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Donor Registries and Search Strategies

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Summary

The optimal donor of hematopoietic progenitor cells shares alleles of the major histocompatibility genes with the recipient. This chapter describes the strategies aimed at identifying such a matched donor from registries of volunteers or from umbilical cord blood banks.

Keywords

Hematopoietic progenitor cell transplantation; histocompatibility; human leukocyte antigen; registries; cord blood banks; histocompatibility; unrelated donor search

1. Introduction

Transplantation of hematopoietic progenitor cells (HPC) is one therapy for a variety of fatal blood diseases such as acute myeloid leukemia and aplastic anemia (1). To provide the best chance for an optimal outcome to a transplant, the patient (i.e., the recipient) and the cell donor must express the same histocompatibility molecules on their cell surfaces (i.e., be “matched”). In humans, the major histocompatibility molecules are the human leukocyte antigens (HLA), a highly polymorphic family of six proteins termed HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP. The genes encoding each HLA protein and their alleles are inherited in traditional Mendelian fashion. Because of the extensive allelic diversity in the human population, a patient requiring a HPC transplant is most likely to find a match among their siblings. However, unrelated donors are the source of HPC for the approximately 70% of patients who do not have a suitable family donor. To facilitate the search for a matched unrelated donor, many countries have established registries of volunteers who offer to provide HPC if matched to a searching patient (2),(3). An alternative source of matched HPC is umbilical cord blood which has been banked for public use (4). This chapter focuses on the procedures for an unrelated donor/umbilical cord blood search and discusses strategies that might be employed to find the optimal HLA matched volunteer donor or umbilical cord blood unit for a specific patient.

2. Materials

2.1. Web sites useful in search

1. Bone Marrow Donors Worldwide: This web site (<http://www.bmdw.org/>) provides a comprehensive listing of almost all registries and cord blood banks in the world

and their contact information. It also provides the tools to perform an initial search of a single worldwide database of donors to assess the likelihood of identifying a matched donor (5). This database does not substitute, however, for a search of a specific registry or cord blood bank because it is only a snapshot of each registry/bank at one recent time and does not directly allow access to specific donors/cord blood units for further testing.

2. HLA nomenclature and allele designations: The web site, <http://hla.alleles.org/nomenclature/>, is the World Health Organization-designated HLA nomenclature web site and it includes both current and previous HLA designations (6),(7). The IMmunoGeneTics/HLA web site (<http://www.ebi.ac.uk/imgt/hla/>) is a source of information on each HLA allele including whether the sequence has been reported more than once (i.e., has been confirmed) and the race/ethnicity of the individuals in whom the allele was first identified (8). It provides tools to compare HLA sequences and provides a listing of alleles and genotypes that can not be distinguished from one another (i.e., are ambiguous) based on the nucleotide sequence of their most variable exons. It also provides a tool to link serologic and DNA-based HLA assignments based on an HLA “dictionary” (9).
3. Allele and haplotype frequencies: The frequencies of alleles and haplotypes (see Note 1) within the U.S. National Marrow Donor Program (NMDP) registry can be found at <http://bioinformatics.nmdp.org/> (see Note 2) (10). A list of rare alleles identifies alleles that have never been observed or have seldom been observed within the NMDP registry. This site also includes a tool to identify the alleles that are contained within the letter codes used to report HLA types (e.g., DRB1*04:AB where AB indicates 01 or 02 defining the assignment DRB1*04:01 or DRB1*04:02)(7). Two sources of world-wide allele frequencies are <http://www.allelefreqencies.net> (11) and <http://www.pypop.org/popdata/>(12). Tools to predict the frequencies of specific haplotypes can be found at <http://www.hlaexplorer.net> and <http://www.haplostats.org/home.do>.

3. Methods

3.1 HLA typing of patient and family

1. Obtain a biological sample from the patient and from nuclear family members if transplantation is being considered as a potential treatment option (Note 3) and perform HLA typing (Note 4). If available, include parents of the patient, siblings, and biological children. The patient should be typed for HLA-A,-B, -C, -DR, -DQ (Note 5) at allele or high resolution (Note 6). The resolution of the typing of the family members should be sufficient to clearly distinguish the HLA types segregating in the family (Note 7).

