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REVIEW

Haematopoietic stem cell transplantation for severe autoimmune diseases in children: A review of current literature, registry activity and future directions on behalf of the autoimmune diseases and paediatric diseases working parties of the European Society for Blood and Marrow Transplantation

Federica R. Achini-Gutzwiller[1] | **John A. Snowden**[2] | **Selim Corbacioglu**[3] | **Raffaella Greco**[4] | **The EBMT Autoimmune Diseases (ADWP) and Paediatric Diseases (PDWP) Working Parties**

[1]Division of Paediatric Stem Cell Transplantation and Haematology, Children's Research Centre (CRC), University Children's Hospital of Zurich, Zurich, Switzerland

[2]Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Sheffield, UK

[3]Department of Paediatric Oncology, Haematology and Stem Cell Transplantation, University Children's Hospital Regensburg, Regensburg, Germany

[4]Unit of Haematology and Bone Marrow Transplantation, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Correspondence
Selim Corbacioglu, Department of Paediatric Oncology, Haematology and Stem Cell Transplantation, University Children's Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany.
Email: selim.corbacioglu@klinik.uni-regensburg.de

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Summary

Although modern clinical management strategies have improved the outcome of paediatric patients with severe autoimmune and inflammatory diseases over recent decades, a proportion will experience ongoing or recurrent/relapsing disease activity despite multiple therapies often leading to irreversible organ damage, and compromised quality of life, growth/development and long-term survival. Autologous and allogeneic haematopoietic stem cell transplantation (HSCT) have been used successfully to induce disease control and often apparent cure of severe treatment-refractory autoimmune diseases (ADs) in children. However, transplant-related outcomes are disease-dependent and long-term outcome data are limited in respect to efficacy and safety. Moreover, balancing risks of HSCT against AD prognosis with continually evolving non-transplant options is challenging. This review appraises published literature on HSCT strategies and outcomes in individual paediatric ADs. We also provide a summary of the European Society for Blood and Marrow Transplantation (EBMT) Registry, where 343 HSCT procedures (176 autologous and 167 allogeneic) have been reported in 326 children (<18 years) for a range of AD indications. HSCT is a promising treatment modality, with potential long-term disease control or cure, but therapy-related morbidity and mortality need to be reduced. Further research is warranted to establish the position of HSCT in paediatric ADs via registries and prospective clinical studies to support evidence-based interspeciality guidelines and recommendations.

KEYWORDS
autoimmune diseases, haematopoietic stem cell transplantation, paediatric

Selim Corbacioglu and Raffaella Greco contributed equally.

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INTRODUCTION

Children suffering from severe rheumatic and non-rheumatic autoimmune diseases (ADs) have a poor quality of life (QoL) and a markedly reduced life expectancy due to persistent/recurring disease activity leading to progressive organ damage and disabilities which tend to increase during adolescence and adulthood. Such limitations may have life-long implications on future health, growth and development, employment, family life and prognosis. Severe paediatric ADs present with heterogeneous autoimmune and autoinflammatory features which are generated from aberrant immune responses targeting organ-specific autoantigens. Whilst defects of either B- or T-cell selection may cause autoimmune manifestations characterised by circulating autoantibodies, mutations in cells or molecules involved in innate immune responses may initiate autoinflammatory symptoms at inflammation-prone sites.[1,2] Current conventional treatments are based on broadly-acting and often potent immunosuppressive 'conventional' agents, as well as on more targeted biological disease-modifying antirheumatic drugs (DMARDs) and disease-modifying therapies (DMTs). Nevertheless, such therapies are rarely curative and mostly need to be administered life-long, following a stepwise scheme which includes dose escalations as well as combinations of different drugs and therapy modalities according to current disease activity.[3] Treatment-related, sometimes severe, adverse effects frequently complicate the primary clinical burden of the AD on both an acute and long-term basis, impacting on morbidity, mortality, QoL and health economic aspects of the disease.[4,5]

In patients with severe ADs refractory to conventional treatments, haematopoietic stem cell transplantation (HSCT) may be considered a potentially curative procedure, through a 'resetting' or replacement (complete or partial) of the dysfunctional immune system.[6–10] Long-term outcome data and genetic features of allogeneic HSCT in children and adults with severe ADs were previously reported.[7] In this review, we provide a summary of the European Society for Blood and Marrow Transplantation (EBMT) registry, discuss past and current indications, efficacy of published conditioning regimens, associated risks and benefits and future directions of HSCT in children with severe autoimmune diseases, focussing on the largest disease groups.

MECHANISTIC ASPECTS

Haematopoietic stem cell transplantation exerts its therapeutic effect in ADs through various biological mechanisms. Firstly, the immunosuppressive conditioning regimen prior to HSCT is able to temporarily eradicate or suppress circulating and tissue-based auto-reactive cells, rapidly halting of inflammatory activity. Secondly, the regeneration/renewal of the immune system resets the aberrant immune response to self-antigens[11] and there is support for various immunological processes, including induction of immune tolerance, associated with longer-term clinical improvements.[11]

Immuno-ablative conditioning and autologous HSCT have been shown to induce depletion or attenuation of the immunological memory as well as generation of *de novo* naïve T cells and T-cell receptor (TCR) repertoire diversification through a revival of the thymopoiesis.[12,13] Since thymus-dependent T-cell regeneration post transplant is strongly determined by age and ability to administer truly lympho-ablative treatments, children may benefit from a physiologically more efficient thymopoiesis and 'thymic re-bound' promoting immune tolerance via 'thymic re-education' post transplant.[14] Moreover, a substantial increase of regulatory T cells (Treg) has been shown to occur after HSCT, supporting the hypothesis that recovery of immune regulation also contributes to induction and/or maintenance of immune tolerance and clinical responses post transplant.[12]

Allogeneic HSCT represents an attractive option for patients with refractory AD, since it has the potential to induce both complete eradication of auto-reactive cells and/or the dysfunctional immune network causing the AD, with the potential regeneration of a 'fresh' immune self-tolerant system.[7,15] Clearly, there are cautions associated with allogeneic HSCT, most notably the potential for graft-versus-host disease (GvHD), graft rejection, delayed immune reconstitution, and infection susceptibility.[16] However, compared with adults, these risks are significantly less in the paediatric age group, and with careful donor selection risks of allo-reactivity can be minimised in a number of ways, including human leukocyte antigen (HLA) compatibility.[17–19] Matched family donors (MFD) are considered as first choice providing lower rates of transplant-related mortality. Matched unrelated donors (MUD) achieve comparable toxicity rates in children with malignant diseases and are thus increasingly used also in children with non-malignant diseases.[20,21] Use of MUD can also remove some concerns of inherent genetic components of ADs within families. If fully matched donors are not available, umbilical cord blood (CB) has been used as a rapidly available source of haematopoietic stem cells.[22–24] However, GvHD prophylaxis remains decisive to success, in particular in non-malignant diseases where no graft-versus-leukaemia (GvL) effect is required. Furthermore, CB lackS antigen-experienced T cells, and IS associated with increased infection risk post transplant.[25–27] Haplo-identical HSCT is an almost universally available alternative donor source with increasing acceptance for malignant and non-malignant diseases, with a variety of techniques for T-cell depletion and tolerance induction. Graft manipulation with combined negative selection of $\alpha\beta^+$ T cells and $CD19^+$ lymphocytes was designed to achieve an ideal graft composition *in vitro*,[28–31] whilst post-transplant cyclophosphamide (PTCy) is used for *in vivo* lympho-depletion, optionally in combination with serotherapy and T-cell add-back procedures.[32–34]

RATIONALE AND CURRENT TRENDS FOR HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH SEVERE AUTOIMMUNE DISEASES

The management of children with severe ADs requires consideration of many, frequently challenging aspects. A broad age range, diversified physical and emotional development, a large variety of disease entities, with a range of proposed pathogenenetic targets,[1] and often fluctuant disease activity lead to heterogeneous clinical phenotypes and severities with variable and highly individualised responses to treatment.

Over the last three decades, both autologous and allogeneic HSCT procedures have been performed in children with severe ADs, largely sporadically on an individual patient basis, with few in clinical trials. In 1996, the first child undergoing a HSCT due to a severe AD (systemic sclerosis, SSc) was registered in the section of the EBMT registry associated with the Autoimmune Disease Working Party (ADWP). Paediatric patients are defined by EBMT as younger than 18 years at time of transplant. By October 2021, 343 HSCT procedures, of which 176 were performed with autologous graft and 167 with donor stem cells, were reported in 326 paediatric patients with severe ADs. For this paediatric AD cohort, median age at autologous and allogeneic transplant was 12.3 years (range 2.7–17.9) and 7.6 years (range 0.13–17.91), respectively. Further information for autologous and allogeneic transplant procedures for ADs reported annually to the EBMT registry are presented in Figure 1, while major transplant indications for both autologous and allogeneic HSCT over time are indicated in Figure 2. Available data on transplant indications are shown in Tables 1 and 2. Available registry information on transplant procedures, including main conditioning regimens, use of serotherapy for lymphodepletion, donor selection and stem cell source are reported in Table 3. A selection of available European studies focussing on or including children with severe ADs are indicated in Table 4.

Overall, data are heterogeneous with paediatric patients mostly undergoing HSCT with centre-specific conditioning regimens, thus limiting systematic comparison of outcome results. Even so there are useful trends. Whilst autologous HSCT procedures were initially preferred in this patient population, there has been a notable shift to allogeneic procedures during the last 15 years, perhaps driven by a relatively high incidence of treatment-related morbidity and mortality (TRM) in autologous HSCT and consistent advances in transplant strategies.[6,7,35–37]

With respect to EBMT registry data for ADs, analyses of the specific paediatric group (<18 years) are relatively limited compared with the adult cohort. The largest experience of allogeneic HSCT in AD is a retrospective EBMT study in a predominantly paediatric population with various haematological and non-haematological severe ADs, where HSCT supported long-term remission and 'cure' with plateauing of the Kaplan–Meier survival curves being achieved in the majority of patients.[7] However, it has to be recognised that in this high-risk population, where individualised treatment decisions may have been taken because of limited treatment options and otherwise poor prognosis, a significant minority suffered TRM of 20% at two years. In support of allogeneic HSCT for paediatric AD patients, significantly better transplant outcomes were achieved for age under 18 years in more recent years.[7]

Many analyses have been performed for autologous HSCT in various ADs, but they have been predominantly in adults and very few specifically relating to children.[38,39] Responses to autologous HSCT are very disease-specific, with high level evidence (randomised controlled trials) supporting its use in adults with multiple sclerosis (MS) and systemic sclerosis (SSc), but variable and unsustained responses in others including Crohn's disease (CD) and rheumatic diseases. In some paediatric ADs, such as juvenile idiopathic arthritis (JIA), autologous HSCT may still have a significant burden of adverse effects, some life-threatening. In paediatrics, autologous HSCT has not been generally followed by the high frequency of profound and sustained drug-free remissions achieved with allogeneic HSCT.

The following sections and Table 4 summarise the reports of various AD indications for allogeneic and autologous HSCT, focussing on responses and toxicity.

MAJOR INDICATIONS FOR HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH SEVERE AUTOIMMUNE DISEASES

Rheumatic diseases

Despite remarkable progress in the treatment of rheumatic diseases in children based on innovative targeted drugs and effective supportive treatment, some children affected by rheumatic diseases will experience ongoing disease activity into adulthood.[35,36] However, current data on rescue therapy with HSCT in selected patients are promising. The EBMT registry currently provides information on 146 children after autologous or allogeneic HSCT for rheumatic diseases. Predominant indications for HSCT are systemic or polyarticular JIA (n = 86), systemic lupus erythematosus (SLE, n = 22) and SSc (n = 16). The majority of patients (75%) were treated with autologous HSCT.

