International retrospective study of allogeneic hematopoietic cell transplantation for activated PI3K-delta syndrome

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Background: Activated phosphoinositide 3-kinase delta syndrome (APDS) is a combined immunodeficiency with a heterogeneous phenotype considered reversible by allogeneic hematopoietic cell transplantation (HCT).

Objectives: This study sought to characterize HCT outcomes in APDS.

Methods: Retrospective data were collected on 57 patients with APDS1/2 (median age, 13 years; range, 2-66 years) who underwent HCT.

Results: Pre-HCT comorbidities such as lung, gastrointestinal, and liver pathology were common, with hematologic malignancy in 26% With median follow-up of 2.3 years, 2-year overall and graft failure-free survival probabilities were 86% and 68%, respectively, and did not differ significantly by APDS1 versus APDS2, donor type, or conditioning intensity. The 2-year cumulative incidence of graft failure following first HCT was 17% overall but 42% if mammalian target of rapamycin inhibitor(s) were used in the first year post-HCT, compared with 9% without mTORi. Similarly, 2-year cumulative incidence of unplanned donor cell infusion was overall 28%, but 65% in the context of mTORi receipt and 23% without. Phenotype reversal occurred in 96% of evaluable patients, of whom 17% had mixed chimerism. Vulnerability to renal complications continued post-HCT, adding new insights into potential nonimmunologic roles of phosphoinositide 3-kinase not correctable through HCT.

Conclusions: Graft failure, graft instability, and poor graft function requiring unplanned donor cell infusion were major barriers to successful HCT. Post-HCT mTORi use may confer an advantage to residual host cells, promoting graft instability. Longer-term post-HCT follow-up of more patients is needed to elucidate the kinetics of immune reconstitution and donor chimerism, establish approaches that reduce graft instability, and assess the completeness of phenotype reversal over time. (J Allergy Clin Immunol 2022;149:410-21.)

Key words: Primary immunodeficiency, activated phosphoinositide 3-kinase delta syndrome, lymphoproliferation, allogeneic hematopoietic cell transplantation, graft failure, mTOR inhibitor, serotherapy

Activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) was first described in 2013, with heterozygous mutations in PI3Kδ catalytic p110δ (PIK3CD) or regulatory p85α (PIK3R1) subunits leading to APDS1 and APDS2, respectively.1,2 PI3Kδ are expressed in various hematopoietic cells and have important roles in T and B lymphocyte homeostasis. The heterogeneous immunological phenotype of APDS may include reduced naive T cells, increased senescent CD8+ T cells, increased transitional B cells, decreased class-switched memory B cells, and dysgranulopoiesis.3-6 Clinical manifestations vary, including, among others, recurrent sinopulmonary infections, enteropathy, autoimmunity, nonneoplastic lymphoproliferation, lymphoma, and impaired EBV, cytomegalovirus (CMV), and varicella-zoster virus control.4,5,7

Supportive care may include antimicrobials and/or immunoglobulin replacement. Corticosteroids, rituximab, and splenectomy may attenuate autoimmune and lymphoproliferative disease manifestations.3,8 The mammalian target of rapamycin (mTOR) activated downstream of PI3K has a significant role in the regulation of immune responses and therefore mTOR inhibitor(s) (mTORi; rapamycin/sirolimus or everolimus) can ameliorate the severity of nonneoplastic lymphoproliferative disease and restore natural killer cell function.9,10 Selective PI3K-delta inhibitors are of interest as a more targeted treatment option and are under continued clinical investigation,11 but the ability of these therapies to prevent the development of life- and organ-threatening complications for the life span of affected individuals remains to be seen. Allogeneic hematopoietic cell transplantation (HCT) offers a potential immunologic cure for patients with APDS1/2;12,13 however, questions remain regarding the optimal timing, intensity, and approach to HCT for APDS1/2, as well as the donor chimerism needed to durably achieve engraftment of donor cells and to prevent immunopathological manifestations of disease.14 Herein, we present the largest international retrospective study of HCT outcomes of patients with APDS1/2 to date.

METHODS

Data collection

We conducted an international case series study of the clinical outcomes of patients with APDS1/2 undergoing HCT. Each participating site obtained approval to contribute deidentified data as per institutional requirements, in accordance with the Declaration of Helsinki, prior to contributing data. Data transfer agreements were put in place when deemed required. The APDS European Society for Immunodeficiencies registry and European Society for Blood and Marrow Transplantation Inborn Errors Working Party were queried to identify European contributors.

Criteria for inclusion were (1) pathogenic germline PIK3CD or PIK3R1 mutation and (2) receipt of HCT for APDS1/2 disease manifestations. A deidentified data query form was completed by participating physicians for each patient.

Data captured included patient demographics; pre-HCT disease manifestations and comorbidities; HCT-comorbidity index (HCT-CI) score;15 prior therapies; HCT approach including conditioning drugs and intensity, graft source, dose, manipulation, and donor demographics; graft-versus-host disease (GVHD) prophylaxis approach; HCT complications; engraftment and chimerism kinetics; immune reconstitution; degree of post-HCT phenotype reversal; follow-up duration; and survival outcomes.

Endpoint definitions and captured complications are detailed in Table E1 in this article’s Online Repository at www.jacionline.org.

Data were locked for analysis on July 13, 2020.
**RESULTS**

Fifty-seven pediatric and adult patients with APDS who received HCT (43 with PIK3CD, 14 with PIK3RI mutations) were included, all with confirmed pathogenic mutations and 20 with previously detailed HCT courses. The cumulative incidences of transplant-related mortality, GF, and subsequent unplanned donor cell infusion (DCI) were determined (competing risk: death), as well as CD4+ T-cell recovery >200 cells/µL (competing risks: death, GF). Cumulative incidence curves were constructed for subgroups based on conditioning intensity, use of serotherapy, HLA match, and use of mTORi post-HCT.

Survival curves, Kruskal-Wallis, and Fisher exact tests were generated using GraphPad Prism, version 8.4.3 (Graph-Pad Software, La Jolla, Calif; www.graphpad.com). Cumulative incidence curves were generated using R program, version 3.6.1 (R Core Development Team, Vienna, Austria; www.r-project.org). Results were considered statistically significant if 2-tailed $P < .05$.

### Statistical analyses

Descriptive statistics were used for patient and HCT characteristics. Conditioning intensity was categorized as myeloablative conditioning (MAC), reduced-toxicity MAC (RT-MAC, regimens using treosulfan as an alkylator), reduced-intensity conditioning (RIC), and nonmyeloablative conditioning based on published consensus definitions and the treating center’s intent.

