or VATS biopsy should be performed, if safe, in order to provide the Pathologist with an optimal sample. Before surgery, bronchoscopy is recommended to rule out a possible infectious explanation for the interstitial picture [108]. The role of Broncho-

Table 2. Main features of GLILD [12,16,107,108,117].

Associated PADs	CVID, SIgAD, and IgG subclass deficiency, CTLA-4 haploinsufficiency and STAT3 GOF mutations, RAG1 and LRBA) deficiency. No evidence in HIGM syndrome and congenital agammaglobulinemia patients [12].
Peripheral B cells	Circulating switched-memory B cells may be reduced, while CD21*low* B cells are often increased [111].
BALF lymphocytes	Lymphocytosis is frequent (>20%); CD4/CD8 ratio has been reported increased or normal in different case series. CD21*low* B cells have been reported as the major B cell population in BALF [117–119].
Associated lung conditions	Frequent infections and possible coexistence of bronchiectasis, COPD and asthma.
Associated extra-pulmonary conditions	Autoimmune cytopenia and splenomegaly are frequently present, Gastrointestinal involvement is reported in 15% of cases; there is an increased likelihood of nodular regenerative hyperplasia of the liver [117].
Main non-infectious differential diagnoses	Sarcoidosis, other ILDs, Malignant lymphoproliferative diseases, metastases or lung cancer
Lung function	DLCO reduction, slowly progressing restrictive lung disease [108].
Main radiologic patterns	Pulmonary lymphoid hyperplasia features (e.g. LIP, follicular bronchiolitis); NSIP; Organizing Pneumonia. Diffuse lung nodules, often > 1 cm, with random or predominantly basal distribution; ground-glass opacities; hilar adenopathy may be present [115,117].
Concomitant radiologic findings	Bronchiectasis, emphysema, post-infectious aspects
Typical histologic findings	Pulmonary lymphoid hyperplasia features, organizing pneumonia, non-necrotizing granulomatous inflammation [100].
Treatment	No evidence-based guidelines [108]. Optimize IgG replacement therapy and consider watchful waiting if asymptomatic and no decline in lung function If treatment is needed: • Steroids as first line or induction treatment • Azathioprine/Mycophenolate as steroid-sparing and/or Rituximab

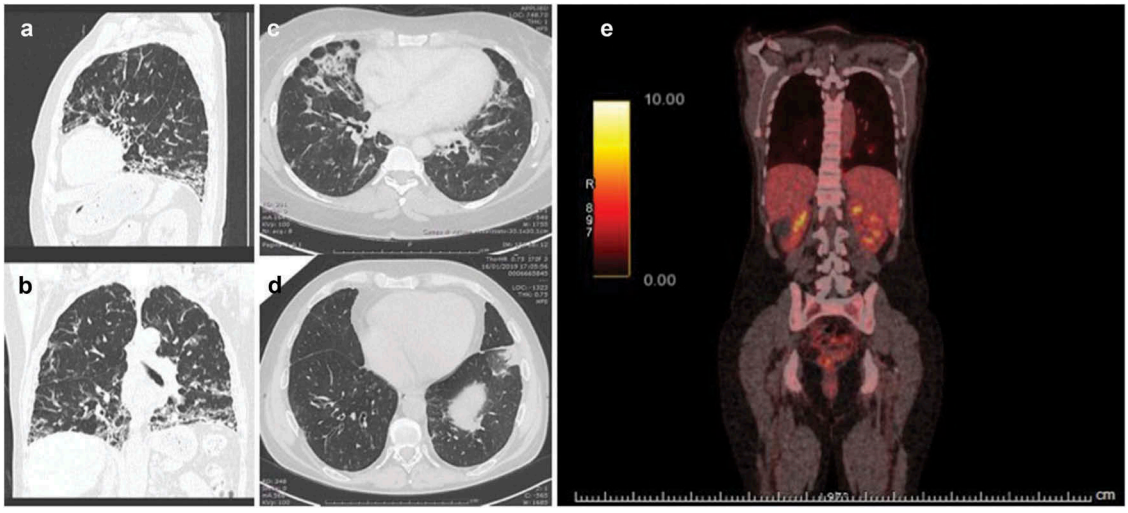

Figure 2. GLILD in CVID patients. Coronal (a) and sagittal (b) view of a CVID patient with a predominantly basal ILD with LIP-like radiological features. Different types of consolidations in CVID patients (c and d). Panel (d) shows an OP-like radiological pattern. All these patients received histologic diagnosis of GLILD. Panel (e) shows PET-CT scan of a 45 yo lady presenting GLILD in CVID; FDG uptake highlight mediastinal lymph-nodes, predominantly basal lung consolidations, liver, and spleen, with significant splenomegaly, bowel, and intraperitoneal lymph-nodes.

