# Latin American consensus on the supportive management of patients with severe combined immunodeficiency



**Juan Carlos Bustamante Ogando, MD,[a] Armando Partida Gaytán, MD,[a] Juan Carlos Aldave Becerra, MD,[b] Aristóteles Álvarez Cardona, MD,[c] Liliana Bezrodnik, MD,[d,e] Arturo Borzutzky, MD,[f] Lizbeth Blancas Galicia, MD, MSc,[a] Diana Cabanillas, MD,[g] Antonio Condino-Neto, MD, PhD,[h] Agustín De Colsa Ranero, MD,[i] Sara Espinosa Padilla, MD, PhD,[a] Juliana Folloni Fernandes, MD,[j] Jorge Alberto García Campos, MD,[k] Héctor Gómez Tello, MD,[l] María Edith González Serrano, MD,[a] Alonso Gutiérrez Hernández, MD,[m] Víctor Manuel Hernández Bautista, MD,[m] Gabriele Ivankovich Escoto, MD,[n,u] Alejandra King, MD,[o] Juliana Lessa Mazzucchelli, MD,[p] Beatriz Adriana Llamas Guillén, MD,[q] Saul Oswaldo Lugo Reyes, MD, MS,[a] Sarbelio Moreno Espinosa, MD,[r] Matías Oleastro, MD,[s] Francisco Otero Mendoza, MD,[i] María Cecilia Poli Harlowe, MD, PhD,[t] Oscar Porras, MD, PhD,[u] Nideshda Ramirez Uribe, MD,[v] Lorean Regairaz, MD,[g] Francisco Rivas Larrauri, MD,[m] Federico José Saracho Weber, MD,[w] Anete S. Grumach, MD,[x] Tamara Staines Boone, MD,[y] Beatriz Tavares Costa-Carvalho, MD,[z] Marco Antonio Yamazaki Nakashimada, MD,[m] and Francisco Javier Espinosa Rosales, MD[aa]** *Mexico City, Aguascalientes, Monterrey, Puebla, Morelos, and Chihuahua, Mexico; Lima, Peru; Buenos Aires and La Plata, Argentina; Santiago, Chile; Sao Paulo, Brazil; and San José, Costa Rica*

**Severe combined immunodeficiency (SCID) represents the most lethal form of primary immunodeficiency, with mortality rates of greater than 90% within the first year of life without treatment. Hematopoietic stem cell transplantation and gene therapy are the only curative treatments available, and the best-known prognostic factors for success are age at diagnosis, age at hematopoietic stem cell transplantation, and the comorbidities that develop in between. There are no evidence-based guidelines for standardized clinical care for patients with SCID during the time between diagnosis and definitive treatment, and we aim to generate a consensus management strategy on the supportive care of patients with SCID. First, we gathered available information about SCID diagnostic and therapeutic guidelines, then we developed a document including diagnostic and therapeutic interventions, and finally we submitted the interventions for expert consensus through a modified Delphi technique. Interventions are grouped in 10 topic domains, including 123 "agreed" and 38 "nonagreed" statements. This document intends to standardize supportive clinical care of patients with SCID from diagnosis to definitive treatment, reduce disease burden, and ultimately improve prognosis, particularly in countries where newborn screening for SCID is not universally available and delayed diagnosis is the rule. Our work intends to provide a tool not only for immunologists but also for primary care physicians and other specialists involved in the care of patients with SCID. (J Allergy Clin Immunol 2019;144:897-905.)**

***Key words:*** *Severe combined immunodeficiency, consensus, transplantation, supportive measures, treatment, immunodeficiency, primary immunodeficiency*

From [a]the Immunodeficiencies Research Unit, [i]the Department of Infectious Diseases, [m]the Department of Clinical Immunology, and [v]the Hematopoietic Stem Cell Transplantation Unit, Instituto Nacional de Pediatria, Mexico City; [b]the Division of Allergy and Immunology, Hospital Nacional Edgardo Rebagliati Martins Lima; [c]Unidad de Investigación en Inmunología Clínica y Alergia, Aguascalientes; [d]the Immunology Department, Hospital de Niños "Ricardo Gutiérrez," Buenos Aires; [e]Centro de Inmunología Clínica "Dra. Bezrodnik," Buenos Aires; [f]the Department of Pediatric Infectious Diseases and Immunology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago; [g]the Immunology Unit, Children's Hospital "Superiora Sor Maria Ludovica," La Plata; [h]the Department of Immunology, Institute of Biomedical Sciences, University of Sao Paulo; [j]Departamento do Hematología e Transplante de Medula Óssea, Hospitalo Israelita Albert Einstein, Sao Paulo; [k]the Infectious Disease Department and [y]the Clinical Immunology Department, Hospital de Especialidades, Monterrey; [l]the Immunology Department, Hospital para el Niño Poblano, Puebla; [n]the School of Medicine, University of Costa Rica, San José; [o]the Division of Pediatric Immunology, Hospital Luis Calvo Mackenna, Santiago; [p]the Department of Pediatrics, Universidade Federal de Sao Paulo; [q]the Immunology Department, Hospital del Niño Morelense, Morelos; [r]Department of Infectious Diseases, Hospital Infantil de México "Federico Gómez," Mexico City; [s]the Department of Immunology and Rheumatology, Hospital de Pediatría J. P. Garrahan, Buenos Aires; [t]Instituto de ciencias e innovación en medicina, Universidad del Desarrollo–Clinica Alemana, Santiago; [u]Pediatric Immunology and Rheumatology, Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera," San José; [w]Hospital Infantil de Especialidades, Chihuahua; [x]the Division of Clinical Immunology, Facultade de Medicina ABC, Sao Paulo; [z]the Allergy and Immunology Unit, Department of Pediatrics, Universidade Federal de Sao Paulo, Santo Andre, Sao Paulo; and [aa]Fundación Mexicana para Niñas y Niños con Inmunodeficiencias Primarias (FUMENI), Mexico City.

