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ORIGINAL ARTICLE

Survey of Infection Control Precautions for Patients with Severe Combined Immune Deficiency

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Abstract

Severe combined immune deficiency (SCID) is caused by an array of genetic disorders resulting in a diminished adaptive immune system due to impaired T lymphocytes. In these patients, active infection at the time of hematopoietic transplantation has been shown to increase morbidity and mortality. To prevent transmission of infections in SCID patients, standardized infection control precautions should be implemented. An online survey regarding SCID-specific protocols was distributed through several immunodeficiency organizations. Seventy-three responses were obtained, with the majority (55%) of responses from the USA, 15% from Canada, and the remainder from 12 other countries. Only 50% of respondents had a SCID-specific infection control protocol at their center, and while a majority of these centers had training for physicians, a small minority had training for other healthcare workers such as nursing and housekeeping staff. Significant variability of infection control practices, such as in-patient precautions, required personal protective equipment (PPE), diet restrictions, visitor precautions and discharge criteria, was found between different treatment centers. There is a paucity of evidence-based data regarding the safest environment to prevent infection in SCID patients. Institutional protocols may have significant impact on infection risk, survival, family well-being, child development and cost of care. From these results, it is evident that further multi-center research is required to determine the safest and healthiest environment for these children, so that evidence-based infection control protocols for patients with SCID can be developed.

Keywords Severe combined immune deficiency · infection control · healthcare-associated infections · transmission

Introduction

Severe combined immune deficiency (SCID) is caused by an array of genetic disorders occurring in approximately 1/58 000 live births, resulting in a diminished adaptive immune system [1]. SCID is diagnosed with newborn screening or presents within the first few months of life with infections due to extremely impaired or absent production and function of T lymphocytes [1, 2]. Consequently, these patients require extensive treatment, and are vulnerable to opportunistic and healthcare associated infections [1–4]. As stated by Heimall et al., "Active infection poses the greatest threat to survival for SCID patients [5]". With the advent of newborn screening in many jurisdictions, there is an opportunity to prevent infection in these infants, and consequently improve morbidity and mortality. For the many countries in which screening is not available, infection control protocols are still important to prevent further infections prior to curative therapy, even though patients may already be infected with one or more organisms.

Currently, there is very little literature on SCID-specific isolation protocols and our experience has been that protocols vary significantly between centers. While there is research regarding infection control protocols for other vulnerable populations, such as hematopoietic stem cell transplant (HSCT) and oncology patients, there is no such research for SCID patients [6–10].

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The main objective of this study was to survey SCID treatment centers internationally in order to collect data on their current infection prevention policies for patients with SCID. This study was designed with the intention of initiating multicenter evidence-based research for infection control practices for patients with severe immune compromise.

Material/Methods

A survey was developed with pediatric hematology/immunology and infectious disease specialists regarding infection control protocols, utilizing Select Survey.NET software (ClassApps, Overland Park, KS). The survey consisted of 45 questions pertaining to SCID treatment center demographics, in-patient facilities, isolation precautions, required personal protective equipment (PPE) for staff, visitors, and patients, as well as diet restrictions, visitor precautions, and discharge criteria (Appendix I, supplemental material). This online survey link was disseminated in 2014 via email by Immunodeficiency Canada and the Clinical Immunology Society, to active members. Note the survey was disseminated prior to widespread availability of newborn screening for SCID in the USA. Descriptive data were analyzed using Microsoft® Excel (2008). This research study was approved by our local Conjoint Health Research and Ethics Board. Informed consent was implied if the member took part in the survey.

Results

Demographics

Seventy-three responses were obtained, with a response rate estimated to be 8% based on organization membership. The majority of responses were from the USA (55%), 15% from Canada, and the remainder from 12 other countries (Australia, Brazil, Bulgaria, Costa Rica, France, Mexico, New Zealand, Portugal, Serbia, Slovenia, Spain, Sweden) (Fig. S1). The main respondents were physicians who worked with HSCT patients (45%) and HSCT specialists (44%); fewer responses were from nurse practitioners (NPs) (6%) and others (pediatrician, allergy/immunology fellow, data manager) (5%). The vast majority of respondents' centers treated between 1 and 5 SCID patients per year (77%), with the remaining treating 6–10 patients.