Survival curves were constructed for overall survival (OS) and graft failure (GF)-free survival (GFFS) using the Kaplan-Meier method and compared using the log-rank test.

Cumulative incidence curves were constructed using the method of Fine and Gray and compared using $K$-sample tests. The cumulative incidences of transplant-related mortality, GF, and subsequent unplanned donor cell infusion (DCI) were determined (competing risk: death), as well as CD4+ T-cell recovery >200 cells/µL (competing risks: death, GF). Cumulative incidence curves were constructed for subgroups based on conditioning intensity, use of serotherapy, HLA match, and use of mTORi post-HCT.

### Clinical history and phenotype

Noninfectious lung pathology 38 (67)
Gastrointestinal pathology 32 (57)
History of immune cytopenias 19 (33)
Hematological malignancy 15 (26)
B-cell lymphoma 13 (23)$§$
Multiple myeloma 1 (2)
Hepatosplenic CD8+ T-cell lymphoma 1 (2)
Liver pathology

**TABLE I.** Patient baseline characteristics

| Genomic defect* | Patients (n = 57) |
|-----------------|------------------|
| **Known at time of first HCT** | |
| Familial (confirmed) | 10 (18) |
| PIK3CD gain of function, heterozygous | 43 (75) |
| c.3061G>A, p.E1021K | 33 |
| Other | 10$†$ |
| PIK3RI splice site mutation, heterozygous | 14 (25) |
| c.1425+1 G>A | 10 |
| Other | 4$‡$ |
| **Clinical history and phenotype** | |
| Noninfectious lung pathology | 38 (67) |
| Gastrointestinal pathology | 32 (57) |
| History of immune cytopenias | 19 (33) |
| Hematological malignancy | 15 (26) |
| B-cell lymphoma | 13 (23)$§$ |
| Multiple myeloma | 1 (2) |
| Hepatosplenic CD8+ T-cell lymphoma | 1 (2) |
| Liver pathology | |
| Known nodular regenerative hyperplasia or portal hypertension | 7 (12) |
| Renal pathology | 8 (14) |
| Cardiac pathology | 4 (7) |
| Prior therapies | |
| Immunoglobulin infusions | 49 (86) |
| nTORi | 28 (49) |
| Rituximab | 23 (40) |
| Nonmalignant indication (lymphoproliferation, autoimmunity) | 15 (26) |
| As part of multidrug chemotherapy for malignancy | 8 (14) |
| Splenectomy | 10 (18) |
| mTORi inhibitor | 4 (7) |
| **Clinical status at HCT** | |
| HCT-CI score at first HCT (n = 48)$§$ | 2 (0-7) |
| Pediatric only (n = 37) | 2 (0-7) |
| Adult only (n = 11) | 4 (1-6) |
| HCT-CI score ≥3 | 21 (44) |
| Pediatric only (n = 37), HCT-CI score ≥3 | 12 (32) |
| Adult only (n = 11), HCT-CI score ≥3 | 9 (82) |
| Karnofsky/Lansky performance status at first HCT (n = 44)$§$ | 90 (30-100) |
| Hematological malignancy status at HCT | |
| In complete remission at HCT | 10 (18) |
| In partial remission or active at HCT | 6 (11) |
| Hepatosplenomegaly | 29 (51) |
| Active infection | 29 (51) |
| Active immune cytopenias | 10 (18) |

Values are n, %, or median (range).

*Pathogenicity was confirmed for all mutations.
†Other PIK3CD mutations: c.1573G>A, p.E525K (n = 3); c.1002C>A, p.N334K (n = 2); c.1264T>C, p.C416R (n = 2); c.3074A>G, p.E1025K (n = 1); c.1574A>C, p.E525A (n = 1); c.371 G>A, p.G124D (n = 1).
‡Other PIK3RI mutations: c.1425+1 G>T (n = 2); n = 1 each: c.1422_1_425+1 delCCAG, c.1425+1 G>C.
§B-cell lymphoma details: diffuse large B-cell lymphoma (n = 7), 1 patient with 2 separate lymphomas: 5 EBV-positive, 2 EBV-negative; Hodgkin lymphoma (n = 6; 2 EBV-positive, 2 EBV-negative, EBV data not available for 2), marginal zone lymphoma (n = 2, EBV-positive, 1 EBV-negative).

$§$ Lung function results, FEV1, and diffusing capacity of carbon monoxide (DLCO) were available in 8 of 37 pediatric patients, FEV1 only in 17, DLCO only in 1, and not performed in 11, due to patient inability or center practices. Thus, HCT-CI scores in pediatric patients may be underestimated. Of 11 adults, FEV1, and DLCO were available for 9, and FEV1, only for 2.

[1] One patient had 2 B-cell lymphomas prior to HCT, EBV-positive nodular sclerosis classical Hodgkin lymphoma in CR1 at time of HCT, and EBV-positive marginal zone lymphoma active and untreated prior to HCT.

Donor, graft, and HCT platform characteristics for 66 HCTs performed are detailed in Tables II and III. Unrelated donors were the most frequent donor source (62%), with unmanipulated bone marrow as the most frequent graft source (48%). Matched sibling donors (MSDs) were used in 11% of HCTs; these recipients also had a lower median HCT-CI score, 1, and younger median age, 9 years, as compared to recipients of grafts from other donor types, although these differences did not reach statistical significance. Most HCTs were either RIC (n = 35, 53%) or MAC (n = 24, 36%). The median age of patients receiving RIC versus MAC/RT-MAC at time of first HCT was the same, 13 years, but age range was wider for recipients of RIC, who also had higher median HCT-CI score (RIC 3, MAC 2, RT-MAC 0, $P = .05$). Most HCTs were performed using serotherapy (n = 55, 83%). Adults were more likely than children to have hematologic malignancy...
as a HCT indication (67% vs 16%, \( P = .001 \)), but age at first HCT did not correlate with survival.

The median follow-up was 27 months overall by the reverse Kaplan-Meier method and 26.3 months (range, 1.5-220.6 months) from first HCT in surviving patients. The 2-year probabilities of OS and GFFS from first HCT were 86% and 68%, respectively (Fig 1). Differences in OS or GFFS were not statistically significant by underlying diagnosis (APDS1 vs APDS2), conditioning intensity, serotherapy choice, or donor source (Fig 2). Subcohorts with 2-year OS and GFFS probabilities of 100% included recipients of RT-MAC (n = 4) or MSD (n = 7), albeit limited by small numbers; in addition, 1 very late GF (day +1862) occurred in 1 RT-MAC HCT. Transplant-related mortality occurred due to late sepsis beyond 6 months post-HCT (n = 3), early post-HCT preengraftment infections (n = 2), viral infection (n = 1), sinusoidal obstructive syndrome (SOS, n = 1), and multiorgan failure in the setting of poor graft function (n = 1); 63% of deaths occurred in the first 100 days post-HCT. Outcomes by number of patients transplanted at individual centers are shown in Table E3 in this article’s Online Repository at www.jacionline.org.