Juvenile idiopathic arthritis (JIA) refers to all forms of arthritis of unknown origin beginning before the age of 16 years and persisting over more than =six weeks.[40] Systemic JIA (sJIA, Stills' disease) is a particular form of this disease characterised by polyarticular arthritis in combination with a prominent systemic auto-inflammatory reaction with overproduction of inflammatory cytokines (in particular IL-6 and IL-1) in the absence of autoantibodies.[41,42] Systemic JIA is associated with recurrent episodes of fever, skin rash, serositis, lymphadenopathy and

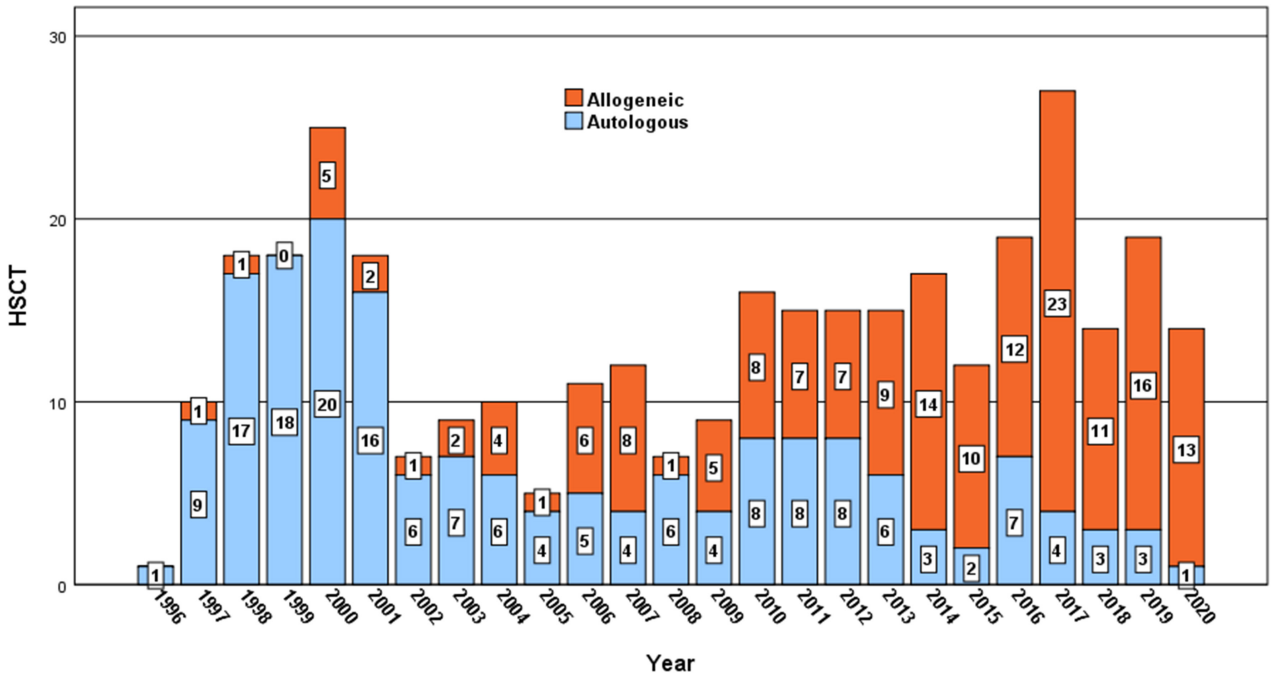

FIGURE 1 Number of autologous and allogeneic haematopoietic stem cell transplantations (HSCT) in children aged 0–18 years with severe ADs reported to the European Society for Blood and Marrow Transplantation data registry associated with the Autoimmune Disease Working Party between 1996 and 2020

hepatosplenomegaly leading to frequent medical consultations and hospitalisations and poor QoL of affected children.[43] First-line JIA treatment is based on non-steroidal anti-inflammatory drugs, mostly in combination with immunosuppressive drugs such as methotrexate and corticosteroids. Targeted therapy with IL-1- (e.g., anakinra) or IL-6-inhibitors (e.g., tocilizumab) has been reported to be highly effective in selected patients refractory to conventional treatment.[42,44–46]

Secondary haemophagocytic lymphohistiocytosis (sHLH) or macrophage activation syndrome (MAS), an heterogenous life-threatening hyperinflammatory complication of severe ADs and, in particular, JIA, occurring in 10% of patients and being a major cause of disability and mortality, may develop despite cytokine inhibitors, thus requiring further therapeutic modalities in affected children.[47–50] Since 1997, a total of 65 autologous HSCT for systemic or polyarticular JIA were identified in the EBMT registry. Available data indicate long-term drug-free complete remission (CR) in around 55% of this patient cohort.[36,51] Published conditioning regimens range from less intensive cyclophosphamide-based with additional anti-thymoglobuline (ATG) serotherapy to more aggressive protocols with combined low-dose total-body irradiation (TBI).[51–53] However, a significant proportion of children treated with this procedure developed severe treatment-related morbidity and mortality (9%–14%), mostly due to infections after profound lympho-depletion and MAS.[51–53] Furthermore, re-emerging auto-reactive T cells stimulated rebounding auto-inflammation in a significant number of children after autologous transplant even several years post transplant, thus opening a therapeutic window for allogeneic procedures.[36,43]

Allogeneic HSCT with an HLA-identical sibling or an unrelated HLA-matched unrelated donor has been successfully performed in a paediatric cohort of 16 patients with JIA, 11 of which (69%) achieved stable CR.[43] Sustained CR was also reached in the first child transplanted with a haploidentical donor for severe JIA.[54] However, allogeneic transplant was associated with significant TRM (13%) and clinically relevant treatment-related toxicity as acute GvHD grade II–IV (19%), infections (56%) and auto- or alloimmune cytopenia (25%), concluding that this procedure should be evaluated in controlled trials.[43,55]

Childhood-onset systemic lupus erythematosus (cSLE) is a rare chronic inflammatory disease affecting multiple systems and occurring before the age of 18 years. Based on a retrospective analysis considering defined diagnostic criteria, a disease incidence of 0.3–0.9 per 100 000 children per year, and a prevalence of 3.3–24 per 100 000 children was reported in the past two decades.[56] The pathogenesis underlying cSLE remains poorly understood, but current reference literature claims SLE as an heterogenous group of genetically distinct disorders.[57–59] Extensive genomic analysis revealed several monogeneic deficiencies and mutations related to the DNA coding of the complement system (e.g. C1q deficiency), of the type I interferon signalling (e.g. TREX1 mutations) and of immune-modulatory protein kinases (e.g. biallelic PRKCD mutations) with high susceptibility to cSLE.[58]

cSLE frequently presents with a severe clinical course characterised by lupus nephritis, cytopenia, haemostatic

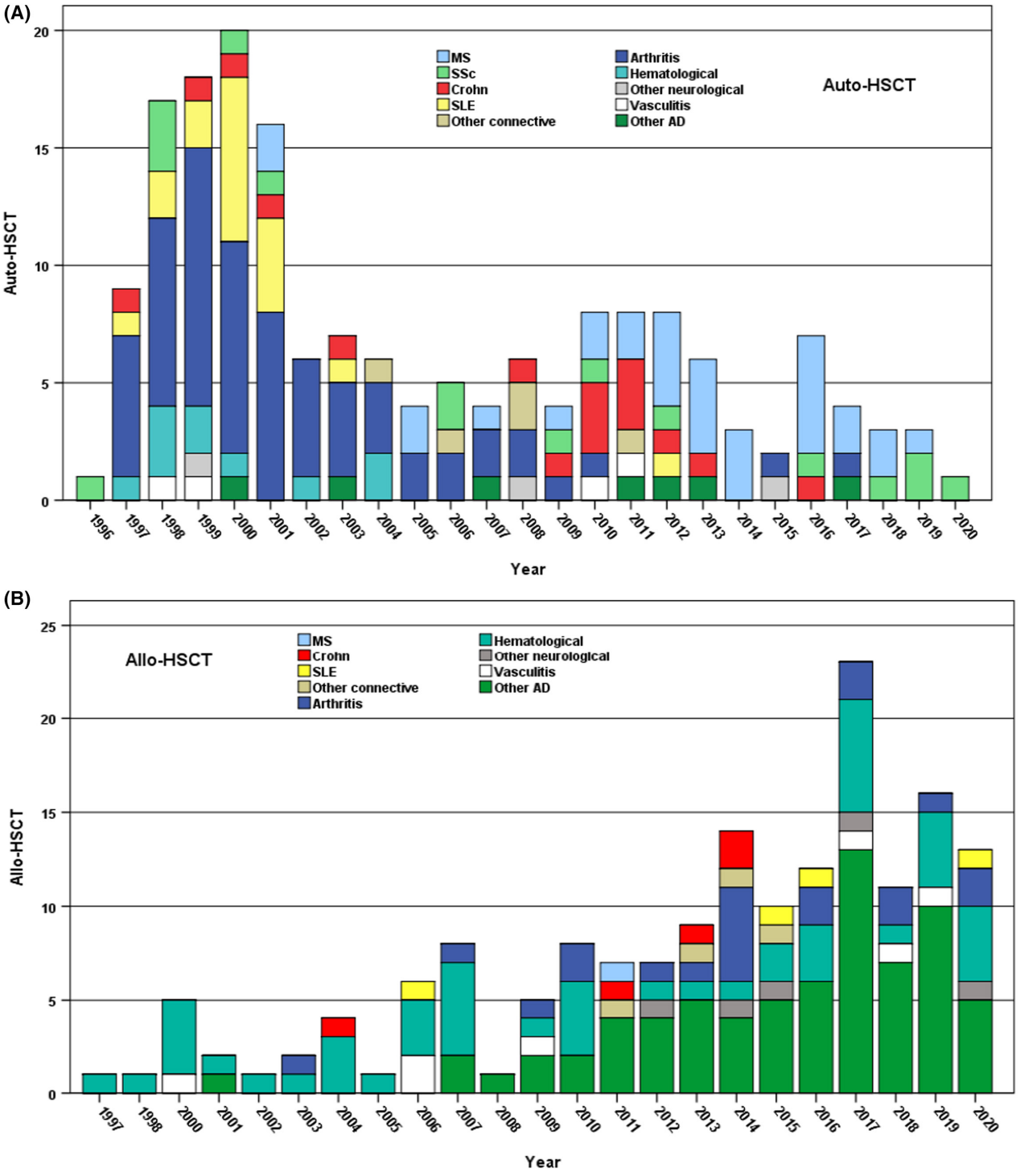

FIGURE 2 Major indications of autologous (A) and allogeneic (B) haematopoietic stem cell transplantation (HSCT) in children aged 0–18 years with severe ADs reported to the European Society for Blood and Marrow Transplantation (EBMT) data registry associated with the Autoimmune Disease Working Party (ADWP) between 1996 and 2020. Abbreviations: AD, autoimmune disease; MS, multiple sclerosis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis

defects, photosensitivity, neuropsychiatric, and mucocutaneous involvement.[60–62] Combined anti-inflammatory and immunosuppressive drugs such as systemic glucocorticoids, mycophenolate mofetil, azathioprine, cyclophosphamide and biologicals (rituximab, belimumab), are currently recommended to rapidly induce disease control, thereby limiting disease-related organ damage.[56] Nevertheless, treatment-related adverse effects including infections and renal failure, may aggravate clinical burdens in children affected with cSLE. For these children, in particular when a genetic component is present, HSCT may represent a feasible alternative.

TABLE 1 Major indications of HSCT for ADs reported to the European Society for Blood and Marrow Transplantation (EBMT) data registry associated with the Autoimmune Disease Working Party (ADWP) and Paediatric Diseases Working Party (PDWP)

	Transplant procedure	
Diagnosis	**Autologous graft (cum. *n* = 176), *n* (relative %)**	**Allogeneic graft (cum. *n* = 167), *n* (relative %)**
Rheumatic diseases, *n* (overall %), 146 (43)		
sJIA	65 (45)	21 (14)
SLE	18 (12)	4 (3)
SSc	16 (11)	
Granulomatosis with polyangiitis	2 (1)	1 (1)
Sjogren syndrome	1 (1)	
PM-DM	1 (1)	
M. Behcet		1 (1)
RA	1 (1)	
Other vasculitis	2 (1)	5 (3)
Other connective diseases	3 (2)	4 (3)
Other arthritis	1 (1)	
Autoimmune cytopenias, *n* (overall %), 60 (17)		
Evans syndrome	3 (5)	13 (22)
AIHA	4 (7)	8 (13)
ITP	3 (5)	2 (3)
Others	1 (2)	26 (43)
Neuroinflammatory diseases, *n* (overall %), 41 (12)		
POMS	32 (78)	1 (2)
NMO		4 (10)
CIDP	1 (2)	
Others	2 (5)	1 (2)
Inflammatory bowel diseases (IBD), *n* (overall %), 35 (10)		
CD	16 (46)	5 (14)
Ulcerative colitis	1 (3)	2 (6)
Others		11 (31)
Monogeneic diseases[a], *n* (overall %), 34 (10)		34 (100)
Other AD, *n* (overall %), 27 (8)	3 (11)	24 (89)

Abbreviations: AD, autoimmune disease; AIHA, autoimmune haemolytic anaemia; CD, Crohn's disease; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; HSCT, haematopoietic stem cell transplantation; ITP, autoimmune thrombopenia; NMO, neuromyelitis optica; PM-DM, polymyositis-dermatomyositis; POMS, paediatric onset multiple sclerosis; RA, rheumatoid arthritis; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

[a]Further patient characteristics are described in Table 2.

