ORIGINAL ARTICLE

Infections in Infants with SCID: Isolation, Infection Screening, and Prophylaxis in PIDTC Centers

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Abstract

Purpose The Primary Immune Deficiency Treatment Consortium (PIDTC) enrolled children with severe combined immunodeficiency (SCID) in a prospective natural history study of hematopoietic stem cell transplant (HSCT) outcomes over the last decade. Despite newborn screening (NBS) for SCID, infections occurred prior to HSCT. This study's objectives were to define the types and timing of infection prior to HSCT in patients diagnosed via NBS or by family history (FH) and to understand the breadth of strategies employed at PIDTC centers for infection prevention.

Methods We analyzed retrospective data on infections and pre-transplant management in patients with SCID diagnosed by NBS and/or FH and treated with HSCT between 2010 and 2014. PIDTC centers were surveyed in 2018 to understand their practices and protocols for pre-HSCT management.

Results Infections were more common in patients diagnosed via NBS (55%) versus those diagnosed via FH (19%) ($p = 0.012$). Outpatient versus inpatient management did not impact infections (47% vs 35%, respectively; $p = 0.423$). There was no consensus among PIDTC survey respondents as to the best setting (inpatient vs outpatient) for pre-HSCT management. While isolation practices varied, immunoglobulin replacement and antimicrobial prophylaxis were more uniformly implemented.

Conclusion Infants with SCID diagnosed due to FH had lower rates of infection and proceeded to HSCT more quickly than did those diagnosed via NBS. Pre-HSCT management practices were highly variable between centers, although uses of prophylaxis and immunoglobulin support were more consistent. This study demonstrates a critical need for development of evidence-based guidelines for the pre-HSCT management of infants with SCID following an abnormal NBS.

Trial Registration NCT01186913

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Abbreviations

CMV	Cytomegalovirus
EBV	Epstein–Barr virus
ERT	Enzyme replacement therapy
FH	Family history
GT	Gene therapy
HSCT	Hematopoietic stem cell transplant
MAC	Myeloablative conditioning
NBS	Newborn screening
PIDTC	Primary Immunodeficiency Treatment Consortium
PPE	Personal protective equipment
PPV	Positive pressure ventilation
SCID	Severe combined immunodeficiency
VOD	Veno-occlusive disease

Introduction

Severe combined immunodeficiency (SCID), characterized by profound cellular and humoral immune defects, leads to lethal infections unless treated by hematopoietic cell transplant (HSCT), gene therapy (GT), or enzyme replacement therapy (ERT) [1–4]. Newborn screening (NBS) for SCID offers the potential to identify affected infants early in life, permitting prompt definitive diagnosis and treatment [4, 5]. The Primary Immune Deficiency Treatment Consortium (PIDTC) has studied SCID since 2010, reporting outcomes for 100 SCID patients receiving HSCT between 2010 and 2014, and demonstrating in larger cohorts that infection at the time of HSCT for SCID was associated with increased mortality [6–9].

While only a minority of infants with SCID were recognized due to a positive family history (FH), the rate of diagnosis via NBS increased during the period of PIDTC study enrollment. Children with SCID diagnosed via NBS or FH, perhaps related to fewer pre-HSCT infections and medical comorbidities, had better neurologic outcomes than did children diagnosed following clinical illness [10].

However, despite lower infection rates in infants with SCID diagnosed via NBS or FH, compared with those presenting with clinical symptoms, 42% of these infants still experienced at least one infection prior to HSCT, and 27% had active infection at the time of HSCT [7]. Moreover, 76% of these infections were identified after the SCID diagnosis was confirmed [7]. We asked whether infection rates were the same in infants diagnosed by NBS versus FH and whether time to HSCT was similar between these groups. Our objective was to retrospectively analyze the types and timing of infections in our existing dataset of patients who received HSCT at PIDTC centers to better define strategies for infection prevention in a future trial. Infection data alone were insufficient to determine sources of exposure or potential approaches to prevention of infections prior to HSCT; we therefore surveyed PIDTC centers to establish the spectrum of current management practices.

Methods

Analysis of Infections in SCID Patients Diagnosed via NBS or FH

The PIDTC, a collaboration of immunology and HSCT centers in the USA and Canada, conducts research to improve the diagnosis and treatment of primary immunodeficiencies [1–3]. PIDTC Protocol 6901 (NCT01186913, www.clinicaltrials.gov) opened in August 2010 as a prospective, natural history study of patients diagnosed and treated for SCID, performed in accordance with the 1964 Declaration of Helsinki and its later amendments and approved by the Institutional Review Boards of individual centers and the UCSF central IRB. Of the 32 participating centers at the time of this analysis, 25 contributed SCID patients, forming the largest North American SCID cohort. Eligibility criteria included diagnosis of typical or leaky SCID based on published definitions [3], and survival to treatment with HSCT. Patients were assigned to stratum A if they were diagnosed with typical SCID and stratum B if they had leaky SCID or Omenn syndrome. Data for the 59 patients diagnosed via NBS or FH within the first 100 patients enrolled and treated with HSCT were reexamined for age at SCID diagnosis, age at infection onset, type of infection, location of pre-HSCT care (inpatient or outpatient) once SCID diagnosis was confirmed, and age at HSCT [5]. Diagnosis by family history is defined as a patient who had a relative with a diagnosis of SCID that was known prior to the patient's delivery; testing for SCID may have been done prenatally or following delivery. Seven patients treated who received GT and/or ERT were not included, as this study focused on rates of infection prior to HSCT. Statistical analyses were primarily descriptive or univariate, with comparisons of categorical outcomes between NBS and FH groups done using Fisher's exact test, and comparisons of quantitative variables between NBS and FH groups done using the Wilcoxon rank-sum test. Infection density, computed as infections per month, was compared between NBS and FH groups using Poisson's regression with a log link and offset equal to the