¹A haplotype is the combinations of HLA alleles that are found on a single copy of chromosome 6. A haplotype may refer to a combination of two or more loci. Some allele combinations such as the combination of DR and DQ alleles found on a haplotype or the combination of HLA-B and HLA-C alleles found on a haplotype can be predicted based on previous population studies. For example, haplotypes with DRB1*01:01 almost always carry DQB1*05:01. Tables of these associations can be found at <http://bioinformatics.nmdp.org/> and at <http://hlaexplorer.net>.

²The excel files on this web site can be filtered and sorted.

³It is important to evaluate the likelihood of finding a suitable HPC donor early during the initial evaluation of the patient when various treatment options are being considered. The outcome of a transplant is more favorable when the patient is transplanted early in the course of their disease (13).

⁴See chapters on HLA typing for more information on the methodology. Blood may not be the best sample source for some patients because of the low number of circulating white cells, because of the possibility of mutations in the HLA genes due to the unstable nature of tumors, or because of the presence of transfused cells from another individual. In these cases, a buccal swab or hair follicles might be the preferred sample source.

2. If sufficient family members are available, confirm the HLA assignments of the patient through observing the same assignments in other family members, identify the HLA types carried by each haplotype segregating in the family (Note 8), and determine if there is a family member who is HLA matched. The latter should be further evaluated to determine if they might serve as a HPC donor (see Note 9).
3. Perform an unrelated donor and umbilical cord blood search as described below so that these options for treatment of the patient can be considered.

3.2 Designing an unrelated donor search strategy

1. Begin by evaluating whether the patient's HLA assignments are complete. For potential 8/8 matches, the typing must include HLA loci HLA-A, -B, -C and – DRB1 (see Note 10). In case 10/10 matches are preferred, the typing must include HLA-A, -B, -C, -DRB1, and -DQB1 assignments. Also determine if the level of typing (i.e., the resolution of the typing) of the patient is adequate (see Note 11).
2. Examine the HLA type of the patient to identify any uncommon or unexpected assignments (See Note 12). This step evaluates the accuracy of the HLA assignments.
3. Establish the patient's HLA haplotypes (See Note 13).

⁵DRB1 and DQB1 genes specify one polypeptide of the DR and DQ heterodimers. These genes are routinely typed during donor selection (14). The DRA and DQA1 genes are not usually typed as they are less polymorphic and provide only limited additional information. The secondary DRB loci, DRB3, DRB4, and DRB5, are often typed. One purpose for typing the HLA loci suggested is to provide further support for the HLA assignments. Specific associations are found between: (1) DRB1 and DQB1 alleles (e.g., DRB1*01:01 is found predominantly associated with DQB1*05:01); (2) HLA-B and -C alleles (e.g., B*07:02 with C*07:02) and (3) DRB1 and the secondary DRB loci (DRB1*15:01 with DRB5 alleles). These associations should be consistent with the HLA assignments.

⁶Allelic resolution is defined as a DNA-based typing result that is consistent with a single allele. An allele is defined as a unique nucleotide sequence for a gene as defined by the use of all of the digits in a current allele name. High resolution typing is defined as a typing which includes alternative alleles that specify the same protein sequence for the region of the HLA molecule that forms the peptide binding site. The peptide binding site is composed of the amino-terminal domains of the HLA proteins (i.e., alpha1 and alpha2 domains for HLA class I molecules and alpha1 and beta1 domains for HLA class II molecules). This is the region that binds self or foreign peptides and that is recognized by T cell receptors. High resolution may also exclude alleles that are not expressed as cell-surface proteins, especially if these null alleles are thought to be common.

⁷In general, low resolution HLA typing may be used for typing the patient's family members except in the cases where the parents are not available or where similar alleles are segregating in the family. A low resolution DNA-based typing result is at the level of the digits comprising the first field in the DNA-based nomenclature (e.g., A*11; B*07).