This work was partially funded by Fundación Mexicana para Niñas y Niños con Inmunodeficiencias Primarias (FUMENI).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication December 4, 2018; revised July 30, 2019; accepted for publication August 5, 2019.

Available online August 13, 2019.

Corresponding author: Juan Carlos Bustamante Ogando, MD, Av. Insurgentes Sur 3700-c, Cuicuilco, Mexico City 04530, Mexico. E-mail: drbustamante_inp@hotmail.com.



0091-6749/$36.00



https://doi.org/10.1016/j.jaci.2019.08.002

*Abbreviations used*
HSCT: Hematopoietic stem cell transplantation
NBS: Newborn screening
PID: Primary immunodeficiency
SCID: Severe combined immunodeficiency

Primary immunodeficiencies (PIDs) comprise more than 350 hereditary diseases that affect the development, function, or both of the immune system.[1] Severe combined immunodeficiencies (SCIDs) constitute a heterogeneous group of genetic defects that result in failure in the number and/or function of T lymphocytes, profoundly affecting cellular and humoral adaptive immunity.[2] SCID affects approximately 1:55,000 live newborns and represents the most lethal spectrum of PIDs.[3] Without timely treatment, SCID results in high mortality rates during the first year of life.[2]

## CLINICAL PICTURE AND DIAGNOSIS OF SCID

SCID typically manifests in the first 6 months of life with severe and/or persistent infections caused by any type of microorganism (ie, bacteria, viruses, fungi, and mycobacteria), poor growth, and chronic diarrhea. Physical examination usually shows the absence of lymphoid tissue, and routine laboratory tests usually document lymphopenia (<3000 cells/mm$^3$) and hypogammaglobulinemia, with absent thymus demonstrated by means of chest radiography or ultrasonography.[4] Peripheral blood lymphocyte subsets typically show low numbers of T lymphocytes (CD3$^+$, CD4$^+$, and CD8$^+$) with or without a decrease in the number of B lymphocytes (CD19$^+$) and/or natural killer cells (CD16$^+$CD56$^+$). Lymphoproliferation studies with different stimuli show defects in the activation and proliferation of T lymphocytes.[2,4] Confirmation of pathogenic variants in genes known to cause SCID helps for a definitive diagnosis, although therapeutic interventions should not be delayed while waiting for a genetic diagnosis when clinical and immunologic features are compatible with SCID.[1] Family history of SCID, consanguinity, early deaths, or severe infections at an early age might be important clues to diagnosis.[4]

Given that SCID is rare and usually asymptomatic at birth, population-based newborn screening (NBS) using a T-cell receptor DNA excision circle assay on dried blood spots is currently a useful strategy to identify patients with SCID earlier and before the development of infectious complications.[5] Universal NBS has been implemented in the United States and some other regions but is still not a reality in most parts of the world.[5,6]

## TREATMENT AND PROGNOSIS

Curative treatments for SCID depending on the molecular defect and availability are hematopoietic stem cell transplantation (HSCT) or gene therapy.[2] However, none of these interventions can be provided immediately, resulting in a lapse between diagnosis and the application of such treatments. This lapse represents a critical period during which the implementation of correct medical interventions allows patients to reach a curative treatment under the best possible clinical conditions. In this sense the observations of several cohorts of patients with SCID treated in different specialized referral centers have given way to recommendations for supportive treatment.[4,7,8]

The prognosis and survival of patients with SCID after HSCT are better when it is performed at an early age and without comorbidities or active infections at the time of the procedure. In an ideal scenario patients with SCID are detected by using neonatal screening, and HSCT at less than 3.5 months of age is performed in the absence of serious and/or active infections, allowing a success rate and survival at 5 years of greater than 90%.[9] However, the most common scenario in Latin America and most parts of the world where NBS is not yet routinely available is the diagnosis of SCID once signs and symptoms have developed, which often include infections and serious complications and delayed referral to a specialized center for definitive treatment.[11] It is very likely that a large number of patients die of serious infections without receiving a proper diagnosis of SCID. Timely diagnosis and treatment affect not only survival but also the quality of life of patients and their families and the economics of health systems.[12-14] The median age at diagnosis in subjects presenting with typical clinical manifestations is 179 days (36-4916 days) compared with the median of 14 days (0-80 days) reported for subjects receiving a diagnosis based on a family history of SCID or neonatal screening ($P < .001$).[15] These differences also affect the time to definitive treatment: patients in Latin America receive curative treatment at a median of 214 days of life compared with 67 days of life for patients in the United States.[15]

In Latin America social, environmental, and demographic conditions introduce added challenges. First, no country has implemented universal neonatal screening, and because of the relative rarity of the diagnosis, there is a low index of diagnostic suspicion by primary care physicians.[16]

Second, with the exception of Ecuador, all countries in the region apply universal vaccination against tuberculosis at birth with the BCG vaccine,[17] causing disseminated BCG in 51% to 65% of patients with SCID.[18]

Third, resource limitations, medical infrastructure, few HSCT centers, and scarce donor registries limit access and opportunities to perform early definitive treatments.[11] In this context less than 30% of patients receiving a diagnosis of SCID receive curative treatment, with a success rate ranging from 40% to 65% (personal communications). The waiting time between diagnosis and HSCT is approximately 4 to 6 months, which adds to the diagnostic delay and reduces the probability of achieving HSCT under optimal conditions (Fig 1).