SCID-Specific Infection Control Protocols

Fifty percent of respondents had a written SCID-specific infection control protocol at their center, and of those, only 30% had a systematic and objective way to monitor and record compliance. The majority of respondents who had written protocols reported that their physicians received training on these protocols (79%), but less than half of centers reported NPs, nurses, allied health professionals, and housekeeping staff received training (Fig. 1).

In-Patient Facilities

Fifty-nine percent of SCID patients were admitted to HSCT/hematology/oncology wards (Fig. 2a), and 89% to a private room. The most common type of air-flow/filter system in the rooms was high-efficiency particulate air (HEPA) filter (59%) and positive pressure air-flow (48%), with 20% reporting laminar air flow (LAF) and 25% of centers reporting no special air-flow/filter system. The majority (54%) of SCID treatment centers had anterooms. Routine environmental microbe screening is illustrated in Fig. 2b.

While 61% of reporting SCID treatment centers allowed washable toys in SCID patient rooms, 4% did not allow any toys or books/magazines in patient rooms (Fig. 2c). SCID patient linens were sterilized in 24% of facilities.

Staff Precautions

The majority of staff are routinely required to don PPE prior to entering the room of a SCID patient with no known contagious infection/antibiotic-resistant organism, with 16% of centers reporting staff are not required to wear any of the specified PPE (Fig. 3a).

In regard to vaccination status, 48% of SCID treatment centers require staff to have vaccines up to date, including the annual injectable, inactivated influenza vaccine (IIV), and 47% were encouraged but did not require staff to have vaccines up to date; the remaining centers had no policy (2%) or did not know their policy (3%).

Caregiver Precautions

Caregivers were defined as parents/guardians or anyone (non-staff) involved in the direct care of the patient. The majority of SCID treatment centers allowed a maximum of 2 caregivers in the room of a SCID patient (40%) (Fig. 3b). Most centers (54%) require caregivers to wear PPE prior to entering the room of a non-infectious SCID patient; however 46% do not (Fig. 3a). Fifteen percent of centers do not allow caregivers to have skin to skin contact with SCID patients.

The majority (64%) of centers reported that they encouraged their SCID patient caregivers to have their vaccines up to date, including the annual IIV, while 18% of reporting centers required caregivers to have their vaccines up to date, including the IIV. Only 18% of centers discouraged caregivers from getting the live attenuated influenza vaccine and 10% of centers reported none of the above vaccine policies.

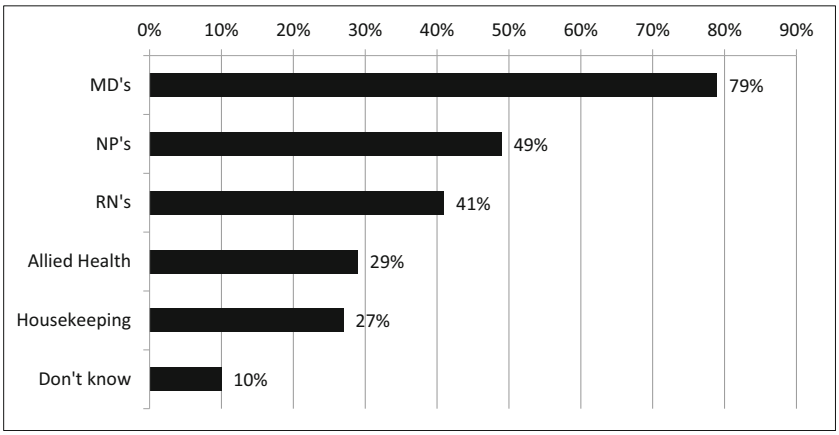

Fig. 1 Percentage of SCID centers that provided training to hospital staff on SCID-specific infection control protocols. MD, medical doctor; NP, nurse practitioner; RN, registered nurse

