

Clinical, Immunological, and Genetic Features in Patients with Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) and IPEX-like Syndrome



Mahnaz Jamee, MD^{a,b}, Majid Zaki-Dizaji, PhD^c, Bernice Lo, PhD^d, Hassan Abolhassani, MD, PhD^{e,f}, Fatemeh Aghamahdi, MD^g, Mehdi Mosavian, MD^g, Zohreh Nademi, MD, PhD^h, Hamed Mohammadi, PhD^g, Farhad Jadidi-Niaragh, PhDⁱ, Manuel Rojas, MD^j, Juan-Manuel Anaya, MD, PhD^j, and Gholamreza Azizi, PhD^g Karaj, Tehran, and Tabriz, Iran; Doha, Qatar; Stockholm, Sweden; Newcastle, UK; and Bogotá, Colombia

What is already known about this topic? Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-like syndromes are rare inborn errors of immunity with similar immune dysregulation phenomena and different monogenic defects. These 2 groups of disorders have not yet been comprehensively compared.

What does this article add to our knowledge? IPEX syndrome is characterized by more frequent endocrinopathies, earlier development of autoimmunities, and also higher serum levels of IgE and autoantibodies, whereas in patients with IPEX-like syndrome, respiratory tract infections, bronchiectasis, and organomegaly are more common.

How does this study impact current management guidelines? IPEX should be considered in male patients with enteropathy, dermatitis, autoimmunity, endocrinopathy, eosinophilia, and elevated serum IgE, and if the *FOXP3* was intact, IPEX-like syndromes are probable. Hematopoietic stem cell transplantation in IPEX may result in favorable outcomes.

BACKGROUND: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare inborn error of immunity caused by mutations in the forkhead box P3 (*FOXP3*) gene.

OBJECTIVE: In this study, we conducted a systematic review of patients with IPEX and IPEX-like syndrome to delineate differences in these 2 major groups.

METHODS: The literature search was performed in PubMed, Web of Science, and Scopus databases, and demographic, clinical, immunologic, and molecular data were compared between the IPEX and IPEX-like groups.

RESULTS: A total of 459 patients were reported in 148 eligible articles. Major clinical differences between patients with IPEX and IPEX-like syndrome were observed in rates of pneumonia (11% vs 31%, $P < .001$), bronchiectasis (0.3% vs 14%, $P < .001$),

diarrhea (56% vs 42%, $P = .020$), and organomegaly (10% vs 23%, $P = .001$), respectively. Eosinophilia (95% vs 100%), low regulatory T-cell count (68% vs 50%), and elevated IgE (87% vs 61%) were the most prominent laboratory findings in patients with IPEX and IPEX-like syndrome, respectively. In the IPEX group, a lower mortality rate was observed among patients receiving hematopoietic stem cell transplantation (HSCT) (24%) compared with other patients (43%), $P = .008$; however, in the IPEX-like group, it was not significant ($P = .189$).

CONCLUSIONS: Patients with IPEX syndrome generally suffer from enteropathy, autoimmunity, dermatitis, eosinophilia, and elevated serum IgE. Despite similarities in their clinical presentations, patients with IPEX-like syndrome are more likely to present common variable immunodeficiency-like phenotype such as respiratory tract infections, bronchiectasis, and

^aStudent Research Committee, Alborz University of Medical Sciences, Karaj, Iran

^bAlborz Office of USERN, Universal Scientific Education and Research Network (USERN), Alborz University of Medical Sciences, Karaj, Iran

^cLegal Medicine Research Center, Legal Medicine Organization, Tehran, Iran

^dSidra Medicine, Division of Translational Medicine, Research Branch, Doha, Qatar

^eResearch Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

^fDivision of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden

^gNon-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

^hChildren's Bone Marrow Transplant Unit, Great North Children's Hospital, Newcastle, United Kingdom

ⁱImmunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

^jCenter for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia

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Corresponding author: Gholamreza Azizi, PhD, Non-communicable Diseases Research Center, Vice Chancellor for Research, Alborz University of Medical Sciences, Karaj, Iran. E-mail: azizi@abzums.ac.ir.

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Abbreviations used

CMCC- Chronic mucocutaneous candidiasis
 FOXP3- Forkhead box P3
 GOF- Gain-of-function
 HSCT- Hematopoietic stem cell transplantation
 IDDM- Insulin-dependent diabetes mellitus
 IPEX- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked
 IQR- Interquartile range
 Treg- Regulatory T cell
 DOCK8- Dedicator of cytokinesis 8
 LRBA- Lipopolysaccharide (LPS)-responsive and beige-like anchor
 MALT1- Mucosa-associated lymphoid tissue lymphoma translocation protein 1
 STAT- Signal transducer and activator of transcription

organomegaly. HSCT is currently the only curative therapy for both IPEX and IPEX-like syndrome and may result in favorable outcome. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:2747-60)

Key words: Immunodysregulation; Polyendocrinopathy; Enteropathy; X-linked; IPEX; IPEX-like; Autoimmunity; FOXP3

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare monogenic inborn error of immunity caused by mutations in the forkhead box P3 (*FOXP3*) gene.¹ The *FOXP3* gene encodes transcription factor FOXP3, a DNA-binding protein belonging to the forkhead/winged-helix family that controls the development and function of regulatory T cells (Tregs), thereby contributing to peripheral immune tolerance.² Thus, *FOXP3* mutations often lead to various combinations of autoimmune manifestations, mostly including insulin-dependent diabetes mellitus (IDDM), autoimmune thyroiditis, autoimmune enteropathy, autoimmune cytopenia, and dermatitis.³ However, some patients develop immune dysregulation phenomena clinically resembling IPEX in the absence of detectable *FOXP3* mutations.⁴ In such individuals, identified as IPEX-like, autoimmunity results from a variety of underlying monogenic defects including *CD25/IL2RA*,⁴⁻⁹ *STAT5B*,^{10,11} *LRBA*,^{9,12,13} *CTLA4*,^{9,14} *DOCK8*,^{15,16} *MALT1*,¹⁷ as well as *STAT1* gain-of-function (GOF),^{9,18-20} *STAT3* GOF,^{9,21} and *CARD11* GOF.²² Aside from autoimmune complications, each defect is characterized by specific associated features²³: lipopolysaccharide-responsive and beige-like anchor (LRBA) deficiency with recurrent infections and inflammatory bowel disease²⁴; cytotoxic T-lymphocyte-associated protein 4 (CTLA4) haploinsufficiency with recurrent infections, enteropathy, interstitial lung disease, and extra-lymphoid lymphocytic infiltration²⁵; mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) deficiency with recurrent infections and normal number of circulating T and B cells²⁶; dedicator of cytokinesis 8 (DOCK8) deficiency with allergy, cutaneous viral infections, and malignancy²⁷; and signal transducer and activator of transcription 3 (STAT3) deficiency with high IgE serum level, chronic mucocutaneous candidiasis (CMCC), lymphoproliferation, enteropathy, and interstitial lung diseases.²⁸

Usually, in most patients with IPEX, laboratory findings include normal specific and total immunoglobulin levels (except for IgE), complements, and lymphocyte subsets.^{9,29} However, they produce a variety of autoantibodies in early infancy even before the onset of autoimmune manifestations against different organs including thyroid, pancreatic islets, erythrocytes, platelets, and small intestine.^{30,31} Although the number of peripheral blood Tregs is often reduced, they could be at normal level but with impaired function without inhibition of proliferation and cytokine production of effector T cells.⁹ Usually, the first manifestation of disease occurs in early infancy and the course is generally fatal if left untreated.³²

Although immunosuppressive therapy can give a transient or partial improvement of disease symptoms, allogeneic hematopoietic stem cell transplantation (HSCT) offers the only possibility of cure.^{29,33,34} In this study, we systematically reviewed the existing evidence of IPEX and IPEX-like syndromes to compare clinical, molecular, and laboratory data in these 2 major groups.

MATERIALS AND METHODS

Search strategy, study selection, and data extraction

The literature search and evaluation were performed in 3 databases including PubMed, Web of Science, and Scopus, and the following search keywords were used: "IPEX," "IPEX like," "Immunodysregulation, Polyendocrinopathy, and Enteropathy, X-Linked," "Autoimmunity-Immunodeficiency Syndrome, X-Linked," "Diarrhea, Polyendocrinopathy, Fatal Infection Syndrome, X-Linked," "X-Linked Autoimmunity-Allergic Dysregulation Syndrome," "IDDM-Secretory Diarrhea Syndrome," and "*FOXP3* mutation" in various combinations. Reference lists of all full-text articles and major reviews were manually searched for additional studies. The study screening and selection based on the eligibility criteria and data extraction were performed as previously described.³⁵

Statistical and genetic analysis

Aggregate data analysis was performed with simple data pooling. By this, an overall summary of subgroup data or data from a number of related studies were combined without weighting. Central and descriptive statistics were reported for quantitative data. For variables with abnormal distribution, median and interquartile ranges (IQR) were calculated. For group comparisons, Mann-Whitney *U*, χ^2 , and Fisher exact tests were applied. A *P* value <.05 was considered statistically significant. All statistical analyses were performed using the SPSS software (v. 25.0; SPSS, Chicago, Ill). For the genetic analysis, we used a uniform mutation nomenclature for all mutations in accordance with the Human Genome Variation Society guidelines; consequently, we had to change some of the mutation numbering from that, which was reported to conform to the guidelines. For the mutations in which the protein effect was not reported (except for splice site mutations and long indels), we used MutationTaster software (<http://www.mutationtaster.org>) to predict the amino acid changes.