log age at HSCT. Survival was estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Multivariable analyses were not done due to limited sample size.

Survey of Current Pre-HSCT Management of SCID Infants at PIDTC Centers

A 29-question survey was initially developed by 18 PIDTC clinical immunologists and transplant specialists. It was then further refined by the larger 6901 protocol working group (Data Supplement 1). The survey aimed to assess the following: patient age at time of SCID diagnosis, timing of HSCT, inpatient versus outpatient pre-HSCT management, inpatient protective environments, outpatient monitoring practices, antimicrobial prophylaxis and immunoglobulin therapies, and practices for monitoring and prevention of viral infections. The survey was completed between October 2017 and January 2018 by the 42 PIDTC centers active at that time. Centers were also asked to share any written protocols for SCID management.

Results

Infection and Survival Outcomes of the Cohort (Birth Years 2010–2014)

Table 1 and Fig. 1 show infections in infants diagnosed with SCID via NBS or FH. Twenty-one of the 38 infants diagnosed via NBS (55%) experienced at least one pre-HSCT infection, compared with 4 of the 21 infants diagnosed via FH (19%) ($p = 0.012$). The median age of diagnosis in patients diagnosed via NBS was 25 days (0–85), versus 6 days (0–32) for those diagnosed via FH ($p < 0.001$). Thirteen infections occurred before a diagnosis of SCID was confirmed; all but one of these occurred in patients diagnosed by NBS. To account for potential differential time to HSCT, we analyzed infection density, which was 0.3 per month in infants diagnosed via NBS compared with 0.1 per month in infants diagnosed via FH ($p = 0.029$). Active infection at the time of HSCT was present in 15 of 38 diagnosed via NBS (39%), but only 1 of the 21 diagnosed via FH (5%) ($p = 0.005$). Several infectious pathogens were seen; some infants had multiple infections (Table 1). The most common were cytomegalovirus (CMV) ($n = 5$), Epstein–Barr virus (EBV) ($n = 2$), and respiratory viruses ($n = 9$). The median time to HSCT was 96.5 days (range 45–251) for those diagnosed via NBS, but only 49 days (range 16–167) for those diagnosed via FH ($p < 0.001$). Two-year post-HSCT survival was 89% in both NBS and FH groups.

Centers were queried to determine if the 59 infants diagnosed by NBS or FH were managed as inpatients or outpatients once the SCID diagnosis was confirmed. Infants initially managed as outpatients, but later hospitalized were considered outpatients for this study. Thirty-six of the 59 infants (61%) were hospitalized continuously once the SCID diagnosis was confirmed, while 23 (39%) were managed as outpatients. The incidence of infection between inpatients (47%) compared with outpatients (35%) was not significantly different ($p = 0.423$; Table 1).

While none of the 21 infants diagnosed by FH was infected with CMV, 5 of the 38 (13%) diagnosed by NBS had CMV ($p = 0.150$), 4 inpatient and 1 initially outpatient. In 2 of these infants, CMV was detected within a month of diagnosis, suggesting that the initial exposure may have occurred prior to confirmation of the SCID diagnosis. Of the 5 patients with CMV, 3 had been breastfed, 1 had not been breastfed, and breastfeeding status was unknown for 1. Both patients with EBV viremia were managed as inpatients from the time of SCID diagnosed by NBS. Eight out of 38 infants (21%) diagnosed by NBS had a respiratory viral infections (4 inpatient and 1 initially outpatient), while 1 of 21 (5%) diagnosed by FH had a respiratory viral infection ($p = 0.138$). Of the respiratory viral infections, 2 were diagnosed prior to confirmation of the SCID diagnosis.

Four of the 38 infants diagnosed via NBS (11%) died after HSCT, all of whom had an active infection at the time of HSCT (Table 1). One of these infants had received no pre-HSCT conditioning, while 3 had received myeloablative conditioning (MAC). Three were initially managed as inpatients, and their causes of death included one or more infections (CMV, EBV, adenovirus, aspergillus, staphylococcal bacteremia, and rhinovirus) and hepatic veno-occlusive disease (VOD), a complication of chemotherapy, in one infant. One infant initially managed as an outpatient died of VOD.

Two of the 21 infants diagnosed via FH died post HSCT (9.5%), neither of whom experienced infection prior to HSCT. One, who did not receive pre-HSCT conditioning, had respiratory failure, while the other, who received MAC, had EBV with post-transplant lymphoproliferative disease.