⁸Haplotypes are defined by segregation in the family. For example, father is typed as A*01, A*02, B*07, B*08; mother as A*11, A*24, B*18, B*35; sib 1 as A*01, A*24, B*08, B*18; and sib 2 as A*01, A*11, B*08, B*35. Based on segregation, the haplotypes are A*01-B*08, A*02-B*07, A*11-B*35, and A*24-B*18.

⁹If there is not a suitable match in the nuclear family, it may be possible to find a match in the extended family (e.g., aunts, uncles, cousins) (15). This is possible if the patient carries a common haplotype which might have been inherited by chance in the extended family. It is also possible if there is a history of consanguinity in the family (e.g., cousin-cousin marriages) or if there are other close family relationships (e.g. two siblings from one family married to two siblings from another family).

¹⁰8/8 means 2 alleles at 4 loci, usually defined as HLA-A, -B, -C, and DRB1.

¹¹Low or intermediate resolution typing will only provide a rough indication of possible donors. Patient typing at this resolution should not be used for an unrelated donor search. Time and money may be wasted if donors with the highest chance of being identical with the patient are not rapidly selected based on the patient's allele/high resolution typing assignment.

¹²It can be useful to know whether the patient has an allele that is rare or an unexpected allele combination as this may be a typing error. Rare alleles in patients should always be confirmed either in the family (i.e., by finding another family member carrying the same rare allele) or by using a different typing technique or reagent set. To know whether the patient has a rare allele is also important as it may affect the likelihood of finding a perfectly matched donor. If no potentially identical donor is available, it is best to look for a donor who is identical for all alleles except the one rare allele. It is also important to realize that there are alleles that may be rare or uncommon in all but one ethnic group. In this case, finding a matched donor can be greatly facilitated by selecting potential donors from the ethnic group in which your patient's allele is less rare or even common.

Furthermore, it may be very difficult to find donors if the patient has a rare HLA association (e.g., HLA-B + HLA-C allele association) and this needs to be identified by using HLA haplotype frequency tables. For example, if the patient has a rare HLA-B + HLA-C association and no potentially identical donors are present, one can substitute the HLA-B allele for another allele that is commonly associated with the patient's HLA-C allele. See Section 3.5 for more information on search strategies to find a mismatched donor.

4. Determine the frequency of the patient's HLA alleles and haplotypes in various ethnic populations based on web sites listing the frequencies of alleles and haplotypes. Table 1a provides an example of the evaluation of the patient's HLA assignments in preparation for a search.

3.3 Submitting a search request to a national or international registry

1. An unrelated donor or umbilical cord blood search should be initiated to identify donors and cord blood units whose HLA typing is potentially identical to the patient's (See Notes 14 and 15).
2. Collect the following information about the patient: HLA typing data, preferably including the patient's HLA haplotypes; date of birth; diagnosis date; gender; weight; cytomegalovirus (CMV) status; ethnicity (see Note 16).
3. Determine the parameters of the search including the type of search to be performed i.e., adult progenitor cell donor, cord blood unit or both (see Note 17); urgency of the search; the specific HLA loci to be considered during matching; and whether or not mismatches are acceptable. These criteria are found in the transplant center protocol (see Note 18).
4. Perform a search of Bone Marrow Donors Worldwide (BMDW) which provides you with a comprehensive overview of almost all HPC sources worldwide (see Notes 19 and 20).
5. Complete a search request form and submit the search request form to all registries of interest or electronically enter the patient's information directly using software or web access where available. A generic form accepted by many registries and cord blood banks (e.g., WMDA Preliminary Search Request Form) can be found under <http://www.worldmarrow.org>. Alternatively, a search can be started through a registry to registry network such as the European Marrow Donor Information System (See Note 21).

¹³Preferentially family typing is available and the patient's haplotypes can be established through family segregation analyses. If family data are not available, there are haplotype frequency tables that can be used to predict which haplotypes the patient might carry and also to provide information whether or not the patient has common haplotypes. Understanding common haplotype or allele associations can be useful for predicting which alleles are most likely to be present in donors who have only low resolution typing information and no family data to define haplotypes. Three useful web sites for haplotype analysis are <http://bioinformatics.nmdp.org>, <http://www.haplostats.org/home.do>, and <http://www.hlaexplorer.net>.

