Review

Severe Combined Immunodeficiency. Microorganisms and Management

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Review

Severe Combined Immunodeficiency. Microorganisms and Management

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Abstract: Severe combined immunodeficiency (SCID) is a primary inherited immunodeficiency that could be fatal, usually due to opportunistic infections caused by bacteria, viruses, fungi, and protozoa if left untreated. Opportunistic infections are the most common presentation of SCID these include viral, fungal, or intracellular bacteria, and infection should prompt immunological investigation. This review aimed to provide a comprehensive approach to the microrganisms associated with severe combined immunodeficiency (SCID) and its management. The authors described SCID as a syndrome and summarized the different microorganisms that affect children and how they are managed.

Keywords: microorganisms; severe combined immunodeficiency; infectious diseases; management; Antibiotics; antifungals; HST

1. Introduction

The innate immune system is the human body's first line of defense against microorganisms [1–3]. Along with the adaptive immune system, they form both the nonspecific and specific systems involved in preventing and destroying microorganisms [4]. There are circumstances in which the immune system fails to function properly after birth; referred to as acquired immunodeficiency. There are rare instances when the immune system fails to mature at birth, this can result in a primary immunodeficiency disease (PID) [5]. Of all the many Primary Immunodeficiency Diseases described, Severe Combined Immunodeficiency Disease (SCID) is the most severe [6]. Affected infants have a severely weakened immune system, leading to an inability to effectively defend against infections, even the mildest microorganisms [1,2]. In this review, the authors described SCID along with the different microorganisms that affect patients, and how they are managed.

SCID or "the bubble boy disease" [7] is a rare disorder in which multiple genes are mutated, which are involved in the development and function of various immune cells. This condition affects both the adaptive and innate immune systems, often resulting in fatal complications within the first two years of life unless treated with HSCT (hematopoietic stem cell therapy), gene therapy, or bone marrow transplant [8,9].In the United States SCID was added to the Recommended Uniform Screening Panel (RUSP) in 2010 and newborns are now screened for this highly fatal disease [10].

More than a dozen genes are involved in the pathogenesis of SCID [11]. SCID is most commonly inherited in an X-linked recessive or autosomal recessive manner [1,9,12]. Although the diagnosis of SCID is usually made by flow cytometry, genetic testing is often needed for genetic counseling and prognostication [11]. However, early diagnosis and management could be delayed or even missed because although SCID is often caused by many genetic factors, as much as 80% of cases of SCID are sporadic, with no known family history of congenital immunodeficiencies [13,14].

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SCID can be defined as typical, atypical/leaky, Variant, or Omenn Syndrome. [15–17]. According to the European Society for Immunodeficiencies (ESID), typical SCID is defined as a patient with: (1) mutation(s) in a gene associated with a typical SCID phenotype; or, (2) presentation with severe or opportunistic infections, persistent diarrhea and failure to thrive, in the presence of low (300/μl) or absent CD3+ or CD4+ or CD8+ T cells, reduced naive CD4+ (CD3+CD4+CD45RA+) and/or CD8+ (CD3+CD8+CD45RA+) T cells, elevated γδ T cells, absence of proliferative responses to mitogens, defined as proliferative response to phytohemagglutinin (PHA) lower than 10% of the control subject; or (3) T cells of maternal origin present. The most common types Typical SCID often include X-linked SCID, Adenosine Deaminase Deficiency SCID, RAG-1/RAG-2, and IL7R SCID [18].

Atypical SCID is characterized by CD3+ > 300 cells/μl and reduced, but detectable, proliferative response to PHA (> 10 < 30% of the control) [18]. In Variant SCID no known gene defect and a persistence of 300–1,500 T cells/L that have impaired function [19]. Atypical SCID can be referred to as "leaky SCID" [20].

2. CID classification and features

2.1. X-linked SCID

40% of SCID cases are X-linked and represent the most common form of SCID [32]. It primarily affects males with mutations in the IL2R gene. This receptor protein is essential for thymic Treg development, regulation of T-reg homeostasis, and suppression. Without these cells, infection occurs frequently [12].

