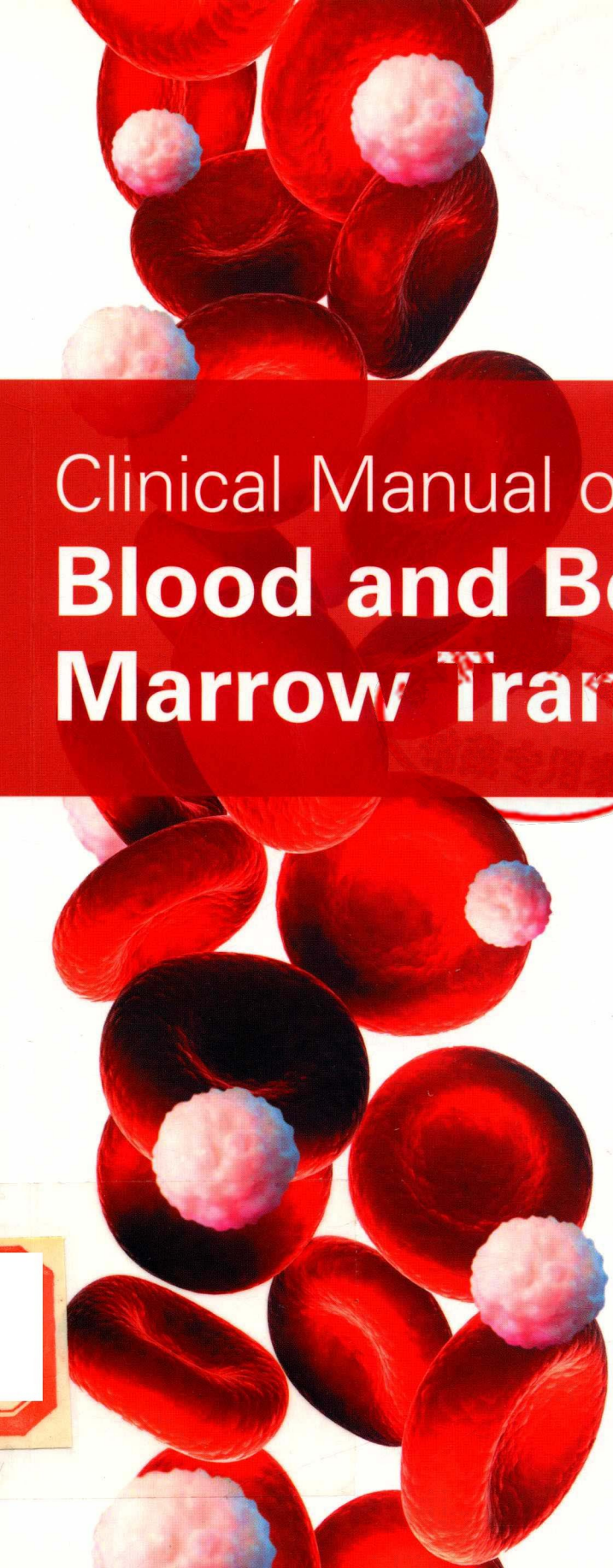

Clinical Manual of Blood and Bone Marrow Transplantation

Edited by
Syed A. Abutalib
and **Parameswaran Hari**

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Dedication

Syed A. Abutalib

I dedicate this book to my everlasting thirst for acquiring medical knowledge, my valued mentors who I strive to emulate in their compassion and advocacy on behalf of the patient, my junior colleagues who continue to teach and remind me that there is always more to learn, and sincerest thanks to my family for their support, most especially my daughter who is the love of my life.

Parameswaran Hari

I dedicate this work mostly to my father who advised me that "your work is to discover your work, and then, to give yourself to it wholeheartedly." Thereafter, I remain grateful to my mentors and mentees, my family and friends, and, above all, my patients who respectively contributed wisdom, equilibrium, and sense of purpose to my work.