RESULTS

Study characteristics

The literature search identified 1271 articles. Of them, 617 articles were duplicates and 506 articles were excluded after title and abstract screening. [Figure E1](#) (available in this article's Online

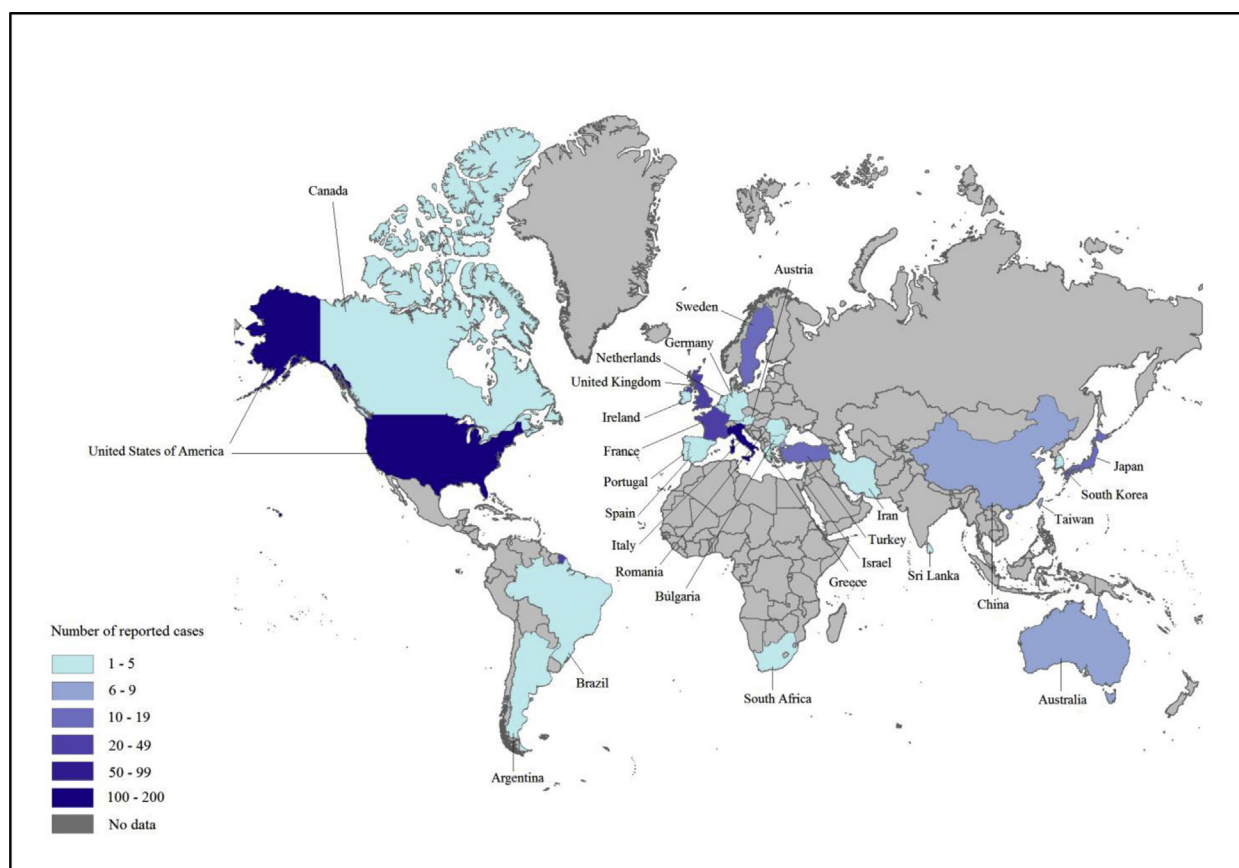


FIGURE 1. Geographical distribution of 459 reported patients with IPEX phenotype. *IPEX*, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

Repository at www.jaci-inpractice.org) summarizes the Preferred Reporting Items for Systematic Reviews and Meta-Analysis diagram. Overall, 148 articles fulfilled the inclusion criteria and were subsequently used for data extraction.^{1,4-9,11-20,22,30,31,33,34,36-162}

A total of 601 patients were reported in these 148 unique articles, and after the removal of duplicate cases, 459 patients remained for data analysis. Among these 459 patients, 49 patients were diagnosed clinically based on the signs and symptoms. Genetic studies were performed in 410 patients, revealing 312 patients with disease-causing *FOXP3* mutation (IPEX group) and 98 patients without any identifiable *FOXP3* mutations (IPEX-like group). Further investigations in these 98 patients identified 12 mutated genes causing IPEX-like phenotype in 58 patients (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Epidemiologic characteristics of patients with IPEX

In this systematic review, 459 patients (285 males, 23 females, and 151 unknown genders) with IPEX and IPEX-like syndrome were evaluated. Figure 1 represents the distribution of patients among different countries. Demographic data of all patients are summarized in Table I. A positive family history of immunodeficiency was reported in 60% (141 of 234) of patients. None of the patients with IPEX syndrome were reported to be born to consanguineous parents, whereas 66% (23 of 35) of patients with IPEX-like syndrome had consanguineous parents ($P < .001$).

Among patients with IPEX, higher rates of death (37% [77 of 210] vs 16% [9 of 56], $P = .003$) and death at younger ages (median [IQR] = 0.7 [0.2-2] vs 14 [4-25], $P < .001$) were reported compared with patients with IPEX-like syndrome. The main reasons for death in patients with IPEX were sepsis, multiorgan failure, and post-transplant complications (Table II), whereas in patients with IPEX-like syndrome, these included pneumonia and respiratory failure.

In patients with IPEX, median (IQR) age at first autoimmune manifestation was 0.2 (0-1) years, and second and third autoimmunity occurred at 2 (0.4-10) and 3 (0.9-13) years, respectively. In patients with IPEX-like syndrome, the first presentations of autoimmunity started at median (IQR) age of 2 (0.7-3) years followed by second and third autoimmune manifestations at 5 (2-11) and 8 (3-15) years, respectively. As depicted in Figure 2, autoimmune complications tend to develop earlier in patients with IPEX, compared with IPEX-like ($P < .001$) syndrome.

Clinical spectrum of patients with IPEX and IPEX-like syndrome

As shown in Figure 3, a large proportion of patients with IPEX primarily presented with enteropathy ($n = 74$, 48%), IDDM with or without diabetic ketoacidosis ($n = 35$, 23%), and dermatitis ($n = 30$, 19%). In patients with IPEX-like syndrome, the most common first presentation was also enteropathy ($n =$

TABLE I. Demographic data of patients with IPEX and IPEX-like syndrome

Parameters	Total [†]	IPEX [‡]	IPEX-like	P value
No. of patients	459	312	98	—
Sex ratio, M/F (n = 308)	285/23	218/3	31/20	<.001*
Family history of PID, n (%) (n = 234)	141 (60)	101 (58)	16 (64)	.551
Consanguinity, n (%) (n = 96)	23 (24)	0	23 (66)	<.001*
Birth weight (kg), median (IQR) (n = 58)	3.09 (2.15-3.48)	3.15 (2.04-3.51)	2.4	.798
Dead, n (%) (n = 306)	112 (37)	77 (37)	9 (16)	.003*
Current age (y), median (IQR) (n = 170)	6 (2-15)	6 (1-17)	7 (3-13)	.980
Age at onset (y), median (IQR) (n = 279)	0.1 (0.1-0.6)	0.1 (0.1-0.4)	0.5 (0.1-2)	<.001*
Age at diagnosis (y), median (IQR) (n = 107)	5 (1-11)	4 (0.4-11)	5 (2-13)	.168
Delay in diagnosis (y), median (IQR) (n = 92)	4 (0.9-10)	4 (0.5-9)	4 (1-12)	.638
Follow-up (y), median (IQR) (n = 320)	4 (0.8-11)	5 (0.8-12.00)	5 (2-11)	.407
Age at death (y), median (IQR) (n = 81)	0.8 (0.3-3)	0.7 (0.2-2)	14 (4-25)	<.001*
Age at presentation of first autoimmunity (y), median (IQR) (n = 102)	0.4 (0-2)	0.2 (0-1)	2 (0.7-3)	<.001*
Age at presentation of second autoimmunity (y), median (IQR) (n = 36)	3 (1-8)	2 (0.4-10)	5 (2-11)	.115
Age at presentation of third autoimmunity (y), median (IQR) (n = 15)	3 (2-12)	3 (0.9-13)	8 (3-15)	.269
Age at presentation of diarrhea (y), median (IQR) (n = 101)	0.2 (0.1-0.6)	0.2 (0.1-0.5)	0.5 (0.3-3)	.001*
Age at presentation of biopsy proven enteropathy (y), median (IQR) (n = 65)	0.5 (0.2-3)	0.3 (0.1-3)	3 (0.5-9)	.007*
Age at presentation of skin disorder (y), median (IQR) (n = 63)	0.2 (0.1-0.5)	0.2 (0.1-0.5)	0.1 (0-1)	.659
Age at presentation of endocrine disorder (y), median (IQR) (n = 101)	0.3 (0-2)	0.1 (0-0.8)	2 (2-4)	<.001*

The median is shown with 25th and 75th percentiles.

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked; IQR, interquartile range; PID, primary immunodeficiency disorder.

*Statistical significance at $P < .05$.

[†]Total patients include clinically and genetically diagnosed patients.

[‡]In the IPEX column, patients with known mutation in the FOXP3 gene are included.

