Leukocyte adhesion deficiency-I: A comprehensive review of all published cases

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Clinical Implications

- Leukocyte adhesion deficiency-I (LAD-I) is a rare, serious disorder with severity determined by defective CD18 expression. LAD-I is characterized by umbilical complications, granulocytosis, and diverse infections. Severe LAD-I is frequently fatal before the age of 2 years without allogeneic transplant. We identified 323 cases published between 1975 and 2017.

TO THE EDITOR:

Leukocyte adhesion deficiency-I (LAD-I) is a rare disorder of leukocyte adhesion and migration, resulting from mutations in the *ITGB2* gene encoding for the β_2-integrin component CD18. Deficiencies in CD18 prevent normal integrin dimerization and leukocyte adhesion to endothelial surfaces, processes essential to extravasation and antimicrobial activity.[1,2]

Severe LAD-I (predominantly classified as <2% of CD18-expressing neutrophils) is characterized by recurrent, life-threatening bacterial and other infections and substantial infant mortality in patients who do not receive allogeneic hematopoietic stem cell transplant (HSCT). Mortality for severe LAD-I was reported as 75% by the age of 2 years in an initial 1988 multicenter retrospective evaluation.[3] Most patients with moderate LAD-I (2%-30% CD18-expressing neutrophils) survive childhood, with recurrent infections of skin and mucosal surfaces; mortality by the age of 40 years reportedly exceeds 50%.[3] LAD-I is also characterized by umbilical cord complications (delayed separation and omphalitis), impaired wound healing, and persistent leukocytosis.[4,5]

Multiple reports have been published in recent decades; however, no comprehensive prognostic assessments are available subsequent to the 1988 report. We sought an updated understanding of severe LAD-I with emphasis on prognosis in the absence of HSCT, HSCT outcomes, and association of CD18 expression with clinical features. We created a database of all published LAD-I cases via PubMed searches and a review of additional references.

Three hundred twenty-three LAD-I cases were reported between 1975 and 2017 in 107 publications (68 of which were single case reports; largest series n = 36). The nations with the highest number of cases were Iran (n = 65), the United States (n = 50), and India (n = 45); the highest number of publications originated in the United States (n = 25) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org for a comprehensive listing of publications and patient numbers by country and Table E2 for a comprehensive listing of references).

Per investigator assessment, 113 patients were considered to have severe LAD-I, 63 moderate, and 147 not classified. Neutrophil CD18 expression was reported for 265 cases and was less than 2% in 135 patients (51%) and 2% or more in 130 patients (49%). Four patients with CD18 greater than or equal to 2% were considered to have severe LAD-I (CD18% range, 2.4-17.3). Sex information was available for 282 patients, of which 148 (52%) were males.

Age at presentation was reported for 146 cases. For 63 patients with CD18 less than 2%, median presentation was at age 1 month (range, 0.03-18 months); for 62 patients with CD18 of 2% or more, median presentation was at age 6 months (range, 0.03-192 months). HSCT was performed for 125 patients; 198 patients did not undergo HSCT.

Infections were described for 248 (77%) of the 323 cases; information regarding anatomic site and CD18% was specified in 154 cases (48%). The most frequent infections in 85 cases with CD18 less than 2% were respiratory tract (39%, including pneumonia), sepsis (29%), and otitis media (27%). The most frequent infections in 69 cases with CD18 of 2% or more were periodontal (52%, including gingivitis and oral ulcers), otitis media (36%), and sepsis (25%). Perianal skin infections and necrotic skin ulcers were each reported in more than 10% of the groups. For additional information, see Table E3 in this article's Online Repository at www.jaci-inpractice.org.

Umbilical cord complications (delayed separation or omphalitis) were more frequent in patients with severe LAD-I, reported in 92 of 110 patients with CD18 less than 2% (84%) and 47 of 81 patients with CD18 of 2% or more (58%; $P = .0001$; χ^2 test). For the subset of patients with severe LAD-I with at least 2 years of follow-up (or death before the age of 2 years), there was significant correlation between absence of umbilical cord complications and survival to 24 months ($P < .001$; Fisher exact test). Tables E4 and E5 in this article's Online Repository at www.jaci-inpractice.org depict umbilical cord complication incidences and 2-year survival.

White blood cell (WBC) counts were reported in 143 cases (median, 45 $\times$ 10^9/L; range, 10-150 $\times$ 10^9/L). Although median WBC was higher in the group with CD18 less than 2% (48 vs 30 $\times$ 10^9/L), there was limited correlation between CD18 expression and WBC ($r < 0.1$) for the entire cohort and when the groups with CD18 less than 2% and of 2% or more were analyzed independently. Expression of β_2-integrin heterodimers CD11a, CD11b, and CD11c was reported in 76, 89, and 69 cases, respectively. Correlations between CD18 and CD11 expressions were also limited ($r < 0.5$), consistent with a recent report.[6] Figures E1 and E2 in this article's Online Repository at www.jaci-inpractice.org depict analyses regarding integrin expression and WBC.