Survey Results

Because the survey focused on general practice patterns, it was not correlated to patient-level data. The response rate was 100%, with 50 evaluable responses from physicians at 42 PIDTC centers, some centers' responses from both a HSCT specialist and an immunologist. The respondents included 25 HSCT specialists, 16 immunologists, and 9 with dual expertise. Responses according to subspecialty are in Supplemental Table 1. Consensus responses for the 7 centers with > 1 respondent were solicited. Twenty-one of the 27 centers with formal supportive care protocols for SCID management submitted their protocol for analysis.

Table 1 Summary of infections seen in 25 of the 59 SCID patients diagnosed via NBS or FH and treated with HSCT on PIDTC 6901. The gray-shaded area indicates that the patients had no active infection at the time of HSCT

| #	Age at SCID Dx (days), FH or NBS	Inpatient or Outpatient once SCID Diagnosed	Infection(s) prior to HSCT, age at onset (days), resolved/active at time of HSCT	Age at HSCT (days)	Genotype; Stratum Assignment	HSCT Donor Source; Conditioning	Status	Reported Cause(s) of Death
1	8, NBS	Inpatient	CMV (viremia), 48, controlled / CMV (urine), 76, active	84	Unknown; A	MMRD; None	Alive	
2	16, NBS	Inpatient	*C. difficile*, 66, active (not clinically significant)	72	IL2RG; A	>=7/8 URD; MAC	Alive	
3	19, NBS	Inpatient	*Candida* (oral), 8, resolved / Rhinovirus (URI), 31, resolved / *Candida* (stool) 35, resolved / *Staphylococcus* (Central Line), 52, resolved / EBV (viremia), 103, active	103	*IL7R*; A	>=7/8 URD; IS	Alive	
4	23, NBS	Inpatient	Rhinovirus (Pneumonia), 23, active	50	*IL2RG*;A	MMRD; None	Alive	
5	23, FH	Inpatient	*C. difficile*, 32, active	45	*RAG1/2*; B	MRD; None	Alive	
6	24, NBS	Outpatient	CMV, 95, active / Parainfluenza, 111, resolved	145	*IL2RG*; B	MMRD; RIC	Alive	
7	25, NBS	Outpatient	*C. difficile*, 144, active (not clinically significant)	151	Unknown; B	>=4/6 UCB; MAC	Alive	
8	25, NBS	Outpatient	Rhinovirus (URI), 82, active	106	*RAG1/2*; B	MMRD; None	Alive	
9	26, NBS	Inpatient	Rhinovirus (Pneumonia), 105, active	139	*RAG1/2*; B	>=7/8 URD; RIC	Alive	
10	26, NBS	Inpatient	*Staphylococcus*, 36, active / *E. coli* (Central Line), 107, resolved	133	Unknown; A	>=7/8 URD; MAC	Alive	
11	27, NBS	Inpatient	Coagulase negative *Staphylococcus* (Central Line), 116, resolved / CMV (viremia), 64, active	86	*RAG1/2*; B	MMRD; RIC	Alive	
12	28, NBS	Outpatient	VRE (Stool), 95, active	113	*RMRP*; B	>=4/6 UCB; MAC	Died	VOD
13	28, NBS	Inpatient	CMV (viremia), 36, active / CMV (pneumonia), 39, active	49	Unknown; A	MMRD; None	Died	CMV
14	32, NBS	Inpatient	*Candida* (oral), 28, resolved / CMV, 31, active / *Staphylococcus* (Central Line), 50, resolved	109	*IL2RG*; A	>=7/8 URD; MAC	Died	EBV, CMV, Aspergillosis
15	34, NBS	Outpatient	Rhinovirus, 60, active / *C. difficile*, 90, active	112	*IL2RG*; A	MMRD; RIC	Alive	
16	41, NBS	Inpatient	Rhinovirus, 36, active	124	*RAG1/2*; A	>=4/6 UCB; MAC	Died	VOD, Rhinovirus, Adenovirus
17	Birth, FH	Inpatient	*Candida* (skin), 18, resolved	36	*IL2RG*; A	>=4/6 UCB; RIC	Alive	
18	5, FH	Outpatient	Coagulase negative Staph, 8, resolved	21	*IL7R*; A	MRD; None	Alive	
19	6, NBS	Outpatient	Rota (stool), 189, resolved	251	Unknown; B	>=4/6 UCB; RIC	Alive	
20	15, NBS	Inpatient	*Klebsiella* (urine), 78, resolved	106	Unknown; B	>=7/8 URD; RIC	Alive	
21	27, FH	Outpatient	Rhinovirus, 27 controlled	55	*IL2RG*; A	MMRD; None	Alive	
22	27, NBS	Inpatient	*Staphylococcus* (Cellulitis), 14 resolved / HSV 1&HSV2 (Blood), 31, controlled / Rhinovirus (URI), 32, controlled	122	*JAK3*; A	>=7/8 URD; RIC	Alive	
23	29, NBS	Inpatient	EBV (Blood), 90, controlled / *Candida* (oral), 22, resolved	50	*IL2RG*; A	MMRD; None	Alive	
24	34, NBS	Inpatient	*Staphylococcus* (bloodstream), 95, resolved	106	*IL7R*; A	>=7/8 URD; IS	Alive	
25	56, NBS	Inpatient	*Niesseria* (pneumonia), 31, resolved / *Klebsiella* (pneumonia), 31, resolved / *Streptococcus* (pneumonia), 31, resolved	70	*ADA*; A	>=4/6 UCB; MAC	Alive	