Neutrophil engraftment occurred at median 16 days (range, 11-127 days) and platelet engraftment at median 21 days (range, 7-162 days). GF or graft instability and requirement for DCI occurred frequently, with 8 patients (14%) requiring a second HCT and 1 patient requiring a third HCT (Table IV). A total of 43 subsequent DCIs were administered to 18 patients (32%), including 24 donor lymphocyte infusions and 10 stem cell boosts. Mixed chimerism was the most common indication for intervention (n = 20), followed by poor graft function (n = 10).

By competing risk analysis, the estimated probability of GF following first HCT was 10% (95% CI, 4%-44%) at 1 year and 17% (95% CI, 8%-30%) at 2 and 3 years (Fig 3). However, when mTORi was used within the first year after HCT (in 13 patients), it rose from 15% (95% CI, 2%-40%) at 1 year to 42% (95% CI, 9%-73%) at 2 and 3 years, compared with a stable and lower incidence of 9% (95% CI, 3%-20%) at 1, 2, and 3 years without mTORi use, \( P = .06 \), approaching statistical significance. More strikingly, the estimated probability of DCI, overall 17% (95% CI, 8%-28%) at 1 year and 28% (95% CI, 15%-42%) at 2 and 3 years, was 55% (95% CI, 23%-79%) at 1 year and 65% (95% CI, 27%-86%) at 2 and 3 years when mTORi was used, compared with 12% (95% CI, 4%-24%) at 1 year and 23% (95% CI, 10%-39%) at 2 and 3 years without mTORi use, \( P = .002 \). The cumulative incidence of DCI, but not GF, also differed by use of serotherapy, where serotherapy-free regimens had 1- and 3-year estimated probabilities of DCI of 48% (95% CI, 12%-78%) and 61% (95% CI, 17%-87%), compared with 18% (95% CI, 8%-30%) and 28% (95% CI, 15%-44%) with serotherapy-containing regimens, \( P = .039 \). The cumulative incidence of GF or DCI did not differ by conditioning intensity or HLA match/relatedness.

Total T cells and CD4+ T cells were slower to recover than CD8+ T cells, B cells, and natural killer cells, were, with median total T cells within normal range at 1-year post-HCT and median CD4+ T cells within normal range at 1.5 years, whereas median counts for other lymphocyte subsets largely recovered by 6 months (Fig 4). Persistent profound T-cell lymphopenia (total T cells range, 46-155 cells/\( \mu \)L) was reported in 5 patients (17% of those with available data) at 10 to 12 months post-HCT; 2 were receiving systemic therapy for GVHD. At 1 year, the estimated probability of CD4+ T-cell count recovery above 200 cells/\( \mu \)L was 41% (95% CI, 27%-54%) and did not differ significantly by conditioning intensity or donor type. CD4+ T-cell recovery during the first year post-HCT was similar for serotherapy-containing and serotherapy-free regimens, although serotherapy-free HCT numbers were small and thus limited post-HCT lymphocyte subset data analyses for this group (see Fig E1 in this article’s Online Repository at www.jacionline.org).

Acute GVHD was reported in 22 patients (39%), 5 post-DCI; maximum grade 3 acute GVHD occurred in 4 patients (7%), 3 post-DCI. Chronic GVHD occurred in 9 patients (16%). The estimated probability of grades 3 and 4 acute GVHD at 1 year was 29% (95% CI, 3%-64%) with MSD, compared with 14% (95% CI, 2%-38%) for HLA haplolidentical, 0% for matched unrelated donors (MUDs), and 0% for umbilical cord blood, \( P = .018 \). The cumulative incidence of grades 2 to 4 acute GVHD did not differ significantly by donor type, conditioning intensity, or serotherapy use, nor did the cumulative incidence of grades 3 and 4 acute GVHD differ by conditioning intensity or serotherapy use. (See Fig E2 in this article’s Online Repository at www.jacionline.org)

Regimen-related and infectious post-HCT complications are summarized in Table V. SOS developed in 3 patients, all recipients of RIC regimens, including 1 patient with a history of pre-HCT EBV-related SOS who developed SOS anew, 1 patient had known prior liver pathology and likely multifactorial liver injury in the setting of sepsis but met Baltimore criteria, and 1 with no

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**TABLE II. Donor and graft characteristics**

| HCTs (n = 66) |  |
|---|---|
| **Graft source** |  |
| Bone marrow | 32 (48) |
| PBSCs | 31 (47) |
| Single umbilical cord | 3 (5) |
| **Graft dose by graft type, TNC \( \times 10^8 \) cells/kg** |  |
| Bone marrow, unmanipulated (n = 29) | 3.47 (0.86-9.67) |
| PBSCs, unmanipulated (n = 21) | 12.1 (4-40.7) |
| PBSCs, manipulated (n = 7) | 8 (0.092-13.3) |
| Single umbilical cord (n = 3) | 0.499 (0.34-0.5) |
| **Donor source** |  |
| Unrelated (non-cord) | 41 (62) |
| HLA-10/10 | 29 (44) |
| HLA-8/8 | 36 (55) |
| Other: HLA-7/8 (n = 3), HLA-5/8 (n = 1), HLA 6/6 (n = 1) | 5 (8) |
| HLA-haploidentical | 15 (23) |
| HLA-matched sibling | 7 (11) |
| Female donor into male recipient* | 16 (28) |
| **Donor age, y** | 27 (4-58) |
| **ABO** |  |
| Matched | 29 (50) |
| Minor mismatch | 15 (26) |
| Major mismatch | 12 (21) |
| Major and minor mismatch | 2 (3) |
| **CMV serostatus D/R** |  |
| D+/R+ | 23 (40) |
| D+/R unknown | 13 (22) |
| D+/R− | 1 (2) |
| D−/R+ | 8 (14) |
| D−/R− | 7 (12) |
| D−/R unknown | 6 (10) |

