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Current Trends in Paediatric Allogeneic Haematopoietic Stem Cell Transplantation: A Systematic Review

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Abstract

Allogeneic-Haematopoietic Stem Cell Transplantation (allo-HSCT) remains the only curative treatment option for many paediatric patients with severe and potentially fatal haematological diseases including leukaemia, primary immunodeficiency, sickle cell disease and thalassaemia. When a Matched Sibling Donor (MSD) is not available, Matched Unrelated Donor (MUD) and haploidentical transplants are alternative options, for which novel techniques have evolved rapidly in recent years.

We conducted a systematic literature review to identify patient outcome and donor availability trends in the last 10 years (January 2009-February 2019) for allo-HSCT in paediatric patients with malignant and non-malignant haematological disorders.

Ninety-nine records of research and real-world evidence had data on patient outcomes and/or donor availability. No comparative clinical outcomes data were found and interpretation of available clinical evidence is confounded by wide variation in practices. No clear differences in outcomes between haploidentical and MUD were observed. However, a substantial increase was found in the number of publications over recent years featuring haploidentical HSCTs, highlighting current research interest. Evidence relating to donor availability was sparse but did suggest that locating MUDs is challenging, especially for non-Caucasian ethnic groups.

Considering the complexity of decision-making, the lack of published data relating to paediatric allo-HSCT is remarkable. Further research is needed to generate high-quality evidence quantifying the comparative benefits of the various paediatric allo-HSCT techniques.

Keywords: Allogeneic haematopoietic stem cell transplantation; Systematic review; Paediatric; Clinical outcomes; Donor availability

Abbreviations

Allo-HSCT: Allogeneic-Haematopoietic Stem Cell Transplantation; CRD: Centre for Reviews and Dissemination; DFS: Disease-Free Survival; GvHD: Graft-Versus-Host Disease; HRQoL: Health-Related Quality of Life; HLA: Human Leukocyte Antigen; mMRD: Mismatched Related Donors; MRD: Matched Related Donors; MSD: Matched Sibling Donor; MUD: Matched Unrelated Donors; OS: Overall Survival; PICOS: Problem/Population, Intervention, Comparator/Control, Outcome, Study Design; PT-Cy: Post-Transplant Cyclophosphamide; UCB: Umbilical Cord Blood

Introduction

Allo-HSCT is a procedure to treat haematological disorders by replacing unhealthy blood-forming cells with healthy stem cells from a donor [1,2]. Malignant and non-malignant haematological disorders collectively contribute to a substantial global mortality and morbidity burden [3]. Many haematological disorders are diagnosed in childhood and allo-HSCT is often part of the paediatric treatment paradigm as it offers a potentially curative therapy. The most common indication for allo-HSCT in children is leukaemia-acute lymphoblastic leukaemia and acute myeloid leukaemia being the most frequently reported sub-types [4]. Other malignant and non-malignant indications include lymphoma, acquired sever aplastic anaemia, haemoglobinopathies, hereditary bone marrow failure syndromes, metabolic diseases and solid tumours [5].

The choice of allo-HSCT technique is largely determined by the availability of donor type [6]. The degree of mismatch between donor and recipient Human Leukocyte Antigen (HLA) alleles heavily influences the likelihood of successful transplant, with greater degrees of HLA mismatch historically associated with poorer Overall Survival (OS) rates, increased transplant-related mortality and Graft-Versus-Host Disease (GvHD)-a reaction of donor cells against host tissues [7].

In paediatrics and adults, MSDs are the preferred choice, providing high long-term survival and limited transplant-related complications [8] but are only available to ≤25% of patients [9]. For patients without access to an MSD, alternative types of allo-HSCT (Umbilical Cord Blood [UCB], MUD, haploidentical) are clinical options [10]. UCB as a donor source for allo-HSCT has the advantage of immediate availability, absence of risk to the donor and reduced risk of GvHD, but is limited by delayed post-transplant haematological recovery and immune reconstitution [11]. MUD grafts are traditionally

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associated with better outcomes than haploidentical, although modern advances in transplant techniques have resulted in significant improvement in patient outcomes with haploidentical HSCT [12]. The use of haploidentical donors has the advantage of rapid universal availability, provision of additional cells should they be needed and carries reduced associated costs and logistical challenges [13,14]. Early HSCT is particularly important in paediatrics presenting with serious or life-threatening infections associated with conditions such as severe primary immunodeficiencies, where life expectancy is rarely beyond 1 year [15].

The minimum matching criteria for MUDs adopted by many transplant centres is four (8/8 alleles; HLA-A, -B, -C and DRB1), five (10/10 alleles, including HLA-DQB1) and, less frequently, six loci (12/12 alleles [including DPB1]). If the choice is to proceed with a haploidentical donor (4/8, 5/10, 6/12 HLA match) the patient is often treated with complementary immuno-suppressive therapy to minimise bidirectional allo-reactivity, risk of graft rejection and GvHD.

A range of graft manipulation, prophylaxis and post-transplant immune suppression techniques for use alongside haploidentical HSCT have evolved over recent years and the choice of technique varies between countries and treatment centres. Unmanipulated haploidentical stem cell grafts with conventional MUD and MSD GvHD prophylaxis (e.g., a calcineurin inhibitor and methotrexate [16-19] are limited by the associated delay to immune reconstitution and high rates of graft failure and GvHD.

