Consensus document

Diagnosis and management of patients with primary immunodeficiencies

Consensus Document of the Spanish Society for Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Immunology (SEI), the Spanish Society for Pediatric Infectious Disease-Spanish Pediatric Association (SEIP-AEP) and the Spanish Society for Clinical Immunology, Allergology and Pediatric Asthma- Spanish Pediatric Association (SEICAP-AEP)

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ABSTRACT

Primary immunodeficiencies (PIDs) are rare, undiagnosed and potentially fatal diseases.

Clinical manifestations of PID can be fatal or leave sequelae that worsen the quality of life of patients. Traditionally, the treatment of PIDs has been largely supportive, with the exception of bone marrow transplantation and, more recently, gene therapy. The discovering of new affected pathways, the development of new molecules and biologics, and the increasing understanding of the molecular basis of these disorders have created opportunities in PIDs therapy. This document aims to review current knowledge and to provide recommendations about the diagnosis and clinical management of adults and children with PIDs based on the available scientific evidence taking in to account current practice and future challenges.

A systematic review was conducted, and evidence levels based on the available literature are given for each recommendation where available.

Keywords:

Primary immunodeficiencies

Vaccination

Treatment

Haematopoietic progenitors transplantation

Antibiotics

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RESUMEN

Las inmunodeficiencias primarias (IDP) son unas enfermedades raras, frecuentemente infradiagnosticadas y potencialmente fatales. Las manifestaciones clínicas de las IDP pueden ser muy graves y ocasionar secuelas que empeoran la calidad de vida de los pacientes. Tradicionalmente, el tratamiento de las IDP ha sido fundamentalmente de soporte, con excepción del trasplante de progenitores hematopoyéticos y, más recientemente, la terapia génica. El descubrimiento de nuevos mecanismos patogénicos, el desarrollo de nuevas moléculas y fármacos biológicos y los avances en el conocimiento de las bases moleculares de estas enfermedades han abierto oportunidades para el tratamiento de esta afección. El objetivo de este documento es revisar el conocimiento actual y aportar recomendaciones para el diagnóstico y el tratamiento clínico de los pacientes adultos y pediátricos con IDP basado en la evidencia científica disponible y teniendo en cuenta la actual práctica y los retos futuros. Se realizó una revisión sistemática, que justifica los niveles de evidencia para cada recomendación.

Palabras clave:

Inmunodeficiencias primarias

Vacunación

Tratamiento

Trasplante de progenitores hematopoyéticos

Antibióticos

Abbreviations

ADA: adenosine deaminase

AGREE: Appraisal of Guidelines Research & Evaluation

ALPS: autoimmune lymphoproliferative syndrome

ANA: antinuclear antibodies

AT: ataxia-telangiectasia syndrome

ATG: anti-thymocyte globulin

AUC: area under the curve

BCG: Bacille de Calmette-Guérin

BM: bone marrow

CBC: complete blood count

CGD: chronic granulomatous disease

CHARGE: coloboma heart defects, atresia choanae, growth retardation

CHH: cartilage-hair hypoplasia

CID: combined immunodeficiencies

CLOVES: congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi, spinal/skeletal anomalies, and/or scoliosis

CMC: chronic mucocutaneous candidiasis

CNS: central nervous system

CSF: cerebrospinal fluid

CVID: common variable immunodeficiency

CyA: cyclosporine

DCLO: diffusing capacity of the lung for carbon monoxide

EBV: Epstein-Barr virus

EBV-PTLD: Epstein-Barr virus post-transplant lymphoproliferative disorder

EDA-ID: ectodermal dysplasia-associated immunodeficiency

EFS: event-free-survival

ERT: enzyme replacement therapy

ESR: erythrocyte sedimentation rate

GOF: gain-of-function

GVHD: graft-versus-host disease

Hib: *Haemophilus influenzae* type b

HIES: hyper-IgE

HLH: hemophagocytic lymphohistiocytosis

HRCT: high resolution computed tomography

HSCT: hematopoietic stem cell transplantation

IDSA: Infectious Diseases Society of America

IFNγ: interferon gamma

IGRT: immunoglobulin replacement therapy

IV: intravenous

KREC: K-deleting recombination excision circles

LAIV: live-attenuated influenza vaccine

LDH: lactate dehydrogenase

MFD: matched-family donor

MMF: mycophenolate mofetil

MMR: measles, mumps, rubella

MMRV: measles, mumps, rubella, varicella

MRI: magnetic resonance imaging

MSD: matched-sibling donor

MTX: methotrexate

NADPH: nicotinamide adenine dinucleotide phosphate

NBS: newborn screening

NEMO: nuclear factor-κB essential modulator

NGS: next generation sequencing

OPV: oral polio virus vaccine

PAD: predominantly antibody deficiencies

PBSC: peripheral blood stem cell

PCV13: 13-valent pneumococcal conjugate vaccine

PFT: pulmonary functional test

PID: primary immunodeficiency

PJP: *Pneumocystis jirovecii* pneumonia

PPSV23: 23-valent polysaccharide vaccine

QoL: quality of life

R-ADA: recombinant adenosine deaminase

RIC: reduced-intensity conditioning

SC: subcutaneous

SCID: severe combined immunodeficiencies

SCID: severe combined immunodeficiency

SCN: severe congenital neutropenia

SEIMC: Sociedad Española de Infectología y Microbiología Clínica

SPURR: severe, persistent, unusual, recurrent infections with a history of PID running in the family

STAT: signal transducer and activator of transcription

TAR: thrombocytopenia and absent radius

TCL: T-cell lymphopenia

TREC: T-cell receptor excision circles

TSH: thyroid stimulating hormone

Ty21a: oral live *Salmonella typhi* vaccine

UD: unmatched donor

US: ultrasound

USA: United States of America

VEO-IBD: very early onset inflammatory bowel disease

WAS: Wiskott-Aldrich syndrome

WES: whole exome sequencing

WGS: whole exome/genome sequencing

WHIM: warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis

XLA: X-linked agammaglobulinemia

Introduction

Justification

The field of primary immunodeficiencies (PIDs) has experienced an enormous increase in the last years. The first PIDs were identified in the 1950s, and in 1970 16 distinct disorders were included in the first World Health Organization report. PIDs were then defined as fully penetrant mendelian traits predisposing to multiple, recurrent, and opportunistic infections.[1,2] Since the mid 1990's, several PIDs predisposing to life-threatening infections in otherwise healthy, even adult, individuals were reported. Some of these PIDs predispose to a narrow range of microorganisms, and frequently, these monogenic diseases do not display a full penetrance.[3] Currently, over 400 PID have been identified, more than 350 out of them with a recognized gene defect. A growing group of PIDs are now known to associate with immune dysregulation often leading to autoimmunity, lymphoproliferation and malignancy, which may be the predominant, and even the only, clinical phenotype.[1,4-8] The descriptor Inborn Errors of Immunity (IEI) is gaining acceptance to encompass dysregulation and autoinflammatory disorders and PIDs, as the latter was traditionally used to define inborn errors of immunity to infection.[1]

Clinical manifestations of PID can be fatal or leave sequelae that worsen the quality of life (QoL) of patients. Traditionally, the treatment of PIDs has been largely supportive, with the exception of bone marrow transplantation and, more recently, gene therapy. The twenty-first century has witnessed exciting advances in immunoglobulin replacement therapy, hematopoietic stem cell transplantation, and gene therapy. Nevertheless, the discovering of new affected pathways, the development of new molecules and biologics, and the increasing understanding of the molecular basis of these disorders, have created opportunities and paved the way for the implementation of precision medicine as a therapy of PIDs.[4,9,10]

It is assumed that PIDs may be greatly underdiagnosed, and their diagnosis and management usually require a multidisciplinary approach. The objective of this consensus document is to provide a practical clinical guide for the suspicion, diagnosis and management of PID patients. Experienced researchers

and clinicians, with expertise in pediatric and adult PIDs and infectious diseases, have developed this consensus document, which was endorsed by four Spanish scientific societies.

Target populations and objectives of the document

The target populations of this document are children and adults with PIDs, healthcare and PIDs relatives. The classification of PIDs was based on the 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity.[1] Patients with autoinflammatory disorders were not included in this document, due to the high variability in symptoms and recommended treatments, which often differ from those used for other PIDs.

The intended guideline audience includes physicians involved in the care of PID patients (including primary care physicians), and other healthcare workers attending PID patients. Here we report a consensus from a public health policy perspective with the objective of assessing the available overall evidences and to propose recommendations on the following key questions:

1. When should a PID be suspected in a child and in an adult? (provided that acquired immunodeficiencies were ruled out).

2. What immunological tests should be performed if a PID is suspected?

3. What other clinical studies and measures should be performed in children and adults with PIDs at diagnosis? And during follow-up?

4. How should PIDs be screened in neonates?

5. When and what type of antimicrobial prophylaxis should be offered to a child and an adult with PIDs?

6. What type of vaccines can be offered to children and adults with PIDs?

7. When can immunoglobulin replacement therapy (IGRT) can be advised? Which route is advisable? How should IGRT be monitored during follow-up?

8. When is a hematopoietic stem cell transplantation (HSCT) considered for a child with PIDs?

9. When is a HSCT considered for an adult with PIDs?

10. Which other immunomodulatory, supportive and curative therapies can be used?

11. When is genetic counselling needed?

General methodology of the document

To develop the recommendations included in the consensus document, the expert panel conducted a systematic review of the literature in PubMed, and established the quality of the evidence using the Infectious Diseases Society of America (IDSA) grading system for ranking recommendations (Table 1).[11]
The contents of the document and the conclusions have been agreed by all the authors and the coordinators of the Statement. Before publication, the manuscript was presented to and approved by the Spanish Society for Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Immunology (SEI), the Spanish Society for Pediatric Infectious Disease-Spanish Pediatric Association (SEIP-AEP) and the Spanish Society for Clinical Immunology, Allergology and Pediatric Asthma-Spanish Pediatric Association (SEICAP-AEP).

1. When should a PID be suspected in a child and in an adult? (provided that acquired immunodeficiencies were ruled out)

Recommendations

- It is critical to maintain a high index of suspicion for PID in patients presenting with recurrent infections, autoimmune disease, malignancy, and combinations of these conditions (A II).
- It is mandatory to obtain a focused family history when the differential diagnosis includes a PID (A II).
- PID must be screened in patients with recurrent infection and at least one of the following ones: family history, failure to thrive, autoimmunity, lymphoproliferative disease, malignancy or requirement of intravenous (IV)

antibiotics for treating and clearing infections that usually do not require it (A II).

- PID must be screened in patients with one or more infections caused by opportunistic organisms that are rarely pathogenic for immunocompetent subjects (A II).
- PID must be screened in patients with one or more severe infections caused by low virulence pathogens (A II).
- PID screening may be considered in children with a sole severe infection, and in patients with recurrent infections depending on the clinical context and the level of suspicion of the physician (B II).

Rationale

PIDs are predominately pediatric diseases. However, they are increasingly being diagnosed during adulthood. Although over 400 PIDs have been identified so far, the main entities can cause similar symptoms in affected patients. Therefore, diagnosis of PIDs in children and adults arises after suspicion of recurrent, long-lasting, severe or unusual infections, severe dermatitis, autoimmune, inflammatory or neoplastic diseases, but the range of warning signs that should lead to the suspicion of a PID is increasingly broad.

PIDs are underdiagnosed diseases worldwide. In recent studies, patients suffering from common variable immunodeficiency (CVID) showed a median diagnosis delay of 3 years ranging from 1 to 10 years.[12]

There are several compendiums of warning signs in children and adults, which are based on clinical presentations —mainly infectious diseases— and, in some cases, on family history. In this regard, in 1993 the Jeffrey Modell Foundation published for the first time the 10 warning signs for PID based on a consensus meeting between different experts; recently, different warning signs for adults and children were included (Table 2).[13,14]

However, some of these warning signs are outdated.[15] Many immunocompetent children may present with recurrent ear, sinus or respiratory tract infections. Asthma, adenoid hypertrophy, cystic fibrosis, abnormal lung anatomy or lifestyle factors such as older siblings, day-care attendance, or smoke exposure

can predispose to infections. These conditions should be thought of firstly in patients with suspected PID.[16]

In addition, these 10 warning signs do not include autoimmune, autoinflammatory or oncological manifestations, despite being relevant presentations in PID patients. There is an increased risk for autoimmune disease in these patients and sometimes it can be the sole manifestation.[15]

A recent study reported that 1 or more autoimmune/inflammatory complications are present in 26% of PID patients, with particular risk for autoimmune cytopenia, inflammatory bowel disease or rheumatoid arthritis when compared with general population.[17] The presence of lymphadenopathy or splenomegaly might be signs of lymphoproliferative disease or malignancy.[16] There is an increased risk for cancer in patients with PID compared to general population, especially for lymphoma[7] or for gastric cancer, being the leading cause of death in some cohorts of patients with CVID.[18]

Nevertheless, the following three specific warning signs would potentially identify about 90% of PID patients: a family history of PID, requirement for IV antibiotics in the management of infections, and failure to thrive in pediatric patients. A focused family history should be obtained when the differential diagnosis includes a PID.[16]

Another useful approach for PID diagnosis is called SPURR. PID should be suspected in patients who have Severe, Persistent, Unusual, Recurrent infections and with a history of PID Running in the family (SPURR). Infections in PIDs usually have special characteristics including recurrence, occurrences in multiple locations, refractoriness to therapy or that are caused by opportunistic microorganisms that are rarely pathogenic for immunocompetent subjects.[16,19] Signs and symptoms found in pediatric patients may be quickly progressive while most of the adults show moderate or mild manifestations, leading to an increased risk of diagnostic delay.[3,11] However, a sole severe infection such as *P. jirovecii* pneumonitis, herpes virus encephalitis, disseminated mycobacteria or invasive pneumococcal disease in a vaccinated-patient, specially due to a vaccine-included serotype, may also reveal the presence of PID, and these cases require appropriate immunological evaluation.[16] In addition, PIDs can

present with diverse symptoms, and all specialties should be made aware of the possibility of PID on patients with atypical clinical presentations.[20]

Further development and refinement of warning signs considering the growing knowledge of PIDs manifestations may allow effective guidelines targeted at different groups to better detect PIDs.[21–23]

Specific documents are necessary for all health professionals who could potentially attend patients with undiagnosed PID, to allow an early diagnosis and adequate management, and recently a Spanish Delphi consensus for a more comprehensive warning signs of PID in pneumonology, hematology and oncology has been recently published.[14–16]

The point at which a patient with a possible PID should be referred to an immunologist will vary depending on the experience of the clinicians involved, but ultimately, the diagnosis or exclusion of PID is best determined by an experienced clinical immunologist, and therefore appropriate early consultation should be encouraged.