¹⁴Registries and banks have guidelines for who can submit a search request. Usually search requests must come from a physician or from a transplant center.

¹⁵Typically searches are performed in two steps. In the preliminary search, a physician will receive a summary indicating whether or not there are potentially matching donors in a registry or cord blood bank. If the registry appears to include suitable donors, a transplant center will formalize the search. In a formal search, the HLA types of each potentially matching donor/unit will be listed individually and the transplant center can request biologic samples from these donors/units for further HLA and infectious disease testing.

¹⁶It is important to confirm the patient's typing using a second biological sample to ensure that no errors are made in the HLA assignments to be used in the unrelated donor/umbilical cord blood search.

¹⁷It is recommended that the search identify the best unrelated donor and the best umbilical cord blood unit to provide alternatives for the physician. An urgent search might focus only on umbilical cord blood units because they are more rapidly available.

¹⁸The level of matching required for optimal outcome has been discussed in the literature, e.g., (14) (13),(16),(17).

¹⁹Access to the search tool in BMDW requires that a transplant center register with BMDW. The search is submitted online. Matches identified in the BMDW worldwide registry will identify one or more countries where potential donors or cord blood units can be found for the patient. The transplant center can then focus the search on registries and cord blood banks from those countries. Contact information for these registries and banks can be found on the BMDW web site.

²⁰The national registry in the country of the transplant center caring for the patient may also assist in contacting multiple registries and banks. For example, a search of the National Marrow Donor Program in the United States will also interrogate the inventory of the BMDW. Any physician may request a search of the NMDP on behalf of a patient through the Office of Patient Advocacy (<http://www.bethematch.org>). There are also several publicly available web sites that provide summarized search results (e.g., MatchView at <http://www.marrow.org>). When using the NMDP, staff will perform all of the contacts and assist with HLA expertise to guide the process of selecting the best potential donor or cord blood unit.

3.4 Reviewing a search report to select potential adult volunteer donors for additional HLA testing

1. Obtain a search report from the registries and banks contacted (see Note 22). Most registries will display adult donor matches based on HLA-A,-B,-DRB1 typing and will list both 6/6 and 5/6 matches. The selection of umbilical cord blood units is described in Section 3.6.
2. Ensure that the correct match criteria are known for the patient (whether an 8/8 or 10/10 match is preferred; which and how many mismatches are allowed; and any other donor-specific characteristics that need to be considered such as gender, age or CMV status). This will guide the selection of the best potential donors and help to increase the likelihood of a successful transplantation (see Note 23).
3. Expand any donor typing results (see Note 24) that may have letter codes (e.g., A*01:CRY) as necessary to understand the full set of alleles in the assignments. See Note 25 for a tool to assist with this task.
4. Evaluate the donor typing results for completeness according to the transplant center match criteria. For example, if an 8/8 match is preferred, do the donor typing results include HLA-A, -B, -C, and DRB1? If incomplete, utilize haplotype frequency data relative to the ethnicity of each donor to help predict the most likely HLA type of the missing loci (see Note 26).
5. Evaluate the donor typing results to determine if the level of resolution at each locus is sufficient in order to make a determination of the likelihood to match the patient's alleles. Utilize allele and haplotype frequency data and the donor's ethnicity to predict the most likely higher resolution types for each locus for the donors of interest on the search report (see Note 27). Table 1b provides an example of the evaluation of a donor's HLA assignments.
6. Prioritize the donors deemed most likely to match the patient's HLA type using all of the information gathered in the analyses above. If multiple, suitably matched donors are available on the search list, apply the additional transplant protocol criteria to the non-HLA information given for each donor to perform a secondary sort. For example, prioritize younger donors over older.
7. Request a biological sample from the selected donors for further typing from the Registry (see Note 28).

²¹Search requests often go from registry to registry using the European Marrow Donor Information System (EMDIS). Transplant centers may have the ability to directly enter the search information into a software application.