Several novel approaches have been developed to overcome these obstacles; some of the most successful methods include myeloablation and immunosuppressive conditioning followed by graft T-cell depletion [20], or the use of high-dose Post-Transplant Cyclophosphamide (PT-Cy) to selectively deplete allo-reactive T cells following T-cell replete (unmanipulated) haploidentical HSCT [21]. Another commonly used protocol is unmanipulated haploidentical HSCT based on immune tolerance induced by Granulocyte Colony Stimulating Factor (G-CSF) and Anti-human Thymocyte Globulin (ATG) [22-24].

Time to finding a suitable MUD from a database is a lengthy process and highly variable. Identifying a match can be difficult, especially for non-Caucasian patients or those from ethnic minorities [25]. The availability of haploidentical donors in most families means that ~95% of patients [26] have access to a donor, which makes them an attractive option especially for patients with imminently life-threatening disease, e.g., high-risk or relapsed malignant disease, or severe combined immunodeficiency [14,27].

To our knowledge, the recent literature of real-world outcomes for paediatric allo-HSCT techniques and evidence of donor availability in paediatric patients has not yet been comprehensively reviewed. The primary objective of this review was to identify current trends in paediatric allo-HSCT outcomes and donor availability.

Materials and Methods

A systematic search of the literature was conducted (following the Centre for Reviews and Dissemination [CRD, York, UK] guidance) to identify the most recent (last 10 years) literature on research and real-world evidence reporting clinical outcomes, donor availability, Health-Related Quality of Life (HRQoL) and economic evaluations in allo-HSCT for paediatric patients with malignant and non-malignant haematological disorders (note: data on clinical outcomes and donor availability was synthesised for this article, that on HRQoL and economic evaluations is reported elsewhere [28]).

Records were considered for review if they met eligibility criteria defined in the PICOS (Problem/Population, Intervention, Comparator/Control, Outcome, Study Design) elements [29] (Table S1). PubMed, Embase and Evidence Based Medicine Reviews through Ovid were searched (see Table S2 for details of search terms) and supplemented by bibliography hand-searches of relevant literature reviews, targeted searches of major conference and congress abstracts and health technology assessment websites.

The titles and abstracts of identified records were screened first, followed by full texts. Records were excluded from the review if they did not fulfil the PICOS criteria (Table S1) or if they lacked outcome data. Studies reporting on adult allo-HSCT patients were included when ≤15 studies per outcome category (i.e., clinical, HRQoL, donor availability, economic) were identified in paediatric populations.

Information about study design, patient characteristics and key outcome measures was extracted from all included records on clinical outcomes and donor availability. A qualitative synthesis of the evidence on clinical outcomes and donor availability was completed and is described in a narrative summary in the results.

Results

Systematic literature review

A total of 7,938 records were retrieved from the database searches. Following removal of duplicates, 4,932 records were title and abstract screened, of which 4,696 were removed from further analysis. The remaining 236 records were screened at full text; 126 were excluded at this stage and the reasons for exclusion are shown

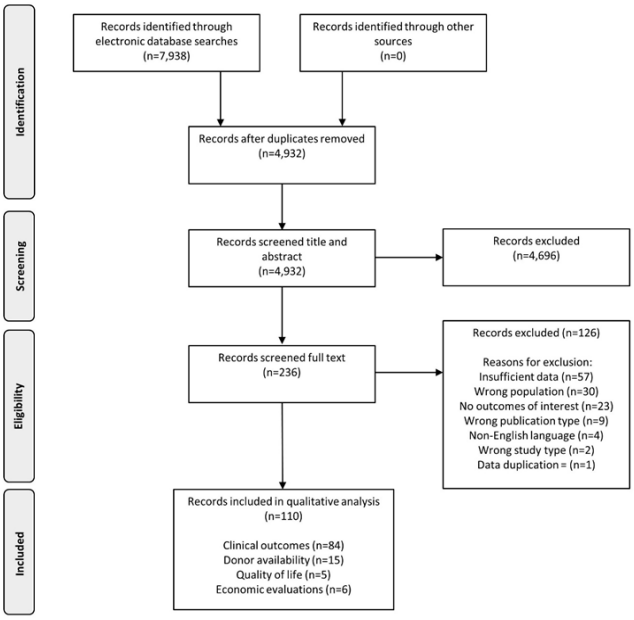
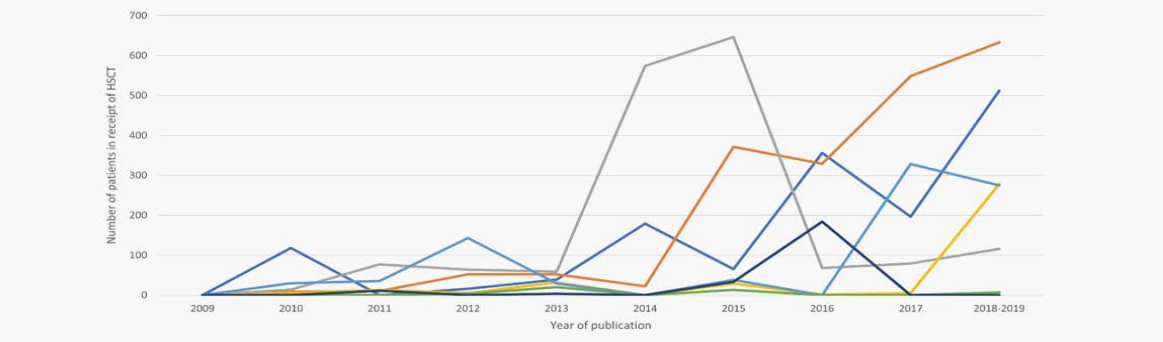