2. What immunological tests should be performed if a PID is suspected?

Recommendations

- Diagnostic process of PID must be done attending clinical phenotype, physical exam and family history (A III).
- A stepwise approach is recommended as the most likely cost-effective strategy for diagnosis of PID (A III).
- Complete blood count (CBC) and immunoglobulins levels should be performed as first line tests for diagnosis of PID (A III).
- Second line (non-disease specific or disease specific) tests include functional, molecular and genetic tests, which must be tailored by experts in PIDs (A III).
- We recommend targeted sequencing of candidate genes if a disease is highly suspected (based on clinical and laboratory findings), a semi-targeted approach in overlapping clinical presentations (PIDs genetic panels), and whole

exome/genome sequencing (WES/WGS) when the previous fail or an unbiased approach to PIDs genetic testing is advantageous (A III).

Rationale

The ultimate aim when studying a PID is to reach a precise diagnosis and to identify the molecular basis of the disease, which is crucial for the management of the patients and their families. When possible, the identification of inborn errors of immunity allows the application of precision medicine in the affected patients and the prevention of clinical manifestations and, when indicated, curative therapy, as well as genetic counselling.

Clinical characterization (phenotype, careful physical exam and familial history including consanguinity or family members who died in early childhood) is extremely important and initiates the immunological diagnosis workflow (Figure 1); further performing of different tests varies depending on the type of suspected immunodeficiency.[1,24] An updated set of clinical, laboratory quantitative and functional features is currently defined for the majority of PIDs, which helps to standardize the classification of these diseases.[25,26]

First and second line studies

Laboratory tests follow stepwise guidelines that can improve timely diagnosis and the appropriate therapy.[27] This usually allows a cost-effective screening for PID in the early phases, with more advanced, expensive tests reserved for their definitive classification in collaboration with the specialists in immunodeficiencies.[28,29]

Relatively inexpensive, rapidly performed, and reasonably sensitive and specific screening, basic or first line tests are available in most centres, even at primary health care level (Figure 1).[29] A CBC and blood smear along with a careful differential cell count provide important information on suspected cytopenias and qualitative cellular changes (Figure 1). Determination of serum immunoglobulins (IgG, IgM, IgA, and IgE) is the first step for the evaluation of defects of antibody production and may reveal other PIDs such as hyper-IgE syndrome (HIES), hyper-IgM syndromes or other combined

immunodeficiencies.[7,17] Low values of calculated globulin (total protein-albumin) should prompt to measure serum immunoglobulin levels.[30] Since CBC, lymphocyte subsets, immunoglobulin and subclasses levels vary throughout life, age-matched reference levels are essential for appropriate interpretation.[31] Second line tests must be done regarding the results of screening tests as well as the clinical phenotype.[13,21,32] They include non-disease-specific assays like T, B, NK immunophenotyping, naïve/memory B and T cell subpopulations, NK cell subsets, lymphocyte T proliferation tests, analysis of TCRVβ repertoire diversity by flow cytometry or spectra-typing, dendritic cells phenotyping or TLR function. Other studies like double negative (CD4– CD8–) T cell counting, protein expression (CD40L, BTK, DOCK8, CD18, WAS, SAP, XIAP, CTLA-4/LRBA...), phosphorylation of signalling proteins (STAT1, STAT3, STAT5, AKT, S6...), DNA repair radio sensitivity, and dihydrorhodamine tests are more disease-specific.

Figure 1 illustrates a diversity of immunological laboratory tests, and how they may be available in routine or at reference laboratories. Some of these tests may move from second to first line depending on the clinical phenotype and the utility of the different tests for the particular suspected PID.

When are functional studies indicated?

In vivo as well as *in vitro* assessment of immune responses are relevant for the diagnosis of many PIDs.[29] Functional studies are usually considered as a second line approach, but in some entities, they point to the pathogenesis and constitute diagnostic criteria. *In vivo* specific antibody responses following immunization are decreased in CVID and other PIDs associated with defects of antibodies; altered *in vitro* cytotoxic activity is found in primary hemophagocytic lymphohistiocytosis (HLH); impairments in the *in vitro* IL-12/IL-23-IFNγ axis is abnormal in mendelian susceptibility to mycobacterial diseases (MSMD); neutrophil oxidative burst is lacking in chronic granulomatous disease (CGD), and C1 esterase inhibitor function is absent in hereditary angioedema type II. Thus, functional studies should be asked as soon as such PIDs are suspected.[25,26]

When should genetic studies be performed (targeted and whole exome/genome sequencing)?

Genetic diagnosis is always desirable as it allows to set the molecular basis and classification of PIDs, an accurate genetic counselling, to get better definitions of genotype/phenotype associations, and to identify patients for gene-specific therapies.

In addition, results of first- and second-line laboratory tests can be normal in several PIDs. This scenario is often found in some defects of the innate immune system or in autoinflammatory diseases. In these cases, genetic analyses should be promptly asked by experts.

On the other hand, most frequent primary antibody immunodeficiencies like IgA deficiency and the majority of CVID patients lack clear genetic backgrounds so far, and they currently do not benefit in most cases of genetic studies.

For many years, the genetic approach for PID diagnosis has been a targeted, gene-to-gene, sequencing analysis based in clinical and/or laboratory findings. Since the advent of next generation sequencing (NGS) tools, there is an increasing worldwide access to panels of immunodeficiency-related genes (semi-targeted sequencing approach) and clinical WES/WGS, requiring a highly specialized interpretation. When available, experts in PID should use NGS for the molecular diagnosis in very complex, overlapping and/or atypical patients with suspected immunodeficiency. In such cases, NGS tools are able to identify the causative genes by consuming less time and costs than conventional studies.[33,34]

3. What other clinical studies and measures should be performed in children and adults with PIDs at diagnosis? And during follow-up?

Recommendations

- A multidisciplinary approach coordinated by an expert in PIDs is recommended in these patients (A III).
- At diagnosis the following tests should be performed:

– Blood analysis: CBC, liver and renal function, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR); in PID related to autoimmunity, include antinuclear antibodies (ANA), thyroid stimulating hormone (TSH) and celiac markers; in T cell defects, include screening for viruses including cytomegalovirus (A III).

– In PID with potential lung involvement, pulmonary functional test (PFT), including diffusing capacity of the lung for carbon monoxide (DLCO), and lung high resolution computed tomography (HRCT), is recommended (A III).

– Chest X-ray and an abdominal ultrasound should be performed in all PID patients (A III).

• During follow-up, the following tests should be performed:

– Yearly blood analysis (CBC, liver and renal function, glucose; include uric acid, LDH, ESR and beta-2-microglobulin in PID at risk of lymphoma and/or with chronic lymphadenopathy; include ANA, TSH and celiac markers in PID related to autoimmunity; besides immunological parameters depending on the PID (A III).

– Yearly PFT, including DLCO, in PID with potential lung involvement (A III).

– Yearly abdominal ultrasound (B III).

– In PID with lung involvement, HRCT should be repeated every 5 years when baseline is normal (A III), or every 1-2 years in case of active bronchiectasis or interstitial lung disease (B III).

– Dental evaluation and QoL scale should be performed at diagnosis and yearly (A III).

– The high variability of PID and their clinical presentations makes it difficult to establish common recommendations. Other tests will be performed depending on the clinical context (A III).

– In patients with bronchiectasis, physiotherapy and respiratory rehabilitation are key in the treatment (A III).

– When there is suspicion of infection in patients with bronchiectasis, it is recommended to optimize general, microbiological and imaging methods (A III).

Rationale

Patients with PID are at risk of multiorgan damage due to infectious complications and/or immune-related complications such as autoimmunity or inflammatory diseases.[35] The presence of secondary complications must be screened for, both at diagnosis and during follow-up (Table 3) and will depend, ultimately, on the clinical manifestations and the underlying PID. The high variability of PIDs and their clinical presentations makes it difficult to establish common recommendations. An expert in PIDs should follow up most patients every 6 to 12 months.[16,36] Patients with secondary complications may need more frequent follow-up and/or more than one specialist.[35,36] A coordinated multidisciplinary approach to management should be considered in these patients.[16]

In every visit, close evaluation of clinical signs is complimentary and will include oral cavity, lymphoid tissue, thyroid gland, skin and joint physical examination. Blood tests of liver and renal function should be checked prior to initiate IGRT and prophylactic antibiotic therapy, and at least once a year thereafter.[16,36] For patients on IGRT, PCR screening for some blood-borne infections (HBsAg and PCR to herpes C virus and human immunodeficiency virus) prior to IGRT is also recommended.[16,36] Serum may be stored for retrospective analysis in the event of future suspected disease transmission.[35,37] Other blood tests might be needed in concrete PIDs linked to autoimmune complications (ANA, TSH, celiac markers).[17] Also, screening tests for malignancy (uric acid, LDH, ESR and beta-2-microglobulin) are recommended yearly in PID at risk of lymphoma and/or with chronic lymphadenopathy.[16,38] In adults, cancer screening should be indicated with the same periodicity than that in general population,[39] except for adult patients with CVID and agammaglobulinemia, who are at high risk of gastric cancer: the frequency at which both *H. pylori* infection and upper endoscopy should be performed in this population is still to be defined.[40]

Immune work-up (T and B sub-phenotyping, proliferation to mitogens, sCD25…) might be recommended in specific PIDs (CVID, CID) yearly; however, a case by case strategy should be pursued.

It is advisable to actively monitor the status of lung disease.[41–43] There is a lack of consensus in assessing and caring for lung disease in patients with CVID, which can be extended to all PIDs. This emphasizes the fact that evidence-based guidelines are missing and urgently needed. Spirometry should be performed annually for all PIDs, or at 6-month intervals if the disease appears to be progressing. Complete pulmonary function testing with measurement of diffusion capacity should also be done yearly in patients with CVID who may have interstitial and/or granulomatous lung disease. HRCT should be performed at diagnosis for all PIDs and repeated every 5 years when baseline is normal, or every 1-2 years in case of active bronchiectasis or interstitial lung disease, according to the progression. The role of lung magnetic resonance imaging (MRI)[44] (specially in patients with demonstrated radiosensitivity) and positron emission tomography-computed tomography in this setting remains to be elucidated.[45] Image studies, HRCT and MRI, as well as specific microbiological or immunological studies, should be performed in selected cases, as well as specific microbiological or immunological studies, and they will vary according to the age and the condition of the patient.[46]

There is a lack of evidence that surveillance cultures, either from collected sputum or an oropharyngeal swab, might prove to be a useful practice, as opposed in cystic fibrosis-bronchiectasis. Sputum cultures before the institution of azithromycin prophylaxis must be taken to exclude nontuberculous mycobacteria and ascertain sensitivity to azithromycin.[16] The most important measure is the early identification and treatment of bacterial sinopulmonary infection, which rarely resolves spontaneously in patients with PIDs. Treatment of bronchiectasis should focus on preventing the progression of structural lung damage. When possible, cultures should be performed, rigorous use of imaging methods to avoid over-exposure to radiation, CBC, C-reactive protein levels and erythrocyte sedimentation rate. Aggressive treatment of other diseases predisposing to infections, such as asthma or allergic rhinitis, is essential to avoid infectious exacerbations. Serial sputum tests, including antibiotic susceptibility tests of the cultured organism, can guide antibiotic treatment.[46,47]

Additional medications that favour bronchodilation, expectorants and mucolytics may be beneficial in symptomatic treatment.

Weight gain must be routinely assessed in the follow-up of pediatric patients.

In patients with bronchiectasis, physiotherapy and respiratory rehabilitation are key in the management. There are available systems for classification (or grading/scoring) of the severity of respiratory complications, such as the St. George questionnaire, which could be useful for controlling symptoms' progression in patients with chronic lung disease.[48] The tools used to control lung disease in other pathologies, such as the quality questionnaire of the British Thorax Society and the severity index of bronchiectasis may also be useful.[49–51]

It is advisable to evaluate the presence of chronic diarrhoea or malabsorption with proper questionnaire and weight control in every visit (which can include faecal calprotectin testing in patients with suspected bowel inflammation). Systematic stool microbiological tests are not recommended. US sonogram to check for granulomatous lesions in the liver, spleen, kidneys, and lymphadenopathies is also recommended yearly for all patients with PIDs that have been linked to lymphoproliferation. In case of any abnormal neurologic or developmental findings, a baseline MRI is recommended. Dental evaluation and a QoL scale should be performed yearly.[52] The clinical screening recommendations for children and adults with PIDs are detailed in Table 3.

4. How should PIDs be screened in neonates?

Recommendations

- In severe combined immunodeficiency (SCID) individuals, haematopoietic stem cell transplantation (HSCT) performed in the first 3-4 months of life and while the newborn is asymptomatic improves the prognosis of patients resulting in a survival rate of >90% (A II).
- Newborn screening (NBS) for T cell deficiencies has shown to reliably identify patients with SCID in the asymptomatic phase (A II).