2.2. Adenosine Deaminase Deficiency

This is the second most common form of SCID, accounting for 15% of all cases [21]. In this particular disorder, the adenosine deaminase (ADA) enzyme is deficient, which mediates the conversion of adenosine into inosine and subsequently deoxyadenosine into deoxyinosine [22,23], leading to an intracellular buildup of deoxyadenosine it's toxic metabolites eg. dATP which is particularly toxic to lymphoid precursors. Consequently ADA deficiency is characterized by lymphopenia. Lack of ADA enzyme leads to neurological issues such as cognitive impairment, hearing and visual impairment, low muscle tone, and movement disorders [2,24].

2.3. RAG-1 and RAG-2 deficiency SCID

This is the third most common form of SCID, as it presents with mutations in RAG-1 and RAG-2 [9,25]. Recombination activation genes (RAGs) are involved in working as a multi-subunit complex to cleave dsDNA molecules between the antigen receptor coding segment and flanking (RSS) recombination signal sequence, as they initiate V(D)J recombination shuffling DNA proteins, which are then expressed on the surface coding for specific antigens [26]. Without these enzymes T-cell receptor development fails, resulting in abnormal T cells, leading to the many infectious complications [2].

2.4. IL-7R deficiency SCID

Interlukin-7 (IL7) and hepatocyte growth factor (HGF) form a heterodimer that functions as a pre-pro–B cell growth stimulating factor [27–29]. It has also been found to be one of the co-factors in the V(D)J rearrangement of the T cell receptor beta (TCRB) for T cell development. This is the fourth most common type of SCID; infants with such a disorder have B cells but few or no T cells; however, because of this lack of T lymphocytes, B lymphocytes would not be able to undergo somatic hypermutation and class switching [29,30].

2.5. LEAKY SCID

Leaky SCID occurs when a person has symptoms similar to typical SCID, but with T cell counts that are not low enough to qualify as typical SCID [31,32]. It is called "leaky" because some T cells

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"leak" through and make a person's blood cell count appear normal [31]. However, T cell production does not help a person fight the infection. In leaky SCID, T cells become overactivated and cause the body to attack itself. Leaky SCID can result in itchy skin, red skin, hair loss, enlarged liver and spleen, swollen lymph nodes, and diarrhea. It can also cause anemia and thyroid problems [23]. A person with leaky SCID might have a different type of gene mutation in the same gene as a person with typical SCID, such as the RAG-1 and RAG-2 genes. Sometimes, children with leaky SCID are not diagnosed until they are older and even into adulthood [33]. In Leaky SCID the defect in a gene allows for a normal, or even elevated, T cell count, which harms the immune system. Omenn Syndrome (OS) is characterized by defects in genes that cause high numbers of non-working T cells, and a lack of B cells resulting in a faulty immune system [17].

2.6. Omenn Syndrome

Omenn Syndrome can present on its own or can be caused by SCID. Genetic mutations that can cause Omenn Syndrome include RAG-1, RAG-2, adenosine deaminase deficiency (ADA), Artemis and DNA ligase 4, all of which are infectious diseases. Infants with Omenn Syndrome suffer from a lack of an immune system as well as autoimmune activity in which the body attacks itself. Symptoms include red and peeling skin, hair loss, enlarged lymph nodes, and enlarged liver and spleen [22]. Omenn syndrome was reported as a distinct form of SCID. Unlike typical SCID, patients with OS have enlarged lymphoid tissue, severe erythroderma, increased IgE levels, and eosinophilia [34]. Clinically, Omenn syndrome is not a 'leaky SCID' and is an extremely serious T+ or T++ SCID [35]

2.7. CD3 Complex Component Deficiency SCID

The CD3 complex is known as a T cell pan marker. The CD3 complex plays an essential role in cell signaling or cell communication down to the nucleus, which is initiated by antigen binding. This is because of the multiple alpha, beta, gamma, delta, epsilon, and zeta transmembrane chains that cause and effect downstream cell signaling to the nucleus, consequently allowing for cytokine formation and release. There are three subtypes: CD3D, CD3E, and CD247/CD3Z. This type of disorder is caused by mutations in these CD3 encoding genes which subsequently results in damage to T cells [36].