Mutation analyses were provided for 139 cases; missense (n = 34) and frame shift (n = 24) mutations were most frequent for the subset (n = 100) in which these were characterized. More than 20 locations within the *ITGB2* gene were specified (n = 120); however, mutations on Exon 6 were most frequent

TABLE I. Survival to age of 2 y in absence of HSCT on the basis of clinical and laboratory assessments of LAD-I severity

LAD-I severity	N	Survival to age 2 y		
		Alive at ≥2 y	Follow-up to 2 y or death by 2 y	% alive to age 2 y
Severe: investigator assessment or CD18 <2%	96	26	66	39%
Severe: CD18 <2%	73	21	48	44%
Severe: CD18 <2% (2000-2017 only)	67	19	43	44%
CD18 2%-4%	17	9	13	69%
CD18 >4%-10%	25	18	19	95%
CD18 >10%	36	29	29	100%

Many reports did not provide precise survival durations (stating only that mortality occurred before the age of 2 y), and hence it was not possible to generate Kaplan-Meier curves incorporating most of the severe LAD-I cases. Several patients were considered to have severe LAD-I despite CD18 expression on >2% neutrophils or unspecified CD18 expression; these cases are included in the top row in addition to those with CD18 expression on <2% neutrophils.

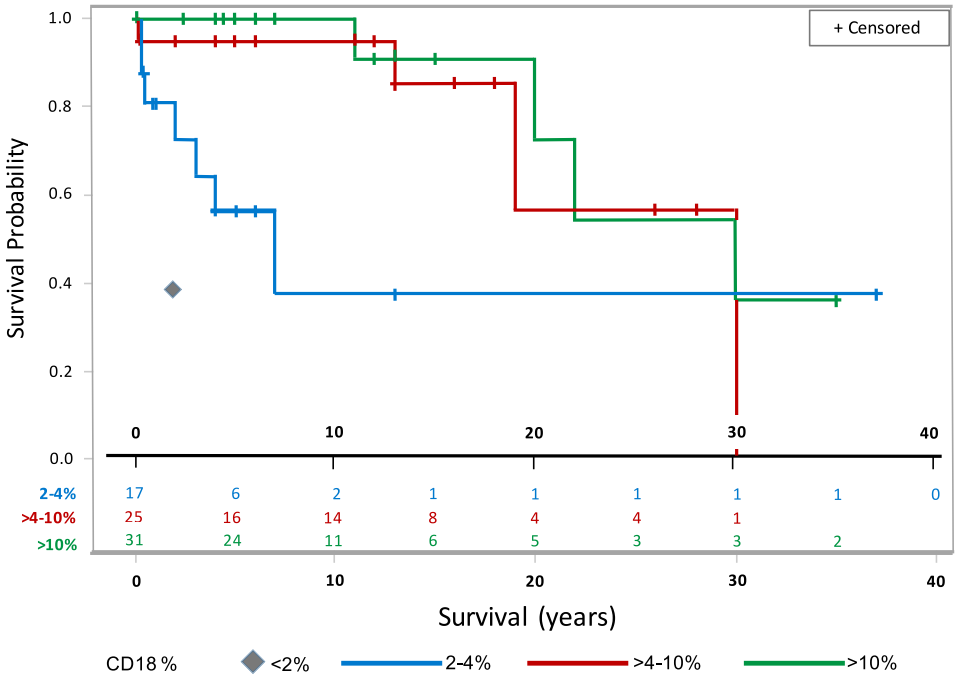

FIGURE 1. Kaplan-Meier survival estimates for patients with moderate LAD-I not receiving allogeneic HSCT, by CD18 expression. Because many reports did not provide precise survival (stating only that mortality occurred before the age of 2 years), it was not possible to generate plots incorporating most of the severe cases. The gray diamond indicates the 39% survival to the age of 2 years for 66 evaluable patients with severe LAD-I not receiving HSCT.

(24%) and mutations on Exons 5, 6, and 7 accounted for 44% of specified cases. We also identified 18 cases in which CD18 expression was more than 30% (range, 31%-99%). In 8 of 12 cases in which CD18 was more than 30% and CD11 information was available, at least 1 CD11 moiety was reported as less than 2%, consistent with recent descriptions of mutations enabling surface expression of nonfunctional CD18.[6] Clinical and genetic details of these cases are provided in Table E6 of this article's Online Repository at www.jaci-inpractice.org.

We sought to understand whether prognosis for severe LAD-I in the absence of HSCT is similar to the initially reported 25% survival to the age of 2 years. There were 66 severe LAD-I cases (per investigator assessment or CD18 less than 2%) for whom survival to 2 years was reported, 40 of whom died before the age of 2 years (61% mortality). As indicated in Table I, survival to the age of 2 years was similar for severe LAD-I subsets defined strictly by CD18 expression, and for severe cases reported since 2000. One patient with severe LAD-I survived beyond the age of 12 years (death at 13.5 years). Because many reports did not provide precise survival durations for severe LAD-I (stating only that mortality occurred before the age of 2 years), it was not possible to generate Kaplan-Meier plots incorporating most of the severe LAD-I cases. Survival to the age of 2 years and throughout early childhood exceeded 90% for patients with more than 4% CD18 expression. Figure 1 shows the survival probability for LAD-I cases on the basis of CD18 expression.