- T-cell receptor excision circles (TREC) is currently the most appropriate biomarker for the early identification of neonates with SCID through systemic NBS programs (A II).
- TREC based SCID NBS programs are cost effective (A II).
- TREC and K-deleting recombination excision circles (KREC) assays allows detection of congenital B cell defects and some additional combined immunodeficiencies may be missed when using TREC alone (A II).

Rationale

SCID is the most severe form of PID, with an estimated prevalence around 1:50 000,[53] characterized by a decrease in the number or function of T lymphocytes, and sometimes B and NK cells. Therefore, patients may suffer from serious infections due to bacteria, viruses and fungi. Patients are usually asymptomatic until the age of 2-4 months and up to 35% die in the first episode. Currently, at least 16 SCID causing molecular defects are known.[24] In addition to SCID, there are other forms of severe T-cell lymphopenia (TCL) associated with high mortality in the first years of life (Table 4). HSCT or gene therapy are curative SCID treatment options with excellent overall survival and QoL.[54]

Early treatment is mandatory, rendering neonatal SCID screening a moral imperative. A sensitive screening test quantifying TRECs has been validated for dried blood spot samples (Guthrie cards). In addition to SCID, it also allows for the detection of other life-threatening T-cell disorders.[55,56] The cost-effectiveness of this NBS is well established and several studies have been performed in different settings and models.[57,58]

The NBS for SCID was incorporated into the Recommended Uniform Screening Panel in 2010 and since 2019 it has been established in all states of the United States of America (USA). Taiwan, Israel, Norway and recently Germany, Switzerland and Austria are other countries with systematic SCID screening and so far, Catalonia is the only region in Spain implementing SCID NBS in January 2017.

Analogous to SCID, efforts have been initiated to set-up KREC-based screening for B-cell deficiency.[59] Several studies have used combined TREC and KREC-screening assays, allowing for a simultaneous detection of T and B-cell defects (Table 4).

Expanded screening for the detection of other PID such as complement deficiencies and granulocyte disorders using protein-based assays has also been proposed. These projects are so far limited to regional pilot studies with a combined case-control and prospective cohort design.[60–62] High throughput targeted mutation analysis or next-generation sequencing, including WES and WGS, is often required to determine the underlying molecular diagnosis in patients with positive NBS tests.[58] Different approaches are currently ongoing in different settings.[63]

TREC-only, TREC/KREC, or TREC/adenosine deaminase (ADA) strategies have been evaluated in national and regional pilot studies and many more regions have approved or applied for the initiation of official screening programs.[60,64–67] The USA has implemented NBS programs producing high quality data that describe benefits and limitations of this method.[20] In addition to SCID cases, the possibility of positive results has been reported for other combined immunodeficiencies (CID) variants, as well as in the context of genetic syndromes such trisomy 21 or DiGeorge syndrome (22q11del), ataxia telangiectasia (AT) or secondary causes (e.g. chylothorax, lymphedema…). Other common sources for positive results are preterm neonates or those born to mothers under immunosuppressive therapy during pregnancy. Importantly, false positive results affect the positive predictive value of the test. Adjusting the cut-off values for the assay to specific populations and settings is necessary to achieve high specificity without sacrificing the sensitivity of the test.[66] Some experts consider that the addition of KREC to the TREC assay may lead to an increase of false positive testing and re-call and re-test rates. However, it may also reduce the numbers of false negative results, as it has shown to detect patients with hypomorphic SCID mutations and delayed-onset ADA-SCID.[60,68]

Infants with combined PIDs that are characterized by variably low numbers of naïve T and B cells cannot be reliably identified by NBS using the TREC or

TREC/KREC assay. Clinicians should be aware of this limitation and investigate those infants for PIDs regardless of the result of the assay.[69] Independently of the used cut-off level, an effective diagnostic infrastructure for further evaluation and clear guidelines for follow-up are necessary to identify, diagnose, register, and if appropriate treat positively tested newborns. Different work-up algorithms have been proposed and although they share many items, regional modifications are common and probably necessary to adjust the screening and confirmation process to the local infrastructure and population characteristics.

5. When and what type of antimicrobial prophylaxis should be offered to a child and an adult with PID?

Recommendations

- Infants older than 4 weeks of age with SCID must receive prophylaxis for *Pneumocystis jirovecii* as soon as they are diagnosed (A II).
- *P. jirovecii* prophylaxis is indicated for other specific T cell deficiencies with a high susceptibility to this microorganism infection (A III).
- All patients with CGD should receive prophylactic cotrimoxazole (A II) and itraconazole (A I).
- Adult patients with humoral immunodeficiency could benefit from prophylaxis with azithromycin when respiratory infections persist despite IGRT (A I). There are no published controlled studies of the benefits of this prophylaxis in children with humoral immunodeficiency, although the same benefit is expected (A III).
- Antibiotic prophylaxis with penicillin V or amoxicillin is recommended for patients with complement component deficiencies and congenital asplenia (A II).
- Other specific antibiotic prophylaxis can be prescribed, chronically or intermittently, according to the type of the primary immunodeficiency. (See specific recommendations, and quality of evidence in Table 5.)

Rationale

There are few studies evaluating the effect of prophylactic antimicrobials in most PID, except for CGD.[16,70–74]

Infants with SCID must receive cotrimoxazole prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) as soon as they are diagnosed, during the waiting period before HSCT/gene therapy, and during the ensuing immune reconstitution.[16,70]

Although cotrimoxazole is not recommended under 6 weeks of age, some centres start it at 1 week of age in term babies with careful monitoring of liver function.[75] Alternative agents include atovaquone, dapsone, and pentamidine.[75] Prophylaxis with palivizumab could be considered during the respiratory syncytial virus season.[16] Antifungal prophylaxis has not been specifically evaluated in these infants, and additional antiviral/antifungal cover depends on local guidelines and clinical circumstances.[76] In patients with parenteral nutrition, prolonged use of broad-spectrum antibiotics, central venous lines and/or mucocutaneous candidiasis, antifungal prophylaxis could be considered.[77] In these cases, fluconazole is prescribed before 1 month of age, at which time itraconazole can be used.[70]

Specific criteria for PJP prophylaxis have not been established for other non-SCID combined immunodeficiencies, although it is widespread used.[16,70] PJP prophylaxis is indicated in specific T-cell deficiencies with high PJP, such as CD40 and CD40L deficiencies or nuclear factor-kappa B essential modulator (NEMO) deficiency.[16]

Patients with partial DiGeorge syndrome present a largely intact T-cell function, and PJP prophylaxis is not usually required.[16,75] Cotrimoxazole or azithromycin prophylaxis could be considered in patients with recurrent respiratory infections.[16,75,78] In contrast, patients with complete DiGeorge syndrome are profoundly immunosuppressed, similar to patients with SCID.[16,75]

Regarding patients with humoral immunodeficiency, many authors propose the use of prophylaxis when infections, such as recurrent pneumonia or multiple otitis media or sinusitis, persist despite well-conducted IGRT.[16] A recently published double-blind, placebo-controlled randomized trial has demonstrated the efficacy and safety of long-term azithromycin prophylaxis in adults with

primary antibody deficiencies under IGRT.[78] This regimen reduced respiratory exacerbations, need of additional antibiotic courses and hospitalizations.[78] However, there are no published controlled studies of its benefit in children,[16,79] and the development of resistances is a concern with long-term antibiotic prescription. Some authors have suggested to "rotate" antibiotics, but studies have not been performed to validate this strategy.[16,79]

All patients with CGD should receive cotrimoxazole and itraconazole prophylaxis if HSCT or gene therapy is not performed.[16,70,75] Voriconazole could be prescribed in small children as oral suspension if available. In older children, itraconazole is recommended as voriconazole could induce photosensitivity in long-term use.[70] Primary prophylaxis with posaconazole has been reported, but its efficacy has not been evaluated, although nowadays this option is increasingly accepted by many clinical experts. Voriconazole serum levels must be measured because of individual absorption variability.

In children with IRAK-4 or MyD88 deficiency, antibiotic prophylaxis of any sort has proved to reduce by half invasive infections.[80] Patients older than 14 years who do not receive prophylaxis, do not use to present further invasive infections, and its discontinuation might be cautiously considered during this age period.[16,80,81]

Antibiotic prophylaxis with penicillin V or amoxicillin is recommended for patients with complement factor deficiencies and congenital asplenia.[16,70,82] An obvious problem is compliance with long-term regimens.

TLR3 pathway defects predispose patients to herpes simplex encephalitis during primary infection, making detection of patients difficult in the absence of a suggestive family history. Given this risk in children less than 3 years of age, and the high incidence of neurological sequelae after the infection, prophylaxis with acyclovir or valacyclovir is advisable for young children until herpes seroconversion is confirmed.[16] Other recommended regimens are described in Table 5 and Table 6.

6. What type of vaccines can be offered to children and adults with PID?

Recommendations

- Live attenuated vaccines, including BCG, are contraindicated in patients with complete T-cell defects because of known or theoretical risks of disseminated infection resulting from viable vaccine organisms (D III).
- PID patients can be safely vaccinated with inactivated vaccines; however, vaccine immune response can be suboptimal (A III).
- Live-attenuated Influenza vaccine is contraindicated in immunocompromised patients, and it is not recommended to the household contacts, except in case of minor antibody deficiencies (D III).
- Annual vaccination with Influenza inactivated vaccines are recommended in all PID patients and their household contacts, including those with CVID receiving IGRT (A II).
- Vaccination of patients receiving IGRT with inactivated antigens could be considered, although efficacy or effectiveness of the intervention has not been yet determined (C III).
- MMR and varicella are not required in PID patients receiving IGRT, however these vaccines may be considered according to their risk of exposure and immune status (C III).
- In children with PID, unless contraindicated, systematic immunization schedule with inactivated vaccines should be completed (A III).
- Pneumococcal vaccination is recommended in PID patients, unvaccinated >60-month-old patients should receive one dose of the 13-valent pneumococcal conjugate vaccine (PCV13) (B III). For those receiving IGRT, pneumococcal vaccination may be considered (safe intervention) although cost-effectiveness remains to be elucidated (C III).
- The 23-valent polysaccharide vaccine (PPSV23) is recommended for PID patients ≥2 years of age with 2-dose scheme 5 years apart (B II). No additional doses of PPSV23 are recommended (D III).
- Vaccination against *H. influenzae* type b is recommended in PID patients, unimmunized patients ≥5 years of age and adults at high risk (complement deficiency, asplenia) (A II).

- Wide protection against serogroups B and ACWY is recommended for patients with PID, especially in those with complement defects or congenital asplenia/hyposplenism (A II).

Rationale

Vaccination of people with PIDs requires especial considerations. These patients can be at increased risk for vaccine preventable diseases, potential serious adverse events following immunization with live attenuated vaccines or poor response to vaccination. The safety and efficacy of vaccines in people with PID are determined by the nature and degree of immune compromise.[83,84] PIDs are usually inherited as single-gene disorders, can involve any part of the immune system, and share the common feature of susceptibility to infection by various microorganisms, depending on the specific deficiency. Specific susceptibilities to certain vaccine preventable diseases entail risk-specific additional recommendations for some vaccines in this population.[83–85]

People with PID can usually be safely vaccinated with inactivated vaccines, with similar or minimally different schemes as for immunocompetent people [85]. However, vaccine immune response can be suboptimal, and in people with humoral PID under IGRT, usefulness of vaccination is controversial,[83,84] although some experts support vaccination based on the possible cellular response.[86,87]

Inactivated antigens, which include recombinant vaccines, are generally not affected by circulating antibodies, so they can be administered before, after, or at the same time as IGRT. Instead, IGRT may interfere with immune responses to measles, mumps, rubella and varicella live vaccines.[83] Vaccination against influenza in patients with CVID receiving IGRT has been studied and, despite conflicting results on humoral and cell responses, available data and current evidence supports annual influenza vaccination in these patients and their close household contacts.[83,88–91] Live vaccines, including BCG, generally are not recommended for many of these patients because of known or theoretical risks of disseminated infection resulting from viable vaccine organisms.[83–85]

Recommendations on immunization of children, adolescents and adults affected by the main types of PIDs are showed in Table 7.