Until now, 22 paediatric patients with severe and refractory SLE who received an autologous (children = 18) or an allogeneic (*n* = 4) HSCT were registered in the EBMT database. Preliminary data on two teenagers suggested acceptable toxicity occurring in both patients and consisting in viral infections. Both patients experienced successful CR after conditioning with cyclophosphamide, ATG and low-dose TBI prior to autologous HSCT.[63] A later retrospective analysis on European adult and paediatric patients receiving autologous HSCT for severe SLE included both above-mentioned patients and 15 further children. Conditioning regimen mostly based on cyclophosphamide with additional ATG and autologous graft re-infusion allowed CR in 66% of all patients and indicated a probability of disease-free survival at five years of 55%. Nevertheless, the incidence of severe adverse events, mostly infections, was high (53%) and TRM rate was significant (13%).[64] The clinical course post transplant of two children in a report from a Chinese centre after comparable conditioning was in line with these results, showing one patient in stable CR after four years and the other relapsing after nine months.[65] Promising long-term remissions have been reported in five severe paediatric SLE, paralleled by a high rate of virus reactivations responding to antiviral treatment (80%) and a low incidence of other adverse reactions (MAS occurred in one child).[66]

The number of adult and paediatric SLE patients having undergone allogeneic HSCT is very limited. To the best of our knowledge, very few children have been reported after allogeneic HSCT for SLE; most of them had coincidental severe haematological diseases or inborn errors of immunity (IEI) as the main transplant indication.

Despite persistent centromere antibodies, a 16-year-old girl suffering from cSLE without monogeneic component experienced complete remission over five years and substantial improvement of QoL after reduced-intensity conditioning with cyclophosphamide, fludarabine and alemtuzumab and infusion of a HLA-identical sibling graft (matched sibling donor — MSD).[67]

Two patients with cSLE and concomitant severe haematological disease (one child with sickle cell disease — SCD[68] — and one other with drug-induced bone marrow aplasia[69]) were transplanted with a MSD graft after cyclophosphamide-based myeloablative conditioning. Whilst the first patient only developed mild acute GvHD and was in CR over 15 years, the child with concomitant SCD experienced severe neurological and gastrointestinal complications before achieving stable CR over 31 months.[68,69]

The clinical course of four children with C1q deficiency and cSLE were reported by different authors. Both conditioning regimens and stem cell donors presented important differences, and outcome results were heterogeneous. One nine-year-old boy with treatment-resistant cerebral SLE required donor lymphocyte infusion due to Epstein–Barr virus (EBV)-mediated post-transplant lymphoproliferative disorder (PTLD) and mesenchymal stem cell (MSC) infusion for treatment-refractory intestinal GvHD which did not resolve. The patient died four months after HSCT due to massive cerebral haemorrhage and multiorgan failure. One 12-year-old girl developed EBV-positive PTLD which

TABLE 2 Patient characteristics of the subgroup transplanted for monogeneic ADs and reported to the the European Society for Blood and Marrow Transplantation (EBMT) data registry associated with the Autoimmune Disease Working Party (ADWP) and Paediatric Diseases Working Party (PDWP)

Patient ID	Year of transplant	Age at transplant (years)	HSCT procedure	Transplant number	Disease classification
1	2011	17.19	Allogeneic	First	Early-onset inflammatory bowel disease with IL10RB deficiency
2	2011	12.85	Allogeneic	First	Early-onset inflammatory bowel disease with IL10R deficiency
3	2012	8.14	Allogeneic	First	Early-onset inflammatory bowel disease with IL10RB deficiency
4	2013	2.98	Allogeneic	First	Early-onset inflammatory bowel disease with IL10RB deficiency
5	2014	0.92	Allogeneic	First	Early-onset inflammatory bowel disease with IL10RB deficiency
6	2014	1.49	Allogeneic	First	Early-onset inflammatory bowel disease with IL10RB deficiency
7	2017	1.33	Allogeneic	First	Early-onset inflammatory bowel disease with IL10RB deficiency
8	2017	4.1	Allogeneic	First	Autoimmune enteropathy, post-infectious
9	2018	0.88	Allogeneic	First	SCID (MHC class 2 deficiency)
10	2018	1.54	Allogeneic	First	SCID (RAG1 deficiency)
10	2018	1.98	Allogeneic	Second	SCID (RAG1 deficiency)
11	2008	3.76	Allogeneic	First	Enteropathy with immune dysregulation
12	2012	0.22	Allogeneic	First	Transfusion-associated GvHD
13	2015	6.46	Allogeneic	First	Inflammatory bowel disease
14	2015	3.07	Allogeneic	First	Early-onset inflammatory bowel disease with IL10RB deficiency
15	2017	4.73	Allogeneic	First	Early onset inflammatory bowel disease and undefined T-cell deficiency
16	2014	2.32	Allogeneic	First	MSMD IF KAPPA B ALPHA deficiency
17	2015	10.29	Allogeneic	First	STAT3 GOF syndrome
18	2016	8.1	Allogeneic	First	Autoinflammatory disease (PAPA-like Syndrome). PSTPIP-I deficiency
19	2016	6.28	Allogeneic	First	STAT3 GOF syndrome
20	2017	6.81	Allogeneic	First	STAT3 GOF syndrome
21	2017	1.06	Allogeneic	First	RALD
22	2014	9.76	Allogeneic	First	Lymphomatoid granulomatosis, grade I
23	2019	10.22	Allogeneic	First	Inflammatory bowel disease with CTLA4 deficiency
24	2018	1.76	Allogeneic	First	SCID
25	2019	3.66	Allogeneic	First	alpha-Mannosidose
26	2019	10.37	Allogeneic	First	RCC
27	2019	3.54	Allogeneic	First	STAT3 GOF syndrome
27	2020	4.48	Allogeneic	Second	STAT3 GOF syndrome
28	2015	16.83	Allogeneic	First	Chediak-Higashi syndrome
29	2017	0.47	Allogeneic	First	SCID (Omenn syndrome)
30	2018	8.45	Allogeneic	First	LRBA deficiency
31	2016	16.47	Allogeneic	First	IPEX syndrome
32	2019	0.85	Allogeneic	First	IPEX syndrome

Abbreviations: AD, autoimmune disease; GOF, gain-of function; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MHC, major histocompatibility complex; MSDM, Mendelian susceptibility to mycobacterial disease; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne; RALD, RAS-associated leucoproliferative disease; RCC, refractory cytopenia of childhood; SCID, severe combined immunodeficiency.

TABLE 3 Treatment procedure of haematopoietic stem cell transplantation for ADs reported to the European Society for Blood and Marrow Transplantation (EBMT) data registry associated with the Autoimmune Disease Working Party (ADWP) and Paediatric Diseases Working Party (PDWP)

Transplant procedure	Autologous graft (cum. *n* = 176), *n* (%)	Allogeneic graft (cum. *n* = 167), *n* (%)
Conditioning regimen		
Cyclophosphamide-based	112 (69.1)	11 (6.6)
Treosulphan-based		67 (40.1)
Busulphan-based	2 (1.2)	42 (25.1)
TBI-based	31 (19.1)	8 (4.8)
Other	17 (10.5)	29 (17.4)
NA	*14*	*10*
Serotherapy for in vivo T-cell depletion		
ATG	139 (97.2)	55 (32.9)
Alemtuzumab	4 (2.8)	77 (46.1)
No		24 (14.4)
NA	*33*	*11*
Donor type for alloHSCT		
MUD		79 (47.3)
MSD		39 (23.4)
MMR		19 (11.4)
MOR		15 (9)
CB		11 (6.6)
NA		*4*
Source of stem cells		
PBSC	128 (72.7)	78 (46.7)
BM	44 (25)	77 (46.1)
CB		11 (6.6)
BM + PBSC	3 (1.7)	
PBSC + CB	1 (0.6)	
NA		*1*

Abbreviations: AD, autoimmune disease; ATG, anti-thymocyte globulin; BM, bone marrow; CB, cord blood; MMR, mismatched related donor; MOR, matched other related donor; MSD, matched sibling donor; MUD, matched unrelated donor; NA, not available; PBSC, peripheral blood stem cells; TBI, total-body irradiation.

resolved after rituximab therapy. Three of four children were alive and experienced stable CR over six months to two years of follow-up.[70–72] Details of four children undergoing allogeneic HSCT for severe SLE, two with a genetic component (C1q deficiency), were included as a personal communication in a recent comprehensive review on HSCT in paediatric rheumatic diseases. Three patients have been reported as alive and well.[36] Furthermore, one child diagnosed with early-onset severe SLE and DOCK8 deficiency tolerated the HSCT procedure well and was in CR over 12 months after transplant.[73]

Systemic sclerosis (SSc) is a rare multisystem disease affecting the macro- and microvasculature and leading to skin and organ fibrosis.[74] An imbalanced T-cell population with reduced regulatory T cells and increased CD4-positive effector memory T cells expressing CD45RA (EMRA) which causes cytokine dysregulation was recently suggested to play a pivotal role in the development of the juvenile form of jSSc.[75,76] However, the aetiology of jSSc remains poorly understood. Current treatments are mainly based on expert opinions, but specific recommendations on behalf of a European initiative (SHARE — Single Hub and Access point for paediatric Rheumatology in Europe) were recently published with the aim to improve clinical outcome.[77,78] Symptomatic therapies (e.g., prokinetics, antihypertensive agents, physiotherapy) are recommended for stable disease. When jSSc progresses, immunosuppressive agents, such as corticosteroids, cyclophosphamide, methotrexate and mycophenolate mofetil, are given. Biologicals (e.g., rituximab, tocilizumab, abatacept) and autologous HSCT addressing the profound immune dysregulation are recommended in children refractory to immunosuppressive treatment.[77] In adults with rapidly progressive disease and thus high risk of mortality, only autologous HSCT was shown to improve the chance of disease control and survival.[79–81] Sixteen children with progressive therapy-refractory SSc have been reported to the EBMT registry after rescue autologous HSCT. The first successful autologous transplantation of a girl with aggressive jSSc clinical course despite several lines of treatment was published in 1999. Pulmonary function, growth and skin findings rapidly improved post transplant and, importantly, the child did not experience any relevant toxicity after myelo-ablation with cyclophosphamide and lymphodepletion with alemtuzumab.[82] A European survey of autologous HSCT trials for SSc including 57 patients, five of which were children, indicated response to transplant in the majority of patients, but only 28% of them experienced long-term CR. Of note, two thirds of the paediatric cohort achieved long-term disease control and 100% survival. However, no data on treatment-related toxicity are available in this cohort.[83]

Until now, allogeneic HSCT for jSSc was restricted to adults. Available case reports showed significant improvement of cutaneous and organ disease manifestation,[84,85] but further research is needed to evaluate the effects of allogeneic transplant in this patient population.

