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Guidelines for Cord Blood Unit Selection

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A B S T R A C T

Optimal cord blood (CB) unit selection is critical to maximize the likelihood of successful engraftment and survival after CB transplantation (CBT). However, unit selection can be complex because multiple characteristics must be considered including unit cell dose, donor-recipient human leukocyte antigen (HLA) match, and unit quality. This review provides evidence-based and experience-based comprehensive guidelines for CB unit selection. Topics addressed include the use of both the TNC and the $CD34^+$ cell dose, as well as the $CD34^+$ cell to TNC content ratio to evaluate unit progenitor cell content and engraftment potential, the acceptable TNC and $CD34^+$ cell dose criteria that define an adequate single-unit graft, and the indication and acceptable cell dose criteria for double-unit grafts. The acceptable criteria for 6-loci (HLA-A, -B antigen, -DRB1 allele) and 8-allele (HLA-A, -B, -C, -DRB1) donor-recipient HLA match, the evaluation of patients with donor-specific HLA antibodies, and the multiple determinants of unit quality are also reviewed in detail. Finally, a practical step-by-step guide to CB searches and the principles that guide ultimate graft selection are outlined.

BACKGROUND

Optimal cord blood (CB) unit selection is critical to maximize the likelihood of successful engraftment and survival after CB transplantation (CBT). Greater availability of high cell content quality units has likely contributed to improving CBT outcomes in recent years [1-6]. However, unit selection can be complex because multiple characteristics must be considered. Several reports have previously outlined country and transplant center-specific selection guidelines [7-12]. This review takes a frequently asked question (FAQ) approach to provide evidence-based guidelines for unit selection and experience-based recommendations when evidence is lacking. Additionally, a step-by-step unit selection guide is provided to simplify the process of performing searches and selecting CB grafts (Table 1).

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FAQ1: What Unit Characteristics Must Be Considered in CB Graft Selection?

Expert centers do not have a uniform approach to unit selection but agree upon the following principles:

1) Precryopreservation total nucleated cell (TNC) and $CD34^+$ cell doses must both be considered.
2) Selection should be based on high-resolution 8-allele donor-recipient HLA match.
3) Selection should be restricted to units of adequate quality.

FAQ2: How Should CB Unit Cell Dose Be Evaluated?

While the importance of TNC dose in CBT is well established, $CD34^+$ cell dose is the most reliable predictor of engraftment [13-17]. Consequently, the current standard is to consider both TNC and $CD34^+$ cell doses in unit selection [7-11]. Consideration of $CD34^+$ cell dose is essential because the TNC and $CD34^+$ cell contents of banked units are not strongly correlated [18], and consequently, units with an adequate or even high TNC dose may have intermediate or low $CD34^+$ cell content [18,19]. Consideration of TNC dose must remain,

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Table 1
Step-by-Step CB Unit Selection Guide in the United States

Step*	Action	Comments
1	Enter patient's high-resolution HLA typing and weight (kg) and sort units in MatchSource®.	2 options for initial unit sorting: I) Sort by $CD34^+$ cell or TNC dose (better HLA-matched units may appear lower on list). II) Sort by HLA match (lower-dose units may appear higher on list). *Note*: If sorted by 8-allele HLA match, units in MatchSource® will be listed based on the highest possible HLA match grade.
2	Filter out units with low TNC dose.	Minimum TNC dose: Single-unit grafts: 2.5×10^7/kg Double-unit grafts: 1.5×10^7/kg for each unit *Note*: Higher minimum TNC cell doses are recommended (see step 9).
3	Filter out units with low $CD34^+$ cell dose.†	Minimum $CD34^+$ cell dose: Single-unit grafts: 1.5×10^5/kg Double-unit grafts: 1.0×10^5/kg for each unit *Note*: Higher minimum $CD34^+$ cell doses are recommended (see step 9).
4	Filter out units that are highly HLA-mismatched.	Minimum 6-loci (HLA-A, -B antigen, -DRB1 allele) match: 4/6 Minimum 8-allele (HLA-A, -B, -C, -DRB1) HLA match: 4/8
5	Filter out old units.	Units collected 15 years or more ago *Note*: Older units may be considered.
6	Filter out nonstandard cryopreservation volumes and/ or RBC-replete units.	Optimal volume: 24-28 mL (1 bag) or 48-54 mL (2 bags each of 24-28 mL/bag) *Notes*: - If unit volume ≥30 mL, verify it is RBC-depleted (filter out if RBC-replete). - Rarely, unit volumes are listed without including the ~5 mL DMSO (19 to 21 mL). If so, verify the correct cryovolume.
7	Filter out units from non-FACT-accredited CB banks.	Prioritize banks with FACT accreditation to optimize unit quality. *Note*: Avoidance of certain banks may also be considered (eg, banks unknown to the transplant center).
8	Sort units *If the search is difficult, above filters can be relaxed or alternative stem cell sources can be considered.*	Two options for unit presentation: I. Sort by $CD34^+$ cell dose (highest to lowest). or II. Sort by 8-allele HLA match grade (if unit typed or by Haplogic predictions): 1) List 8/8 HLA-matched units (highest to lowest $CD34^+$ cell dose). 2) Repeat for 7/8, 6/8, 5/8, 4/8 units (within each match grade sort by dose).
9	Review and select units for confirmatory typing. *Units already typed at high resolution can be placed on hold. Will need 1 to 2 units for the graft and 1 to 2 domestic units as backups.*	Must consider cell dose, HLA match, and unit quality. 1) Select 4 to 6 (if possible) units with adequate TNC and CD34+ cell dose/kg and acceptable HLA match. 2) Assess specificities and titers of DSA (if present). *Notes*: - Minimum cell dose thresholds capture all potentially acceptable units. - Selection of units with higher cell doses is now recommended: Single units: TNC cell dose ≥3.0×10^7/kg and $CD34^+$ cell dose ≥2.0×10^5/kg Double units: $CD34^+$ cell dose ≥1.5×10^5/kg for each unit - If the $CD34^+$/ TNC content ratio is unexpectedly high (≥1.5% to 2%), the listed $CD34^+$ cell dose should be verified. - How to trade off dose versus HLA match is not well established. If all units have a low cell dose, selection of highly HLA-mismatched units may be necessary to achieve acceptable dose. HLA match can be optimized if multiple high cell dose units are available. - For patients with hematologic malignancies, units that are very well HLA matched (ie, 8/8 HLA-allele matched) may be avoided to reduce the risk of relapse. - For patients with nonmalignant diseases, both cell dose and HLA match need to be optimized. - Units targeted by high DSA titers should be avoided if possible. - Additional center-specific criteria may be applied in final CB unit selection.