General considerations

Proper immunization does not replace other infection prevention measures on these patients when recommended (antibiotic prophylaxis, IGRT, avoidance of disease exposure). Herd-protection effects should be achieved by vaccinating close contacts whenever is not contraindicated for safety issues (transmission of viable vaccine organism).[84,85]

In specific PID disorders, secondary immunodeficiencies caused by medical therapy or concomitant disorders could influence vaccine indications and contraindications. In case HSCT is indicated, especial considerations should be taken before the procedure and revaccination after transplant is recommended (timing dependent on vaccine and immune recovery after the procedure); these recommendations are beyond the scope of these guidelines, but can be found in the provided references.[84]

Influenza vaccination

Inactivated influenza vaccines are recommended for all immune-deficient individuals and their close contacts aged ≥6 months.[84,85,92–95] For children receiving influenza vaccination for the first time, 2 vaccine doses at least 4 weeks apart are recommended. After that, 1 dose should be given annually.[84,93,94] Inactivated influenza vaccine is also recommended in patients receiving IGRT, as effective antibodies against the ongoing seasonal influenza virus are not included in immunoglobulin products, because of the viral antigen variability. Patients with hypogammaglobulinemia can mount a CD4-mediated antibody response after influenza vaccination.[96] Furthermore, it could also stimulate an adequate protective response providing a residual immune function.[84,85,90]

Whenever is possible, quadrivalent inactivated influenza vaccines are preferred.[95] Live-attenuated influenza vaccine is contraindicated in immunocompromised patients, and it is not recommended to the household

contacts for potential virus transmission, except in case of minor antibody deficiencies.[85]

Pneumococcal vaccination

Pneumococcal conjugated vaccine (13-serotypes) is indicated in all patients with PID at any age (>2 months of age).[85] The vaccine should be given to infants as a 4-dose series at 2, 4, 6, and 12-15 months of age. Catch-up immunization is recommended for all children through 59 months of age, with fewer doses depending on age. Children aged 24 to 59 months should be given a 2-doses scheme. Unvaccinated >60-month-old children, adolescents and adults with PID should receive 1 dose of PCV13.[85] The PPSV23 vaccine is recommended for people ≥2 years of age with PID, administered after the dose of PCV13.[85] A 2-dose scheme 5 years apart is recommended in these patients. Additional doses of PPSV23 are not recommended. Unvaccinated people >2 years of age with severe forms of PIDs should always receive PCV13 first, followed by PPSV23 at least 8 weeks later ("sequential pneumococcal vaccination").[84,97] For those patients >18 years old who received PPSV23 previously, PCV13 should be administered ≥1 year after the last PPSV23 dose.[97] For patients 2-18 years old, an 8-week interval for PPSV23-PCV13 sequence is appropriate.[97] The efficacy of any vaccine that is reliant on a T-cell independent humoral response, such as PPSV23, is doubtful. However, a PCV13/PPSV23 combined schedule might be used to extend antibody responses to additional serotypes.[84,85]

Meningococcal vaccination

Wide protection against serogroups B and ACWY is recommended for patients with PID, but especially in those with complement defects or congenital asplenia/hyposplenia.[98,99] There are 2 available meningococcal B vaccines: MenB-4C approved for people aged >2 months old, and MenB-fHbp for people ≥10 years old. MenB-fHbp is licensed as a 2-dose series (administered at 0 and 6 months) or a 3-dose series (administered at 0, 1-2, and 6 months); the choice of dosing schedule depends on the patient's risk for exposure and

susceptibility to serogroup B meningococcal disease. Currently, there are 2 meningococcal ACWY vaccines, commercialized: one approved for ≥6 weeks of age and another licensed for ≥2 years of age. Patients with high-risk (complement deficiency, asplenia) should receive additional doses every 5 years.[84,85,98]

Haemophilus influenzae type b vaccination

Vaccination against *H. influenzae* type b is recommended in PID patients, especially unimmunized patients ≥5 years of age and adults at high risk (complement deficiency, asplenia, MyD88/IRAK-4 deficiency), if the later an unique dose is indicated.[84,98]

Human Papillomavirus vaccination

Papillomavirus vaccine is recommended in patients with PID aged ≥9 years old who have not been previously vaccinated or have not completed the dose series.[84,100] A 3-dose scheme is always recommended in these patients for both females and males adolescents and adults.[100] Especial consideration for WHIM syndrome (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis syndrome) should be considered.[101]

Travel immunization in PIDs

According to the travel itinerary, patients with PID can safely receive the following inactivated vaccines: hepatitis A and B vaccines, parenteral typhoid vaccine, inactivated polio vaccine, rabies vaccine, the inactivated Japanese encephalitis vaccine, inactivated influenza vaccine, tetanus, diphtheria, and pertussis combined vaccine, tetanus and diphtheria combined vaccine and meningococcal vaccines. Live vaccines that could be considered for travellers (yellow fever, BCG…) are not recommended, as previously mentioned (Table 7). Before travelling, it is recommended to discuss travel plans with the specialist who will advise on safety issues and individualize the need for vaccinations.

Immunization in patients receiving IGRT

For patients receiving IGRT, live attenuated vaccines containing viable agents like measles, mumps, rubella and varicella are not required, considering that these antigens are neutralized by antibodies included in therapeutic IgG preparations.[83–85] Other live attenuated vaccines like OPV, BCG, yellow fever, oral typhoid and cholera are also contraindicated for safety issues.[83–85] There are controversies between guidelines regarding vaccination with inactivated vaccines containing non-viable agents.[83–85] Although immunization with these vaccines is safe, efficacy and effectiveness of the intervention are variable, and mostly of the antibodies against these vaccine preventable diseases are well represented in IgG preparations (except for *H. influenza* b and hepatitis B).[83] Some studies including few patients receiving IGRT have documented positive vaccine responses to polysaccharide vaccines, peptide vaccines and conjugated vaccines in a small proportion of subjects, while other studies reported reduced but protective responses to meningococcal polysaccharide vaccines.[83] All guidelines recommend annual influenza vaccination in patients receiving IGRT,[83–85] whilst they support immunization with inactivated vaccines in patients with major antibodies deficiencies with some residual antibody production.[84] Recent guidelines support that IGRT patients may receive pneumococcal and other inactivated vaccines, as the intervention is safe and there could be protective antibody responses in a small proportion of patients (and maybe potential unknown cellular protective responses).[83,85,86] Nonetheless, it remains to be determined if this approach is cost-effective.[83]

7. When can immunoglobulin replacement therapy (IGRT) be advised? Which route is advisable? How should IGRT be monitored during follow-up?

Recommendations

- IGRT is indicated in cases of agammaglobulinemia due to absence of B cells and hypogammaglobulinemia with low antibody production function (A II).
- The use of IGRT should be individually assessed in patients with normal Ig and deficiency of antibody production, hypogammaglobulinemia with normal antibody function, isolated deficiency of an IgG subclass with recurrent

infections, and recurrent infections due to a complex immune mechanism related to a genetically defined PID disease (C III).

- Intravenous and subcutaneous route for IGRT are equivalent in terms of efficacy (A I).
- The route of administration should be selected individually in every patient (A I).
- Patients' preferences should be considered when choosing the route of administration (B III).
- In patients with humoral immune defects on IGRT, trough serum IgG levels >500 mg/dL are effective in prophylaxis against bacterial infections, particularly against pneumonia (A I).
- Patients on IGRT should be periodically monitored for trough IgG levels: first control after 3 months except for the loading dose; then every 3-6 months in children, and at least once a year in adults afterwards to ensure they are kept above the recommended levels (600-800 mg/dL), depending on the underlying PID and the presence of lung disease) (A III). More frequent studies should be performed in presence of complications such as cancer, chronic lung disease or malabsorptive syndrome (A III).
- It is recommended to stratify patients with antibody production deficits according to lung damage, and to maintain trough IgG levels consequently: >600 mg/dL for patients without pulmonary abnormalities and >800 mg/dL for those with chronic lung damage (A III).
- The presence of low trough IgG levels despite adequate IGRT must prompt the search of protein loss (urinary and gastrointestinal) or consumption due to pneumopathy, complications to be considered in the follow-up (B II).
- Dose IGRT adjustments are required in special situations, such as acute illnesses, before or after surgery, chronic diarrhoea or weight changes, and during pregnancy (B III).
- It is advisable to maintain serum bank during IGRT (B III).

Rationale

When IGRT can be advised?

The indications of IGRT in patients with PID are summarized in Table 8 and Figure 2.[102–104] This therapy may be lifesaving in patients with PID and a deficient antibody production, such as X-linked agammaglobulinemia (XLA) or CVID, among many others. However, as new PIDs are continuously discovered and understood, defined indications of IGRT are likely to broaden.[105]
As reported in recently published guidelines, there are several general conditions in which IGRT should be considered —with different degrees of evidence— for patients with PIDs.[102]

- Patients with agammaglobulinemia due to absence of B cells. It has been demonstrated that maintaining IgG through levels >700 mg/dL reduces the risk of serious bacterial infections and enteroviral meningoencephalitis.[103–106] Immunoglobulin replacement should be immediately started at diagnosis of severe congenital PID, since maternal IgG levels decrease over time. It should also be started after HSCT and during gene therapy or enzyme replacement, until normalization of B-cell function.[107,108]
- Patients with recurrent bacterial infections, hypogammaglobulinemia and impaired specific antibody production.[41,102] This include patients with CVID, XLA and hyper-IgM syndrome. Early diagnosis is essential, since IGRT has demonstrated to reduce the incidence of acute and chronic infections and of long-term lung disease and functional impairment.[109–112] Doses and through levels should be individualized to attain an infection-free status instead of following a fixed protocol.[113–116] Patients with unspecified IgG deficiency (not fulfilling CVID diagnostic criteria) should be followed clinically.[41] When the severity, frequency of infections, associated deterioration or ineffectiveness of antibiotic prophylaxis justify the use of IGRT, patients and/or their caregivers should be informed that treatment may be discontinued after a period of time (preferably during spring in temperate regions) and that the immune response will be re-evaluated at least 3-5 months after discontinuation.[117] Recurrence after 1 or 2 periods of treatment (6-24 months) will identify the subset of patients with permanent immunological defect that deserve continuous therapy.

- Patients with normal immunoglobulin levels, but selective antibody deficiency (impaired specific-antibody production to pneumococcal polysaccharides). In this population, IGRT should be administered at least during a period of time, when there is clear documentation of non-response to polysaccharide vaccination and recurrent infections requiring antimicrobial therapy (e.g. recurrent otitis at risk for permanent hearing loss, bronchiectasis, failed antimicrobial prophylaxis, impaired QoL due to recurrent infections, or multiple antimicrobials intolerance or allergy that impair prophylaxis and treatment).[102,118–120] While antibiotic prophylaxis may represent a first-line intervention in some patients, the severity of infection and/or the efficacy of antibiotic prophylaxis should be the most influential aspects in making any decision to recommend IGRT.[102] Additional indications for IGRT include abnormal findings in sinus or lung imaging, or analytical signs of inflammation (C-reactive protein, ESR, white blood cell count).
- Patients with hypogammaglobulinemia. The indication for IGRT will depend both on the hypogammaglobulinemia degree and on the frequency and severity of the infections. Overall, less than 10% of these patients need treatment.[121] In patients with IgG levels lower than 150 mg/dL (severe hypogammaglobulinemia), treatment will be administered immediately, while in patients with IgG levels between 150 and 250 mg/dL, the production of specific antibodies may be considered to better define functionality, always depending on the clinical course.[122] In patients with higher IgG levels, the indication for IGRT will follow the same clinical criteria as in the previous section, always considering that hypogammaglobulinemia may be transient and, in many cases, secondary to some medication (anticonvulsants, rituximab, corticosteroids) or to protein loss,[122,123] among other causes.
- Patients with normal immunoglobulin levels, but with isolated deficiency in IgG subclasses. Recent studies suggest that IGRT should be considered as an option in patients when other measures, such as antimicrobial prophylaxis and treatment of underlying conditions such as asthma or allergies, have failed. In these cases, IGRT can improve QoL and reduce the need for antibiotics.[124–129]

- Patients with recurrent infections and unknown or different immunodeficiencies due to a complex immune mechanism.[102] An example might be patients with HIES syndrome due to STAT3 LOF or Wiskott-Aldrich syndrome (WAS).[130–132] Approximately 12-15% of patients with AT require IGRT. The immunological abnormalities observed in AT that have been best characterized are IgA and IgG2 deficiencies, which affect between 50% and 80% of cases, as well as low concentrations of IgG. The consideration for WAS also applies to AT, as well as to other of these types of combined PIDs, including deficiencies in STAT-3, NEMO or in patients with *STAT1* gain-of-function mutations.
- In general, IGRT for patients with selective IgA deficiency is not recommended. It should be remembered that its administration may condition anaphylaxis in IgA-deficient patients with IgE anti-IgA antibodies, or complement activation in the presence of IgG anti-IgA antibodies.[133,134] If treatment is necessary, subcutaneous route or IgA-depleted IV preparations may be considered.[135,136] However, IGRT may be considered when a deficient IgG production coexists in the setting of recurrent infections.

In summary, IGRT is a clear and vitally important indication in patients with PID that affects B-cell function and antibody production as the hallmark or as a part of their immunologic disorder. In this type of patients, IGRT is essential to prevent potentially lethal infections, chronic organ dysfunctions and to improve their QoL. Given the growing description of immunodeficiencies in which these dysfunctions are not easily detectable by means of the routine diagnostic tests, this is a dynamic indication that is increasing with the appearance of more sensitive diagnostic tests. More trials and studies on the functional antibody responses, as well as improved clinical and microbiological evaluation and characterization of recurrent infections in patients with antibody deficiency, are needed.[137] The interval and doses of IGRT should be individualized according to clinical manifestations and trough levels.

Which route is advisable?

There are currently 2 main routes for IGRT administration: IV and subcutaneous (SC); although some products for the intramuscular route are still available.[138] Preparations for the IV route are mainly distinguished on the different immunoglobulin concentration (5% [50 mg/dL] and 10% [100 mg/dL]). However, the differences between products are beyond the concentration and also affect their composition. Thus, the composition of stabilizers, the presence of IgA, or proteins other than IgG, should be known by the prescriber to accurately fit to the patient's needs, to improve tolerance to treatment and to minimize adverse events.[139,140] Given that half-life of human IgG is around 21-23 days, the periodicity of the infusions when using IV IGRT should be adjusted to this frequency. Nevertheless, the optimal frequency of infusions should be individualized in function of several clinical and analytical parameters.[139–141]

The SC route for IGRT administration allows a greater comfort and family conciliation for the patient and caregivers.[142–145] However, it requires patient or caregivers to receive training for self-administration in order to meticulously perform the infusion. Although products for the SC route may differ in concentration (10%, 16% or 20%), the main distinction between them lies in the addition or absence of facilitating agents (hyaluronidase) to allow the administration of important volumes in the perfusion sites. These facilitated preparations show a pharmacokinetic profile similar to that obtained by IV infusion with a peak of high initial serum concentration and a subsequent gradual decrease. It may require, depending on case, up to a single monthly administration like that offered by the IV route, but with self-administration by the patient at home.[146,147] However, long term safety of this approach needs to be studied more deeply. When not helped by facilitating agents, traditional products for SC IGRT administration are limited to the maximum volume per perfusion point (increased now to 50 mL per site). This may force a higher frequency of administrations, oscillating the periodicity approved from daily to biweekly.