alveolar lavage fluid (BALF) cytology and flow-cytometric analysis, instead, is not yet defined. BALF has been described as lymphocyte-enriched (>20%) in adult CVID patients affected by GLILD. An increased CD4/CD8 ratio of BALF lymphocytes has been reported, but not confirmed in other case series [117–119]. CD21low B cells have also been suggested as the dominant cells in the BALF of patients diagnosed with GLILD [109]. It has been hypothesized that different BALF lymphocytes distributions might imply distinct pathogenic mechanisms of GLILD, possibly deriving from diverse triggers correlating with specific clinical and prognostic phenotypes [118,119]. Further evidence is needed to define the exact pathogenic, diagnostic and prognostic role of these lymphocyte sub-populations in GLILD. The role of trans-bronchial biopsy is not defined, being cryo-biopsy, as for other ILDS, a more promising approach than EBUS-TBNA [108,120].

Specific therapeutic guidelines for GLILD are currently lacking. No evidence from controlled trials is available regarding the appropriate timing for treatment initiation or about specific therapeutic protocols. The only published data derive from retrospective studies [109].

The above-mentioned UK consensus statement summarizes the limited available evidence and recommendations based on experts' experience/opinion, together with some open questions [108]. The first point is to decide whether to treat or not GLILD once a diagnosis has been made. The choice should be based on a combination of clinical and functional parameters. There is no evidence about benefits of treating asymptomatic patients with normal lung function (not declining over time). Optimization of the IgG replacement has been suggested, but there is no demonstration that increasing the dose of administered IgG has a direct impact on GLILD progression [121,122]. There is also no evidence about the use of antimicrobial prophylaxis. However, considering that GLILD occurs in PAD patients and may be associated with bronchiectasis, it is likely that maintaining an adequate IgG trough level may be helpful; for the same reason, the antimicrobial and anti-inflammatory properties of antibiotic prophylaxis, as previously discussed, may contribute to lower the degree of lung inflammation.

Symptomatic patients presenting an abnormal or at least declining lung function might be first-line treated with oral corticosteroids [108,123]. The decision on whether or how to treat may also be influenced by concomitant extra-pulmonary involvement. A general consensus has been reported for the use, as second-line agents, of azathioprine or mycophenolate, and/or rituximab (95). Successful treatment of GLILD with a combination regimen including rituximab and azathioprine has been recently reported in a retrospective case series [109]. Few recently published case report/series suggested that Rituximab monotherapy might also be a reasonable option [115,124,125]. Rationale and outcome of anti-CD20 treatment in CVID have been recently discussed in a comprehensive review [126]. The use of other drugs as hydroxychloroquine, methotrexate, sirolimus, tacrolimus, and anti-TNF agents has been described in case reports [108,127,128]. When an underlying genetic defect is known, e.g. LRBA deficiency or activated PI3K-δ syndrome, a more targeted immunomodulator (respectively, abatacept and rapamycin) might be considered [129,130]

The reported efficacy of immune suppressants suggests that, despite infectious agents potentially acting as initial triggers, persistent infection may not substantially contribute to GLILD progression. The promising results obtained with drugs commonly used both in T-cell and B-cell mediated diseases suggest that both lymphocyte sub-populations may play an active role in disease progression. It is not clear, however, if different GLILD phenotypes may be distinguished on the basis of the prominent pathogenic role of either of these two lymphocytes subgroups. Rituximab and Azathioprine may improve Treg cells count [100,131,132]. Moreover, Rituximab has been successfully used for T-mediated and granulomatous diseases [133]. Recently, a B cell activating factor (BAFF)-driven B cell hyperplasia has been shown to be involved in the pathogenesis of

ILD in CVID [125]. This further strengthens the rationale of anti-CD20 therapy, opening the way also to anti-BAFF therapy. Whether a tailored choice of the most appropriate treatment might be extrapolated by the histologic pattern or by any disease biomarker (e.g peripheral blood or BALF-derived mediators or lymphocyte distribution) is still an open question.