*Number of HCTs for which data were available: donor sex, ABO compatibility, and CMV serostatus (n = 58); donor age (n = 53).
known baseline liver pathology. Interestingly, renal failure requiring dialysis was observed in 6 patients (11%), of whom 3 had known immune-mediated renal pathology prior to HCT. Additionally, 1 patient developed papillary renal cell carcinoma 1-year post-HCT, in complete remission postcryoablation at last follow-up. Infectious complications were notable for EBV in blood requiring therapy in 11% of patients, CMV and adenovirus organ involvement in 7% and 2%, respectively, and lower respiratory tract viral infection other than CMV or adenovirus in 14%. CMV disease (1 fatal) and EBV-posttransplantation lymphoproliferative disease occurred exclusively in patients who received proximal serotherapy (within 8 days of HCT), with the exception of 1 case of primary CMV infection (seronegative donor and recipient) after

### TABLE III. Transplant platform characteristics, by donor type

| Conditioning intensity | Total HCTs (n = 66) | MSD HCTs (n = 7) | 8/8 MUD HCTs (n = 36) | Haplo HCTs (n = 15) | Other HCTs (n = 8) |
|------------------------|---------------------|-----------------|-----------------------|--------------------|------------------|
| MAC                    | 24 (36)             | 7 (100)         | 11 (31)               | 5 (33)             | 1 (13)           |
| RT-MAC                 | 6 (9)               | 0               | 6 (17)                | 0                  | 0                |
| RIC                    | 35 (53)             | 0               | 19 (53)               | 9 (60)             | 7 (88)           |
| Nonmyeloabative conditioning | 1 (2)             | 0               | 0                     | 1 (7)              | 0                |
| Serotherapy use        | 55 (83)             | 5 (71)          | 34 (84)               | 11 (73)            | 5 (63)           |
| Antithymocyte globulin | 33 (50)             | 4 (57)          | 18 (50)               | 8 (53)             | 3 (38)           |
| Rabbit                 | 29 (44)             | 4 (57)          | 15 (42)               | 7 (47)             | 3 (38)           |
| Horse                  | 4 (6)               | 0               | 3 (8)                 | 1 (7)              | 0                |
| Alemtuzumab            | 22 (33)             | 1 (14)          | 16 (44)               | 3 (20)             | 2 (25)           |
| Proximal timing (administered day −8 or closer to HCT) | 15 (23) | 1 (14) | 12 (33) | 0 | 2 (25) |
| Intermediate timing (administered between days −16 and −9) | 7 (11) | 0 | 4 (11) | 3 (20) | 0 |
| Total body irradiation (total dose, 2-4 Gy) | 12 (18) | 0 | 6 (17) | 3 (20) | 3 (38) |
| GVHD prophylaxis | | | | | |
| Calcineurin inhibitor-based | 48 (73) | 7 (100) | 29 (81) | 5 (3) | 7 (88) |
| Posttransplantation cyclophosphamide-based | 13 (20) | 0 | 5 (14) | 8 (53) | 0 |
| Graft manipulation | 8 (13) | 0 | 4 (11) | 3 (20) | 1 (13) |
| α/β T-cell/CD19+ depletion, with or without CD45RA+ add-back | 6 (9) | 0 | 3 (8) | 2 (13) | 1 (13) |
| α/β T-cell depletion | 1 (2) | 0 | 0 | 1 (7) | 0 |
| CD34+ positive selection | 1 (2) | 0 | 1 (3) | 0 | 0 |
| No pharmacologic prophylaxis apart from serotherapy | 3 (5) | 0 | 0 | 2 (13) | 1 (13) |
| Other*/incomplete information | 2 (3) | 0 | 2 (6) | 0 | 0 |

Values are n or n (%).

*In addition to rabbit antithymocyte globulin and graft manipulation, patient received abatacept and mycophenolate mofetil early post-HCT, followed by methotrexate.

FIG 1. Kaplan-Meier survival curves depicting OS and GFFS for all patients (n = 57) with median follow-up of 27 months overall by the reverse Kaplan-Meier method and 26.3 months (range, 1.5-220.6 months) from first HCT in survivors.
One patient developed renal failure requiring ongoing hemodialysis due to biopsy-proven, BK polyomavirus-associated nephropathy; BK nephropathy may have predated HCT, as this patient had renal insufficiency at baseline in the presence of BK viremia, but no pre-HCT renal biopsy was performed.
Of evaluable, engrafted survivors (n = 47), 45 (96%) are alive and well with phenotype reversal, 8 (17%) in the setting of mixed chimerism in either whole blood or myeloid and/or CD3+ compartments (Table VI). One patient has continued disease manifestations (immune thrombocytopenia, hypogammaglobulinemia) over 2 years post-HCT in the setting of mixed donor chimerism (85% myeloid, 58% CD3+) despite having received 9 DCIs, although with improvement of the disseminated Mycoplasma orale infection that prompted HCT. Another has resolution of recurrent respiratory infections, enteropathy, CMV and EBV infection, and immunoglobulin replacement requirement but had alphaherpesvirus infections 2 years post-HCT despite prophylaxis, in the context of continued mixed chimerism (26% myeloid, 34% CD3+). Four other patients have significant ongoing complications related to GVHD or chronic kidney disease in the setting of 100% donor chimerism and resolution of underlying reversible disease manifestations. Of 46 engrafted survivors with available data, 83% are off immunoglobulin replacement as of last follow-up. Of 8 patients remaining on immunoglobulin replacement, 6 have <2 years follow-up so may still have evolving humoral reconstitution.

No clear correlation was noted between OS and donor chimerism. Infectious deaths occurred in the setting of full donor chimerism (n = 2, at days +175 and +340), preengraftment (n = 2, at days +6 and +17), split donor chimerism and profound lymphopenia (n = 1 at day +238; 0.06% CD3+, 99.6% myeloid chimerism at day +141), and mixed donor chimerism (n = 1 at day +663 and attributed to prior splenectomy; prior to death had phenotype reversal despite 50% whole blood chimerism at day +515). Whole blood, myeloid, and CD3+ donor chimerism trends expectedly showed a trend of more frequent mixed chimerism in patients who received RIC, but not all patients with mixed chimerism across compartments required intervention (see Fig E3 in this article’s Online Repository at www.jacionline.org). Of note, the ability to analyze chimerism trends and differences between platforms was limited by intercenter variability in the type

### TABLE IV. Engraftment and subsequent unplanned cell infusions

|                          | First HCT, patients (n = 57) | Second HCT, patients (n = 8) | Third HCT, patients (n = 1) |
|--------------------------|-------------------------------|-------------------------------|-----------------------------|
| Engraftment              |                               |                               |                             |
| Primary graft failure     | 2 (4)                         | 0                             | 0                           |
| Secondary graft failure   | 7 (12)                        | 1 (13)                        | 0                           |
| Unstable chimerism or threatened graft failure (not progressing to graft failure) | 4 (7) | 2 (25) | 0 |
| Poor graft function       | 9 (16)                        | 3 (38)                        | 0                           |
| Subsequent unplanned cell infusion, no. of patients* | 18 (32) | 4 (50) | 0 |
| Donor lymphocyte infusion† | 7 (12)                        | 2 (25)                        | 0                           |
| Repeat HCT‡               | 8 (14)                        | 1 (13)                        | 0                           |
| Peripheral blood stem cell boost§ | 5 (9) | 1 (13) | 0 |

Values are n or n (%).