Regarding the decision to use the SC or IV route, both administration routes have been shown to be equivalent in terms of efficacy and safety,[142–145]

although with a higher incidence of serious systemic adverse effects with the IV route and mild local effects with the SC route.[142–145] Despite the inconvenience of needing patient training, more equipment and infrastructure for proper administration, the SC route presents several important advantages: it is associated with a higher QoL for both patients and their caregivers,[147–150] has been shown to be more cost-effective (mainly due to less missed work and school days),[150] it is more appropriate for patients with venous access difficulties, and does not seem to have a negative impact on the kidney. There are no differentiated indications for the choice of the product within the SC route, so the decision should be based on the necessary treatment dose, the expected frequency of infusions, the aggravating factors of IgG losses such as intestinal losses or burns, and the social and work circumstances of each patient. Finally, the patient's preferences should be considered when deciding.[151]

How should IGRT be monitored in children and adults with PID during follow-up?

Numerous studies have shown that trough serum IgG levels above 500 mg/dL are effective in the prophylaxis against recurrent infections, particularly against pneumonia.[16,143,144,152–157] There are, however, few studies regarding the effects of IGRT on the incidence of recurrent sinopulmonary infection and structural lung damage, such as the presence of bronchiectasis.[158] In most clinical guidelines of IGRT, starting doses between 400 to 600 mg/kg/3-4 weeks are proposed.[103,113,159] For each 100 mg/kg of infused IgG, the initial peak of serum IgG increases in 250 mg/dL and the trough levels in 100 mg/dL.[160] Several studies have shown that when IGRT is administered at high dose (600 mg/kg for adults and 800 mg/kg for children) the frequency and duration of the infections decrease, resulting in better lung prognosis.[103,113,160,161] Therefore, it is recommended to stratify patients with predominantly antibody deficiencies (PAD) according to lung damage and to maintain trough IgG levels consequently. For patients without pulmonary abnormalities, trough IgG levels above 600 mg/dL are recommended, while in those with chronic lung damage

trough IgG levels above 800 mg/dL must be targeted.[113] A meta-analysis showed that the incidence of pneumonia decreased by 27% with each increase of 100 mg/dL at the minimum level of IgG. The incidence of pneumonia with a minimum level of 500 mg/dL was 0.113 cases/patient-year versus 0.023 cases/patient-year with a minimum level of 1000 mg/dL.[103] Trough levels >700 mg/dL may be prevent autoimmune thrombocytopenia in adult patients with CVID.[162] Patients on IGRT should be periodically monitored for trough IgG levels: first control after 3 months, then every 3-6 months, and at least once a year afterwards to ensure they are kept above the recommended levels (>600-800 mg/dL, depending on the underlying PID and the presence of lung disease).[16]

The presence of low trough IgG levels despite adequate IGRT must prompt the search of protein loss (urinary and gastrointestinal) or consumption due to pneumopathy complications, which should be considered in the follow-up.[163]

Immunoglobulin replacement does not prolong the hypogammaglobulinemia or affects maturation of the immune system, as demonstrated in a study in a series of patients with transient hypogammaglobulinemia of childhood with severe or recurrent infections.[121]

Dose adjustments are required in special situations, such as acute illnesses, before or after surgery, chronic diarrhoea or insufficient growth, and during pregnancy.[164,165] No specific protocols have been published for pregnant women; usually, frequent monitoring is recommended to adjust IgG levels. Despite the available evidence is scarce, case series suggests that replacement therapy is not only beneficial for the mother but also for the foetus.[166–170]

8. When is a HSCT considered in a child with PID?

Recommendations

- Allogeneic (allo-) HSCT in children is recommended as potentially curative procedure for SCID and CGD (A II).
- In patients with CIDs, allo-HSCT is recommended in the following conditions: CD40L, WAS, cartilage-hair hypoplasia (CHH), ZAP70, MHC-class II deficiency and NEMO (A II).

- Allo-HSCT is recommended in severe congenital neutropenia if treatment with colony stimulating factor lacks efficacy, or when the disease progresses to myelodysplastic syndrome or acute myeloid leukaemia (B II).
- Allo-HSCT should be performed in all patients with primary HLH (A II). Remission of the disease is recommended to avoid relapses (A II). In CVID with immune dysregulation (*CTLA4, LRBA, PI3Kδδ/R1, STAT3* gain-of function [GOF] mutations), HSCT should be considered after failing first-line therapies with abatacept, PIK3 or JAK inhibitors, or in cases of incomplete response (C III).
- Allo-HSCT is recommended in: patients with complete IFNγ-receptor defects and complete STAT-1 deficiency, complete LAD 1, and DOCK8 deficiencies and severe forms of IPEX non-responsive to other treatments, (B II), patients with IL-10 receptor-deficiency and selected patients with ADA2 deficiency (CECR1), *STAT-1* GOF and *STAT-3* GOF (B III).
- Indication of allo-HSCT in SCID, CID and CGD is preferred during childhood, the earlier the better but not sooner than 2 months of age, provided that there's a suitable donor and the patient is at the best expected condition (A II).
- Whenever possible, a matched sibling donor should be used (A II). Otherwise, a fully matched unrelated donor is the recommended alternative (A II).
- If only haploidentical or mismatched unrelated donors are available, T-cell depletion techniques (TCRab and CD19+ depletion) ensure the lowest risk of acute graft-versus-host-disease, along with serotherapy (antithymocyte globulin or alemtuzumab) (B II).

Rationale

In HSCT, donor engraftment occurs after ablation of the recipient's marrow and immune system by conditioning chemoradiotherapy (before the transplantation), and by the alloimmune action (graft-versus-host marrow) of the engrafted donor cells against residual cells in the recipient. These processes are not always easy to control, and can lead to graft-versus-host disease (GVHD), when non-hematopoietic cells (e.g., gut, skin, liver, and lung) are

targeted. HSCT is a risky procedure; therefore, a weighted risk-benefit assessment is essential. The difficulty lies in that although HSCT has shown to increase long-term survival, the early post-transplant mortality rate is remarkable. This is also true for adolescents and young adults with PIDs.[171]

In SCID individuals, HSCT performed early in life (under the age of 4 months), and prior to active infection, harbours the best prognosis leading to a survival rate around 95%.[54,172–175] Radiosensitive SCID (patients with T cells <300/μL and very low T cell function or T cells of maternal origin) present benefits from a tailored conditioning regimen avoiding myeloablation due to unacceptable toxicity.[172,176]

Phagocyte defects, such as CGD and severe congenital neutropenia (SCN), benefit from HSCT. In CGD, HSCT should be considered in all patients.[177] HSCT in patients with SCN is recommended particularly in 2 scenarios: when there is a lack of response to treatment with colony stimulating factors, and in patients who develop myelodysplastic syndrome or acute myeloid leukaemia.[177–180]

CID comprise a vast group of more than 20 genes that deserves HSCT.[181] In these patients, allo-HSCT is recommended in the following conditions: CD40L, WAS, CHH, ZAP70 and NEMO.[166] The molecular characterization of the defect should not defer HSCT, except for radiosensitive defects. Patients with CD40L deficiency show an ongoing risk for cholangiocarcinoma and liver failure after *Cryptosporidium parvum* infection. Despite long-term survival is similar in transplanted compared with non-transplanted patients, there is a trend towards higher survival in transplanted patients during the last decade.[184] Overall survival was 74% in patients with hypomorphic NEMO mutations who received HSCT.[182] Ataxia telangiectasia may show a CID phenotype; however, due to the severe extra-immunological features of this disease, there is no current curative treatment.

In patients with immune dysregulation (CTLA4, LRBA, PI3K$\delta\delta$ type 1 and 2, STAT1 or 3 GOF mutations) HSCT should be considered carefully after first line therapies (abatacept, PIK3 or JAK inhibitors) failure or in case of incomplete response, keeping in mind the so far non-optimal survival results.[185–193] Careful

consideration includes age, available matched donor, organ damage and active disease.[194–198]

Complete IFNγ-receptor defects require HSCT to correct the predisposition to mycobacterial infection (and other intracellular pathogens).[199,200]

In ADA2 deficiency *(CECR1)* HSCT has been successful in a group of patients presenting with haematological manifestations. For this reason, it might be considered for selected patients.[201]

The HLH is a lethal disease only cured by HSCT.[202,203] In this condition, remission of the disease is recommended to avoid relapses. Mixed chimerism is common in reduced-intensity conditioning. However, relapses with donor chimerism above 30% are uncommon.

Thymic transplant is an evolving technique for athymic patients (complete DiGeorge, CHARGE, FOXN1). However, due to the lack of availability and risk of autoimmunity, it is only performed in selected centers.[173,204]

Very early onset inflammatory bowel disease may be caused by 50 monogenic diseases. HSCT is a curative tool in some of them (CGD, IL10/R).[205,206]

In all patients undergoing allo-HSCT, close follow-up of immune reconstitution is required to identify patients who may need additional intervention to prevent poor long-term outcome.[54]

In general, reduced-intensity conditioning (RIC) regimens (busulfan/fludarabin or treosulfan/fludarabin) are preferred over full myeloablative conditioning, even though the risk of mixed chimerism is higher. However, other conditions such as PID due to GOF mutations (STAT3 and STAT1 among others), Wiskott-Aldrich disease, Artemis disease, and RAG mutations require myeloablative conditioning.[207]

Careful donor selection is one of the key factors to ensure full chimerism and minimum rate of graft failure with lowest rate of acute/chronic GVHD. In this regard, the use of T-cell depleted haploidentical donors or haploidentical donors with the administration of cyclophosphamide after transplant seems promising.[208]

The source of stem cell progenitors influences the outcome. In this regard, the recommended source for genetic disease are bone marrow and umbilical cord

blood, in order to avoid the risk of sequelae due to chronic GVHD. Peripheral blood stem cell source is recommended in patients with SCID or CID receiving a related or unrelated 10/10 HLA-identical donor with a reduced-intensity regimen. This strategy could help ensuring adequate engraftment without excessive risk of GVHD. Additional GVHD prophylaxis should be administered in this setting.[208]

9. When is a HSCT considered in an adult with PID?

Recommendations

- Chronic granulomatous disease and CVID are the most common indications of allo-HSCT in adolescents and young adults with PID, mainly in patients presenting with a complicated disease course (B II).
- Allo-HSCT is also recommended in other PID, such as T-lymphocyte immunodeficiencies, WAS, phagocyte disorders, hemophagocytic syndromes, and a growing number of other immunodeficiencies (B II).
- An adapted strategy with a reduced-intensity conditioning regimen based on the combination of fludarabine and melphalan or busulfan, with *in vivo* T-cell depletion (with antithymocyte globulin or alemtuzumab), minimizes the risk of graft-versus-host disease and transplant related mortality (C III).

Rationale

PIDs with allogeneic HSCT (allo-HSCT) indications in adults are extremely rare because allo-HSCT is usually indicated in the early ages.[209,210] Although allo-HSCT is preferred for PIDs in early childhood, sometimes is not possible because of atypical forms with late presentation lack of a suitable donor, or in the case of non-severe forms of CGD. However, advances in an earlier diagnosis, a more accurate HLA typing, increasing stem cell sources, less toxic conditioning regimens (RIC and *in vivo* T-cell depletion), and better supportive care have improved overall outcomes of allo-HSCT, with reported survival rates higher than 85% for these indications.[211–214]

Chronic granulomatous disease is one of the most common indications in adolescents and young adults, although classically overall outcomes for allo-

HSCT are frequently complicated because of pre-transplant conditions of patients. In some forms of CGD, patients retain some activity of the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase complex, but commonly reach adolescence and older ages with organ dysfunction, that significantly increase transplant related mortality. Nonetheless, promising results have been reached with a RIC regimen. In a series of 56 patients including 25 patients older than 13 years-old (range, 14-39), with both related and unrelated donors, the 2-year probability of overall survival was 96% (95%CI, 86.46-99.09) and of event-free-survival (EFS) was 91% (95%CI, 79.78-96.17). Graft failure occurred in 5% of patients. The cumulative incidence of III-IV acute GVHD and chronic GVHD was 4% (2/56) and 7% (4/56), respectively, with stable myeloid donor chimerism in 93% of cases.[177]
A series of 29 adult patients (range, 17-50 years old) undergoing RIC allo-HSCT (both related and unrelated donors) for an heterogeneous group of patients with different PIDs, has recently reported a 3 year-overall survival of 85.2% (even higher if excluding CGD out of analysis), very low transplant related mortality with only 4 deaths (median follow-up of 3.5 years), no cases of early or late rejection, with either stable mixed or full donor chimerism.[215] Moreover, it is highlighted that no evidence of persistent or recurrent infections were documented in the majority of surviving patients (87%), bearing in mind the trend for a high burden of infectious complications that these patients had pre-transplantation (82% of patients had prior recurrent or severe infections). Most post-transplant infections had a viral aetiology (Cytomegalovirus, Epstein-Barr virus), with no viral infection-related mortality. The causes of death were refractory GVHD, sepsis and multiorgan failure. In another recent study, a total of 18 adolescents and young adults (median age, 18.5 years) with PID undergoing allo-HSCT were reported.[216] The most frequent diagnosis was CGD (n=6) and the donors were unrelated in 89% of cases. Overall survival and EFS were both 94%. No patient experienced severe acute or chronic GVHD, and immunosuppressive therapy could be retired in all of them.
These results indicate that adolescents and young adults with PIDs have surprisingly little transplant-related mortality and GVHD when using reduced-

toxicity conditioning regimens based on fludarabine plus melphalan or targeted busulfan with *in vivo* T-cell depletion (Table 9). However, in any case, specific pre-transplant risk factors must be considered to accurate transplantation planning, such as age, type of PI and clinical condition before transplant (active infection), presence of an active or steroid-dependent inflammatory disease, or pre-existing malignancy.[216,217]

Recently, a comprehensive review reported a survival rate post-HSCT of 74% in 130 patients suffering from GATA2 deficiency, optimal timing still to be determined.[183]

Common variable immunodeficiency is another PID with potential allo-HSCT indication in specific cases, and is usually well controlled with IGRT and immunomodulatory drugs. However, there is a subgroup of patients presenting a complicated disease course with high morbidity and mortality, for whom allo-HSCT has been offered as the only potentially curative treatment. In this setting, a multicenter study from the European Bone Marrow Transplantation group reported a series of 25 patients with CVID, 22 of them older than 13 years old (range, 14-50 years) at the time of transplantation. The main indication for allo-HSCT was immunologic dysregulation (60%), but it was also indicated in 6 cases (24%) with lymphoma and 3 cases (12%) with severe infections despite standard treatment. The overall survival rate was 48% and the major causes of death were treatment refractory GVHD and infectious complications. Half of the surviving patients stopped IGRT. In 92% of surviving patients, the condition constituting the indication for HSCT resolved. Overall outcomes were poor, when compared with other reports of allo-HCST for PIDs, but heterogeneous conditioning regimens were used including 10 cases of myeloablative conditioning. A better patient selection, type of conditioning and timing for transplantation are future challenges.[218]

Both, the European Bone Marrow Transplant and European Society for Immunodeficiencies Inborn Errors Working Party have recently reviewed HSCT indications and the guidelines of treatment for PIDs.[207,217] Allo-HSCT is indicated as standard of care generally in suitable patients, with level of evidence II, regardless of donor type (related, unrelated, alternative).[217] On the

other hand, and more specifically, European guidelines have defined in detail inclusion and exclusion criteria for each type of PIDs as well as recommended conditioning and GVHD prophylaxis, source and stem cell cellularity.[207] Recommendations regarding the types of donors, conditioning regimens, and sources of stem cell progenitors are addressed in the previous section.