3.3. Neoplastic diseases involving the lung

Cancer is a relevant cause of morbidity and mortality in Primary Antibody Deficiencies. Lymphoma and gastric carcinoma are the most represented neoplastic diseases [6,13,56]. Primary lymphoid lesions may affect the lung of PAD patients, including non-Hodgkin lymphomas, as low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), and Hodgkin disease [134,135]. Of note, the diagnosis of Epstein-Barr Virus (EBV)-driven lymphoproliferative diseases in patients with hypogammaglobulinemia and history of recurrent bacterial infections should raise the suspicion of a CD27-CD70 axis deficiency [136]. In this case, diagnosis relies on genetic analysis moving the investigated PID from the '*predominantly antibody deficiencies*' to the '*diseases of Immune dysregulation with Hemophagocytic Lymphohistiocytosis and EBV susceptibility*' group of the IUIS classification [1]. Neoplastic lymphoproliferative diseases should be considered in the differential diagnosis of GLILD [137]. Different case series reported also lung carcinoma in CVID patients, but lung infiltration with metastases of other cancers appears to be more common than primary lung tumors [56,92,135]. Even if an increased prevalence of malignant lymphoma and of gastric cancer has been observed in an Italian cohort of 455 CVID patients, the prevalence of lung cancer in that cohort was 0.9%, lower than that reported in general population, with a significantly lower mortality if compared to normative Italian population [13]. A Thymic enlargement/mass at chest CT scan in a patients with hypogammaglobulinemia, finally, should raise the suspicion of a Thymoma-associated Good's Syndrome [138].

4. Conclusions

Lung disease is a common and relevant clinical feature of Primary Antibody Deficiency. The availability of different options of IgG replacement therapy, allowing treatment personalization, has significantly reduced the recurrence of infections, particularly in early diagnosed patients. However, diagnostic delay still represents a great concern, particularly for PAD presenting in the adulthood, and once the lung damage is established, the risk of colonization and further infections increases [10]. Moreover, IgG replacement does not fulfill all the patients' requirements, and the persistence of IgA and IgM deficiency and other concomitant immune defects have extensively been highlighted as risk factors for the progression of lung disease [31]. Apart from replacement therapy, no specific and evidence-based guidelines for diagnostic and therapeutic management of lung diseases in PADs are currently available [14]. The most relevant new data, in the field, are those recently published about antibiotic prophylaxis with azithromycin [70]. The management of bronchiectasis, asthma, and COPD might be somehow borrowed from the same conditions occurring in non-PAD patients, provided that the PAD condition had been diagnosed and Ig replacement therapy had been established. Nonetheless, further specific evidence is needed in cohorts of PAD patients. On the contrary, the management of ILD is much more challenging. Too little is known about pathogenesis, and about correlations between histology, radiology, serum markers, and disease behavior. Moreover, the need for a tailored treatment which could maximize the effect on lung disease while minimizing the immune suppressive power, particularly when acting broader than on B-cell mediated immunity, is definitely higher in PAD than in immune competent patients [139]. Immune-mediated diseases, indeed, do not necessarily occur separately from chronic infection-related lung disease.

Thus, future studies are needed, as well as a broader degree of awareness of epidemiologic and etiologic relationships between PADs and specific pulmonary manifestations. A better understanding of the specific mechanisms leading from immunodeficiency to immune dysregulation, particularly when an underlying monogenic defect cannot be demonstrated, will open the way to more personalized diagnostic and therapeutic approaches. The reduction of diagnostic delay and a better understanding of lung diseases mechanisms and consequent therapeutic options will have a strong impact on Quality of Life and long-term prognosis of PAD patients.