TABLE II. Causes of death (where stated)

Type of disease	Cause	No. of patients	References
IPEX syndrome	Sepsis	9	18,64,74,86,90,123,124,128
	Multiorgan failure	9	1,18,64,74,76,81,90
	IUFD	4	17,123
	Transplantation complications	7	27,45,48,71,90,127
	Cardiac disorders	2	57,90
	Respiratory insufficiency	5	18,48,57,108,137
	ARDS	1	18
	Fungemia	1	119
	Hemorrhage	1	18
	Intestinal perforation	1	137
	Hemophagocytic lymphohistiocytosis	1	42
	RTI	1	81
	Undernutrition	2	86,108
	Meningoencephalitis	1	128
	Severe EBV infection	1	117
IPEX-like syndrome	RTI	2	19,70
	Sepsis	1	16
	Pulmonary insufficiency	1	102
	Intestinal perforation	1	87
	Invasive fungemia	1	18
	Intracranial bleeding	1	18
	ARDS	1	163
	Multiorgan failure	1	19

ARDS, Acute respiratory distress syndrome; EBV, Epstein-Barr virus; IUFD, intrauterine fetal death; RTI, respiratory tract infections.

13, 37%), but it was followed by dermatitis (n = 10, 29%) and respiratory tract infections (n = 5, 14%). Among patients with an established primary clinical diagnosis (n = 60), most patients

were diagnosed initially with enteropathy (n = 16, 27%), neonatal diabetes (n = 11, 18%), food allergy (n = 7, 12%), and IPEX itself (n = 9, 15%). Figure 4 shows the wide range of

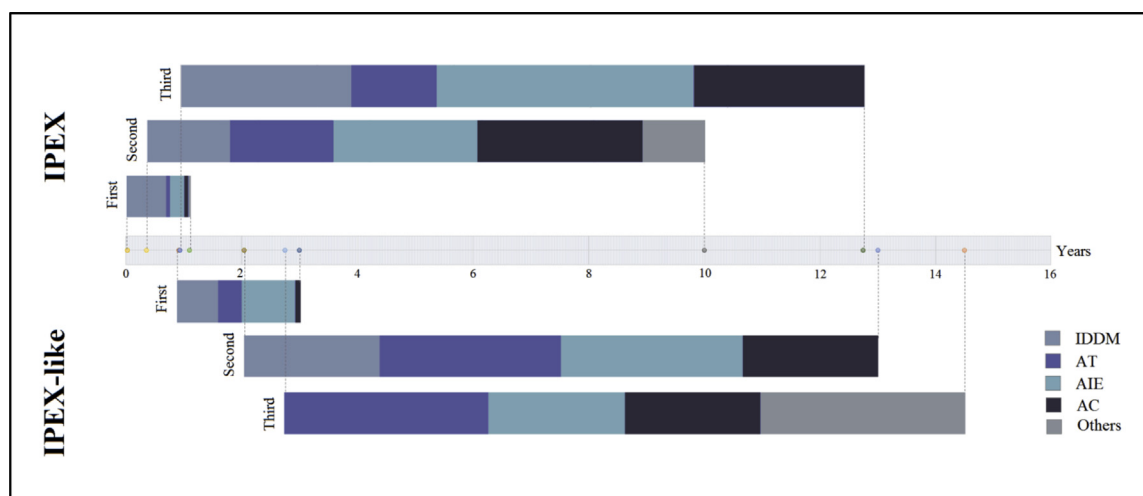


FIGURE 2. Temporal timeline of autoimmune manifestations in IPEX and IPEX-like syndromes. Autoimmune manifestations developed significantly at an earlier age in patients with IPEX, compared with those with IPEX-like syndrome. The most common first autoimmune manifestation in IPEX and IPEX-like syndromes was IDDM and autoimmune enteropathy, respectively (see text for detailed information). AC, Autoimmune cytopenia; AIE, autoimmune enteropathy; AT, autoimmune thyroiditis; First, first autoimmune manifestations; IDDM, insulin-dependent diabetes mellitus; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; Second, second autoimmune manifestations; Third, third autoimmune manifestations.

initial clinical diagnosis of patients with IPEX and IPEX-like syndrome. Of note, only 15% of patients were diagnosed correctly at the first time of presentation.

Patients with IPEX and IPEX-like syndrome are affected by a variety of autoimmune complications summarized in Table III. Almost half of the patients (50% [212 of 425]) had at least 1 autoimmune endocrinopathy. IDDM (123 [39%] vs 21 [25%], $P = .012$) and thyroiditis (50 [16%] vs 26 [31%], $P = .002$) were most commonly reported endocrinopathies in patients with IPEX and IPEX-like syndrome, respectively. Aside from autoimmune endocrine disorders, in patients with IPEX and IPEX-like syndrome, autoimmune cytopenia (including immune thrombocytopenic purpura, autoimmune hemolytic anemia, neutropenia, Evans syndrome) (68 [22%] vs 17 [20%]), autoimmune gastrointestinal disorders (37 [12%] vs 21 [25%]), and autoimmune cutaneous disorders (eg, vitiligo and/or alopecia) (13 [4%] vs 12 [14%]) were frequently reported. Other rare autoimmune manifestations such as autoimmune hepatitis, primary sclerosing cholangitis, chronic inflammatory demyelinating polyneuropathy, psoriatic arthritis, and autoimmune nephritis in 12 (4%) patients with IPEX and autoimmune hepatitis, cholangitis, ankylosing spondylitis, vasculitis, and autoimmune interstitial pneumonitis in 7 (8%) patients with IPEX-like syndrome were also reported.

The prevalence of polyautoimmunity (ie, 2 or more concurrent autoimmune disorders) in patients with IPEX and IPEX-like syndrome was 28% (86 of 312) and 35% (30 of 85), respectively. Figure 2 also illustrates the temporal time-line and proportional frequency of each type of autoimmunity in these 2 groups of patients. The most common first autoimmune manifestation in IPEX was IDDM (62% [48 of 78]), whereas most of the patients with IPEX-like syndrome (44% [10 of 23]) primarily developed autoimmune gastrointestinal disorders. The combination of IDDM and autoimmune thyroiditis was the

most common concurrent autoimmune disease in individuals with IPEX (7%) and IPEX-like (5%) syndrome.

Overall, biopsy-proven enteropathy was the most common finding in both IPEX (212 [70%]) and IPEX-like (67 [77%]) groups. In patients complicated with enteropathy, the histopathological presentations were rather variable and mostly included villous atrophy ($n = 111$, 26%), inflammatory infiltration ($n = 78$, 18%), and thin mucosa ($n = 9$, 2%) in the small intestine as well as inflammation ($n = 54$, 13%), mucosal erosion ($n = 13$, 3%), and crypt abscesses ($n = 7$, 2%) in the colon.

Skin disorders including eczematous, atopic, or psoriasiform dermatitis as well as alopecia complicated 200 (66%) individuals with IPEX and 53 (63%) with IPEX-like syndrome ($P = .593$).

Life-threatening infections including pneumonia, sepsis, meningitis, and peritonitis were reported in more than a quarter of all patients (87 [28%] IPEX vs 33 [39%] IPEX-like, $P = .052$). Respiratory tract complications such as sinusitis (10% vs 4%, $P = .042$), pneumonia (31% vs 11%, $P < .001$), and bronchiectasis (14% vs 0.3%, $P < .001$) were more prevalent in patients with IPEX-like syndrome compared with IPEX syndrome. Moreover, ear nose throat disorders such as otitis media, rhinitis, and tonsillitis were reported more frequently among patients with IPEX-like syndrome (16% vs 7%, $P = .015$) (Table IV). The most common microorganisms identified were *Staphylococcus* spp. (IPEX 8% vs IPEX-like 6%, $P = .494$), Cytomegalovirus (IPEX 5% vs IPEX-like 8%, $P = .283$), and *Candida* spp. (IPEX 4% vs IPEX-like 15%, $P < .001$).

Immunological findings of patients with IPEX and IPEX-like syndrome

Table V represents the available immunological data of patients with IPEX and IPEX-like syndrome. Lymphocyte counts in the majority of patients (71% [37 of 52]) were within the

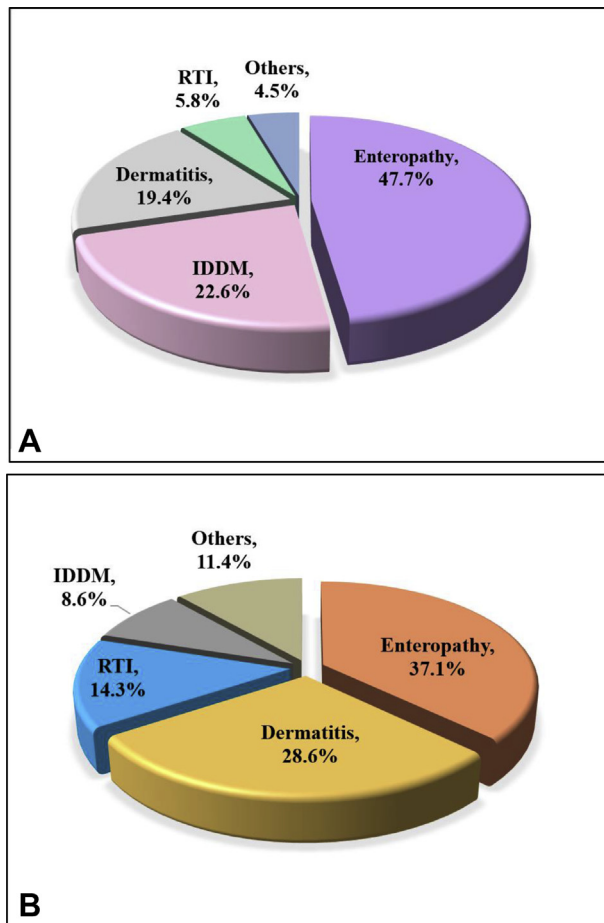


FIGURE 3. The first presentation of 190 patients with (A) IPEX and (B) IPEX-like syndromes. Enteropathy has been observed as the first presentation in most of the patients with IPEX phenotype. IDDM, Insulin-dependent diabetes mellitus; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; RTI, respiratory tract infection.