CMV cytomegalovirus, *EBV* Epstein–Barr virus, *FH* family history, *MAC* myeloablative conditioning, *MMRD* mismatched related donor, *MRD* matched related donor, *MUD* matched unrelated donor, *NBS* newborn screening, *RIC* reduced intensity conditioning, *SCID* severe combined immunodeficiency, *UCB* umbilical cord blood

Median Age at the Time SCID Management Commenced

At the time of the survey, 91% of PIDTC centers were in states with SCID NBS programs. Based on survey responses, abnormal NBS results were reported to the specialist at a median age of 16 days from birth (range 1–28 days). Delays in reporting included local NBS program process issues and delays where only the primary care provider was notified of abnormal results and took a variable amount of time to notify specialists. Initiation of management as a SCID patient (when protective actions and prophylaxis were started) was at a median age of 21 days (range 2–30) and was based on lymphocyte subset values in most centers (38 centers, 90%). Additional testing used to determine when an infant should be managed as a SCID patient included as follows: naïve T cells, 25 centers (60%); T cell proliferation, 16 centers (38%); genetic testing, 6 centers (14%); maternal engraftment, 7

Fig. 1 Infection in patients diagnosed with SCID based on positive NBS or FH
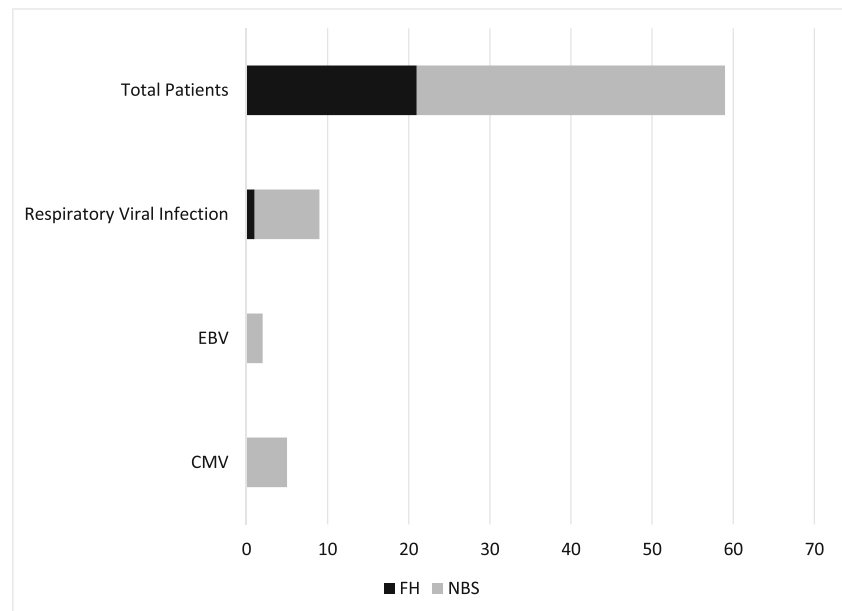
centers (17%); repeat TREC, 2 centers (5%); and negative results from testing for DiGeorge syndrome, 1 center (2%).

Timing of Transplant for all Infants with SCID

When asked for criteria regarding timing of an HSCT with no chemotherapy ("unconditioned"), 69% of centers proceeded as soon as possible. Others cited these criteria to determine timing of an unconditioned HSCT: resolution of infection (29%), return of genetic test results (24%), return of an unrelated donor search (19%), and development of infection (7%). Timing for conditioned HSCT was not assessed in this study as this may have been influenced by multiple factors including time required to find a donor and type of donor selected, time to rule out radiosensitivity, and controversy regarding how soon it is safe to use specific conditioning agents in an infant.

Outpatient Versus Inpatient Management Pre-HSCT

For 52% of centers, the pre-HSCT management location for infants with SCID varied, while 31% routinely planned for inpatient and 17% for outpatient care. Criteria to determine an appropriate home environment varied greatly between centers (Fig. 2). Centers having multiple provider responses cited their criteria inconsistently prior to providing center consensus responses. Of 11 centers that addressed disposition in their written protocol, 64% of these were consistent with their survey responses.

Inpatient Protective Environments

In addition to universal hand hygiene, 20% of centers required a 2-min scrub. Most centers required staff to wear some form of personal protective equipment (PPE) in SCID patient rooms. This included reverse isolation (gown, glove, mask) either with ($n = 25$) or without ($n = 10$) positive pressure ventilation (PPV); gown and gloves, but no mask ($n = 1$); and mask only ($n = 2$). Six centers did not indicate a requirement for staff to wear any PPE. Of 16 centers that addressed protective isolation components in their written protocol, 92% were consistent with their survey responses.