Figure 1: PRISMA diagram.



Patient population	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018-2019	Total
Haploidentical	0	118	0	16	39	179	65	356	196	512	1,481
MUD	0	8	10	52	52	22	371	329	548	633	2,025
MSD	0	14	77	64	59	574	646	68	79	116	1,697
MRD	0	30	35	143	29	0	38	0	328	275	878
mMUD	0	5	13	5	32	0	29	1	5	278	368
mMRD	0	0	0	3	20	0	13	0	0	7	43
UCB[a]	0	0	11	0	3	0	33	184	0	0	231
Other[b]	0	0	0	74	24	15	132	0	362	295	902
Total	0	175	146	357	258	790	1327	938	1518	2116	7,625

Figure 2: Number of HSCT recipients in the included studies (January 2009-February 2019). For illustrative purpose, the graph depicts the seven major donor types only. [a]UCB reported separately in studies as a donor source or a donor type, presented as defined by original publication. [b]Unrelated donor, mismatched donor, mismatched sibling donor, related donor, matched donor, sibling donor, other donor.

in the PRISMA diagram in (Figure 1). A total of 110 unique records (66 [59.5%] full text articles, 45 [40.5%] abstracts) reported at least one outcome of interest and were included in the final analysis, comprising: 84 reports on clinical outcomes, 15 on donor availability, 5 on HRQoL (not analysed in this report) and 6 economic evaluations (not analysed in this report). (Table S3) contains a full reference list of included reports.

The geographical distribution of the clinical outcome and donor availability studies was wide; the largest number were conducted in Europe (37/99, 37.3%) and Asia (34/99, 34.3%), followed by the Americas (23/99, 23.2%), Africa (3/99, 3.0%) and Australia (1/99, 1.0%). One study was intercontinental (1/99, 1.0%).

Most reports (76/99, 76.8%) presented data from retrospective analyses, 16 (16/99, 16.2%) from non-randomised controlled trials, 2 (2/99, 2.0%) from prospective surveys and 2 (2/99, 2.0%) from prospective observational (cohort) studies. One population model, 1 prospective single arm trial and 1 randomised control trial (1/99, 1.0% respectively) were included. Due to the marked heterogeneity of included studies and non-comparative nature of this review, an overview of report type, study type and population size were used to assess the quality of the evidence identified.

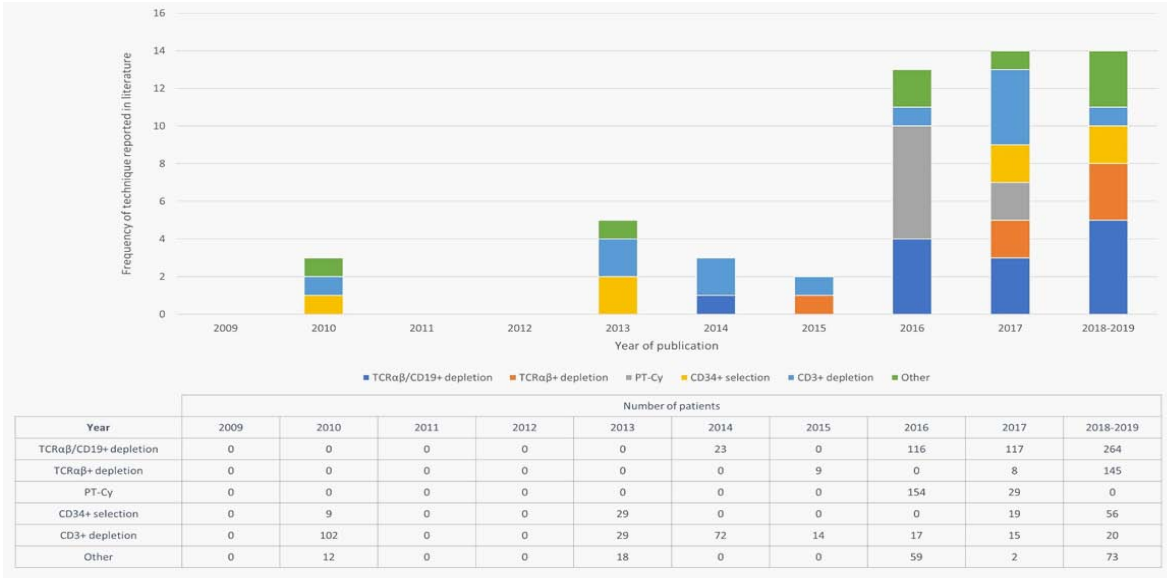
A summary of the key findings for both clinical outcomes and donor availability is presented hereafter. Findings for HRQoL and economic evaluations are reported elsewhere [28].