10. What other immunomodulatory and curative therapies can be used?

Recommendations

- The identification of underlying disease-causing or -modifying pathways is encouraged as this might direct immune suppression treatment strategies (B II).
- Immune suppression in PID should be considered in order to treat autoimmune, autoinflammatory, lymphoproliferative or granulomatous disease manifestations (A II).
- Infectious prevention with IFNγ should be considered for CGD patients (B I).
- ADA enzyme-replacement therapy should be given to all patients with a new diagnosis of ADA deficiency or ADA-SCID (A I).
- Gene therapy should be pursued for all ADA-SCID patients with no matched-sibling or matched family donor (A II).
- Gene therapy should be considered and might be indicated as a suitable alternative to HSCT even for those ADA-SCID patients with matched-sibling donor (MSD) or matched-family donor (MFD) (C III).
- Gene therapy should be considered in patients with CGD or WAS if HSCT cannot be performed (A III).
- Treatment with granulocyte colony-stimulating factor is recommended as first-line treatment for patients with congenital neutropenia (A I).

Rationale

Given the wide heterogeneity of the possible immune modulators therapy, these guidelines will focus on the most commonly used immune modulators.

Recommendations for targeted treatment are mainly based on case reports, smaller case series and expert opinion, instead of solid clinical data, since patient numbers are too low and disease manifestations are to heterogeneous to allow for appropriate clinical trials.

Immunosuppressant agents in PIDs

The use of immunosuppressant drugs in PID might appear counterintuitive. However, in the last years, PID patients with important immune dysregulation features has experienced a substantial increase,[219] which is probably related to an increased overall survival of infections due to early and better diagnostics and therapy. The most commonly reported manifestations are autoimmune cytopenias, arthritis, enteropathy and lung disease,[17,219] but clinical manifestations may vary largely even between patients with the same mutations. The management is complex as these patients are not only at risk of recurrent and/or severe infections, but also of a broad variety of non-infectious features (autoinflammatory, autoimmune and granulomatous diseases, lymphoproliferation or malignancies). In order to apply the most appropriate diagnostic and therapeutic strategy to these patients, the evaluation and correct interpretation of disease triggering pathways will be extremely helpful.[220–222].

Anti-CD20 agent (rituximab)

Rituximab, a chimeric anti-CD20 monoclonal antibody, is found to be effective in the treatment of granulomatous disorders, such as granulomatous and lymphocytic interstitial lung disease and autoimmune cytopenias, in most B cell associated pathologies, such as CVID.[223,224] Rituximab might be of clinical benefit in PIDs with autoantibody production as part of their pathogenesis such as autoimmune lymphoproliferative syndrome (ALPS), WAS (mostly autoimmune cytopenias), autoimmune polyendocrinopathy type 1 syndrome, RAG1/2 deficiency, and STAT1 and STAT3 GOF mutations. However, a careful risk-benefit analysis is warranted. The baseline B cell phenotype should be evaluated before prescription.[220–222] If available, other less toxic treatment

options, such as mycophenolate mofetil (MMF) and sirolimus (e.g. in ALPS), should be considered first.[221,222,225] Rituximab has been successfully used in PID phenocopies that are characterized by the production of anti-IFNγ or anti-GM-CSF autoantibodies that confer patients with increased infection susceptibility (e.g. non-mycobacterial or cryptococcal disease, chronic mucocutaneous candidiasis, etc.).[220–222] In this particular setting, rituximab has been successfully used. Furthermore, patients with severe Epstein-Barr virus (EBV) infections or EBV positive malignancies may benefit from B cell directed therapies.[220–222]

CTLA4 agonist (abatacept)

CTLA4 is a receptor of immunoglobulin superfamily expressed on T cells that competes with CD28 in binding with CD80/CD86. Binding of CD28 to CD80/CD86 is the required second stimulatory signal for effector T lymphocytes. CTLA4 haploinsufficiency as well as LRBA deficiency (involved in the effective lysosomal recycling of CTLA4) are clinically characterized by the occurrence of multiple autoimmune features as well as increased infection susceptibility with hypogammaglobulinemia.[194,226] Abatacept, a fusion protein formed of IgG1 linked to the extracellular domain of CTLA4, mimics CTLA4 function and acts therefore as an immunosuppressant. In patients with CTLA4 or LRBA deficiency, abatacept has produced a significant improvement of autoimmune manifestations (particularly lung and gastrointestinal tract) which is accompanied by an improvement of Treg function, including an increase in FOXP3 expression. An increased risk to develop severe viral infections needs to be considered.[194,226]

Janus-associated kinase (JAK)/signal transducer and activator of transcription (STAT) inhibitors

The GOF mutations in *STAT1* gene result in enhanced and sustained phosphorylation of STAT1, which results in increased expression of interferon-stimulated genes. Clinical effects of GOF *STAT1* are chronic mucocutaneous candidiasis (CMC), autoimmunity and vasculopathy, whereas *STAT3* GOF

mutations often lead to multi-organ autoimmunity and lymphoproliferation.[227] Blocking the upstream cytokine receptor-associated JAKs reduces excess STAT activation and its downstream effects. Promising results have been reported in a recent case series summarizing the effects of the JAK inhibitors tofacitinib (mostly *STAT3* GOF) and ruxolitinib (mostly *STAT1* GOF). However, side effects such as dyslipidemia, cytopenias and infectious complications (fungus and virus) need to be closely monitored.[228]

Rapamycin (mTOR inhibitors)

ALPS is characterized by defective lymphocyte apoptosis, and clinically manifests as abnormal lymphoproliferation, elevated double-negative T cells (DNT) (CD4−/CD8−, CD3+, TCRαβ+) and autoimmunity. Rapamycin (sirolimus), an mTOR inhibitor, has been shown to induce lymphocyte apoptosis and reduce lymphocyte survival. Reduction of lymphoproliferation, decrease in DNT cells, and improvement in autoimmune cytopenias were successfully achieved with sirolimus in ALPS.[220–222,225]

Impaired regulatory T cell production or survival is characteristic of IPEX (-like), CTLA4 haploinsufficiency, LRBA deficiency or *STAT3* GOF mutations and can be improved with mTOR inhibitors (e.g. sirolimus) resulting in clinical benefit.[220–222]

The phenotype of patients with APDS1 (activating mutations in *PI3K*) and APDS2 (mutations in *PIK3R*) is characterized by recurrent sinopulmonary infections, recurrent or persistent *Herpesviridae* family virus infections, lymphoproliferation, enteropathy and an increased lymphoma risk.[229] The effect of rapamycin on these patients has been evaluated in an international cohort study.[230] Physicians rated the overall effect as good in 10, moderate in 9, and poor in 7; lymphoproliferation showed the best response (8 complete, 11 partial, 6 no remission), whilst bowel inflammation (3 complete, 3 partial, 9 no remission) and cytopenia (3 complete, 2 partial, 9 no remission) responded less well.[230]

Other treatments (non-immunosuppressive) — IFNγ

Chronic granulomatous disease: Long-term prospective studies and randomized controlled trials have shown a prophylactic (effect reduced infection frequency) of IFNγ in CGD patients, which was independent of concomitant antibiotic usage, age, and CGD type.[231] However, the role of IFNγ in patients with CGD and acute infections remains unclear. Prophylactic IFNγ therapy is safe and well-tolerated in all types of CGD patients. Minor side effects noted were flu-like reactions, loose stools, and fever.[220–222,231]

Mendelian susceptibility to mycobacterial diseases: IFNγ therapy should be considered, in conjunction with antibiotics, in all patients who are able to mount, even partially, cellular responses to IFNγ. Subcutaneous administration at 50-100 μg/m^2 as an initial dose is recommended, and scaling the dose may be required in some patients.[232]

Other treatments (non-immunosuppressive) — PEG-ADA enzyme replacement therapy (ERT)

ADA deficiency is a systemic metabolic disease and the substitution with ADA ERT has shown to reverse accumulation of toxic metabolites and results in the restoration of the immune function (B cells, first 4-6 weeks; T cells, 2-4 months). Positive effects on other organs such as liver, lungs and bones have also been observed. Although it appears to prevent neurologic damage, there is still uncertainty about its impact on already established neurologic injury. In all ADA-SCID patients ERT should be initiated and used as a short term, usually <2 years, "bridging therapy" whilst awaiting curative treatment options such as HSCT or gene therapy. Depending on the protocol, this therapy should be maintained throughout the transplant or stopped before the selected curative procedure. The initial total weekly dose is generally 60 U/kg (based on ideal body weight). Once clinical stability has been achieved and immune function has been restored (recovery of T cell counts and antigen-specific responses usually after 4-6 months) dosing might be reduced to 30 U/kg/week.[233]

In patients with severe congenital neutropenia, substitution with G-CSF is strongly recommended.[234–236]

Gene therapy (indications, experience)

The success of allogeneic HSCT as a curative therapy for PIDs since 1968 paved the way for gene therapy efforts aiming to provide normal copies of the mutated gene (i.e., gene addition) to autologous HSCT *ex vivo* by means of viral vectors. Except for ADA-SCID,[237] only cases lacking an alternative therapy are eligible for gene therapy, as HSCT remains the current definitive treatment of choice.[238–240] Current protocols use HIV-1-based lentiviral vectors to reduce the risk of insertional oncogenesis associated to early gamma-retroviral vectors. Partial cytoablation is included to enhance engraftment, particularly in non-SCID cases. More than 150 patients suffering several PIDs have been treated with gene therapy in the last two decades, with excellent safety profiles and strong evidence of clinical benefit, particularly when there is selective advantage of the corrected lymphoid cells.[237–240] Primary immunodeficiencies for which gene therapy has shown safety and efficacy are detailed in Table 10. The strong progress in the field led to market authorization in Europe of a first gene therapy medicine approved for PID conditions indicated for ADA-SCID.[233,241] The most common side effect with gene therapy products is fever.[237–240] Serious side effects may include autoimmunity and inflammation (anaemia, hepatitis, thrombocytopenia, and Guillain-Barré syndrome).[237–240] Primary immunodeficiencies for which gene therapy has shown safety and efficacy are detailed in Table 10.

Future challenges for PID gene therapy medicines include: *a)* reaching all patients in need by scaling production; *b)* reducing the toxicity of conditioning regimens; *c)* producing and testing new vectors for other PIDs; *d)* generating new products for use *in vivo, and e)* gene edition (CRISPR/Cas9-mediated) rather than addition.

Concluding remarks

By identifying the genetic basis of PIDs and the detailed description of altered pathways related to their pathogenesis, the clinicians are now able to prescribe targeted therapies aiming to correct these specific alterations.[4,5,10] Due to the heterogeneity of the clinical manifestations, penetrance and symptoms

expressivity even in the same family, the generation of clinical evidence via prospective, randomized clinical trials is very unlikely.

As advances in management and treatment are commonly derived from clinical experience, mechanistic extrapolations and anecdotal case reports, the collaboration of physicians and patients within international registries is highly important in order to produce reliable data.

11. When is genetic counselling needed?

Recommendations

- Genetic counselling must be always ensured when a genetic study with medical purposes is conducted (A III).
- Genetic counselling for PIDs must be conducted by a professional with deep knowledge in these diseases (B II).
- New therapeutic approaches are improving the prognosis of PID patients and must be considered during the genetic counselling process (A II).
- Prenatal and preimplantation diagnosis are ways to ensure healthy offspring and must be explained to mutation carriers during the genetic counselling act (A III).
- Voluntary interruption of pregnancy may be a possibility when a PID is detected in the fetus and must be considered in the context of the current law (B III).

Rationale

As the Spanish Society of Genetic Counselling addresses, genetic counselling is a communicative process by which a specialized professional provides medical complex information to patients and/or family members in a simple way about the genetic disease, its inheritance pattern, the recurrence risk and the available options.[242] The final objective is to facilitate the decision-making process according to the values and beliefs of the patient and to act in accordance with it. Genetic counselling must therefore be a non-directive act. Different countries have distinct regulations and recommendations that define either the figure of the genetic counsellor or the counselling process itself.

Genetic counselling is a non-dissociable part of a genetic study and must always be offered.

