**Allogeneic Hematopoietic Stem-Cell Transplantation for Leukocyte Adhesion Deficiency**

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**What’s Known on This Subject**

Leukocyte Adhesion Deficiency is a rare inherited immune disorder characterized by defective immune cell migration. Bone marrow and peripheral blood stem cell transplantation offers the possibility of cure, but can be associated with significant complications.

**What This Study Adds**

Hematopoietic stem cell transplantation is advocated in LAD, especially when suitable HLA-matched donors are available. Matched unrelated donor transplants can be successful in combination with less toxic, reduced intensity conditioning regimens. Haplo-identical transplants should be procedures of last resort.

**ABSTRACT**

**OBJECTIVES.** Leukocyte adhesion deficiency is a rare primary immune disorder caused by defects of the CD18 β-integrin molecule on immune cells. The condition usually presents in early infancy and is characterized by deep tissue infections, leukocytosis with impaired formation of pus, and delayed wound healing. Allogeneic hematopoietic stem-cell transplantation offers the possibility of curative therapy, and with patient numbers at any individual center being limited, we surveyed the transplant experience at 14 centers worldwide.

**METHODS.** The course of 36 children with a confirmed diagnosis of leukocyte adhesion deficiency who underwent hematopoietic stem-cell transplantation between 1993 and 2007 was retrospectively analyzed. Data were collected by the registries of the European Society for Immunodeficiencies/European Group for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research.

**RESULTS.** At a median follow-up of 62 months (extending to 14 years), the overall survival rate was 75%. Myeloablative conditioning regimens were used in 28 patients, and reduced-intensity conditioning in 8 patients, with no deaths in this subgroup. Survival rates after matched family donor and unrelated donor transplants were similar, with 11 of 14 matched family donor and 12 of 14 unrelated donor recipients alive; mortality was greatest after haploidentical transplants, after which 4 of 8 children did not survive. Twenty-seven transplant recipients were alive, with full donor engraftment in 17 cases, mixed multilineage chimerism in 7 patients, and mononuclear cell-restricted chimerism in an additional 3 cases.

**CONCLUSIONS.** Hematopoietic stem-cell transplantation offers long-term benefit in leukocyte adhesion deficiency and should be considered as an early therapeutic option if a suitable HLA-matched stem-cell donation is available. Reduced-intensity conditioning was particularly safe, and mixed-donor chimerism seems sufficient to prevent significant symptoms, although careful long-term monitoring will be required for these patients. *Pediatrics* 2009;123:836–840

**Key Words**

leukocyte adhesion deficiency, stem-cell transplantation, reduced-intensity conditioning

**Abbreviations**

ATG—antithymocyte globulin
CLAD—canine leukocyte adhesion deficiency
CMV—cytomegalovirus
EBV—Epstein-Barr virus
GVHD—graft-versus-host disease
HSCT—hematopoietic stem-cell transplantation
LAD—leukocyte adhesion deficiency
LFA-1—lymphocyte function-associated antigen-1
MFD—matched family donor
PBSC—peripheral blood stem-cell collection
RIC—reduced-intensity conditioning

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**RIC**—reduced-intensity conditioning

**EUKOCYTE ADHESION DEFICIENCY (LAD)** type 1 is a rare autosomal recessive immunodeficiency documented in ~300 patients worldwide. Defective expression of the β-2 integrin, CD18, on immune cells results in impaired leukocyte...
adhesion, egression, and migration. CD18 forms the dimeric complexes lymphocyte function associated antigen-1 (LFA-1) in association with CD11a, Mac-1 in combination with CD11b, and p150-95 with CD11c. These molecular complexes are essential for effective migration and homing of immune cells, including neutrophils, dendritic cells, and T lymphocytes.1,2 Defective neutrophil migration can result in omphalitis and delayed separation of the umbilical cord, a characteristic and early presenting hallmark of LAD.1 Other features include recurrent deep tissue bacterial infections affecting the skin and mucosa. Leukocytosis in peripheral blood and the absence of pus formation at sites of infection is characteristic. Poor postoperative wound healing may be a presenting feature. Patients with <1% CD18 expression are considered to have the most severe phenotype, with serious infections leading to life-threatening complications in early infancy. Allogeneic hematopoietic stem-cell transplantation (HSCT) offers the possibility of curative therapy for LAD, but, as the condition is extremely rare, experience at any particular center is limited.4,5 A 2-center study has previously reported the outcomes of 14 matched-family and haploidentical donor transplants, undertaken between 1982 and 1993. The findings noted particular difficulties associated with transplantation for LAD, including graft rejection and graft-versus-host disease (GVHD). In some patients, additional chemotherapy with agents such as etoposide was used to supplement conventional myeloablative conditioning with busulphan and cyclophosphamide.6 There was an overall mortality rate of 28%, but interestingly no difference in survival rate after HLA-identical or nonidentical procedures was detected, and the study has broadly influenced the subsequent approach to stem-cell transplantation for LAD. We surveyed the results of transplantation undertaken in the subsequent period, between 1993 and 2007, of children who were treated at 14 centers worldwide and have compiled a series of 36 patients. Our findings provide the most comprehensive picture of outcomes after transplantation and highlight an increased use of alternative stem-cell sources and reduced-intensity regimens.