5. Expert opinion

5.1. Practical approach to lung disease in PADs

Lacking internationally recognized guidelines about screening and management of lung diseases in PAD patients, different approaches are ongoing in distinct Countries and, sometimes, even in different referral centers within the same Country [14]. What we currently recommend in Italy is to adopt a standardized approach at diagnosis and a personalized approach during follow-up, keeping in mind the above-mentioned possible pulmonary complications and their pre-clinical and clinical signs [140]. The initial work-up of a possible lung disease in PAD includes high-resolution chest CT scan and Pulmonary function tests encompassing spirometry (with eventual post-bronchodilator test or methacholine challenge), gas transfer measurement and blood gas analysis [12]. It is indeed important to establish whether patients present or not bronchiectasis, lymph-node enlargement, radiological signs of ILDs, as well as an obstructive, restrictive or combined respiratory disorder, possibly associated with an impairment in gas transfer or blood oxygenation. As discussed above, this initial assessment allows clinicians to optimize Ig replacement therapy and all the possible add-ons, including antibiotic prophylaxis and inhalation therapy. At the time of the initial assessment, a lung MRI may be considered as a complementary investigation. Lung MRI is performed in contexts where recurrent lung imaging may be required, as a radiation-sparing techniques, e.g. in cystic fibrosis; radiologists may thus be used to evaluate signatures of chronic lung disease, including bronchiectasis. The reliability of lung MRI in PAD patients has already been demonstrated in previous studies, and its use in routine monitoring will likely increase in the next future [141,142]. This radiation-sparing technique has

indeed a great potential for application in PAD patients, which are often young and more prone to cancer than the general population.

The initial work-up has to include a genetic screening for the well-known mutations associated to PAD phenotypes and related lung involvement, together with all the investigations possibly highlighting risk factors for specific lung disease patterns (we already discussed the putative risk factors for GLILD, e.g. splenomegaly and percentage expansion of CD21low B cells).

Ig replacement therapy has to be established at the dosage of 400–800 mg/kg every 4 weeks, adjusting the initial dose according to the frequency of infections and IgG trough levels. The route and the schedule of administration and the optimal replacement dosage have to be individualized [143]. No specific difference between intravenous (IVIg) and subcutaneous (SCIg) administration of Ig has been clearly demonstrated, in terms of impact on PAD-related lung complications, despite a lower degree of bronchiectasis under SCIg treatment having been described in certain cohorts of patients [76]. The main goal is to obtain and keep stable the optimal IgG trough level for each single patient, independent on route of Ig administration. According to recent evidence, apart from Ig replacement therapy, in patients presenting bronchiectasis or COPD, we recommend to establish an antibiotic prophylaxis with azithromycin, if not contraindicated. A supervised Pulmonary Rehabilitation and Exercise Training programs should be recommended to patients suffering from bronchiectasis and/or COPD complaining frequent acute exacerbations.

In case of suspicion of ILD raising from the initial work-up, 6-MWT and/or a CPET test should be promptly performed. According to the results of functional assessment and to the presence or absence of symptoms, patients might be then recommended either a therapeutic approach or a watchful waiting strategy. In this second circumstance, not only a functional but also a radiologic close monitoring is needed. Thus, despite HRCT being the current gold standard imaging technique, the importance of Lung MRI is destined to increase [144,145].

Once a clinical and radiologic suspicion of GLILD has been formulated, a bronchoalveolar lavage is recommended to rule out an infection as cause of the interstitial lung disease. The role of BALF lymphocyte flow-cytometric analysis in the diagnostic process is not yet defined. Nonetheless, preliminary data suggested a possible relationship between the lymphocyte subpopulations distribution and the clinical behavior of GLILD [117–119]. BALF lymphocytes may be helpful in the diagnostic work-up of ILDs, including sarcoidosis. In this last case, in specific circumstances, a definite diagnosis of sarcoidosis may rely on the combination between a suggestive clinical-radiologic picture and a CD4/CD8 ratio [90]. Moreover, an increase in B cells may allow to assess a possible clonal restriction of surface Ig light chains and, in case malignancies had been ruled out, might suggest a more B-cell targeted approach with anti-CD20 treatment. Positron emission tomography with Fluoro-D-glucose (FDG-PET) combined with CT scan (or with MRI, when available) represents a reasonable option in the work-up, combining a well-established role in the differential diagnosis of lymphoproliferative disease and a recently described value in initial work-up and in response-to-treatment evaluation of GLILD. Finally, to confirm a diagnosis of GLILD versus the suspicion of lymphoma, a histologic examination is required. Transbronchial biopsy generally offers small samples, that may be inadequate to observe the typical histologic heterogeneity of GLILD and to exclude a malignant lymphoproliferative disease. Thus, an open-lung or VATS biopsy is currently recommended as above described. However, in the field of ILDs, transbronchial cryo-biopsy has been gaining importance over the last few years, offering more adequate samples while sparing the higher risks potentially related to surgery [108,120]. At present, in light of the just mentioned risks and of the lack of evidence about any specific treatment of GLILD, in absence of symptoms and without signs of functional decline, the opportunity of an invasive approach should be carefully evaluated by clinicians and discussed with patients. In our opinion, in these circumstances and once ruled out infections and lymphomas (a lymph-node transbronchial biopsy might be enough in many cases and a bronchoalveolar lavage might offer much information), a watchful waiting might be more cost-effective than an immediate surgical lung biopsy. Thus, we suggest establishing a close monitoring schedule, with the evaluation of lung function after 3 months and, later, every 6 months. Chest CT scan should be repeated after 6 months and, subsequently, once a year or according to specific requirements. Once more, lung MRI is destined to become a cornerstone of the watchful waiting strategy. However, at the first evidence of disease progression, surgical lung biopsy is still recommended, provided that we still do not know how a specific histologic or histochemical pattern of GLILD may influence our therapeutic strategy.

