Outcome of Hematopoietic Stem Cell Transplantation in patients with Mendelian Susceptibility to Mycobacterial Diseases

Nesrine Radwan1,2 · Zohreh Nademi2,3 · Su Han Lum2 · Terry Flood2 · Mario Abinun1,2 · Stephen Owens2 · Eleri Williams2 · Andrew R. Gennery2,3 · Sophie Hambleton2,3 · Mary A. Slatter2,3,4

Received: 25 March 2021 / Accepted: 29 July 2021 / Published online: 13 August 2021
© Crown 2021

Abstract
Predisposition to mycobacterial infection is a key presenting feature of several rare inborn errors of intrinsic and innate immunity. Hematopoietic stem cell transplantation (HSCT) can be curative for such conditions, but published reports are few. We present a retrospective survey of the outcome of 11 affected patients (7 males, 4 females) who underwent HSCT between 2007 and 2019. Eight patients had disseminated mycobacterial infection prior to transplant. Median age at first transplant was 48 months (9 - 192); three patients were successfully re-transplanted due to secondary graft failure. Donors were matched family (1), matched unrelated (3), and mismatched unrelated and haploidentical family (5 each). Stem cell source was peripheral blood (9), bone marrow (4), and cord blood (1). TCRαβ/CD19+ depletion was performed in 6. Conditioning regimens were treosulfan, fludarabine (4), with additional thiotepa (in 8), and fludarabine, melphalan (2); all had serotherapy with alemtuzumab (8) or anti T-lymphocyte globulin (6). Median hospital stay was 113 days (36–330). Three patients developed acute grade I-II skin and one grade IV skin graft versus host disease. Four patients had immune-reconstitution syndrome. Two reactivated cytomegalovirus (CMV), 1 Epstein-Barr virus, and 3 adenovirus post HSCT. Nine are alive, 1 died early post-transplant from CMV, and the other was a late death from pneumococcal sepsis. Patients with active mycobacterial infection at HSCT continued anti-mycobacterial therapy for almost 12 months. In conclusion, HSCT is a successful treatment for patients with mycobacterial susceptibility even with disseminated mycobacterial infection and in the absence of an HLA matched donor.

Keywords Mendelian susceptibility to mycobacterial disease · Hematopoietic stem cell transplant · Inborn errors of immunity · Immune reconstitution syndrome

Abbreviations
AD Autosomal dominant
Alem Alemtuzumab
AR Autosomal recessive
ATG Anti-thymocyte globulin
BCG Bacille Calmette-Guérin
BM Bone marrow
CB Cord blood
CMV Cytomegalovirus
CYBB Cytochrome b-245, beta
EBV Epstein Barr virus
Flu Fludarabine
GATA2 GATA-binding factor 2
GVHD Graft versus host disease
HLA Human leukocyte antigen
HSCT Hematopoietic stem cell transplantation
HHV6 Human herpes virus type 6
IEI Inborn errors of immunity
IFN-γ Interferon-gamma
IFNGR Interferon gamma receptor
IRF8 Interferon regulatory factor 8
MFD Matched family donor

Clinical Implications • HSCT for mycobacterial susceptibility can be curative
• Outcome is good even in patients with previous disseminated mycobacterial infection
• Modern methods of T-lymphocyte depletion enable successful outcome in patients with mismatched donors

Capsule Summary HSCT for patients with mycobacterial susceptibility has a good outcome even in patients with disseminated mycobacterial disease and without an HLA identical donor.

Mary A. Slatter
Mary.slatter@nhs.net

Extended author information available on the last page of the article
Introduction

Mendelian susceptibility to mycobacterial disease (MSMD) is a group of rare inborn errors of immunity (IEI) characterized by selective susceptibility to mycobacteria including BCG-derived Mycobacterium bovis and environmental mycobacteria [1, 2]. The main underlying pathogenic mechanism is impaired production of or responses to interferon gamma (IFN-γ) [3, 4]. In addition, mycobacterial susceptibility is a prominent feature of several other non-SCID, non-CGD disorders that also confer vulnerability to other pathogens and are thus classified separately by the IUIS [5, 6]. In common with classical MSMD, these disorders generally impair intrinsic and innate immunity.