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Preface

Cellular therapy in general, and hematopoietic cell transplantation in particular, has rapidly expanded in scope, practice, and basic understanding in the past 30 years. The indications now encompass a wide and diverse range of inherited and acquired disorders, malignant and non-malignant indications, conditioning therapies of varying intensities and numerous "constantly growing" strategies with novel cells, *ex vivo* processed cells and genetically re-engineered products. Concomitant advances in supportive and ancillary technologies now allow better immune matching, rapid diagnosis, and risk stratification of complications such as graft-versus-host disease and viral illnesses. Parallel development in treatments have also occurred that have reduced transplant related mortality and morbidity. Our saga of success in transplant has been built on the basis incremental small gains in technology. Assimilating and applying these new diagnostic and therapeutic modalities to daily patient care can be challenging and, often times, overwhelming.

We have attempted to describe the state of practice in hematopoietic cell transplantation in this manual. Developed with both the teacher and learner in mind, our book offers trainees and practitioners an excellent opportunity to enhance their knowledge and practice skills. Physicians in training, physicians in other disciplines who see transplant survivors, in fact all health care providers wishing to increase their knowledge in this sub-specialty area, will find the format engaging and robust with direct relevance to daily practice. Our book provides a concise "practical expert review" non-exhaustive format in 42 chapters with each chapter annotated with numerous practical headings for focused learning. Without the intention to write it as a text book, we attempted to include the diagnosis and management of as many transplant related practical questions faced by hematologists and transplant physicians. We hope that the accessible format will enable reader to become familiar with both the basics and nuances of clinical transplant care. The authors are experts in the field of hematopoietic cell transplant and cell therapy and have all followed the same basic format. Readers will find that this *Clinical Manual of Blood and Marrow Transplantation* has clear take-away points that are informative and valuable for clinical practice beyond transplant in the management of hematologic disorders. Ultimately, we hope that the professionals using this book will find the content of value and of benefit in their own interactions with patients.

Syed A. Abutalib, MD
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Contents

CHAPTER 1
Donor and graft selection strategy

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Introduction

A key component of the decision-making process of an allogeneic hematopoietic cell transplant is selection of the appropriate donor and graft. The best donor is an HLA-matched sibling. However, this option is available only for one third of patients. While the choice of a graft type is often determined by the transplant center preference and experience, there are advantages and disadvantages with each option.

What are the donor options?

In the absence of an HLA-matched sibling, an alternative donor is pursued. The options of donors are:

1. HLA-matched sibling (including one antigen/allelic mismatch)
2. Unrelated volunteer adult donor (MUD donor) (including one antigen/allelic mismatch).
3. Umbilical cord blood (UCB).
4. Haploidentical donor.

What are the graft sources?

Initial allogeneic transplants were done using bone marrow grafts. However, more options are currently available. The sources of hematopoietic grafts are:

1. Peripheral blood (PB).
2. Bone marrow (BM).
3. UCB.

Donor options

HLA matching is the most relevant factor when choosing a donor. Details of HLA typing are explained in Chapter 2. Some pertinent details are outlined next.

HLA matching for donor selection

HLA antigens are either "high expression" such as HLA-A, B, C (class I), DRB1 (class II), or "low expression" such as DQB1, DPB1, and DRB3/4/5 (all class II). The "high expression" antigens play a pivotal role in the transplant setting because of *high antigen density* on the cells. (We will refer to DRB1, DQB1, and DPB1 as DR, DQ, and DP, respectively, throughout this chapter.) An HLA-matched sibling is usually the preferred donor. A haploidentical donor (≥ 4/8 match) is defined as a first degree relative that shares at least one full haplotype with the recipient (i.e., it cannot be mismatched in both loci of any HLA alleles).

For unrelated donors, HLA matching at the allele level of HLA-A, B, C and DRB1 (8 alleles) is done according to National Marrow Donor Program (NMDP) recommendation. An ideal donor is 8/8 HLA-match. When there is more than one 8/8 HLA-matched donor, additional HLA matching at the DQ and DP may be helpful to identify a better candidate (see Chapter 2). For example, with DQ typing, 10/10 matched donors may be favored. On the other hand, DP matching is only seen in about 20% of 10/10 HLA-matched unrelated donors. Nevertheless, groups of "permissive" versus "non-permissive" mismatching have been identified based on cross-reactivity profiles. Permissive mismatching (found in ~70% of 10/10 HLA-matched donors) means two mismatched DP alleles will have a favorable outcome (less non-relapse mortality (NRM)) similar to

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a HLA-matched DP. The use of DQ and DP matching has not been universally recommended.