Clinical practice

Median age at HSCT was <1.0-19 years and gender distribution ranged between 18.9-65.2% female. The definition of 'paediatric' patients varied, ranging from patients ≤18 years-21 years. Over half of the included records (n=44, 52.4%) reported HSCT treatment of patient populations with non-malignant haematological disease, 39.3% (n=33 reports) with malignant haematological disease and 8.3% (n=7 reports) on mixed populations.

Studies used either single or multiple sources of haematological stem cells derived from bone marrow, peripheral blood stem cells and umbilical cord blood (Table 1). Single or multiple donor types were also used in each study; the most frequently reported donor types were MUD (26.5% of all patients treated with HSCT identified in this review), followed by MSD (22.2%) and haploidentical HSCT (19.4%). Other commonly reported donor types were Matched Related Donors (MRD) (11.5%), mMUD (4.8%) and Mismatched Related Donors (mMRD) (0.6%) (Table 1). The overall frequency of paediatric HSCTs reported in the included studies increased more than 12-fold between 2010 and 2018-2019 (Figure 2). Since 2016, greater numbers of haploidentical and MUD HSCTs relative to MSD have been reported (1,064, 1,540 and 263 patients respectively) in 2018-2019, 24.2% of paediatric patients were treated with haploidentical grafts, 29.9% with MUD grafts and 18.6% with MSD or MRD grafts.

HLA match distribution was described in 16.9% (15/89) of studies reporting haploidentical donors or MUD. The majority (7/11, 63.6%) of studies reporting haploidentical HLA matches reported "5-8/10" (alleles) and the remainder (4/11, 36.4%) reported "4-6/8" or "3-6/6". Almost all studies reporting MUD HLA matches (13/14, 92.9%) reported "9-10/10" or "10/10", with a single study reporting "8/8" (Table 1). Of the 50 studies reporting use of haploidentical as a donor type, 41 (1,481 patients) featured one or more graft manipulation and GvHD prophylaxis techniques (Table 1). The most frequently reported techniques were TCRαβ+/CD19+ depletion, followed by αβ T-cell depletion, CD3+ depletion, T-cell replete grafts with post-transplant cyclophosphamide (PT-Cy) and CD34+ selection. Notably, we categorised αβ T-cell depletion and TCRαβ+/CD19+ depletion separately where authors of reports did not specify CD19+ depletion as part of a combined regimen-however in reality these studies may employ parallel techniques.



	Number of patients									
Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018-2019
TCRαβ/CD19+ depletion	0	0	0	0	0	23	0	116	117	264
TCRαβ+ depletion	0	0	0	0	0	0	9	0	8	145
PT-Cy	0	0	0	0	0	0	0	154	29	0
CD34+ selection	0	9	0	0	29	0	0	0	19	56
CD3+ depletion	0	102	0	0	29	72	14	17	15	20
Other	0	12	0	0	18	0	0	59	2	73

Figure 3: Frequency of haploidentical HSCT techniques in the included studies (January 2009-February 2019).