Mycobacterial infection complicating non-SCID IEI shows a wide range of clinical manifestations, from localized to disseminated, acute to chronic infections, plus immature or mature granulomas [7–9]. Typically, age of onset is in childhood, but there are reported cases in adults [4]. Owing to BCG vaccination at birth in many parts of the world, some affected newborn infants may present as a consequence of this vaccination [5]. Some patients develop non-typhoidal Salmonella infection [8–10], and a significant proportion experience mucocutaneous candidiasis [4]. In some disorders, viral infections, in particular due to herpesviruses, have been reported [8, 9]. Standard hematological and immunological screening results for IEI are often normal [1], making diagnosis challenging. The overall prognosis for MSMD depends on its specific molecular basis but is often poor [11]. Although patients with some genetic mutations benefit from recombinant IFN-γ, treatment of mycobacterial infection may not be curative without correction of the underlying condition as is the case with absent IFNGR where hematopoietic stem cell transplantation (HSCT) is the only treatment [11].

There are few reported data on patients transplanted for MSMD or related disorders conferring mycobacterial susceptibility. We report outcome of patients transplanted in our center, excluding those with CGD who have recently been reported [12, 13]. Patients 9 and 11 have previously been published [14, 15].

Clinical and laboratory data were retrieved from patients’ medical files and laboratory records. Written informed consent was obtained from the parents or legal guardians as per institutional practice.

The donor hierarchy was (i) matched family donor, (ii) matched unrelated donor, followed by a single antigen mismatched unrelated or haploidentical donor. High-resolution HLA typing was performed for class I and II alleles. Six products underwent TCRαβ/CD19+ depletion using the Clinimacs (Miltenyi Biotec Ltd, Surrey, UK) systems [16].

Prior to transplant, all patients were screened for viruses in blood, stool, and respiratory samples including a bronchoalveolar lavage. Routine surveillance for cytomegalovirus (CMV), adenovirus, Epstein Barr virus (EBV), and human herpes virus type 6 (HHV6) in blood was performed weekly. All patients received prophylaxis against fungi, Pneumocystis jiroveci (PCP), and viral reactivation and received immunoglobulin replacement until normal IgM was demonstrated. Donor chimerism was measured by labeling peripheral blood with anti-CD3, -CD19, or -CD15 microbeads. Cell lines were separated using an autoMACS® automated bench-top magnetic cell sorter (Miltenyi Biotec Ltd, Surrey, UK). Separated cells were assayed using variable number of tandem repeats.

Results and Discussion

Between 2007 and 2019, we transplanted 8 children with a history of infection with atypical mycobacteria or disseminated BCG due to 6 different genetic diseases (deficiency of IRF8 (AR), NEMO (IKBKGC), GATA2, STAT1 (AR), IFNGR2 (AR), gain of function in NFKBIA (AD)). A further 3 patients underwent HSCT for the same genetic disorders in the absence of preceding mycobacterial infection and were included for comparison (IRF8 (AR/AD), GATA2).

Patient characteristics (n = 11, 7 female, 4 male) are shown in Table 1. Eight had proven infection, either due to BCG vaccination (4/8) or atypical mycobacteria (4/8). Five (45%) patients presented with failure to thrive, 6 (55%) with lymphadenopathy and or hepatosplenomegaly, and 3 (27%) each had neurodevelopmental delay, eczema, and dental abnormalities.

A detailed description of transplant characteristics is summarized in Table 2.

Eleven patients received 14 transplants. Median age at first transplant was 48 months (range 9–192). Median time lag between presentation and transplantation was 31 months (range 6–89).

| Abbreviation | Definition |
|--------------|------------|
| MMF | Mycophenolate mofetil |
| MUD | Matched unrelated donor |
| MMUD | Mismatched unrelated donor |
| MSMD | Mendelian susceptibility to mycobacterial disease |
| NEMO | Nuclear factor Kappa B essential modulator |
| NFKBIA | NF-kappa-B inhibitor alpha |
| PBSC | Peripheral blood stem cell |
| STAT1 | Signal transducer and activator of transcription 1 |
| Treo | Treosulfan |
One patient had a graft from an HLA-matched family donor (MFD), 3 from matched unrelated donors (MUD), and 5 each from mismatched unrelated donors (MMUD) and haploidentical parental donors. TCRαβ/CD19 depletion was performed in all haploidentical and 1 MMUD grafts. Stem cell source was peripheral blood (PBSC) for 9 transplants, bone marrow (BM) for 4, and cord blood (CB) for 1, with median CD34+ cell doses of $3.3 \times 10^6$/kg for BM, $8.7 \times 10^6$/kg for unmanipulated PBSC, $1.5 \times 10^6$/kg for CB, and $13.9 \times 10^6$/kg in TCR αβ-depleted grafts.

