A Primer on Immunology for the Pulmonologist

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What are Primary Immune Deficiencies

Primary Immune Deficiency disorders (PIDD) refer to a group of over 150 distinct defects of the immune system, many of which are due to single gene defects. Congenital defects in various parts of the immune system have been described in humans. Although, the underlying immunologic defects are present at birth, individuals may not become symptomatic until adulthood. Most primary immune deficiencies (PIDDs) are due to single gene defects causing either the absence of a specific protein or a non-functional protein. This distinguishes them from secondary immune defects due to medications, malignancies, or other infections. PIDD can be inherited in an X-linked, autosomal recessive or autosomal dominant fashion. One of the largest clinical phenotypes, Common Variable Immune Deficiency (CVID), has a pattern of variable inheritance, with both AR and AD forms being reported and genetic linkage studies showing a familial predisposition. Despite the differing patterns of disease severity and onset, all patients with PIDD suffer from recurrent infections which cause significant morbidity and mortality.

The true prevalence of PIDD is not known, but it is estimated that 1:1,200 individuals in the United States has been diagnosed with a PIDD. This number is in contrast to previous minimal estimates of 1:10,000 to 1:500,000 based on data from disease registries and suggests that many cases of PIDD remain undiagnosed. PIDD are typically classified by the nature of the immune defect, whether it affects antibody production by B cells (humoral immunity), T cell function (cellular immunity), both T and B cell function (combined immune defect), killing of bacteria by neutrophils (phagocytic defect) or complement. Figure 1 shows the breakdown of PIDD by the underlying defect with the largest proportion resulting in defects of antibody production. About 40% of individuals with PIDD present with infections or other findings of PIDD in the first few years of life. The most severe defects, such as Severe Combined Immune Deficiency (SCID), are fatal in early childhood if not treated. Previously PIDD were thought to be pediatric diseases, but the mean age of diagnosis for CVID is 29 years for males and 33 years for females. Most will have a history of infections for several years prior to diagnosis. In adults the average delay in diagnosis is 5 years. Diagnosis of PIDD, even in the face of symptoms starting early in childhood, may be delayed until adolescence because of a lack of clinical suspicion, underscoring the need for improved awareness of these disorders. Recent results from a UK national audit show that the median delay in diagnosis has decreased from 3.5 years to 1 year. Early diagnosis and treatment has been shown to reduce morbidity and mortality in many PIDD. (Buckley SCID BMT) End organ damage, particularly in the lungs, frequently occurs in the first decade of life as a sequelae of infection.
Normal Host Defenses of the Respiratory Tract

The respiratory tract communicates with the outside environment, thus host defenses against respiratory pathogens are critical. Innate immune defenses are the first line responders against pathogens. The components of the innate immune system in the respiratory tract are the mechanical barriers, the mucous membranes, the mucin containing antimicrobial peptides such as defensins and secretory IgA, the cilia, the cellular effector cells, the phagocytes and NK cells which engulf and kill microbes, the natural antimicrobial agents, defensins, lactoferrin, lysozyme and myeloperoxidase, reactive oxygen species, cytokines and chemokines to recruit effector cells to the site of infection.

Innate Immunity

Innate immune responses are generally the first line of defense against viral, bacterial and fungal pathogens and involve the activation and recruitment of macrophages, neutrophils and Natural Killer cells with release of chemokines, cytokines, or antimicrobial peptides. Clearance of infectious organisms can be accomplished through binding of serum complement facilitating opsonization of microbes, or by phagocytosis and intracellular killing in phagocytes through reactive oxygen or nitrogen molecules.

Humoral Immunity

The humoral immune system relies on adaptive immunity to produce antigen specific responses against infectious pathogens. Microbial peptides are presented on the surface of antigen presenting cells (dendritic cells, monocytes/macrophages, B cells) associated with costimulatory major histocompatibility class II (MHCII) molecules. Cognate interaction between T cells and B cells by binding of T cell receptor (TCR) with B cell receptor (BCR) complex and binding of secondary signal (CD40-CD40L or CD28-CTLA4) results in intracellular signaling to trigger clonal proliferation and maturation of antigen specific cells with immunoglobulin heavy chain isotype switching to produce specific IgG or IgA antibodies.

Cellular Immunity

Cellular immunity involves the activation and proliferation of naïve T cells in response to an antigen. Macrophages or dendritic cells can express microbial peptides on their cell surface with MHCI or MHCII. Recognition of foreign peptides on the cell surface signals T cells to differentiate into effector cells, cytotoxic T cells that kill infected cells, or T helper cells (T\textsubscript{H}1) that activate infected macrophages. Cytotoxic T cells exert their effects through enzymes (perforin, granzyme), Fas Ligand, and cytokines.
IFN gamma, TNFβ, TNFα). T_{h}1 cells produce interferon gamma, and TNFβ and TNFα, activating infected macrophages.