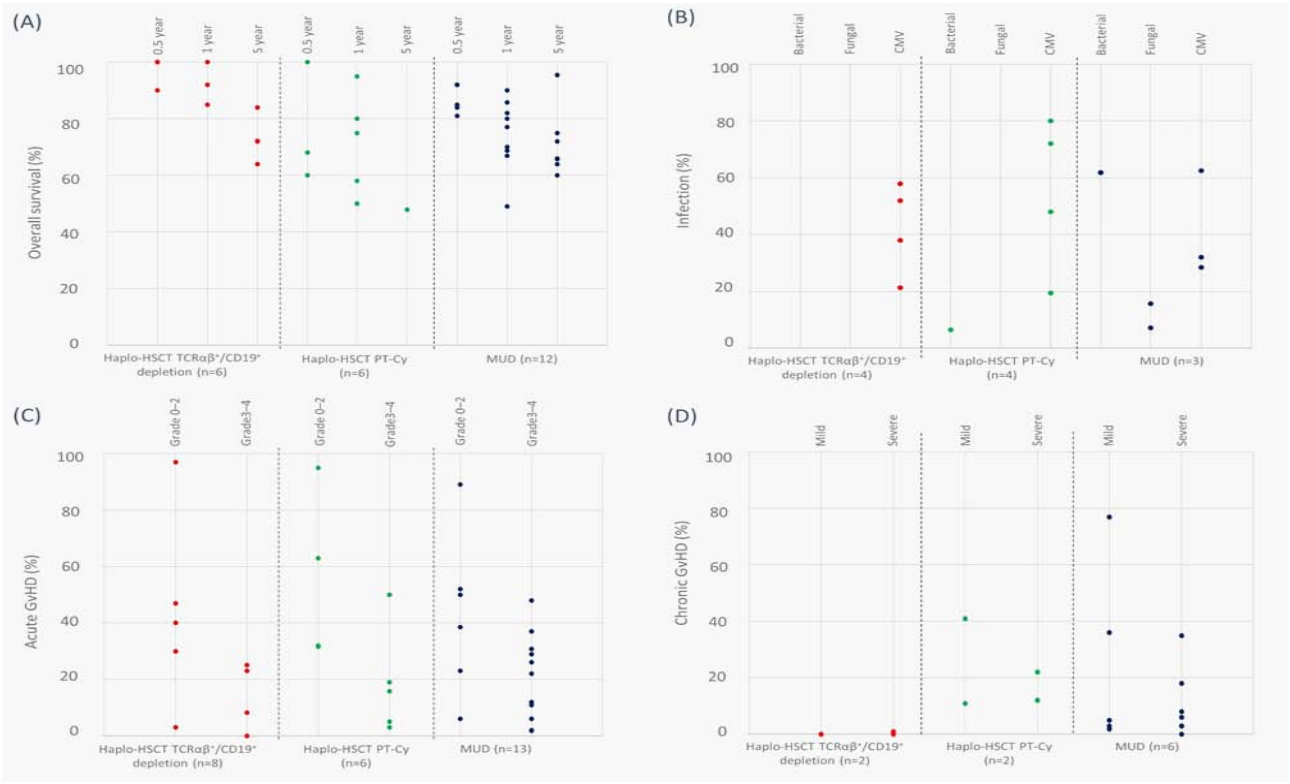


Figure 4: Comparative spread of outcome data between MUD, haploidentical with TCRαβ+/CD19+ depletion and haplo-PT-Cy. (A) Overall survival, (B) Infections, (C) Acute GvHD, (D) Chronic GvHD.

The number of haploidentical HSCT studies and the range of techniques reported have increased over the last 10 years (Figure 3). Notably, the majority of studies reporting TCRαβ+/CD19+ depletion, αβ T-cell depletion, PT-Cy, CD34+ selection and CD3+ depletion was published in the last 3 years (2015-2019). Overall, TCRαβ+/CD19+ depletion is the most frequently reported with the highest total patient number.

Clinical outcomes

Studies were too heterogenous to allow direct comparison and most were single institution, single arm studies. Generally, outcome ranges were wide across all studies, donor types and graft manipulation techniques, therefore common trends were difficult to

Table 1: Characteristics of included studies reporting clinical outcomes.

Stem cell source	Number of reports in which technology was applied (relative frequency, %)	Year of publication (range)	Number of patients treated with technology (% of total patients, n=6,634)
BM	56 (40.6)	2010-2018	3,481 (52.5)
UCB[a]	26 (18.8)	2012-2018	2,319 (35.0)
PBSC	56 (40.6)	2010-2019	834 (12.6)
Donor type	**Number of reports in which technology was applied (relative frequency, %)**	**Year of publication (range)**	**Number of patients treated with technology (% of total patients, n=7,625)**
Haploidentical	50 (27.9)	2010-2019	1,481 (19.4)
MUD	39 (21.8)	2010-2018	2,025 (26.6)
MSD	25 (14.0)	2010-2018	1,697 (22.2)
MRD	18 (10.1)	2010-2018	878 (11.5)
mMUD	15 (8.4)	2010-2018	368 (4.8)
mMRD	7 (3.9)	2012-2018	43 (0.6)
UCB[a]	5 (2.8)	2011-2016	231 (3.0)
Other[b]	20 (11.2)	2012-2019	902 (11.8)
Graft manipulation/GvHD prophylaxis techniques used for haplo-HSCT	**Number of reports in which technology was applied (relative frequency, %)**	**Year of publication (range)**	**Number of patients treated with technology (% of total patients, n=1,411)**
TCRαβ+/CD19+ depletion	14 (25.5)	2014-2018	520 (36.9)
TCRαβ+ depletion	6 (10.9)	2015-2018	162 (11.5)
PT-Cy	8 (14.5)	2016-2017	183 (13.0)
CD34+ selection	7 (12.7)	2010-2019	113 (8.0)
CD3+ depletion	12 (21.8)	2010-2018	269 (19.1)
Other[c]	8 (14.5)	2010-2018	164 (11.6)
HLA match distribution (haploidentical)	**Number of haploidentical studies reporting match type (relative frequency, %)**	**Year of publication (range)**	
"5-8/10"	7 (63.6)	2013-2018	
"4-6/8"	2 (18.2)	2010-2013	
"3-6/6"	2 (18.2)	2013-2016	
HLA match distribution (MUD)	**Number of MUD studies reporting match type (relative frequency, %)**	**Year of publication (range)**	
"10/10"	5 (35.7)	2015-2018	
"9-10/10"	8 (57.1)	2013-2018	
"8/8"	1 (7.1)	2011	

Abbreviations: BM: Bone Marrow; haplo: Haploidentical; HSCT: Haematopoietic Stem Cell Transplant; mMRD: Mismatched Related Donor; MRD: Matched Related Donor; MSD: Matched Sibling Donor; mMUD: Mismatched Unrelated Donor; MUD: Matched Unrelated Donor; PBSC: Peripheral Blood Stem Cells; PT-Cy: Post-Transplant Cyclophosphamide; UCB: Umbilical Cord Blood. Footnotes: [a]UCB reported separately in studies as a donor source or a donor type, presented as defined by original publication. [b]Unrelated donor, mismatched donor, mismatched sibling donor, related donor, matched donor, sibling donor, other donor. [c]CD3+/CD19+depletion, T-cell repletion, CD45RA-depletion and cryopreservation.