Each single locus mismatching in classical HLA loci (A, B, C, and DRB1) is associated with ~10% reduction in overall survival particularly for "early stage" disease. Earlier data showed that the worst "bone marrow" mismatches were HLA-A or HLA-DRB1 alleles, and the worst PB mismatch was HLA-C antigen. However, more recent data showed that the type (allele/antigen) and locus (HLA-A, B, C, or DR) of mismatch have equal impact on survival outcome. The only exception is a favorable outcome with the permissive mismatch of C*03:03/C*03:04.

HLA matching of UCB

Due to the immaturity of UCB T-cells, HLA matching is less stringent when using this graft source. UCB should be at least a 4/6 (A/B and DRB1) match using HLA-A and B (DNA-based low resolution/antigen level) and DRB1 (DNA-based high resolution/allele level). Outcomes of 4/6 UCB transplants are comparable to that of HLA-matched unrelated donors, albeit with an increased risk of NRM. When using a "single" unit of UCB, HLA-C antigen mismatching was shown to increase transplant-related mortality (TRM), particularly, if combined with HLA-DRB1 mismatching. When using double UCB units (as in most adult patients), there are no guidelines for HLA matching *between* the two units as long as minimum requirement of 4/6 HLA matching is present of each unit with the patient's HLA. Nevertheless, some centers prefer to use at least a 4/6 matching *between* the two units.

When a HLA-matched unrelated donor or a mismatched unit is used, it is essential to test the recipient for pre-formed donor-specific anti-HLA as described next.

HLA antibodies

About one-third (33%) of recipients have antibodies directed against HLA class I or II. However, only 5–10% of those recipients have "donor-specific" HLA antibodies (DSA). High titer (>1,000–2,000 MFI; mean fluorescent intensity) of DSA is associated with risk of graft rejection. Risk of graft rejection with DSA is higher when using NMA, compared to myeloablative regimens. Testing recipients for DSA is crucial when using HLA-mismatched, unrelated, haploidentical donors or mismatched cord units. Higher $CD34^+$ cell/kg in PB grafts compared to BM grafts may overcome negative impact of DSA, particularly when the titer is considered low, that is, <1,000 MFI.

How is DSA tested?

HLA antibody testing is done by initial screening of the recipient's serum using the "Panel Reactive Antigen" (PRA) assay. PRA determines the percentage of random people's sera against which the recipient could have antibodies. If PRA is positive, "Single Antigen Beads" (SAB) test is performed to identify whether the antibodies are against DSA or not (requires blood test from the donor). DSA may be mitigated by therapeutic plasma exchange (TPE), rituximab, bortezomib, and/or intravenous immunoglobulin.

The following is a description of the pros and cons with each of the donor options.

HLA-matched sibling

An HLA-matched sibling is favored in most cases, if available. Any full biological sibling (same biologic parents) of the patient would have a 25% chance of being fully HLA-matched, 25% of being HLA-non-matched and 50% of being HLA-haploidentical matched. DSA testing is not required in the setting of HLA-MSD. In addition, another advantage of a HLA-MSD is that he/she would be readily available for graft procurement for the potential need for future cell donations such as donor lymphocyte infusion (DLI) or a $CD34^+$ cell boost-"graft boost".

Unrelated volunteer adult donor (MUD donor)

When a fully HLA-MSD is not available, a HLA-MUD donor is sought through registries. In the United States, the NMDP represents a major source for volunteer donors. In addition, The Bone Marrow Donors Worldwide (BMDW) organization has data for over 25 million volunteer donors. Once again, the ideal donor is 8/8 HLA-matched with the patient. HLA-MUD donors are typically available for donation after about 8 weeks but may not be available for another cell donation for DLI or graft boost. Thus, transplant centers may opt to store an extra portion of the HLA-MUD graft (if feasible) for future use.

UCB

When a fully HLA-matched donor (whether a MSD or MUD donor) is not available, an UCB donor can be considered. UCB would be promptly available, but is not available again for DLI or graft boost. More details on UCB use is outlined below under graft sources.