Regarding GLILD treatment, first of all, we recommend treating symptomatic patients and those presenting a clear decline in lung function. Treatment of asymptomatic patients without decline in lung function might only be considered in those patients with radiologic evidence of disease progression and a specific underlying genetic defect (e.g. LRBA deficiency), where disease biology may at present be better predicted and targeted. The increase in serum IgM levels has also been suggested as a marker of more severe disease behavior that should be taken into account [125]. Optimization of Ig replacement therapy is reasonable, both for preventing acute respiratory exacerbations and for down-modulating any possible infection-related inflammatory trigger. The first-line steroid treatment is a standard approach in inflammatory ILDs and may be considered in the presence of an Organizing Pneumonia predominant pattern. In most of other cases and particularly when granulomatous inflammation is detected, in the absence of therapeutic guidelines, we take some hints from our experience in the treatment of chronic sarcoidosis. Since a long-term treatment is generally needed, the use of steroids alone is generally burdened by many side effects even in immunocompetent patients. Thus, we prefer to use corticosteroids as induction treatment while starting an immunosuppressant as Azathioprine or Mycophenolate to be continued as long-term treatment. However, when a rapid clinical response is needed, our first choice tends to be the anti-CD20 treatment with Rituximab, that has been shown effective in different ILD contexts, including selected cases of sarcoidosis and GLILD [125,133].

In terms of routine follow-up, finally, lung function (particularly FEV1 and DLCO) is known to decline slowly over time in patients with PID, despite appropriate replacement therapy [67]. Thus, annual testing with spirometry and CO transfer measurement is recommended in PAD patients, with or without functional or radiologic evidence of chronic lung disease. As already discussed, DLCO reduction may be an early signal of an ongoing, clinically not evident, interstitial lung disease, even in the absence of a restrictive pattern at PFTs. HRCT scan can be even more sensitive, showing interstitial modifications before any impairment in gas transfer. However, due to the exposure to ionizing radiations, CT scan is generally recommended to be performed once every 5 years in the absence of specific clinical indications. The increasing performances of chest MRI will hopefully allow clinicians to prescribe more frequent imaging assessments, particularly in selected patients with known risk factors for ILD. This will also be helpful in those patients with a diagnosis of GLILD without immediate indication to treatment. Figure 3 recapitulates the step-by-step approach to lung monitoring in PADs.

Starting from recent evidence and open questions already discussed in this review, in the next 3–5 years we expect to have some major advances that will significantly modify (and standardize) the management of lung disease in PAD:

(1) In PAD patients, IgG replacement therapy has been shown to enhance survival and reduce severe and invasive infections. However, patients might still develop chronic infection-related lung disease (CLD). Recurrent respiratory tract infections are indeed linked to low serum IgA levels, reflecting a severely impaired isotype switching process leading to a loss of function of memory B cells. It has been recently suggested that there have been limited innovations over the last 65 years in Ig