Outcomes for 101 patients receiving HSCT were consistent with recent series.[7,8] Phenotypic correction was reported in 83% of HLA-identical sibling allograft recipients. Transplant-related mortality was 19% across all groups (11% for HLA-matched sibling recipients). Seven of 22 (32%) haploidentical recipients had HSCT-related mortality and 12 (55%) received at least 1

subsequent transplant. HSCT outcomes were not markedly different for cases in publications before 2000 (n = 23) versus those from 2000 to 2017 (n = 78), although the more recent interval included matched unrelated donor (n = 24) and cord blood (n = 6) transplants. Additional transplant information is provided in Table E7 in this article's Online Repository at www.jaci-inpractice.org.

Our findings indicate that severe LAD-I remains a life-threatening condition with limited 2-year survival in the absence of allogeneic HSCT. Potential publication biases may include predilection for reporting more severe cases and those with favorable treatment outcomes; there is also potential underreporting from regions with higher disease incidence, in which LAD-I management is a component of regular practice. Umbilical cord complications and granulocytosis are frequent early LAD-I manifestations. Respiratory tract, ear, sepsis, oral, and skin infections are common. HSCT is the only available curative therapy; transplant-related mortality and other complications occur frequently, especially in haploidentical transplants. In addition to flow cytometry, genetic evaluation may confer meaningful diagnostic and prognostic information. Rapid identification of patients with potential LAD-I (unusual or severe infections during infancy, granulocytosis, and umbilical cord complications) is essential to enable referral to centers with disease expertise and early implementation of definitive therapy.

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Conflicts of interest: E. Almarza has received personal fees for lecturer participation and has patent licensing agreements for the development of LAD gene therapies from Rocket Pharmaceuticals. S. Kasbekar and J. D. Schwartz are full-time employees of Rocket Pharmaceuticals. A. Thrasher is a consultant for Rocket Pharmaceuticals. D. Kohn declares no relevant conflicts of interest. J. Sevilla serves as an advisory board member for Rocket Pharmaceuticals and has patent licensing agreements for the development of gene therapies from Rocket Pharmaceuticals. T. Nguyen is a full-time employee of RTW Investments and a stockholder of Rocket Pharmaceuticals. J. Bueren is a consultant for Rocket Pharmaceuticals, has patent licensing agreements for the development of LAD gene therapies from Rocket, and has also obtained financial support for research.
Received for publication October 18, 2017; revised December 11, 2017; accepted for publication December 12, 2017.
Available online January 20, 2018.
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2213-2198

https://doi.org/10.1016/j.jaip.2017.12.008

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2. Schmidt S, Moser M, Sperandio M. The molecular basis of leukocyte recruitment and its deficiencies. Mol Immunol 2013;55:49-58.
3. Fischer A, Lisowska-Grospierre B, Anderson DC, Springer TA. Leukocyte adhesion deficiency: molecular basis and functional consequences. Immunodefic Rev 1988;1:39-54.
4. Hanna S, Etzioni A. Leukocyte adhesion deficiencies. Ann NY Acad Sci 2012; 1250:50-5.
5. Van de Vijver E, Van den Berg TK, Kuijpers TW. Leukocyte adhesion deficiencies. Hematol Oncol Clin North Am 2013;27:101-16.
6. Levy-Mendelovich S, Rechavi E, Abuzaitoun O, Vernitsky H, Simon AJ, Lev A, et al. Highlighting the problematic reliance on CD18 for diagnosing leukocyte adhesion deficiency type 1. Immunol Res 2016;64:476-82.
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8. Hamidieh AA, Pourpak Z, Hosseinzadeh M, Fazlollahi MR, Alimoghaddam K, Movahedi M, et al. Reduced-intensity conditioning and hematopoietic SCT for pediatric patients with LAD-1: clinical efficacy and importance of chimerism. Bone Marrow Transplant 2012;47:646-50.

