Management of Cellular Immunodeficiencies

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Abstract

In this chapter, we will highlight the general strategies and tools in the clinical management of primary cellular immunodeficiency with predominant T cell and/or B cell dysfunction. Hematopoietic stem cell transplantation (HSCT) represents a curative treatment in certain patients with cellular immunodeficiency; enzyme replacement therapy and gene therapy may be further options in very specific settings. Apart from disease-specific treatments, antibiotic therapy and prophylaxis and replacement of immunoglobulin G are therefore the mainstay of treatment, also after HSCT. The monitoring of long-term consequences of infections on airways architecture and function is pivotal in cellular immunodeficiency. Moreover, the management of immune-mediated complications, encompassing a range of clinical issues as interstitial lung diseases, systemic granulomatosis, immune dysregulation, autoimmune cytopenia, and enteropathy, requires a multidisciplinary approach. Finally, a proper management of T and B cellular immune deficiencies allows an early detection of lymphoproliferative complications and cancer.

Keywords

Management · Cellular immunodeficiencies · Immunoglobulin replacement therapy · Antibiotic prophylaxis · Noninfectious complications

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17.1 Introduction

Primary cellular immunodeficiencies are a group of rare genetic disorders characterized mainly by deficiencies of T lymphocyte counts and/or function and/or B lymphocyte defect. The clinical spectrum of primary immunodeficiencies (PID) is extremely broad, and the management mostly depends on the underlying immunological defect and its functional consequences that may have infectious and noninfectious implications. Together with infections, T and B cell immunodeficiencies, indeed, predispose to the development of autoimmunity, allergy, chronic lung disease (including bronchiectasis, asthma, COPD, interstitial lung diseases), gastrointestinal disease with or without malabsorption, systemic or localized granulomatous disease, liver disease, splenomegaly, lymphadenopathy, and neoplastic conditions [1] (see Fig. 17.1). The management of these noninfectious conditions needs to be integrated with the prophylaxis and management of infections, requiring a multidisciplinary approach; pediatric and adult immunologists should thus favor the interplay between different healthcare professionals as pulmonologists, cardiologists, geneticists, gastroenterologists, and neurologists. Finally, primary immunodeficiencies are lifelong conditions: a psychological support could also be necessary, especially for younger patients. This chapter will recapitulate the milestones of the clinical management of primary cellular immunodeficiency associated with predominantly T cell and/or B cell dysfunction, which have been partly discussed in previous chapters.