* A total of 43 subsequent unplanned cell infusions were administered.
† A total of 24 unplanned donor lymphocyte infusions were administered, for mixed chimerism (n = 18), viral infection (n = 2), lymphoma relapse (n = 2), poor graft function (n = 1), promoting immune reconstitution (n = 1).
‡ Indications for repeat HCT included graft failure (n = 6), mixed chimerism (n = 2), and lymphoma relapse (n = 1).
§ A total of 10 stem cell boosts were administered, for poor graft function (n = 9) and to promote immune reconstitution (n = 1, included CD3+ add back).
of chimerism study and frequency of assessment, as well as by lymphopenia hindering the ability to assess CD3\(^+\) chimerism early post-HCT.

**DISCUSSION**

Since the original description of APDS in 2013,\(^1,2\) increased understanding of this disease has prompted interest in earlier
Infectious complications

- Developed following RIC in all 3 patients, 2 of whom had known prior liver disease requiring hemodialysis.
- Segmental glomerulosclerosis on immunosuppression; BK-associated nephropathy included transplant-related mortality.
- Two patients had concurrent respiratory failure requiring ECMO; outcomes were noted based on donor type. Importantly, particularly in an autosomal dominant disease, unaffected MSD options may be particularly scarce. Our findings suggest that having only MUD or HLA-haploidentical donor options should not dissuade or delay HCT for patients with APDS1/2 in need. Similarly equivalent outcomes between MUD and HLA-haploidentical HCTs for nonmalignant diseases and/or lymphoma have been reported in both TCRαβ+/CD19+ depletions-based and in posttransplantation cyclophosphamide-based platforms.

Conditioning intensity, with historical preference for myeloablative regimens in hard-to-engraft diseases, does not appear to be a key factor in the outcomes reported here. The high risk of graft failure or need for DCI was a consistent finding, with no statistically significant differences in the probabilities of OS, GFFS, GF, or need for DCI based on conditioning intensity. The 100% 2-year GFFS in the RT-MAC subgroup may suggest particular promise with this approach, but the outcome estimates for this subgroup are limited by small numbers, and more patient outcomes data are required to draw conclusions. Given the activated, dysregulated immune function that predominates this disease, it is not surprising that the use of serotherapy and thus the intensity of host lymphodepletion, rather than myeloblation, contributed to the risk of graft instability and need for DCIs in this study. The importance of robust host lymphodepletion was also demonstrated through the relationship between post-HCT mTORi use and the risk of graft instability or need for DCIs. It is known that mTORi ameliorate the function and survival of lymphocytes from patients with APDS by reducing T-cell senescence, increasing naive T-cell percentage, and normalizing IL-2–mediated lymphoproliferation. Therefore, mTORi use early post-HCT may actually provide an undesirable survival advantage to residual host lymphocytes, thus mediating graft instability. Whether these results are applicable to other clinical HCT situations, such as somatic PI3K mutations in patients with lymphoma without underlying primary immunodeficiency diagnosis or in patients with non-APDS immunodeficiency with disease pathophysiology that includes mTOR pathway activation, merits further investigation. For patients with APDS1/2, progress toward improving HCT outcomes may come from work related to tailoring serotherapy dosing, optimizing lymphodepletion over myeloablation, avoidance of post-HCT mTORi until there is confidence that residual host lymphocytes are eradicated, and optimizing the immune dysregulation pre-HCT as best possible.

In comparing the clinical manifestations pre-HCT in our cohort and in the cohort described by Coulter et al, in which 91% of patients did not proceed to HCT, patients in our cohort who all ultimately proceeded to HCT had a greater baseline frequency of enteropathy (57% vs 25%), immune cytopenias (33% vs 17%), and hematologic malignancy (26% vs 13%), suggesting access to definitive treatment such as HCT, necessitating improved awareness of factors that might optimize the approach to HCT. Prior reports have confirmed that HCT is potentially curative for patients with APDS1/2, but those reports have also highlighted barriers to achieving better success rates in HCT for this disease, including high risk of graft instability, significant comorbidities, and poorly controlled infections, autoimmunity, and lymphoproliferative pre-HCT. Herein, we further characterized the international experience with the largest cohort of patients with APDS1/2 who have received transplants to date and examined the relative contribution of HCT-related factors such as donor type, conditioning regimen, and post-HCT therapies to HCT outcomes in these patients.

Whereas MSDs are typically the preferred donor type in practice, no statistically significant differences in outcomes were noted based on donor type. Importantly, particularly in an autosomal dominant disease, unaffected MSD options may be particularly scarce.

TABLE V. Outcomes for all patients

| Outcome                                             | Patients (n = 57) |
|-----------------------------------------------------|------------------|
| Transplant-related mortality                         | 8 (14)           |
| Infection*                                           | 6 (11)           |
| Organ toxicity (regimen-related)                     | 2 (4)            |
| Acute GVHD                                           | 22 (39)          |
| Grade 2-4                                            | 13 (23)          |
| Grade 3-4                                            | 4 (7)            |
| Chronic GVHD†                                        | 9 (16)           |
| Mild                                                 | 3 (11)           |
| Moderate                                             | 1 (2)            |
| Severe                                               | 2 (4)            |

Organ toxicities

- Renal failure requiring dialysis‡ 6 (11)
- Sinusoidal obstructive syndrome§ 3 (5)
- Congestive heart failure 3 (5)
- ARDS 3 (5)
- Respiratory failure requiring ECMO‡ 2 (4)
- DAH, IPS, BO, or COP 0