PATIENTS AND METHODS

Data Sources
Patient data, transplant characteristics, and outcomes were reported to the European Society for Immunodeficiencies/European Group for Blood and Marrow Transplantation registry and the Center for International Blood and Marrow Transplant Research. Fourteen centers treated between 1 and 9 patients each (median: 1.5 per center). Included are patients documented as having reduced or absent expression of CD18 by flow-cytometric analysis and transplanted after 1993. Excluded are patients with a clinical suspicion of LAD but without proven reduction in CD18 expression. Although this is the largest series to date, patients treated under identical transplant regimens were small, limiting the power of any statistical analysis.

Transplantation
Thirty-six patients underwent their first transplant for LAD between 1993 and 2007. Patients received bone marrow (n = 27), peripheral blood progenitor cells (n = 4), or umbilical cord blood grafts (n = 5) from 14 HLA-matched family donors, 8 haploidentical donors, and 14 unrelated donors (Table 1). The median age at stem-cell transplantation was 9 months (range: 2 months to 14 years). Most patients (n = 28) received fully myeloablative regimens with combinations of busulphan (16–20 mg/kg), cyclophosphamide (100–200 mg/kg), and etoposide (900 mg/m²). Additional serotherapy included Campath 1G, anti-LFA-1, anti-CD2 antibody, anti-CD3 antibody, or antithymocyte globulin (ATG). The remaining 8 patients received reduced-intensity conditioning (RIC) with combinations of fludarabine (150 mg/m²), melphalan (140 mg/m²), treosulphan (42 mg/m²), Campath 1H (1 mg/kg), and rabbit ATG (10 mg/kg). In the haploidentical setting, T-cell depletion was achieved by E-Rosetting or CD34⁺ stem-cell selection from marrow or mobilized peripheral blood stem-cell collection (PBSC). Most patients received cyclosporine either alone or in combination with mycophenolate, methotrexate and/or prednisolone for GVHD prophylaxis. Chimerism after stem-cell transplantation was monitored by a variety of techniques including fluorescent in situ hybridization for gender mismatched grafts, polymerase chain reaction analysis using microsatellite probes, and flow cytometry for CD18.7,8 Six patients received a second stem-cell transplant for graft failure (n = 5) or secondary malignancy (Epstein-Barr virus [EBV] lymphoma, n = 1) and 2 patients underwent a third procedure for graft failure or low-level donor chimerism. All but 1 of these multiple grafts was in the haploidentical setting.

RESULTS
In general, outcomes after HSCT for primary immunodeficiencies have improved over time.7 We found that the long-term survival rate after transplantation for LAD undertaken between 1993 and 2007 was ~75%; little changed from results reported for the period of 1982 through 1993.6 Previous transplant experience had suggested that nonidentical, T-cell–depleted grafts could be as successful as HLA-identical procedures in LAD, but our survey found a high level of primary graft failure, which resulted in secondary (or tertiary) grafting in all 8 haploidentical transplants. Consequently, only 4 of 8 (50%) children in this subgroup survived. The increased availability of matched unrelated adult and cord blood stem-cell grafts has been an important change in recent years, and survival rates after either matched family donor or unrelated donor transplantation were notably better. Thus, 12 of 14 (86%) recipients of unrelated donor HSCT survived, and this was comparable to 11 of 14 (79%) of the matched family donor recipients.

