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Consensus document

Executive Summary of the Consensus Document on the Diagnosis and Management of Patients with Primary Immunodeficiencies☆,☆☆,☆☆☆

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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 Calmette-Guérin; BM, bone marrow; CBC, complete blood count; CGD, Chronic Granulomatous Disease; CHH, cartilage-hair hypoplasia; CSF, cerebrospinal fluid; CHARGE, coloboma heart defects, atresia choanae, growth retardation; CID, combined Immunodeficiencies; CLOVES, congenital; lipomatous; overgrowth; vascular malformations; epidermal nevi; spinal/skeletal anomalies; and/or scoliosis; CMCchronic mucocutaneous candidiasis; CNS, central nervous system; CVID, common variable immunodeficiency; CyA, Cyclosporine; DCLO, Diffusing capacity of the lung for carbon monoxide; EFS, event-free-survival; EBV, Epstein-Barr virus; EBV-PTLD, Epstein-Barr virus post-transplant lymphoproliferative disorder; EDA-ID, ectodermal dysplasia-associated immunodeficiency; ERT, enzyme replacement therapy; ESR, erythrocyte sedimentation rate; GVHD, graft-versus-host disease; GOF, gain-of-function; 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; IFNg, 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; NBS, newborn screening; NADPH, nicotinamide adenine dinucleotide phosphate; NEMO, nuclear factor-kappa B essential modulator; NGS, next generation sequencing; OPV, oral polio virus vaccine; PAD, predominantly antibody deficiencies; PBSCs, Peripheral Blood Stem Cell; PCV13, 13-valent pneumococcal conjugate vaccine; PFT, pulmonary functional test; PID(s), Primary immunodeficiency(es); PJP, *Pneumocystis jirovecii* pneumonia; PPSV23, 23-valent polysaccharide vaccine; QoL, quality of life; RIC, reduced-intensity conditioning; R-ADA, recombinant adenosine deaminase; SC, subcutaneous; SCID, Severe Combined Immunodeficiencies; SCN, severe congenital neutropenia; STAT, Signal Transducer and Activator of Transcription; TAR, thrombocytopenia and absent radius; TCL, T-cell lymphopenia; SCID, severe combined immunodeficiency; SEIMC, Sociedad Española de Infectología y Microbiología Clínica; SPURR, severe; persistent; unusual; recurrent infections with a history of PID running in the family; 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; WHIM, warts; hypogammaglobulinemia; immunodeficiency; and myelokathexis; WGS, whole exome/genome sequencing; XLA, X-linked agammaglobulinemia.

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☆☆☆ The complete consensus document is available as Appendix in supplementary material.

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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.

Resumen ejecutivo del Documento de consenso sobre diagnóstico y manejo de pacientes con inmunodeficiencias primarias

Palabras clave:
Inmunodeficiencias primarias
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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.

Introduction

Justification

The field of Primary Immunodeficiencies (PID) has experienced an enormous increase in the last years. The first PID 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 fulling penetrant mendelian traits predisposing to multiple, recurrent, and opportunistic infections. Since the mid 1990s, 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. Currently, over 400 PID have been identified, more than 350 out of them with a recognized gene defect.[1] 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.[2] The descriptor Inborn Errors of Immunity (IEI) is gaining acceptance to encompass dysregulation and autoinflammatory disorders and PID, 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.[3–8] The twenty-first century has witnessed exciting advances in immunoglobulin replacement therapy, hematopoietic stem cell transplantation, and gene therapy.[6–8] 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.[9]

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 PID, healthcare and PID 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 PID.

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 primary immunodeficiency (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 PID be screened in neonates?
5. When and what type of antimicrobial prophylaxis should be offered to a child and an adult with PID?
6. What type of vaccines can be offered to children and adults with PID?
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 in a child with PID?
9. When is a HSCT considered in an adult with PID?
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.[10]

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 Paediatric Infectious Disease-Spanish Paediatric Association (SEIP-AEP) and the Spanish Society for Clinical Immunology, Allergology and Paediatric Asthma-Spanish Paediatric 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 (AII).
- It is mandatory to obtain a focused family history when the differential diagnosis includes a PID (AII).
- 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 (AII).
- PID must be screened in patients with one or more infections caused by opportunistic organisms that are rarely pathogenic for immunocompetent subjects (AII).
- PID must be screened in patients with one or more severe infections caused by low virulence pathogens (AII).
- 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 (BII).

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 (AIII).
- A stepwise approach is recommended as the most likely cost-effective strategy for diagnosis of PID (AIII).
- Complete blood count (CBC) and immunoglobulins levels should be performed as first line tests for diagnosis of PID (AIII).
- Second line (non-disease specific or disease specific) tests include functional, molecular and genetic tests, which must be tailored by experts in PID (AIII).
- 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 (PID genetic panels), and whole exome/genome sequencing (WES/WGS) when the previous fail or an unbiased approach to PID genetic testing is advantageous (AIII).

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 PID is recommended in these patients (AIII).
- 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 (AIII).
  - 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 (AIII).
  - Chest X-ray and an abdominal ultrasound should be performed in all PID patients. (AIII).
- 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 (AIII).
  - Yearly PFT, including DLCO, in PID with potential lung involvement (AIII).
  - Yearly abdominal ultrasound (BIII).
  - In PID with lung involvement, HRCT should be repeated every 5 years when baseline is normal (AIII), or every 1–2 years in case of active bronchiectasis or interstitial lung disease (BIII).
  - Dental evaluation and QoL scale should be performed at diagnosis and yearly (AIII).
  - 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 (AIII).
  - In patients with bronchiectasis, physiotherapy and respiratory rehabilitation are key in the treatment (AIII).
  - When there is suspicion of infection in patients with bronchiectasis, it is recommended to optimize general, microbiological and imaging methods (AIII).