In the period between diagnosis and curative treatment, infectious, inflammatory, and autoimmune complications affect the prognosis of patients, even if they manage to receive such treatment. Viral, bacterial, fungal, and often polymicrobial infections are responsible for the greatest mortality.[10,15] The supportive treatment provided during the waiting period for curative treatment is critical to achieve ideal conditions in patients and improve survival, and measures should be implemented from the time SCID diagnosis is considered (Fig 2).[19] In our clinical practice we have identified great heterogeneity in the diagnostic and therapeutic interventions received by patients with SCID among different centers and even among different physicians within the same center. We consider this heterogeneity to result in deleterious effects for these patients, and furthermore, it should be considered that in most cases, the initial supportive treatment given to patients with SCID will be initiated by primary care

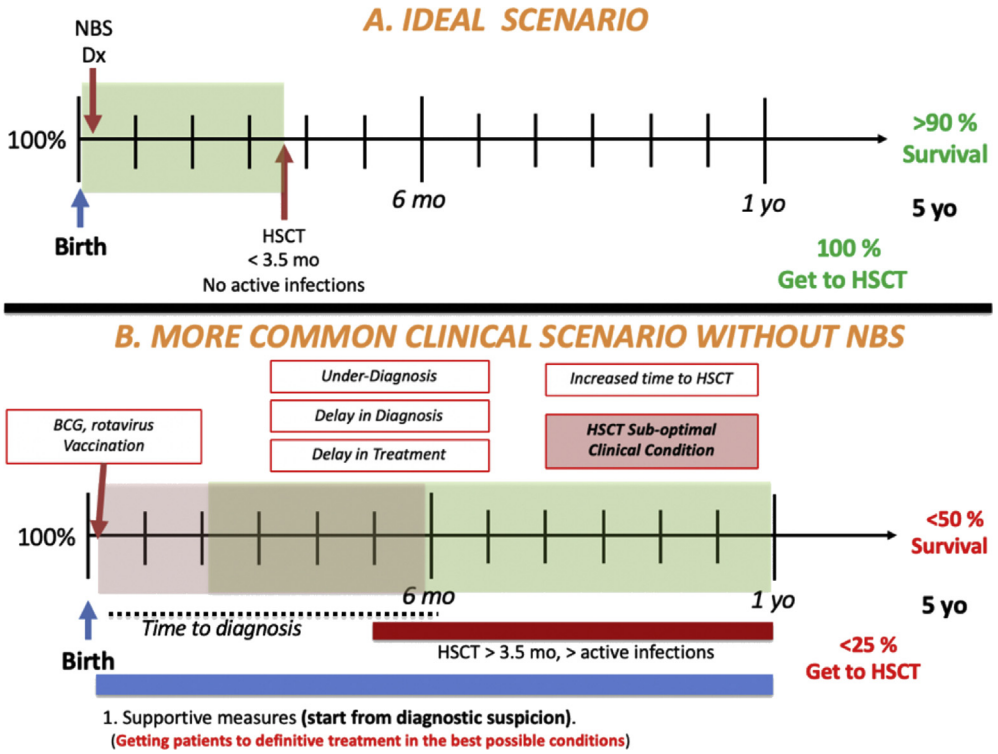


**FIG 1.** Ideal versus common scenarios for patients with SCID. In places where SCID NBS is not routinely available, delayed diagnosis and treatment have a considerable effect on survival and overall prognosis. Clinical awareness and initiation of supportive measures from the time of diagnostic suspicion might allow patients with SCID to receive definitive treatment in better clinical conditions.

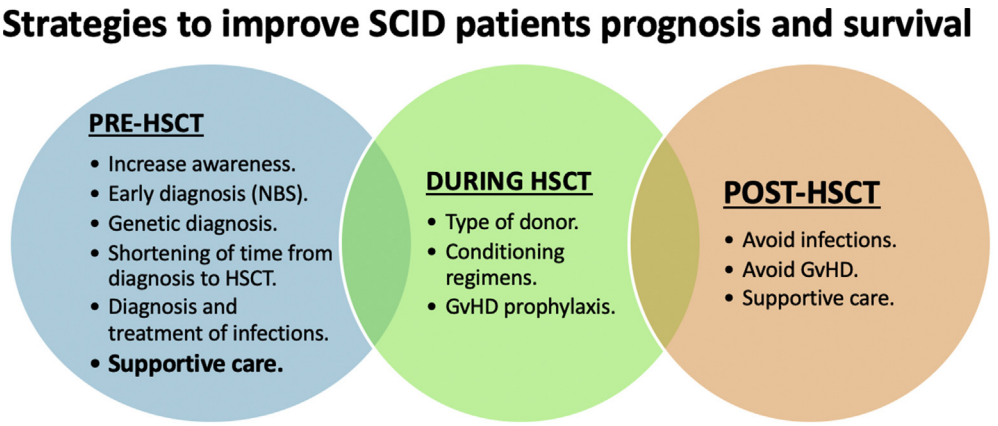


**FIG 2.** Strategies to improve SCID prognosis. SCID treatment requires specialized and multidisciplinary clinical care. Many strategies can be implemented at different time points and health care levels to improve prognosis and survival. *GvHD,* Graft-versus-host disease.

physicians, pediatricians, and physicians in emergency services and not by an immunologist with experience with these diseases.

For these reasons, the creation of a document that is agreed upon by experts and allows the establishment of sequential guidelines for patients with a suspected or confirmed diagnosis of SCID is a useful tool with a potential beneficial effect on patient care, with the ultimate objective of facilitating curative treatments under better clinical conditions. To the best of our knowledge, there are no published clinical practice guidelines or consensus that focus particularly on specific recommendations for such a period between diagnosis and curative treatment and certainly not in the context of developing countries, such as those in the region of Latin America.