normal range, and lymphopenia was reported in 25% (13 of 52) of patients. Eosinophilia was a prevalent finding, reported in nearly all patients with IPEX and IPEX-like syndrome (95% [57 of 60] vs 100% [11 of 11]). Thrombocytopenia was detected in a small fraction of patients with IPEX and IPEX-like syndrome (13% [39 of 302] vs 11% [9 of 84], respectively). Most of the patients with IPEX and IPEX-like syndrome had normal lymphocyte subsets including CD3+ (81% [33 of 41] vs 62% [16 of 26]), CD4+ (73% [29 of 40] vs 72% [18 of 25]), CD8+ (85% [34 of 40] vs 72% [18 of 25]), CD19+ (77% [30 of 39] vs 65% [20 of 31]), and natural killer cells (59% [13 of 22] vs 68 [21 of 31]). However, low Treg count was reported in 68% (34 of 50) and 50% (10 of 20) of evaluated patients with IPEX and IPEX-like syndrome, respectively. Adjusted to the age-matched normal ranges, normal IgG (67% [31 of 46] vs 59% [16 of 27]), normal IgA (73% [29 of 40] vs 46% [13 of 28]), normal IgM serum (82% [31 of 38] vs 58% [15 of 26]) levels and elevated IgE levels (87% [104 of 120] vs 61% [17 of 28]) were observed in patients with IPEX and IPEX-like syndrome, respectively. The median IgE serum level was significantly higher

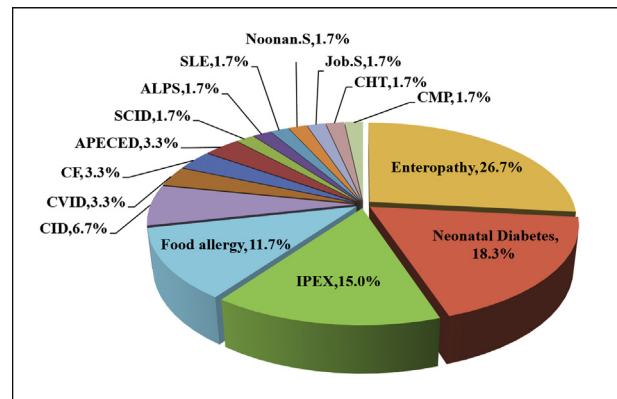


FIGURE 4. Distribution of available initial clinical diagnoses given to 60 patients with IPEX and IPEX-like syndromes at the presentation. Patients with IPEX and IPEX-like syndrome are often diagnosed with enteropathy or neonatal diabetes. ALPS, Auto-immune lymphoproliferative syndrome; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; CF, cystic fibrosis; CHT, congenital hypothyroidism; CID, combined immune deficiency; CMP, congenital myopathy; CVID, common variable immunodeficiency; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; S, syndrome; SCID, severe combined immune deficiency; SLE, systemic lupus erythematosus.

among patients with IPEX compared with those with IPEX-like syndrome (1670.0 vs 40.5, $P = .001$). Patients with IPEX also had higher rates of autoantibodies (71% vs 23%, $P < .001$) than patients with IPEX-like syndrome. Autoantibodies detected in patients with IPEX are listed in Table VI. The most common reported autoantibodies in patients with IPEX-like syndrome were anti-glutamic acid decarboxylase antibody and antithyroglobulin antibody, each reported in 3 (3%) patients.

The most frequently detected autoantibodies were those directed against enterocytes, found in 63 (15%) (57 [19%] IPEX and 1 [1%] IPEX-like) patients. In addition, antienterocyte antibodies were detected more frequently in patients with villous atrophy (30 [40%] IPEX and 1 [5%] IPEX-like patients).

Molecular findings of patients with IPEX and IPEX-like syndrome

In total, 370 (322 families) of the 459 patients (393 families) had a definitive genetic diagnosis, whereas the other 89 patients were diagnosed based on clinical signs and symptoms (no genetic testing in 49 and no genetic cause identified after genetic testing in 40 patients). Among the 370 patients, 312 patients (275 families) had mutations in *FOXP3* (IPEX patients) and 58 patients (47 families) had mutations in other genes (IPEX-like patients) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). The specific mutations for 8 of the patients (6 patients with *FOXP3* deficiency and 2 patients with *IL2RA* deficiency) were not reported, so we did not have access to those details.^{4,7,62,87} Overall, there were 111 different *FOXP3* gene mutations identified in the 306 patients from 270 families (Figure 5). These variants consisted of 50 missense, 29 splice site, 27 inDel (5 mutations with long deletions), 2 nonsense, 1 silent,

TABLE III. Autoimmune disorders in IPEX and IPEX-like syndrome

Autoimmunity	Total (n = 459)	IPEX (n = 312)	IPEX-like (n = 98)	P value
Insulin-dependent diabetes mellitus, n (%)	164 (37)	123 (39)	21 (25)	.012*
Autoimmune thyroiditis, n (%)	81 (18)	50 (16)	26 (31)	.002*
Autoimmune enteropathy, n (%)	64 (14)	37 (12)	21 (25)	.003*
Autoimmune cytopenia, n (%)	90 (20)	68 (22)	17 (20)	.721
Autoimmune skin disorders, n (%)	27 (6)	13 (4)	12 (14)	.001*
Others, n (%)	21 (5)	12 (4)	7 (8)	.146

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

*Statistical significance at $P < .05$.**TABLE IV.** Clinical manifestations of patients with IPEX and IPEX-like syndrome

Parameters	Total† (n = 459)	IPEX‡ (n = 312)	IPEX-like (n = 98)	P value
Pneumonia, n (%)	61 (14%)	32 (11%)	26 (31%)	<.001*
Sinusitis, n (%)	19 (5%)	11 (4%)	8 (10%)	.042*
Ear nose throat disorders, n (%)	35 (8%)	21 (7%)	13 (16%)	.015*
Bronchiectasis, n (%)	13 (3%)	1 (0.3%)	12 (14%)	<.001*
Asthma, n (%)	17 (4%)	15 (5%)	1 (1%)	.212
Food allergy, n (%)	69 (16%)	56 (19%)	8 (10%)	.049*
Diarrhea, n (%)	233 (55%)	169 (56%)	35 (42%)	.020*
Enteropathy, n (%)	301 (71%)	212 (70%)	67 (77%)	.196
Failure to thrive, n (%)	145 (34%)	102 (34%)	32 (38%)	.462
Hepatobiliary disorders, n (%)	58 (14%)	43 (14%)	9 (11%)	.403
Organomegaly, n (%)	53 (13%)	29 (10%)	19 (23%)	.001*
Hematologic disorders, n (%)	133 (31%)	103 (34%)	21 (25%)	.114
Malignancy, n (%)	7 (2%)	5 (2%)	2 (2%)	.650
Autoimmunity, n (%)	310 (70%)	214 (69%)	62 (73%)	.440
Rheumatologic disorders, n (%)	38 (9%)	22 (7%)	12 (14%)	.045*
Skin disorders, n (%)	270 (64%)	200 (66%)	53 (63%)	.593
Endocrine disorders, n (%)	212 (50%)	153 (51%)	38 (45%)	.379
Neurologic/learning disorders, n (%)	36 (9%)	23 (8%)	9 (11%)	.362
Cardiovascular disorders, n (%)	18 (4%)	14 (5%)	2 (2%)	.539
Renal disorders, n (%)	81 (19%)	61 (20%)	14 (17%)	.469
Abscess, n (%)	11 (3%)	7 (2%)	4 (5%)	.264
Sepsis, n (%)	71 (17%)	58 (19%)	11 (13%)	.196

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

*Statistical significance at $P < .05$.

†Total patients include clinically and genetically diagnosed patients.

‡In the IPEX column, patients with known mutation in the FOXP3 gene are included.

1 new start site (c.-7G>T), and 1 poly-A site (g.14372A>G) mutations.

Mutations were located throughout the *FOXP3* gene, and there did not appear to be any mutational hot spot. However, the forkhead domain had a large proportion of the mutations. Four patients had 2 mutations in their *FOXP3* gene, 1 patient with c.748delAAG/c.543C>T (p.K250del/p.S181S) mutations and 3 patients with c.970T>C/c.543C>T (p.F324L/p.S181S). There was no correlation between clinical and laboratory findings with the site of mutation in the different domains.

In 58 patients from 47 families with IPEX-like phenotype (harboring mutations in 11 genes), 39 different variants were identified including 22 missense, 8 nonsense, 4 splice site, and 5 InDel mutations. Mutations in the *STAT1* and *LRBA* genes account for 51% of the patients identified with IPEX-like phenotypes. In 1 family, DOCK8 homozygous mutation was associated with homozygous CLEC7A mutation that might intensify phenotype severity¹⁶ (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

The therapeutic approach in patients with IPEX and IPEX-like syndrome

Immunosuppressive drugs, including cyclosporine, mycophenolate mofetil, tacrolimus, rapamycin, rituximab, azathioprine, infliximab, alemtuzumab, and abatacept, in combination with systematic corticosteroids, were prescribed in 133 of 401 (33%) patients, including 104 of 290 (36%) patients with IPEX and 22 of 74 (30%) patients with IPEX-like syndrome.