Autoimmune cytopenias

Several forms of autoimmunity are directed against various stages of haematopoietic cells, from early precursors with forms of bone marrow aplasia, generalised in aplastic anaemia and more lineage-specific forms, such as pure red cell aplasia (PRCA), to the predominantly peripheral destruction of autoimmune haemolytic anaemia (AIHA), immune thrombocytopaenia (ITP) and combined involvement of both red cells and platelets (Evans syndrome). In children, severe haematological cytopenias caused by autoreactive antibodies (mostly IgG) against blood cell surface antigens are rare, but frequently relapse over years despite multimodal therapy approaches, thus leading to prolonged

TABLE 4 Overview of European studies on autologous and allogeneic HSCT for severe ADs in children <18 years of age

Disease	HSCT procedure	First author	Year	Study design	Children aged <18 years/total	Conditioning regimen
Rheumatic diseases						
JIA	Autologous	De Kleer	2004	Multicentre, retrospective	*n* = 34/34	Cyclophosphamide+low dose TBI + rabbitATG, or
					Median age = 9.4 years (4.3–17)	Cyclophosphamide+rabbitATG, or
						Cyclophosphamide + rabbitATG, or
						Fludarabine + cyclophosphamide + ATG + methylprednisolone
JIA	Autologous	Brinkman	2007	Multicentre, prospective, phase II	*n* = 22[b]/22	Cyclophosphamide + low-dose TBI + rabbit ATG, or
					Median age = 8.5 years (4–18)	fludarabine + cyclophosphamide + rabbit ATG
JIA	Autologous	Abinun	2009	Multicentre, prospective	*n* = 9/9	Cyclophosphamide + rabbit ATG ± TBI, or
					Median age = 7 years (6–17)	Fludarabine + cyclophosphamide + rabbit ATG
JIA	Allogeneic	Silva	2017	Multicentre, prospective	*n* = 16/16	Fludarabine + melphalan + alemtuzumab, or
					Median age = 8.4 years (range, 2.6–16)	fludarabine + treosulphan + alemtuzumab
JIA	Allogeneic	Morelle	2021	Case report	*n* = 1, 3.7-year-old	Busulphan + fludarabine + alemtuzumab + rituximab + post-cyclophosphamide
SLE	Autologous	Wulffraat	2001	Case report	*n* = 2/2	Cyclophosphamide + low dose TBI + ATG
					both 14-year-old	
SLE	Autologous	Jayne	2004	Multicentre, retrospective	*n* = 17[c]/53	Cyclophosphamide-based ± ATG, or
					Median age = 29 years (9–52)	melphalan + VPl6, or
						BEAM + ATG, or
						BEAM alone, or
						busulphan + fludarabine + ATG, or
						melphalan alone
SLE/C1q deficiency	Allogeneic	Arkwright	2014	Case report	*n* = 1, 16-year-old	Treosulphan + fludarabine + alemtuzumab
SLE/C1q deficiency	Allogeneic	Olsson	2016	Case report	*n* = 2/2, 9- and 12-year-old	Treosulphan + fludarabine + ATG

Disease remission	Relapse	Survival	Complications	TR mortality	Follow-up	Reference
CR = 53%	21%	OS = 85%	Virus infection/reactivation	9%	2.3 years (1–5)	51
PR = 18%			Bacterial infection			
			Fungal infection			
			MAS			
CR = 36%	60%	OS 5 years = 82%	Virus infection/reactivation	9%	6.6 years (4.3–8.6)	52
PR = 35%		EFS 5 years = 36%	MAS			
CR = 57%	29%	OS = 86%	Virus reactivation	14%	5 years (4.3–8.6)	53
			Autoimmune tyhroiditis			
			MAS			
CR = 69%	13%	88%	Virus infection/reactivation	12%	2.4 years (0.2–8)	43
			aGvHD			
			Alloimune thrombo-cytopaenia and neutropaenia			
			Pneumo-mediastinum/ pneumothorax			
CR	No	Alive	Virus infection/reactivation	No	3 years	54
			Bacterial infection			
			Autoimmune thrombo-cytopaenia			
			aGvHD			
			Hypothyreoidism			
CR	No	Alive	Virus infection/reactivation	No	1 and 1.5 years	63
			Sinus bronchitis			
CR = 66%	19%	OS 1 year = 84%	Virus infection/ reactivation	13%	1.9 years (0–6.5)	64
PR = 14%		OS 4 years = 62%	Antiphospholipid syndrome			
		DFS 5 years = 55%	Haemolytic anaemia			
			EBV-associated PTLD			
			AML			
CR	No	Alive	EBV-reactivation (subclinical)	No	6 months	72
CR = 50%	50%	OS 2 years = 50%	EBV-associated PTLD	50%	4 months and 2 years	71
			aGvHD			

(Continues)

Disease	HSCT procedure	First author	Year	Study design	Children aged <18 years/total	Conditioning regimen
SSc	Autologous	Martini	1999	Case report	n = 1, 11-year-old	Cyclophosphamide + alemtuzumab
SSc	Autologous	Farge	2004	Report of open	*n* = 5[a]/57	Cyclophosphamide + TBI + ATG
				Multicentre	12 years (range 9–17)	Cyclophosphamide + alemtuzumab
				Uncontrolled phase I–II studies		Cyclophosphamide
Autoimmune cytopaenias						
Evans syndrome	Allogeneic	Raetz	1997	Case report	*n* = 1, 5-year-old	Cyclophosphamide + TBI
Evans syndrome	Autologous and allogeneic	Urban	2006	Case report	*n* = 1, 7-year-old	1st autologous HSCT: cyclophosphamide + rabbitATG
						2nd autologous HSCT: fludarabine + alemtuzumab
						1st allogeneic HSCT: busulphan + thiotepa + etoposide + rabbit ATG
AIHA, ITP, Evans syndrome, ALPS	Autologous and allogeneic	Rabusin	2013	Retrospective analysis	Overall autologous cohort: *n* = 7/7	Cyclophosphamide-based ± ATG, or
					Median age = 6.99 years (1.73–17.34)	cyclophosphamide + fludarabine ± ATG, or
						fludarabine ± ATG ± others, or
						melphalan alone
					Overall allogeneic cohort: *n* = 17/17	Busulphan-based, or
					Median age 8.24 years (0.61–17.77)	cyclophosphamide-based ± ATG, or
						cyclophosphamide + fludarabine ± ATG, or
						fludarabine ± ATG ± other, or
						data not available (n = 2)
Outcome by disease						
Evans syndrome	Autologous				*n* = 2	
	Allogeneic				*n* = 9	
AIHA	Autologous				*n* = 1	
	Allogeneic				*n* = 5	
ITP	Autologous				*n* = 4	
ALPS	Allogeneic				*n* = 3	
Neuroinflammatory diseases						
POMS	Autologous	Burman	2017	Multicentre retrospective	*n* = 21/21	BEAM (BCNU, etoposide, cytosine arabinoside, melphalan), or cyclophosphamide-based ± rabbit or horse ATG
					Median age = 16 years (9–18)	

TABLE 4 (Continued)

Disease remission	Relapse	Survival	Complications	TR mortality	Follow-up	Reference
CR	no	Alive	no	No	2 years	[82]
CR = 60% PR = 20%	20%	OS = 100%	NA	No	3.1 years (1.1–5.6)	[83]
CR	No	Died	Hepatic failure Transient pulmonary insufficiency aGvHD	Died	0.8 years	[97]
No	day +12					[96]
NO	+2 months		Massive intracranial bleeding			
CR	NO	Alive	Virus infection/reactivation aGvHD Muscle atrophy	No	1.5 years	
CR = 43%	43%	EFS = 42%	Virus infection/reactivation	No	10.5 years (9.4–11)	[39]
CR = 60%	13%	EFS = 58%	Virus infection/reactivation aGvHD cGvHD	12%	6.3 years (0.5–13)	
No	50%			No		
56%	11%			33%		
No (DP)	no			No		
CR = 40%				40%		
CR = 75%				25%		
CR = 100%				No		
PFS 3-year = 100%	10%	OS 3 years = 100%	Virus infection/reactivation Bacterial infection	No	2.8 years (0.1–13.2 years)	[38]

Disease	HSCT procedure	First author	Year	Study design	Children aged <18 years/total	Conditioning regimen
NMO	Allogeneic	Ceglie	2019	Case report	*n* = 1, 15 years old	Thiotepa+treosulphan + fludarabine + rabbit ATG + RTX
Inflammatory bowel diseases (IBD)						
CD	Autologous	Burt	2010	Prospective phase 1/2	*n* = 5/24 Median age = 16 years (15–18)	Cyclophosphamide + horse or rabbit ATG

Abbreviations: AD, autoimmune disease; aGvHD, acute GvHD; AIHA, autoimmune haemolytic anaemia; ALPS, autoimmune lymphoproliferative syndrome; AML, acute myeloid leukaemia; ATG, anti-thymoglobuline; BCNU, bis-chloroethylnitrosourea, carmustine; CD, Crohn's disease; cGVHD, chronic GvHD; CR, complete remission; DFS, disease-free survival; DP, disease progression; EBV, Epstein–Barr virus; EFS, event-free survival; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; ITP, autoimmune thrombopenia; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; NA, not available; NMO, neuromyelitis optica; OS, overall survival; PFS, progression-free survival; POMS, paediatric onset multiple sclerosis; PR, partial remission; PTLD, post-transplant lymphoproliferative disorder; RFS, relapse-free survival; RTX, rituximab; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TBI, total-body irradiation; TR, treatment-related.

[a]Data refer to the paediatric cohort.

[b]Subset of the previous cohort of 34 patients.

[c]Including previously published patients.

immunosuppressive treatment, repeated transfusions, and life-threatening situations. Furthermore, autoimmune cytopenias may occur in children with underlying monogeneic diseases or after HSCT for any indication.[86,87] The production of autoantibodies by the donor immune system which reacts against haematological antigens produced by the graft itself as well as discordant T- and B-cell recovery post transplant with persistent host B- and plasma cells producing antibodies against donor blood cells antigens were recently hypothesised.[88,89] Importantly, the clinical course of post-transplant cytopenias is generally more severe and more frequently resistant to conventional treatments than spontaneous cytopenias. A distinct pathogenesis has been proposed.[88,89]

First-line treatments with steroids (AIHA) and/or immunoglobulins (ITP) and second-line drugs, such as sirolimus, ciclosporin, mycophenolate mofetil, rituximab, daratumumab and bortezomib, address the pathogenic B-cell clone.[90,91] In children with persistent ITP, thrombopoietin receptor agonists (TPO-RAs), such as eltrombopag and romiplostim, may increase circulating platelet count by stimulating proliferation and maturation of megakaryocytes.[92,93] Both drugs were shown to be a feasible treatment option in paediatric patients, but randomised controlled trials comparing both drugs and data on long-term toxicity are lacking.[92,94]

In children refractory to several therapy lines and experiencing life-threatening bleeding, immunosuppressive conditioning treatment with profound B-cell depletion prior to HSCT may be a curative option. As of October 2021, the EBMT registry holds data on 61 paediatric autologous or allogeneic HSCT recipients for autoimmune cytopenia, of whom 16 suffered from Evans syndrome, 13 from AIHA, five from ITP and 27 from other forms of autoimmune cytopenia. More than 80% of these children were transplanted following an allogeneic procedure. Of note, one child with Evans syndrome was diagnosed with a concomitant CTL4-deficiency. However, the number of patients with autoimmune cytopenias and underlying monogeneic disorders may be higher, since further genetic findings diagnosed after the primary patient registration in the EBMT registry are potentially underreported in the database due to the limited availability of routine genetic testing at the time of HSCT.

An early, mixed EBMT analysis included 36 adults and children with autoimmune cytopenia indicated long-term progression-free survival (PFS) after autologous or allogeneic HSCT of 45% [95% confidence interval (CI) ± 21%] and 78% (95% CI ± 28%) respectively, but risks of treatment-related toxicity after cyclophosphamide-based conditioning were concerning. Unfortunately, no specific data on the paediatric subgroup are available.[95,96] An updated EBMT retrospective analysis of 22 paediatric patients undergoing allogeneic (*n* = 17) or autologous (*n* = 7) HSCT confirmed successful complete remission (CR) in 43% of patients after autologous and in 59% after allogeneic HSCT. Again, TRM provided further concerns reaching 16% in autologous and 29% in allogeneic HSCT recipients. However, risks of recurrent disease are also significant in this population, as two children (18%) died due to disease progression after allogeneic HSCT.[39]

Specific reports of paediatric patients receiving allogeneic HSCT for severe Evans syndrome (ES) are limited. Two children were reported to achieve complete disease remission over nine and 18 months after a conditioning with cyclophosphamide/TBI or busulphan/thiotepa/etoposide/ATG, respectively, with significant toxicity post transplant.[96,97]

In summary, available data suggest successful control of severe haematological autoimmunity by both autologous and allogeneic HSCT in paediatric patients. However, the consistent risk of TRM currently restricts this procedure to children with severe autoimmune cytopenias resistant

TABLE 4 (Continued)

Disease remission	Relapse	Survival	Complications	TR mortality	Follow-up	Reference
PFS and clinical improvement	No	Alive	No	No	2 years	[99]
CR = 70%–80%	40%	RFS 5 years = 19%	Virus infection/reactivation Bacterial infection Fungal infection	No	5 years	[107]

to multiple immunosuppressive treatments and TPO-RAs. Further data registration and ideally prospective studies are needed to support safer transplant protocols and other guidance in these rare patients who are resistant to modern treatment strategies.