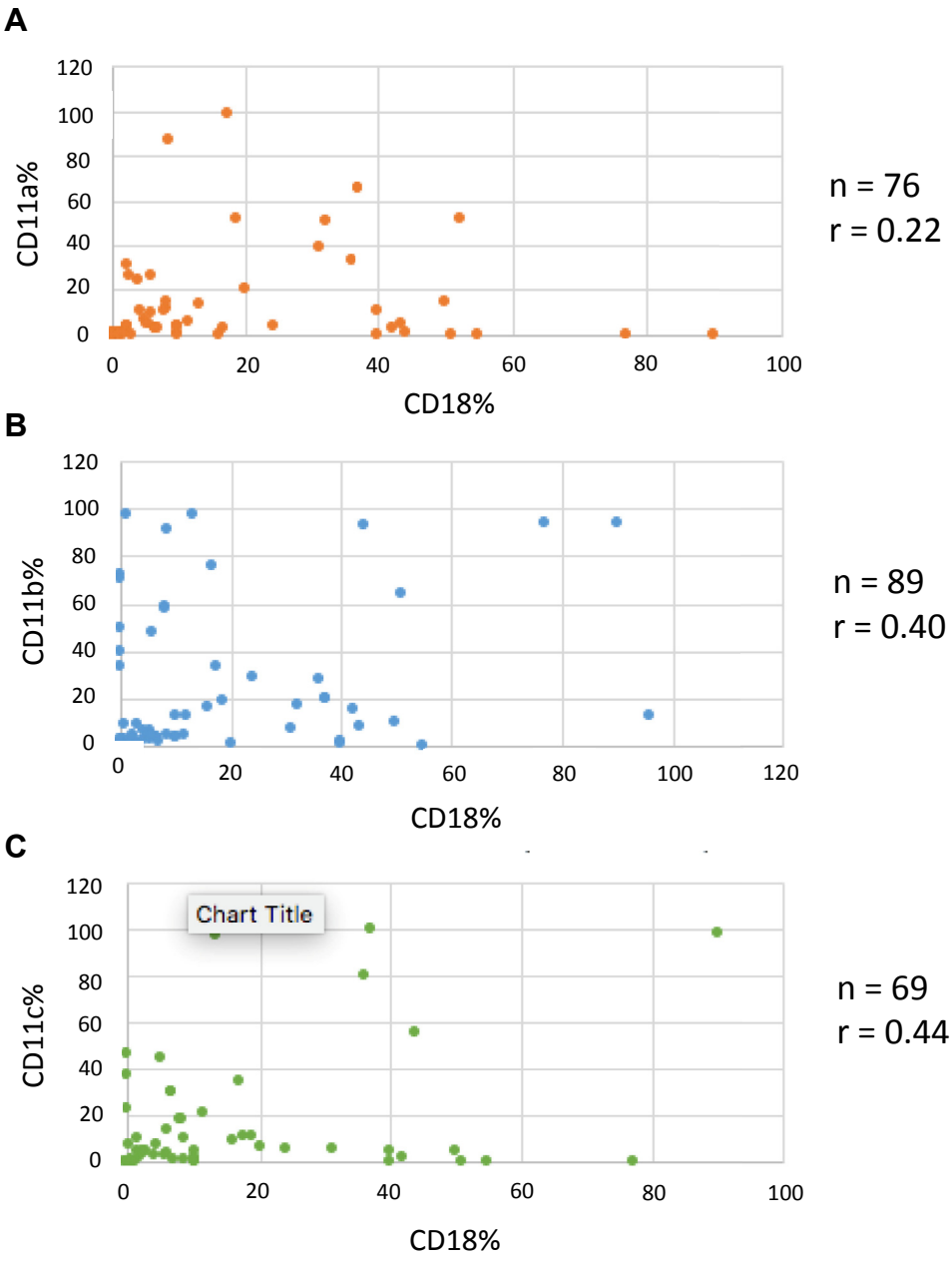

FIGURE E1. Correlation of neutrophil CD18 expression with β_2-integrin heterodimer expression. CD18 expression by **(A)** CD11a, **(B)** CD11b, and **(C)** CD11c. Most publications did not provide precise mechanism by which β_2-integrin expression was assessed; the percentage of neutrophils expressing CD18 (or CD11) via flow cytometry (relative to normal) is the most frequent modality for determination of CD18 expression.

