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A Guide for Pulmonologists

IDFA Immune Deficiencies Foundation Australia

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

ABBREVIATIONS

ILD	Interstitial lung disease
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency
RTI	Respiratory tract infection
SCID	Severe combined immunodeficiency
IG	Immunoglobulin

Primary immunodeficiencies: A guide for pulmonologists (1st edition).

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INTRODUCTION

This booklet is about patients with primary immunodeficiencies (PIDs) who may be referred to pulmonology services due to respiratory symptoms before receiving a formal PID diagnosis. Clinical indicators that may raise a suspicion for PID are reviewed as are the needs for members of a multidisciplinary team to care for such patients.

Primary immunodeficiencies (PIDs) are rare diseases that occur when components of the immune system are either not present or are not functioning normally, rendering the patient susceptible to potentially life-threatening infections.

The presentation of PIDs are often complex with clinical indicators suggestive of multiple potential diagnosis. Recurrent lung infections are one of the first warning signs of an underlying PID in both adults and paediatric patients and often cause permanent lung damage if appropriate treatment is delayed. Such patients may be referred to a pulmonologist who, therefore, has an opportunity to identify patients with PIDs ensuring they receive a timely diagnosis and intervention to minimise the chronic effects of PIDs and initiate prophylactic therapies.

The following sections review the complex clinical presentations of patients with PIDs and the clinical indicators that may raise a suspicion for PIDs. Management strategies, including building a multidisciplinary team, are also explored.

PIDs: NOT JUST A PAEDIATRIC DIAGNOSIS

To date, over 400 different PIDs have been identified ranging from the very rare (e.g. severe combined immunodeficiency [SCID]) to the relatively common (e.g. selective immunoglobulin A deficiency).

The diagnosis of PIDs often emerges from a picture of recurrent or unusual infections (including respiratory tract infections [RTIs]), autoimmune diseases, inflammatory processes or cancers. Recurrent RTIs are often the first clinical warning sign of an underlying PID and are often the primary cause of death among adults with PID. [a,b]

The most severe forms of PIDs are diagnosed in childhood. However, others are frequently identified during adulthood because of their late onset and because they have been misdiagnosed or undiagnosed.

PIDs can have widely differing presentations, from relatively mild to life-threatening. Some develop over time and worsen as late manifestations or complications take effect. Many patients with PIDs go undiagnosed for several years, during which time they are often treated several times with antimicrobial agents. Delayed diagnosis can result in inadequate or inappropriate treatment and accumulated lung damage. [c]

PULMONARY INDICATORS FOR PIDs

Lung complications caused by PID include RTIs and interstitial lung disease (ILD). Typical respiratory symptoms in patients with PIDs include recurrent and chronic bronchial infections and pneumonias, the need for prolonged antibiotic treatment for respiratory infections and infections caused by rare or opportunistic microorganisms.

[a] Hampson FA, et al. Respiratory disease in common variable immunodeficiency and other primary immunodeficiency disorders. Clin Radiol 2012;67:587-95

[b] Verma N, et al. Lung disease in primary antibody deficiency. Lancet Respir Med 2015;3:651-60

[c] Soler-Palacin P, et al. Primary immunodeficiency disease in lung disease: wrining signs, diagnosis and management. Respir Res 2018;19:219

RESPIRATORY MANIFESTATIONS OF PIDs [d]

ADULT AND PAEDIATRIC PATIENTS:

- Recurrent bronchial infections (≥2/year) with cough and purulent expectoration
- Idiopathic bronchiectasis
- Recurrent pneumonias
- Chronic bronchial infection
- Need for prolonged antibiotic treatment for respiratory infections
- Pulmonary abscess and pneumatocele
- Infections caused by rare or opportunistic microorganisms

INFANTS:

- Severe infantile bronchiolitis or pneumonia

NON-INFECTION DISEASES (ADULTS AND PAEDIATRIC PATIENTS):

- Granulomatous-lymphocytic interstitial lung disease (GLILD)
- Bronchiolitis obliterans
- Lymphoproliferative syndrome
- Alveolar proteinosis
- Recurrent serositis

Common respiratory manifestations of PID differ by type of PID.