Visitor Precautions

Visitors were defined as anyone other than hospital staff or caregivers. The majority of SCID treatment centers allowed visitors (62%), including grandparents, siblings, other relatives, and friends (Fig. 3b). Many centers reported no screening tool to assess the infectious status of a visitor (47%), while 39% did have a visitor screening tool, and 14% did not know. The majority of centers (74%) require visitors to wear some form of PPE prior to entering a SCID patient room where there is no known contagious infection or antibiotic-resistant organism (Fig. 3a). With regard to vaccination status, 44% reported visitors are encouraged to have vaccines up to date, including the annual IIV, while 12% reported this was required of visitors.

Patient Hygiene

Most responding SCID treatment centers recommend that their SCID patients bathe daily (33%), and 29% of centers have no frequency recommendations. While most centers do not have specific restrictions on bathing, 17% require in-bed bathing (sponge/cloth baths) and 9% require showers only. Sixty percent do not allow the use of sinks in their rooms, and 6% do not allow the use of in-room sinks, showers, or bath tubs. The majority of centers use normal hospital water for bathing (66%) and regular soap (30%). Oral hygiene practices varied: 28% prefer mouth swabbing/sponging, 26% antiseptic mouth wash, and 13% use a sterile water mouth rinse.

Dietary Restrictions

Various breastfeeding restrictions exist among reporting SCID centers, with the most common being restricting breastfeeding to cytomegalovirus (CMV) seronegative mothers (48%), and mothers without upper respiratory tract infection (URTI) or gastro-intestinal infection (33%) (Fig. 4). The majority of centers reported use of a low microbial diet or HSCT diet (46%), whereas 25% of centers do not have any dietary restrictions or precautions. Most centers use standard infant formula (65%).

Pre-HSCT Management

With regard to prophylaxis for infections for SCID patients pre-HSCT, the majority of centers report use of intravenous or subcutaneous immunoglobulin replacement (88%) and *Pneumocystis jirovecii* pneumonia (PJP) standard first-line prophylaxis (trimethoprim-sulfamethoxazole, pentamidine, dapsone) (82%). Further, 70% of centers report use of a prophylactic antifungal (standard first line, e.g., fluconazole, itraconazole, micafungin), 40% report using prophylactic antivirals (standard first line, e.g., acyclovir, ganciclovir) and 26% report using a prophylactic antibacterial (standard first line, e.g., amoxicillin or penicillin, fluoroquinolone) regimen.

The majority of SCID treatment centers do viral surveillance, using blood PCR, for CMV (85%), Epstein Barr Virus (EBV) (79%), and adenovirus (55%) (Fig. 5).

Discharge Management and Criteria

For discharge of a clinically well SCID infant prior to HSCT, the majority of centers have some restrictions to discharge, 10% had no restrictions, and 28% do not discharge clinically well SCID infants prior to HSCT (Fig. 6). After HSCT, the majority (70%) of SCID treatment centers discharge SCID patients as soon as the patient has engrafted and all medical care can be handled within the home, regardless of the number of days post-HSCT.

Discussion

Overall, this survey of infection control precautions for SCID patients shows large variation and lack of consensus. This may be due to a paucity of evidence as to what is efficacious. Most recommendations for similar populations, such as HSCT patients, are based on expert opinion or consensus guidelines created by specialists in the field, such as the Center for Disease Control (CDC) HSCT guidelines, and not based on high-quality research [4]. Results of this survey