Infectious complications

- CMV infection requiring treatment; CMV disease 26 (46); 4 (7)
- EBV in blood requiring therapy; EBV-PTLD 6 (11); 3 (5)
- Adenoviremia requiring treatment; adenovirus with organ involvement 4 (7); 1 (2)
- HHV-6 in blood requiring treatment; HHV-6 encephalitis 5 (9); 0
- BK virus-associated hemorrhagic cystitis; biopsy-proven BK nephropathy 10 (18); 1 (2)
- CMV or adenovirus 8 (14)
- HSV requiring treatment 6 (11)
- VZV requiring treatment 3 (5)
- Bacteremia, with or without sepsis; sepsis 19 (33); 9 (16)
- Other significant bacterial infection 10 (18)
- Fungal infection requiring systemic treatment 3 (5)
- Pneumocystis jiroveci pneumonia 1 (2)
- Toxoplasmosis reactivation 0

ARDS, Acute respiratory distress syndrome; BO, bronchiolitis obliterans; COP, cryptogenic organizing pneumonia; DAH, diffuse alveolar hemorrhage; ECMO, extracorporeal membranous oxygenation; HHV-6, human herpesvirus-6; HSV, herpes simplex virus; IPS, idiopathic pneumonia syndrome; PTLD, post-transplantation lymphoproliferative disease; VZV, varicella zoster virus.

Values are n or n (%).

*Attributed to *Pseudomonas aeruginosa *(n = 3, at days +6, +238, +340), *Rhizomucor pusillus *(n = 1, day +17), sepsis in asplenic patient (n = 1, day +663), and CMV (n = 1, day +75). Only the last patient had active GVHD (grade 2, skin only) requiring systemic corticosteroids, diagnosed a week before death; 1 other patient had grade 2, skin only GVHD that developed following donor lymphocyte infusion for lymphoma relapse, treated with calcineurin inhibitor alone, but died of multidrug-resistant *Pseudomonas.*

†Chronic skin GVHD without available data on severity reported for 3 patients. One patient had probable ocular-only chronic GVHD, not diagnostic of GVHD per 2014 consensus criteria and not included above.

‡Occurred in the setting of severe infection (n = 5), SOS, and thrombotic microangiopathy (n = 1). Three patients had significant known preexisting renal pathology. Two patients had concurrent respiratory failure requiring ECMO; outcomes included transplant-related mortality (n = 4) and chronic kidney disease (n = 2, focal segmental glomerulosclerosis on immunosuppression; BK-associated nephropathy requiring hemodialysis).

§Developed following RIC in 3 all patients, 2 of whom had known prior known liver pathology (n = 2). The remaining patient, without prior known liver pathology, received 16 mg/kg total of busulfan, targeting area under the curve of 60 mg h/L.
that these manifestations may be particularly refractory to standard therapy and may justify sooner consideration of HCT once identified. Many patients in our cohort entered HCT with active, uncontrolled manifestations of immune dysregulation. Optimizing pre-HCT disease status with disease-attenuating agents such as mTORi, rituximab, and PI3K inhibitors, as well as moving patients to HCT before significant organ dysfunction develops, might reduce some of the struggles with graft stability and failure while also affording utilization of lower toxicity approaches to successful HCT. Baseline liver pathology was observed frequently, and SOS developed even after RIC. Poor pulmonary function pre-HCT was also frequent, and severe post-HCT respiratory complications such as acute respiratory distress syndrome or extracorporeal membrane oxygenation requirement were seen in 9% of patients. The long-term impact of these transplant-related organ toxicities on morbidity and longevity is of concern. Thus, the choice of conditioning intensity for these patients must be closely guided by underlying comorbidities; full lung function evaluations including spirometry and diffusion capacity of carbon monoxide whenever possible, in children as well as adults, along with a low threshold for detailed liver evaluation prior to HCT, may help inform these decisions.

The incidence of pre-HCT renal pathology and post-HCT renal complications was also notable in this cohort, with 2 cases of severe chronic kidney disease long term. One of these patients developed post-HCT focal segmental glomerulosclerosis, a feature reported pre-HCT in other patients with APDS, in the setting of full donor chimerism. It has been shown that hyperactivated PI3K-Akt signaling within kidney podocytes sensitizes them to injury and apoptosis and has also been linked to renal tissue hyperproliferation and renal cell carcinoma, a complication observed post-HCT in 1 patient in this cohort.

These findings suggest that patients with APDS may remain at risk of renal complications post-HCT even if the hematopoietic system is fully donor and may merit closer observation in this regard, both due to possible increased vulnerability to renal insults early post-HCT and for chronic complications long term.

The minimum donor chimerism necessary for phenotype reversal remains to be defined, but it is notable that phenotype reversal has been observed in the setting of stable mixed chimerism in some patients. Regardless, given the risk of graft loss or instability, close monitoring of donor chimerism, including CD3⁺ donor chimerism when possible, is necessary to identify declining donor chimerism early enough to intervene and should continue long term even after full donor chimerism is established, as illustrated by secondary GF and return of disease manifestations 5 years post-RT-MAC MUD HCT in a patient who ultimately required 3 HCTs.

Identifying the HCT approach associated with the most desirable immune reconstitution profile was not feasible based on the data available and given the heterogeneity of platforms, donors, and graft sources used in this cohort, along with the numerous DCIs administered for various indications. In terms of infectious complications, CMV and EBV requiring treatment, which are particularly problematic pre-HCT in patients with APDS, occurred with similar frequency as would be expected in a general HCT recipient population.

There was a subset of patients in this cohort with prolonged, profound lymphopenia and future studies should aim to characterize whether such occurrences are related to the HCT approach/comlications or might be inherent, nonhematopoietic disease features for a subset of patients with APDS1/2. Immune reconstitution may be affected by serotherapy use, but serotherapy-free HCTs were few in this cohort, thus not providing ample comparison to serotherapy-containing approaches. Given the probable importance of serotherapy in the conditioning of these patients as well as the tendency for patients with APDS1/2 to enter HCT with poor viral control and/or virus-associated malignancy, fine-tuning serotherapy exposure to the graft is future work of utmost importance when striving to improve immune reconstitution and avoid viral complications, while also optimally preventing GVHD.

In conclusion, this large international investigation of HCT outcomes for patients with APDS1/2 has yielded important insights into the breadth and severity of pre-HCT comorbidities, ongoing limitations in disease optimization pre-HCT, the incidence of major HCT complications, and key factors that may affect graft stability and loss. Use of mTORi post-HCT appears to be detrimental to graft stability and should be avoided in the setting of clinically significant mixed or split donor chimerism. Longer detailed follow-up of graft stability, late toxicities, immune reconstitution, and phenotype reversal is needed to further inform the optimal timing of and approach to HCT for patients with APDS1/2.