General considerations in genetic counselling for PIDs

Primary immunodeficiencies are a highly heterogeneous group of diseases, both from a genetic and clinical point of view. Nowadays, more than 350 causative genes are known,[1] some of them associated to various phenotypes, either as a continued clinical spectrum dependent on *a)* the severity of symptoms, as in the case of *NLRP3* or *TNRT1,*[243,244] *b)* the different inheritance patterns, as for *IRF8, IFNGR1, IFNGR2, STAT1,* or *TREX1,*[245,246] *c)* the functional significance of the mutation (complete versus partial deficiency or loss-of-function versus GOF mutations), as for *IFNGR1, IFNGR2, STAT1, STAT3,* or *PIK3R1,*[247,248] or *d)* the location of the mutation within the gene, as in the case of WAS.[249]

The ever-increasing description of incomplete penetrance of PIDs, in which individuals with the mutated genotype can be nearly asymptomatic, as in CTLA4 deficiency,[194] also contributes to the complexity of the genetic context of PID. Other relevant concerns must also be considered, as the possible presence of parental post-zygotic mutations that can modify the recurrence risk in future descendants characteristic of Mendelian diseases,[250] or the existence of few X-linked pathologies in which females can show phenotypic features, as is the case with WAS or X-linked CGD.[251,252]

The increasing use of NGS for PID diagnosis is revealing new scenarios in which a consensus may be necessary, for example, whether incidental findings or variants of uncertain significance should or not be informed. The informed consent given to the proband is a binding document that results indispensable to clarify these aspects.

Furthermore, available therapeutic approaches that may significantly improve the QoL of patients are increasing over time, ranging from substitutive or prophylactic treatments to curative ones, as allogeneic HSCT or gene therapy.[2] Actual efforts are focused in designing molecules which directly act in the cellular pathway that remains altered, such as biological treatments and immunosuppressive specific therapies. Altogether, the potential existence of

successful therapeutic approaches is changing the prognosis of PID patients, and consequently it should be considered during the genetic counselling process.

Genetic counselling for PID should be undertaken by professionals that are able not only to conduct the different aspects of counselling, but also to deepen the different and complex aspects of PID and the available therapeutic options for which specialized training in the field is required.

Options for future offspring in mutation carriers: prenatal diagnosis and pre-implantation diagnosis

A fundamental part of the process of genetic counselling is clarifying the options for a PID carrier individual —or couple— to conceive a healthy biological offspring.

A usual approach is to conduct a prenatal diagnosis that consists in the analysis of the gene mutation/s in foetal DNA obtained from chorionic villus or amniotic fluid. Often the final objective of a prenatal diagnosis is to undergo the voluntary interruption of the pregnancy in those cases where the foetus has the disease-causing genotype according to the laws in each country.[225,226] Another option that enables the achievement of healthy biological offspring is pre-implantation diagnosis.[253]

Concluding remarks

Independently of the legislative context valid in each country and on the intrinsic characteristics of each patient or family, PIDs must be addressed by a multidisciplinary team. Besides, diagnosing and managing the index patient, it also provides the pertinent information and support to other implicated members, such as relatives.

Conflict of interests

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Table 1

Strength of recommendation and quality of evidence

Level of scientific evidence	
I	Evidence obtained from ≥1 randomized clinical trial
II	Evidence obtained from ≥1 well-designed non-randomized clinical trial, or cohort studies, or case-control studies, especially if they have been performed in more than one center
III	Evidence obtained from documents or opinions of experts, based in clinical experience or case series
Grades of recommendation	
A	Good evidence to recommend the use of a measure or practice
B	Moderate evidence to recommend the use of a measure or practice
C	Poor evidence to recommend the use of a measure or practice
D	Moderate evidence to discourage the use of a measure or practice
E	Good evidence to discourage the use of a measure or practice

Table 2

Jeffrey Modell Foundation's warning signs for primary immunodeficiencies[14,15]

Children	Adults
• Failure to thrive • Recurrent need for intravenous antibiotics to clear infections • A history of a primary immunodeficiency in the family • Four or more new ear infections within 1 year • Two or more new sinus infections within 1 year • Two or more months on at least 2 antibiotics at a stretch with little effect • Two or more pneumonias within 3 years • Having frequent deep skin or organ abscesses • Persistent thrush or fungal infection on the skin or elsewhere • Two or more deep-seated infections, including septicaemia, within 3 years	• Two or more new ear infections within 1 year • Two or more new sinus infections within 1 year, in the absence of allergy • 1 pneumonia/year for more than 1 year • Chronic diarrhoea with weight loss • Recurrent viral infections (colds, herpes, warts, condyloma) • Recurrent need for intravenous antibiotics to clear infections • Recurrent, deep abscesses of the skin or internal organs • Persistent thrush or fungal infection on skin or elsewhere • Infection with normally harmless tuberculosis-like bacteria • A family history of primary immunodeficiency

Table 3

Recommendation for clinical screenings for PID children and adults

	Specifications	Strength of quality of evidence	References
*Physicians should perform the following tests **at diagnosis** in a patient with a confirmed primary immunodeficiency*			
Blood analysis	Includes CBC, liver, renal function, LDH, ESR • In PID related to autoimmunity include ANA, TSH and celiac markers • In T cell defects, include screening for viruses (cytomegalovirus)	A III A III A III	16,36
Stool analysis	Not systematically recommended	A III	36
Sputum culture	Not systematically recommended	A III	41–43
PFT	• In PID with lung involvement; includes lung volumes and DLCO	A III	41–43
Lung CT scan	• In PID with lung involvement; HRCT	A III	41–43
Chest X-ray and abdomen US	All PID	A III	
CNS MRI +/– CSF analysis	If neurological symptoms	A III	
Dental evaluation	All PID	A III	
QoL scale	All PID	A III	52
*Physicians should perform the following tests **during follow-up** in a patient with a confirmed primary immunodeficiency*			
Blood analysis	Includes CBC, liver, renal function. Also, uric acid, LDH, ESR and β2-microglobulin in PIDs at risk of lymphoma and/or with chronic lymphadenopathy	A III A-B III	37

	• Include ANA, TSH and celiac markers in PID related to autoimmunity • IgG trough level if on IGRT • Immune work-up (T and B subphenotyping, proliferation to mitogens, sCD25…) in selected PID		
Stool analysis	Not systematically recommended	B III	[36]
Sputum culture	Not systematically recommended	B III	[41–43]
PFT	• In PID with potential lung involvement; Includes lung volumes and DLCO	A III	[41–43]
Lung CT scan	• In PID with lung involvement; HRCT: repeated every 5 years in case baseline is normal, or every 1-2 years in case of active bronchiectasis or interstitial lung disease	B III	[41–43]
Abdomen US	All PID	B III	
CNS MRI +/- CSF analysis	If neurological symptoms	A III	
Dental evaluation	All PID	A III	
QoL scale	All PID	A III	[52]

CNS: central nervous system; CSF: cerebrospinal fluid; DCLO: diffusing capacity of the lung for carbon monoxide; ESR: erythrocyte sedimentation rate; HRCT: high resolution computed tomography; IGRT: immunoglobulin replacement therapy; MRI: magnetic resonance imaging; PFT: pulmonary function test; PID: primary immunodeficiency; QoL: Quality of Life; US: ultrasound..

Table 4

Diseases detectable by TREC and KREC screening[58]

TREC	KREC
Severe combined immunodeficiency[a]	*Severe combined immunodeficiency (T-B–)*[b]
Other immunodeficiencies	
DiGeorge syndrome or 22q deletion	X-linked agammaglobulinemia (XLA)
Combined immunodeficiency (CID)	XLA-like disorders
Ataxia telangiectasia	Nijmegen breakage syndrome[b]
DOCK8 deficiency	Ataxia teleangiectasia
EDA-ID	Late onset ADA Severe combined immunodeficiency (T-B)[b]
Kabuki syndrome	
CHARGE syndrome	
Nijmegen breakage syndrome	
Schimke immuno-osseous dysplasia	
Cartilage hair hipoplasia	
Rac2 defect	
Other diseases	
Trisomy 21, 18	
Noonan syndrome	
Jacobsen syndrome	
Fryns syndrome	
CLOVES	
ECC	
Renpenning syndrome	
TAR	
Cytogenetic abnormalities	

CHARGE: coloboma heart defects, atresia choanae, growth retardation, genital abnormalities, ear abnormalities; CID: combined immunodeficiency; CLOVES: congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi, spinal/skeletal anomalies, and/or scoliosis; ECC: ectrodactyly ectodermal dysplasia-clefting syndrome; EDA-ID: ectodermal dysplasia-associated immunodeficiency; TAR: thrombocytopenia and absent radius; XLA: X-linked agammaglobulinemia.

[a]Excluding Zap70 deficiency, MHCII deficiency, late-onset ADA deficiency and ORAI1 deficiency.

[b]Low TREC and KREC levels.

Table 5

Antimicrobial prophylaxis for patients with primary immunodeficiencies

Type of immunodeficiency	Type of prophylaxis	Evidence
Chronic granulomatous disease	Daily cotrimoxazole + itraconazole	A II + A I
Hyper IgE syndrome (Job syndrome) (STAT3 deficiency)	Daily cotrimoxazole for *Staphylococcus aureus* infections Alternative: cloxacillin for relapsing methicillin-sensitive *S. aureus* If bronchiectasis/ symptomatic bronchial infections: azithromycin Inhaled tobramycin to treat chronic *Pseudomonas aeruginosa* colonization with frequent exacerbations and/or bronchiectasias If pneumatocele or previous fungal infection: Itraconazole/voriconazol	A II A III A II A I A III
Hyper IgM syndrome (CD40 L deficiency)	If frequent respiratory tract infections/bronchiectasis: azithromycin Cotrimoxazole 3 times/week for *P. jirovecii*	A I A II
Agammaglobulinemia	In frequent symptomatic respiratory tract infections, consider intermittent or continuous prophylaxis in addition to IGRT Cotrimoxazole; azithromycin; amoxicillin with or without clavulanate	A III
Undefined antibody deficiency	In frequent symptomatic respiratory tract infections, consider intermittent or continuous prophylaxis for those not receiving immunoglobulin replacement or despite immunoglobulin replacement Cotrimoxazole; azithromycin; amoxicillin with or without clavulanate	A III

Common variable immunodeficiency	Considered for those with recurrent infections (especially respiratory infections) or bronchiectasis despite immunoglobulin replacement	A I
Idiopathic CD4+ lymphocytopenia	Patients with <200 CD4+/mm^3 as recommended for subjects with HIV infection (example: cotrimoxazole to prevent *P. jirovecii* pneumonia)	A III
Inherited disorders of the complement system	Limited data available. Antibiotic prophylaxis with penicillin V or amoxicillin with or without clavulanate may be indicated	B III
Combined immunodeficiencies	Cotrimoxazole 3 times/week for *P. jirovecii* prophylaxis If bronchiectasis/symptomatic bronchial infections, azithromycin	A II A III
Severe combined immunodeficiency	Cotrimoxazole 3 times/week for *P. jirovecii* prophylaxis	A II
Ataxia-telangectasia	Antibiotic prophylaxis in subjects with recurrent respiratory infections: cotrimoxazole; azithromycin; amoxicillin with or without clavulanate	B III
Chronic mucocutaneous candidiasis	Chronic suppressive therapy to prevent recurrences. Fluconazole as first choice drug	A III
IRAK-4 or MyD88 deficiency	Daily cotrimoxazole and/or penicillin until 14 years old for preventing *S. pneumoniae/S. aureus* infections	A III
Isolated congenital asplenia	Penicillin until at least 5 years of age	A III

HIV: human immunodeficiency virus; IGRT: immunoglobulin replacement therapy.

Table 6

Frequently used antibiotics for prophylaxis in primary immunodeficiencies

	Regimen for children	Regimen for adults
Cotrimoxazole[16,254]	5-8 mg/kg (trimethoprim component), daily or intermittent (3 days/week) 150 mg/m^2/day, daily or 3 days/week	160 mg of trimethoprim daily or 3 times a week
Amoxicillin (consider clavulanate, if necessary)[16]	10-20 mg/kg daily or twice daily	500 to 1000 mg daily or twice daily
Azithromycin[16,78]	10 mg/kg/week or 5 mg/kg 3 days/week	500 mg/week or 250 mg 3 days/week
Itraconazole[74]	<13 years or <50 kg: 5-10 mg/kg daily	200 mg/day (capsules)
Alternatives[16]		
Penicillin V	50 000 IU/kg/day in 2 intakes per day (oral) Alternative: intramuscular benzathine penicillin G 2.4 MU every 2-3 weeks)	250 mg twice daily (oral) Alternative: intramuscular benzathine penicillin G (2.4 MU every 2–3 weeks)
Clarithromycin	7.5 mg/kg daily or twice daily	500 mg daily or twice daily
Doxycycline	>8 years 25-50 mg/daily or twice daily	100 mg daily or twice daily
Pentamidine	5 mg/kg every 4 weeks (inhaled)	300 mg monthly (inhaled)
Dapsone	1-2 mg/kg/day (oral)	100 mg daily (oral)

Atovaquone	30 mg/kg/day (oral)	1500 mg daily with food (oral)

Table 7

Recommendations on vaccination of children, adolescents and adults with primary immunodeficiencies[70,83–85,92–94,98,255–257]

Predominant immunodeficiency	Specific immunodeficiency	Vaccines		Comments
		Contraindicated	Risk-specific recommended	
T-lymphocyte (cell-mediated and humoral)	Complete defects (e.g.: severe combined immunodeficiency, complete DiGeorge syndrome)	Live viral[a] and bacterial[b] vaccines (D III)	Pneumococcal (B III)[c] Inactivated influenza (B III) Hib (B III)	• All inactivated vaccines could be given (A III) • Low or absent efficacy of immunizations
	Partial defects: most patients with DiGeorge syndrome, ataxia telangiectasia, Wiskott-Aldrich syndrome	Live viral[a,d] and bacterial[b] vaccines (D III)	Pneumococcal (B III)[3] Hib (B III) Inactivated influenza (B III)	• All inactivated vaccines should be given (B III) • Effectiveness of any vaccine depends on degree of immunodepression
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g.: X-linked agammaglobulinemia, common variable immunodeficiency)	Live viral[a] and bacterial[b,e] vaccines (D III)	Inactivated vaccines (C III) Pneumococcal (PCV13) (C III)[c]	• The effectiveness of any vaccine is uncertain if it depends only on the humoral response (e.g.: PPSV)