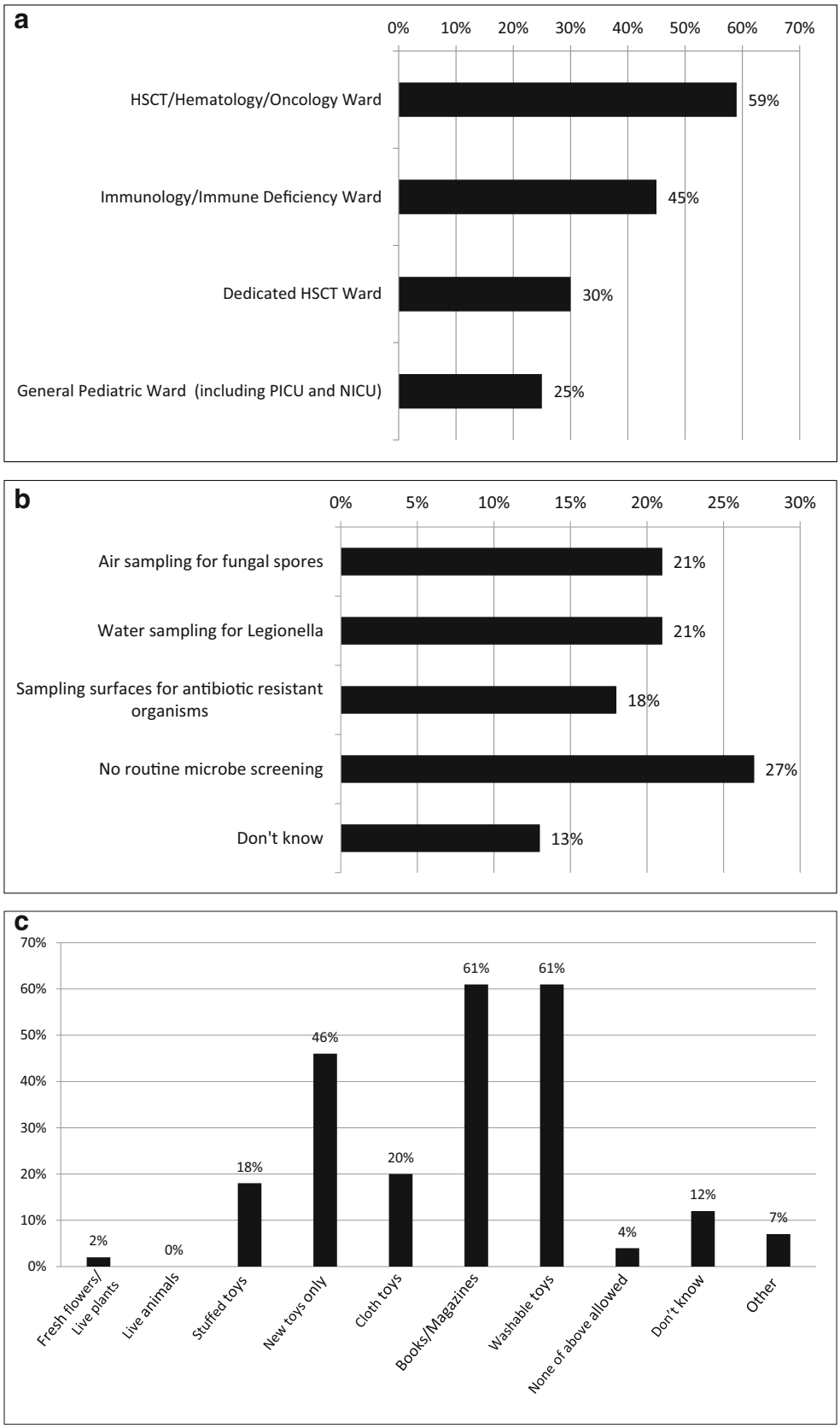

Fig. 2 Percentage of SCID patients admitted to pediatric wards (**a**). Percentage of SCID centers reporting routine environmental microbe screening (**b**). Percentage of SCID centers reporting items allowed in SCID patient rooms (**c**). HSCT, hematopoietic stem cell transplant; PICU, pediatric intensive care unit; NICU, neonatal intensive care unit