Neuroinflammatory diseases

Neuroinflammatory diseases such as MS and neuromyelitis optica (NMO) are chronic autoimmune-mediated demyelinating disorders of the central nervous system (CNS) mostly occurring in young adults and gradually leading to severe neurological disability.[98,99] Although *increasing*, the incidence of NMO and MS in children (paediatric-onset MS, POMS) is rare and reaches a peak at the age of 12 years and in the age group of 13–16-year-olds, respectively.[100,101]

A relapsing–remitting clinical course characterised by severe cerebral damage leading to severe disability and a high relapse rate are unfavourable peculiarities of POMS.[102,103] In patients with POMS unresponsive to treatment with modern disease-modifying drugs (DMDs) such as interferon beta (IFN β), glatiramer acetate (GA), natalizumab or rituximab, autologous HSCT may successfully suppress CNS inflammation. Until now, 32 children treated with autologous transplant and one child with allogeneic HSCT for POMS were reported to the EBMT registry. Encouraging data on 21 young patients (patients' age range was 9–18 years) after autologous HSCT have been recently published.[38] In this patient cohort, the incidence of severe treatment-related toxicity after conditioning with bis-chloroethylnitrosourea (BCNU), etoposide, cytosine arabinoside, melphalan (BEAM)/ATG or cyclophosphamide/ATG was low: one patient experienced *Pseudomonas aeruginosa* sepsis and one other child developed gastrointestinal bleeding and disseminated intravascular coagulation (DIC). Outcome was impressive with 100% overall survival and PFS at three years.[38] To our knowledge, no data on children undergoing allogeneic HSCT for POMS have been published yet.

Recurrent autoinflammatory episodes primarily involving the optic nerves and spinal cord are characteristic clinical signs of NMO. This disease was previously considered a subtype of MS, but the occurrence of specific antibodies against aquaporin-4 defined it as an independent neuroinflammatory disease.[101] Limited experience is available regarding the use of HSCT in children with NMO, but one significant case report was recently published. A girl of 15 years with a severe disease course resistant to multiple treatments had undergone a haploidentical allogeneic procedure after *ex-vivo* depletion of $\alpha\beta^+$ T cells and CD19 lymphocytes of the graft, and experienced long-term disease control and significant clinical improvement at 2 years of follow-up.[99] Three further children receiving allogeneic HSCT for NMO have been registered in the EBMT database.

Inflammatory bowel diseases

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and CD, have a rising incidence in children. A dysregulated T-cell-mediated mucosal immune response against the commensal intestinal microbiota results in chronic relapsing auto-inflammation.[104,105] In children, IBD commonly presents with weight loss, recurrent abdominal pain and bloody diarrhoea, but also has a major impact on growth and psychosocial development.[106] Despite biological tumour necrosis factor alpha.

(TNFα)-targeted therapies such as infliximab and adalimumab having been proven to be highly effective by inducing disease remission in the majority of children with UC or CD,[106] immune escape mechanisms causing disease relapse are frequent and new therapy strategies are needed.

Both autologous or allogeneic HSCT procedures have been performed in children with recurrent UC or CD after exhaustion of multiple treatments. Until now, 21 children with CD, 16 of whom received autologous HSCT and five an allogeneic HSCT, and three patients with UC (two after allogeneic and one after autologous transplant) have been registered in the EBMT database. While no published data on HSCT in children with UC are currently available, an American trial including five paediatric patients with CD after conditioning with cyclophosphamide/ATG and autologous HSCT showed no severe treatment-related toxicity, 100% overall survival and 40% (two out of five children) PFS at five years. One patient experienced partial disease remission and two patients relapsed, qualifying thus for colectomy and ileostomy 18 and 30 months after transplant, respectively.[107]

To our knowledge, there are no published results on allogeneic HSCT procedures in children with IBD. However, encouraging data on monogeneic diseases manifesting with severe IBD [e.g. X-linked inhibitor of apoptosis (XIAP) deficiency[108] and homozygous loss of function mutations in interleukin-10 (IL10) and IL10 receptors (IL10R)[109]] pave the way for the potential use of allogeneic HSCT as an effective treatment option for the most severe, treatment-refractory cases of polygeneic IBD. Further trials are needed to explore benefits and reduce treatment-related toxicity in children undergoing autologous or allogeneic HSCT for IBD.

Autoimmune diseases with genetic features

All ADs have a genetic component, but some, usually presenting in childhood, have a strong and increasingly well-defined monogeneic basis. Such diseases typically present with an overlapping spectrum of autoimmune (adaptive immunity) and autoinflammatory (innate immunity) features, and there is a high degree of overlap with primary immunodeficiency diseases and other IEI, for which allogeneic HSCT is standard of care. In the recently updated phenotypical classification of the International Union of Immunological Societies (IUIS), more than 20 monogeneic diseases leading to clinical syndromes characterised by severe autoimmunity are reported.[110] Diseases such as chronic granulomatous disease (CGD), XIAP deficiency, immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX, based on mutation FOXP3), CD25 deficiency, CTLA4 deficiency, and IL10 deficiency represent a particularly rare but expanding and clinical heterogenous subgroup of IEI which can be cured with allogeneic HSCT.[111–113] Some of these molecular defects affecting immunological cells therefore increase the risk of malignancy significantly.[114] Allogeneic HSCT following expert guidelines[115] may thus improve life expectancy as well as QoL in this patient population and current outcome data are promising.[116] A recent analysis on 635 children with chronic granulomatous disease (CGD), a monogeneic disorder frequently presenting with inflammatory bowel disease, and undergoing allogeneic HSCT indicates excellent outcomes with 86% overall survival, 76% event-free survival (meaning also disease control) and <10% incidence of acute GvHD at three years post transplant.[117] A further recent study on children with XIAP deficiency, a rare genetic disease which causes severe autoimmunity such as treatment-refractory IBD and life-threatening sHLH, reports encouraging survival data after allogeneic HSCT following reduced-intensity or reduced-toxicity conditioning. Forty children and young adults with a median age at HSCT of 6.5 years (0.45–27) reached an overall survival rate of 74% and a rate of event-free survival of 64% at two years post transplant, but the incidence of severe treatment-related toxicities like respiratory distress syndrome or life-threatening bleeding was high (25% and 23%, respectively).[108]

In summary, further characterisation of genetic components of paediatric ADs will evolve our understanding, and direct appropriate treatment, including allogeneic HSCT, which is a standard of care according to EBMT guidelines.[118] 'Standard' autologous HSCT is clearly ineffective in these patients as a means of long-term cure. However, gene therapies using autologous HSCs are increasingly developed and evaluated as discussed below.

FUTURE DEVELOPMENTS

Genetic analysis

In children with severe ADs, genetic analysis increasingly reveals monogeneic backgrounds in a significant proportion of patients. If a monogeneic disease is identified, an allogeneic HSCT is the transplant modality of choice and should be evaluated as curative treatment. Therefore, genetic analysis should be considered in all patients where an HSCT is discussed in order to allow a proper decision between allogeneic and autologous HSCT. Furthermore, genetic findings may provide better discrimination between relevant disease subgroups, thereby supporting specific treatments and improved outcomes. The development of specifically designed next-generation sequencing (NGS) panels can facilitate the application of more detailed genetic analysis in routine clinical practice.

Transplant technique and supportive care

The goal of modern highly effective reduced-intensity conditioning (RIC)/reduced-toxicity conditioning (RTC) regimens leading to consistent myeloid engraftment even in the presence of mixed donor chimerism may support the beneficial development of an immunological balance

and allow long-term remission whilst significantly reducing the risk of severe treatment-related morbidity such as infertility, organ damage and late cancers, as well as TRM.[36,119–124]

There are a variety of modern chemotherapy and serotherapy agents used in conditioning to deliver lympho- and/or myelo-ablation, whilst having an improved toxicity profile. These may include modified drugs in the same disease class (such as treosulphan) and also targeted therapies, such as antibody-linked agents. Irradiation, which is not favoured in a non-malignant paediatric setting, can be delivered more safely through antibody-targeted means. Recently, sophisticated techniques for profound depletion of $\alpha\beta^+$ T cells and $CD19^+$ lymphocytes from the graft whilst maintaining immune-modulating $\gamma\delta^+$ T cells have been shown to lead to excellent outcome results with low rates of acute GvHD and stronger immune reconstitution in children undergoing haploidentical HSCT.[29,30,125,126] Furthermore, post-transplant cyclophosphamide (PTCy) is increasingly used as a pharmacological strategy to overcome HLA barriers in the setting of allogeneic HSCT, initially from haploidentical donors, but more recently also in matched related and unrelated donors.[34,127–129] Although both techniques have been used interchangeably in the broader field of non-malignant diseases, experience is limited in the setting of ADs and pivotal outcome parameters, including incidence of complications such as acute and chronic GvHD and rejection, need to be reported in an accurate and timely manner to registries and published in order to inform decision-making in this area.

Recent expert guidelines,[115] opinions,[36] and pharmacokinetic studies on conditioning drugs as well as accurate analysis of immune reconstitution post transplant support the development of more and more individualised therapy regimens, thereby promising further reduction of the risk of severe transplant-related morbidity and mortality.[8,130–136]

Other advanced therapies in autoimmune diseases

In patients with severe ADs, the disruption of the central and/or peripheral immunologic tolerance causes unwanted immune reactions against self-antigens. The activated endogenous cytokine network may thus play an important role in terms of effectiveness of immunosuppressive therapy. Alongside allogeneic HSCT, innovative therapy approaches with consistent immune-regulatory properties, including gene therapy based on both autologous and donor cells, MSC infusion and regulatory T-cell (T-reg) administration have been developed over the last decades for treating severe ADs. Published trials on advanced cellular therapies in patients with ADs report a benign toxicity profile, while showing controversial beneficial effects from direct cell-to-cell interaction and paracrine action.[137–140] Nevertheless, there is great variability among different trials and numbers of patients are small, warranting further studies in this setting.

T-regs are a subset of $CD4^+$ T lymphocytes, endowed with immune-regulatory capacities. These cells maintain the physiological immune homeostasis, avoiding excessive inflammatory reactions or responses against self-antigens. Adoptive T-reg therapies have been envisaged for inflammatory and autoimmune conditions.[141] Several clinical trials employed polyclonal regulatory cells and proved these approaches to be safe, but showed limited efficacy in controlling the underlying disease, potentially explained by low numbers of true disease-relevant antigen-specific cells in the product.

Considering the relevance of antigen-specific T-regs, different strategies have been designed to increase their numbers in patients with severe ADs. Chimaeric antigen receptor (CAR)-T cells represent one of the most promising therapy approaches in this respect. CAR-T-cell therapies have become an effective treatment in B-cell acute lymphoblastic leukaemia and other malignant diseases.[142] However, in addition the ability of CAR-T cells to confer new antigen-specificities whilst boosting cell activation may be employed in autoimmune models. In early experimental studies on autoimmune encephalomyelitis and pemphigus vulgaris, CAR-T cells were used to eliminate auto-reactive T and B cells.[143,144] The successful treatment of a patient with refractory SLE with CD19-targeted CAR-T cells has been recently reported.[145] Complete resolution of symptoms was accompanied by sustained depletion of circulating B cells and rapid disappearance of anti-double-stranded DNA antibodies. Thus, T-regs may represent ideal candidates for an immune-modulatory CAR-T-cell therapy. Pre-clinical studies have evaluated the efficiency of CAR-T-regs in controlling the inflammatory response in various murine models of ADs and supporting further evaluation and potential clinical development.[146]

Haematopoietic stem cell gene therapy for monogeneic diseases and the adoptive transfer of engineered donor T cells including a suicide mechanism, have been proven to be safe in early clinical trials and may bring consistent advantages over the allogeneic transplant strategy.[147,148] Whilst only mild conditioning treatment is required prior to re-infusion of autologous gene-edited stem cells, thus limiting treatment-related toxicity, donor T cells were infused at the day of allogeneic transplant and shown to support thymic recovery, thereby promoting immune reconstitution after HSCT.[147–149] However, the risk of lymphoproliferation and the achievement of long-term T-cell persistence post transplant remain delicate challenges of such approaches. Novel sophisticated techniques are in development and may be able to provide efficacious T-cell therapies in patients with severe ADs.[148]

Other non-haematopoietic stem cell transplantation (HSCT) treatments in combination with HSCT

While it is likely that current and future developments in transplant technique and greater experience will improve

outcomes, there will inevitably be advances in 'standard' treatments as well. While these treatments may be successful in their own right, there may be opportunity to combine them with HSCT, for example, as post-transplant maintenance or early salvage treatments. Evidence for using conventional drugs in this context was provided by clinical trials in young adults undergoing autologous HSCT for severe CD and responding to anti-TNF therapy post transplant for relapsing disease activity despite being resistant/refractory prior to HSCT.[150–152] Development of future trials and studies should be done in collaboration with disease specialist groups, in order that meaningful conclusions can be delivered in a continually moving field.