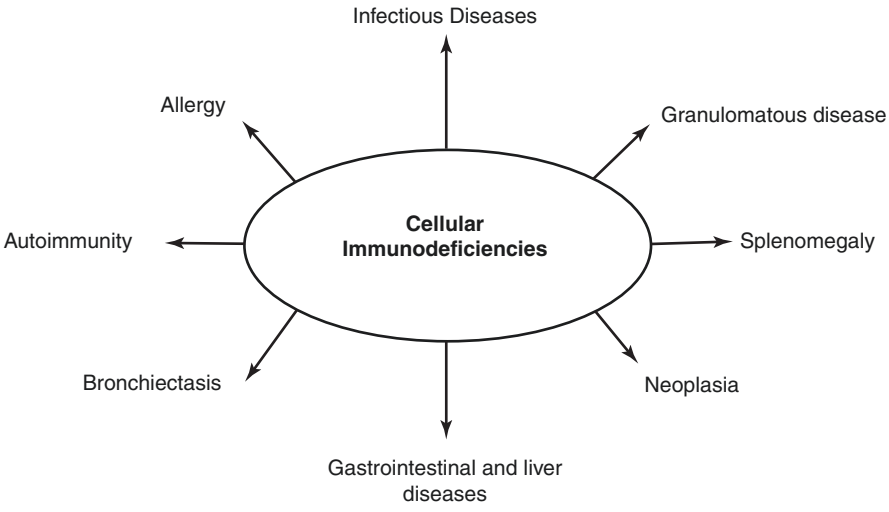

Fig. 17.1 Complications of cellular immunodeficiencies

17.2 Management of T Cell Immune Deficiencies

Patients are classified as severe combined immune deficiency (SCID) if their mature peripheric T lymphocytes are absent or extremely low (CD3+ T cells <500 cell/mL) [2]. Patients affected by SCID usually present during the first year of life recurrent invasive bacterial, viral (particularly cytomegalovirus, parainfluenza, and rotavirus), and opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PJP), *Candida,* and *Aspergillus* species. The clinical manifestations are often characterized by respiratory and gastrointestinal infections, although meningitis, arthritis, urinary tract infection, and systemic infections can also occur [3]. Epstein-Barr virus (EBV) infection has been reported and it can rarely determine immune dysregulation phenomena together with the development of B cell lymphoma or hemophagocytic lymphohistiocytosis [4]. Patients with SCID should be placed in protective isolation and receive symptomatic treatments, parenteral nutritional support due to chronic diarrhea, intensive treatment of ongoing infections, and/or prophylaxis for infections. Although B cells are present in many types of SCID (common gamma chain deficiency [IL2RG], JAK3 deficiency), antibody production results profoundly impaired due to the absence of adequate co-stimulation by CD4+ T cells [5]. Moreover, patients with SCID often present with recurrent sinopulmonary infections caused by encapsulated organisms (*Streptococcus pneumoniae* and *Haemophilus influenzae*), as well parainfluenza, respiratory syncytial virus, adenovirus, and CMV. Thus, patients with SCID must be treated with antibiotic prophylaxis for PJP and immunoglobulin replacement therapy (IgRT) (see Table 17.1). Both of these therapies have been shown to reduce the risk of infection before and after treatment with hematopoietic stem cell transplantation (HSCT). Enzyme replacement therapy with intramuscular injections of ADA (adenosine deaminase) coupled with polyethylene glycol has been successfully used to improve immune system function in patients with ADA-SCID.

17.2.1 Management of Immune Dysregulation

A diagnosis of primary immunodeficiency does not represent an absolute contraindication to immune suppressive therapy, in the presence of immune-mediated complications. Corticosteroids are indeed widely used in treating autoimmune disease and immune dysregulation, especially as first-line therapy, in T cell dysfunction. Ciclosporin is frequently used as “steroid-sparing” agents. Rapamycin inhibits T cell proliferation while selectively increasing the number of Treg cells, then it can be used in the treatment of patients with autoimmune lymphoproliferative syndrome (ALPS) [6]. A wide variety of biologicals are already being used to block cytokines

Table 17.1 Differences in clinical manifestations and management of cellular PID

Cellular PID	Clinical infections and noninfectious complications	Pathogens	Management
SCID, CID *(T and B cell defects)*	Systemic, invasive, or opportunistic infections are common. Diarrhea, eczema and infections. Unusual infection or unusually severe course of infection Failure to thrive Autoimmune or chronic inflammatory disorders Chronic lung diseases Lymphoproliferative disorders Cancer	Viruses (CMV, EBV, VZV, HSV, adenovirus, HHV8, HPV, molluscum contagiosum, RSV) Fungi (*Candida, Aspergillus, Cryptococcus, Histoplasma*, PCJ) Protozoa (*Toxoplasma*, *Microsporidium*, *Cryptosporidium*) Intracellular bacteria (*Mycobacterium* spp., *Salmonella*, *Listeria*) Extracellular bacteria	*PJP prophylaxis*: TMP-SMX dosed as 4–6 mg/kg/day of TMP component divided twice daily 3 days per week (after 30 days of life) *Fungal prophylaxis*: fluconazole 6 mg/kg daily or oral amphotericin B Treatment of acute infections Avoid environmental exposure and live vaccines IgRT Enzyme replacement therapy (ADA-SCID) HSCT Gene therapy
CVID, Bruton agammaglobulinemia, TACI deficiency, class-switch recombination defects (CD40L deficiency) *(B cells defects)*	Recurrent bacterial sinopulmonary infections (otitis media, sinusitis, and pneumonia). Diarrhea due to *Giardia lamblia*. Sometimes meningitidis. Systemic, invasive, or opportunistic infections are uncommon Enteropathy Autoimmunity Interstitial lung disease Chronic lung disease Lymphoproliferative disorders Cancer	Encapsulated bacteria (*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis*)	IgRT *Antibiotic prophylaxis*: azithromycin 5 mg/kg 3 times weekly (maximum 250 mg three times weekly) Treatment of acute infections Appropriate vaccinations Diet, nutritional support, diagnosis and management of inflammatory bowel diseases Immune suppressive treatment Early detection of pulmonary complications, asthma/COPD treatment, pulmonary rehabilitation when required Surveillance for early detection (and treatment) of neoplastic complications