A total of 36 of 437 (8%) and 69 of 238 (15%) patients received systemic corticosteroids or immunosuppressive agents alone, respectively, for autoimmune and inflammatory complications. However, definitive control using immunosuppressive therapy was achieved in only 27 (6%) patients, and 106 (23%) patients (87 [28%] patients with IPEX and 11 [11%] patients with IPEX-like syndrome, $P = .001$) received HSCT at the median (IQR) age of 0.8 (0.5-5) years. Among the HSCT complications, acute or chronic graft-versus-host disease occurred in approximately 17% (15 of 87) and 9% (1 of 11) of the

TABLE V. Immunologic profile of patients with IPEX and IPEX-like syndrome

Parameters	Total	IPEX	IPEX-like	P value
WBC $\times 10^3$ (cell/ μ L), median (IQR) (n = 29)	11.2 (8.2-15.7)	11.7 (9.9-16.7)	10.7 (5.3-13.7)	.183
Absolute lymphocytes counts $\times 10^3$ (cells/ μ L), median (IQR) (n = 35)	2.4 (1.3-3.2)	2.5 (1.6-4.7)	2.4 (1.3-3.1)	.370
Absolute neutrophils counts $\times 10^3$ (cells/ μ L), median (IQR) (n = 18)	3.0 (0.04-4.1)	2.2 (0.2-4.9)	3.1 (0.008-4.3)	.851
Absolute eosinophils counts $\times 10^3$ (cells/ μ L), median (IQR) (n = 42)	1.2 (0.5-2.8)	1.1 (0.5-3.1)	1.2 (0.1-2.5)	.859
CD3 ⁺ T cells $\times 10^3$ (cell/ μ L), median (IQR) (n = 41)	1.7 (0.9-3.3)	2.7 (1.2-4.3)	1.5 (0.9-2.8)	.103
CD4 ⁺ T cells $\times 10^3$ (cell/ μ L), median (IQR) (n = 50)	0.9 (0.4-2.0)	1.6 (0.6-3.1)	0.8 (0.3-1.1)	.069
CD8 ⁺ T cells $\times 10^3$ (cell/ μ L), median (IQR) (n = 47)	0.6 (0.3-1.0)	0.7 (0.4-1.0)	0.6 (0.3-1.0)	.770
NK cell (cell/ μ L), median (IQR) (n = 42)	152.0 (74.5-415.5)	200.0 (98.0-566.0)	137.0 (49.0-280.0)	.265
CD19 ⁺ B cells (cell/ μ L), median (IQR) (n = 41)	308.0 (73.5-851.0)	0.6 (0.1-0.8)	269.5 (48.2-687.5)	.239
IgG (mg/dL), median (IQR) (n = 69)	680.0 (296.0-1103.5)	656.0 (257.0-873.0)	735.0 (302.0-1150.0)	.307
IgA (mg/dL), median (IQR) (n = 59)	34.0 (10.0-120.0)	29.0 (8.0-94.0)	78.0 (16.0-192.0)	.243
IgM (mg/dL), median (IQR) (n = 56)	68.5 (35.0-177.7)	52.6 (31.5-182.2)	68.5 (35.5-177.5)	.840
IgE (IU/mL), median (IQR) (n = 109)	1179.0 (120.0-3276.0)	1670.0 (230.0-3698.0)	40.5 (3.3-1009.2)	.001*
Autoantibodies, n (%) (n = 272)	176 (65%)	153 (71%)	9.0 (23%)	<.001*

The median is shown with 25th and 75th percentiles.

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked; IQR, interquartile range; NK, natural killer; WBC, white blood cell.

*Statistical significance at $P < .05$.

transplants in patients with IPEX and IPEX-like syndrome, respectively. Seventeen patients with IPEX died within 3 years after HSCT. Among patients with post-transplant follow-up, the mean duration of follow-up was longer for patients with IPEX (2 years) compared with individuals with IPEX-like syndrome (1 year), $P = .563$. The HSCT survivors (including 53 patients with IPEX and 11 patients with IPEX-like syndrome) had a mean follow up of 3 and 1 years, respectively. The transplantation ameliorated survival outcome of patients with IPEX ($P = .016$); however, for patients with IPEX-like syndrome, it was not significant ($P = .189$) (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). Detailed information on HSCT of 48 cases is presented in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org). Surgical procedures, including gastrectomy, abscess resection, tonsillectomy, myringotomy, and ear tube placement, were performed on 22 patients (5%).

DISCUSSION

Herein we presented a systematic review of IPEX and IPEX-like syndromes in terms of epidemiologic features, clinical, molecular, and immunological characteristics, and also available therapeutic options. In recent years, the discovery of multiple monogenic primary immunodeficiency disorders resulting in immune dysregulation and sharing the overlapping clinical manifestations²³ has made diagnosis challenging. The early diagnosis of IPEX and IPEX-like syndromes is pivotal and helps prevent life-threatening outcomes. About one-fifth of patients with IPEX phenotype have no mutation in the *FOXP3* gene identified. We have investigated clinical and laboratory clues that may help differentiate this group of patients from those with similar disorders in immune dysregulation category. It is worth noting that in some of the demographic, clinical, and laboratory parameters, data belong to a relatively small proportion of patients available in the literature; therefore, they may or may not reflect the findings in the larger group of patients, and due to the low sample size, the statistical comparison between 2 groups may not be valid.

TABLE VI. Autoantibodies found in patients with IPEX syndrome*

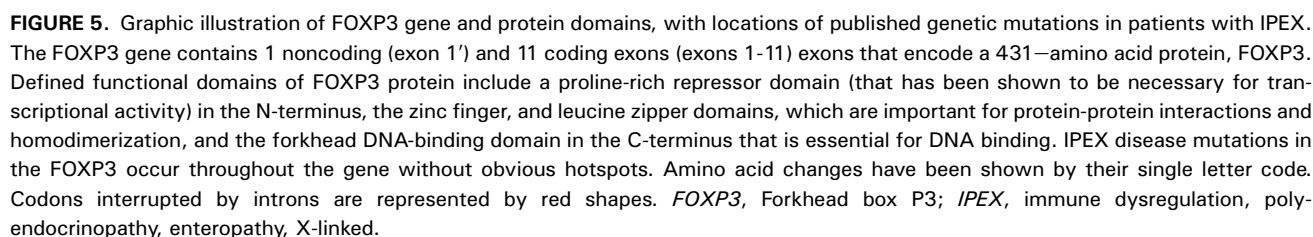
Autoantibodies	No. of positive patients (%)
Anti-islet cell Ab	23 (7)
Anti-insulin Ab (AIA)	18 (6)
Antiglutamic acid decarboxylase Ab (Anti-GAD)	28 (9)
Antinuclear Ab (ANA)	18 (6)
Antineutrophil cytoplasmic Ab (ANCA)	10 (3)
Anti-Saccharomyces-cerevisiae-mannan Ab (ASCA)	4 (1)
Antismooth muscle Ab (SMA)	8 (3)
Antimicrosomal Ab	6 (2)
Antithyroglobulin Ab (TgAb)	7 (2)
Antithyroid peroxidase (TPO)	9 (3)
Antienterocyte Ab (AEA)	57 (19)
Antivillin Ab (actin-binding 95 kDa protein)	19 (6)
Antihormonin Ab (75 kDa protein)	61 (20)

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

*Data regarding autoantibodies in patients with IPEX-like syndrome are scarce and therefore are not shown in this table.

In this review, 89 (30%) patients with IPEX syndrome fulfilled the classic triad of symptoms (enteropathy, skin disorders, and endocrinopathy), and the presence of this triad was comparable with those with IPEX-like syndrome (23 [27%]). Recently, it has been suggested that patients with IPEX are more likely to have full triad, whereas patients with IPEX-like syndrome are mainly affected by thyroid disease and cardiovascular abnormalities.⁹ Our findings demonstrate that most patients with IPEX present with the incomplete triad and atypical phenotype.

IPEX syndrome tends to develop at lower ages, often within the first year of life, compared with IPEX-like syndrome such as LRBA deficiency (median age of onset = 1.8 years)²⁴ and STAT3 GOF mutations (average age of onset = 3 years).²⁸ In patients with IPEX-like syndrome, detailed history taking was more likely to reveal consanguineous parents, positive family history, or miscarriages in previous generations.