CONCLUSION

Severe ADs are rare in childhood and present with a wide range of clinical features and variable genetic components, but lead to challenging and frequently complex management strategies involving multiple treatment regimens. Eventually, some patients exhaust all 'standard of care' options and are considered refractory to treatment. Literature suggests that autologous and allogeneic HSCT offer a consistent therapeutic role for treating severe autoimmune syndromes in children, albeit with a significant but defined profile of complications and TRM. Data on this specific patient population remains limited, but early disease recognition, careful patient selection and multidisciplinary approach, before patients are compromised by their AD and ongoing attempts at disease control with corticosteroid, immunosuppressive and biological treatments, should improve the efficacy and safety of this procedure. While evaluation of retrospective registry data continues to be a valuable resource, prospective clinical studies addressing current clinical practice are necessary in highly selected patient groups to define the safety and efficacy of HSCT and support expert consensus. It is likely that current and future developments in transplant technique and greater experience will improve outcomes, but at the same time significant advances in 'standard of care' treatments are inevitable, and therefore decision-making should always be multidisciplinary, whether this be on an individual patient basis, in developing guidelines and recommendations for wider use, or in designing prospective clinical studies. The field is continually moving and the development of advanced cell and gene therapies using haematopoietic stem cells will evolve and is likely to be supported by experience of HSCT for ADs in the paediatric age group.

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CONFLICT OF INTERESTS

Federica R. Achini-Gutzwiller and Selim Corbacioglu declare that they have no conflict of interest. Raffaella Greco discloses honoraria for speaking at educational events supported by Biotest, Pfizer, and Magenta. John A. Snowden declares honoraria for speaking from Jazz, Gilead, Janssen, Actelion, advisory board work from Medac and IDMC membership for Kiadis Pharma.

AUTHOR CONTRIBUTIONS

The experts on this panel are active members of the EBMT. All authors participated in the concept and design of the astudy, contributed to the analysis and interpretation of data, and wrote sections of the manuscript. Federica R. Achini-Gutzwiller and Raffaella Greco coordinated and gave lead to thed ata analysis, provided expert and analytical feedback, and were involved in reviewing, writing, and editing the manuscript. All co-authors were involved in drafting the

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ORCID

Federica R. Achini-Gutzwiller https://orcid.org/0000-0002-0797-8146
John A. Snowden https://orcid.org/0000-0001-6819-3476
Selim Corbacioglu https://orcid.org/0000-0003-1070-8486
Raffaella Greco https://orcid.org/0000-0002-6117-5328

REFERENCES

1. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med. 2006;3(8):e297.
2. Davidson A, Diamond B. Autoimmune diseases. N Engl J Med. 2001;345(5):340–50.
3. Rabusin M, Andolina M, Maximova N, EBMT Paediatric, Autoimmune Diseases Working Parties. Haematopoietic SCT in autoimmune diseases in children: rationale and new perspectives. Bone Marrow Transplant. 2008;41(Suppl 2):S96–9.
4. Dumaine C, Bekkar S, Belot A, Cabrera N, Malik S, von Scheven A, et al. Infectious adverse events in children with Juvenile Idiopathic Arthritis treated with Biological Agents in a real-life setting: data from the JIRcohorte. Joint Bone Spine. 2020;87:49–55.
5. Woerner A, Ritz N. Infections in children treated with biological agents. Pediatr Infect Dis J. 2013;32(3):284–8.
6. Alexander T, Greco R, Snowden JA. Hematopoietic stem cell transplantation for autoimmune disease. Annu Rev Med. 2021;72:215–28.
7. Greco R, Labopin M, Badoglio M, Veys P, Furtado Silva JM, Abinun M, et al. Allogeneic HSCT for autoimmune diseases: a retrospective study from the EBMT ADWP, IEWP, and PDWP working parties. Front Immunol. 2019;10:1570.
8. Snowden JA, Badoglio M, Labopin M, Giebel S, McGrath E, Marjanovic Z, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. Blood Adv. 2017;1:2742–55.
9. Greco R , Lorentino F, Albanese S, Lupo Stanghellini MT, Giglio F, Piemontese S, et al. Posttransplantation Cyclophosphamide- and Sirolimus-Based Graft-Versus-Host-Disease Prophylaxis in Allogeneic Stem Cell Transplant. Transplant Cell Ther. 2021;27:776.e771–776.e713.
10. Passweg JR, Baldomero H, Chabannon C, Basak GW, de la Cámara R, Corbacioglu S, et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. Bone Marrow Transplant. 2021;56:1651–64.
11. Muraro PA, Martin R, Mancardi GL, Nicholas R, Sormani MP, Saccardi R. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. Nat Rev Neurol. 2017;13:391–405.
12. Muraro PA, Douek DC. Renewing the T cell repertoire to arrest autoimmune aggression. Trends Immunol. 2006;27(2):61–7.
13. Delemarre EM, van den Broek T, Mijnheer G, Meerding J, Wehrens EJ, Olek S, et al. Autologous stem cell transplantation aids autoimmune patients by functional renewal and TCR diversification of regulatory T cells. Blood. 2016;127:91–101.
14. Krenger W, Blazar BR, Holländer GA. Thymic T-cell development in allogeneic stem cell transplantation. Blood. 2011;117(25):6768–76.
15. Greco R, Bondanza A, Vago L, Moiola L, Rossi P, Furlan R, et al. Allogeneic hematopoietic stem cell transplantation for neuromyelitis optica. Ann Neurol. 2014;75:447–53.
16. Ros-Soto J, Burt RK, Snowden JA. Allogeneic HSCT and graft-versus-host disease (GvHD). General principles with reference to autoimmune diseases. In: Burt RK, Farge D, Ruiz MA, Saccardi R, Snowden JA, editors. Hematopoietic stem cell transplantation and cellular therapies for autoimmune diseases. 1st ed. Boca Raton: CRC Press; 2021.
17. Hough RE, Snowden JA, Wulffraat NM. Haemopoietic stem cell transplantation in autoimmune diseases: a European perspective. Br J Haematol. 2005;128(4):432–59.
18. Marmont AM, Gualandi F, Van Lint MT, Bacigalupo A. Refractory Evans' syndrome treated with allogeneic SCT followed by DLI. Demonstration of a graft-versus-autoimmunity effect. Bone Marrow Transplant. 2003;31:399–402.
19. Van Wijmeersch B, Sprangers B, Rutgeerts O, Lenaerts C, Landuyt W, Waer M, et al. Allogeneic bone marrow transplantation in models of experimental autoimmune encephalomyelitis: evidence for a graft-versus-autoimmunity effect. Biol Blood Marrow Transplant. 2007;13:627–37.
20. Locatelli F, Zecca M, Messina C, Rondelli R, Lanino E, Sacchi N, et al. Improvement over time in outcome for children with acute lymphoblastic leukemia in second remission given hematopoietic stem cell transplantation from unrelated donors. Leukemia. 2002;16:2228–37.
21. Peters C, Schrappe M, von Stackelberg A, Schrauder A, Bader P, Ebell W, et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: a prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. J Clin Oncol. 2015;33:1265–74.
22. Vander Lugt MT, Chen X, Escolar ML, Carella BA, Barnum JL, Windreich RM, et al. Reduced-intensity single-unit unrelated cord blood transplant with optional immune boost for nonmalignant disorders. Blood Adv. 2020;4:3041–52.
23. Ruggeri A, Paviglianiti A, Gluckman E, Rocha V. Impact of HLA in cord blood transplantation outcomes. HLA. 2016;87:413–21.
24. Spees LP, Martin PL, Kurtzberg J, Stokhuyzen A, McGill L, Prasad VK, et al. Reduction in mortality after umbilical cord blood transplantation in children over a 20-year period (1995–2014). Biol Blood Marrow Transplant. 2019;25:756–63.
25. Rocha V, Cornish J, Sievers EL, Filipovich A, Locatelli F, Peters C, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood. 2001;97:2962–71.
26. Rocha V, Locatelli F. Searching for alternative hematopoietic stem cell donors for pediatric patients. Bone Marrow Transplant. 2008;41(2):207–14.
27. Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. Blood. 2013;122(4):491–8.
28. Or-Geva N, Reisner Y. The evolution of T-cell depletion in haploidentical stem-cell transplantation. Br J Haematol. 2016;172(5):667–84.
29. Bertaina A, Merli P, Rutella S, Pagliara D, Bernardo ME, Masetti R, et al. HLA-haploidentical stem cell transplantation after removal of αβ+ T and B cells in children with nonmalignant disorders. Blood. 2014;124:822–6.
30. Bertaina A, Pitisci A, Sinibaldi M, Algeri M. T cell-depleted and T cell-replete HLA-haploidentical stem cell transplantation for nonmalignant disorders. Curr Hematol Malig Rep. 2017;12:68–78.
31. Aversa F, Pierini A, Ruggeri L, Martelli MF, Velardi A. The evolution of T cell depleted haploidentical transplantation. Front Immunol. 2019;10:2769.
32. Fernandes JF, Nichele S, Arcuri LJ, Ribeiro L, Zamperlini-Netto G, Loth G, et al. Outcomes after haploidentical stem cell transplantation with post-transplantation cyclophosphamide in patients with primary immunodeficiency diseases. Biol Blood Marrow Transplant. 2020;26:1923–9.
33. Torres Canizales J, Ferreras C, Pascual A, Alonso L, Regueiro A, Plaza M, et al. Haploidentical transplantation in pediatric nonmalignant diseases: a retrospective analysis on behalf of the Spanish Group for Hematopoietic Transplantation (GETH). Eur J Haematol. 2021;106:196–204.
34. Oostenbrink LVE, Pool ES, Jol-van der Zijde CM, Jansen-Hoogendijk AM, Vervat C, van Halteren AGS, et al. Successful mismatched hematopoietic stem cell transplantation for pediatric hemoglobinopathy by using ATG and post-transplant cyclophosphamide. Bone Marrow Transplant. 2021;56:2203–11.
35. Mori M. Pediatric rheumatic diseases: a review regarding the improvement of long-term prognosis and the transition to adults. Immunol Med. 2018;41(1):2–5.