Nine patients (4 haploidentical, 3 sibling donor, and 2 matched unrelated donor) did not survive after transplantation (Table 2). All had received myeloablative conditioning and donor engraftment was established in 7 patients, albeit after repeat procedures in 5 cases. Infection-related deaths occurred in 5 cases, with 3 deaths.
linked to veno-occlusive disease and 1 case of secondary malignancy (EBV lymphoma). We noted that 6 deaths occurred in the first 7-year period of this analysis (1993–1999) compared with 3 deaths in the subsequent period (2000–2007). This probably reflects the reduced use of busulphan-based conditioning regimens undertaken at 14 centers worldwide over a 14-year period. There is general agreement that infants presenting with significant infections in the first weeks or months of life who have a diagnosis of LAD confirmed

**DISCUSSION**

We report the transplant experience for LAD for procedures undertaken at 14 centers worldwide over a 14-year period. There is general agreement that infants presenting with significant infections in the first weeks or months of life who have a diagnosis of LAD confirmed

### Table 1: Patients Who Survived After Allogeneic Transplantation for LAD

<table>
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<tr>
<th>Donor</th>
<th>Age, mo</th>
<th>Year of BMT</th>
<th>Follow-up, mo</th>
<th>Conditioning</th>
<th>Graft</th>
<th>Prophylaxis</th>
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**AMM** indicates antigen mismatched; **ARA-C**, cytarabine; **ARDS**, acute respiratory distress syndrome; **BM**, bone marrow; **BMT**, bone marrow transplantation; **Bu**, busulphan; **Cam1G**, Campath 1G; **Cam1H**, Campath 1H; **CMV**, cytomegalovirus; **EBV**, Epstein-Barr virus; **Flu Mel**, Fludarabine, Melphalan; **Flu Treo**, Fludarabine, Treosulfan; **HAPL**, haploidentical donor (P, paternal; M, maternal); **MFD**, mismatched family donor; **MSD**, matched sibling donor; **MUD**, matched unrelated donor; **MNC**, mononuclear cells; **Mtx**, methotrexate; **MMF**, mycophenolate mofetil; **PBSC**, peripheral blood stem cell collection (CD34 selected where indicated); **PMN**, polymorphonuclear cells; **Prd**, prednisolone; **TBI**, total body irradiation; **T dep**, T-cell depleted; **TP**, thiopeta; **UCB**, umbilical cord blood; **VOD**, veno-occlusive disease; **VP16**, etoposide; **VZV**, varicella zoster virus.

* Indicates RIC.
on the basis of CD18 expression should undergo early HSCT if a suitable HLA-matched family donor can be identified. In the absence of a HLA-matched family donor, the ready availability of a maternal haploidentical donor has obvious attractions, and previous experience of successful haploidentical transplantation in LAD has suggested that T-cell–depleted family mismatched grafts could be as successful as HLA-identical (T-cell replete) procedures in LAD. It was postulated that this may relate to the reduced ability of the LAD host to mediate graft rejection.5,6 This observation has not been borne out in the current series, where all the haploidentical grafts were successfully transplanted without evidence of rejection.7

In more recent years, there has been increased availability of unrelated volunteer donors and umbilical cord stem-cell donations, and this is reflected in our series, which included 14 such procedures. Until now there have been only isolated reports describing the successful transplantation for LAD using matched unrelated adult donors and umbilical cord blood grafts.15 As unrelated donor transplants undertaken with conventional myeloablative conditioning can be associated with significant toxicity, especially in the context of preexisting organ dysfunction, a number of these procedures were performed using modified, reduced-intensity regimens. We previously documented improved survival rates in children with primary immune deficiencies who underwent RIC procedures.8 These transplants are generally less toxic and rely on intense immunosuppression to engineer host:donor tolerance sufficient for reliable engraftment. In the LAD setting, the RIC regimens were well tolerated, and although a number of children have mixed chimerism, all remain alive and free of significant symptoms. The long-term consequences of RIC preconditioning in these patients will be of particular interest considering that intact fertility and uncomplicated pregnancies have been reported in dogs with canine LAD (CLAD) after nonmyeloablative stem-cell transplantation.16 Interestingly, low levels of donor neutrophil engraftment as measured in peripheral blood seem sufficient for patients to remain symptom free. The minimum level of functional CD18 expression on leukocytes required to prevent complications is not known. Somatic reversion events, leading to normal CD18 expression on a small fraction of peripheral blood T cells, have been reported in LAD.17,18 Somatic mosaicism in patients with other inherited immunodeficiencies has been linked to milder phenotypes,19,20 but in LAD the reversion phenomena have mixed chimerism, all remain alive and free of significant symptoms. The long-term consequences of RIC preconditioning in these patients will be of particular interest considering that intact fertility and uncomplicated pregnancies have been reported in dogs with canine LAD (CLAD) after nonmyeloablative stem-cell transplantation.16