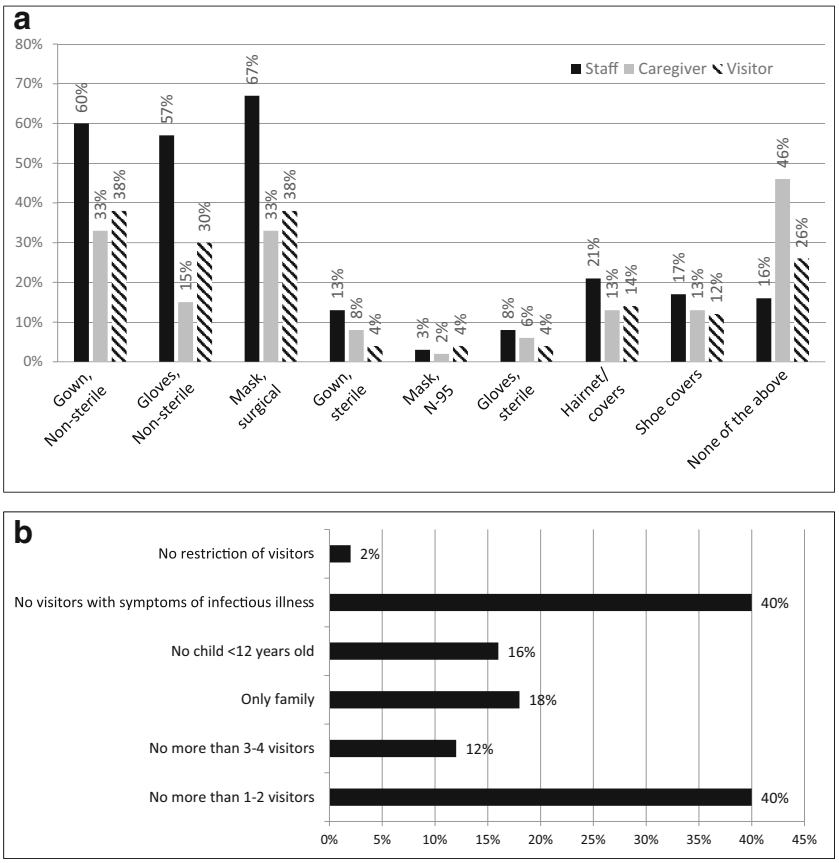

Fig. 3 Personal protective equipment required prior to entering room of SCID patient without known infection, by staff, caregiver, and visitor (**a**). Visitor restrictions reported by SCID centers (**b**)

demonstrate a great need to develop evidence-based isolation protocols, with strategies for implementation and compliance monitoring.

Infection prevention is even more important with SCID newborn screening, currently performed throughout the USA and a number of other countries [2]. Prior to screening, many patients with SCID presented at diagnosis already infected; this likely contributed to the worsening survival rates seen when infants received curative therapy at an older age. A European review of SCID patients found 3-year survival dropped from 85% for patients transplanted prior to 6 months of age, compared with 53% if transplanted over 6 months of age [11]. Buckley et al. showed that overall survival dropped from 95% in patients transplanted at < 3.5 months of age compared with 76% in those transplanted at > 3.5 months of age [12]. This is supported by data from the Primary Immune Deficiency Treatment Consortium (PIDTC) that patients transplanted at < 3.5 months had fewer active infections going into transplant compared with those > 3.5 months of age (66% vs 46%, $p = < 0.001$) [5]. Retrospective review of SCID transplant outcomes by Haddad et al. and Pai et al. through the PIDTC confirmed in multivariate analysis that active infection at the time of transplant significantly affected survival and was associated with increased risk of treatment failure [13, 14].