Developing a consensus regarding the diagnostic and therapeutic interventions to be implemented in this critical period will establish a starting point to (1) know our practices, (2) create a reference document to homogenize clinical care, (3) compare our care against other references, and (4) allow improvement of the clinical care of these patients and, consequently, their prognosis and survival.

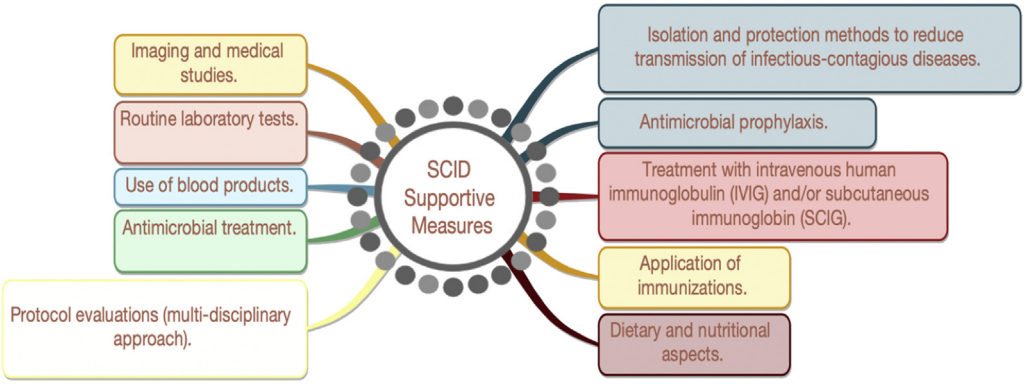


**FIG 3.** Supportive measures for patients with SCID are classified in 10 domains based on the main clinical objectives.

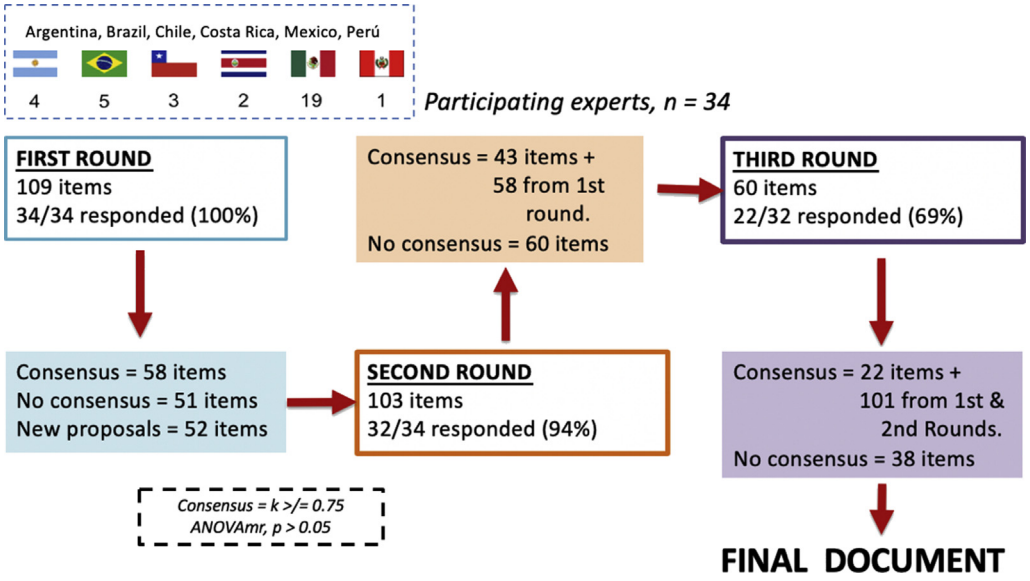


**FIG 4.** Consensus document flowchart. The Delphi method has been widely used to establish guidelines in areas of health care and research. It is particularly useful in situations in which there is a lack of agreement, incomplete knowledge, uncertainty, or lack of evidence.[22] The final document includes 161 interventions, of which 123 (76.4%) achieved consensus (Table I) and 38 (23.6%) did not reach consensus (see Table E1). *ANOVAmr*, Repeated-measures ANOVA.

## CONSENSUS ON SCID SUPPORTIVE MEASURES

Using a defined methodology and a modified Delphi technique, our objective is to propose a Latin American consensus for the supportive treatment of patients with SCID, from diagnostic suspicion to the execution of curative treatment, considering the clinical and sociodemographic particularities of the region.

First, we conducted a structured and exhaustive search of the literature on diagnostic and therapeutic interventions for the support and treatment of patients with SCID. We also contacted SCID experts from PID reference centers (see the Acknowledgements section) in Europe, the United States, Canada, and Latin America and specifically requested written documents that guide the clinical care of patients with SCID in their institutions. We found a lack of specific written protocols for the management of patients with SCID in specialized centers in developed countries, and even in these centers, most clinical decisions are based on the experiences of the local clinicians (personal communications).

A document concerning the management of patients with SCID detected by using neonatal screening in the United States was recently published in which diagnostic and therapeutic interventions are proposed to be performed before definitive treatment, many of which coincide with the strategies expressed in our consensus.[20] During the annual Clinical Immunology Society meeting in Toronto 2018, an abstract by Heimall et al presented a survey of 51 specialists from 43 specialized centers in the United States belonging to the Primary Immune Deficiency Treatment Consortium on the management of patients with SCID detected by means of neonatal screening during the period from diagnosis to HSCT. The survey showed that one third of the centers lack established practice guidelines, as well as significant heterogeneity in intercenter practices, with respect to antimicrobial prophylaxis and infection monitoring, performance of diagnostic studies, and general measures to avoid infectious complications. Despite neonatal screening, up to 42% of the