2.8. JAK3 Deficiency SCID

The Janus kinase 3 gene works synonymously with IL2RG (interleukin 2 receptor gene) for interleukin 2, which promotes the growth of T lymphocytes (helper, cytotoxic, and regulatory) and natural killer cells. Due to this deficiency patient with JAK3 deficiency SCID show very similar attributes of patients presenting with lymphopenia. However, since JAK3 is not located on the X chromosome, both male and female infants can be affected [37,38].

3. Microorganisms affecting SCID patients

3.1. Viruses

Opportunistic Viral Infections eg. Cytomegalovirus, Epstein–Barr virus, Adenovirus, Enterovirus, Herpes Simplex Virus and Parainfluenza virus can cause severe disseminated infections in SCID patients, which can be fatal if left untreated or undiagnosed [39–41]. Cytomegalovirus (CMV) has been found to be excreted in breastmilk and breastfeeding should not be advised for SCID patients, unless the mother is found to be CMV antibody-negative [11].

Infection with Adenovirus can manifest as ocular, respiratory, gastrointestinal, or hepatic diseases in immunocompetent patients and is often mild and self-limiting [42]. However, in patients with SCID, adenovirus may produce severe and prolonged viral Pneumonia, Bronchiolitis, Hepatitis, or Gastroenteritis, with a potentially fatal outcome [43].

Rotavirus is the leading cause of severe gastroenteritis in children, and vaccination is the mainstay of prophylaxis [44]. However, the live rotavirus vaccine has been found to cause severe

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diarrhea in children with SCID, and should therefore be avoided [45]. Epstein–Barr virus infections affect over 95% of the human population at some point but are usually asymptomatic [46]. Symptomatic infections in adolescents may result in infectious mononucleosis characterized by fever, sore throat, splenomegaly, and lymphadenopathy. The virus typically attacks B cells;-therefore, SCID patients with impaired or absent B cells are at an increased risk of EBV associated lymphomas as a result of persistent viremia and lymphoproliferation [47].

ParvoVirus-B19 is a common infection in rapidly dividing erythroid progenitor cells, with children being the main source of infection [48].Immunocompetent host infections can be asymptomatic or symptomatic, and include erythema infectiosum, arthropathy, anemia, thrombocytopenia, hepatitis, and myocarditis. In immunocompromised hosts, infection with Parvovirus B-19, chronic red cell aplasia, Acute Lymphoblastic Leukemia (ALL), and Virus-Associated Hemophagocytic Syndrome (VAHS) [49].

Varicella-zoster virus (VZV) infection occurs primarily via respiratory inoculation and establishes lifetime latency in the sensory ganglia of immunocompetent patients [50]. Immunocompromised patients are at an increased risk of complications, such as reactivation, Herpes zoster, retinal necrosis, and even death [50]. Worldwide vaccination via live VZV vaccines has prevented many of the complications of VZV infection [51], however, vaccination in SCID patients has been associated with disseminated infection [52] including vaccine-associated pneumonia [53] and should therefore be avoided.

3.2. Bacteria

Recurrent sinopulmonary infections are characteristic of primary immunodeficiencies such as SCID, and can result in severe complications. Lung abscess, empyema, and pneumatocele. The bacterial causes of pneumonia include Staphylococcus aureus, Pseudomonas spp., Mycobacterium bovis, and other atypical mycobacteria [54]. On clinical imaging, an important diagnostic clue in acute pulmonary infections in children with primary immunodeficiencies as they often lack a thymic shadow [55].

Clinical manifestations of SCID include gastrointestinal infections, chronic diarrhea, and failure to thrive. Gram-positive bacteria such as Staphylococcus aureus and gram-negative bacteria such as Klebsiella pneumoniae, Pseudomonas aeruginosa, Burkholderia, and Chryseobacterium [56]. SCID patients who lack immunoglobulins are at constant risk of recurrent infections with encapsulated bacteria [57].