²²Searches performed electronically using BMDW or NMDP generate donor lists immediately. Most registries and cord blood banks will provide a search report within 24 hours when using the EMDIS system. The matches displayed usually include 6/6 (HLA-A,-B,-DRB1) and 5/6 matched donors but the criteria for the donors displayed on a search should be confirmed with the registry.

²³Non-HLA factors that are often considered in donor selection have been reviewed by Confer et al. (18).

²⁴The donors/units listed on the report are sorted by the extent of matching with the patient. It is possible, however, that the optimal donor may not appear at the top of the list so it is critical to examine all of the donors on the report.

²⁵An HLA typing result may include a two or more letter code following the first colon in the allele name (e.g., A*02:AF where AF is a code standing for 01 or 09 indicating that an individual carries A*02:01 or A*02:09). The web site, <http://bioinformatics.nmdp.org>, has a tool to define alleles included in any letter codes. Further information on HLA assignments can be found at <http://hla.alleles.org> and <http://www.ebi.ac.uk/imgt/hla/>.

²⁶There are several approaches that can be used to predict the most likely missing data. The Haplostats tool and the HLA Explorer will generate a table of the most frequently seen HLA-C types associated with a known HLA-B and the most frequently seen HLA-DQB1 types associated with a known DRB1 antigen sorted by likelihood and ethnicity. The complete list of HLA-A, B, C, DRB1, and DQB1 haplotypes found on bioinformatics.nmdp.org can be used by searching on the known HLA-A, B and DRB1 haplotype and then viewing the possibilities of full haplotype combinations considering the frequencies of each and the racial/ethnic group of the donor (if known).

²⁷The Haplostats and HLA Explorer tools will each display the possible high resolution types given any low resolution input. The difference in the two tools is that Haplostats requires all known loci to be entered and HLA Explorer will provide data on any single low resolution type. They both sort by frequency within racial/ethnic populations.

8. Perform HLA typing of the samples to obtain more information as to the HLA alleles carried at key loci and to verify the HLA typing assignment (see Note 29).
9. Select the best donor based on the transplant center criteria (see Note 30 and ³¹).
10. Contact the registry to request that a specific volunteer be medically evaluated for donation.

3.5 Refining the search strategy to identify a mismatched or mistyped donor

1. When the search report or the analyses performed above does not yield donors who potentially match the patient, a strategy to locate the best potential mismatch may need to be implemented. In these instances, a donor with only one mismatch (7/8 or 9/10) may be considered as an alternative depending on the transplant center protocol (see Note 32). The search reports from most registries include 5/6 matched donors (i.e., with one mismatch at one of the three loci, HLA-A, -B, -DRB1). A longer list of potential donors may be needed if the search was initiated through EMDIS since some registries limit the search results to either 50 or 100 donors.
2. Evaluate the patient for the presence of IgG antibodies directed to specific HLA antigens (Note 33).
3. Evaluate the methodology that may have been utilized to generate the HLA data of the potential donors. Assignments made using older serologic typing techniques have a higher likelihood of appearing falsely disparate than typing techniques that utilize DNA-based methodologies. If the patient carries an antigen that is known to be difficult to distinguish by serologic methods, then donors typed serologically who have a high likelihood of matching the patient may appear as mismatched on the search report (see Note 34). Utilize the HLA dictionary to identify any of these antigens (see Note 35). Perform a new search if needed by substituting the patient's difficult allele or antigen with an alternate choice as indicated by the HLA dictionary "assigned type" field (see Note 36).
4. Evaluate the possibility that allele level differences between a donor and the patient may be permissible mismatches due to the location of the disparity. Some alleles that have different assignments are actually identical, either genotypically or

²⁸High or allele resolution typing should be performed to identify those donors who carry the same HLA alleles as the patient. This extended typing should include all loci to be considered for matching. Verification typing using a fresh biological sample from the donor should be performed in order to ensure that this individual was the one with the HLA assignment appearing on the search report. The resolution of verification typing should be sufficient to confirm the original HLA assignments.