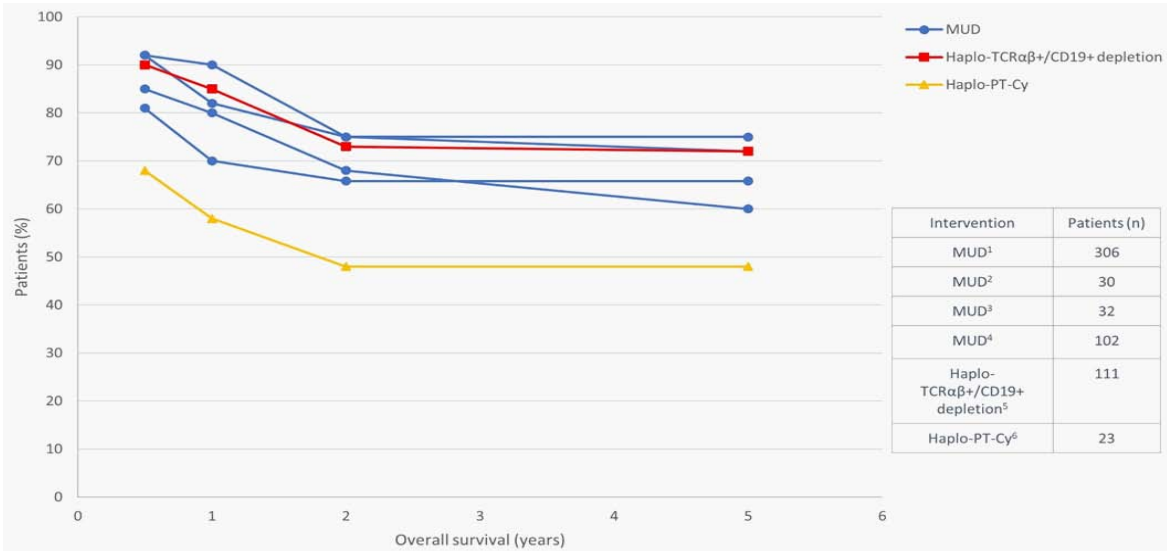


Figure 5: Overall survival of paediatric patients with malignant disease who received MUD or haploidentical HSCT (with PT-Cy or TCRαβ+/CD19+ depletion). [1]Peters *et al.,* 2015 [4], [2]Beier *et al.,* 2013 [27], [3]Erbey *et al.,* 2018 [28], [4]Bakhtair *et al.,* 2019 [29], [5]Merli *et al.,* 2018 [25], [6]Dufort *et al.,* 2016 [26].

identify (Table 2).

No discernible differences in clinical or safety outcomes were apparent between transplant modalities. Overall, engraftment rates across all studies ranged from 22-100 %, graft failure from 0-45 %, median days to neutrophil recovery 10-42 days and platelet recovery 10-45 days. Transplant-related mortality ranged from 1-100 % and

Table 2: HSCT outcomes of included studies reporting clinical outcomes.

Outcome category	All studies	Donor source				
		Haploidentical			MUD	MSD
		Other[a]	TCRαβ+/CD19+ depletion	PT-Cy		
	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)
Immune reconstitution and haematological recovery						
Engraftment, mean %	22-100 % (36)	22-100 % (12)	86-98 % (5)	68-94 % (4)	87-95 % (3)	90-94 % (2)
Graft failure, mean %	0-45 % (45)	1-45 % (14)	2-17 % (5)	2-6 % (3)	0-13 % (6)	0-10 % (5)
Neutrophil recovery, median days	10-42 (59)	10-15 (19)	12-16 (6)	14-18 (5)	14-22 (11)	11-21 (7)
Platelet recovery, median days	10-45 (42)	11-19 (13)	10-15 (3)	15-30 (4)	12-32 (9)	12-40 (5)
Survival and relapse outcomes, mean %						
Transplant-related mortality	1-100 % (42)[b]	4-33 % (9)	5-37 % (6)	13-26 % (3)	2-37 % (10)	5-17 % (4)
Relapse incidence (malignant disease)	2-73 % (36)	6-73 % (16)	12-40 % (3)	23-42 % (3)	16-32 % (6)	2–38% (4)
Overall survival at 6 months	60-100 % (41)	60-100 % (8)	90-100 % (2)	60-100 % (3)	81-92 % (4)	85-100 % (3)
Overall survival at 1 year	45-100 % (47)	45-100 % (11)	85-100 % (3)	50-95 % (5)	49-90 % (9)	78-100 % (5)
Overall survival at 5 year	29-100 % (45)	29-78 % (6)	64-84 % (5)	48% (1)	60-96 % (6)	76-100 % (6)
Disease-free survival at 6 months	68-100 % (19)	68-75 % (2)	83-100 % (4)	NR	85-90 % (2)	74-80 % (2)
Disease-free survival at 1 year	34-100 % (25)	38-64 % (4)	72-100 % (4)	69% (1)	75-77 % (2)	64-94 % (3)
Disease-free survival at 5 year	27-95 % (22)	27-87 % (4)	62-71 % (4)	NR	60-81 % (3)	74% (1)
Event-free survival at 6 months	42-100 % (15)	45-77 % (3)	100% (1)	42-94 % (2)	79-100 % (4)	80-100 % (2)
Event-free survival at 1 year	33-96 % (17)	40-60 % (4)	92% (1)	33-94 % (2)	70-77 % (4)	75-86 % (3)
Event-free survival at 5 year	34-83 % (19)	35% (1)	58-70 % (3)	NR	53-68 % (4)	55-87 % (4)
Graft-versus-host disease and infections, mean %						
Incidence of acute GvHD, grade 0-2	3-97 % (47)	16-93 % (8)	3-97 % (5)	32-95 % (4)	6-89 % (6)	7-89% (3)
Incidence of acute GvHD, grade 3-4	0-50 % (55)	7-36 % (7)	0-25 % (4)	3-50 % (5)	2-48 % (10)	4-15 % (4)
Incidence of chronic[c] GvHD, mild[d]	0-77 % (22)	0-40 % (4)	0% (1)	11-41 % (2)	2-77 % (5)	7-20 % (3)
Incidence of chronic[c] GvHD, severe[d]	0-35 % (25)	0-9 % (3)	0-1 % (2)	12-22 % (2)	0-35 % (6)	0-32 % (4)
Infections[e]	1-81 % (30)	4-81 % (8)	78-58 % (4)	6-80 % (4)	7-63 % (3)	6% (1)