Omenn syndrome is an autosomal recessive form of SCID that is usually T-B-NK+ and is highly fatal owing to recurrent opportunistic infections [58,59]. Skin sepsis is observed in patients with Omenn syndrome. Skin sepsis in Omenn syndrome can occur due to colonization by bacteria such as Staphylococcus Aureus, Streptococcus Pyogenes, Enterococcus, and gram-negative bacteria, such as Pseudomonas [58,60,61]. Cutaneous manifestations of bacterial infections include recurrent and life-threatening skin abscesses, folliculitis, impetigo, and furunculosis [62]. Survival rarely exceeds several months after birth in the absence of curative treatment.

3.3. Fungi

Invasive fungal infections (IFI) rarely occur in immunocompetent individuals and are more likely to occur in patients with primary immunodeficiencies. –Opportunistic fungal infections seen in SCID are similar to those in patients with AIDS, and are usually caused by opportunistic fungi. Pneumocystis carinii, Histoplasma capsulatum, and Cryptococcus Neoformins [63]. Pneumocystis carinii pneumonia is the most common respiratory infection in SCID, and is often co-infected with a respiratory virus [60]. Patients with SCID may be offered prophylactic treatment against Pneumocystis carinii to prevent fatal complications.

Patients with SCID are at increased risk of disseminated fungal infections, with invasive Candida albicans and Aspergillus being the most prominent microorganisms [64]. Other rare microorganisms implicated in SCID include Acremonium and Pichia [65,66]. Colonization of the skin, oropharynx, and gut by Candida albicans, typically manifests as persistent oral thrush, Pneumonia

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or Meningitis [65]. Hematopoietic stem cell transplantation is the definitive treatment for SCID, and fluconazole (3 mg/kg OD) is administered as prophylaxis against candidiasis and is generally tolerated [67].

Invasive aspergillosis (IA) is a life-threatening condition in immunocompromised children. Infection is typically acquired in the community or via nosocomial infections during hospital construction, renovation, and air--conditioning systems [68]. Bronchopneumonia is the most common presentation of infection with Aspergillosis in SCID, and other primary immunodeficiencies [69]. Other clinical manifestations of invasive aspergillosis include pleural effusion, pulmonary infarction, pulmonary thrombosis, and pleural effusion [70,71].

Cryptococcosis is a subacute or chronic systemic mycosis caused by-Cryptococcus neoformans [72,73]. Cryptococcus neoformans is an opportunistic fungus that infects immunocompromised individuals. The respiratory tract is the primary portal of entry and has been found to be fatal because of overwhelming pneumonia in patients with SCID[72]. Cryptococcus neoformans was found in the skin lesions of a patient with SCID who presented with a maculopapular rash along with lobar consolidation. The treatment was refractory to medical management, but responsive to hematopoietic stem cell therapy [74].

3.4. Parasites

Parasitic infections are the dominant cause of gastrointestinal disease in patients with SCID. Protozoans eg. Giardia lamblia and Cryptosporidium spp. are the most common parasites affecting patients with SCID. Other implicated parasites included Schistosoma species, Blastocystis hominis, Fasciola species, and Trichostrongylus species. [75]. The gastrointestinal tract is the largest lymphoid organ of the body [76]. GI manifestations are the second most common manifestations of PID after pulmonary disease [77]. Gastrointestinal disorders, such as chronic diarrhea, malabsorption, and abdominal pain, are seen in as many as 50% of patients with primary immunodeficiencies [78]. Giardia lamblia is a zoonotic protozoan parasite typically found in the small intestine of humans and various animals. Infections can be asymptomatic to mild diarrhea in immunocompetent patients or severe and chronic diarrhea and malabsorption in immunocompromised patients[79–81].

Cryptosporidium can cause severe and chronic enteropathy by releasing proinflammatory cytokines such as interleukin-8 (IL-8) in intestinal epithelial cells in patients with primary immunodeficiencies [82,83]. Disseminated cryptosporidiosis can lead to biliary tract disease, pancreatitis, pulmonary disease, and stunted growth in patients with SCID[82]. Disseminated cryptosporidiosis leading to overwhelming sepsis and death has been observed in patients with SCID[84]. Although the International Agency for Research on Cancer (IARC) has not considered protozoans as carcinogens for humans [85], Cryptosporidium has been associated with colonic adenocarcinoma in SCID mice [86]; therefore, this possible complication should be made aware and infection in SCID patients treated promptly.