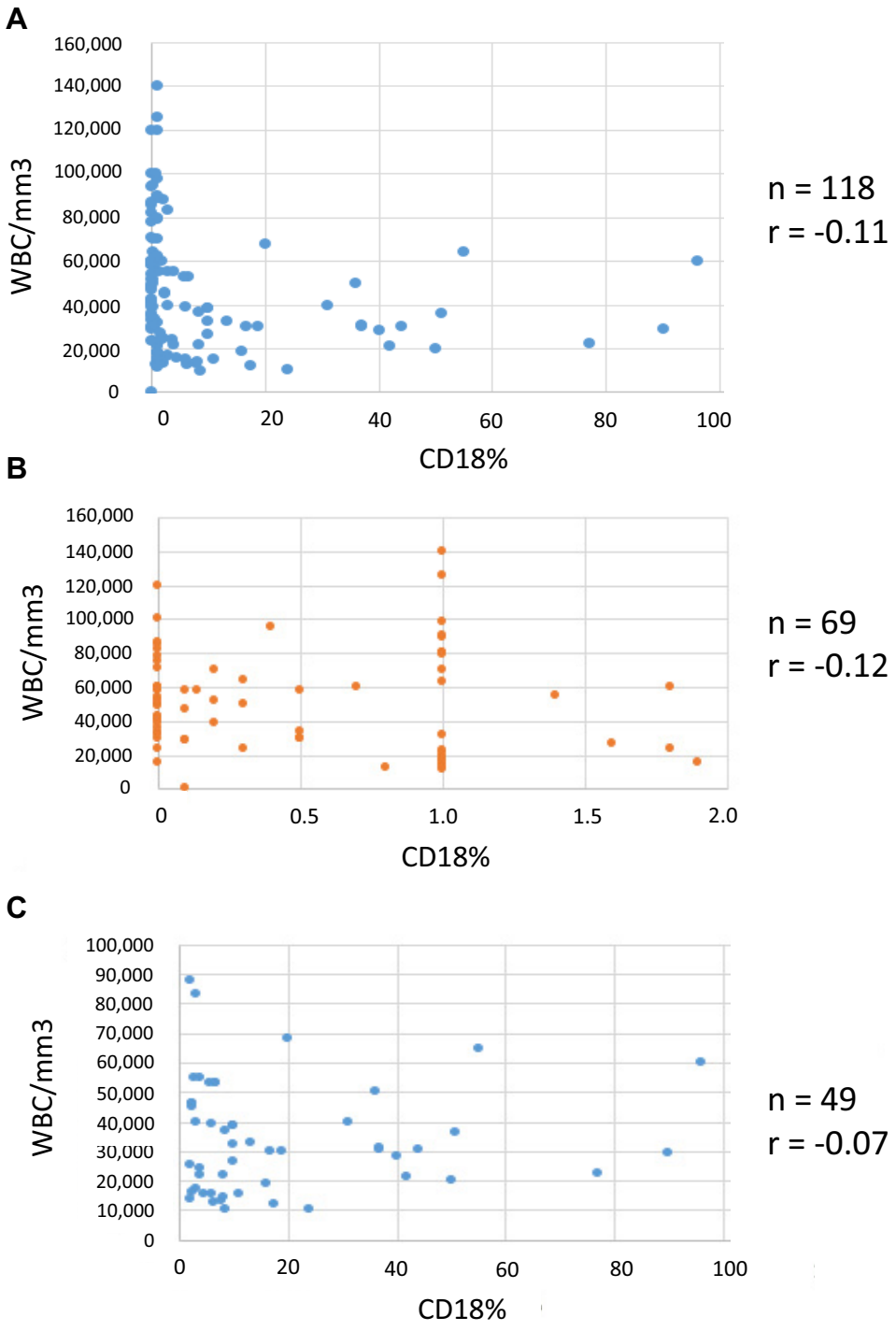

FIGURE E2. Correlation of neutrophil CD18 expression with highest reported WBC count for **(A)** all patients for whom information was reported, **(B)** patients with CD18 <2%, and **(C)** patients with CD18 ≥2%. Upper limits of normal for WBC counts vary between clinical laboratories, but are generally in the range of 9800/mm^3.

TABLE E1. Publications and patient numbers by country

Country	No. of publications	No. of patients
United States	25	50
Iran	12	65
India	10	45
United Kingdom	8	16
The Netherlands	5	9
Japan	5	5
Italy	4	5
Mexico	3	4
Canada	3	5
France	3	6
Taiwan	3	2
Israel	2	12
Spain	2	2
European Union*	2	10
Saudi Arabia	2	13
Turkey	2	2
Chile	2	2
Jordan	2	2
Pakistan	2	3
United States/European Union*	1	36
Germany/France	1	14
Switzerland	1	4
Tunisia	1	5
Argentina	1	1
Brazil	1	1
Egypt	1	1
Norway	1	1
Singapore	1	1
China	1	1

*Publications with multiple contributing nations.