In patients with IPEX, the most common autoimmune disorders were endocrinopathy and cytopenia, whereas in patients with IPEX-like syndrome, endocrinopathy and enteropathy predominate. In some patients with IPEX-like syndrome such as STAT3 GOF mutation, other conditions such as CMCC also develop. Therefore, the concurrent development of autoimmune disorders observed in monogenic PIDs seems to be more

Renal complication was generally observed in 19% of patients and almost equally affected patients with IPEX and IPEX-like syndromes. In line with previous studies, the most frequently described renal disorder was membranous nephropathy.^{126,139} Previously, it has been proposed that the detection of autoantibody against the 75-kD antigen may be of diagnostic and predictive value for the development of intestinal and renal damage.¹⁶⁴ However, in our study, this correlation was much more significant for the development of enteropathy than renal abnormalities. This is consistent with previous observations that

high titers of anti-75-kD autoantibodies in IPEX syndrome could potentially be predictive of the associated enteropathy.³¹

Totally, 111 unique mutations in the *FOXP3* gene and 39 different mutations in 11 other genes associated with IPEX-like phenotype were reviewed. Despite the loss of function mutations in the *FOXP3* gene in IPEX disease, other 11 genes with IPEX-like phenotype showed loss (*LRBA*, *DOCK8*, *MALT1*, *STAT5B*, *TTC7A*, *TTC37*, *IL2RA*), haploinsufficiency or dominant negative (*CTLA4*, *CARD11*), and gain (*STAT3*, *STAT1*) of function mutations. The structure of the *FOXP3* gene limits the number of possible exon deletions,¹⁶⁵ and most of the mutations tended to occur at the most highly conserved residues.⁹ Mutations were located throughout the *FOXP3* gene, and there did not appear to be any mutational hot spot. However, the 3 most frequent mutations in the families were the c.1150G>A/p.A384T mutation found in 23 families (9%) and the c.1040G>A/p.R347H mutation detected in 15 families (5%), both of which are in the forkhead domain, and c.751_753del-GAG/p.E251del in the leucine zipper domain that was discovered in 11 families (4%). As shown in Figure 5, the mutations mostly aggregated in within the functional domains. The silent mutation, c.543C>T (p.S181S), has been reported in 3 families. Its effect on FOXP3 mRNA processing, stability, or expression still requires clarification; however, in 1 report, 5% of the FOXP3 transcripts were found to be misspliced around exons 4–5 in activated lymphocytes from patients with this silent mutation.⁹ Because identical *FOXP3* mutations can cause profoundly different phenotypes in patients, it is difficult to link the location of the mutation with disease course or outcome. Also because of the variable expression of FOXP3 protein in patients with IPEX, this factor cannot be used as a reliable tool for the diagnosis or determining the disease severity.⁷⁸ We did not find any correlation between clinical and laboratory factors with the site of the mutation (different domains). This clinical heterogeneity may reflect the complex transcription and splicing regulation, intracellular interactions of FOXP3, effects of modifier genes, and the role of epigenetic regulation/environmental factors in determining the clinical image and outcome.^{163,165}

As indicated in the Results section, disease control with immunosuppressive therapy was achieved in only 27 (6%) patients, whereas 106 (23%) (28% IPEX and 11% IPEX-like) patients underwent HSCT. The HSCT improved survival outcome in both IPEX and IPEX-like groups. Initially, HSCT was only proposed after multiple relapses and when combination immunosuppressive therapy had been tried and failed. However, early HSCT seems to lead to better outcomes in patients with IPEX when it is applied before the development of severe organ damage.¹ It was revealed that early HSCT is also associated with better outcomes in patients with IPEX-like syndrome. Successful HSCT has been reported in several patients with *DOCK8* mutations and is shown to cure nearly all clinical and laboratory manifestations by reconstituting the normal function of the immune system.^{166–168} Recently reported HSCT in cases with *STAT3* and *LRBA* mutations has also been associated with promising outcomes.^{169,170}

SUMMARY AND CONCLUSION

This is the most extensive review of previously published cases of patients with IPEX and IPEX-like syndromes that provided a comparison between 2 diseases and may help discriminate “true

IPEX” from “IPEX like” syndrome. Patients with IPEX syndrome tend to develop autoimmune manifestations at lower ages and within more narrow intervals. The prevalence of endocrinopathies is higher among patients with IPEX, whereas in patients with IPEX-like syndrome, respiratory tract infections, bronchiectasis, and organomegaly are more frequent. Furthermore, patients with IPEX have higher serum levels of IgE and also autoantibodies compared with patients with IPEX-like syndrome. As patients with IPEX syndrome have lower survival rates, early diagnosis and management may help prevention from life-threatening complications.

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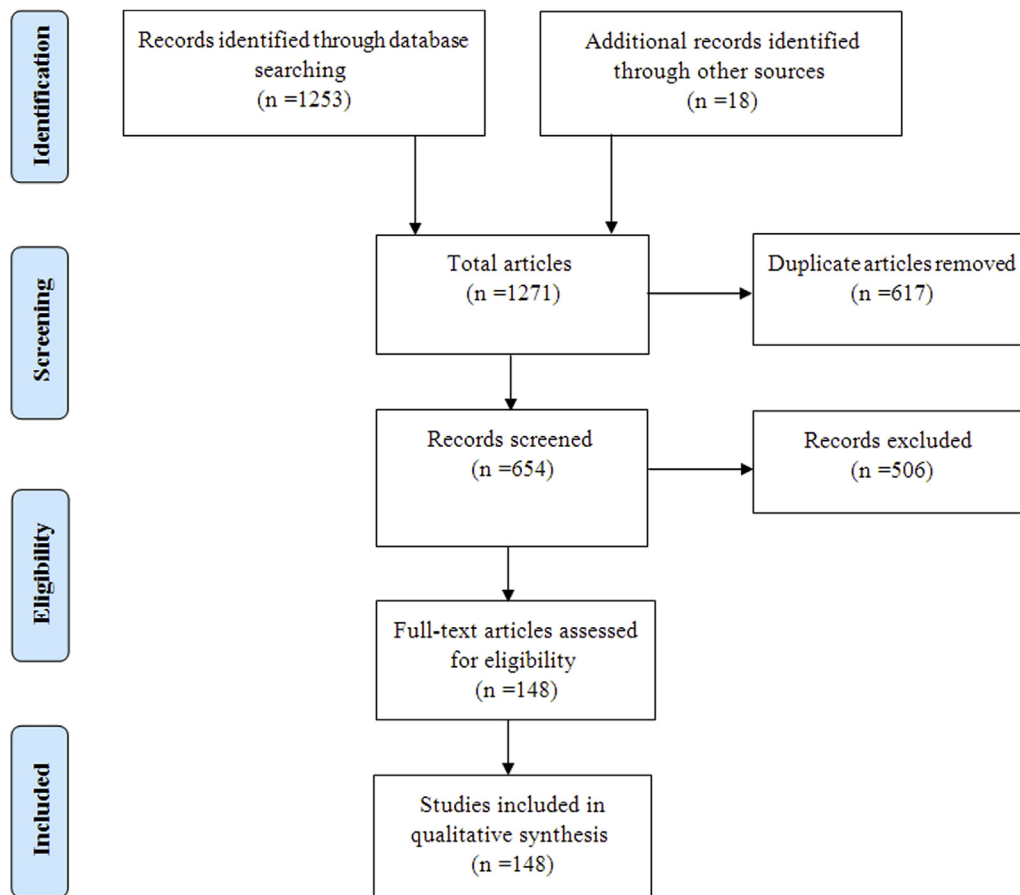


FIGURE E1. Flowchart of the systematic search and study selection process.

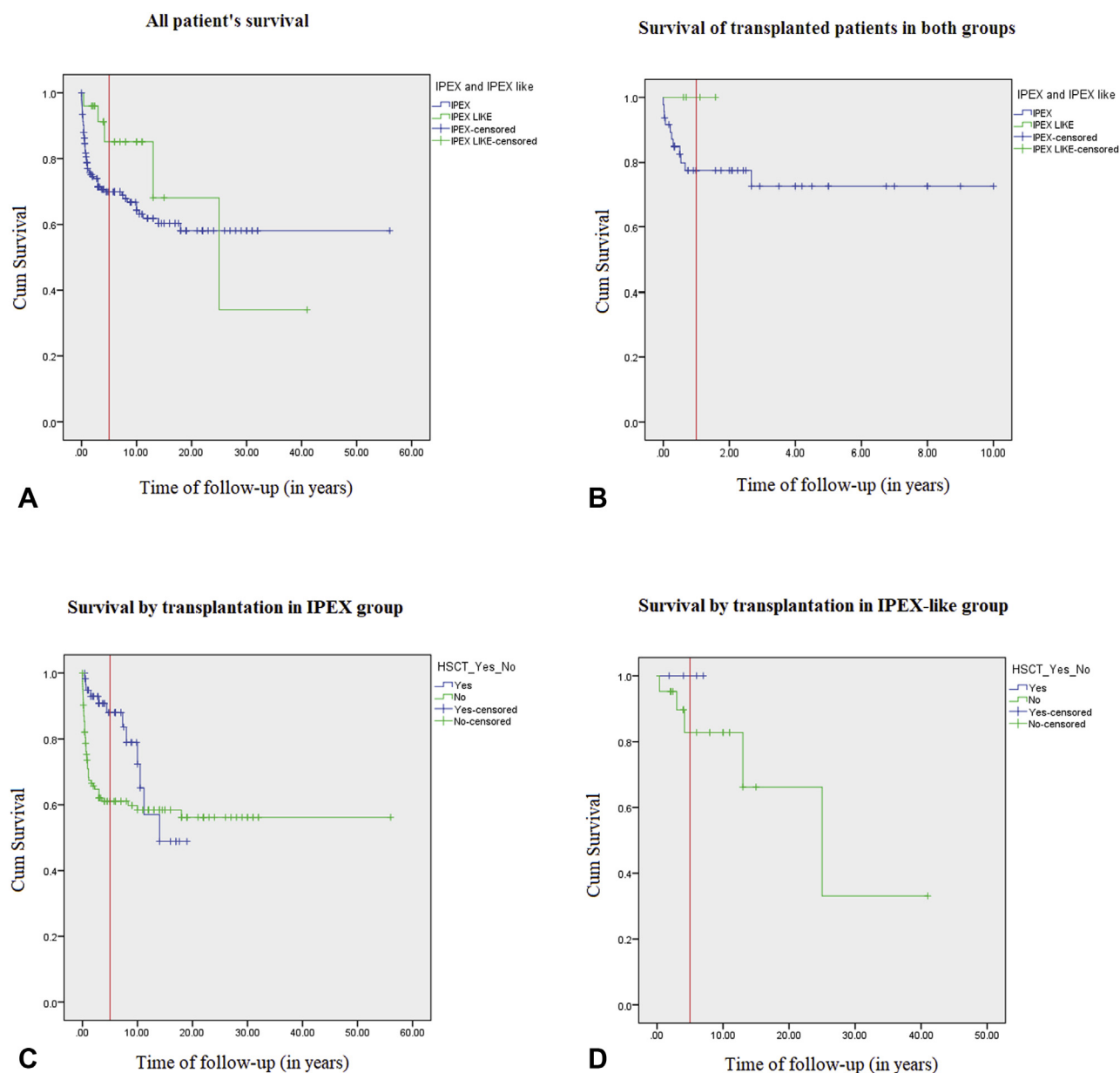


FIGURE E2. The Kaplan-Meier survival curve of patients. **A**, The overall survival in all patients is evaluated, and differences among survival curves are assessed by the log-rank test, $P = .161$. **B**, Transplanted patients with IPEX vs IPEX-like are compared, $P = .322$. **C**, Patients with IPEX stratified whether or not they underwent HSCT, $P = .016$. **D**, Patients with IPEX-like syndrome stratified whether or not they underwent HSCT, $P = .471$. *HSCT*, Hematopoietic stem cell transplantation; *IPEX*, immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