4. Management of SCID

4.1. Hematopoietic Sem Cell Therapy (HSCT).

Hematopoietic stem cell transplantation (HSCT) is the recommended treatment for SCID as it is potentially curative [27,87]. Although lifesaving, HSCT only partially restores immunity as recovery is a dynamic process [88]. SCID patients who had transplants before the age of 3.5 months had the highest survival rates [89]. Therefore, the best outcomes for SCID newborns are achieved through early transplantation [28]. PEF-ADA, an enzyme replacement medication, has been used to treat SCID in children with ADA deficiency with modest effectiveness [2].

Infants diagnosed with SCID are often treated with hematopoietic stem cell therapy (HSCT), which is also known as bone marrow transplantation. This is, in fact, no easy medical task to perform, as this takes time and a lot of preparation to get done [1,2]. After a suitable donor is identified, hematopoietic stem cells are drawn and infused into infants with SCID. Hematopoietic stem cells are immature, and they then develop into red blood cells, white blood cells, and platelets. These cells

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then multiply over time, where immunity is consequently achieved, which is proven as the survival rate for such a procedure ranges from 70-95% [90,91].

Factors that affect and influence the outcome of this transplantation method include:

1.Age and clinical condition at the time of diagnosis, as this method is best performed at an earlier time (first few months of life 1-4 months). This time will disallow and mitigate the chances of opportunistic infections and failure to thrive [28].

2. Hematopoietic stem cell donor, it is very unlikely that the affected infant possesses HLA-matched siblings; therefore locating HLA-compatible volunteers is time consuming, giving way to new and worsening infections or disorders.

3. Pre-treatment Conditioning. Prior to HSCT, children may be subjected to conditioning with such chemotherapy or to equip the child's body to receive new stem cells. Patients undergoing this treatment experience frequent defective B cell reconstitution, requiring lifelong immunoglobulin replacement therapy [1,2].

4.2. Gene Therapy

Gene therapy can be a successful treatment, particularly for X-linked SCID [92,93]. In this process, stem cells are drawn from the patient's bone marrow, the normal gene is inserted using a carrier known as a vector, and the repaired cells are returned to the patient [1]. Early attempts to use gene therapy to treat X-linked SCID were successful in restoring T-cell function in children [12], but approximately 25% of the children developed leukemia two to five years after [94]. The vectors employed in using gene therapy were proposed to inappropriately activate genes that regulate cell development, resulting in leukemia [25]. Modern gene therapy techniques often employ modified vectors that are more efficient and associated with less potential complications [95].

Artemis SCID gene therapy is now available for infants diagnosed with X-linked SCID. In this procedure the hematopoietic stem cells containing the mutated gene is extracted from the bone marrow or blood, this extracted gene is now sent to the lab where "correct" copies are made. This copy is now infused into a deactivated virus, which efficiently penetrates hematopoietic stem cells. After the virus penetrates the cell, the normal HSC of the patient mixes with the new copy and is allowed to be a part of hematopoietic stem cells. This corrected form of the cell is now allowed to be divided and placed in a cryogenic state. The infant then receives conditioning whether it is in [2,96] the form of chemotherapy or immunosuppressive agents, where the sample is then inserted via a simple IV infusion where corrected hematopoietic stem cells are able to spread throughout the body[28]

4.3. Enzyme replacement therapy (ERT)

Patients with adenosine deaminase deficiency (ADA) lack the vital enzyme adenosine deaminase; therefore, infants receive a weekly intramuscular injection of Revcovi containing adenosine deaminase. As simple and pain-free as this procedure sounds, it does not cure or permanently fix the case SCID, but merely as a temporary step before a much more permanent procedure such as HSCT or GENE THERAPY[1]. It has also been proven that using enzyme replacement therapy before stem cell therapy can actually enhance and increase the number of T lymphocytes, which results in a lower occurrence of infection until a definitive method is used [97,98].