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Clinical implications: HCT for patients with APDS reverses phenotype but is associated with high incidence of graft instability, regardless of conditioning intensity or donor type, which is increased by post-HCT mTORi use.

REFERENCES

1. Angulo I, Vadás O, Garcon F, Banham-Hall E, Plagnol V, Leahy TR, et al. Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory infection and airway damage. Science 2013;342:866-71.
2. Lucas CL, Kuehn HS, Zhao F, Niemela JE, Deenick EK, Palendira U, et al. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency. Nat Immunol 2014;15:88-97.
3. Coutlier TJ, Chandra A, Bacon CM, Babar J, Curtis J, Screean N, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase delta syndrome: a large patient cohort study. J Allergy Clin Immunol 2017;139:597-606.e4.
4. Elkaim E, Neven B, Bruneau J, Mitsui-Sekinaka K, Yanardi R, Jadhut-Niaragh F, et al. Clinical, immunologic, and genetic features in patients with activated PI3Kdelta syndrome (APDS): a systematic review. Clin Rev Allergy Immunol 2020;59:323-33.
5. Elgizouli M, Lowe MD, Speckmann C, Schubert D, Hulsduncker J, Eskandari Z, et al. Activating PI3Kdelta mutations in a cohort of 669 patients with primary immunodeficiency. J Immunol Exp Med 2016;183:221-9.
6. Maccari ME, Abolhassani H, Aghamohammadi A, Aiuti A, Aleinikova O, Bangs H, et al. Activating PI3Kdelta mutations in a cohort of 669 patients with primary immunodeficiency diseases. Pediatr Blood Cancer 2018;65(1):e26783.
7. Takeda AJ, Zhang Y, Dornan GL, Siempelkamp BD, Jenkins ML, Matthews HF, et al. Prospective study of a novel, radiation-free, reduced-intensity bone marrow transplantation platform for primary immunodeficiency diseases referred for allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2019;25:1666-73.
8. Dreger P, Sureda A, Ahn KW, Eapen M, Litovchik C, Finel H, et al. PTCy-based haplotype-matched vs matched related or unrelated donor reduced-intensity conditioning transplant for DLBCL. Blood Adv 2019;3:360-9.
9. Burroughs LM, O’Donnell PV, Sandmaier BM, Storer BE, Luznik L, Symons HJ, et al. Comparison of outcomes of HLA-matched related, unrelated, or HLA-haploidentical hematopoietic cell transplantation following nonmyeloablative conditioning for relapsed or refractory Hodgkin lymphoma. Biol Blood Marrow Transplant 2008;14:1279-87.
10. Rastogi N, Katewa S, Thakkar D, Kohli S, Nivargi S, Yadav SP. Reduced-toxicity alternative-donor stem cell transplantation with posttransplant cyclophosphamide for primary immunodeficiency diseases. Pediatr Blood Cancer 2016;63:1055-63.
11. Bertaina A, Merli P, Rutella S, Pagliara D, Bernardo ME, Masetti R, et al. HLA-matched versus HLA-matched unrelated haploidentical transplantation in primary immune deficiency. J Allergy Clin Immunol 2018;141:1152-6.e10.
12. Hong CR, Lee S, Hong KT, Choi JY, Shin HY, Choi M, et al. Successful haploidentical transplantation with post-transplant cyclophosphamide for activated phosphoinositide 3-kinase delta syndrome. J Allergy Clin Immunol Pract 2019;7:1034-7.e1.
13. Crank MC, Grossman JK, Moir S, Pittaluga S, Buckner CM, Kardava L, et al. Mutations in PIK3CD can cause hyper IgM syndrome (HIGM) associated with increased cancer susceptibility. J Immunol 2014;34:372-6.
14. Crank MC, Zhang Y, Venda A, Wang Y, Hughes J, McElwee J, et al. Heterozygous splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K. Exp Med 2014;211:2537-47.
15. Wang Y, Wang W, Liu L, Hou J, Ying W, Hui X, et al. Report of a Chinese cohort with activated phosphoinositide 3-kinase delta syndrome. J Clin Immunol 2018;38:854-63.
16. Kazita Y, Mitsu-Sekinaka K, Imai K, Yeh TW, Mitsuuki N, Asano T, et al. Phosphatase and tensin homolog (PTEN) mutation can cause activated phosphatidylinositol-3-kinase delta syndrome-like immunodeficiency. J Clin Immunol 2016;36:1672-80.e10.
17. Deau MC, Heurtier L, Frangi P, Suarez F, Bole-Feysoy C, Nitschke P, et al. A human immunodeficiency caused by mutations in the PIK3R1 gene. J Clin Invest 2014;124:3923-8.
18. ClinVar accession: VC000827331.6. ClinVar [Internet]. Available at: https://www.ncbi.nlm.nih.gov/clinvar/variation/827331/. Accessed April 10, 2021.
19. Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG, et al. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation 1987;44:778-83.
20. Lucas CL, Chandra A, Nejentsev S, Condiffe AM, Okkenhaug K. PI3Kdelta and primary immunodeficiencies. Nat Rev Immunol 2016;16:702-14.
21. van Hagen PM, Holland S, et al. Successful haploidentical transplantation with post-transplant cyclophosphamide for activated phosphoinositide 3-kinase delta syndrome 2: a cohort study. J Allergy Clin Immunol 2016;138:210-8.e9.
22. Hong CR, Lee S, Hong KT, Choi JY, Shin HY, Choi M, et al. Successful haploidentical transplantation with post-transplant cyclophosphamide for activated phosphoinositide 3-kinase delta syndrome 1 and 2 (APDS 1 and APDS 2): similarities and differences based on clinical presentation in two boys. Allergy Asthma Clin Immunol 2020;16:22.
42. Garner KL, Betin VMS, Pinto V, Graham M, Abgueguen E, Barnes M, et al. Enhanced insulin receptor, but not PI3K, signalling protects podocytes from ER stress. Sci Rep 2018;8:3902.
43. De Santis MC, Sala V, Martini M, Ferrero GB, Hirsch E. PI3K signaling in tissue hyperproliferation: from overgrowth syndromes to kidney cysts. Cancers (Basel) 2017;9:30.
44. Guo H, German P, Bai S, Barnes S, Guo W, Qi X, et al. The PI3K/AKT pathway and renal cell carcinoma. J Genet Genomics 2015;42:343-53.
45. Melendez-Munoz R, Marchalik R, Jerussi T, Dimitrova D, Nussenblatt V, Beri A, et al. Cytomegalovirus infection incidence and risk factors across diverse hematopoietic cell transplantation platforms using a standardized monitoring and treatment approach: a comprehensive evaluation from a single institution. Biol Blood Marrow Transplant 2019;25:577-86.
46. Ljungman P, de la Camara R, Robin C, Crocchiolo R, Einsele H, Hill JA, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis 2019;19:e260-72.
47. de Koning C, Nierkens S, Boelens JJ. Strategies before, during, and after hematopoietic cell transplantation to improve T-cell immune reconstitution. Blood 2016;128:2607-15.
REFERENCE