TABLE E1. Distribution of reported mutations in genes other than *FOXP3* in 58 patients with IPEX-like syndromes

Genes	No. of patients	No. of families	DNA mutation	Protein	Mutation type	Zygosity	Reference
<i>TTC37</i>	1	1	c.859-3_859-7delTTTT/ c.3364delA	Miss-spliced protein/ p.T1122Qfs*10	Splicing/ InDel-Frameshift	C. Het	E1
<i>TTC7A</i>	1	1	c.1817A>G/A/c.2086T>C	p.E606G/p.S696P	Missense/Missense	C. Het	E2
<i>STAT5B</i>	2	1	c.1680+1del		Splicing	Hom	E3
<i>MALT1</i>	2	1	c.550G>T	p.D184Y	Missense	Hom	E4
<i>IL2RA</i>	7	7	c.151T>G c.452A>C c.151T>G c.497G>A c.692_692delA	p.C51G p.Q151P p.C51G p.S166N p.Q231Hfs*23	Missense Missense Missense Missense InDel-Frameshift	Hom Hom Hom Hom Hom	E1,E5-E8
<i>CARD11</i>	2	2	c.1483C>T c.88C>T	p.P495S p.R30W	Missense Missense	Het Het	E9
<i>CTLA4</i>	3	3	c.442C>T c.410C>T c.436G>A	p.Q148* p.P137L p.G146R	Nonsense Missense Missense	Het Het Het	E1,E10,E11
<i>STAT3</i>	4	4	c.832C>T/C c.986T>G/T c.1079A>G/A c.1243 G>C/G	p.R278C p.M329R p.Y360C p.E415Q	Missense Missense Missense Missense	Het Het Het Het	E1
<i>DOCK8</i> <i>DOCK8/CLEC7A</i>	7	3	c.1498C>T c.2402-1G>A c.3193delA/c.576T>G	p.R500* p.S1065Afs*17/p.T238*	Nonsense Splicing InDel-Frameshift/Missense	Hom Hom Hom	E12,E13
<i>STAT1</i>	13	13	c.1154C>T c.983 A>G c.1053G>T/G c.1073T>G c.1153C>T c.629G>T c.796G>A	p.T385M p.H328R p.L351F p.L358W p.T385M p.R210I p.V266I	Missense Missense Missense Missense Missense Missense Missense	Het Het Het Het Het Het Het	E14-E17
<i>LRBA</i>	16	11	c.1496C>A c.2032C>T c.2496C>A c.2617_2620del c.3549_3550insA c.5172-2A>G c.5680A>T c.6657_6658delGA c.865_866delTG	p.S499* p.Q678* p.C832* p.L873Afs*13 p.A1184Sfs*34 p.R1894* p.E2219Dfs*3 p.V290Efs*3	Nonsense Nonsense Nonsense InDel-Frameshift InDel-Frameshift Splicing Nonsense Nonsense Nonsense	Hom Hom Hom Hom Hom Hom Hom Hom	E1,E18-E20

C. Het, Compound heterozygous; Hom, homozygous.

TABLE E2. Detailed available data on 48 of 106 transplanted patients with IPEX and IPEX-like syndrome

Pt ID	Gene defect	Type	Sex	Age at HSCT (y)	Donor	HLA match	Source	Conditioning	GvHD prophylaxis	CD34 ($\times 10^6$ cells/kg)
1	FOXP3, c.1113T>G, p.F371C	IPEX	M	0.3	MSD	HLA-identical	BM	r-ATG, Bu, CY	CSA, IV and then orally	—
2	FOXP3, c.748delAAG/c.543C>T, p.K250del/p.S181S	IPEX	M	9.0	URD	HLA matched	BM	CY, 1.2 GY TBI, and r-ATG	—	5.1
3	FOXP3, c.1040G>A, p.R347H	IPEX	M	13.5	MSD	HLA matched	BM	CY, 1.2 GY TBI, and r-ATG	Low dose steroids and CSA	2.3
4	FOXP3, c.1117T>G, p.F373V	IPEX	M	6.0	MSD	—	BM	Flu, CY, and low-dose TBI (RIC)	MTX and CSA	—
5	FOXP3, c.-6600del	IPEX	M	1.0	MSD	HLA-identical	BM	Flu, Bu, CY, anti-T-lymphocyte globulin (MAC)	—	7.85
6	No FOXP3 coding mutation	IPEX-like	M	6.0	URD	5 of 6	Cord	Flu, Bu, and r-ATG (sub-MAC)	CSA, MMF	0.3
7	FOXP3, c.816+4A>G, p.273fs*286	IPEX	M	7.0	URD	8 of 8	BM	ALM, Flu, Melph (RIC)	CSA, Tacro, MTX, MP	34.7
8	FOXP3, c.303_304 del TT, p.F102Hfs*103	IPEX	M	1.4	URD	7 of 8 (A-antigen mismatched)	BM	ALM, Flu, Melph (RIC)	CSA, Tacro, MTX, MP	5.8
9	FOXP3, c.1271G>A, p.C424Y	IPEX	M	4.0	MSD	8 of 8	BM	ALM, Flu, Melph (RIC)	CSA, Tacro, MTX, MP	5.0
10	FOXP3, c.1226A>G, p.D409G	IPEX	M	0.5	URD	8 of 8	BM	ALM, Flu, Melph (RIC)	CSA, Tacro, MTX, MP	12.7
11	FOXP3, c.1139C>T, p.T380I	IPEX	M	0.4	URD	—	BM	Flu, CY, ALM, anti-CD45 monoclonal antibodies	CSA and MMF	2.7
12	FOXP3, g.14372A>G/3'UTR	IPEX	M	0.6	URD	10 of 10	BM	ALM, Flu, Mel (RIC)	CSA, MTX, prednisone	4.7
13	—	IPEX*	M	0.9	URD	10 of 10	BM	ALM, Flu, Melph (NMA)	—	2.0
14	FOXP3, c.210+2delT	IPEX	M	0.7	URD	HLA matched	PBSC	Flu, TBI 4 GY (RIC)	CSA, MMF	1.0
15	FOXP3, c.816+7G>C	IPEX	M	16.0	MSD	HLA matched	BM	Flu, TBI 4 GY (RIC)	CSA, MMF	1.0
16	—	IPEX*	—	0.5	URD	10 of 10	Cord	Treo, ALM	—	—
17	—	IPEX*	—	0.7	URD	8 of 10	Cord	Treo, ALM	—	—
18	FOXP3, c.1150G>A, p.A384T	IPEX	M	0.6	URD	10 of 10	BM	ALM, Flu, Thio, Melph (NMA)	CSA	4.7
19	TTC7A, c.1817A>G/A; c.2086T>C, p.E606G/p.S696P	IPEX-like	M	0.25	MSD	—	BM	r-ATG	—	—
20	FOXP3, c.1157G>A, p.R386H	IPEX	F	0.5	MSD	12 of 12	BM	Bu, CY	CSA	6.0
21	FOXP3, c.*876A>G	IPEX	F	0.8	URD	8 of 10	Cord	Bu, CY	CSA	0.6
22	FOXP3, c.758T>C, p.L253P	IPEX	M	0.8	URD	12 of 12	BM	Bu, CY	CSA, MMF	4.3
23	FOXP3, c.816+5G>A	IPEX	M	0.8	URD	—	Cord	Treo, CY	CSA, MMF	2.7
24	FOXP3, c.1037T>C, p.I346T	IPEX	M	0.5	URD	11 of 12	Cord	Treo, Flu	Tacro, MMF	1.9
25	FOXP3, c.1037T>C, p.I346T	IPEX	M	0.5	URD	1 DP mismatch	Cord	ALM, Flu, Treo (sub-MAC)	Tacro, MMF	—
26	No FOXP3 coding mutation	IPEX*	—	0.8	MSD	Mismatched	PBSC	Bu, Flu, r-ATG (RIC)	—	9.37
27	—	IPEX*	—	0.6	URD	—	Cord	Bu, Flu, r-ATG (RIC)	—	0.11
28	FOXP3, c.1189C>T, p.R397W	IPEX	—	0.5	URD	8 of 8	BM	ALM, Flu, Melph (RIC)	Tacro, MTX	12.7
29	FOXP3, c.750_752delGGA, p.E251del	IPEX	—	2.4	URD	7 of 8	BM	ALM, Flu, Melph (RIC)	CSA	8.0
30	FOXP3, c.542+1G>C	IPEX	—	1.3	URD	5 of 8	Cord	Bu, CY, ATG	CSA	1.5
31	FOXP3, c.817-5C>G	IPEX	—	5.4	URD	7 of 8	BM	ALM, Flu, Melph (RIC)	Tacro, CSA	5.7
32	FOXP3, c.737T>C, p.L246P	IPEX	—	10.9	URD	7 of 8	BM	ALM, Flu, Melph (RIC)	CSA	5.0
33	FOXP3, c.1227_1235delTGAGCTGGA, p.N409E/p.E410_E412del	IPEX	M	0.4	URD	—	BM	RIC	—	—
34	FOXP3, c.1163A>G, p.N388S	IPEX	M	3.5	URD	Matched	BM	ALM, Flu, Melph (RIC)	Tacro	—
35	FOXP3, c.1190G>A, p. R397Q	IPEX	M	7.5	MSD	Matched	PBSC	Bu, Flu, CY, ATG (RIC)	CSA, MP	7.0
36	—	IPEX*	—	—	URD	9 of 10	BM	ALM, Flu, Melph (RIC)	Tacro, MP	—
37	—	IPEX*	—	—	URD	10 of 10	BM	ALM, Flu, Melph (RIC)	Tacro, MP	—
38	MALT1, c.550G>T, p.D184Y	IPEX-like	F	—	URD	10 of 10	PBSC	Flu, ALM, and Bu (RIC)	CSA, MMF	—
39	MALT1, c.550G>T, p.D184Y	IPEX-like	M	—	URD	10 of 10	PBSC	Flu, ALM, and Bu (RIC)	CSA, MMF, Tacro	—
40	—	IPEX*	—	—	URD	10 of 10	BM	Bu, Flu, ATG	MMF, Tacro	—
41	FOXP3, g.-4859_-6247del	IPEX	M	10.5	URD	—	PBSC	Flu, ALM, and Bu (RIC)	Steroids, MMF	—
42	FOXP3, c.751_753delGAG, p.E251del	IPEX	M	12.8	MSD	—	PBSC	Flu, ALM, and Bu (RIC)	CY, MMF	—
43	FOXP3, c.210_210delG	IPEX	M	1.0	MSD	—	PBSC	ATG, BU, and CY (MAC)	CSA, MMF	—
44	FOXP3, c.264_264delC, p.L92Yfs*37	IPEX	M	7.0	MSD	—	PBSC	Flu, Cx, TBI 2GY, and CY (NMA)	CSA, MMF	—
45	FOXP3, c.1010G>A, p.R337Q	IPEX	M	1.0	URD	—	PBSC	Flu, Bu, and ALM	CSA, MMF	—
46	FOXP3, c.1015C>T, p.P339S	IPEX	M	0.46	MSD	—	PBSC	Ritu, ALM, Bu, Flu, and CY (MAC)	CSA, MMF	—
47	FOXP3, c.816+2T>A	IPEX	M	4.0	URD	10 of 10	PBSC	ALM, Flu, Treo, and Thio (reduced toxicity MAC)	CSA, MMF	—
48	FOXP3, c.1040G>A, p.R347H	IPEX	—	16	URD	8 of 8	BM	Flu, Melph, r-ATG, TBI (NMA)	—	—