TABLE E2. LAD-I publications evaluated to comprise database

Reference	No. of cases
Akbari H, Zadeh MM. Leukocyte adhesion deficiency. Indian J Pediatr 2001;68:77-9.	1
Al-Dhekri H, Al-Mousa H, Ayas M, Al-Muhsen S, Al-Ghonaium A, Al-Ghanam G, et al. Allogeneic hematopoietic stem cell transplantation in leukocyte adhesion deficiency type 1: a single center experience. Biol Blood Marrow Transplant 2011;17:1245-9.	11
Alizadeh P, Rahbarimanesh AA, Bahram MG, Salmasian H. Leukocyte adhesion deficiency type 1 presenting as leukemoid reaction. Indian J Pediatr 2007;74:1121-3.	1
Allende LM, Hernandez M, Corell A, García-Pérez MA, Varela P, Moreno A, et al. A novel CD18 genomic deletion in a patient with severe leukocyte adhesion deficiency: a possible CD2/lymphocyte function-associated antigen-1 functional association in humans. Immunology 2000;99:440-50.	1
Al-wahadneh A, Haddadin I, Hamouri M, Omari K, Aejellat F. Bone marrow transplantation for leukocyte adhesion deficiency-I: case report. Saudi J Kidney Dis Transpl 2006;17:564-7.	1
Anderson DC, Schmalsteig FC, Finegold MJ, Hughes BJ, Rothlein R, Miller LJ, et al. The severe and moderate phenotypes of heritable Mac01, LFA-1 deficiency: their quantitative definition and relation to leukocyte dysfunction and clinical features. J Infect Dis 1985;152:668-89.	10
Anderson DC, Springer TA. Leukocyte adhesion deficiency: an inherited defect in the Mac-I, LFA-l, and pI50,95 glycoproteins. Ann Rev Med 1987;38:175-94.	10*
Arnaout MA, Pitt J, Cohen HJ, Melamed J, Rosen FS, Colten HR. Deficiency of granulocyte-membrane glycoprotein (gp150) in a boy with recurrent bacterial infections. N Engl J Med 1982;306:693-9.	1
Arshi S, Bahrami A, Faranoush M, Mehrvar A, Rezaei N. Non-Hodgkin's lymphoma in a patient with leucocyte adhesion deficiency. Iran J Pediatr 2014;24:31-2.	2
Bedlow AJ, Davies EG, Moss AL, Rebuck N, Finn A, Marsden RA. Pyoderma gangrenosum in a child with congenital partial deficiency of leucocyte adherence glycoproteins. Br J Dermatol 1998;139:1064-7.	1
Bissenden JG, Haeney MR, Tarlow MJ, Thompson RA. Delayed separation of the umbilical cord, severe widespread infections, and immunodeficiency. Arch Dis Child 1981;56:397-9.	1
Bowen TJ, Ochs HD, Altman LC, Price TH, Van Epps DE, Brautigan DL, et al. Severe recurrent bacterial infections associated with defective adherence and chemotaxis in two patients with neutrophils deficient in a cell, associated glycoprotein. J Pediatr 1982;101:932-40.	2
Buescher ES, Gaither T, Nath J, Gallin JI. Abnormal adherence-related functions of neutrophils, monocytes, and Epstein-Barr virus-transformed B cells in a patient with C3bi receptor deficiency. Blood 1985;65:1382-90.	1
Cabanillas D, Regairaz L, Deswarte C, García M, Richard ME, Casanova JL, et al. Leukocyte adhesion deficiency type 1 (LAD1) with expressed but nonfunctional CD11/CD18. J Clin Immunol 2016;36:627-30.	1
Castriconi R, Dondero A, Cantoni C, Della Chiesa M, Prato C, Nanni M, et al. Functional characterization of natural killer cells in type I leukocyte adhesion deficiency. Blood 2007;109:4873-81.	2
Cher BTH, Chan HS, Klein GF, Jabkowski J, Schadenböck-Kranzl G, Zach O, et al. A novel 3' splice-site mutation and a novel gross deletion in leukocyte adhesion deficiency (LAD)-1. Biochem Biophys Res Commun 2011;404:1099-104.	1
Chowdary S, Kumar M. Leukocyte adhesion defect: a rare cause of immunodeficiency. Indian J Child Health 2014;1:153-4.	1
Cox DP, Weathers DR. Leukocyte adhesion deficiency type 1: an important consideration in the clinical differential diagnosis of prepubertal periodontitis: a case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:86-90.	1
Crowley CA, Curnutte JT, Rosin RE, André-Schwartz J, Gallin JI, Klempner M, et al. An inherited abnormality of neutrophil adhesion: its genetic transmission and its association with a missing protein. N Engl J Med 1980;302:1163-8.	1
Dababneh R, Al-wahadneh AM, Hamadneh S, Khouri A, Bissada NF. Periodontal manifestation of leukocyte adhesion deficiency type I. J Periodontol 2008;79:764-8.	1
D'Agata, Paradis K, Chad Z, Bonny Y, Seidman E. Leucocyte adhesion deficiency presenting as a chronic ileocolitis. Gut 1996;39:605-8.	1
Davies EG, Isaacs D, Levinsky RJ. Defective immune interferon production and natural killer activity associated with poor neutrophil mobility and delayed umbilical cord separation. Clin Exp Immunol 1982;50:454-60.	2
Deist F, Blanche S, Keable H, Gaud C, Pham H, Descamp-Latscha B, et al. Successful HLA nonidentical bone marrow transplantation in three patients with the leukocyte adhesion deficiency. Blood 1989;74:512-6.	3

(continued)