* Steps 1 to 5 need to be performed in MatchSource® as of June 2020. Units of interest should then be exported into an Excel file for further sorting and final unit selection.

† Units with adequate $CD34^+$ cell dose that do not meet minimum TNC dose criteria may be considered if the $CD34^+$/TNC ratio is within an acceptable range. Bank accreditation, processing, and year of cryopreservation must be considered for such units.

however, due to potential interlaboratory variability and lack of standardization of $CD34^+$ cell enumeration assays [20]. Rarely, units may be listed with unexpectedly high $CD34^+$ cell content, and exclusion of erroneous data entry for such units is recommended. The $CD34^+$ cell to TNC content ($CD34^+$/TNC) ratio can be used to identify "out-of-range" $CD34^+$ cell values that should be confirmed before final graft selection. An expected median $CD34^+$/TNC ratio of 0.34% (interquartile range, 0.23% to 0.48%) has been reported in an analysis of the US inventory [18]. However, a higher ratio of 0.78% (interquartile range, 0.6% to 1.07%) has been observed in units selected for transplantation when $CD34^+$ cell dose is also considered in unit selection [21].

FAQ3: What Are the Minimum Cell Dose Criteria for an "Adequate" Single-Unit Graft?

The minimum TNC and $CD34^+$ cell dose thresholds for single unit grafts vary between countries and are influenced by additional factors such as HLA mismatch and malignant or nonmalignant CBT indications.

Minimum TNC dose

- The United States uses a minimum TNC dose of $>2.5 \times 10^7$/kg [9,10,22], based on studies showing improved engraftment, transplant-related mortality, and survival above this threshold [23-25].
- The United Kingdom and Europe have adopted a minimum dose of $>3.0 \times 10^7$/kg for single-unit grafts [7,8,26], given 2 registry studies demonstrated a TNC dose greater than this higher threshold was associated with reduced mortality [27,28].
- Japan has adopted a lower TNC dose threshold of 2.0×10^7/kg [12,29] to extend access to single-unit CBT.
- TNC doses significantly greater than the accepted minimum TNC thresholds of 2.0 to 3.0×10^7/kg have been associated with improved engraftment and potentially lower mortality, especially in the presence of high degrees of HLA disparity [5,24,29-31].
- Higher minimum TNC thresholds (eg, TNC $\geq$4.0-5.0×10^7/kg) are recommended for CBT for nonmalignant diseases [7,8,32-37].

Minimum $CD34^+$ cell dose

The $CD34^+$ cell dose is the most critical determinant of hematopoietic recovery [5,12,13,15,19,38-40]. However, an association with survival outcomes has been shown in some [13,39,40] but not all single-unit CBT series [5,12,15,19]. At this time, the minimum acceptable $CD34^+$ cell dose threshold is not fully established. Existing US [9,10] and updated Eurocord guidelines [11] accept a minimum $CD34^+$ cell dose of 1.5×10^5/kg for single-unit grafts. However, a higher minimum $CD34^+$ cell dose is now recommended to mitigate prolonged post-transplant cytopenia (Table 1).

FAQ4: When Is a Double-Unit CB Graft Indicated and How Should It Be Selected?

Patients who lack a suitable single unit can be considered for a double-unit CB (dCB) graft [41,42]. It is well established that 2 units, each considered inadequate as single-unit grafts, can be successfully combined in a double-unit graft [41,42]. Two randomized studies of myeloablative CBT in children and young adults have demonstrated that adding a second unit to an adequate single-unit graft is not beneficial [22,26]. These findings suggest that double-unit CBT (dCBT) should be avoided in patients who have a unit of adequate TNC dose and donor-recipient HLA match [22,26]. However, the 2 trials used different minimum TNC criteria and did not incorporate consideration of $CD34^+$ cell dose and 8-allele HLA match. Moreover, caution is required when extrapolating these findings to adults who are more likely to receive reduced-intensity conditioning and therefore may benefit from the potentially enhanced graft-versus-leukemia effects associated with double-unit grafts [43,44]. Use of 2 units also increases the chance of at least 1 unit with optimal engraftment potential being infused.