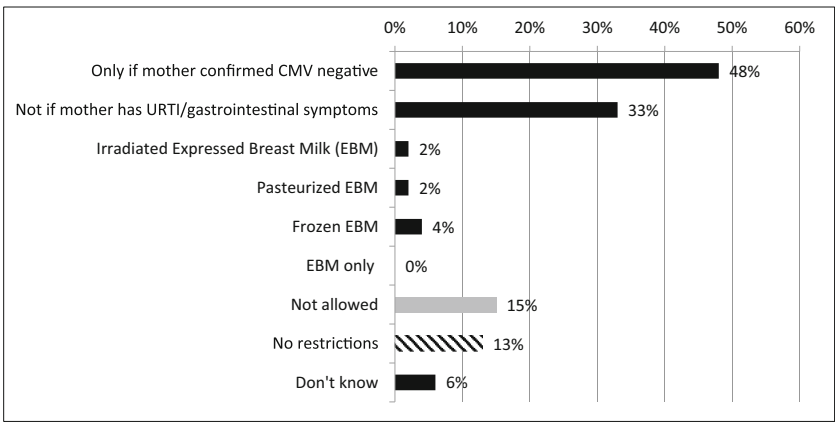

Fig. 4 Breastfeeding practices reported across SCID centers. CMV, cytomegalovirus; URTI, upper respiratory tract infection; EBM, expressed breastmilk

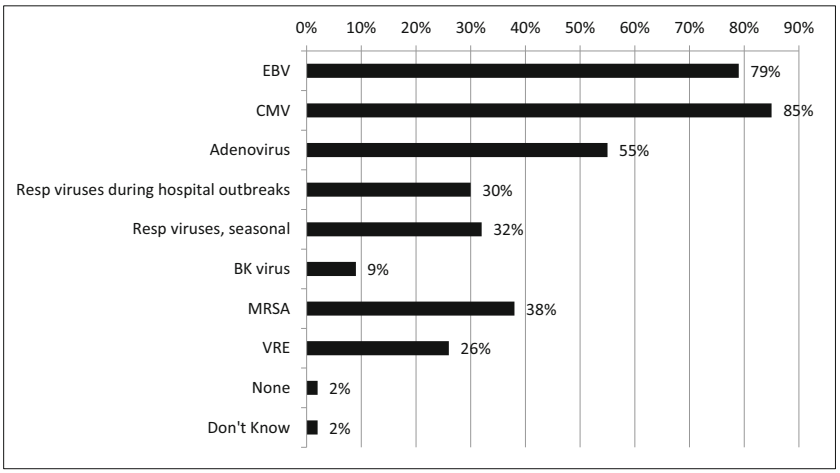

Fig. 5 Organisms routinely screened for pre-HSCT by SCID centers. EBV, Epstein Barr virus; CMV, cytomegalovirus; MRSA, methicillin resistant *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococci

With the ability to diagnose these infants in the neonatal period, there is now an opportunity to keep them free of infection prior to receiving curative therapy. However, despite early diagnosis, recent review of SCID patients diagnosed with newborn screening or family history showed that 42% of infants still developed infections prior to definitive treatment, and over three quarters of these infections were identified after the SCID diagnosis was made [5]. Overall survival dropped from 95 to 81% (p 0.009) if patients had infection prior to transplant; infection at the time of transplant was the only variable found to significantly impact survival [5]. Many of the infections were transmissible diseases, such as CMV, EBV, herpes simplex viruses, adenovirus, other respiratory viruses, *Clostridioides difficile*, and rotavirus [5]. Improving current infection prevention control strategies in these patients may have significant impact on overall morbidity and mortality.

Our survey demonstrated significant variability in visitor restrictions, use of PPE, discharge criteria, and breastfeeding practices. The large majority of SCID treatment centers surveyed reported SCID patients are admitted to a one-bed room, which is consistent with what is recommended by multiple HSCT organizations and the CDC [4, 15–18]. Fifty-nine percent of SCID centers use HEPA filters; however, this is much lower compared with similar surveys of HSCT centers (86%) [15–18]. Similarly low numbers of SCID centers report use of LAF compared with HSCT centers (20–40%) [4, 15–17, 19, 20]. The low report of HEPA with LAF in SCID treatment centers could be due to a lack of concrete evidence, as well as the expense of LAF. There is evidence of benefit for HEPA filters in HSCT based on expert opinion and descriptive studies; however, no survival benefit has been demonstrated in HSCT patients with LAF [4].