²⁹It is recommended that more than one donor be selected for additional HLA testing. This is because some donors may not carry the same alleles as the patient following higher resolution testing or because some volunteers will be unwilling or unable to donate or can not be located. The number of donors to select will depend on the likelihood of the patient's alleles and haplotypes being present in the donors. For common alleles and haplotypes, 3–5 donors might be selected for further HLA testing. Uncommon alleles and haplotypes may require 10 or more donors to be selected for extended HLA typing. The registry may have information on the rate of donor availability to help with this decision.

³⁰The donor's registry or the cord blood bank will request that your extended HLA typing results be provided to them to update the donor/unit file. Follow the policy of the registry for the loci and level of resolution to be tested when reporting the results for each donor.

³¹If there are multiple suitable matched donors, HLA assignments at other HLA loci, not routinely considered by the transplant center in determining the match, can be used to select among the donors. For example, if the transplant center requests an 8/8 match and there are several 8/8 matched donors, matching for HLA-DQB1, HLA-DRB3/DRB4/DRB5, or HLA-DPB1 alleles might be used to prioritize donors.

³²A single mismatched donor is defined as a 7/8 or 9/10 matched donor (14).

³³Prior sensitization to specific HLA antigens may result in rejection of grafts expressing those antigens (19),(20). Antibody assays are described in Chapter??.

³⁴For example, if the patient carries A*01:01, A*74:01, it may be possible that those donors typed only as HLA-A1 using serology might actually carry HLA-A74 since HLA-A74 was frequently missed by serology. Lists of frequently missed or mis-assigned serologic antigens have been reported (21),(22).

³⁵The HLA dictionary can also be found online at [http://www.ebi.ac.uk/imgt/hla/\(9\)](http://www.ebi.ac.uk/imgt/hla/(9)).

phenotypically, in the region that encodes the peptide binding site and may not impact the transplant outcome (see Notes 37 and 38).

5. Review the patient's HLA assignment to determine if an uncommon haplotype or allele may be present (see Section 3.2.4). In these cases, it may be possible to substitute a donor with a single mismatched allele at the locus in question and meet the 7/8 or 9/10 transplant center criteria (see Note 39).
6. Prioritize the loci involved and the selection of potentially mismatched donors according to the transplant center criteria and using recommendations given in recent publications (see Note 40). Avoid choosing donors carrying HLA antigens to which the patient is sensitized.

3.6 Searching for a cord blood unit

1. Review the cord blood units that have been listed on the patient's search report (see Note 41).
2. Identify units with greater than a minimal required cell dose based on the transplant center protocol (see Note 42).
3. Identify units that may meet the transplant center's HLA matching criteria for a cord blood unit (see Note 43). The units will likely be HLA typed at a low resolution and higher resolution testing may be required for optimal donor selection.

³⁶An example from the HLA dictionary is B*39:20 that has an assigned type of "blank" (67%) or B38 (33%). If the patient carries B*39:20, B*07:02, an alternative phenotype search might be submitted in which the patient's HLA-B assignment is listed as B*38:XX, B*07:02. In some cases, acceptable donors may not appear on the search report because their HLA typing appears to be more mismatched than the registry's minimum criteria. For example, a search report usually lists 6/6 and 5/6 matched donors. A donor who appears as a 4/6 match will not be shown on the report. An example for a patient typed as A*02:01, A*03:01, B*39:20, B*07:02 is a donor typed as A11, A3, B38, B7. Submission of an alternative phenotype search replacing B*39:20 with B38 may yield additional 5/6 donors who didn't appear on the initial search.

³⁷For example, a patient may carry DRB1*14:01 and a potential donor might carry DRB1*14:54. These two alleles specify proteins that are identical in amino acid sequence in the portion of the HLA molecule called the peptide binding site. Note 6 further defines this region of the HLA molecule. Since it is thought that allorecognition focuses on this region of the HLA molecule, the single amino acid difference outside of the peptide binding site that distinguishes these two HLA molecules is thought to be unlikely to trigger allorecognition (23). Thus, differences in HLA molecules that fall outside of the peptide binding site might be considered permissive. A list of alleles that share the sequence of their peptide binding site can be found at <http://hla.alleles.org/nomenclature/>.

³⁸Several studies have discussed permissive mismatches (24) (25),(13),(26),(23) or have evaluated tools to select these mismatches (27),(28).