36. Abinun M, Slatter MA. Haematopoietic stem cell transplantation in paediatric rheumatic disease. Curr Opin Rheumatol. 2021;33(5):387–97.
37. Abinun M, Lane JP, Wood M, Friswell M, Flood TJ, Foster HE. Infection-related death among persons with refractory juvenile idiopathic arthritis. Emerg Infect Dis. 2016;22:1720–7.
38. Burman J, Kirgizov K, Carlson K, Badoglio M, Mancardi GL, De Luca G, et al. Autologous hematopoietic stem cell transplantation for pediatric multiple sclerosis: a registry-based study of the Autoimmune Diseases Working Party (ADWP) and Pediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2017;52:1133–7.
39. Rabusin M, Snowden JA, Veys P, Quartier P, Dalle J-H, Dhooge C, et al. Long-term outcomes of hematopoietic stem cell transplantation for severe treatment-resistant autoimmune cytopenia in children. Biol Blood Marrow Transplant. 2013;19:666–9.
40. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet. 2011;377(9783):2138–49.
41. Martini A, Lovell DJ. Juvenile idiopathic arthritis: state of the art and future perspectives. Ann Rheum Dis. 2010;69(7):1260–3.
42. Pardeo M, Bracaglia C, De Benedetti F. Systemic juvenile idiopathic arthritis: new insights into pathogenesis and cytokine directed therapies. Best Pract Res Clin Rheumatol. 2017;31(4):505–16.
43. Silva JMF, Ladomenou F, Carpenter B, Chandra S, Sedlacek P, Formankova R, et al. Allogeneic hematopoietic stem cell transplantation for severe, refractory juvenile idiopathic arthritis. Blood Adv. 2018;2:777–86.
44. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011;70:747–54.
45. Cabrera N, Avila-Pedretti G, Belot A, Larbre J-P, Mainbourg S, Duquesne A, et al. The benefit-risk balance for biological agents in juvenile idiopathic arthritis: a meta-analysis of randomized clinical trials. Rheumatology (Oxford). 2020;59:2226–36.
46. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367:2385–95.
47. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol. 2016;12(5):259–68.
48. Minoia F, Davì S, Horne A, Demirkaya E, Bovis F, Li C, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis Rheumatol. 2014;66(11):3160–9.
49. Minoia F, Davì S, Horne A, Bovis F, Demirkaya E, Akikusa J, et al. Dissecting the heterogeneity of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Rheumatol. 2015;42(6):994–1001.
50. Sandler RD, Tattersall RS, Schoemans H, Greco R, Badoglio M, Labopin M, et al. Diagnosis and management of secondary HLH/MAS following HSCT and CAR-T cell therapy in adults; a review of the literature and a survey of practice within EBMT centres on behalf of the Autoimmune Diseases Working Party (ADWP) and Transplant Complications Working Party (TCWP). Front Immunol. 2020;11:524.
51. De Kleer IM, Brinkman DM, Ferster A, Abinun M, Quartier P, Van Der Net J, et al. Autologous stem cell transplantation for refractory juvenile idiopathic arthritis: analysis of clinical effects, mortality, and transplant related morbidity. Ann Rheum Dis. 2004;63:1318–26.
52. Brinkman DMC, de Kleer IM, ten Cate R, van Rossum MAJ, Bekkering WP, Fasth A, et al. Autologous stem cell transplantation in children with severe progressive systemic or polyarticular juvenile idiopathic arthritis: long-term follow-up of a prospective clinical trial. Arthritis Rheum. 2007;56:2410–21.
53. Abinun M, Flood TJ, Cant AJ, Veys P, Gennery AR, Foster HE, et al. Autologous T cell depleted haematopoietic stem cell transplantation in children with severe juvenile idiopathic arthritis in the UK (2000–2007). Mol Immunol. 2009;47:46–51.
54. Morelle G, Castelle M, Pinto G, Breton S, Bendavid M, Boussard C, et al. Sustained remission after haploidentical bone marrow transplantation in a child with refractory systemic juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2021;19:27.
55. Abinun M, Lum SH, Lazareva A, Veys P, Slatter MA. Hematopoietic stem cell transplantation for juvenile idiopathic arthritis. In: Burt RK, Farge D, Ruiz MA, Saccardi R, Snowden JA, editors. Hematopoietic stem cell transplantation and cellular therapies for autoimmune diseases, 1st ed. Boca Raton: CRC Press; 2021.
56. Harry O, Yasin S, Brunner H. Childhood-onset systemic lupus erythematosus: a review and update. J Pediatr. 2018;196:22–30.e2.
57. McClellan J, King MC. Genetic heterogeneity in human disease. Cell. 2010;141(2):210–7.
58. Omarjee O, Picard C, Frachette C, Moreews M, Rieux-Laucat F, Soulas-Sprauel P, et al. Monogenic lupus: dissecting heterogeneity. Autoimmun Rev. 2019;18:102361.
59. Crow YJ. Lupus: how much "complexity" is really (just) genetic heterogeneity?Arthritis Rheum. 2011;63(12):3661–4.
60. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol. 2010;6(9):538–46.
61. Malattia C, Martini A. Paediatric-onset systemic lupus erythematosus. Best Pract Res Clin Rheumatol. 2013;27(3):351–62.
62. Tarr T, Dérfalvi B, Győri N, Szántó A, Siminszky Z, Malik A, et al. Similarities and differences between pediatric and adult patients with systemic lupus erythematosus. Lupus. 2015;24:796–803.
63. Wulffraat NM, Sanders EAM, Kamphuis SSM, Rijkers GT, Kuis W, Lilien M, et al. Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus. Arthritis Rheum. 2001;44:728–31.
64. Jayne D, Tyndall A. Autologous stem cell transplantation for systemic lupus erythematosus. Lupus. 2004;13(5):359–65.
65. Chen J, Wang Y, Kunkel G, Zhao H, Xue H, Xie X, et al. Use of CD34+ autologous stem cell transplantation in the treatment of children with refractory systemic lupus erythematosus. Clin Rheumatol. 2005;24:464–8.
66. Su G, Luan Z, Wu F, Wang X, Tang X, Wu N, et al. Long-term follow-up of autologous stem cell transplantation for severe paediatric systemic lupus erythematosus. Clin Rheumatol. 2013;32:1727–34.
67. Abinun M. Haematopoietic stem cell transplantation for rheumatological conditions. Paediatr Child Health. 2011;21:558–62.
68. Lee AC, Al-Saad KK. Successful hematopoietic cell transplantation in a child with sickle cell disease and systemic lupus erythematosus. Bone Marrow Transplant. 2013;48(1):151–2.
69. Gur-Lavi M. Long-term remission with allogenic bone marrow transplantation in systemic lupus erythematosus. Arthritis Rheum. 1999;42(8):1777.
70. Matsumura R, Mochizuki S, Maruyama N, Morishita Y, Kawaguchi H, Okada S, et al. Bone marrow transplantation from a human leukocyte antigen-mismatched unrelated donor in a case with C1q deficiency associated with refractory systemic lupus erythematosus. Int J Hematol. 2021;113:302–7.
71. Olsson RF, Hagelberg S, Schiller B, Ringdén O, Truedsson L, Åhlin A. Allogeneic hematopoietic stem cell transplantation in the treatment of human C1q deficiency: the karolinska experience. Transplantation. 2016;100:1356–62.
72. Arkwright PD, Riley P, Hughes SM, Alachkar H, Wynn RF. Successful cure of C1q deficiency in human subjects treated with hematopoietic stem cell transplantation. J Allergy Clin Immunol. 2014;133:265–7.
73. Seo E, Lee BH, Lee JH, Park YS, Im HJ, Lee J. Hematopoietic stem cell transplantation in an infant with dedicator of cytokinesis 8

(DOCK8) deficiency associated with systemic lupus erythematosus: a case report. Medicine (Baltimore). 2021;100:e20866.
74. Foeldvari I. Update on juvenile systemic sclerosis. Curr Rheumatol Rep. 2015;17(3):18.
75. Reiff A, Weinberg KI, Triche T, Masinsin B, Mahadeo KM, Lin C-H, et al. T lymphocyte abnormalities in juvenile systemic sclerosis patients. Clin Immunol. 2013;149:146–55.
76. Fuschiotti P. T cells and cytokines in systemic sclerosis. Curr Opin Rheumatol. 2018;30(6):594–9.
77. Foeldvari I, Culpo R, Sperotto F, Anton J, Avcin T, Baildam E, et al. Consensus-based recommendations for the management of juvenile systemic sclerosis. Rheumatology (Oxford). 2021;60:1651–8.
78. Wulffraat NM, Vastert B, SHARE consortium. Time to share. Pediatr Rheumatol Online J. 2013;11(1):5.
79. Farge D. Stem cell transplantation for systemic sclerosis in Israel: a new star is rising. Isr Med Assoc J. 2020;22(2):116–8.
80. Farge D, Ait Abdallah N, Marjanovic Z, Del Papa N. Autologous stem cell transplantation in scleroderma. Presse Med. 2021;50:104065.
81. Cipriani P, Ruscitti P, Giacomelli R. Stem cell therapies for systemic sclerosis. Br J Haematol. 2015;168(3):328–37.
82. Martini A, Maccario R, Ravelli A, Montagna D, De Benedetti F, Bonetti F, et al. Marked and sustained improvement two years after autologous stem cell transplantation in a girl with systemic sclerosis. Arthritis Rheum. 1999;42:807–11.
83. Farge D, Passweg J, van Laar JM, Marjanovic Z, Besenthal C, Finke J, et al. Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. Ann Rheum Dis. 2004;63:974–81.
84. Nash RA, McSweeney PA, Nelson JL, Wener M, Georges GE, Langston AA, et al. Allogeneic marrow transplantation in patients with severe systemic sclerosis: resolution of dermal fibrosis. Arthritis Rheum. 2006;54:1982–6.
85. Loh Y, Oyama Y, Statkute L, Verda L, Quigley K, Yaung K, et al. Non-myeloablative allogeneic hematopoietic stem cell transplantation for severe systemic sclerosis: graft-versus-autoimmunity without graft-versus-host disease? Bone Marrow Transplant. 2007;39:435–7.
86. Miller PDE, Snowden JA, De Latour RP, Iacobelli S, Eikema D-J, Knol C, et al. Autoimmune cytopenias (AIC) following allogeneic haematopoietic stem cell transplant for acquired aplastic anaemia: a joint study of the Autoimmune Diseases and Severe Aplastic Anaemia Working Parties (ADWP/SAAWP) of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2020;55:441–51.
87. Dimitrova D, Nademi Z, Maccari ME, Ehl S, Uzel G, Tomoda T, et al. International retrospective study of allogeneic hematopoietic cell transplantation for activated PI3K-delta syndrome. J Allergy Clin Immunol. 2022;149:410–421.e417.
88. Neely JA, Dvorak CC, Pantell MS, Melton A, Huang JN, Shimano KA. Autoimmune cytopenias in pediatric hematopoietic cell transplant patients. Front Pediatr. 2019;7:171.
89. Barcellini W, Fattizzo B. The changing landscape of autoimmune hemolytic anemia. Front Immunol. 2020;11:946.
90. Berentsen S, Barcellini W. Autoimmune hemolytic anemias. N Engl J Med. 2021;385(15):1407–19.
91. Miano M. How I manage Evans syndrome and AIHA cases in children. Br J Haematol. 2016;172(4):524–34.
92. Neunert CE, Rose MJ. Romiplostim for the management of pediatric immune thrombocytopenia: drug development and current practice. Blood Adv. 2019;3(12):1907–15.
93. Kuter DJ. The biology of thrombopoietin and thrombopoietin receptor agonists. Int J Hematol. 2013;98(1):10–23.
94. Giordano P, Lassandro G, Barone A, Cesaro S, Fotzi I, Giona F, et al. Use of eltrombopag in children with chronic immune thrombocytopenia (ITP): a real life retrospective multicenter experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Front Med (Lausanne). 2020;7:66.
95. Passweg JR, Rabusin M, Musso M, Beguin Y, Cesaro S, Ehninger G, et al. Haematopoetic stem cell transplantation for refractory autoimmune cytopenia. Br J Haematol. 2004;125:749–55.
96. Urban C, Lackner H, Sovinz P, Benesch M, Schwinger W, Dornbusch HJ, et al. Successful unrelated cord blood transplantation in a 7-year-old boy with Evans syndrome refractory to immunosuppression and double autologous stem cell transplantation. Eur J Haematol. 2006;76:526–30.
97. Raetz E, Beatty PG, Adams RH. Treatment of severe Evans syndrome with an allogeneic cord blood transplant. Bone Marrow Transplant. 1997;20(5):427–9.
98. Sharrack B, Saccardi R, Alexander T, Badoglio M, Burman J, Farge D, et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). Bone Marrow Transplant. 2020;55:283–306.
99. Ceglie G, Papetti L, Figà Talamanca L, Lucarelli B, Algeri M, Gaspari S, et al. T-cell depleted HLA-haploidentical HSCT in a child with neuromyelitis optica. Ann Clin Transl Neurol. 2019;6:2110–3.
100. Waldman A, Ness J, Pohl D, Simone IL, Anlar B, Amato MP, et al. Pediatric multiple sclerosis: clinical features and outcome. Neurology. 2016;87:S74–81.
101. Tenembaum S, Chitnis T, Nakashima I, Collongues N, McKeon A, Levy M, et al. Neuromyelitis optica spectrum disorders in children and adolescents. Neurology. 2016;87:S59–66.
102. Margoni M, Rinaldi F, Perini P, Gallo P. Therapy of pediatric-onset multiple sclerosis: state of the art, challenges, and opportunities. Front Neurol. 2021;12:676095.
103. Gordon-Lipkin E, Banwell B. An update on multiple sclerosis in children: diagnosis, therapies, and prospects for the future. Expert Rev Clin Immunol. 2017;13(10):975–89.
104. Caprilli R, Angelucci E, Clemente V. Recent advances in the management of Crohn's disease. Dig Liver Dis. 2008;40(9):709–16.
105. Bamias G, Nyce MR, De La Rue SA, Cominelli F, Physicians ACo, Society AP New concepts in the pathophysiology of inflammatory bowel disease. Ann Intern Med. 2005;143:895–904.
106. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. JAMA Pediatr. 2015;169(11):1053–60.
107. Burt RK, Craig RM, Milanetti F, Quigley K, Gozdziak P, Bucha J, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up. Blood. 2010;116:6123–32.
108. Arnold DE, Nofal R, Wakefield C, Lehmberg K, Wustrau K, Albert MH, et al. Reduced-intensity/reduced-toxicity conditioning approaches are tolerated in XIAP deficiency but patients fare poorly with acute GVHD. J Clin Immunol. 2022;42(1):36–45.
109. Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K, et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. Gastroenterology. 2012;143:347–55.
110. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, et al. Human inborn errors of Immunity: 2019 update of the IUIS phenotypical classification. J Clin Immunol. 2020;40:66–81.
111. Slatter MA, Engelhardt KR, Burroughs LM, Arkwright PD, Nademi Z, Skoda-Smith S, et al. Hematopoietic stem cell transplantation for CTLA4 deficiency. J Allergy Clin Immunol. 2016;138:615.e611–619.e1.
112. Nademi Z, Slatter M, Gambineri E, Mannurita SC, Barge D, Hodges S, et al. Single centre experience of haematopoietic SCT for patients with immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. Bone Marrow Transplant. 2014;49:310–2.
113. Barzaghi F, Amaya Hernandez LC, Neven B, Ricci S, Kucuk ZY, Bleesing JJ, et al. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: an international multicenter