Our survey did not address hand hygiene as this is a well-accepted procedure with strong evidence for preventing healthcare-associated infection, though visitor compliance with hand hygiene may be an area for further study. The use of gowns and masks was similar to that reported in HSCT literature (60–73% and 65–74% respectively), though use of hair and shoe covers was lower in SCID treatment centers (50% in HSCT vs 17–21% in SCID centers) [17]. CDC HSCT guidelines only recommend appropriate PPE when interacting with a potentially contagious HSCT patient [4]. We are not aware of any studies demonstrating a benefit in

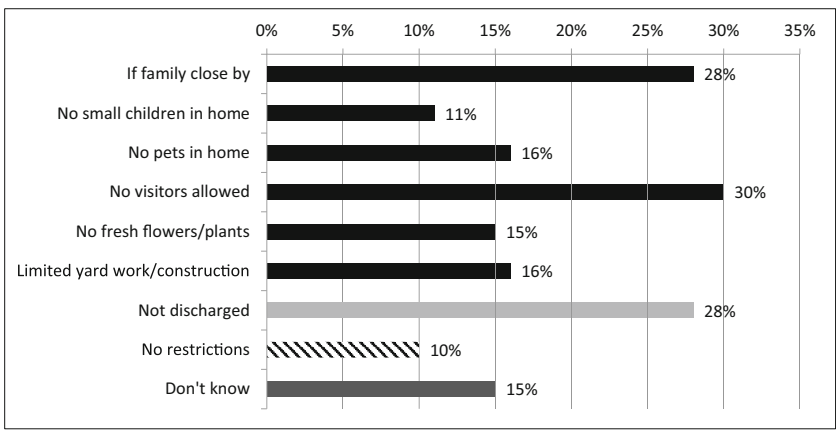

Fig. 6 Discharge restrictions of a clinically well infant with SCID pre-HSCT

SCID or HSCT patient infection prevention with staff or visitors routinely wearing gowns and hair or shoe covers. There are data that universal use of non-sterile gloves for patient and intravenous catheter contact reduces the incidence of infections [21–23]. Our survey found 67% of centers required staff to wear masks and 33% required visitors to wear masks. In a prospective study by Sung et al., the incidence of respiratory viral infections dropped from 10.3 to 4.4% ($p < 0.001$) with universal mask usage for all individuals in contact with HSCT patients [24]. We recommend the policy for mask and glove usage around SCID patients should be evaluated.

There is large variability in what is reported to be allowed in SCID patient rooms across treatment centers. Most experts strongly discourage plants and flowers in rooms for severely immunocompromised patients based on *Aspergillus* spores being isolated from the soil or flowers, not due to conclusive reports of fungal infection [4, 15, 19]. HSCT guidelines have no strict policy of type of toys that are allowed in patient rooms, but it is recommended based on expert opinion that only those that can be cleaned regularly be allowed [4, 15, 19]. While this may be beneficial from an infection control perspective, other aspects of patient health such as development and psychological wellness must also be kept in mind.

Overall, there was variability in visitor restrictions for SCID patients, and restrictions largely did not follow HSCT guidelines. Munoz-Price et al. describe that visitors are capable of and have started nosocomial outbreaks, which are especially significant in the SCID population [25]. It has also been found that visitor infection control compliance, including hand hygiene and PPE, is generally poor and that there should be protocols in place to improve adherence [25].

HSCT guidelines recommend antimicrobial prophylaxis for HSCT patients [26]. PJP prophylaxis is strongly recommended and has been found by the European BMT database as a significant factor in HSCT outcome [17]. European review of SCID data also confirmed that PJP prophylaxis improved outcomes; however, not all SCID centers are complying with this pre-HSCT [11]. Although the CDC HSCT guideline does not recommend immunoglobulin replacement unless the patient's IgG is < 4 g/dL, a large majority of SCID treatment centers report giving immunoglobulin replacement to SCID patients pre-HSCT; it should be kept in mind that this CDC guideline may not be translatable to the SCID population. The HSCT guideline also recommends fluconazole to prevent candidiasis, which a majority, but not all, of SCID treatment centers report using pre-HSCT [27]. Review of SCID patients diagnosed by newborn screening shows a decrease in incidence of PJP and Candida infections, suggesting efficacy of prophylaxis for these patients [5]. Overall, SCID treatment centers are largely following HSCT guidelines for pre-HSCT antimicrobial prophylaxis.