**Pulmonary disease in Primary Immunodeficiency**

The majority of patients with antibody deficiencies, up to 80%, and neutrophil defects will have more than one episode of pneumonia prior to diagnosis\(^{11,14,15}\). Frequently the pattern of infection or identification of the causative pathogen will serve as an indicator to the nature of the immune defect. Table 1 summarizes clinical characteristics of pulmonary infections in different PIDD.

Defects in interferon gamma (IFNg) and IL12 axis cause an increased susceptibility to mycobacteria. Defects in IFNgR1, IFNgR2, IL12/IL23 and IL12R are inherited in an AR fashion and affected individuals develop disseminated and life threatening infections with mycobacterium, including BCG and nontuberculous mycobacteria.\(^{16,17}\)

Individuals with cellular immune defects such as Severe Combined Immune Deficiency (SCID) or an absence of the thymus (complete DiGeorge syndrome) present early in life with opportunistic infections, frequently pneumonia due to *Pneumocystis jirovecii*. Other viral pathogens, parainfluenza 3 and respiratory syncytial virus (RSV), cytomegalovirus (CMV) and Herpes viruses, can cause severe interstitial pneumonitis and may be fatal. Without immune reconstitution, usually achieved by hematopoietic stem cell transplantation in SCID, affected patients will succumb to recurrent viral, fungal and bacterial infections.

Combined immune deficiencies include disorders such as Wiskott-Aldrich Syndrome (WAS), Ataxia-Telangiectasia (AT), and Hyper-IgE syndrome. Recurrent pulmonary infections are a common feature for all these disorders. Pyogenic bacteria are the most frequent pathogen, but *pneumocystis* and other viral pathogens also cause infections. Bronchiectasis is a common complication of respiratory infections in WAS and AT. Pneumatocoeles are characteristic for *S. aureus* infections in Hyper-IgE.

Individuals with antibody deficiencies typically develop bacterial infections of the sinopulmonary tract after maternal antibodies wane after six months of life. Infants with X-linked agammaglobulinemia have an increased frequency of bacterial pneumonias, along with recurrent otitis media, and chronic diarrhea. While many individuals with selective IgA deficiency are asymptomatic, others have a history of frequent otitis media and sinusitis. Some individuals will also be more susceptible to lower respiratory infections and gastrointestinal infections. Many individuals with CVID do not have a notable history of infections until the 2nd decade of life or later. Infections of the sinopulmonary tract occur more frequently than in the general population, with an increase in severity, and are often associated with other sites of infection. Pyogenic bacteria, such as *Staph. aureus, Strep. pneumonia, Haemophilus influenza* and *Moraxella catarrhals*, are responsible for the majority of the pulmonary infections, but infections with
atypical mycobacterium, and opportunistic organisms may be seen in patients with impaired T cell function and in patients with hyper-IgM syndrome. Other antibody deficiencies (NEMO, AR-HyperIgM, selective antibody deficiency) also predispose affected individuals to upper and lower respiratory tract infections.

Pneumonia associated complications, bronchiectasis, empyemas, granulomatous lung disease, are seen more frequently in patients with antibody deficiencies (except SAD and IgA deficiency).\textsuperscript{18} Bronchiectasis may already be present at the time of diagnosis (Figure 2) and end-stage lung disease with respiratory insufficiency is the most frequent cause of death in CVID.\textsuperscript{11} Frequently progression of lung disease occurs despite replacement of serum IgG with gammaglobulins\textsuperscript{19}.

In Chronic Granulomatous Disease (CGD), infections with catalase positive organisms (\textit{S.aureus, Pseudomonas sp., Aspergillus, Nocardia, Serratia, Klebsiella}) can involve multiple sites. The majority of patients will present with a history of pneumonia\textsuperscript{14}. The hallmark of the respiratory infections in patients with CGD is the unusually invasive nature of infections with \textit{Pseudomonas or Aspergillus}, the propensity for abscess formation and the development of noncaseating granulomas. Bronchiectasis is seen less frequently in patient with CGD compared to individuals with antibody deficiency, but can develop after recurrent \textit{S. aureus} infections. Necrotizing pneumonias due to \textit{Pseudomonas} species may necessitate lobectomy.