Conditioning regimen used for unmanipulated grafts was either treosulfan (Treo) and fludarabine (Flu) alone (4/8), or with additional thiopeta (TT) (2/8), or Flu and melphalan (2/8), and alemtuzumab (Alem) was used as serotherapy. TCRαβ/CD19-depleted graft recipients received Treo/Flu/TT with rituximab and anti-thymocyte globulin according to institutional practice. Post-HSCT graft versus host disease (GVHD) prophylaxis with cyclosporin and mycophenolate mofetil was given to all patients except those receiving TCRαβ/CD19+-depleted products.

Table 1 Clinical phenotype

| Patients | Mutated gene (mode of inheritance) | Age at presentation in months | Sex | Clinical picture | Infections Pre-HSCT | Treatment Pre-HSCT |
|----------|-----------------------------------|-----------------------------|-----|------------------|--------------------|-------------------|
| P1       | IRF8 (AR)                         | 3                           | F   | FTT, neurodevelopmental delay, intracranial calcification with ventriculomegaly, hepatosplenomegaly | Disseminated BCG | Antimycobacterial |
| P2       | IRF8 (AR)                         | 2                           | M   | Eczema, neurodevelopmental delay, paronychia | Recurrent chest infection, pyelonephritis | None |
| P3       | IRF8 (AD)                         | 8                           | M   | Small tonsils, hepatosplenomegaly, lymphadenopathy, warts, barrel shaped chest, clubbing | Recurrent chest infections, bronchiectasis, warts | None |
| P4       | IFNGR2 (AR)                       | 9                           | M   | FTT, neurodevelopmental delay, mycobacterium abscess | Mycobacterium abscess, MRSA in stool | Antimycobacterial |
| P5       | IFNGR2 (AR)                       | 5                           | F   | Hepatosplenomegaly, lymphadenopathy | Disseminated BCG, cryptosporidium in stool, enterovirus, norovirus, CMV, HHV6, adenovirus, influenza B | Antimycobacterial |
| P6       | IKBKG (X-L)                       | 6                           | M   | FTT, eczema, hair loss, ichthyosis, spiky teeth, lymphadenopathy | PCP, norovirus, rotavirus, Mycobacterium intracellulare in BAL | Antimycobacterial |
| P7       | IKBKG (X-L)                       | 9                           | M   | Hypodontia, ectodermal dysplasia, xeroderm pigmentosa, eczema | Pneumococcal meningitis, disseminated Mycobacterium avium infection | Antimycobacterial IFNg |
| P8       | GATA2 (AD)                        | 2                           | M   | Poor wound healing, vasculitic skin rash, clubbing, oral candidiasis | Recurrent upper respiratory tract infections, disseminated BCG | Antimycobacterial IFNg |
| P9       | GATA2 (AD, de novo)               | 168                         | M   | FTT, hepatosplenomegaly, lymphadenopathy, skin nodules, jaundice | Disseminated BCG, RSV bronchiolitis | Antimycobacterial Steroids IFNg |
| P10      | STAT1 (AR)                        | 1.5                         | F   | FTT, diarrhea, fever, skin rash, hepatomegaly, tooth abnormalities | Salmonella enteritis + osteomyelitis candida esophagitis disseminated Mycobacterium malmoense Sapo- and norovirus | Antimycobacterial |
| P11      | NFKBIA (AD, de novo)              | 1.7                         | F   | FTT, neurodevelopmental delay, intracranial calcification with ventriculomegaly, hepatosplenomegaly | | |