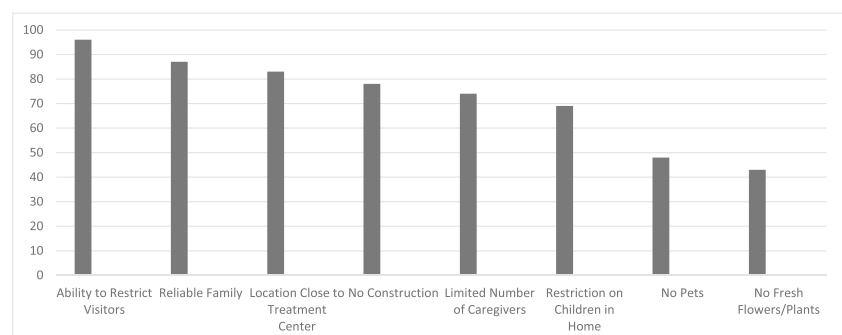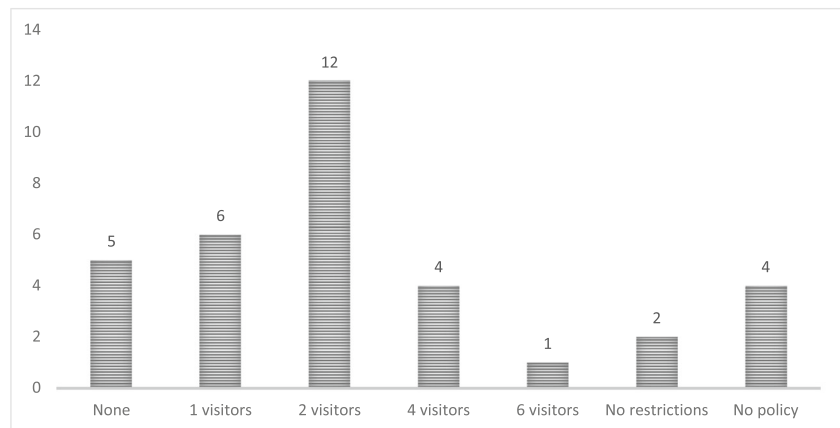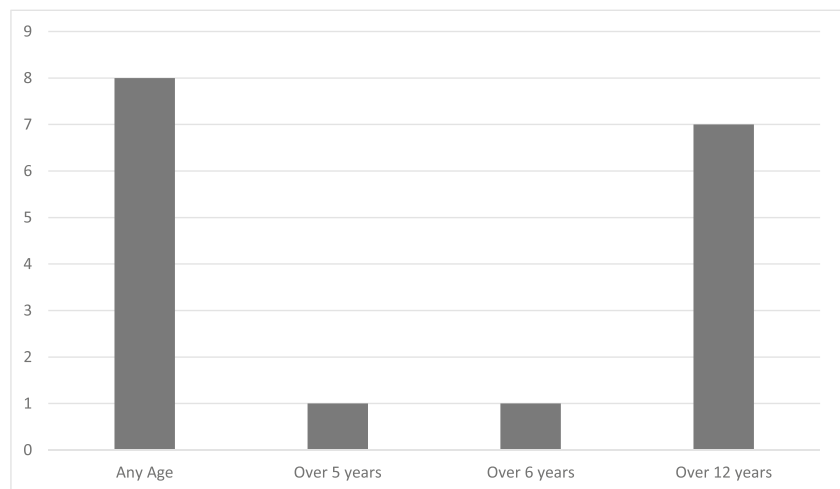**Fig. 2** Criteria for safe home management of SCID infants

Fig. 3 **a** Visitor policies for inpatients. **b** Age sibling visitors permitted

a: Visitor Policies for Inpatients

b: Ages Sibling Visitors permitted

Most centers (79%) restricted non-staff caregivers to a maximum of 2 individuals; 7% reported no restrictions. There was significant variability with regard to the allowed number of non-care-providing visitors, including siblings (Fig. 3a and b).

Thirty-five (83%) centers required non-staff caregivers and visitors to perform hand hygiene prior to entering a SCID patient room. Thirteen (31%) required these individuals to wear gowns, gloves and masks.

Outpatient Monitoring

Infants managed as outpatients resided in private homes ($n = 22$), accommodations near the hospital ($n = 1$), or a communal hospital-associated facility ($n = 2$). When queried regarding recommended frequency for outpatient clinic follow-up of these patients, 8 indicated no formal policy, 8 recommended weekly visits, 5 twice a week, 4 every other week, and 1 monthly.

Prophylaxis and Immunoglobulin Replacement

Prophylaxis against *Pneumocystis jiroveci* (PJP) infection was started universally, although age at initiating trimethoprim/ sulfamethoxazole (TMP-SMX) varied (Fig. 4a and b). Fungal prophylaxis was routinely started by 79% of centers with various agents (Fig. 4c). Most centers (98%) administered immunoglobulin to all patients with varied routes (Fig. 4d). Of 17 centers that addressed use of immunoglobulin and antimicrobial prophylaxis in a written protocol, 70% were consistent with their survey responses.