³⁹For example, if the patient carries an uncommon HLA-B locus allele, the search may yield a donor carrying a differing HLA-B locus allele that still matches the patient's HLA-C alleles. For example, if the patient carries B*35:15-C*07:02, the rare B*35:15 may be substituted by B*07:02, as B*07:02 is strongly associated with C*07:02. Likewise, this strategy can be utilized to identify an HLA-DRB1 mismatched donor who may mismatch the patient's uncommon HLA-DRB1 yet has high potential to match the patient's HLA-DQB1 allele. For example, if the patient carries DRB1*04:07-DQB1*03:01, the rare DRB1*04:07 may be substituted by DRB1*11:01 as DRB1*11:01 is strongly associated with DQB1*03:01.

⁴⁰The selection of which locus to mismatch has been discussed in the literature (14) (13),(16). Evidence guiding the selection of a donor with the most permissive mismatch at a locus is limited; most studies have evaluated strategies that ultimately did not predict permissive mismatches (13),(26),(27),(28).

⁴¹The units shown on the search report likely meet some minimum HLA match and/or total nucleated cell (TNC) criteria defined by the registry or cord blood bank. The units may be sorted into categories based on the degree of match or size of the unit. It should not be assumed that the optimal unit is found at the top of the list; all units on the report should be evaluated.

⁴²Cell dose is one of two critical factors in the selection of a unit; HLA match is the second critical factor. The unit selected must contain a minimum of $2.5-3 \times 10^7$ pre-cryopreserved total nucleated cells (TNC) per kilogram of recipient body weight (29). If the possibility of using two cord blood units is being considered, the minimum TNC/kg for a unit as part of a double cord transplantation may be lower, but together the two units should have at least $2.5-3 \times 10^7$ TNC/kg.

⁴³The criteria that are often used for matching is a minimum of a 4 of 6 match, two antigen level matches at HLA-A and HLA-B and an allele match at DRB1. An antigen match is defined as a match at the first two digits of the allele name. For example, a patient typed as A*02:05 and a unit typed as A*02:01 would be considered an antigen match. Matching among B*15 and B*40 alleles is the exception. In these cases, the serologic assignment of the allelic products determines whether the patient and donor are matched at the antigen level. For example, a patient typed as B*15:01 (serologic B62) would not be an antigen match with a donor typed as B*15:03 (serologic B70). Use the HLA dictionary to obtain the serologic types associated with B*15 and B*40 alleles (9).

4. Select one or more units that have both an acceptable cell dose and an acceptable HLA match. Request that the Registry/Cord Blood Bank initiate further HLA testing of the selected unit or request a sample for typing at your local HLA laboratory (see Note 44). Also request a Unit Report that gives more information about the unit plus the maternal health history.
5. Consider whether the unit has attached segments for verification typing (see Note 45) in making your decision about whether to request the unit for transplant.
6. Request that the Registry/Cord Blood Bank reserve the unit for your patient until you have completed your evaluation.

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⁴⁴Recent reports suggest that better matching of the patient and the umbilical cord unit may result in better outcome (29). Therefore, it is recommended that the unit be tested at allele to high level resolution at HLA-A, -B, -C, -DRB1 so that the best matched unit can be selected for the patient.

⁴⁵It is important to insure that the cord blood unit is the one with the HLA typing found on the search report. This verification typing should be performed on a biological sample found in an aliquot physically attached to the unit.

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Table 1a

Example of how a patient typing is evaluated.