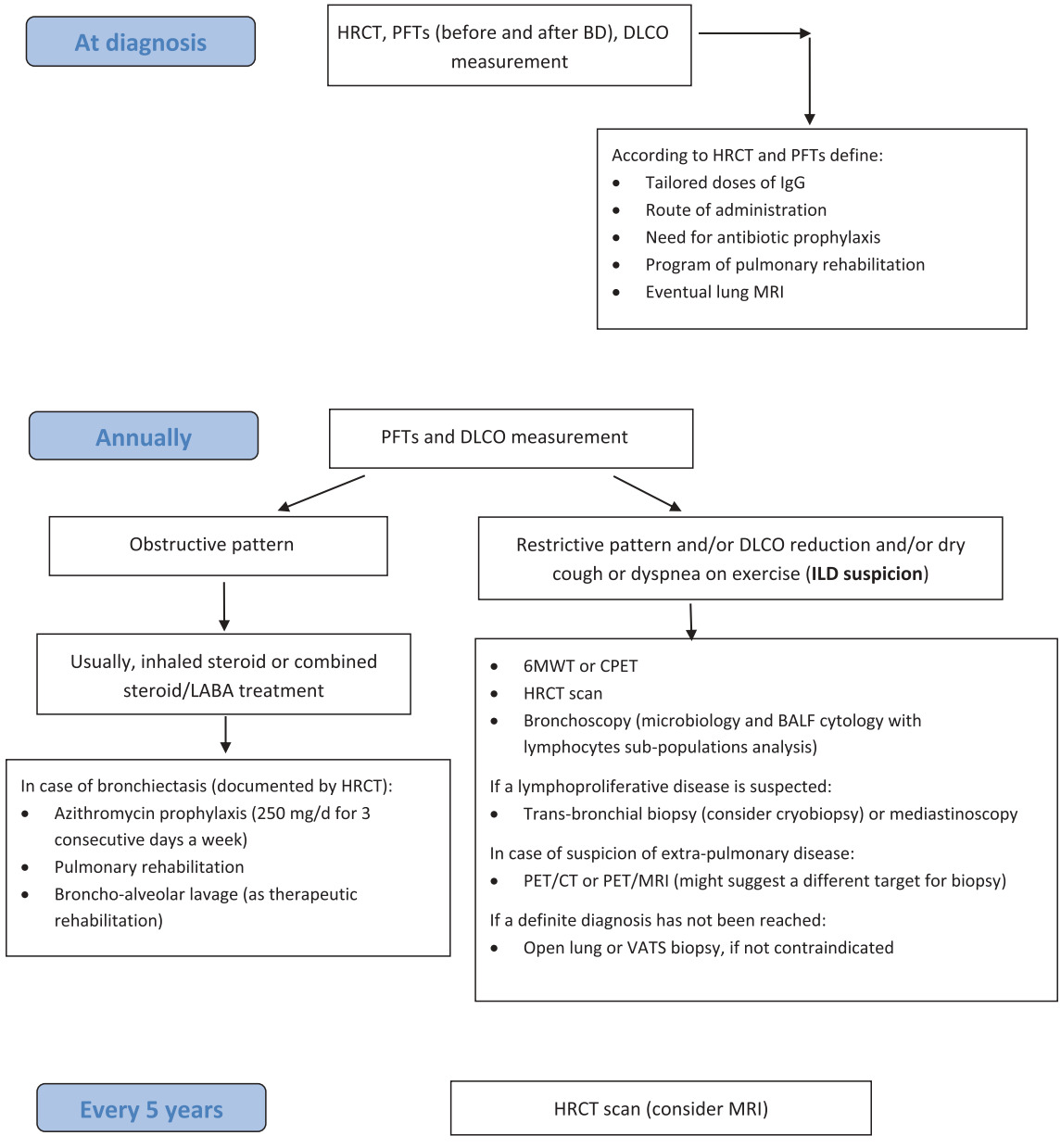

Figure 3. Monitoring and management of lung disease in primary antibody deficiencies.