HLA-haploidentical donor (haplo donor)

Recent introduction of post-transplant cyclophosphamide (PTCy) made HLA-haploidentical transplant a feasible option even in a center not specialized on this type of transplant. When a fully HLA-matched donor (whether a MSD or MUD donor) is not available, a haplo donor can be considered. A haplo donor is typically a first degree relative like a parent, a child or a sibling. The majority of patients have a haplo donor (exceptions include adopted and old patients with no children). While the haplo donor would be readily

available for the donation transplant centers with no adequate expertise in performing HLA-haploidentical transplants may opt to use HLA-mismatched from unrelated donors. The choice between haplo- and UCB- transplant often depends on the center preference and experience. The choice between UCB and haploidentical transplant remains controversial until the CTN 1101 clinical trial comparing haplo BM *vs* UCB with reduced intensity regimen, is completed.

Clinical differences among different types of donors are summarized in Table 1.1.

Graft composition

There are biological differences among the three sources of grafts (PB, BM and UCB) due to their different composition. These grafts are primarily composed of:

- $CD34^+$ cells, which make ~1% of the entire graft composition.
- Lymphocytes (mainly T-cells, and also B-cells and natural killer (NK) cells).
- Myeloid precursors.
- Monocytes (with potential for cytokine release).
- Other cells (e.g., endothelial progenitor cells and mesenchymal cells).

The $CD34^+$ cell dose is the primary determinant of successful engraftment. However, other components (in particular, the T-cells = $CD3^+$ cells) play pivotal roles in transplant outcomes. Simply stated, $CD3^+$ cells (T-cells) mediate the following four immunological processes:

1 Engraftment.
2 Immune reconstitution to prevent infection.
3 Graft-versus-tumor (GvT) effect to prevent relapse.
4 Graft-versus-host-disease (GvHD).

While engraftment, immune reconstitution, and GvT are favorable processes, GvHD is not.

PB graft

Although the initial transplants were done with BM grafts, PB grafts are now more commonly used. Main advantages of using PB grafts are faster and more secure engraftment (thus preferred for NMA and RIC regimens) and immune reconstitution, and less relapses (via GvT effect). However, chronic GvHD (cGvHD) continues to be a major long-term complication of PB grafts.

A PB graft is collected by apheresis procedure. Typically, donors receive growth factor injection for 4 days and then undergo leukapheresis for 1–2 days. The recommended $CD34^+$ cell dose in a PB graft is at least 4×10^6 $CD34^+$ cells/kg of recipient weight, while a dose of $< 2 \times 10^6$ $CD34^+$ cells/kg is discouraged to avoid risk of engraftment failure (See chapters 5 and 6).

BM graft

BM was the initial graft source used for allogeneic transplantation. BM grafts, by virtue of having less T-cells, have higher risk of engraftment failure (particularly when using NMA conditioning regimens), delayed immune reconstitution, and potential risk of neoplastic disease relapse (less GvT effect). However, they are associated with less risk of cGvHD and clinical trials have shown equivalent survival outcomes when compared with PB in hematologic malignancies.

BM is harvested in the operating room under general anesthesia. It is typically a 1-day surgery with the risks of complications common to general anesthesia, as well as bleeding, pain, and, rarely, traumatic surgical injury. The recommended cell dose in a BM graft is 4×10^8 TNC

Table 1.1 Comparison of the different graft sources.

	HLA-MSD	HLA-MUD	Haplo Donor	UCB
Priority	First Priority	First alternative	Next alternative	Next alternative
Availability	Readily available	Procurement time of 4–8 weeks or longer	Readily available	Promptly available
Cost	Donor testing and collection	Registry search, donor testing and collection	Donor testing and collection	Expensive: A single UCB unit is ~$30,000 –$50,000
DLI and graft boost	Available	May be available	Available	NOT available*
Graft manipulation trials	Donor available to consent	Requires Registry approval	Donor available to consent	NOT possible*

*Once thawed, the whole UCB unit is infused and generally not amenable for cellular manipulation in usual circumstances.

(total nucleated cells)/kg of recipient weight for hematologic malignancies. A dose of $<2\times10^8$ TNC/kg is discouraged. The TNC (rather than the $CD34^+$ cell count) is used to determinate the cell dose in the BM graft since the interim cell dose evaluation (during the harvest procedure) is routinely done using the quick hemocytometer cell counter of TNC.