**TABLE I.** Consensus interventions for supportive management of patients with SCID

| Intervention | Kappa value |
|---|---|
| 1. Isolation and protection methods to reduce transmission of infectious-contagious diseases | |
| All patients who are hospitalized should be admitted to isolated rooms. | 0.94 |
| All hospitalized patients must be kept in conditions of strict protective isolation (single-patient rooms with positive pressure and high-efficiency particulate air filters, restriction of visits, and use of gloves, face masks, hats, boots, hand washing with a 3-step technique with 4% chlorhexidine or iodopovidone or equivalent, and a sterile diet). | 0.89 |
| If the patient is in good general condition (asymptomatic), he or she can be taken care of at home under the following home conditions:<br>● The house where the child is cared for must have drinking water, electricity, drainage, and some means of communication (telephone or cell phone).<br>● Patient care is limited to 1 or 2 family members.<br>● There is no exposure to contact with other children.<br>● Visits are strictly restricted.<br>● There is no exposure to animals of any kind.<br>● Hand washing by caregivers must be done with alcohol, chlorhexidine, or similar.<br>● Exposure to sick family members must be restricted.<br>● Reliable parents and/or caregiver must have been previously trained in the diagnosis and care of the patient.<br>● There must be no vaccination of caregivers with live agents (varicella, rotavirus, yellow fever, oral polio, rubella, mumps, cholera, or oral typhoid). | >0.75 |
| At the entrance to the room of a patient with SCID, there must be visible notifications of the preventive and general care measures to be carried out by health care and related personnel before entering the room. | 1.00 |
| All persons (caregivers, students, nurses, medical personnel, and cleaning staff) who enter the patient's room should:<br>● wear face masks and<br>● use a gown that is exclusive for that room. | >0.75 |
| Student (eg, medicine, nursing, or nutrition) access must be restricted to the rooms of patients with SCID in teaching hospitals. | 0.82 |
| The nurse in charge of the care of patients with SCID should avoid simultaneous contact with other patients with infectious diseases. | 1.00 |
| Specific nursing staff should be assigned for the care of patients with SCID, attempting to reduce as much as possible the rotation of nursing staff for these patients. | 0.93 |
| Entry of people to the room should be restricted as much as possible. | 1.00 |
| Avoid contact with any person with symptoms of any infectious process, including mild symptoms (eg, cold, cough, or diarrhea). | 1.00 |
| Avoid contact with other children to avoid contagious infectious diseases. | 0.94 |
| In case the patient requires a study that cannot be performed in his or her room (ie, imaging studies), the patient should be treated in the respective area without waiting and without being in contact with other patients. | 0.94 |
| All medical and nursing staff participating in the care of these patients should receive special training. | 1.00 |
| Disinfect toys and electronic devices, such as telephones, tablets, and video games, before they enter the room of a patient with SCID. | 1.00 |
| Medical equipment (eg, stethoscope, sphygmomanometer, or monitor) should be exclusively assigned for use in a patient with SCID. | 1.00 |
| 2. Antimicrobial prophylaxis | |
| Prophylaxis against bacteria and *Pneumocystis jirovecii* should be administered with TMP/SMX. | 1.00 |
| Prophylaxis with TMP/SMX can begin after 2 weeks of life, as long as the concentration of bilirubin is normal. | 0.78 |
| Prophylaxis against fungal infections should be administered with itraconazole (10 mg/kg/d) every day or fluconazole (impregnation, 12 mg/kg/d; followed by 6 mg/kg/day) every day for all patients. | 0.89 |
| Breast-feeding should be suspended until there is certainty of the maternal status with respect to CMV infection. Breast-feeding will be contraindicated in every mother who can transmit CMV. (If it is not possible to perform these examinations in a timely manner, it will be preferable to suspend breast-feeding and feed with milk formula.) | 0.88 |
| Patients who have been vaccinated with BCG (regardless of symptomatology) should receive antimycobacterial drugs. | 0.82 |
| Use of pyrazinamide should be avoided as part of the antimycobacterial treatment of those patients who have received the BCG vaccine (*Mycobacterium bovis*) because of the intrinsic resistance of the microorganism. | 0.83 |
| Patients who have been vaccinated with BCG and who have BCGitis should receive rifampicin + ethambutol + isoniazid + clarithromycin. | 0.82 |
| Patients who have been vaccinated with BCG and who have BCGosis should receive rifampicin + ethambutol + isoniazid + clarithromycin. | 1.00 |
| 3. Treatment with IVIG, SCIG, or both | |
| Replacement treatment with human immunoglobulin should be started immediately in all patients. | 1.00 |
| The first dose of human immunoglobulin should always be administered intravenously. | 0.89 |
| The minimum substitutive IVIG dose should be 400-600 mg/kg/d every 3 to 4 weeks. | 1.00 |
| The minimum substitutive SCIG dose is 100-200 mg/kg/d every 1 to 2 weeks. | 0.82 |
| Additional doses of human immunoglobulin should be administered during active infections. | 0.77 |
| The serum concentration of IgG must be monitored to modify the treatment dose. | 0.88 |