In addition to bronchiectasis, other chronic lung changes occur in PIDD. Hilar and mediastinal adenopathy is frequently seen. Bronchiolitis obliterans may develop, or involvement of the airways and the parenchyma can lead to pulmonary fibrosis and pulmonary hypertension. Subsequent to opportunistic viral or fungal infections, persistent focal ground-glass opacities may be seen on CT scan. Interstitial lung disease occurs in patients over 40 years of age with antibody deficiencies\textsuperscript{20}. Multiple pulmonary noncaseating granulomas, sometimes calcified can be seen in patients with CGD and CVID. In both disorders, intracellular pathogens (PJP, mycobacterium) can sometimes be identified in the granulomas (Figure 3). In CVID these granulomas have been termed “sarcoid-like”\textsuperscript{21}. Benign lymphoid hyperplasia involving the lung and gastrointestinal tract occur in as many as 30\% of patients with CVID\textsuperscript{22}. Non-Hodgkin lymphomas are more prevalent in patients with CVID\textsuperscript{11,23}. Thoracic lymphomas may present with enlarged mediastinal nodes, or an anterior mediastinal mass which may compress the airway or blood vessels. The presence of an anterior mediastinal mass in a patient with hypogammaglobulinemia and low or absent B cells is characteristic of Good syndrome\textsuperscript{24}. In these cases the development of a thymoma carries a poor prognosis.

\textbf{Evaluation of the patient with suspected Primary Immunodeficiency}
Any patient with a history of recurrent, unusually severe pneumonias, or infection with atypical or opportunistic pathogens should undergo evaluation to identify a possible immune deficiency. The types of infections, their frequency, severity, pathogens involved and the age of onset may suggest the clinical phenotype and can be used to direct the laboratory evaluation. In addition to the history of infections, clinicians should inquire about associated problems and a family history of PIDD. Clinical algorithms have been suggested to help identify individuals with possible PIDD (Figure 4:JMF 10WS). Laboratory testing can then be used to delineate the immune defect. The pattern of infection is the most useful element to discriminate the different immunologic defects. Table 1 shows the pathogens typically associated with defects in different arms of the immune system. Figure 5 shows a testing algorithm for screening patients for a PIDD\textsuperscript{25}. It is worth noting that some tests are available only in specialized laboratories.

Treatment

Therapy is aimed at preventing infections and sequelae of infections. For antibody deficiencies, gamma globulin replacement is effective at reducing the incidence of infections, although it may not be as effective in treating bronchiectasis\textsuperscript{19}. Recommended dosing is 400-500mg/kg/month of gammaglobulin given IV or 100-150 mg/kg/wk given subcutaneously\textsuperscript{26}. Prophylactic antibiotics are first line therapy to prevent PJP (co-trimoxazole), and to prevent infections in IgA deficiency and selective antibody deficiency (SAD). Antibiotics may also be adjunctive therapy in CVID, XLA and HyperIgM. Patients with CGD require prophylaxis with co-trimoxazole and itraconazole. In addition, therapy with IFN gamma given three days a week was shown to reduce the rate of serious infections\textsuperscript{27}. 
References


Frequency of various primary immune deficiencies.

Table 1:

Pulmonary Infections in PIDD

<table>
<thead>
<tr>
<th>Immune defect</th>
<th>T cell or combined</th>
<th>B cell- antibody</th>
<th>Phagocyte</th>
<th>Complement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common pathogens (respiratory)</td>
<td><em>Pneumocystis</em> jirovecii, CMV, EBV, herpes viruses, mycobacteria, pseudomonas</td>
<td><em>S. pneumoniae</em>, <em>H. influenza</em>, <em>S. aureus</em></td>
<td><em>S. aureus</em>, <em>Pseudomonas sp.</em>, <em>Serratia sp</em>, <em>Klebsiella sp</em>, <em>Nocardia</em>, <em>Aspergillus</em></td>
<td><em>S. pneumonia</em>, <em>Neisseria meningitides</em>, <em>E. coli</em> (usually non-pulmonary)</td>
</tr>
<tr>
<td>Pathology</td>
<td>Interstitial pneumonia</td>
<td>Lobar pneumonia, empyema</td>
<td>Necrotizing pneumonia, lung abscess</td>
<td>Pneumonia infrequent</td>
</tr>
<tr>
<td>Sequelae</td>
<td>Pulmonary fibrosis</td>
<td>Granulomas, bronchiectasis, interstitial fibrosis</td>
<td>Granulomas, bronchiectasis</td>
<td>Rare</td>
</tr>
<tr>
<td>Associated features</td>
<td>Failure to thrive, GVHD from maternal cells, BCGosis, dermatitis</td>
<td>Malabsorption, chronic diarrhea autoimmune disease, thymoma</td>
<td>Other organ abscesses, adenitis, osteomyelitis, periodontitis, delayed separation of umbilical</td>
<td>Bacteremia, meningitis, SLE, glomerulonephritis</td>
</tr>
</tbody>
</table>
Figure 2: CT of bronchiectasis

Bronchiectasis, bronchial wall thickening in XLA patient

Figure 3: Granulomatous pneumocystis in CVID

Pulmonary nodules containing *pneumocystis*
courtesy of L Kobrynski

Figure 4: JMF 10 Warning signs at www.info4PI.org
Figure 5: Laboratory Testing Algorithm