BAL bronchoalveolar lavage, BCG Bacillus Calmette–Guérin, CMV cytomegalovirus, F female, FTT failure to thrive, HHV6 Human herpes simplex virus, HSCT Hematopoietic stem cell transplantation, IFNg interferon gamma, M male, MRSA methicillin-resistant Staphylococcus aureus, PCP pneumocystis jiroveci, RSV respiratory syncytial virus, AD autosomal dominant, AR autosomal recessive, X-L X-linked
| Patient | Diagnosis | Age at HSCT (months) | Mycobacterial infection | Donor | Source | Conditioning | CD34+ (× 10^6/kg) | CD3+ | GVHD prophylaxis | Outcome | Last chimerism |
|---------|-----------|----------------------|-------------------------|-------|--------|-------------|-------------------|-------|------------------|---------|----------------|
| P1      | IRF8      | 9                    | Yes                     | MUD   | CB     | FT Alemtuzumab | 0.15              | 2.4×10^7/kg       | Ciclosporin, MMF | Alive  | 100% at 3 years |
| P2      | IRF8      | 48 (1st HCT)         | No                      | MUD   | PBSC   | FT Alemtuzumab | 8.1               | 3.7×10^7/kg       | Ciclosporin, MMF | Alive  | 100% at 1 year after 2nd HSCT |
|         |           | 93 (2nd, HSCT)       | No                      | New MUD | PBSC   | FTT Alemtuzumab | 9.3              | 2.4×10^8/kg       | Ciclosporin, MMF |       |                   |
| P3      | IRF8      | 97                   | No                      | MMUD (mismatch A) | TCRαβ/CD19 depleted PBSC | FTT, ATG, RTX | 4.7              | 0.72×10^8/kg      | –                  | Alive  | 100% at 1.5 years |
| P4      | IFNGR2    | 18                   | Yes                     | Maternal haploidentical | TCRαβ/CD19 depleted PBSC | FTT, ATG, RTX | 20               | CD3+ + TCRαβ + 0.43 × 10^8/kg | Alive | 100% at 6 months after 2nd HSCT |
|         |           | 24 (2nd, HSCT)       | Yes                     | Maternal haploidentical | TCRαβ/CD19 depleted PBSC | FTT, ATG, RTX | 12.4             | CD3+ + TCRαβ + 3.3 × 10^7/kg | – |                   |
| P5      | IFNGRa    | 34                   | Yes                     | Maternal haploidentical | TCRαβ/CD19 depleted PBSC | FTT, ATG, RTX | 12.1             | CD3+ + TCRαβ + 8.2 × 10^7/kg | None | Alive  | 100% at 1 year |
| P6      | IKBKG     | 54                   | Yes                     | MMUD (single A + C mismatches) | BM | FT Alemtuzumab | 3.0              | 5.8×10^6/kg       | Ciclosporin, MMF | Dead  | 100% at 7 years |
| P7      | IKBKG     | 78                   | Yes                     | MMUD (A mismatch) | PBSC | Fludarabine, melphalan, Alemtuzumab | 4.4              | 7.3×10^7/kg       | Ciclosporin, MMF | Alive  | 100% at 12 years |
| P8      | GATA2     | 43                   | No                      | MFD   | BM     | FTT Alemtuzumab | 4.3              | 6.3×10^7/kg       | Ciclosporin, MMF | Alive  | T 93%, B 96% CD15 18% at 18 months |
| P9      | GATA2     | 192                  | Yes                     | MMUD (C mismatch) | BM | Fludarabine, melphalan, Alemtuzumab | 1.9              | 3.2×10^7/kg       | Ciclosporin, MMF | Alive  | 100% at 11 years |
| P10     | STAT1     | 12                   | Yes                     | Paternal haploidentical | TCRαβ/CD19 depleted PBSC | FTT, ATG, RTX | 26.5             | CD3+ + TCRαβ + 3.97 × 10^4/kg | – | Dead | – |
| P11     | NFKBIA    | 51                   | Yes                     | MMUD (A mismatch) | BM | FT Alemtuzumab | 3.6              | 4.7×10^7/kg       | Ciclosporin, MMF | Alive  | 100% at 30 months after 2nd HSCT |
|         |           | 71 (2nd, HSCT)       | Yes                     | Paternal haploidentical | TCRαβ/CD19 depleted PBSC | FTT, ATG, RTX | 15.3             | CD3+ + TCRαβ + 3.1 × 10^4/kg | – |                   |