FAQ5: What Are the Minimum TNC and $CD34^+$ Cell Doses for a Double-Unit CB Graft?

Both TNC and $CD34^+$ cell doses are important in dCBT [16,45-50]. Historically, a TNC dose $\geq 1.5 \times 10^7$/kg and a $CD34^+$ cell dose $\geq 1 \times 10^5$/kg for each unit in a dCB graft have been the accepted minimum thresholds so as to extend transplant access to the majority of patients [7-9,11]. However, a higher minimum $CD34^+$ cell dose for each unit is now recommended (Table 1). In dCBT, while 1 unit will typically provide long-term hematopoiesis, the dominant unit cannot be reliably predicted at the time of selection [49]. Therefore, the characteristics of both units are equally important and identical selection criteria should be applied to each unit. There are no data to support the consideration of the combined unit cell dose in dCB graft selection.

FAQ6: How Should Donor-Recipient HLA Match Be Evaluated?

Donor-recipient HLA match of CB units should be evaluated at 6 HLA loci (HLA-A, -B antigen, -DRB1 allele-level typing) and 8 HLA loci (HLA-A, -B, -C, -DRB1 allele-level resolution).

FAQ7: What Is the Minimum Required Donor-Recipient HLA Match?

Historically, unit-recipient HLA matching has been based on HLA-A, -B antigen, -DRB1 allele-level typing (6-loci HLA match grade) [9,51], with the exception of Japan, which accepts antigen-level HLA typing for all 6 loci [12]. However, a minimum of 8-loci HLA-A, -B, -C, -DRB1 allele-level typing (8-allele HLA match grade) is now required in Europe [11], the United Kingdom [7], and the United States [9,10].

HLA -A, -B antigen, -DRB1 allele HLA match (6-loci HLA match grade)

A minimum requirement of donor-recipient 4/6-loci HLA match has been widely accepted [7-11,22,23,26,51,52]. In CBT for hematologic malignancies, HLA mismatch has been associated with inferior engraftment, as well as increased risk of graft-versus-host disease and potentially transplant-related mortality [4,12,13,23,30,52,53], but also lower relapse risk [4,12,52,53]. Consequently, a higher degree of HLA disparity at 6 loci has been associated with inferior survival in some single-unit CBT studies [13,23,30,53] but not in others [4,5,12,22,25,52,54]. One study has suggested that the deleterious effect of HLA mismatch on survival is limited to children [29].

HLA-A, -B, -C, -DRB1 allele HLA match (8-allele HLA match grade)

In CBT for malignant diseases, a higher degree of 8-allele HLA mismatch has been associated with inferior engraftment, higher rates of acute graft-versus-host disease and transplant-related mortality, but also a lower incidence of relapse [5,27,55]. Inferior survival has been observed only with <4/8 HLA-matched grafts [5,27] or <5/8 HLA-matched grafts in children [5]. Consequently, avoidance of units that are <4/8 HLA allele matched is generally recommended [9,10], if possible.

HLA match in double-unit CBT

Presently, the recommendations for the minimum 6-loci HLA match of each unit of a dCB graft are the same as for single units. Several studies have shown either no detrimental effect, or even benefit, of higher degrees of HLA-allele mismatch on survival post-dCBT [48,56-58]. Consequently, a minimum donor-recipient 8-allele HLA match requirement is not well

established in dCBT. The unit-unit HLA match does not need to be considered in dCBT [59].

Nonmalignant diseases

In CBT for nonmalignant diseases, prioritization of well-matched units at the HLA allele level is recommended as it has been associated with improved outcomes [6,60,61].

Other HLA match considerations

Finally, for all populations, there are insufficient or conflicting data regarding CBT outcomes according to locus-specific HLA mismatches [12,27,28,62-64], direction of mismatch [65-68], or 10 or 12 HLA allele level matching [64,69]. It is also not practical to consider noninherited maternal antigen or inherited paternal antigen matching in most patients [70-73].

FAQ8: How Should Unit Quality Be Evaluated?

Unit quality is determined by banking practices and will be influenced by processing and cryopreservation techniques. The goal is to select units of high quality to maximize post-thaw cell dose recovery and potency and, thereby, the engraftment potential. The following characteristics must be considered:

Bank accreditation and licensure

Standardization of banking practices is crucial to ensure consistent product quality and reliability of testing results such as the correlation between pre- and post-thaw viable $CD34^+$ cell content [16]. Accordingly, banks accredited by the Foundation for the Accreditation of Cellular Therapy (FACT) are preferred [9,10]. In the United States, Food and Drug Administration (FDA) licensure is associated with high quality. FDA regulations ensure safety, identity, potency, and product purity, and provide assurance that all steps from collection to unit release undergo rigorous monitoring and results meet predetermined standards. Nonlicensed units banked under similar conditions are also acceptable [6].

Cryopreservation volume

Most automated processing systems have a predefined, standardized final volume (approximately 25 mL with DMSO, or 50 mL in two 25-mL bags). In contrast, the volumes of manually processed units vary. Units with nonstandard cryovolumes have been associated with lower post-thaw viability and, consequently, inferior engraftment potential [16,74].

Red Blood Cell content

Red blood cell (RBC)-replete units are no longer recommended given the increased likelihood of serious infusion reactions [6,75]. Additionally, washing these units can lead to significant cell loss given the lack of a clear interface after centrifugation. RBC-replete units usually have larger cryopreservation volumes. RBC-depleted units with standard cryovolumes that result from automated processing are preferred.