[d] Soler-Palacin P, et al. Primary immunodeficiency disease in lung disease: warning signs, diagnosis and management. Respir Res 2018;19:219


SID
72 IN
180 CM
40 IN
100 CM

COMMON RESPIRATORY MANIFESTATIONS OF PIDs

Pulmonary symptom/condition	Predominantly T-cell deficiency	Antibody deficiencies	Immune dysregul
Recurrent bronchitis	✓	✓	
Idiopathic bronchiectasis	✓	✓	
Recurrent pneumonias	✓	✓	
Chronic bronchial infection	✓	✓	
Prolonged antibiotic treatment with poor response	✓	✓	
Pneumonia due to encapsulated bacteria	✓	✓	
Abscess and pneumatocele	✓		
Infections caused by rare microorganisms	✓		
Pneumonitis or bronchitis with hospitalization in infants	✓	✓	
ILD	✓	✓	
Bronchiolitis obliterans	✓	✓	
Alveolar proteinosis	✓		
Absent thymus or aplasia	✓		
Pulmonary lymphoma	✓	✓	
Thymoma		✓	
Recurrent serositis			

ation	Phagocyte disorders	Innate immunity disorder	Complement deficiency	Autoinflammatory disease
✓			✓	
✓			✓	
	✓	✓	✓	
✓			✓	
✓	✓			
✓		✓	✓	
	✓	✓		
✓	✓	✓		
✓	✓			
✓	✓			✓
✓				
	✓			
✓				
				✓

ACHIEVING A DIAGNOSIS OF PID

Initial investigations that may have been performed in the primary care setting should include complete blood count including leucocytes and differentiation, IgA, IgM, IgG and IgE. A computerised tomography (CT) scan should be requested in cases of recurrent pulmonary infections to assess lung damage.

Tests to be performed by respiratory specialists for adults with suspected PID-related respiratory symptoms include spirometry, carbon monoxide diffusing capacity (DLCO), high-resolution computerised tomography (HRCT; with or without abdominal ultrasound [US]), sputum culture (bacteria, mycobacteria, fungi) if expectoration present. For children with suspected PID-related respiratory symptoms, work-up should include spirometry if technically possible, plethysmography if available, DLCO (≥6–7 years), lung HRCT (with or without abdominal US), sputum culture of expectoration (induced sputum if no expectoration).

It is usually necessary to involve additional specialities to achieve a diagnosis, frequently an immunologist but possibly also a specialist in infectious diseases or haematologist. A key step is to rule out haematological malignancy as an alternative diagnosis.

CARING FOR THE LUNGS OF PATIENTS WITH PIDs

Early diagnosis and antimicrobial prophylaxis and/or Ig replacement therapy treatment are critical to optimising outcomes for patients with PID. Treatment of the respiratory manifestations of PID may include acute pharmacological management of upper and lower RTIs, antibiotic prophylaxis, antiviral treatment, management of lung inflammation: oral/inhaled antibiotics, inhaled hyperosmolar agents, mucolytics,[e] and immunosuppressive therapy (e.g GLILD) and also asthma-related therapy (inhaled beta-mimetics or corticosteroids). Non-pharmacological interventions may include airway clearance techniques, nasal irrigation, exercise, physiotherapy, and home and personal hygiene (avoidance of tobacco or other inhaled products such as e-cigarettes), rarely lobectomy or pulmonectomy. Lung transplantation may be considered for patients with PID in cases of severe lung disease (caused by severe extended bronchiectasis, for instance).

Ongoing monitoring of patients with PID and respiratory symptoms should include respiratory tests (annual lung function tests; spirometry every 4–6 months in the absence of lung disease; and sputum culture), as well as lung computed tomography every 2–3 years for patients with pulmonary involvement.

[e] Baumann U, et al. The lung in primary immunodeficiencies: New concepts in infection and inflammation. Front Immunol 2018;9:1837

BUILDING A MULTIDISCIPLINARY TEAM FOR PATIENTS WITH PIDs

Patients with PIDs may present with comorbid conditions (including hypercholesterolaemia and type 2 diabetes mellitus) that may require the involvement of additional specialist physicians. An additional complication is the risk associated with intravenous immunoglobulin treatment, which can increase a patient's risk of congestive heart disease and haemolytic anaemia and requires input from cardiology and haematology specialists.

Patients with PIDs are more vulnerable to the development of malignancies, especially GI cancers and lymphoma. Hence, oncology specialists may need to be included as part of a multidisciplinary team. Referral to centres specialising in the management of PIDs may be appropriate where available.

PIDs: A GUIDE FOR PULMONOLOGISTS

- Lung complications caused by PID include RTIs, ILD, and cancer.
- Recurrent RTIs are often the first clinical warning sign of an underlying PID and are often the primary cause of death among adults with PID.
- Patients with PIDs may require care from a range of specialties depending on their individual symptoms and the organ systems affected.

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI).

Other booklets are available in this series.

For further information and details of PID patient organisations in 63 countries worldwide please visit www.ipopi.org

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