*(Continued)*

**TABLE I**. *(Continued)*

| Intervention | Kappa value |
|---|---|
| 4. Application of immunization | |
| In newborns with suspected or diagnosed SCID, it must be reported in the patient's file and cradle (eg, on a sign) that BCG vaccine should NOT be applied for any reason. | 1.00 |
| The complete vaccination scheme should be ensured/corroborated in all adults who have close contact with patients with SCID. | 0.93 |
| Application of vaccines derived from live attenuated microorganisms (ie, BCG, rotavirus, varicella, measles, rubella, parotitis, yellow fever, typhoid fever, cholera, oral polio, and intranasal influenza) is contraindicated in patients with SCID. | 0.94 |
| Application of vaccines derived from live attenuated microorganisms (ie, BCG, rotavirus, varicella, measles, rubella, mumps, yellow fever, typhoid fever, cholera, oral polio, and intranasal influenza) is contraindicated in close relatives of patients. | 0.83 |
| Application of all vaccines that are not attenuated live microorganisms should be ensured in close relatives of the patients. | 0.88 |
| The influenza vaccine should be applied annually to all close relatives, as well as medical and paramedical personnel who have contact with patients with SCID. | 1.00 |
| 5. Dietary and nutritional aspects | |
| In case of suspension of breast-feeding, feeding should be provided with formula prepared under sterile conditions. | 1.00 |
| All patients should be evaluated by gastroenterology and nutrition specialists to establish an intensive nutritional plan (considering even total or mixed parenteral nutrition or nutrition by means of an orogastric/nasogastric tube). | 0.83 |
| The ideal formula to administer will obey clinical conditions (starting with formula according to age), and only in the case of specific symptoms will some specialized formula be selected. | 0.94 |
| Somatometry (weight, height, and head circumference) should be evaluated weekly in all patients. | 0.82 |
| The diets of ablated patients should be low in bacteria and/or sterile. | 1.00 |
| Avoid storage of food in the rooms of patients with SCID. | 1.00 |
| 6. Antimicrobial treatment | |
| Given the suspicion of an infectious process, broad-spectrum empiric antimicrobial treatment (covering gram-positive, gram-negative, mycobacterial, fungal, and viral agents) should be initiated in all patients. | 0.82 |
| Appropriate initial empiric antimicrobial treatment of a suspected infectious process in patients with SCID should include coverage for gram-positive and gram-negative organisms (eg, third-generation cephalosporin). | 0.88 |
| In patients with a suspected infectious process, the infectious focus and microorganism responsible for directing treatment should be exhaustively searched through the following studies:<br>● complete blood count with differential;<br>● urine test for bacteria, fungi, and mycobacteria;<br>● stool test;<br>● CMV viral load;<br>● EBV viral load; and<br>● thoracic radiography. | >0.75 |
| In patients with a suspected infectious process, fungal forms should be looked for in urine. | 0.77 |
| In patients with a suspected infectious process, fungal forms should be looked for in nail, mouth, and skin lesions. | 0.88 |
| In patients with a suspected infectious process, *Candida* species antigen should be looked for in blood. | 0.77 |
| In patients with a suspected infectious process, *Aspergillus* species antigen should be looked for in blood. | 0.77 |
| In patients with a suspected infectious process, PCR should be performed for mycobacteria. | 0.82 |
| In patients with a suspected infectious process, acid-resistant bacteria should be sought with Ziehl-Neelsen stain in gastric juice. | 0.75 |
| In patients with a suspected infectious process, an ophthalmologic evaluation should be performed to rule out infectious processes at this level. | 0.9 |
| In patients with a suspected infectious process, abdominal ultrasonography should be performed (eg, search for fungomas, abscesses, and collections). | 0.82 |
| In patients with SCID younger than 6 months of age who present with fever without an identified infectious focus, lumbar puncture should be performed. | 0.9 |
| Bronchoscopy and bronchoalveolar lavage should be performed only in the case of respiratory symptoms. | 0.77 |
| Echocardiography should be performed in patients with SCID who present with fever without an obvious focus. | 0.82 |
| When there is information about an involved microorganism, antimicrobial coverage should be adjusted without suspension of habitual prophylaxis. | 0.88 |
| If already started, empiric treatment with ganciclovir will be suspended once there is a negative viral load for CMV. | 0.88 |
| If CMV infection is confirmed (ie, positive viral load), treatment should be continued for 14 days after symptoms are resolved and a negative CMV viral load result is determined by using PCR. | 0.77 |
| 7. Use of blood products | |
| All blood products must be negative for CMV serology, leuko-reduced, and irradiated to eliminate the risk of graft-versus-host disease and CMV infection. | 1.00 |
| Use of blood products should be limited to situations that place the lives of these patients at risk. | 0.83 |