4. How should PID 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% (AII).
- Newborn screening (NBS) for T cell deficiencies has shown to reliably identify patients with SCID in the asymptomatic phase (AII).
- T-cell receptor excision circles (TREC) is currently the most appropriate biomarker for the early identification of neonates with SCID through systemic NBS programs (AII).
- TREC based SCID NBS programs are cost effective (AII).
- 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 (AII)

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 (AII).
- *Pneumocystis jirovecii* prophylaxis is indicated for other specific T cell deficiencies with a high susceptibility to this microorganism infection (AIII).
- All patients with CGD should receive prophylactic cotrimoxazole (AII) and itraconazole (AI).
- Adult patients with humoral immunodeficiency could benefit from prophylaxis with azithromycin when respiratory infections persist despite IGRT (AI). There are no published controlled studies of the benefits of this prophylaxis in children with humoral immunodeficiency, although the same benefit is expected (AIII).
- Antibiotic prophylaxis with penicillin V or amoxicillin is recommended for patients with complement component deficiencies and congenital asplenia (AII).
- Other specific antibiotic prophylaxis can be prescribed, chronically or intermittently, according to the type of the primary immunodeficiency.

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 (DIII).
- PID patients can be safely vaccinated with inactivated vaccines, however, vaccine immune response can be suboptimal (AIII).
- 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 (DIII).
- Annual vaccination with influenza inactivated vaccines are recommended in all PID patients and their household contacts, including those with CVID receiving IGRT (AII).

- Vaccination in patients receiving IGRT with inactivated antigens could be considered, although efficacy or effectiveness of the intervention has not been yet determined (CIII).
- 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 (CIII).
- In children with PID, unless contraindicated, systematic immunization schedule with inactivated vaccines should be completed (AIII).
- Pneumococcal vaccination is recommended in PID patients, unvaccinated > 60-month-old patients should receive one dose of the 13-valent pneumococcal conjugate vaccine (PCV13) (BIII). For those receiving IGRT, pneumococcal vaccination may be considered (safe intervention) although cost-effectiveness remains to be elucidated (CIII).
- The 23-valent polysaccharide vaccine (PPSV23) is recommended for PID patients ≥ 2 years of age with 2-dose scheme five years apart (BII). No additional doses of PPSV23 are recommended (DIII).
- 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) (AII).
- Wide protection against serogroups B and ACWY is recommended for patients with PID, especially in those with complement defects or congenital asplenia/hyposplenism (AII).

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 (AII)
- 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 (CIII).
- Intravenous and subcutaneous route for IGRT are equivalent in terms of efficacy (AI).
- The route of administration should be selected individually in every patient (AI).
- Patients' preferences should be considered when choosing the route of administration (BIII).
- In patients with humoral immune defects on IGRT, trough serum IgG levels above 500 mg/dL are effective in prophylaxis against bacterial infections, particularly against pneumonia (AI).
- 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) (AIII). More frequent studies should be performed in presence of complications such as cancer, chronic lung disease or malabsorptive syndrome) (AIII).
- It is recommended to stratify patients with antibody production deficits according to lung damage, and to maintain trough IgG levels consequently: above 600 mg/dL for patients without pulmonary abnormalities and above 800 mg/dL for those with chronic lung damage (AIII).
- 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 (BII).
- Dose IGRT adjustments are required in special situations, such as acute illnesses, before or after surgery, chronic diarrhoea or weight changes, and during pregnancy (BIII).
- It is advisable to maintain serum bank during IGRT (BIII).

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 (AII).
- In patients with CID, allo-HSCT is recommended in the following conditions: CD40L, WAS, CHH, ZAP70, MHC-class II deficiency and NEMO (AII).
- 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 (BII).
- Allo-HSCT should be performed in all patients with primary HLH (AII). Remission of the disease is recommended to avoid relapses (A-II). In CVID with immune dysregulation (CTLA4, LRBA, PI3Kδ/R1, STAT3 gain-of function mutations), HSCT should be considered after failing first-line therapies with abatacept, PIK3 or JAK inhibitors, or in cases of incomplete response (CIII).
- 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, (BII), patients with IL-10 receptor-deficiency and selected patients with ADA2 deficiency (CECR1), STAT-1 GOF and STAT-3 GOF. (BIII).
- 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 (AII).
- Whenever possible, a matched sibling donor should be used (AII). Otherwise, a fully matched unrelated donor is the recommended alternative (AII).
- 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) (BII).

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 (BII).
- 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 (BII).
- 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 (CIII).

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 (BII).
- Immune suppression in PID should be considered in order to treat autoimmune, autoinflammatory, lymphoproliferation or granulomatous disease manifestations (AII).
- Infectious prevention with Interferon gamma should be considered for CGD patients (BI).
- ADA enzyme-replacement therapy should be given to all patients with a new diagnosis of ADA deficiency or ADA-SCID (AI).
- Gene therapy should be pursued for all ADA-SCID patients with no matched-sibling or matched family donor (AII)
- 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) (CIII).
- Gene therapy should be considered in patients with CGD or WAS if HSCT cannot be performed (AIII)
- Treatment with granulocyte colony-stimulating factor is recommended as first-line treatment for patients with congenital neutropenia (AI).

11. When is genetic counselling needed?

Recommendations

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

Conflict of interest

This document has not received any financial funding's by private institutions.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eimc.2020.07.001.

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