			Inactivated influenza (A III)	
	Less severe antibody deficiencies (e.g.: selective IgA or IgM deficiency, IgG subclasses deficiency)	OPV (D III)[f] BCG (D III)[g] Yellow fever (D III)[g]	Pneumococcal (PCV13) (B III) Inactivated influenza (A III)	• Other live vaccines appear to be safe • All indicated vaccines are likely effective (A III) • Patients should receive vaccines according to the immunization schedule for healthy patients (A III)
Innate immunity	Phagocytic defects (e.g.: congenital neutropenia,	Live bacterial[b] vaccines (D III)	Pneumococcal: PCV (A III) and PPSV (B II) vaccines[c]	• All inactivated vaccines are safe and likely effective (A III) • Live viral vaccines are likely safe and effective (A III)

	chronic granulomatous disease, leukocyte adhesion deficiency, Chediak-Higashi syndrome)		Inactivated influenza (A III) Live viral vaccines (A III)	
	Complement, congenital asplenia-hyposplenia	None	Meningococcal: ACWY and B (AI I) Pneumococcal: PCV13 (A II) and PPSV (B II) vaccines (A II)[c]	• All routine vaccines are likely effective (A III) • No contraindications for attenuated vaccines have been raised (A III)

			Hib (A II) Inactivated influenza (A III)	
	MyD-88 deficiency, IRAK-4 deficiency	None	Pneumococcal: PCV13 (A II) and PPSV23 (B II) vaccines[c]	• All routine vaccines are likely effective

BCG: bacille de Calmette-Guérin; Hib: *Haemophilus influenzae* type b vaccine; LAIV: live-attenuated influenza vaccine; MMR: measles, mumps, rubella vaccine; MMRV: measles, mumps, rubella, varicella vaccine; OPV: oral polio virus vaccine (no longer available in Spain); PPSV: polysaccharide pneumococcal vaccine; SCID: severe combined immunodeficiency; Ty21a: oral live *Salmonella typhi* vaccine.

[a]Live viral vaccines: MMR, varicella, MMRV, herpes zoster, rotavirus, yellow fever, OPV, LAIV. Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

[b]Live bacterial vaccines: BCG, Ty21a, oral cholera.

[c]Pneumococcal immunization: PCV13 and PPSV23 ("sequential pneumococcal vaccination", see text).

[d]Patients with partial DiGeorge syndrome should receive MMR and varicella vaccines (or MMRV vaccine) if immune system assessment shows normal mitogen response and:

• CD4 T lymphocytes ≥500/mm^3 and CD8 T lymphocytes ≥200/mm^3 [84,85].

According to CDC criteria [85,255]:

• <1 year old: CD4 T lymphocytes ≥1500/mm^3 and CD8 T lymphocytes ≥200/mm^3.

• 1-6 year old: CD4 T lymphocytes ≥1000/mm^3 and CD8 T lymphocytes ≥200/mm^3.

• >6 year old: CD4 T lymphocytes ≥500/mm^3 and CD8 T lymphocytes ≥200/mm^3.

[e]MMR and varicella are not required because the individual is on immunoglobulin replacement therapy that provides passive protection and interfere with the immune response to MMR vaccine and possibly varicella vaccine. These vaccines may be considered in these patients according to their risk of exposure and immune status. MMR and varicella may be considered in patients with CVID (C III).

[f]Vaccination is also contraindicated for their close contacts.

[g]No data available.

*Household contacts vaccination: most live-attenuated vaccines are considered safe in PID patient's close contacts, except for oral polio, which is contraindicated and live-attenuated influenza vaccine (see text). If a close contact develops skin lesions after varicella vaccination, contact avoidance and Zoster-immunoglobulin administration to the PI patient is recommended.

Table 8

Evidence-based indications of IGRT in patients with PID[102]

Disease[a]	Evidence
Primary immune defects with absent B cells	A II
Primary immune defects with hypogammaglobulinemia and impaired specific antibody production	A II
Distinct genetically defined primary immunodeficiencies with variable defects in antibody quality and quantity[b]	C III
Transient hypogammaglobulinemia of infancy	C III
Other immune mechanisms driving recurrent infections that affect B-cell function	C III
Primary immune defects with normal IgG and impaired specific antibody production	C III
Selective antibody deficiency ‘‘memory phenotype’’	C III
Isolated IgG subclass deficiency (IgG1, IgG2, IgG3) with recurrent infections	C III
Isolated IgG4, IgA, IgE or IgM deficiency	D III

[a]Indication of IGRT should be individualized according to the clinical symptoms and complications of the patient.

[b]Hyper-IgE syndrome, dedicator of cytokinesis 8 (DOCK8), STAT-1, nuclear factor-κB essential modulator (NEMO), among others.

Table 9

Conditioning regimens[207]

Mieloablative conditioning			
Protocol	Chemotherapy	Serotherapy	GVHD prophylaxis
A	Busulfan (IV) (wt or AUC dosing)[a] Fludarabine 160 mg/m^2	Alemtuzumab (TD 0.6-1 mg/kg) or ATG (TD 10 mg/kg)	CyA or CyA + MMF or MTX (as 2nd agent)
Reduced intensity conditioning			
B	Busulfan (IV) (AUC dosing) Fludarabine 180 mg/m^2	Alemtuzumab (TD 0.6-1 mg/kg) or ATG (TD 7.5-10 mg/kg)	CyA or CyA + MMF or MTX (as 2nd agent)
C	Fludarabine 150 mg/m^2 Melphalan 140 mg/m^2	Alemtuzumab (TD 0.6-1 mg/kg)	CyA or CyA/MMF
D	Treosulfan 42 g/m^2 Fludarabine 150 mg/m^2	None or Alemtuzumab (TD 0.6-1 mg/kg)	CyA or CyA/MMF

ATG: anti-thymocyte globulin; AUC: area under the curve; BM: bone marrow; CyA: cyclosporin; EBV-PTLD: Epstein-Barr virus post-transplant lymphoproliferative disorder; GVHD: graft versus host disease; HLH: hemophagocytic lymphohistiocytosis; MFD: matched-family donor; MMF: mycophenolate mofetil; MTX: methotrexate; PBSC: peripheral blood stem cell; UD: unmatched donor; VOD: veno-occlusive disease; WAS: Wiskott-Aldrich syndrome.

- AUC dosing for IV busulfan in myeloablative conditioning, 90±5 mg*h/L.
- AUC dosing for IV busulfan in reduced intensity conditioning, 60±5 mg*h/L.
- Avoid melphalan 140 mg/m^2 <1 year of age unless HLH.
- Treosulphan 36 g/m^2 <1 year of age.
- If using ATG with protocols C or D, be aware of increased incidence of EBV-PTLD.
- For these protocols if using matched UD or MFD–PBSCs are stem cell source of choice.
- If using BM, consider decrease in alemtuzumab dose to 0.6 mg/kg, especially if condition requires full donor chimerism as in WAS or MHC class II deficiency.
- Busulfan/cyclophosphamide conditioning is no longer recommended by the EBMT/IEWP because of the increased risk of VOD.

Table 10

Experience of gene therapy in primary immunodeficiencies[241]

		Number of patients (published)					
Indications	Mutated gene/protein	Treated	Benefited	Exitus[b]	Busulphan	Longest follow-up (years)	Level of evidence
ADA-SCID	Adenosine deaminase	116	114	0	0-4 mg/kg	7	A II
X-SCID[b]	IL2RG/γ common	37	33	2		9	A II
WAS[b]	Wiskott-Aldrich syndrome	32	30	3	0-10 mg/kg	4	A II
X-CGD[b] AR-CGD	CYBB/gp91phox NCF-1/p47phox	12	2	0		3	B II

[a]Related to procedure.

[b]Oncogenic adverse events reported with retroviral vectors.

Figure 1. Main clinical and laboratory features to be assessed in suspected PID patients. ANA: anti-nuclear antibodies; BTK: Bruton tyroxin kinase; C1inh: C1 inhibitor; C3: complement factor 3; C4: complement factor 4; Ca: calcium; CD: cluster of differentiation; CRP: C-reactive protein; CTL: cytotoxic T lymphocyte; FASL: FAS ligand; Foxp3: forkhead box P3 transcription factor; gp91phox: 91-kDa subunit of the phagocyte oxidase; HLA: human leucocyte antigen; IFN: interferon; Ig: immunoglobulins; IL: interleukin; iNKT: invariant NKT-cells; IRAK: interleukin-1 receptor-associated kinase; MyD88: myeloid differentiation factor 88; Mg: magnesium; NK: natural killer; SAA: serum amyloid protein A; STAT: signal transducer and activator of transcription; Treg: regulatory T-cells; WAS: Wiskott-Aldrich syndrome protein.

Figure 1.

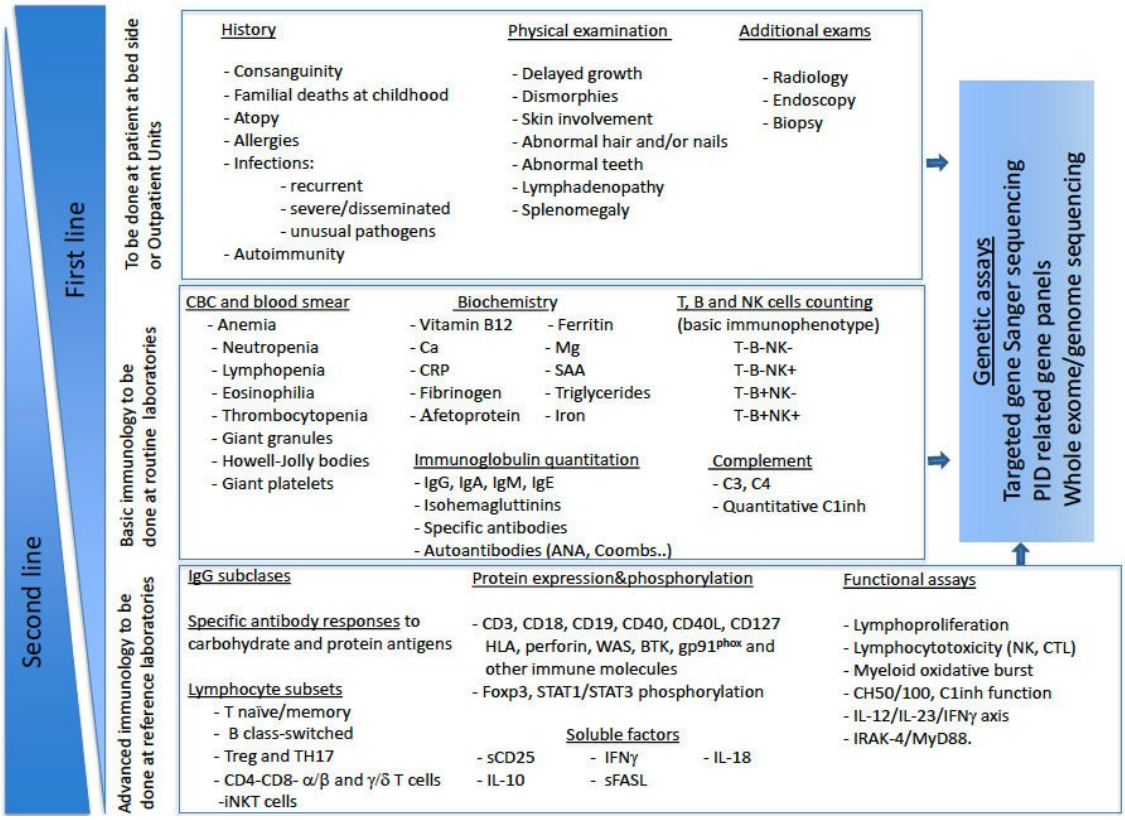

Figure 2. Proposal of a scoring decision tree for indication of immunoglobulin replacement therapy in patients with hypogammaglobulinemia based on laboratory and clinical history parameters. Adapted from Agarwal et al.[258]
AB: antibiotic; AI: autommune; AIHA: autoimmune hemolytic anemia; DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; ITP: idiopathic thrombocytopenic purpura; TLC: total lung capacity; IGRT: immunoglobulin replacement therapy; IV: intravenous; RTI: respiratory tract infection; SC: subcutaneous. Reproduced with permission from Agarwal and Cunningham-Rundles.[258]

Figure 2.

	POINT VALUE	0	1	2	3	4	5
LABORATORY	IgG (mg/dL)	600+	350-590		150-349		0-149
	IgA (mg/dL)	Normal			Reduced		
	IgM (mg/dL)	Normal			Reduced		
	Diphteria or tetanus	Protective					Nonprotective
	% of protective pneumococcal serotype	≥50%			20-49%		0-19%
CLINICAL	Pneumonia/lifetime	None	1	2	3	4	>4
	Upper RTI/year	None	1	2	3		>3
	Antibiotic courses/year	None	1	2	3	4	>4 or prophylactic
	AI diseases: ITP, AIHA, others	None			Present		
	Sepsis, meningitis, septic arthritis, osteomyelitis, empyema	None					Present
	Splenomegaly or splenectomy	None			Present		
	Lymphadenopathy	None			Present		
	Infectious diarrhea (excluding *Clostridium difficile*)	None			Present		
	Malabsorption, chronic gastroenteritis, inflammatory bowel-like disease	None			Present		
	Weight loss or failure to thrive	None			Present		

	Hospitalizations/5 years	None	1	2	3	4	≥5
OTHER	Pulmonary function tests	Normal	FEV1/FVC or TLC <80% predicted		FEV1/FVC or TLC <70% predicted		FEV1/FVC or TLC <60% predicted
	Bronchiectasis	None					Present