*(Continued)*

**TABLE I**. *(Continued)*

| Intervention | Kappa value |
|---|---|
| 8. Routine laboratory tests | |
| Laboratory tests that should be requested for ALL patients at the time the patient is classified with SCID or probable SCID, when available, are as follows:<br>● lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$/56+, $CD19^+$);<br>● studies of lymphoproliferation with different stimuli (phorbol 12-myristate 13-acetate, PHA, and anti-CD3/CD28);<br>● viral load for CMV and EBV;<br>● Immunoglobulins (IgG, IgM, IgA, and IgE);<br>● TCR diversity studies; and<br>● thymic ultrasonography. | >0.75 |
| T-lymphocyte subsets ($CD45RA^+$ and $CD45RO^+$) should be measured only in the case of lymphocytes present in blood counts or on flow cytometry. | 0.75 |
| Conduct studies to evaluate the TCR diversity in patients with SCID. | 0.75 |
| Radiosensitivity tests should be performed in all patients with microcephaly (under suspicion or a diagnosis of SCID). | 0.82 |
| Radiosensitivity tests should be performed in all patients with microcephaly and a T-B- immunophenotype. | 0.93 |
| Studies to determine maternal graft or previous transfusion graft ($CD3^+CD45RA^+$ and $CD3^+D45RO^+$/karyotype/determination of chimerism by HLA) should be performed only in patients with symptoms of graft-versus-host disease. | 0.75 |
| TREC quantitative analysis should be performed in ALL patients at the time the patient is classified with SCID or probable SCID. | 0.77 |
| Search for mycobacteria should be performed in all patients who have received the BCG vaccine (Ziehl-Neelsen stains, PCR in the corresponding fluids, and staining in biopsy specimens). | 0.82 |
| Biopsy of any obvious skin lesion should be performed (in addition to light microscopy, request stains for fungi and mycobacteria and send tissue to culture for bacteria, fungi, and mycobacteria). | 0.77 |
| Multiorgan functional evaluation (ie, complete blood count with differential, liver function tests, blood chemistry, serum electrolytes, and general urinalysis) should be part of the blood tests requested should be performed for ALL patients at the time the patient is classified with SCID or probable SCID. | 0.87 |
| Save a blood sample on filter paper for all patients with SCID before carrying out any type of transfusion. | 0.82 |
| Save samples of genetic material from both the patient and both parents when possible. | 1.00 |
| Request HLA studies of the patient and immediate family members from the moment the diagnosis is confirmed. | 1.00 |
| Request the viral load for HIV in all patients. | 0.93 |
| 9. Imaging and other studies | |
| Perform chest radiography in all patients (evaluate parenchyma, infiltrates, and bone changes and the presence or absence of thymic shadow). | 0.94 |
| Perform high-resolution lung computed tomographic scans in all patients who present or have presented with respiratory symptoms to determine the presence and/or extent of lung damage. | 0.93 |
| Imaging studies involving ionizing radiation should be minimized in patients with the T-B- immunophenotype (unless radiosensitivity has been ruled out). | 1.00 |
| Perform auditory and visual screening in all patients with SCID. | 0.82 |
| Perform bone marrow aspiration in all patients with SCID and suspicion of reticular dysgenesis. | 0.77 |
| 10. Protocol evaluations | |
| Request early consultation and assessment for specialists as follows:<br>● immunology;<br>● transplantation of hematopoietic progenitor cells;<br>● infectious diseases;<br>● gastroenterology;<br>● nutrition;<br>● psychology;<br>● genetics;<br>● neurology;<br>● rehabilitation;<br>● hematology;<br>● ophthalmology; and<br>● cardiology. | >0.75 |
| Notify and request early assessment of critical care specialists (even when the patient is stable) and establish intrahospital programs that ensure immediate access of patients with SCID to critical care areas, as needed. | 0.87 |
| Notify blood bank directly about admission of patients with suspicion or a diagnosis of SCID to the hospital. | 0.93 |
| Ensure early intervention of social support services in conjunction with the medical team. | 1.00 |
| Always request a postmortem study in all patients with SCID who die. | 0.87 |
| Perform and append the pedigree chart of all patients with SCID, with a minimum of 3 generations. | 1.00 |
| Implement a special data collection sheet for patients with SCID in the clinical file. | 0.87 |

*CMV*, Cytomegalovirus; *IVIG*, intravenous immunoglobulin; *SCIG*, subcutaneous immunoglobulin; *TCR*, T-cell receptor; *TMP/SMX*, trimethoprim-sulfamethoxazole; *TREC*, T-cell receptor DNA excision circle.

identified newborns with SCID had infections before transplantation, among whom 76% were acquired in the period between the confirmation of diagnosis and the performance of HSCT.[21] All the above reflects the complexity of these diseases and the need to establish strategies that improve the prognosis of patients with SCID.

Based on available information, we developed an initial document with diagnostic and therapeutic interventions for patients with SCID to be submitted for evaluation by qualified SCID experts. We divided supportive measures into 10 main domains (Fig 3).

The expert panel was composed of 34 clinicians (30 clinical immunologists and 4 infectious disease specialists) from 6 countries (Argentina, n = 4; Brazil, n = 5; Chile, n = 3; Costa Rica, n = 2; Mexico, n = 19; and Peru, n = 1). We carried out a consensus under the Delphi-modified technique electronically and anonymously by using the Google Forms platform and used Microsoft Excel to register and analyze data. Each of the interventions was analyzed successively until a "consensus" criterion defined by a kappa concordance index among experts of 0.75 or greater or "no consensus" when a kappa value of less than 0.75 was reached. We measured stability of responses between rounds using repeated-measures ANOVA, and we stopped the consensus when the *P* value was greater than .05. Finally, we asked the experts to present their arguments in favor or against the "no consensus" interventions to provide relevant information for clinicians to use this document.

After 3 rounds of consensus (Fig 4),[22] we gathered a final document, which is presented here (Table I), including 123 interventions that achieved consensus and therefore should be implemented in every patient with SCID as soon as the diagnosis is suspected. Another 38 interventions did not reach consensus and are presented in Table E1 in this article's Online Repository at www.jacionline.org.

## DISCUSSION AND RECOMMENDATIONS

The time elapsed from SCID diagnosis until the completion of definitive treatment is essential because appropriate interventions can prevent complications. We found that no evidence-based clinical guidelines exist on the supportive treatment for patients with SCID, and the creation of a document allowing the establishment of sequential guidelines for patients with a suspected or confirmed diagnosis of SCID is a useful tool with a potential beneficial effect on patient care, with the ultimate objective of facilitating curative treatment under better clinical conditions. This consensus will serve to assist in clinical decision making for all physicians who encounter a patient with SCID, and it can also help to establish care policies at the institutional level in different centers by adapting it to the local availability of human and material resources. This consensus also has the advantage of including Latin American experts who in their daily practice face the care of patients with SCID and who know the limitations for their care in our region, allowing the creation of a guide that takes into consideration important practical aspects for its local implementation. Most of the experts in the panel are clinical immunologists, but because the main clinical manifestations of patients with SCID are infections, infectious disease specialists who have contact with these patients are included because they are often a fundamental part of the multidisciplinary management of patients with SCID.