relapse (for malignant disease) ranged from 2-73 %. Mean OS ranged from 60-100% at 6 months, 45-100 % at 1 year and 29-100 % at 5 years. Mean Disease-Free Survival (DFS) ranged from 68-100 % at 6 months, 34-100 % at 1 year and 27-95 % at 5 years. Mean event-free survival ranged from 42-100 % at 6 months, 33-96 % at 1 year and 34-83 % at 5 years. Incidence of acute GvHD ranged from 3-97 % for grade 1-2 and 0-50 % for grade 3-4. Incidence of mild chronic GvHD ranged from 0-77 %, of severe chronic GvHD from 0-35 %. Incidence of infection ranged from 1-80 %. The spread of OS, GvHD and infection outcome data for MUD, haploidentical HSCT with TCRαβ+/CD19+ depletion and haplo-PT-Cy HSCT is illustrated in (Figure 4).

Mean OS and DFS ranges for patients with malignant and non-malignant disease are presented in (Table 3). Outcome ranges were wide and varied and meaningful comparisons between disease background and transplant modalities could not be made due to study heterogeneity and low study number. However, we identified 6 studies in patients with malignant disease (604 patients, 7.9% of total patients treated with HSCT identified in this review) who received either MUD or haploidentical HSCT (with TCRαβ+/CD19+ graft depletion or PT-Cy) reporting OS at more than one timepoint up to 5 years [8,30-34]. Evidence from these studies suggest that regardless of donor source, risk of death is most acute during the first year after transplant, with survival typically plateauing during the second year (Figure 5).

Donor availability

Of the 15 studies (comprising >31,500 patients or donor registrants) reporting on donor availability in allo-HSCT, all reported

Table 3: HSCT outcomes of included studies reporting clinical outcomes by disease background.

Outcome category	Disease background					
	Malignant			Non-malignant		
	Haploidentical	MUD	MSD	Haploidentical	MUD	MSD
	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)	Outcomes range (number of studies reporting outcome)
Overall survival at 6 months	60-90 % (8)	81-100 % (4)	85-100 % (4)	82-100 % (4)	NR	100% (2)
Overall survival at 1 year	50-90 % (11)	67-90 % (5)	78-88 % (4)	80-100 % (4)	86% (1)	94-100 % (2)
Overall survival at 5 year	29-72 % (11)	60-75 % (5)	67-76 % (3)	75-84 % (2)	64-96 % (3)	86-100 % (3)
Disease-free survival at 6 months	68-90 % (3)	90% (1)	80% (1)	75-100 % (3)	85% (1)	NR
Disease-free survival at 1 year	64-78 % (3)	75% (1)	60% (1)	50-100 % (3)	77% (1)	64-94 % (2)
Disease-free survival at 5 year	27-70 % (3)	60-65 % (2)	60% (1)	38-69 % (2)	NR	NR

Abbreviations: MSD: Matched Sibling Donor; MUD: Matched Unrelated Donor; NR: Not Reported

on factors affecting the likelihood of donor selection, 7 reported length of donor search and 9 reported centre experiences of HSCT (Table S4). Two reports were specific to paediatric patients and the remainder (12 reports) included mixed age populations or did not specify patient age.

Three studies presented evidence that larger family size and greater number of siblings increases the probability of finding an MSD [35-37]. Two studies showed that considerable variation in the likelihood of finding an MSD is based on patient age, race and ethnicity (13-51 %) [35,38] and 5 studies reported ethnicity as a significant factor affecting MUD identification and transplant [36,39-42].