ATG anti-thymocyte globulin, BM bone marrow, CB cord blood, GvHD graft versus host disease, FT fludarabine, treosulfan, FTT fludarabine, treosulfan, thiopeta, HSCT hematopoietic stem cell transplantation, MFD matched family donor, MMF mycophenolate mofetil, MMUD mismatched unrelated donor, MUD matched unrelated donor, PBSC peripheral blood stem cells, RTX rituximab
Median days to neutrophil and platelet engraftment were 18 and 17 days, respectively. Three patients were successfully re-transplanted due to secondary graft failure. One patient with IRF8 deficiency who had a MUD PBSC with Treo/Flu/Alem conditioning for the first transplant received the second graft from a different MUD with additional TT. A patient with IFNGR2 deficiency received a second haploidentical TCRαβ/CD19 + -depleted PBSC. The patient with NFKBIA gain of function lost the graft following a MMUD BM with Treo/Flu/Alem conditioning but achieved sustained engraftment from a haploidentical TCRαβ/CD19 + -depleted PBSC. There is limited data on the addition of thiopeta to treosulfan and fludarabine, but it is increasingly being used to try to improve engraftment in reduced toxicity regimens. A report from 3 Israeli centers documented 44 patients, who received treosulfan-based conditioning for non-malignant diseases. A comparison in engraftment rates was made between those who received treosulfan and fludarabine (66.7%), treosulfan and cyclophosphamide (16.7%), and treosulfan, fludarabine, and thiopeta (94.7%). This did not translate into any difference in overall or disease free survival [17]. Nine of 11 patients are alive. One patient with autosomal recessive STAT1 deficiency died early post-transplant due to CMV pneumonitis. Another child with NEMO deficiency succumbed 8 years post-HSCT from pneumococcal sepsis. He had normal immune reconstitution, but post-transplant colitis was on topical oral budesonide and 6 weekly infliximab. He had stopped immunoglobulin replacement and was on pneumococcal prophylaxis and awaiting pneumococcal vaccination.

Eight patients received total parental nutrition for a median number of 25.5 days. Median hospital stay was 113 days (36–330). Three patients had grade I-II skin acute GVHD treated either by topical steroids, tacrolimus and/or systemic steroids. The patient with late death had grade IV acute skin GVHD that necessitated a prolonged course of combined immunosuppressive treatment and extra-corporeal photopheresis. Five patients had post-transplant immune-reconstitution syndrome (IRES) related to mycobacterial infection, manifesting as fever, raised inflammatory markers, malaise, and chronic relapsing lesions of skin, bones, and/or viscera. All 8 patients with a history of mycobacterial infection received long-term (median 12 months) antimycobacterial therapy with 2–4 agents. Those with severe IRES also received judicious anti-inflammatory treatment with steroids and cytokine blocking agents in cases that were steroid refractory (anakinra, infliximab). One patient developed late, renal biopsy–proven, thrombotic microangiopathy 7 months post-transplant. Six patients had viral reactivation: 2 CMV, 3 adenoviremia, and 1 EBV.

Long-term complications were assessed in 8 patients with more than 2 years’ follow up. The only late complication was in a patient with GATA2 deficiency who developed a melanocytic melanoma 7 years post-transplant which was surgically removed.

We investigated the impact of mycobacterial infection on outcome, but numbers were small with only 3 patients who did not have mycobacterial infection pre-transplant. There was a trend for a longer hospital stay in those with mycobacterial infection compared to those without (median of 87 and 71.5 days, respectively). Immune reconstitution was assessed at 6 months according to numbers of CD4 + lymphocytes, with no significant delay in CD4 + reconstitution in those with mycobacterial infection compared to those without (median CD4 + counts of 400 cells/ul and 392 cells/ul, respectively). Patients with more than 2 years follow up maintained chimerism between 90 and 100%. Patient 8 has mixed chimerism at 18 months with good immune reconstitution and no signs of disease.