Patient typing: A*02:05, 68:04; B*35:DNXXN, 53:01; DRB1*03:01, 13:03; C*04:01; DQB1*02:01, 02:02			
Issue noted	Web site providing information	Action/Resolution	
Is information included on all the loci required for matching?		If the transplant center would like to search for a 10/10 match, assignments must be included for 5 loci; for a 8/8 match, 4 loci. The typing includes all the required loci for either level of match.	
Evaluate resolution of testing: Allele B*35:DNXXN has an allele code	http://Bioinformatics.nmdp.org/DNA_Type_Lookup_Tool	Expand to full allele string. Depending on the assignments, request additional typing to increase the resolution. In this case, the assignment includes only alleles that share the sequence of exons 2 and 3: B*35:01, B35:40N, B35:42, B35:57, B35:94.	
Evaluate resolution of testing: C*04:01 allele is at high resolution but this level of resolution required special testing by the HLA laboratory	http://hla.alleles.org/alleles/index.html G groups	Ask the laboratory if it specifically excluded the other alleles that carry the same nucleotide sequence as C*04:01 in the HLA-C exons specifying the peptide binding site. For example, did the laboratory specifically exclude the non-expressed allele C*04:09N? (see Note 46)	
Evaluate frequency of alleles: Allele A*68:04 is uncommon	http://Bioinformatics.nmdp.org/Rare Allele List	In family? If yes, acceptable. If no, repeat HLA typing of HLA-A preferably with different reagents/method.	
Investigate B/C and DR/DQ haplotypes: B*35:DNXXN with C*04:01 B*53:01 with C*04:01 DRB1*03:01 with DQB1*02:01 or *02:02 DRB1*13:03 with DQB1*02:01 or *02:02	http://www.haplostats.org/home.do	Concordant with family typing? Common or uncommon? In this case, the B-C associations are common. Both DRB1 alleles are frequently observed with DQB1*02:01 but not with DQB1*02:02 so this is unusual. The laboratory should be asked to confirm the DQB1*02:02 assignment if it is not observed in the family.	
Investigate multi-locus haplotypes (A/B/C/DRB1/DQB1)	http://www.haplostats.org/home.do	Concordant with family typing? Common or uncommon?	

⁴⁶The specifications for the resolution of HLA typing should be established by the transplant center in discussion with the histocompatibility laboratory. The resolution of the patient's typing assignment will determine which donors appear on a search report and may vary among registries. For example, donors listed on a search report for a patient typed as C*04:01 may differ from the donors listed for a patient typed as C*04:01:01G (which includes alternative alleles C*04:01:01:01, C*04:01:01:02, C*04:01:01:03, C*04:01:01:04, C*04:09N, C*04:28, C*04:30, C*04:41, C*04:79, C*04:82, C*04:84) or typed as C*04:FEAS (which includes alternative alleles C*04:01, C*04:09N, C*04:28, C*04:30, C*04:41).

Table 1b
Examples of how a potential donor typing is evaluated for the patient in Table 1a.

Patient typing: A*02:05, 68:04; B*35:DNXX, 53:01; DRB1*03:01, 13:03; C*04:01			
Donor 1 Typing: A2, 68; B35, 53; DRB1*03:DHJB, 13:BGTY			
Issue noted	Web site providing information	Action/Resolution	
Allele codes need expansion	http://Bioinformatics.nmdp.org/DNA_Type_Lookup_Tool_Haplostats	DHJB: 03:01/03:06/03:18/03:19/03:22/03:28/03:37 BGTY: 13:03/13:33/13:66 The patient's DR alleles are included in the donor assignments and, based on the frequency of the alleles in the code, are likely to be matched (i.e., DRB1*13:03 is more common than DRB1*13:33 or DRB1*13:66).	
Determine likelihood for allele match: Serologic typing at HLA-A and B	Haplostats HLA Explorer DNA Dictionary	Predict higher resolution and likelihood of allele match with patient based on ethnicity. A*02:01 is more frequent than A*02:05; it is unlikely that the donor carries A*6804. B*35:01 is common and may be present in B35 typed individual although other B*35 alleles (B*35:02, B*35:03) are possible; B*53:01 is likely to be present.	
Evaluate typing for completeness: HLA-C not typed	http://bioinformatics.nmdp.org/index.html , Haplotype table	Predict HLA-C alleles that might be present. If B*35:01 and B*53:01 are present, both B alleles are frequently found with C*04:01.	
Is resolution sufficient to make a determination of match?		The donor is likely an HLA-A mismatch (i.e., not A*68:04). A donor matched at 7/8 or 9/10 may be acceptable to the transplant center. Depending on other donors available on the search report, determine whether this donor should be typed at higher resolution.	