To our knowledge, this is the first document trying to standardize supportive treatment in patients with SCID. The interventions should be implemented from the moment there is suspicion of an SCID diagnosis to reduce the risk of complications. Although consensus is based on the perspectives of Latin American clinicians, this document will also serve as a guide in other parts of the world mainly but not exclusively in places where neonatal screening for SCID is not yet available. In the near future, we are planning to spread the consensus among the most significant possible number of primary care physicians and specialists through the network of immunologists belonging to PID societies (the Latin American Society for Primary Immunodeficiencies, Clinical Immunology Society, and European Society for Immunodeficiencies among others) and through its publication in English and Spanish. We will develop a user-friendly format as an intervention checklist for supportive measures and as an electronic tool to facilitate sharing of information and clinical implementation.

We also present the interventions that did not reach a consensus in Table E1, and it is noteworthy to mention that besides the lack of consensus, these interventions must be revised, and many of them might be considered in particular clinical scenarios. Also, they represent gray areas for clinical care, where more discussion and evidence are needed.

The authors know that SCID management decisions are complex and depend on many factors, including local experience, the patient family's preferences, available resources, and institutional policies. This consensus might help improve outcomes for patients with SCID and represents a guideline that can be adapted and implemented in the different centers facing SCID. It also represents a joint effort of clinicians belonging to the Latin American Society for Primary Immunodeficiencies and the commitment of that society to improve the diagnosis and treatment of patients with PID.

We acknowledge the PID experts who helped us during the first phase of this work and kindly provided input and comments about clinical practices in their centers: Kathleen Sullivan, Luigi Notarangelo, Jordan Orange, Richard Stiehm, Chaim Roifman, Jean-Laurent Casanova, Anders Fasth, and Cristoph Klein. We also want to acknowledge the Latin American Society for Primary Immunodeficiencies and Fundación Mexicana para Niñas y Niños con Inmunodeficiencias Primarias A.C. (FUMENI) for their support in this work.

### REFERENCES

1. Picard C, Bobby Gaspar H, Al-Herz W, Boufisha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol 2018; 38:96-128.
2. Fischer A, Notarangelo LD, Nelen B, Cavazzana M, Puck JM. Severe combined immunodeficiencies and related disorders. Nat Rev Dis Primers 2015;1:15061.
3. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. JAMA 2014;312:729-38.
4. McWilliams L, Railey MD, Buckley R. Positive family history, infection, low absolute lymphocyte count (ALC), and absent thymic shadow: diagnostic clues for all molecular forms of severe combined immunodeficiency. J Allergy Clin Immunol Pract 2015;3:585-91.
5. Puck J. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia. Immunol Rev 2019;287:241-52.
6. Kwan A, Puck J. History and current status of newborn screening for severe combined immunodeficiency. Semin Perinatol 2015;39:194-205.
7. Gaspar HB, Qasim W, Davies EG, Rao K, Amrolia PJ, Veys P. How I treat severe combined immunodeficiency. Blood 2013;122:3749-58.
8. Chinn IK, Shearer WT. Severe combined immunodeficiency disorders. Immunol Allergy Clin North Am 2015;35:671-94.

9. Rivers L, Gaspar HB. Severe combined immunodeficiency: recent developments and guidance on clinical management. Arch Dis Child 2015;100:667-72.
10. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med 2014;371:434-46.
11. Folloni J, Nichele S, Daudt L, Tavares R, Seber A, Kerbauy F, et al. Transplantation of hematopoietic stem cells for primary immunodeficiencies in Brazil: challenges in treating rare diseases in developing countries. J Clin Immunol 2018;38:917-26.
12. Chan A, Scalchunes C, Boyle M, Puck J. Early vs delayed diagnosis of severe combined immunodeficiency: a family perspective survey. Clin Immunol 2011;138:3-8.
13. Nichols S, Krance R, Hanson IC, Mamlok R, Roifman C, Shearer W. Early versus delayed diagnosis of SCID: triumph versus tragedy. Clin Immunol 2011;139:360-2.
14. Gardulf A, Winiarski J, Thorin M, Arnlind MH, von Döbeln U, Hammarström L. Costs associated with treatment of severe combined immunodeficiency (SCID) —rationale for newborn screening in Sweden. J Allergy Clin Immunol 2017; 139:1713-6.
15. Dvorak CC, Cowan MJ, Logan BR, Notarangelo LD, Griffith LM, Puck JM, et al. The natural history of children with severe combined immunodeficiency: baseline features of the first fifty patients of the primary immune deficiency treatment consortium prospective study 6901. J Clin Immunol 2013;33:1156-64.
16. Espinosa-Rosales FJ, Condino-Neto A, Franco JL, Sorensen RU. Into action: improving access to optimum care for all primary immunodeficiency patients. J Clin Immunol 2016;36:415-7.
17. Available at: http://www.bcgatlas.org/. Accessed November 2018.
18. Marciano BE, Huang CY, Joshi G, Rezaei N, Carvalho BC, Allwood Z, et al. BCG vaccination in SCID patients: complications, risks and vaccination policies. J Allergy Clin Immunol 2014;133:1134-41.
19. Griffith L, Cowan M, Notarangelo L, Puck J, Buckley R, Candotti F, et al. Improving cellular therapy for primary immune deficiency diseases: Recognition, diagnosis, and management. J Allergy Clin Immunol 2009;124:1152-60.
20. Dorsey M, Dvorak C, Cowan M, Puck J. Treatment of infants identified as having severe combined immunodeficiency by means of newborn screening. J Allergy Clin Immunol 2017;139:733-42.
21. Abstract presented at 2018 CIS Annual Meeting: Immune Deficiency & Dysregulation North American Conference. Abstract #454131 by Heimall J, Wright N, Miller H, et al. Diagnosis and pre-transplant management of SCID patients in the era of newborn screening: a survey of practices in the Primary Immune Deficiency Consortium. J Clin Immunol 2018;38:330-44.
22. Trevelyan E, Robinson N. Delphi methodology in health research: how to do it? Eur J Integr Med 2015;7:423-8.