TABLE E2. *(Continued)*

Reference	No. of cases
El-Sayed ZA, El-Ghoneimy DH, Abd-Allah H, Afifi HM. A rare association between leukocyte adhesion deficiency type I and psoriasis in humans. Allergy Asthma Immunol Res 2011;3:138-40.	1
Engel ME, Hickstein DD, Bauer TR Jr, Calder C, Manes B, Frangoul H. Matched unrelated bone marrow transplantation with reduced-intensity conditioning for leukocyte adhesion deficiency. Bone Marrow Transplant 2006;37:717-8.	1
Esmaeili B, Ghadami M, Fazlollahi MR, Niroomanesh S, Atarod L, Chavoshzadeh Z, et al. Prenatal diagnosis of leukocyte adhesion deficiency type-1 (five cases from Iran with two new mutations). Iran J Allergy Asthma Immunol 2014:13:61-5.	4
Farinha NJ, Duval M, Wagner E, Champagne J, Lapointe N, Barrette S, et al. Unrelated bone marrow transplantation for leukocyte adhesion deficiency. Bone Marrow Transplant 2002;30:979-98.	3
Fathallah DM, Jamal T, Barbouche MR, Bejaoui M, Hariz MB, Dellagi K. Two novel frame shift, recurrent and *de novo* mutations in the ITGB2 (CD18) gene causing leukocyte adhesion deficiency in a highly inbred North African population. J Biomed Biotechnol 2001;1:114-21.	5
Fiorini M, Piovani G, Schumacer RF. ITGB2 mutation combined with deleted ring 21 chromosome in a child with leukocyte adhesion deficiency. Allergy Clin Immunol 2009;124:1356-8.	1
Fischer A, Descamps-Latscha B, Gerota I, Lisowska-Grospierre B, Gerota I, Perez N, et al. Bone-marrow transplantation for inborn error of phagocytic cells associated with defective adherence chemotaxis, and oxidative response during opsonised particle phagocytosis. Lancet 1983;2:473-6.	2
Garcia MB, Dominguez O, Juan M, Aróstegui JI, Badell I, Chapman E, et al. Type I leucocyte adhesion deficiency (LAD I): report of a case. Allergol Immunolpathol (Madr) 2012;40:254-8.	1
Guneser S, Altintas DU, Aksungur P, Hergüner O, Sanal O. An infant with severe leucocyte adhesion deficiency. Acta Paediatr 1996;85:622-4.	1
Hamidieh AA, Pourpak Z, Alimoghaddam K, Movahedi M, Bahoush G, Behmanesh F, et al. Successful allogeneic stem cell transplantation with a reduced-intensity conditioning in a leukocyte adhesion deficiency type I patient. Pediatr Transplant 2009;15:E30-3.	1
Hamidieh AA, Pourpak Z, Hosseinzadeh M, Fazlollahi MR, Alimoghaddam K, Movahedi M, et al. Reduced-intensity conditioning and hematopoietic SCT for pediatric patients with LAD-1: clinical efficacy and importance of chimerism. Bone Marrow Transplant 2012;47:646-50.	10
Harvath L, Andersen BR. Defective initiation of oxidative in polymorphonuclear leukocytes. N Engl J Med 1979;300:1130-5.	1
Hattori H, Tsuruta S, Horikoshi Y, Amano K, Takashima Y, Sakashita K, et al. Successful human leukocyte antigen one antigen-mismatched related bone marrow transplantation in a 6-year-old boy with leukocyte adhesion deficiency syndrome. Pediatr Int 2001;43:306-9.	1
Hayward AR, Harvey BA, Leonard J, Greenwood MC, Wood CB, Soothill JF. Delayed separation of the umbilical cord, widespread infections, and defective neutrophil mobility. Lancet 1979;1:1099-101.	6
Hinze CH, Lucky AW, Bove KE, Marsh RA, Bleesing JH, Passo MH. Leukocyte adhesion deficiency type 1 presenting with recurrent pyoderma gangrenosum and flaccid scarring. Pediatr Dermatol 2010;27:500-3.	1
Hixson P, Smith C, Shurin SB, Tosi MF. Unique CD18 mutations involving a deletion in the extracellular stalk region and a major truncation of the cytoplasmic domain in a patient with leukocyte adhesion deficiency type 1. Blood 2004;103:1105-13.	1
Hogg N, Stewart MP, Scarth SL, Newton R, Shaw JM, Law SK, et al. A novel leukocyte adhesion deficiency caused by expressed but nonfunctional β2 integrins Mac-1 and LFA-1. J Clin Invest 1999;103:97-106.	1
Hu TC, Wang LC, Chiang BL. Type 1 leukocyte adhesion deficiency complicated by the presence of idiopathic liver cirrhosis. J Formosan Med Assoc 2014;113:877-8.	1
Hung CH, Cheng SN, Hua YM, Wang CL, Chen YH, Yang KD. Leukocyte adhesion deficiency disorder: report of one case. Acta Paediatr Taiwan 1999;40:128-31.	1
Jabbari Azad F, Ardalan M, Hoseinpoor Rafati A, Sotoudeh S, Pourpak Z. Osteomyelitis in leukocyte adhesion deficiency type 1 syndrome. J Infect Dev Ctries 2010;4:175-8.	1

(continued)

TABLE E2. *(Continued)*

Reference	No. of cases
Jabado N, Le Deist F, Cant A, De Graeff-Meeders ER, Fasth A, Morgan G, et al. Bone marrow transplantation from genetically HLA-nonidentical donors in children with fatal inherited disorders excluding severe combined immunodeficiencies: use of two monoclonal antibodies to prevent graft rejection. Pediatrics 1996;98:420-8.	2
Jain S, Gozdziak P, Morgan A, Burt RK. Remission of Crohn's disease after cord blood transplantation for leukocyte adhesion deficiency type 1. Bone Marrow Transplant 2013;48:1006-7.	1
Jasani BB, Nanavati R, Kabra N. Unusual neonatal presentation of type I leukocyte adhesion deficiency. J Clin Neonatol 2014;3:109-11.	1
Jothilakshmi K, Priva S, Matthai J. Leucocyte adhesion defect-1. Indian Pediatr 2008;45:507-9.	1
Kavehmanesh Z, Matinzadeh ZK, Amirsalari S, Torkaman M, Afsharpayman S, Javadipour M. Leukocyte adhesion deficiency: report of two family related newborn infants. Acta Med Iran 2010;48:273-6.	2
Kobayashi K, Fujita K, Okino F, Kajii T. An abnormality of neutrophil adhesion: autosomal recessive inheritance associated with missing neutrophil glycoproteins. Pediatrics 1984;73:606-10.	1
Kuijpers TW, van Lier RAW, Hamann D, de Boer M, Thung LY, Weening RS, et al. Leukocyte adhesion deficiency type 1 (LAD-1)/variant: a novel immunodeficiency syndrome characterized by dysfunctional β2 integrins. J Clin Invest 1997;100:1725-33.	1
Levy-Mendelovich S, Rechavi E, Abuzaitoun O, Vernitsky H, Simon AJ, Lev A, et al. Highlighting the problematic reliance on CD18 for diagnosing leukocyte adhesion deficiency type 1. Immunol Res 2016;64:476-82.	10
Li L, Jin YY, Cao RM, Chen TX. A novel point mutation in CD18 causing leukocyte adhesion deficiency in a Chinese patient. Chin Med J (Engl) 2010;123:1278-82.	1
Madkaikar M, Currimbhoy Z, Gupta M, Desai M, Rao M. Clinical profile of leukocyte adhesion deficiency type I. Indian Pediatr 2011;49:43-5.	7
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Majorana A, Notarangelo LD, Savoldi E, Gastaldi G, Lozada-Nur F. Leukocyte adhesion deficiency in a child with severe oral involvement. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87:691-4.	1
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Mancias C, Infante AJ, Kamani NR. Matched unrelated donor bone marrow transplantation in leukocyte adhesion deficiency. Bone Marrow Transplant 1999;24:1261-3.	1
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TABLE E2. *(Continued)*