Year of collection

It is well documented that CB potency and engraftment potential are preserved after many years of cryopreservation [16,76-78]. However, most centers consider unit age in selection as banking practices have improved over time, and recent units (ie, those collected in the past 10 to 15 years) are more likely to have undergone more optimized procedures and testing compared to those collected in earlier years.

Post-thaw segment potency

Evaluation is not widely standardized. NetCord-FACT specifications require a minimum thawed segment $CD34^+$ cell viability $\geq$70%. However, transplantation of units with a higher minimum segment $CD34^+$ cell viability of $\geq$80% by flow cytometry is preferred, and units with lower viability should potentially be avoided.

FAQ9: What Are Other Measures of Unit Quality?

- Unit identity should be verified by HLA confirmatory typing (or a similar DNA-based assay) of an attached segment.
- Donor eligibility is based on maternal risk factors and maternal infectious disease marker screening. Units from ineligible donors can be used based on FDA requirements of "Urgent Medical Need" after evaluating the potential risk associated with the reason for ineligibility versus the potential benefit of CBT with these unit(s), relative to other units or options for therapy.

FAQ10: Are Units Targeted by Donor-Specific HLA Antibodies Contraindicated?

The impact of donor-specific HLA antibodies (DSAs) on engraftment after CBT for hematologic malignancies is controversial, but points to consider include the following:

- Some [8,79-83] but not all [84,85] studies suggest the presence of DSAs increases the risk for graft failure.
- DSA number, titer, locus specificity, and complement binding capacity of the DSA, as well as the graft cell dose, must be considered on a case-by-case basis [86,87].
- Additional important factors include recipient diagnosis, patient's prior immunosuppressive therapy, and planned conditioning intensity because they will also influence the potential for graft rejection.
- Consideration of DSAs should not significantly compromise the cell dose of the selected graft.
- Antibody debulking strategies are not standardized and cannot be relied upon to guarantee engraftment.

In CBT for nonmalignant diagnoses, DSA-targeted units should be avoided.

FAQ11: What Factors Do Not Need to Be Taken into Consideration in Unit Selection?

ABO mismatch has not been established as a determinant of inferior survival in CBT [88-91]. Also, as the importance of killer cell immunoglobulin-like receptor (KIR) typing in CBT remains inconclusive, it should not be included in unit selection at this time [92-97]. Other unit characteristics that do not require consideration are nucleated RBC content and donor sex or ancestry.

FAQ12: What Are the Practical Steps in CB Unit Selection?

A suggested step-by-step guide to the process of CB search and ultimate graft selection is shown in Table 1. Selection steps may be further modified by transplant centers according to expertise and center-specific needs.

FAQ13: Should Cell Dose or HLA Match Take Priority in CB Graft Selection?

How to prioritize cell dose versus HLA match in CB graft selection is unknown. While analyses have evaluated the

relative importance of TNC dose and 4-6/6 HLA match [29,30,53], information as to the relative importance of $CD34^+$ cell dose versus 8-allele HLA match is limited [5]. Moreover, it is important to make a distinction between the minimal acceptable cell dose or HLA match versus what is considered optimal.

In patients (such as many children and some adults with common haplotypes) who have several units with high cell doses (eg, TNC $\geq 3 \times 10^7$/kg and $CD34^+$ cells $\geq 2 \times 10^5$/kg), HLA match can be prioritized. Conversely, for most adults and some larger children, cell dose may need to take priority over HLA match, and double-unit grafts may be needed. In patients with difficult searches, achieving an adequately dosed graft may mandate the transplantation of units with a high degree of HLA mismatch. Avoidance of very well matched units (ie, 8/8 HLA allele matched) in patients with hematologic malignancies may also be considered due to the increased risk of relapse [5,55]. In contrast, in patients with nonmalignant diseases, optimization of HLA match is very important [60].

Overall, expert centers agree that TNC and $CD34^+$ cell dose thresholds that are higher than the minimum should be considered to minimize the risk of graft failure and avoid protracted post-transplant cytopenia (Table 1). Also, many centers will restrict selection to units with a donor-recipient HLA match of at least 4/8.

FAQ14: What Are Important Future Considerations in CB Unit Selection?

There are many unanswered questions in CB unit selection. Two of the most common are how to prioritize cell dose versus HLA match and the criteria for choosing single- versus double-unit grafts. Whether CB expansion will permit the safe transplantation of lower cell dose but better HLA-matched units is also unknown.