replacement therapy. Despite having improved the therapeutic options in terms of route and schedule of administration and tolerability of the different preparations, indeed, we are still not able to provide IgA or IgM replacement [146]. IgA and IgM enriched preparations are currently under evaluation, being the lack of the secretory domain the main limitations, at present. Recently, recombinant secretory component to be combined with plasma-derived IgA and IgM have been tested in animal studies with promising results. Human plasma-derived polyreactive IgA and IgM antibodies reconstituted as secretory-like immunoglobulins have been shown to be effective when used for oral passive immunization in murine models of experimental salmonellosis [147]. Nebulized inhaled Ig (IgA/IgM), will also be available in the near future [148]. These new preparations might be useful to prevent the progression of CLD and will offer a therapeutic option for SIgAD and selective IgM deficiency patients. The potential limitation might be represented by the development of anti-IgA IgG (and possibly IgM) antibodies, potentially inducing anaphylactoid reactions to IgA-containing preparations [149,150]. However, the risk will be limited to those patients with absolute IgA deficiency (undetectable IgA) and still able to produce specific IgG (or IgM); the subcutaneous route of administration has been shown to be safer, in these patients [149].

(2) As suggested above, recent evidence supports the possible role of lung magnetic resonance imaging (MRI) in diagnosing and monitoring chronic lung disease in PAD patients. On the other hand, in ILDs the potential of MRI is much more uncertain. Accordingly, future multicentric studies will be needed due to the lower number of PAD patients presenting GLILD if compared to bronchiectasis. However, thin-slices chest CT scan cannot distinguish pure inflammatory from fibrotic ground-glass opacity. On the contrary, recently developed chest MRI techniques, while not adding information to HRCT scan in terms of image quality, may provide in ILDs both structural and functional information in a single examination. They can indeed add information about inflammation, ventilation, and perfusion, being potentially helpful in assessing ILD progression and in predicting its response to treatment [144,145]. All these considered, without exposure to ionizing radiation, chest MRI will offer also in PAD-associated ILDs better tissue characterization, differentiating between inflammatory and purely fibrotic ground-glass opacities [144]. Recent and near-future advances will thus hopefully lead to the routine use of lung MRI at diagnosis, in a combined approach together with HRCT, and as gold standard for the 3–5 years follow-up in PAD patients, being HRCT used only on demand.

(3) The recent controlled trial on Azithromycin prophylaxis will be helpful in designing a more standardized approach to CLD in PAD patients. However, further multicenter-controlled trials are needed, in order to define PAD-specific evidence-based guidelines for the management of infection-related lung diseases.

(4) The diagnosis of GLILD is currently based on a multi-step process culminating in an invasive open-lung or VATS biopsy. The increasing awareness of this lung complication will hopefully lead to earlier suspicion and to more limited risks eventually related to a surgical biopsy. However, the world of ILDs is moving towards clinical-radiologic diagnoses based on the exclusion of causes of secondary lung diseases and on a Multi-Disciplinary Team (MDT) discussion. Thus, the diagnosis of GLILD is also destined to move to a more clinical-radiological-plus -MDT -discussion-based approach. VATS and open-lung biopsy will then be limited to those cases when other lung diseases cannot be ruled out in a different way (e.g. transbronchial biopsy or biopsy of a different tissue in the context of a systemic disease). Cryo-biopsy will likely become the first-line approach when a lung tissue biopsy is needed.

(5) The treatment of GLILD definitely represents the major concern. Observational studies are ongoing but, due to the rarity and heterogeneity of this condition, we are still far from multicenter interventional-controlled studies possibly leading to evidence-based guidelines. Thus, the next advances will still derive from case series and retrospective/prospective observational studies. Nonetheless, these studied will start providing interesting correlations between possible predisposing factors, concomitant conditions, peripheral blood or BALF lymphocytes distribution (e.g. CD4/CD8 ratio, CD21lo B cells or large granular lymphocytes expansion), histochemical characterization of tissue samples and GLILD behavior. The recent paper published by Maglione et al. represents an appropriate paradigm of this kind of studies [125]. Response to treatment will also be put in relation to all the above and to possible underlying genetic defects sustaining a peculiar pathogenic pathway. This will allow clinicians either to classify patients in different subgroups in terms of prognosis and predicted response to specific treatment, or to take into account all the possible immunologic mechanisms or biomarkers of each single patients in order to design a tailored treatment strategy.

(6) Starting from these data that will hopefully be published in the next 3–5 years, it will be possible to design relatively large multicenter-controlled trial with existing drugs that will be the basis for PAD-specific evidence-based treatment guidelines for ILDs.

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