retrospective study. J Allergy Clin Immunol. 2018;141:1036–1049. e1035.
114. Neven B, Mamessier E, Bruneau J, Kaltenbach S, Kotlarz D, Suarez F, et al. A Mendelian predisposition to B-cell lymphoma caused by IL-10R deficiency. Blood. 2013;122:3713–22.
115. Lankester AC, Albert MH, Booth C, Gennery AR, Güngör T, Hönig M, et al. EBMT/ESID inborn errors working party guidelines for hematopoietic stem cell transplantation for inborn errors of immunity. Bone Marrow Transplant. 2021;56(9):2052–62.
116. Lum SH, Buddingh EP, Slatter MA, Lankester AC. Hematopoietic cell transplantation in monogenic autoimmune diseases. In: Burt RK, Farge D, Ruiz MA, Saccardi R, Snowden JA, editors. Hematopoietic stem cell transplantation and cellular therapies for autoimmune diseases, 1st ed. Boca Raton: CRC Press; 2021.
117. Chiesa R, Wang J, Blok H-J, Hazelaar S, Neven B, Moshous D, et al. Hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults. Blood. 2020;136:1201–11.
118. Duarte RF, Labopin M, Bader P, Basak GW, Bonini C, Chabannon C, et al. Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. Bone Marrow Transplant. 2019;54:1525–52.
119. Chan AY, Torgerson TR. Primary immune regulatory disorders: a growing universe of immune dysregulation. Curr Opin Allergy Clin Immunol. 2020;20(6):582–90.
120. Chan AY, Leiding JW, Liu X, Logan BR, Burroughs LM, Allenspach EJ, et al. Hematopoietic cell transplantation in patients with primary immune regulatory disorders (PIRD): a primary immune deficiency treatment consortium (PIDTC) survey. Front Immunol. 2020;11:239.
121. Swart JF, Delemarre EM, van Wijk F, Boelens J-J, Kuball J, van Laar JM, et al. Haematopoietic stem cell transplantation for autoimmune diseases. Nat Rev Rheumatol. 2017;13:244–56.
122. Milanetti F, Abinun M, Voltarelli JC, Burt RK. Autologous hematopoietic stem cell transplantation for childhood autoimmune disease. Pediatr Clin North Am. 2010;57:239–71.
123. Faraci M, Diesch T, Labopin M, Dalissier A, Lankester A, Gennery A, et al. Gonadal function after Busulfan compared with treosulfan in children and adolescents undergoing allogeneic hematopoietic stem cell transplant. Biol Blood Marrow Transplant. 2019;25:1786–91.
124. Slatter MA, Rao K, Abd Hamid IJ, Nademi Z, Chiesa R, Elfeky R, et al. Treosulfan and fludarabine conditioning for hematopoietic stem cell transplantation in children with primary immunodeficiency: UK experience. Biol Blood Marrow Transplant. 2018;24:529–36.
125. Locatelli F, Bauquet A, Palumbo G, Moretta F, Bertaina A. Negative depletion of α/β+ T cells and of CD19+ B lymphocytes: a novel frontier to optimize the effect of innate immunity in HLA-mismatched hematopoietic stem cell transplantation. Immunol Lett. 2013;155:21–3.
126. Bethge WA, Eyrich M, Mielke S, Meisel R, Niederwieser D, Schlegel PG, et al. Results of a multicenter phase I/II trial of TCRαβ and CD19-depleted haploidentical hematopoietic stem cell transplantation for adult and pediatric patients. Bone Marrow Transplant. 2022;57(3):423–430.
127. Greco R, Lorentino F, Albanese S, Lupo Stanghellini MT, Giglio F, Piemontese S, et al. Posttransplantation cyclophosphamide- and sirolimus-based graft-versus-host-disease prophylaxis in allogeneic stem cell transplant. Transplant Cell Ther. 2021;27:776.e771–776.e713.
128. Ruggeri A, Galimard J-E, Paina O, Fagioli F, Tbakhi A, Yesilipek A, et al. Outcomes of unmanipulated haploidentical transplantation using post-transplant cyclophosphamide (PT-Cy) in pediatric patients with acute lymphoblastic leukemia. Transplant Cell Ther. 2021;27:424.e421–9.
129. McCurdy SR, Luznik L. Post-transplantation cyclophosphamide for chimerism-based tolerance. Bone Marrow Transplant. 2019;54(Suppl 2):769–74.
130. Admiraal R, van Kesteren C, Jol-van der Zijde CM, Lankester AC, Bierings MB, Egberts TCG, et al. Association between anti-thymocyte globulin exposure and CD4+ immune reconstitution in paediatric haemopoietic cell transplantation: a multicentre, retrospective pharmacodynamic cohort analysis. Lancet Haematol. 2015;2:e194–203.
131. Admiraal R, Boelens JJ. Individualized conditioning regimes in cord blood transplantation: towards improved and predictable safety and efficacy. Expert Opin Biol Ther. 2016;16(6):801–13.
132. Admiraal R, Nierkens S, de Witte MA, Petersen EJ, Fleurke GJ, Verrest L, et al. Association between anti-thymocyte globulin exposure and survival outcomes in adult unrelated haemopoietic cell transplantation: a multicentre, retrospective, pharmacodynamic cohort analysis. Lancet Haematol. 2017;4:e183–91.
133. Admiraal R, Jol-van der Zijde CM, Furtado Silva JM, Knibbe CAJ, Lankester AC, Boelens JJ, et al. Population pharmacokinetics of alemtuzumab (Campath) in pediatric hematopoietic cell transplantation: towards individualized dosing to improve outcome. Clin Pharmacokinet. 2019;58:1609–20.
134. de Koning C, Admiraal R, Nierkens S, Boelens JJ. Immune reconstitution and outcomes after conditioning with anti-thymocyte-globulin in unrelated cord blood transplantation; the good, the bad, and the ugly. Stem Cell Investig. 2017;4:38.
135. Willemsen L, Jol-van der Zijde CM, Admiraal R, Putter H, Jansen-Hoogendijk AM, Ostaijen-ten Dam MM, et al. Impact of serotherapy on immune reconstitution and survival outcomes after stem cell transplantations in children: thymoglobulin versus alemtuzumab. Biol Blood Marrow Transplant. 2015;21:473–82.
136. Penack O, Peczynski C, Mohty M, Yakoub-Agha I, Styczynski J, Montoto S, et al. How much has allogeneic stem cell transplant-related mortality improved since the 1980s? A retrospective analysis from the EBMT. Blood Adv. 2020;4:6283–90.
137. Wang D, Zhang H, Liang J, Li X, Feng X, Wang H, et al. Allogeneic mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus: 4 years of experience. Cell Transplant. 2013;22:2267–77.
138. Zappia E, Casazza S, Pedemonte E, Benvenuto F, Bonanni I, Gerdoni E, et al. Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. Blood. 2005;106:1755–61.
139. Velier M, Daumas A, Simoncini S, Arcani R, Magalon J, Benyamine A, et al. Combining systemic and locally applied cellular therapies for the treatment of systemic sclerosis. Bone Marrow Transplant. 2021;57(1):17–22.
140. Uccelli A, Laroni A, Ali R, Battaglia MA, Blinkenberg M, Brundin L, et al. Safety, tolerability, and activity of mesenchymal stem cells versus placebo in multiple sclerosis (MESEMS): a phase 2, randomised, double-blind crossover trial. Lancet Neurol. 2021;20:917–29.
141. Romano M et al. Past, present, and future of regulatory T cell therapy in transplantation and autoimmunity. Front Immunol. 2019;10:43.
142. Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017;129:3322–31.
143. Rossig C. CAR T cell immunotherapy in hematology and beyond. Clin Immunol. 2018;186:54–8.
144. Jyothi MD, Flavell RA, Geiger TL. Targeting autoantigen-specific T cells and suppression of autoimmune encephalomyelitis with receptor-modified T lymphocytes. Nat Biotechnol. 2002;20(12):1215–20.
145. Mougiakakos D, Krönke G, Völkl S, Kretschmann S, Aigner M, Kharboutli S, et al. CD19-targeted CAR T cells in refractory systemic lupus erythematosus. N Engl J Med. 2021;385:567–9.
146. Sadeqi Nezhad M, Seifalian A, Bagheri N, Yaghoubi S, Karimi MH, Adbollahpour-Alitappeh M. Chimeric antigen receptor based therapy as a potential approach in autoimmune diseases: how close are we to the treatment? Front Immunol. 2020;11:603237.

147. Biasco L, Scala S, Basso Ricci L, Dionisio F, Baricordi C, Calabria A, et al. In vivo tracking of T cells in humans unveils decade-long survival and activity of genetically modified T memory stem cells. Sci Transl Med. 2015;7:273ra213.
148. Panchal N, Ghosh S, Booth C. T cell gene therapy to treat immunodeficiency. Br J Haematol. 2021;192(3):433–43.
149. Vago L, Oliveira G, Bondanza A, Noviello M, Soldati C, Ghio D, et al. T-cell suicide gene therapy prompts thymic renewal in adults after hematopoietic stem cell transplantation. Blood. 2012;120:1820–30.
150. Snowden JA, Panés J, Alexander T, Allez M, Ardizzone S, Dierickx D, et al. Autologous haematopoietic stem cell transplantation (AHSCT) in severe Crohn's disease: a review on behalf of ECCO and EBMT. J Crohns Colitis. 2018;12:476–88.
151. Snowden JA, Ansari A, Sachchithanantham S, Jackson G, Thompson N, Lobo A, et al. Autologous stem cell transplantation in severe treatment-resistant Crohn's disease: long-term follow-up of UK patients treated on compassionate basis. QJM. 2014;107:871–7.
152. López-García A, Rovira M, Jauregui-Amezaga A, Marín P, Barastegui R, Salas A, et al. Autologous haematopoietic stem cell transplantation for refractory Crohn's disease: efficacy in a single-centre cohort. J Crohns Colitis. 2017;11:1161–8.

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