REFERENCES

1. Konuma T, Kanda J, Inamoto Y, et al. Improvement of early mortality in single-unit cord blood transplantation for Japanese adults from 1998 to 2017. *Am J Hematol*. 2020;95:343–353.
2. Spees LP, Martin PL, Kurtzberg J, et al. Reduction in mortality after umbilical cord blood transplantation in children over a 20-year period (1995-2014). *Biol Blood Marrow Transplant*. 2019;25:756–763.
3. Hayashi H, Volt F, Sanz J, et al. Myeloablative unrelated cord blood transplantation in adolescents and young adults with acute leukemia. *Biol Blood Marrow Transplant*. 2019;25:2438–2446.
4. Kanda J, Hayashi H, Ruggeri A, et al. Prognostic factors for adult single cord blood transplantation among European and Japanese populations: the Eurocord/ALWP-EBMT and JSHCT/JDCHCT collaborative study. *Leukemia*. 2020;34:128–137.
5. Yokoyama H, Morishima Y, Fuji S, et al. Impact of HLA allele mismatch at HLA-A, -B, -C, and -DRB1 in single cord blood transplantation. *Biol Blood Marrow Transplant*. 2020;26:519–528.
6. Ballen K, Logan BR, Chitphakdithai P, et al. Unlicensed umbilical cord blood units provide a safe and effective graft source for a diverse population: a study of 2456 umbilical cord blood recipients. *Biol Blood Marrow Transplant*. 2020;26:745–757.
7. Hough R, Danby R, Russell N, et al. Recommendations for a standard UK approach to incorporating umbilical cord blood into clinical transplantation practice: an update on cord blood unit selection, donor selection algorithms and conditioning protocols. *Br J Haematol*. 2016;172:360–370.
8. Ruggeri A, Paviglianiti A, Gluckman E, Rocha V. Impact of HLA in cord blood transplantation outcomes. *HLA*. 2016;87:413–421.
9. Barker JN, Kurtzberg J, Ballen K, et al. Optimal practices in unrelated donor cord blood transplantation for hematologic malignancies. *Biol Blood Marrow Transplant*. 2017;23:882–896.
10. Dehn J, Spellman S, Hurley CK, et al. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. *Blood*. 2019;134:924–934.
11. Ruggeri A. Optimizing cord blood selection. *Hematology Am Soc Hematol Educ Program*. 2019;2019:522–531.
12. Yanada M, Konuma T, Kuwatsuka Y, et al. Unit selection for umbilical cord blood transplantation for adults with acute myeloid leukemia in complete remission: a Japanese experience. *Bone Marrow Transplant*. 2019;54:1789–1798.
13. Wagner JE, Barker JN, DeFor TE, et al. Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. *Blood*. 2002;100:1611–1618.
14. Terakura S, Azuma E, Murata M, et al. Hematopoietic engraftment in recipients of unrelated donor umbilical cord blood is affected by the CD34+ and CD8+ cell doses. *Biol Blood Marrow Transplant*. 2007;13:822–830.
15. Konuma T, Kato S, Oiwa-Monna M, et al. Cryopreserved CD34(+) cell dose, but not total nucleated cell dose, influences hematopoietic recovery and extensive chronic graft-versus-host disease after single-unit cord blood transplantation in adult patients. *Biol Blood Marrow Transplant*. 2017;23:1142–1150.
16. Purtill D, Smith K, Devlin S, et al. Dominant unit CD34+ cell dose predicts engraftment after double-unit cord blood transplantation and is influenced by bank practice. *Blood*. 2014;124:2905–2912.
17. Lemarie C, Esterni B, Calmels B, et al. CD34(+) progenitors are reproducibly recovered in thawed umbilical grafts, and positively influence haematopoietic reconstitution after transplantation. *Bone Marrow Transplant*. 2007;39:453–460.
18. Barker JN, Kempenich J, Kurtzberg J, et al. CD34(+) cell content of 126 341 cord blood units in the US inventory: implications for transplantation and banking. *Blood Adv*. 2019;3:1267–1271.
19. Nakasone H, Tabuchi K, Uchida N, et al. Which is more important for the selection of cord blood units for haematopoietic cell transplantation: the number of CD34-positive cells or total nucleated cells. *Br J Haematol*. 2019;185:166–169.
20. Spellman S, Hurley CK, Brady C, et al. Guidelines for the development and validation of new potency assays for the evaluation of umbilical cord blood. *Cytotherapy*. 2011;13:848–855.
21. Politikos I, Mazis CM, Naputo KA, et al. Analysis of the CD34+ cell to total nucleated cell content ratio of 619 transplanted and back-up cord blood units. *Bone Marrow Transplant*. 2020. https://doi.org/10.1038/s41409-020-01042-7. Online ahead of print. PMID: 32862197.
22. Wagner Jr JE, Eapen M, Carter S, et al. One-unit versus two-unit cord-blood transplantation for hematologic cancers. *N Engl J Med*. 2014;371:1685–1694.
23. Rubinstein P, Carrier C, Scaradavou A, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *N Engl J Med*. 1998;339:1565–1577.
24. Kurtzberg J, Prasad VK, Carter SL, et al. Results of the Cord Blood Transplantation Study (COBLT): clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies. *Blood*. 2008;112:4318–4327.
25. Cohen YC, Scaradavou A, Stevens CE, et al. Factors affecting mortality following myeloablative cord blood transplantation in adults: a pooled analysis of three international registries. *Bone Marrow Transplant*. 2011;46:70–76.
26. Michel G, Galambrun C, Sirvent A, et al. Single- vs double-unit cord blood transplantation for children and young adults with acute leukemia or myelodysplastic syndrome. *Blood*. 2016;127:3450–3457.
27. Eapen M, Klein JP, Ruggeri A, et al. Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy. *Blood*. 2014;123:133–140.
28. Eapen M, Klein JP, Sanz GF, et al. Effect of donor-recipient HLA matching at HLA A, B, C, and DRB1 on outcomes after umbilical-cord blood transplantation for leukaemia and myelodysplastic syndrome: a retrospective analysis. *Lancet Oncol*. 2011;12:1214–1221.
29. Atsuta Y, Kanda J, Takanashi M, et al. Different effects of HLA disparity on transplant outcomes after single-unit cord blood transplantation between pediatric and adult patients with leukemia. *Haematologica*. 2013;98:814–822.
30. Barker JN, Scaradavou A, Stevens CE. Combined effect of total nucleated cell dose and HLA match on transplantation outcome in 1061 cord blood recipients with hematologic malignancies. *Blood*. 2010;115:1843–1849.
31. Ballen KK, Logan BR, Laughlin MJ, et al. Effect of cord blood processing on transplantation outcomes after single myeloablative umbilical cord blood transplantation. *Biol Blood Marrow Transplant*. 2015;21:688–695.
32. Gluckman E, Rocha V, Ionescu I, et al. Results of unrelated cord blood transplant in Fanconi anemia patients: risk factor analysis for engraftment and survival. *Biol Blood Marrow Transplant*. 2007;13:1073–1082.
33. Peffault de Latour R, Chevret S, Jubert C, et al. Unrelated cord blood transplantation in patients with idiopathic refractory severe aplastic anemia: a nationwide phase 2 study. *Blood*. 2018;132:750–754.
34. Peffault de Latour R, Purtill D, Ruggeri A, et al. Influence of nucleated cell dose on overall survival of unrelated cord blood transplantation for patients with severe acquired aplastic anemia: a study by Eurocord and the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2011;17:78–85.
35. Gluckman E, Rocha V. Donor selection for unrelated cord blood transplants. *Curr Opin Immunol*. 2006;18:565–570.