Viral Infection Testing, Surveillance, Prophylaxis, and Prevention

Viral Testing

Routine viral monitoring for CMV was performed at 93% of centers, with blood PCR the most common method. Routine

a: PJP Prophylaxis medications
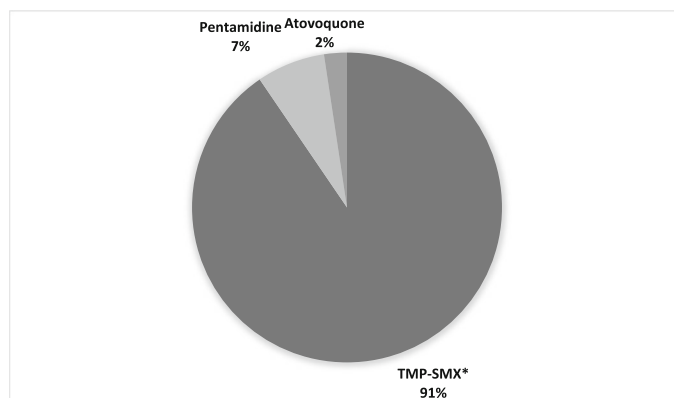
*Dose varied, but generally ranged between 2.5-5mg/kg/day of the trimethoprim component divided to twice a day administration and given 2-3 times a week.

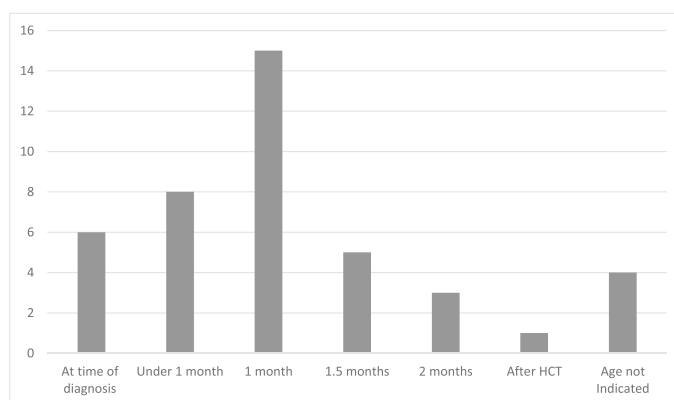b: Age at initiation of TMP-SMX

Fig. 4 a PJP prophylaxis medications. *Dose varied, but generally ranged between 2.5 and 5 mg/kg/day of the trimethoprim component divided to twice a day administration and given 2–3 times a week. **b** Age at initiation of TMP-SMX. **c** Fungal prophylaxis medications. *Dose varied, but generally ranged between 3 and 6 mg/kg/day. **d** Route of immunoglobulin replacement

monitoring for EBV and adenovirus via blood PCR was performed by 69% and 57% of centers, respectively. Respiratory virus monitoring was routine at 7% of centers. Of the 13 centers that addressed CMV screening in a written protocol, 40% were consistent with their survey responses.

CMV and Breastfeeding Recommendations

Of the 36 centers that made recommendations regarding breastfeeding, 81% recommended against breastfeeding if the mother was CMV seropositive. Of these, 45% based their recommendations on anti-CMV IgG alone, 45% considered anti-CMV IgG and/or IgM, and 3% considered anti-CMV IgM alone. Twenty-eight percent of centers recommended against breastfeeding if mothers had infectious symptoms.

Viral Prophylaxis

A minority of centers (45%) routinely started all patients on prophylaxis against herpes viruses with acyclovir and

continued through HSCT. If used, 94% started either at diagnosis or within the first month of life.

Discussion

Despite diagnosis following NBS, some SCID patients enrolled in PIDTC Protocol 6901 developed respiratory viral (21%) and/or CMV (13%) infections prior to HSCT. These infections may have contributed to the surprising lack of difference in overall survival between patients diagnosed clinically compared with those diagnosed via NBS or FH noted in our recent PIDTC analysis [7]. Prior to the era of NBS, improved outcomes in patients diagnosed via FH versus as sporadic cases have been attributed to earlier institution of protective measures resulting in reduced infections, so our findings were unexpected [11]. To address this issue, we reassessed the patient data and surveyed the clinical practices of PIDTC providers regarding diagnosis and management of newborn SCID prior to HSCT.