AIHA, Autoimmune hemolytic anemia; *ALM*, alemtuzumab; *BM*, bone marrow; *Bu*, busulfan; *CMV*, cytomegalovirus; *CSA*, cyclosporine A; *CVL*, central venous line; *CY*, cyclophosphamide; *EBV*, Epstein-Barr virus; *Flu*, fludarabine; *GI*, gastrointestinal; *GvHD*, graft-versus-host disease; *IPEX*, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; *MAC*, myeloablative conditioning; *Melph*, melphalan; *MMF*, mycophenolate mofetil; *MP*, methylprednisolone; *MSD*, matched sibling donor; *MTX*, methotrexate; *NMA*, nonmyeloablative conditioning; *PBSC*, peripheral blood stem cell; *r-ATG*, rabbit antithymocyte globulin; *RIC*, reduced-intensity conditioning; *Ritu*, Rituximab; *Tacro*, tacrolimus; *TBI*, total body irradiation; *Thio*, thiopeta; *TNC*, total nucleated cell; *TPN*, total parental nutrition; *Treo*, treosulfan; *URD*, unrelated donor; *VOD*, veno-occlusive disease.

* Clinically diagnosed IPEX.

TABLE E2. (Continued)

TNC ($\times 10^8$ cells/kg)	Latest chimerism, % donor	GvHD (organ, grade)	Other complications	Off TPN	Outcome	Duration of follow-up (y)	Reference, year
—	30	No	Hemophagocytic syndrome, hepatitis	D+90	Deceased (at 2.41 y)	1.91	E21, 2000
6.0	70	No	Hemorrhagic cystitis, CMV infection, lymphoproliferative disorders	Less than 1 mo	Deceased (at 10 y)	0.25	E22, 2002
0.5	50	No	Neutropenic fever and mild hemorrhagic cystitis, adenovirus infection, pneumonia	D+21	Deceased (at 0.53 y)	0.53	E22, 2002
4.3	—	Yes (Skin, I)	—	D+204	Alive	1.00	E23, 2004
5.0	Mixed: T: 70 B: 30 PMN: 50	Yes (Skin and GI, II)	—	D+480	Alive	1.33	E24, 2005
1.1	98	Yes (Colon)	EBV reactivation, lymphoproliferative disorders	—	Alive	1.16	E25, 2007
12.6	100	Yes (Skin and GI, II)	CMV infection	—	Alive	2.08	E26, 2007
6.0	100	No	Acute respiratory distress due to pulmonary hemorrhage	—	Alive	1.58	E26, 2007
3.1	89	No	Hypotension and malaise, histoplasma infection	—	Alive	0.91	E26, 2007
5.3	84.6	No	—	—	Alive	0.50	E26, 2007
8.0	100	Yes (Skin and GI, II and III)	—	D+900	Alive	2.50	E27, 2008
—	100	Yes (Skin)	<i>Staphylococcus epidermidis</i> bacteremia, significant hypertension, <i>Enterobacter cloacae</i> bacteremia	D+125	Alive	0.34	E28, 2009
—	100	Yes (Skin, II)	—	D+30	Alive	6.00	E29, 2009
15.0	100	Yes (Acute: Skin, II, Chronic)	Bacteremia	—	Alive	4.00	E30, 2010
5.1	60	Yes (Acute: GI, II)	Bacteremia	—	Alive	1.00	E30, 2010
—	Mixed: T: 94 B: 82 CD15: 58	No	Tracheostomy, gut resection, nephrotic syndrome	—	Alive	0.50	E31, 2011
—	Mixed: T: 35 B: 45 CD15: 38	Yes (gut, skin, III)	Perineal ulceration, nephrotic syndrome	—	Alive	1.08	E31, 2011
2.1	—	No	Coagulase negative <i>Staphylococcus</i> and <i>Staphylococcus aureus</i> bacteremia, dehydration, adenovirus and <i>Clostridium difficile</i> diarrhea	—	Alive	2.42	E32, 2011
—	95%	No	—	—	Alive	1.58	E2, 2013
—	Mixed: T: 68 B: 57 CD15: 66	No	Cholestasis, jaundice	D+26	Alive	10.0	E33, 2014
—	100	No	GI bleeding, pneumonitis LVH	D+65	Alive	9.00	E33, 2014
4.1	100	No	CVL infection, pneumonitis	D+45	Alive	8.00	E33, 2014
8.6	Mixed: T: 32 B: 36 CD15: 21	Yes (Skin, II)	CVL infection	D+100	Alive	5.00	E33, 2014
1.7	Mixed: T: 41 B: 35 CD15: 34	No	GI obstruction, nephrotic syndrome, AIHA	D+390	Alive	3.50	E33, 2014
—	70	No	Upper intestinal obstruction	D+360	Alive	0.75	E34, 2015
—	—	No	—	—	Alive	0.61	E35, 2015
—	—	No	—	—	Alive	0.08	E35, 2015
5.0	100	Yes (Skin)	—	—	Alive	8.00	E36, 2016
6.9	93	No	Autoimmune cytopenia	—	Alive	7.00	E36, 2016
—	100	Yes (Acute: Skin, Chronic)	—	—	Alive	5.00	E36, 2016
6.7	31	No	Autoimmune cytopenia	—	Alive	4.00	E36, 2016
8.8	—	No	Norovirus, CMV	—	Deceased (at 11.18)	0.21	E36, 2016
—	—	No	VOD, pulmonary hemorrhage, and candidemia	—	Deceased (at 0.44)	0.03	E37, 2016
—	57	No	—	D+630	Alive	1.75	E38, 2017
—	100	No	—	—	Alive	0.50	E39, 2017
—	—	No	—	—	Alive	0.16	E40, 2017
—	—	No	—	—	Alive	0.16	E40, 2017
—	100	No	CMV reactivation	—	Alive	1.11	E4, 2017
—	75	No	CMV reactivation	—	Alive	0.69	E4, 2017
—	—	No	—	—	Alive	—	E41, 2017
—	—	Yes (Acute: II)	Microangiopathies and renal failure	—	Deceased (at 10.5)	0.00	E42, 2018
—	—	No	—	—	Alive	4.20	E42, 2018
—	—	No	—	—	Deceased (at 1.50)	0.50	E42, 2018
—	—	Yes (GI, III)	—	—	Deceased (at 7.30)	0.30	E42, 2018
—	—	Yes (III)	—	—	Alive	1.00	E42, 2018
—	—	Yes (Chronic)	—	—	Alive	0.04	E42, 2018
—	<20	No	Neutropenic bacteremia and asymptomatic CMV reactivation	—	Alive	3.00	E43, 2018
—	—	Yes (GI, III)	—	—	Alive	1.66	E44, 2019

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