36. Fernandes JF, Rocha V, Labopin M, et al. Transplantation in patients with SCID: mismatched related stem cells or unrelated cord blood. *Blood*. 2012;119:2949–2955.
37. Boelens JJ, Aldenhoven M, Purtill D, et al. Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. *Blood*. 2013;121:3981–3987.
38. Sanz J, Sanz MA, Saavedra S, et al. Cord blood transplantation from unrelated donors in adults with high-risk acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2010;16:86–94.
39. Page KM, Zhang L, Mendizabal A, et al. Total colony-forming units are a strong, independent predictor of neutrophil and platelet engraftment after unrelated umbilical cord blood transplantation: a single-center analysis of 435 cord blood transplants. *Biol Blood Marrow Transplant*. 2011;17:1362–1374.
40. Laughlin MJ, Barker J, Bambach B, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *N Engl J Med*. 2001;344:1815–1822.
41. Barker JN, Weisdorf DJ, DeFor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood*. 2005;105:1343–1347.
42. Scaradavou A, Brunstein CG, Eapen M, et al. Double unit grafts successfully extend the application of umbilical cord blood transplantation in adults with acute leukemia. *Blood*. 2013;121:752–758.
43. Verneris MR, Brunstein CG, Barker J, et al. Relapse risk after umbilical cord blood transplantation: enhanced graft-versus-leukemia effect in recipients of 2 units. *Blood*. 2009;114:4293–4299.
44. Balligand L, Galambrun C, Sirvent A, et al. Single-unit versus double-unit umbilical cord blood transplantation in children and young adults with residual leukemic disease. *Biol Blood Marrow Transplant*. 2019;25:734–742.
45. Avery S, Shi W, Lubin M, et al. Influence of infused cell dose and HLA match on engraftment after double-unit cord blood allografts. *Blood*. 2011;117:3277–3285. quiz 3478.
46. Purtill D, Stevens CE, Lubin M, et al. Association between nondominant unit total nucleated cell dose and engraftment in myeloablative double-unit cord blood transplantation. *Biol Blood Marrow Transplant*. 2015;21:1981–1984.
47. Bejanyan N, Rogosheske J, DeFor T, et al. Higher dose of mycophenolate mofetil reduces acute graft-versus-host disease in reduced-intensity conditioning double umbilical cord blood transplantation. *Biol Blood Marrow Transplant*. 2015;21:926–933.
48. Brunstein CG, Petersdorf EW, DeFor TE, et al. Impact of allele-level HLA mismatch on outcomes in recipients of double umbilical cord blood transplantation. *Biol Blood Marrow Transplant*. 2016;22:487–492.
49. Tozatto-Maio K, Giannotti F, Labopin M, et al. Cord blood unit dominance analysis and effect of the winning unit on outcomes after double-unit umbilical cord blood transplantation in adults with acute leukemia: a retrospective study on behalf of Eurocord, the Cord Blood Committee of Cellular Therapy, Immunobiology Working Party, and the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2018;24:1657–1663.
50. Haspel RL, Kao G, Yeap BY, et al. Preinfusion variables predict the predominant unit in the setting of reduced-intensity double cord blood transplantation. *Bone Marrow Transplant*. 2008;41:523–529.
51. Barker JN, Byam C, Scaradavou A. How I treat: the selection and acquisition of unrelated cord blood grafts. *Blood*. 2011;117:2332–2339.
52. Gluckman E, Rocha V, Arcese W, et al. Factors associated with outcomes of unrelated cord blood transplant: guidelines for donor choice. *Exp Hematol*. 2004;32:397–407.
53. Eapen M, Rubinstein P, Zhang MJ, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *Lancet*. 2007;369:1947–1954.
54. Arcese W, Rocha V, Labopin M, et al. Unrelated cord blood transplants in adults with hematologic malignancies. *Haematologica*. 2006;91:223–230.
55. Sanz J, Jaramillo FJ, Planelles D, et al. Impact on outcomes of human leukocyte antigen matching by allele-level typing in adults with acute myeloid leukemia undergoing umbilical cord blood transplantation. *Biol Blood Marrow Transplant*. 2014;20:106–110.
56. Ponce DM, Hilden P, Devlin SM, et al. High disease-free survival with enhanced protection against relapse after double-unit cord blood transplantation when compared with T cell-depleted unrelated donor transplantation in patients with acute leukemia and chronic myelogenous leukemia. *Biol Blood Marrow Transplant*. 2015;21:1985–1993.
57. Oran B, Cao K, Saliba RM, et al. Better allele-level matching improves transplant-related mortality after double cord blood transplantation. *Haematologica*. 2015;100:1361–1370.
58. Delaney M, Cutler CS, Haspel RL, et al. High-resolution HLA matching in double-umbilical-cord-blood reduced-intensity transplantation in adults. *Transfusion*. 2009;49:995–1002.
59. Brunstein C, Zhang MJ, Barker J, et al. The effect of inter-unit HLA matching in double umbilical cord blood transplantation for acute leukemia. *Haematologica*. 2017;102:941–947.
60. Eapen M, Wang T, Veys PA, et al. Allele-level HLA matching for umbilical cord blood transplantation for non-malignant diseases in children: a retrospective analysis. *Lancet Haematol*. 2017;4:e325–e333.
61. Mallhi KK, Smith AR, DeFor TE, Lund TC, Orchard PJ, Miller WP. Allele-level HLA matching impacts key outcomes following umbilical cord blood transplantation for inherited metabolic disorders. *Biol Blood Marrow Transplant*. 2017;23:119–125.