Careful donor selection and preparation of the patient prior to HSCT including treatment of active mycobacterial infection are extremely important [18]. In our series, only 4 patients had fully matched donors available. The 2 patients that died had mismatched donors, but the rest of the cohort are alive and well. The presence of active or disseminated mycobacterial infection did not affect survival, but there was a trend toward more prolonged hospitalization. Roessler et al. reported a multicenter survey in which 2 children with active mycobacterial infection died post-HSCT and recommended optimal control of mycobacterial infection before HSCT and use of a non-T-cell–depleted transplant from an HLA-identical sibling after a fully myeloablative conditioning regimen [19]. Other authors report that achieving disease remission before HSCT affects outcome and immune reconstitution [20, 21]. Rottman et al. recommended use of non-T-cell−depleted PBSC or BM in order to achieve stable donor chimerism [22]. In our series, 6 out of 9 patients with a good outcome had TCRαβ/CD19 + -depleted stem cells from mismatched donors. New methods of T cell depletion for mismatched grafts such as CD3 + TCRαβ/CD19 + depletion show promising results in terms of good engraftment but reduced risk of GVHD in IEI. In the absence of a suitable mismatched family donor which is usually easier and faster to organize, a mismatched unrelated donor can be used with success [16, 23].

In conclusion, most of the literature to date concerning HSCT for these disorders consists of case reports and advises transplant only if active infection is controlled and there is a fully matched donor. Our series suggests that improvement in conditioning regimens, graft manipulation, and prolonged anti-microbial treatment have made HSCT a successful option for patients with mycobacterial susceptibility including those with disseminated mycobacterial infection and without a fully HLA-matched donor in centers of expertise where these options are available.
Author Contribution NR collected and analyzed the data of the patients. NR, SH, and MS wrote the manuscript. ZN, SHEL, TF, MA, SO, EW, and ARG all reviewed and edited the manuscript.

Data Availability Clinical data files are stored at the Great North Children’s hospital and may be shared according to institutional guidelines.

Code Availability This is not applicable.

Declarations

Ethics Approval No formal ethical approval was obtained for this retrospective study.

Consent to Participate Freely given written informed consent was obtained from participants/parents or legal guardians for data collection and participation as per institutional practice.

Consent for Publication Freely given written informed consent was obtained from participants/parents or legal guardians for publication as per institutional practice.