Abbreviations: *SCID* severe combined immune deficiency, *CID* combined immune deficiency, *ADA* adenosine deaminase, *CVID* common variable immunodeficiency, *IgRT* immunoglobulin replacement therapy, *HSCT* hematopoietic stem cell transplantation, *TMP-SMX* trimethoprim-sulfamethoxazole, *COPD* chronic obstructive pulmonary disease, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *VZV* varicella-zoster virus, *HSV* herpes simplex virus, *HHV8* human herpesvirus 8, *HPV*, human papillomavirus, *RSV* respiratory syncytial virus, *PCJ Pneumocystis jiroveci*

(such as TNF-alpha, IL-1, IL-6, IL-12/23, and IL-17) in the treatment of autoimmune diseases, and their potential in patients with T cell deficiencies has to be carefully considered. Finally, in patients with thrombocytopenia, as in Wiskott-Aldrich syndrome (WAS), the use of recombinant thrombopoietin may be an option for supportive treatment [7].

17.2.2 Management of Complications of HSCT

HSCT is a high-risk treatment but can potentially provide a definitive correction for most PID. A major concern when a patient undergoes a HSCT is infections. Common infectious diseases occur after HSCT. Post-HSCT infectious complications are usually classified according to the time after HSCT: pre-engraftment, immediate post-engraftment, and late post-engraftment period. The infectious diseases that occur before the engraftment are similar to those that develop during the neutropenic phase after chemotherapy. The majority of infections in this period are due to bacteria, with Gram-positive organisms predominating over Gram negatives, *Clostridium difficile*, fungal infections, and herpes simplex virus (HSV) reactivation (see Table 17.2) [8]. In neutropenic patients during the pre-engraftment phase, infections can progress rapidly and it can be difficult to distinguish between

Table 17.2 Common pathogens, risk factors, and antimicrobial prophylaxis according to the various time periods after HSCT

	Pre-engraftment period (1st 2–4 weeks)	Immediate post-engraftment period (2nd and 3rd month)	Late post-engraftment period (after 2nd and 3rd month)
Pathogens	Gram-negative bacteria (especially enteric bacteria)	Gram-negative bacteria (especially enteric bacteria)	Encapsulated bacteria (*S. pneumoniae, H. influenzae*)
	Gram-positive cocci (mainly viridans group streptococci)	Gram-positive cocci	*Nocardia*
	Clostridium difficile		Tuberculosis, NTM
	Candida, Aspergillus	*Aspergillus* and PCJ	*Aspergillus* and PCJ
	HSV	EBV, CMV, HHV-6, JC virus	EBV, CMV, VZV
Risk factors	Mucositis, central venous catheter, neutropenia, organ dysfunction due to conditioning regimen	Acute GVHD	Chronic GVHD
		Immune-modulating viruses	Hyposplenism, decrease in opsonization
Antimicrobial prophylaxis	Consider fluoroquinolone and fluconazole during neutropenia	PCJ prophylaxis	PCJ prophylaxis
		Antiviral prophylaxis	Antiviral prophylaxis

Abbreviations: *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *VZV* varicella-zoster virus, *HSV* herpes simplex virus, *HHV-6* human herpesvirus 6, HHV8; *PCJ Pneumocystis jiroveci*, *JC* John Cunningham virus (human polyomavirus 2), *NTM* nontuberculous mycobacteria