62. Konuma T, Kato S, Ishii H, et al. HLA-DRB1 mismatch is associated with a decreased relapse in adult acute myeloid leukemia after single-unit myeloablative cord blood transplantation. *Ann Hematol*. 2015;94:1233–1235.
63. Brunstein CG, Cutler CS, DeFor TE, et al. Matching at human leukocyte antigen-C improved the outcomes after double umbilical cord blood transplantation for recipients of two to four of six human leukocyte antigen-matched grafts. *Biol Blood Marrow Transplant*. 2017;23:126–133.
64. Yabe T, Azuma F, Kashiwase K, et al. HLA-DPB1 mismatch induces a graft-versus-leukemia effect without severe acute GVHD after single-unit umbilical cord blood transplantation. *Leukemia*. 2018;32:168–175.
65. Stevens CE, Carrier C, Carpenter C, Sung D, Scaradavou A. HLA mismatch direction in cord blood transplantation: impact on outcome and implications for cord blood unit selection. *Blood*. 2011;118:3969–3978.
66. Matsuno N, Wake A, Uchida N, et al. Impact of HLA disparity in the graft-versus-host direction on engraftment in adult patients receiving reduced-intensity cord blood transplantation. *Blood*. 2009;114:1689–1695.
67. Cunha R, Loiseau P, Ruggeri A, et al. Impact of HLA mismatch direction on outcomes after umbilical cord blood transplantation for hematological malignant disorders: a retrospective Eurocord-EBMT analysis. *Bone Marrow Transplant*. 2014;49:24–29.
68. Kanda J, Atsuta Y, Wake A, et al. Impact of the direction of HLA mismatch on transplantation outcomes in single unrelated cord blood transplantation. *Biol Blood Marrow Transplant*. 2013;19:247–254.
69. Kogler G, Enczmann J, Rocha V, Gluckman E, Wernet P. High-resolution HLA typing by sequencing for HLA-A, -B, -C, -DR, -DQ in 122 unrelated cord blood/patient pair transplants hardly improves long-term clinical outcome. *Bone Marrow Transplant*. 2005;36:1033–1041.
70. Rocha V, Spellman S, Zhang MJ, et al. Effect of HLA-matching recipients to donor noninherited maternal antigens on outcomes after mismatched umbilical cord blood transplantation for hematologic malignancy. *Biol Blood Marrow Transplant*. 2012;18:1890–1896.
71. Van der Zanden HG, Van Rood JJ, Oudshoorn M, et al. Noninherited maternal antigens identify acceptable HLA mismatches: benefit to patients and cost-effectiveness for cord blood banks. *Biol Blood Marrow Transplant*. 2014;20:1791–1795.
72. van Rood JJ, Scaradavou A, Stevens CE. Indirect evidence that maternal microchimerism in cord blood mediates a graft-versus-leukemia effect in cord blood transplantation. *Proc Natl Acad Sci U S A*. 2012;109:2509–2514.
73. van Rood JJ, Stevens CE, Smits J, Carrier C, Carpenter C, Scaradavou A. Reexposure of cord blood to noninherited maternal HLA antigens improves transplant outcome in hematological malignancies. *Proc Natl Acad Sci U S A*. 2009;106:19952–19957.
74. Scaradavou A, Smith KM, Hawke R, et al. Cord blood units with low CD34+ cell viability have a low probability of engraftment after double unit transplantation. *Biol Blood Marrow Transplant*. 2010;16:500–508.
75. Barker JN, Scaradavou A. Response: the controversy of red blood cell–replete cord blood units. *Blood*. 2011;118. 480.
76. Jaing TH, Chen SH, Wen YC, Chang TY, Yang YC, Tsay PK. Effects of cryopreservation duration on the outcome of single-unit cord blood transplantation. *Cell Transplant*. 2018;27:515–519.
77. Nikiforow S, Li S, Snow K, et al. Lack of impact of umbilical cord blood unit processing techniques on clinical outcomes in adult double cord blood transplant recipients. *Cytotherapy*. 2017;19:272–284.
78. Mitchell R, Wagner JE, Brunstein CG, et al. Impact of long-term cryopreservation on single umbilical cord blood transplantation outcomes. *Biol Blood Marrow Transplant*. 2015;21:50–54.
79. Takanashi M, Atsuta Y, Fujiwara K, et al. The impact of anti-HLA antibodies on unrelated cord blood transplantations. *Blood*. 2010;116:2839–2846.
80. Takanashi M, Fujiwara K, Tanaka H, Satake M, Nakajima K. The impact of HLA antibodies on engraftment of unrelated cord blood transplants. *Transfusion*. 2008;48:791–793.
81. Cutler C, Kim HT, Sun L, et al. Donor-specific anti-HLA antibodies predict outcome in double umbilical cord blood transplantation. *Blood*. 2011;118:6691–6697.
82. Fuji S, Oshima K, Ohashi K, et al. Impact of pretransplant donor-specific anti-HLA antibodies on cord blood transplantation on behalf of the Transplant Complications Working Group of Japan Society for Hematopoietic Cell Transplantation. *Bone Marrow Transplant*. 2020;55:722–728.
83. Yamamoto H, Uchida N, Matsuno N, et al. Anti-HLA antibodies other than against HLA-A, -B, -DRB1 adversely affect engraftment and nonrelapse mortality in HLA-mismatched single cord blood transplantation: possible implications of unrecognized donor-specific antibodies. *Biol Blood Marrow Transplant*. 2014;20:1634–1640.
84. Brunstein CG, Noreen H, DeFor TE, Maurer D, Miller JS, Wagner JE. Anti-HLA antibodies in double umbilical cord blood transplantation. *Biol Blood Marrow Transplant*. 2011;17:1704–1708.
85. Dahi PB, Barone J, Devlin SM, et al. Sustained donor engraftment in recipients of double-unit cord blood transplantation is possible despite donor-