In addition, observations from animal studies are encouraging and suggest that low levels of functional CD18 expression on leukocytes can reverse disease phenotype.21 Transplant studies in CLAD have indicated that <500 CD18+ donor neutrophils per μL in peripheral blood can prevent complications and mediate important beneficial effects at target sites such as the oral mucosa. Thus, in dogs, selective accumulation of donor neutrophils was demonstrated in the oral mucosa resulting in significantly higher levels of donor chimerism in the saliva of animals compared with peripheral blood after transplantation.22 Evidence from gene therapy studies in the CLAD model also supports donor neutrophils per mL in peripheral blood can prevent complications and mediate important beneficial effects at target sites such as the oral mucosa. Thus, in dogs, selective accumulation of donor neutrophils was demonstrated in the oral mucosa resulting in significantly higher levels of donor chimerism in the saliva of animals compared with peripheral blood after transplantation.22 Evidence from gene therapy studies in the CLAD model also supports

### TABLE 2 Patients not Surviving After Allogeneic Transplantation for LAD

<table>
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<tr>
<th>Donor</th>
<th>Age, mo</th>
<th>Year</th>
<th>BM T dep</th>
<th>TBI CY ATG</th>
<th>BM T dep</th>
<th>CyA Mtx</th>
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<td>Bu CY ATG</td>
<td>BM</td>
<td>CyA</td>
<td>Yes</td>
<td>Infection</td>
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<td>I</td>
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<td>4</td>
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<td>Bu CY VP16</td>
<td>BM</td>
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<td>No ARDS</td>
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ARDS indicates acute respiratory distress syndrome; BM, bone marrow; Bu, busulphan; Cam1G, Campath 1G; CY, cyclophosphamide; CyA, cyclosporine; HAPL, haploidentical donor (P, paternal; M, maternal); MSD, matched sibling donor; MUD, matched unrelated donor; Mtx, methotrexate; PBSC, peripheral blood stem cell collection (CD34 selected where indicated); Prd, prednisolone; T dep, T-cell depleted; VOD, veno-occlusive disease; VP16, etoposide.
the notion that low numbers of functional cells can prevent disease. The infusion of autologous hematopoietic stem cells transduced to express canine CD18 corrected 5% to 10% of circulating leukocytes, and this was sufficient to mediate durable reversal of the disease. Presently, a number of patients with mixed-donor chimerism, including those with only mononuclear lineage engraftment, remain free of significant disease. Additional investigation of these patients may be warranted, including detailed lineage-specific chimerism in tissues (in the bone marrow and gingival tissues) and the exclusion of host-mediated cellular or autoantibody responses against donor-derived cells.

CONCLUSIONS

LAD1 is a serious primary immune disorder that can be corrected by allogeneic HSCT. Matched family donor and unrelated donor procedures were equally successful and mixed chimerism in peripheral blood seems sufficient to keep patients free of significant symptoms. The study has highlighted the impressive safety profile of RIC regimens, and the greater availability of suitable unrelated donors in combination with tailored conditioning regimens should improve outcomes further.

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REFERENCES

An error occurred in this article published in the January 2009 issue of Pediatrics (doi:10.1542/peds.2007-2680). The authors inadvertently omitted the list of participating centers, principal investigators, and research coordinators from the manuscript:

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An error occurred in this article published in the March 2009 issue of Pediatrics (doi:10.1542/peds.2008-1191). On page 836, in the authorship list, line 4 reads “Mary Slatten, MBBSr.” This should have read: “Mary Slatter, MBChB.”

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