E1. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21:389-401.e1.
**FIG E1.** Total T-cell (A) and T-cell subset (B and C) recovery by serotherapy use in conditioning regimen; cumulative incidence of CD4+ T-cell recovery >200 cells/µL by serotherapy use (D). Data points are as follows: pre-HCT, n = 42; +6 months, n = 38 (n = 6 serotherapy-free); +1 year, n = 30 for total T cells and n = 28 for each subset (n = 4 serotherapy-free); +1.5 years, n = 14 (n = 4 serotherapy-free); +2 years, n = 15 for total T cells and CD8+ T cells and n = 16 for CD4+ T cells (n = 1 serotherapy-free); +3 or more years, n = 12 (n = 2 serotherapy-free). Gray shading represents normal adult reference ranges.
FIG E2. Cumulative incidence of grades 2 to 4 (A) and grades 3 to 4 (B) acute graft-versus-host disease (aGVHD) after hematopoietic cell transplantation (HCT) by donor type (“Other unrelated” includes unrelated donors less than HLA-A/-B/8/8 match, n = 5, and single umbilical cords, n = 3), conditioning intensity, and serotherapy use during conditioning, with graft failure or death as competing risks. For 1 patient, grade 2 aGVHD diagnosis date was not available, so last recorded date of follow-up (day 133) was utilized in an effort to include all events.
FIG E3. Whole blood, myeloid, and CD3⁺ donor chimerism post-HCT, by outcome (need for subsequent DCI or GF) and by conditioning intensity.
## TABLE E1. Endpoint definitions and complications compiled for each patient

| Endpoint definitions | Neutrophil engraftment: the first of 3 days after count nadir of absolute neutrophil count >500 cells/μL. |
|----------------------|--------------------------------------------------------------------------------------------------|
|                      | Platelet engraftment: the first of 3 days postnadir of platelets >20,000 without transfusion in the prior 7 days. |
|                      | Graft failure: 5% or fewer donor cells (whole blood or myeloid). |
|                      | Primary graft failure: no donor chimerism was demonstrated at any post-HCT time point. |
|                      | Secondary graft failure: donor cells were demonstrated to be present post-HCT and then subsequently declined to 5% or fewer donor cells (whole blood or myeloid). |
|                      | Mixed chimerism: <95% donor in whole blood, myeloid, or CD3⁺ lineages. |
|                      | Overall survival: the time from first HCT to death of any cause, with surviving patients censored at last follow-up. |
|                      | Graft failure-free survival: the time from first HCT to graft failure or death of any cause, with event-free patients censored at last follow-up. |
|                      | Transplant-related mortality: any death from the start of conditioning on, apart from external (accidental) causes. |

| Infectious complications | Cytomegalovirus: infection requiring therapy, disease. |
|--------------------------|-----------------------------------------------------|
|                          | EBV: viremia requiring intervention, EBV-posttransplantation lymphoproliferative disease. |
|                          | Adenovirus: adenoviremia requiring therapy, adenovirus disease. |
|                          | HHV-6: viremia requiring therapy, encephalitis. |
|                          | BK virus–associated hemorrhagic cystitis. |
|                          | Toxoplasmosis reactivation. |
|                          | Pneumocystis jiroveci pneumonia. |
|                          | Viral lower respiratory tract infection. |
|                          | HSV requiring therapy. |
|                          | VZV requiring therapy. |
|                          | Fungal infection requiring systemic therapy. |
|                          | Bacteremia. |
|                          | Sepsis. |
|                          | Other significant infections. |

| Organ toxicities | SOS. |
|------------------|----------------------------------|
|                  | Pulmonary complications: diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, cryptogenic organizing pneumonia. |
|                  | Renal failure requiring dialysis. |
|                  | Thrombotic microangiopathy. |
|                  | Central nervous system complications: posterior reversible encephalopathy syndrome, stroke, seizure. |
|                  | Congestive heart failure. |
|                  | Other organ toxicities. |

| Other complications | GVHD. |
|---------------------|----------------------------------|
|                     | Acute: incidence, timing of diagnosis, maximum grade, treatment, outcome. |
|                     | Chronic: incidence, severity. |
|                     | Need for subsequent donor cell infusions. |
|                     | Cell infusion type, indication, timing, and number of infusions. |
|                     | Stem cell boost was defined as CD34⁺ selected stem cells with or without CD3⁺ T cell add back, or peripheral blood stem cells, and determined by contributor to not meet criteria for an additional HCT procedure. |

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*The diagnosis and severity of chronic GVHD was as reported by the treating institution, with 2014 National Institutes of Health consensus criteria applied to data with discrepancies.¹¹
TABLE E2. Details of indication for HCT

| Indication for HCT, no. of patients | Total (n = 57) |
|-------------------------------------|---------------|
| Hematologic malignancy              | 15 (26)       |
| Nonmalignant lymphoproliferation    | 28 (49)       |
| Autoimmune cytopenias               | 8 (14)        |
| Chronic or recurrent infections     | 26 (46)       |
| End organ damage                    | 24 (42)       |
| Lung                                | 16 (28)       |
| Gastrointestinal tract              | 9 (16)        |
| Liver                               | 6 (11)        |
| Kidney                              | 2 (4)         |
| Multiple organs                     | 7 (12)        |
| Multiple indications                | 30 (53)       |

Values are n (%).
TABLE E3. Outcomes by number of patients transplanted at individual centers

| Patients transplanted, n | Centers, n | Year of first HCT, range | Crude mortality, % | Crude graft failure, % |
|-------------------------|------------|--------------------------|--------------------|------------------------|
| 8                       | 1          | 2015-2020                | 12.5               | 25                     |
| 7                       | 1          | 2009-2019                | 0                  | 14                     |
| 5                       | 1          | 2014-2019                | 20                 | 40                     |
| 4                       | 1          | 2011-2019                | 0                  | 25                     |
| 3                       | 1          | 2015-2017                | 33                 | 0                      |
| 2                       | 5          | 2000-2019                | 30                 | 10                     |
| 1                       | 20         | 2004-2019                | 10                 | 5                      |