The time to finding an unrelated donor differed between studies and countries, with medians ranging between 44–140 days (reported in 3 studies [1,610 patients], [43-45]. One study reported that white patients and those with common haplotypes (≥ 1/2000; [46]) are significantly more likely to find a "10/10" MUD donor and proceed to transplant than non-white patients and those with uncommon haplotypes [39]. Higher donor registry attrition rates were found amongst racial and ethnic minorities compared with donors of white ethnicity (reported in 1 study, [47]); the most consistent factor associated with opting out of a registry being ambivalence about donation. Interestingly, 1 study (242 patients) comparing all transplant types suggested there were no significant differences between ethnic groups or haplotype when searching or proceeding to transplant [39].

Discussion

Literature published over the last decade reporting clinical outcomes in paediatric allo-HSCT is heterogenous and very little data exists on donor availability. Considerable variation was observed within and between, studies in terms of patient characteristics, study design and treatment modalities and available evidence on clinical outcomes is mostly observational. No randomised-controlled trials were identified from which to make indirect comparisons or quantitatively assess the relative treatment effects between donor types, or haploidentical HSCT graft manipulation and GvHD prophylaxis techniques. Firm conclusions were therefore difficult to draw, although several trends were identified.

This systematic literature review revealed an increased interest in paediatric haploidentical HSCT, however, whether this has translated into routine clinical practice remains unknown no comprehensive patient-registry studies reporting the proportion of paediatric allo-HSCT compared to other donor types in real-world routine practice were identified. Overall, in the included studies, the largest number of patients over the last 10 years were treated with MUD, followed by MSD and haploidentical HSCTS (Figure 2). However, since 2016, MUD and haploidentical HSCTs have been reported more frequently than MSD the highest numbers for both reported in 2018-19 (Figure 2). Our findings align with trends reported elsewhere in studies of both adult and paediatric patients, which describe a continued rapid increase in haploidentical grafts [48,49] and slower rates of growth for HSCT with other donor sources in recent years [49]. Smaller real-world studies also indicate that paediatric haploidentical HSCT is becoming more prevalent in routine practice; the EMBT activity survey report in 2017 shows the increasing use of haploidentical graft manipulation techniques [50] and a continued rapid increase in paediatric haploidentical grafts [51]. Another indication of the increasing relevance of paediatric haploidentical HSCT to routine practice is the upgrading of EBMT guidelines (2019), which stipulate the level of evidence and recommendations for haploidentical HSCT [10,13]. Based on the paucity of available data in the literature and absence of randomised controlled trials, it is not possible to compare survival or relapse outcomes by donor types, let alone segment outcomes by malignant *vs* non-malignant disease type. That said, for the 6 studies in patients with malignant disease reporting OS up to 5 years, no distinguishable differences in mortality or relapse incidence between TCRαβ+/CD19+ depleted grafts, PT-Cy and MUD treatment groups, or in survival outcomes between donor types were observed. For all studies, OS followed a similar trend, levelling-off at 2 years.

Patterns of acute GvHD also appeared similar across all reported donor types. Few studies overall reported infection rates stratified by donor type; those that did, reported wide ranges of infection rates from bacterial, fungal and viral organisms therefore conclusions about infection rates cannot be drawn other than that infection remains a significant issue in patients undergoing allo-HSCT, regardless of procedure selected and (presumably) prophylaxis used.

Donor availability can be a considerable issue if an MSD is not available and this should be factored into the decision-making process when establishing the most appropriate treatment pathway for individual allo-HSCT patients. Evidence suggests that patients with small family size, less common HLA haplotypes and those from non-white ethnic backgrounds face the greatest challenges in sourcing suitable HSC donors and are significantly more likely to have longer waiting times for transplantation or not receive an HSCT at all [35-39,46]. Whilst these issues are well known, the literature documenting donor availability is relatively sparse, perhaps reflecting the difficulties in analysing donor matches and consistent reporting of molecular typing.

Geographical distribution of included studies was wide, suggesting our findings are reflective of practices around the world, although we acknowledge a potential bias introduced by inclusion of English-language texts only [52]. In addition to the limitations on available head-to-head data in the field of paediatric allo-HSCT, this review highlights numerous reporting biases across the literature and a lack of consensus in defining therapy-specific terms and patient populations. Variability was identified in the definition of 'paediatric' patients, categorisation of UCB (as both a stem cell source and a donor type), assessment criteria for GvHD and the terms used for defining donor types. To avoid improper assumptions, we report data consistent with definitions given by authors and study centres.

Conclusion

The scarcity and heterogeneity of published literature on clinical outcomes and donor availability relating to paediatric allo-HSCT is striking considering the complexity of decision-making in this therapy area. The increased frequency of haploidentical HSCTs and associated graft manipulation and GvHD prophylaxis techniques reported in recent years, indicates that this treatment modality is becoming an increasingly commonly adopted option in the paediatric setting, conferring future benefits for donor availability. Available evidence indicates that treatment options are not well differentiated in terms transplant outcomes, survival, GvHD, or infection, highlighting the need.

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