Competing Interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol. 2002;20:581–620.
2. Casanova JL, Jouanguy E, Lamhamedi S, Blanche S, Fischer A. Immunological conditions of children with BCG disseminated infection. Lancet. 1995;346(8974):581.
3. Nathan CF, Murray HW, Wiebe ME, Rubin BY. Identification of interferon-gamma as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity. J Exp Med. 1983;158(3):670–89.
4. Bustamante J. Mendelian susceptibility to mycobacterial disease: recent discoveries. Hum Genet. 2020;139(6–7):993–1000.
5. Boushiha A, Jeddane L, Picard C, Al-Herz W, Ait Al, Chatila T, et al. Human inborn errors of immunity: 2019 update of the IUIS Phenotypical Classification. J Clin Immunol. 2020;40(1):66–81.
6. Tangye SG, Al-Herz W, Boushiha A, Chatila T, Cunningham-Rundles C, Ettzioni A, et al. Human Inborn errors of immunity: 2019 update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2020;40(1):24–64.
7. Poyhonen L, Bustamante J, Casanova JL, Jouanguy E, Zhang Q. Life-threatening infections due to live-attenuated vaccines: early manifestations of inborn errors of immunity. J Clin Immunol. 2019;39(4):376–90.
8. Rosain J, Kong XF, Martinez-Barricarte R, Oleaga-Qintas C, Ramirez-Alejo N, Markle J, et al. Mendelian susceptibility to mycobacterial disease: 2014–2018 update. Immunol Cell Biol. 2019;97(4):360–7.
9. Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. Semin Immunol. 2014;26(6):454–70.
10. Rosain J, Oleaga-Qintas C, Deswarte C, Verdin H, Marot S, Syridou G, et al. A variety of Alu-mediated copy number variations can underlie IL-12Rbeta1 deficiency. J Clin Immunol. 2018;38(5):617–27.
11. Bandari AK, Muthusamy B, Bhat S, Govindaraj P, Rajagopalan P, Dalvi A, et al. A novel splice site mutation in IFNγR2 in patients with primary immunodeficiency exhibiting susceptibility to mycobacterial diseases. Front Immunol. 2019;10:1964.
12. Lum SH, Flood T, Hambleton S, McNaughton P, Watson H, Abinun M, et al. Two decades of excellent transplant survival in children with chronic granulomatous disease. Blood. 2019;133(23):2546–9.
13. Chiesa R, Wang J, Blok HJ, Hazelaar S, Neven B, Moshou D, et al. Hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults. Blood. 2020;136(10):1201–11.
14. Tholouli E, Sturgess K, Dickinson RE, Genney A, Cant AJ, Jackson G, et al. In vivo T-depleted reduced intensity transplantation for GATA2-related immune dysfunction. Blood. 2018;131(12):1383–7.
15. Staples E, Morillo-Gutierrez B, Davies J, Petersheim D, Massaad M, Slater M, et al. Disseminated Mycobacterium malmoense and Salmonella infections associated with a novel variant in NFkBIA. J Clin Immunol. 2017;37(5):415–8.
16. Shah RM, Elfeoky R, Nademi Z, Qasim W, Amrolia P, Chiesa R, et al. T-cell receptor αβ+ and CD19+ cell-depleted haploidentical and mismatched hematopoietic stem cell transplantation in primary immune deficiency. J Allergy Clin Immunol. 2018;141(4):1417–26.
17. Dinur-Schejter Y, Krauss AC, Erlich O, Gorelik N, Yahel A, Porat I, et al. Bone marrow transplantation for non-malignant diseases using treosulfan-based conditioning. Pediatr Blood Cancer. 2015;62:299–304.
18. Patel S, Uppuluri R, VellaichamySwaminathan H, Ravichandran M, NarmacodeRamanan K, Raj R. Mendelian susceptibility to mycobacterial disease-challenges in hematopoietic stem cell transplantation. Pediatr Blood Cancer. 2020;67(5):e28187.
19. Roesler J, Horwitz ME, Picard C, Bordigoni P, Davies G, Koscielniak E, et al. Hematopoietic stem cell transplantation for complete IFN-γ receptor one deficiency: a multi-institutional survey. J Pediatr. 2004;145(6):806–12.
20. Chantrain CF, Bruwier A, Brichard B, Largent V, Chapgier A, Feinberg J, et al. Successful hematopoietic stem cell transplantation in a child with active disseminated Mycobacterium fortuitum infection and interferon-gamma receptor 1 deficiency. Bone Marrow Transplant. 2006;38(1):75–6.
21. Olbrich P, Martinez-Saavedra MT, Perez-Hurtado JM, Sanchez C, Sanchez B, Deswarte C, et al. Diagnostic and therapeutic challenges in a child with complete interferon-γ receptor 1 deficiency. Pediatr Blood Cancer. 2015;62(11):2036–9.
22. Rottman M, Soudais C, Vogt G, Renia L, Emile JF, Decaluwe H, et al. IFN-γ mediates the rejection of hematopoietic stem cells in IFN-eR1-deficient hosts. PLoS Med. 2008;5(1):e26.
23. Balasov D, Shcherbina A, Maschman M, Trakhtman P, Skvortsova Y, Shelikhova L, et al. Single-center experience of unrelated and haploidentical stem cell transplantation with TCRαβ and CD19
depletion in children with primary immunodeficiency. Biol Blood Marrow Transplant. 2015;21:1955–62.

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

Authors and Affiliations

Nesrine Radwan¹,² · Zohreh Nademi²,³ · Su Han Lum² · Terry Flood² · Mario Abinun¹,² · Stephen Owens² · Eleri Williams² · Andrew R. Gennery²,³ · Sophie Hambleton²,³ · Mary A. Slatter²,³,⁴

¹ Pediatric Allergy and Immunology Unit, Children’s Hospital, Ain Shams University, Cairo, Egypt
² Children’s Stem Cell Transplant Unit, Great North Children’s Hospital, Newcastle upon Tyne, UK
³ Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
⁴ Paediatric Immunology, CRB level 4, Block 2, Royal Victoria Infirmary, Queen Victoria Rd, Newcastle upon Tyne, UK