specific human leukoctye antigen antibodies. *Biol Blood Marrow Transplant*. 2014;20:735–739.
86. Ciurea SO, Cao K, Fernandez-Vina M, et al. The European Society for Blood and Marrow Transplantation (EBMT) consensus guidelines for the detection and treatment of donor-specific anti-HLA antibodies (DSA) in haploidentical hematopoietic cell transplantation. *Bone Marrow Transplant*. 2018;53:521–534.
87. Gladstone DE, Bettinotti MP. HLA donor-specific antibodies in allogeneic hematopoietic stem cell transplantation: challenges and opportunities. *Hematology Am Soc Hematol Educ Program*. 2017;2017:645–650.
88. Wada S, Asano-Mori Y, Yamamoto H, et al. No post-transplant pure red cell aplasia development in 106 major ABO incompatible cord blood transplantation. *Bone Marrow Transplant*. 2019;54:765–768.
89. Kudek MR, Shanley R, Zantek ND, McKenna DH, Smith AR, Miller WP. Impact of graft-recipient ABO compatibility on outcomes after umbilical cord blood transplant for nonmalignant disease. *Biol Blood Marrow Transplant*. 2016;22:2019–2024.
90. Konuma T, Kato S, Ooi J, et al. Effect of ABO blood group incompatibility on the outcome of single-unit cord blood transplantation after myeloablative conditioning. *Biol Blood Marrow Transplant*. 2014;20:577–581.
91. Romee R, Weisdorf DJ, Brunstein C, et al. Impact of ABO-mismatch on risk of GVHD after umbilical cord blood transplantation. *Bone Marrow Transplant*. 2013;48:1046–1049.
92. Brunstein CG, Wagner JE, Weisdorf DJ, et al. Negative effect of KIR alloreactivity in recipients of umbilical cord blood transplant depends on transplantation conditioning intensity. *Blood*. 2009;113:5628–5634.
93. Tanaka J, Morishima Y, Takahashi Y, et al. Effects of KIR ligand incompatibility on clinical outcomes of umbilical cord blood transplantation without ATG for acute leukemia in complete remission. *Blood Cancer J*. 2013;3:e164.
94. Tarek N, Gallagher MM, Chou JF, et al. KIR and HLA genotypes have no identifiable role in single-unit dominance following double-unit umbilical cord blood transplantation. *Bone Marrow Transplant*. 2015;50:150–152.
95. Rettman P, Malard F, Legrand N, et al. Impact of KIR/HLA genetic combinations on double umbilical cord blood transplantation outcomes: results of a French multicentric retrospective study on behalf of the Societe Francophone de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC) and the Societe Francophone d'Histocompatibilite et d'Immunogenetique (SFHI). *Bone Marrow Transplant*. 2016;51:1499–1503.
96. Sekine T, Marin D, Cao K, et al. Specific combinations of donor and recipient KIR-HLA genotypes predict for large differences in outcome after cord blood transplantation. *Blood*. 2016;128:297–312.
97. Rocha V, Ruggeri A, Spellman S, et al. Killer cell immunoglobulin-like receptor-ligand matching and outcomes after unrelated cord blood transplantation in acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2016;22:1284–1289.