CMV is a large cause of morbidity and mortality in HSCT patients; screening for CMV is recommended, and most SCID centers report screening by blood PCR [26]. CMV is a significant concern with breastfeeding patients as there is large risk for transmission from mother to child. Only 70% of respondents reported taking any measures to prevent CMV transmission through breastmilk, with half of respondents allowing breastfeeding if the mother is confirmed CMV negative, a few centers allowing irradiated or pasteurized breastmilk and less than one-fifth of centers do not allow any breastmilk. One study found an approximately 80% secretion rate of CMV through breast milk detected as early as 1 week into breastfeeding and peaking at around 3–5 weeks [28]. From these studies and our data, it is evident that more research is needed to determine the safest breastfeeding and CMV prevention practices for SCID patients.

Limited literature regarding safe discharge criteria could explain variations in discharge practices across SCID centers. Families may have a greater quality of life while in a home setting. Review of the literature for home versus hospital care for patients with hematologic malignancies and cytopenias found there are not enough data to conclude if home care is as safe as hospital care in protective isolation [29].

A limitation of this study was that respondents could select "do not know" answers; these responses illustrate issues with awareness of local protocols. Another limitation was the anonymous collection of data, as multiple responses from one site could have occurred from different practitioners. However, we felt that anonymous collection of results was appropriate in order to obtain confidential answers. The low response rate was a challenge in this study, though responses were obtained from the majority of provinces and states where there are major immunology treatment centers, and nearly one quarter of responses were from large centers treating more than 6 SCID patients per year. Finally, though our survey was conducted prior to widespread availability of newborn screening, we feel the results are still currently representative, as there have not been any significant practice changing research or revision of HSCT infection prevention guidelines since the survey was completed.

While the impetus for the implementation of infection control precautions is to minimize the morbidity and mortality of infections in SCID patients, treatment centers must be cautious of over-protection to the point of causing harm to the psychological well-being of these children and their families. One study found that length of hospital stay had a major impact on neuro-developmental outcomes, such as adaptive behavior development [30]. Another study reported decreased quality of life in mothers of SCID babies due to protective isolation, with 25% reporting depression [31]. Evidence is also required to justify the increased cost of more intensive isolation protocols.

Conclusion

Overall, we found most centers had a high rate of agreement on the following practices: managing patients in one-bed rooms; avoiding plants and animals in patient rooms; use of prophylaxis for PJP and candidiasis; immunoglobulin replacement; and CMV surveillance. There was significant variability in the use of air filters in patient rooms; types of toys allowed; type of PPE required and vaccination policies for staff, caregivers, and visitors; policies for visitor restrictions; breastfeeding policies; surveillance for viruses other than CMV; and discharge criteria.

We recommend centers treating patients with SCID should institute practices for preventing infectious complications for which there is reasonable evidence: patients should be in single HEPA-filtered rooms; staff, caregivers, and visitors should be encouraged or required to have up-to-date vaccinations, including the annual IIV [32]; antimicrobial prophylaxis for PJP and *Candida* should be used; and CMV surveillance should be performed. Centers should develop a policy to prevent transmission of CMV through breastmilk based on the best available evidence. The majority of centers currently recommend restricting breastmilk from mothers who are CMV positive [33].

We recommend further multicenter research be done to determine the most efficacious practices for infection control policies for patients who are severely immunocompromised. Utility of PPE, and in particular mask and glove use for staff, caregivers, and visitors, should be studied. Strategies to prevent CMV and safest breastfeeding practices need to be determined. The safest policies for caregiver and visitor restrictions require further evaluation. There are also no data on whether it is safest to manage a well patient with SCID prior to curative therapy at home or in the hospital.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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