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(continued)

TABLE E2. *(Continued)*

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Note. A total of 323 LAD-I cases were evaluated and included in the database, identified in the 107 publications listed in the table.
*Because the 10 cases noted here were described in more than 1 publication, the sum of cases in the table is 333.

TABLE E3. Infections specified (by LAD-I severity)*

	CD18 <2% (n = 85)		CD18 ≥2% (n = 69)	
Infection	**n**	**%**	**n**	**%**
Otitis media	23	27	25	36
Respiratory tract including pneumonia	33	39	16	23
Sepsis	25	29	17	25
Periodontal including gingivitis and oral ulcers	20	24	36	52
Perianal skin infections	17	20	10	14
Necrotic skin ulcers	11	13	8	12

*Includes conditions reported as >10% of specified infections.

TABLE E4. Umbilical cord complications by neutrophil CD18 expression (LAD-I severity)

	LAD-I severity	
Umbilical cord complications	**CD18 <2% (n = 110)**	**CD18 ≥2% (n = 81)**
Yes	92 (84%)	47 (58%)
No	18 (16%)	34 (42%)

Note. Umbilical cord complications include delayed cord separation and omphalitis. Umbilical cord complication information was available for 110 of 135 patients with CD18 <2% and 81 of 130 patients with CD18 ≥2%.

TABLE E5. Umbilical cord complications and 2-y mortality in LAD-I with CD18 <2%

Umbilical cord complications	**Death before 24 mo**	**Alive at 24 mo**
Complications	28	8
No complications	0	6

Umbilical cord complications include delayed cord separation and omphalitis. Table includes information for 42 patients from whom information regarding umbilical cord complications was available, and for whom follow-up to age 2 y (or death before the age 2 of y) was provided.

TABLE E6. LAD-I cases with CD18 >30% and at least 1 CD11 moiety <2%

Patient	Pheno	Sex	Mutation	Loc	Type	CD18%	CD11a%	CD11b%	CD11c%	Nation	Year of publication
Levi-Mendel-ovich 2016-2	M	Male	c.n.C562T; p.R188X	Exon 6	Nonsense	44	1	93	55	Israel	2016
Levi-Mendel-ovich 2016-5	M	Female	10-bp deletion, c.n.119-GGCCCGGCTG	Exon 3	Frame shift	51	0	64	0	Israel	2016
Levi-Mendel-ovich 2016-7	M	Female	1-bp deletion, c.n.1096-G	Exon 10	Frame shift	77	0	94	0	Israel	2016
Levi-Mendel-ovich 2016-8	M	Male	1-bp deletion, c.n.1096-G	Exon 10	Frame shift	90	0	94	98	Israel	2016
Levi-Mendel-ovich 2016-9	M	Male	c.850G>A, G284S	Exon 7	Missense	55	0	0	0	Israel	2016
Mortezaee 2015-8	NS	Female	c.691G>C	Exon 6	Missense	42	2.4	15	1.9	Iran	2015
Esmaeili 2014-1	NS	Female	c.382G>A; p. Asp128Asn	Exon 5	Missense	40	11	1.5	5	Iran	2014
Hinze 2010-1	NS	Male	314T>C	NS	Missense	40	0	1	0	United States	2010

Loc, Location on *ITGB2* gene; *Pheno*, phenotype per investigator.

TABLE E7. Allogeneic HSCT

		Phenotypic correction		Engraftment failure		Subsequent HSCT		HSCT-related mortality	
HSCT type	n	n	%	n	%	n	%	n	%
MSD	36	30	83	2	6	2	6	4	11
MFD	10	8	80	0	–	0	–	2	20
MMFD	2	2	100	0	–	0	–	0	–
MUD	25	19	76	0	–	2	8	6	24
Haplo	22	11	50	4	18	12	55	7	32
CB	6	4	67	2	33	3	50	0	–

CB, Cord blood; *Haplo*, haploidentical donor; *MFD*, matched family donor; *MMFD*, mismatched family donor; *MSD*, matched sibling donor; *MUD*, matched unrelated donor; *NS*, not stated.

Note. Outcomes were available for 101 of 125 patients reported to have received HSCT, of which LAD-I severity was as follows: severe, n = 46; moderate, n = 11; not specified, n = 44. Phenotypic correction is defined as a reversal of the underlying immunodeficiency.