4.4. Treatment of infections

While definitive management is SCT, the use of reverse isolation, that is,-keeping the patient in a protected environment, avoiding live vaccines, therapeutic use of immunoglobulins, an early prophylactic use of antimicrobials can help infections.[99]. The early use of prophylactic antibiotic therapy is quite widespread in the management of SCID, to reduce the frequency and severity of infections, especially bacterial sinopulmonary infections, while prophylactic antiviral and antifungal therapy is warranted in SCID[100]. Prophylaxis with TMP-SMX, while awaiting definitive SCT, is aimed at addressing PCP. Fluconazole is often administered to prevent mucocutaneous candidiasis

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and acyclovir to prevent Herpes Simplex Virus infection. Antifungals have been used to treat invasive pulmonary aspergillosis in patients with SCID. New antifungal agents have been developed over the last two decades, including lipid formulations of amphotericin B (liposomal amphotericin B, amphotericin B lipid complex), new azoles (voriconazole, posaconazole, and isavuconazole), and echinocandins (caspofungin, micafungin, and anidulafungin) [22].

5. Examples of antibiotic prophylaxis regimens used in patients with immunodeficiency

Table 1. The following table adapted from Segundo and Condino-Neto [100,101] via an open access resources illustrates treatment options for infections affecting SCID patients.

Prevention intention	Preferential regimen	Alternative regimen
Pneumocystis jirovecii	Sulfametoxazol-trimetoprim (SXT-TMP): Infants> 4 weeks of age and children: 5 mg/kg/day divided into two doses 3x/week (Based on TMP, maximum 160 mg per day) Adults and adolescents with normal kidney function: based on TMP 80 mg/day or 160 mg daily or 160 mg 3x/week	Dapsone: Infants and children: 2 mg/kg/day daily 1x/day (maximum: 100 mg/day) Adults: 100 mg 1x/day or 50 mg 2x/day Pentamidine: Children <5 years: 9 mg/kg (maximum: 300 mg/dose) nebulized inhalation every 4weeks Children> 5 years, adolescents and adults: 300 mg nebulized inhalation every 4 weeks
Staphylococcus spp, Gram-negative spp	SXT-TMP Infants> 4 weeks of age and children: 5 mg/kg/day divided into 2 daily doses (Based on TMP, maximum 160 mg per day) Adults and adolescents: based on TMP 160 mg daily	Amoxicillin: Children: 10---20 mg/kg per day, single dose or divided into 2x (maximum: 875 mg/day) Adolescents and adults: 875 mg Ciprofloxacin: Children: 10 mg/kg/dose 2x/day (maximum: 500 mg) Adults: 500 mg Amoxicillin and clavulanate: Children: 20 mg/kg per day single dose or divided into 2x (maximum: 875 mg/day based on amoxicillin) Adolescents and adults: 875 mg (based on amoxicillin)

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Mycoplasma spp, Streptococcus spp	Azithromycin Children: 5---10 mg/kg/oral dose 3x/week (maximum: 250 mg) Adolescents and adults: 250 mg oral dose 3x/week	
Atypical mycobacteriosis	Azithromycin Children: 20 mg/kg/oral dose 1x/week (maximum dose of 1200 mg/week; can be given up to 600 mg 2x/without causing nausea at high doses) Adolescents and adults: 1200 mg 1x/week (or 600 2x/week in case of nausea)	
Aspergillus spp	Itraconazole: Children: 5 mg/kg/day orally (maximum: 200 mg) Adolescents and adults: 200 mg oral daily	Voriconazole: ≤ 50 kg: 8 mg/kg/oral dose 2x/day (maximum per dose: 350 mg) > 50 kg: 4 mg/kg/oral dose 2x/day (maximum per dose: 200 mg
Candida spp	Fluconazole: Children: 6 mg/kg orally daily (maximum: 400 mg) Adolescents and adults: 400 mg orally daily	
HSV/VZV	Acyclovir: Children <40 kg: 600 mg oral dose 4x/day Children> 40 kg: 800 mg oral dose 4 x/day Adults: 800 mg oral dose 2x/day	
CMV	Valganciclovir: Children 1 month to 16 years: oral dose (mg) = 7 × body surface area × creatinine clearance Adolescents ≥17 years and adults with normal renal function: 900 mg oral dose 1x/day	

6. Conclusion

This review could serve as a foundation for further mechanistic and clinical studies in understanding the disease pathogenesis as well as the development of effective treatment strategies for patients with SCID.

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