c: Fungal prophylaxis medications
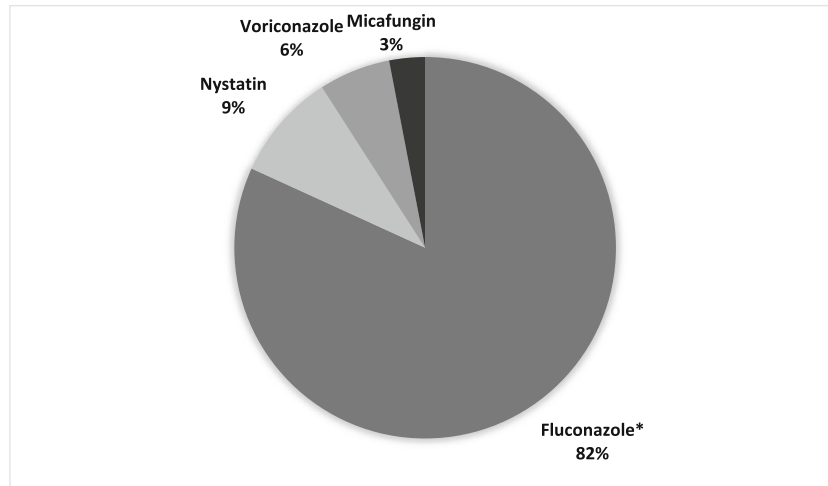
*Dose varied, but generally ranged between 3-6mg/kg/day
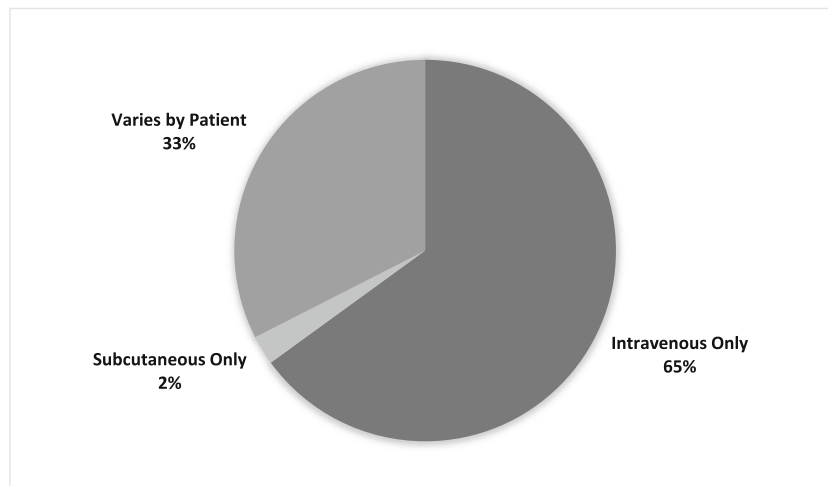
d: Route of Immunoglobulin Replacement

Fig. 4 (continued)

The rate of pre-HSCT infections in patients diagnosed via NBS (55%) was nearly 3-fold higher than that of patients diagnosed based on family history (19%). Furthermore, patients diagnosed by FH received HSCT at a younger age than those diagnosed via NBS (median 49 vs 96 days). We hypothesize that awareness of genetic risk and early testing (including prenatal testing) in the setting of recognized FH prompted planning for birth to occur in a controlled environment with immediate protection from infectious exposures and rapid progression to HSCT. In addition, psychosocial factors and awareness of the importance of infection prevention may have contributed to the advantages of infants with positive FH; families who have had a prior child with SCID likely require less time to adjust to the diagnosis, are experienced in instituting isolation protocols, and may have organized the support

required to manage a SCID baby prior to the child's delivery. Notably, no CMV infections occurred in the FH cohort, possibly reflecting differences in prospective monitoring, prophylaxis, or adherence to prevention counseling from the time of birth (i.e., avoiding breastfeeding from CMV seropositive mothers, isolation from potentially infectious contacts).

In contrast, infants diagnosed via NBS in the absence of FH were not diagnosed immediately at birth; as noted in our survey, NBS results took as long as 28 days to return. Time required to obtain results of confirmatory testing resulted in further delays; some centers reported not initiating SCID management until results of T cell proliferation studies, genetics, and maternal engraftment studies have returned. These investigations can take 2 or more weeks to be reported, which may result in significant delays in initiating protective measures

and commencing work-up for HSCT in infants diagnosed with NBS. Thirteen potentially preventable infections were seen in the period prior to confirmation of SCID diagnosis in our cohort. Thus, delays between birth, reporting of screening results, and referral for diagnosis and definitive therapy allowed for exposures to infections. Additionally, as we learned from the survey, some centers always awaited genetic testing results before HSCT, lengthening the window for infections to develop. Families who were not aware of SCID may have needed more counseling and time to comprehend the impact of their child's condition, including the importance of infection prevention through isolation. Although NBS afforded an opportunity for sporadic SCID cases to have earlier diagnosis, further improvements in isolation, preventative care, and infectious screening practices, as well as shorter time to definitive therapy, should be sought so that infection risk can be further decreased.

Analysis of the early life data did not demonstrate a clear advantage for inpatient versus outpatient management prior to HSCT in terms of survival or risk of development of infections. Based on our survey of PIDTC centers, there was no consensus regarding inpatient versus outpatient management prior to transplant. Practices for inpatients commonly included hand hygiene and PPE, as well as a protective PPV environment. The clinical status of the patient and appropriateness of the home environment were important factors contributing to the decision to allow outpatient management. However, what comprised an appropriate home environment was multifactorial. The recommended frequency of follow-up while awaiting HSCT varied. Notably, there were also discrepancies between respondents from a single center, the majority of which concerned isolation of patients prior to HSCT. Standard practice documents existed at many centers, but were not always consistently followed. Further study is needed to determine which environmental factors provide best protection from infection for SCID patients diagnosed via NBS.

An area of unanimity in the SCID provider community was the routine use of antimicrobial prophylaxis and immunoglobulin for SCID patients prior to definitive therapy, although timing of initiation and dosing were not uniform.