bacterial infection and noninfectious fever. For this reason, empirical antimicrobial therapy is strongly recommended in all patients with febrile neutropenic episodes: the broad-spectrum β-lactam antibiotic is the primary choice. After HSCT, PCJ prophylaxis with trimethoprim/sulfamethoxazole (single-strength 80/400 mg daily or double-strength 160/800 mg three times weekly) is recommended from engraftment to at least ≥6 months and as long as receiving immunosuppressive therapy is ongoing [9]. CMV can reactivated after HSCT and the spectrum of CMV infection is extensive extremely broad: from asymptomatic DNAemia to esophagitis, gastritis, colitis, hepatitis, pneumonia, retinitis, and encephalitis. In addition, CMV reactivation can determine a state of graft failure or immunosuppression that may permit the development of concurrent bacterial and/or fungal infections. CMV pneumonia or encephalitis can be fatal despite aggressive anti-CMV therapy [10]. Management of CMV is categorized into prevention, preemptive treatment, and definitive treatment. Preemptive therapy is anti-CMV treatment even in the absence of clinical symptoms in cases with CMV infection (reinfection or reactivation). Most transplantation centers introduce preemptive therapy rather than routine prevention because of cost-benefit ratio and adverse drug reactions. In 2017, the U.S. Food and Drug Administration has approved letermovir for the prevention of CMV infection in adult CMV-seropositive patients undergoing allogeneic HSCT, after the evidence that letermovir prophylaxis resulted in a significantly lower risk of clinically significant CMV infection than placebo [11]. Currently available anti-CMV agents are ganciclovir, valganciclovir, foscarnet, and cidofovir. Moreover, it has been noted that graft versus host disease (GVHD) or the use of monoclonal antibodies can increase the incidence of CMV infections [12, 13]. Finally, acyclovir prophylaxis is recommended to reduce the incidence of HSV and varicella-zoster virus (VZV) infections not only before engraftment but also in the long term until the immunosuppressant is stopped: some studies showed that acyclovir shall be maintained for at least 1 year after allogeneic HSCT and for 6 to 12 months after autologous HSCT [14].

17.3 Management of B Cell Immune Deficiencies

B cell defects are a heterogeneous group of disorders with variable reduction in B cell numbers and function, sharing the reduction in or absence of serum Ig and/or specific antimicrobial antibodies [15]. Most infections are caused by encapsulated bacteria, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae* (Table 17.1). Both recurrent or chronic bronchitis and pneumonia can result in chronic lung disease such as bronchiectasis and interstitial lung disease due to the chronic inflammation and fibrotic process in the pulmonary interstitium. Patients affected by B cell defects frequently suffer from recurrent otitis media and chronic sinusitis since childhood. Infants typically present first bacterial infections once maternal IgG have disappeared from circulation, which occurs between 3 and 18 months of age. Also common are gastrointestinal infections with *Giardia lamblia* and *Cryptosporidium* spp. (the latter mainly in patients with certain class-switch recombination defects) or CNS infection with bacterial meningitidis [16].

Despite an appropriate IgG replacement therapy, as described for combined immunodeficiencies, low IgM and particularly low IgA serum levels may be risk factors for *S. pneumoniae* and *H. influenzae* lung colonization [17]. In contrast to T cell defects, most B cell defects are associated with an otherwise normal response to viral infection. Numerical or functional B cell defects can be divided into three major categories: (i) defects in early B cell development (agammaglobulinemia), (ii) class-switch recombination defects (e.g., hyper-IgM syndromes), and (iii) common variable immunodeficiency (CVID). In the presence of B cell defects, as in CVID and X-linked agammaglobulinemia, the management may include IgRT, antibiotics for treatment, and prophylaxis of infections, but also respiratory rehabilitation programs and proper therapy for noninfectious complications [18]. Despite the reduction of bacterial infections due to IgRT [19], patients with cellular immunodeficiencies remain more susceptible to complications because of an associated T cell defect that requires particular attention.

17.3.1 Management of Pulmonary Complications

Among B cell immunodeficiencies, CVID is the most associated with pulmonary complications, such as bronchiectasis and noninfectious interstitial lung diseases (ILDs) [20]. Bronchiectasis presents as atypical bronchial and bronchiolar dilatations, resulting from repeated episodes of infection and inflammation with the destruction of the airways and lung parenchyma, consequent decline in lung function [21]. Also, it has also been demonstrated that, once the remodeling process is ongoing, airway inflammation gets worse even in the absence of bacterial infection, facilitated by the neutrophil accumulation and the augmentation of pro-inflammatory milieu. The management of bronchiectasis, apart from antibiotic prophylaxis, may require physiotherapy programs. Some studies have evidenced how the high incidence of chronic lung diseases in B cell immunodeficiencies is a direct consequence of diagnostic delay, severity of the infectious respiratory phenotype, and difficulty to find appropriate treatment strategies [22]. Thus, screening for chronic lung disease by high-resolution chest tomography (HRCT) scan is a cornerstone of disease management. Chronic airway inflammation due to recurrent infections may also lead to airway hyper-reactivity state with reversible or fixed obstruction [23]. Thus, annual testing with spirometry and CO transfer measurement is recommended (see Table 17.3). Another great challenge is currently represented by the management of ILDs [24]. ILD has not been only described in CVID but also in patients with CID such as cytotoxic T lymphocyte antigen 4 (CTLA-4) haploinsufficiency, lipopolysaccharide (LPS)-responsive and beige-like anchor protein (LRBA) deficiency, and signal transducer and activator of transcription 3 (STAT-3) gain of function (GOF). Interestingly, it is not found in hyperimmunoglobulin (IgM) syndromes or in XLA [25]. Different ILD patterns have been described in lung biopsies, including granulomas and all forms of pulmonary lymphoid hyperplasia. The term "granulomatous-lymphocytic interstitial lung disease" (GLILD) has been adopted to encompass all these features of ILD in CVID patients [26]. Its pathogenesis and appropriate management are currently under investigation. GLILD is usually described as part of a