Why is BM graft is preferred in children with hematologic malignancies?

In children, BM graft is used more than PB mainly to avoid the long-term complications of cGvHD. The risk of engraftment failure in children is less with BM graft as they always receive enough $CD34^+$ cells (due to their small body weight compared to the donor). Children may also tolerate infectious complications (if delayed immune reconstitution) better than adults, who often have medical comorbidities. The risk of relapse of neoplastic diseases (by virtue of less GvT) of the BM graft may be reduced by myeloablative regimens, which children can tolerate better than adults.

UCB graft

UCB units are cryopreserved (voluntarily donated) in several cord banks. UCB banking is recommended for public use. Storing UCB for personal use (i.e., reserved for the same baby if he/she develops disease in the future) is generally discouraged, because the probability of a newborn using his/her own UCB is too small, around 0.04–0.001%. While cord blood baking started in the 1980s in the United States, FDA regulations have only been imposed since 2011. Any UCB unit stored without conforming with the FDA regulations issued in late 2011 is considered "unlicensed", and its use is currently available only under FDA approval (considered investigational use). Units stored according to the FDA regulations are "licensed," and are available for routine use in the United States. One of the advantages of UCB units is that they are promptly available. They are typically of small volume with 1 log fewer TNCs and $CD34^+$ cells/recipient weight (compared to PB and BM grafts). However, for most adults, 2 units (double cord transplant) are used for a successful transplant. When double cord units are used, eventually only one UCB engrafts and the other one vanishes after providing cellular immune support during the early post-transplant time. UCB has more immature T-cells and, thus, is less immunologically reactive. Consequently, they are associated with higher risk of engraftment failure (particularly with NMA regimen), delayed immune reconstitution and potential for neoplastic disease relapse (limited GvT effect). The risk of GvHD with UCB depends on the degree of HLA disparity with the recipient. Due to the immaturity of the cord blood T-cells, HLA matching is less restrictive. An ideal UCB unit should have at least 3×10^7 TNC/kg of recipient weight. When performing a double UCB transplant in adults, each unit has to have at least 1.5×10^7 TNC/kg of recipient weight. Since the $CD34^+$ cell dose in the UCB is about a log less than that in PB or BM graft, at an average of 3×10^5/kg (~1% of TNC) for an adult, slow engraftment is expected. It is also to be noted that UCB is typically negative for antibodies to CMV. In routine clinical practice (outside clinical trials), UCB is not available for future use (e.g., DLI).

Differences among the three sources of graft sources are summarized in Table 1.2.

Which graft type should I use?

Although several transplant centers tend to use one type of graft more than another, it is often prudent to consider several factors when selecting the type of the graft for each individual patient. As a general rule, UCB or haploidentical graft are typically reserved for recipients with no available HLA-matched donors. The decision-making to choose between PB and BM is summarized in Table 1.3.

Non-HLA factors

What if more than one HLA-matched donor is available?

HLA matching is the most relevant factor when choosing a donor. However, the following factors are to be considered when there is more than one equivalent donor. The order of preference of these factors is often based on institutional preference.

1. CMV status of the donor and patient.
2. ABO blood matching with the patient.
3. Gender of the donor.
4. Age of the donor.
5. Weight discrepancy between the donor and the patient.
6. Availability (domestic or international) and timeframe of availability.
7. Killer cell Immunoglobulin-like Receptors (KIR) status of the donor using techniques such as KIR B content score.

CMV status

Most of the population acquire CMV infection when young and remain seropositive for life. CMV remains dormant in leukocytes and can be re-activated when the host becomes immunocompromised. For a CMV negative patient, ideally, a CMV negative donor should be used, whenever possible. However, for patients who are CMV positive, either CMV negative or positive donor can be used. Some centers prefer to use CMV positive donors for CMV positive patients (i.e., CMV matching) to allow the transfer of CMV immune lymphocytes (from the donor) to the patient to combat post-transplant CMV reactivation. The latter approach, although not systematically studied, may be beneficial with T-cell depleted transplants (in particular with anti-thymocyte