Viral infections led to significant morbidity and mortality, even in this cohort of SCID patients diagnosed as newborns. While screening for CMV, EBV, and adenovirus was widespread, respiratory virus screening was less common in the absence of symptoms. With regard to CMV, blood-based PCR screening was routinely performed, and a majority of providers recommended against breastfeeding by CMV-seropositive mothers. A prior retrospective analysis of patients in the UK suggested that CMV disease disproportionately occurred in those who were breastfed [12]. A recent single-center study had equal cases in breastfed and non-breastfed babies, but had very low overall rates of CMV infection [13]. Further study is needed to determine what screening should be performed and at what interval, in order to best detect and treat CMV. Similarly, there is a need to determine whether interventions will be effective in preventing CMV in the pre-HSCT SCID population, and whether newer anti-CMV antivirals and cellular therapies will make treatment more successful. Based on current understanding of CMV transmission in neonates, we propose the following management strategy [14–16]:

- Infants suspected of having SCID should discontinue breastfeeding and start ready-to-feed infant formula until maternal CMV status is known.
- Infant should undergo work-up for CMV infection with blood CMV DNA PCR and urine CMV DNA PCR; and mother should undergo CMV IgG testing. While awaiting maternal CMV results consider valganciclovir for baby and advise mother to hold breastfeeding (provide breast pump and lactation consult) [17, 18].
- If mother is CMV IgG negative, encourage resumption of breastfeeding and stop infant valganciclovir; if mother is CMV IgG positive, CMV may be shed in breastmilk, so nursing should not continue.
- Infant CMV DNA PCR studies should be conducted weekly for a total of 4 tests; if all are negative, recommend testing every 3 weeks. If infant has any positive CMV PCR, give provide treatment with ganciclovir and/or other effective anti-CMV therapy and work with local transplant team to plan for urgent HCT.

More complete recommendations for prophylactic medications in the pre-transplant period are available in Table 2. The PIDTC 6901 study prospectively collected patient data via standardized case report forms that assessed infections at a baseline visit prior to HSCT, but did not collect details of each patient's state SCID NBS program nor pre-HSCT management. The wide variation in management pre- and post-HSCT limited our ability to assess the impacts of these circumstances, the incidence of infections, and ultimate survival following HSCT. A planned prospective protocol tracking pre-HSCT management will assess the impact of pre-HSCT interventions on patient outcomes. Additionally, while all PIDTC centers participated in our survey of management practices, some questions were left unanswered by the participants, decreasing our statistical power. Finally, the survey did not assess factors contributing to delay of conditioned versus unconditioned HSCT specifically. For example, some centers using conditioning delayed HSCT until an infant reached a certain age, while presence of infection could have required an urgent, unconditioned HSCT.

Ideally, consistent care guidelines should be established for management of SCID prior to definitive therapy. These guidelines should address outpatient versus inpatient pre-HSCT

Table 2 Recommended prophylactic medications

Medication	Dose	Notes
Immunoglobulin replacement	400–600 mg/kg every 4 weeks for intravenous administration 100–150 mg/kg weekly for subcutaneous administration	Start within a few weeks of life. Maintain IgG trough > 800 mg/dL
PJP prophylaxis		
TMP/SMX	2.5 mg/kg TMP component PO BID twice weekly	Start when infant > 30 days old; monitor bilirubin and CBC
Pentamidine	4 mg/kg per dose IV every 2 weeks	If < 30 days old and high risk; give once, then re-evaluate in 2 weeks
Folinic acid	1.25 mg QD twice a week	Used to minimize TMP/SMX neutropenia
Valganciclovir for CMV prophylaxis	Valganciclovir 16 mg/kg PO QD	Start immediately only if there are clinical indications, such as abnormal physical exam or liver abnormalities. Otherwise, wait for mother's CMV IgG. If mother CMV IgG+, give valganciclovir until infant weekly blood PCR CMV is neg ×4 and then stop, provided infant remains well and CMV PCR negative May elect not to not treat if mother CMV negative and infant healthy
Acyclovir for HSV prophylaxis	Acyclovir 12.5 mg/kg PO BID or 8 mg/kg IV q12hr (≤ 12 kg)	Start immediately only if HSV risk identified; do not give in addition to valganciclovir
Fluconazole for fungal prophylaxis	3 or 6 mg/kg/day PO QD; check NICU dose for infants younger than 30 days	Start immediately; ensure normal LFTs prior to starting and follow
Palivizumab	Per institutional protocol, monthly	During RSV season

management, use of PPE and isolation, clinical monitoring, virologic screening, and administration of immunoglobulin and antimicrobial prophylaxis. Pre- and post-implementation assessment of outcomes may help centers to fine-tune their local practices to improve patient outcomes. While suggested practices for management of SCID have been published based on single-center experiences [19–22], evidence-based practice parameters are needed to assist in establishing universal standards of care for these infants, ultimately maximizing the potential of NBS to bring all babies with SCID to definitive treatment infection-free.

Authorship Contributions • Morna Dorsey, Nicola AM Wright, Natalia S. Chaimowitz, Blachy J Dávila Saldaña, Holly Miller, Michael D. Keller, Monica S. Thakar, and Ami J. Shah, MD, designed data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the final manuscript.

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• All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability Deidentified individual participant data will not be made available.

Compliance with Ethical Standards

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

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Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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