Table 17.3 Monitoring and management of complications in B cell immune deficiencies

At diagnosis	During follow-up	
	Annually	Every 5 years
According to HRCT and PFTs (before and after BD) with DLCO measurement: • Tailored doses of IgG • Route of administration • Need for antibiotic prophylaxis • Pulmonary rehabilitation	PTFs and DLCO measurement • **Obstructive pattern** → inhaled steroid or steroid/LABA: In case of bronchiectasis → azithromycin prophylaxis + pulmonary rehabilitation + toilet bronchoscopy • **Restrictive pattern and/or DLCO reduction** with/without dry cough or dyspnea on exercise (**ILD suspicion**) → 6MWT, CPET, HRCT scan, bronchoscopy (microbiology, BALF analysis) → consider transbronchial biopsy (or cryobiopsy) to rule out a lymphoproliferative disorder Abdominal ultrasound EGDS	HRCT scan

Abbreviations: *HRCT* high-resolution chest tomography, *PFTs* pulmonary function tests, *DLCO* diffusing capacity for carbon monoxide, *6MWT* 6-minute walking test, *CPET* cardiopulmonary exercise testing, *BALF* bronchoalveolar lavage fluid, *LABA* long-acting beta agents, *EGDS* esophagogastroduodenoscopy

multisystem granulomatous/inflammatory disease, potentially involving the lymph nodes, spleen, liver, gastrointestinal tract, and other organs. The presence of splenomegaly, immune cytopenia, low serum IgA levels, higher IgM levels, and percentage expansion of CD21low B have been suggested as clinical predictors of GLILD [27]. A reduction in DLCO/gas transfer at routine lung function tests may be the earlier sign of an underlying ILD, deserving radiologic investigation. In case of radiological suspicion of ILD, a bronchoscopy in order to obtain a bronchoalveolar lavage fluid (BALF) analysis (microbiology and lymphocytic subpopulation study) should be performed, as well as a lung or nodal biopsy in order to confirm GLILD diagnosis and rule out hematological malignancies, when appropriate. Specific therapeutic guidelines for GLILD are currently lacking, but there are promising results with immunosuppressive agents on T cell and B cell (methotrexate, azathioprine [28], mycophenolate [29], sirolimus [30], anti-CD20 and anti-TNF agents [31]), thus suggesting how both lymphocyte subpopulations may play an active role in disease progression.

17.3.2 Management of Other Immunological Complications

Noninfectious complications of B cell immune deficiencies also include autoimmune cytopenias, enteropathy, and neoplastic diseases. Treatment of autoimmune cytopenias (mainly autoimmune thrombocytopenia and autoimmune hemolytic anemia) is mainly based on corticosteroids and anti-CD20 treatment. Currently, there is no evidence of advantages in splenectomy for the treatment of cytopenias in CVID [32]. Moreover, the indication for any immunosuppressive therapy in PID

should be considered very carefully for the risk of developing opportunistic infections like PCJ pneumonia. At least 20% of CVID patients have chronic gastrointestinal symptoms (including bloating, discomfort, malabsorption, and diarrhea) [33]. The histological evidence of mucosal inflammation in CVID enteropathy is similar to villous atrophy in celiac disease, although recent works underlined the different immunologic hallmarkers of T cell subpopulations [34]. About 5% of CVID with enteropathy present severe symptoms and may also benefit from treatment with low-dose immunomodulators, rituximab, and anti-TNF agents [35]. Finally, another relevant complication and cause of morbidity and mortality during the management of B cell immune deficiencies is cancer. Lymphoma and gastric carcinoma are the most represented neoplastic diseases [36]. The finding of EBV-driven lymphoproliferative diseases in patients with hypogammaglobulinemia and history of recurrent bacterial infections should raise the suspicion of a CD27-CD70 axis deficiency [37]

17.4 Immunoglobulin Replacement Therapy and Antibiotic Prophylaxis

SCID is a medical emergency as patients are extremely susceptible to developing additional severe and debilitating infections. When pulmonary infections are severe and recurrent, patients may develop irreversible lung damage such as bronchiectasis [38]. Many patients cannot produce appropriate antibodies; therefore, immunoglobulin G (IgG) replacement therapy should be initiated as soon as the immune deficit is diagnosed [39]. Both intravenous IgG (IVIG) and subcutaneous IgG (SCIG) have been regarded therapeutically equivalent (same efficacy for prevention of bacterial infections) [17]. Moreover, SCIG have showed some advantages in less systemic adverse events, improved quality of life, and stable IgG levels and disadvantages in having more local infusion site reactions and requirement of frequent infusions (weekly vs. monthly) [40] (see Table 17.4). The serum

Table 17.4 Differences in intravenous vs. subcutaneous IgRT

IVIG	SCIG
Intravenous administration, 100% and immediate bioavailability	Subcutaneous administration, gradual absorption, venous access is not required
Monthly infusions	Frequent infusions (generally weekly, up to every 3–4 weeks with fSCIG)
Higher peaks, less stable serum IgG levels	Stable and possibly higher serum IgG trough levels
No difference in quality of life	Improved quality of life [41]
More systemic adverse events	Less systemic adverse events, but more local infusion site reactions
Hospital-based, may be home-based according to the single country	Home-based after initial training

Abbreviations: *fSCIG* facilitated subcutaneous immunoglobulin

IgG trough level, defined as concentration preceding the next dose of IgG infusion, has been regarded as an important guide to therapy. An IVIG dose of 400–600 mg/kg every 4 weeks or a dose that maintains serum IgG trough levels above 500 mg/dL is desirable. Measurement of serum IgG trough level is necessary every 3 months until a steady state is achieved and then every 6 months if the patient is stable. For persons who have a high catabolism of infused IgG (e.g., during a period of active infection), measuring serum IgG levels and adjusting to higher dosages or shorter intervals may be required. Recent recommendations have noticed that individualized treatment plans and route of administration based on patient's preferences increase the therapeutic compliance to IgRT [42]. Adjunct therapy as azithromycin prophylaxis has been suggested for its antimicrobial, immunomodulatory, and anti-inflammatory properties. A recent study showed that long-term oral azithromycin prophylaxis (250 mg once daily for 3 consecutive days per week) in patients affected by XLA and CVID presenting chronic infection-related pulmonary diseases significantly may reduce the number of acute respiratory exacerbations per patient-year [43].

17.5 Neonatal Screening and Vaccination in the Management of T and B Cell Immune Deficiencies

Analysis of thymopoiesis can also help in the management of T cell immune deficiencies. T cell receptor excision circles (TREC), which are fragments of genomic DNA formed during V(D)J recombination in thymocytes, have been shown to reflect thymus activity. TREC levels in patients with cellular immunodeficiencies are typically below 400/mg DNA. TREC levels can be quantified by PCR, even from Guthrie cards, and it has become the mainstay of neonatal screening programs of SCID/CID. Thus, an early diagnosis can help in the management of cellular immunodeficiency. Moreover, detection of kappa-deleting recombination circles (KRECs), co-products during B cell formation, by PCR can estimate the average number of B cell divisions and may be a possible target for neonatal screening of B cell immunodeficiencies. KREC concentration in CVID patients has been found to be lower than in controls (58). This may enable an earlier diagnosis and management, especially starting sooner the IgRT, providing better clinical outcome and prevention of chronic immunologic complications. The role of vaccination in cellular immunodeficiencies will be discussed in the next chapter. In addition, vaccination is also used as diagnostic tool to assess specific antibody response to protein and/or polysaccharide antigens [44]. In particular, the specific IgG measured in pre- and post-vaccination in response to 23-valent pneumococcal polysaccharide vaccine is the most used test to evaluate a T-independent antibody response and the residual function of B lymphocytes. A recent 6-year longitudinal study showed that anti-23 pneumococcal serotype IgA level is a parameter capable of detecting CVID patients at risk of developing greater frequency of respiratory infections, chronic lung damage, and noninfectious complications over time [45].

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