ANTHONY NOLAN SEARCH ALGORITHM
FOR A BASIC CORD BLOOD UNIT
SELECTION

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PRINCIPLES FOR A NEW ALGORITHM

Once cord blood transplantation (CBT) is indicated, a cord blood search can be initiated to find a compatible donor of an appropriate cell dose from more than 500,000 cord blood grafts available worldwide. The term compatibility is used here to measure the degree of HLA matching according to predefined criteria, following published evidence on its impact on outcomes, mostly TRM and Survival.

Cell dose is based on total nucleated cell count and, in addition, CD34+ cell amount can be used as a complementary factor to accelerate engraftment. But, quality is also critical in the search process. Identifying reliable units early in the process is very important to minimize time and effort and to decrease transplantation risks. The most common qualitative differences between banks in the preliminary lists are: eligibility criteria including IDM testing, levels of HLA resolution, cell counting methodology especially for CD34+ cells and accreditation status.

Integrating HLA compatibility, cell dose and quality in a practical search process may be difficult unless issues are properly discussed and agreed in a logical decision-making process. This document aims to identify key search variables and propose a practical algorithm to simplify pathways to finding a reliable donor on time.

Anthony Nolan procedure for CB searches is based on the interactive connection of an experienced search hub and the transplant centre search unit. This Anthony Nolan (AN) algorithm (see Figure 1) defines 7 consecutive steps leading to the identification of the most suitable CB unit/s:

1. **Search request** (TC search unit). Aim: to make a formal request for CB search to avoid exploratory searches due to the work burden CB searches create. Request should contain request date, Transplant Centre, contact person’s name, Patient ID, age, weight, disease and its phase, optimal transplant date, ABO/RhD blood group and molecular HLA typing for HLA-A, -B, -C, -DRB1 and -DQB1 genes.

2. **Matching and listing** (AN Search Department). Aim: to generate lists of potential matched units after contacting local (AN and BBMR) and international (BMDW or other if appropriate, i.e. Netcord, New York Cord Blood Bank, NMDP, etc) sources. Matching will be based on HLA-A, -B at antigen level, and HLA-DRB1 at allele level, actual or potential, depending on the level of resolution. Listing of local CBUs will be presented in blocks based on level of matching (6/6, 5/6 and 4/6) and sorted by TNC dose within the blocks. Listing of international CBUs could have different format depending on the source.

3. **Search report** (AN Search Department). Aim: to send all CBU lists generated to the TC search unit for consideration.

4. **Short listing** (TC search unit or AN Search Department for GIAS users). Aim: to identify up to six suitable units from those listed according to the following criteria (note: certain clinical trials may require specific selection criteria that should be applied accordingly).
   a. For a single CB transplant, identify units containing more than 2.5x10^7 TNC/kg, first at 6/6 HLA matching level, then 5/6 and finally 4/6. For double CB transplant, cell dose cut-off could be reduced to 1.5x10^7 TNC/kg.
   b. From those identified, select units originating from “preferential qualified banks”. There are many cord blood banks worldwide with substantial differences in quality. In order to ensure reliability, predefining a group of *preferential qualified banks* might help in the search efficiency. These preferential banks must be locally licensed and internationally accredited to fulfill mandatory criteria (preferentially FACT-Netcord or AABB accreditation). A consensus engaging UK transplant centres experience and Anthony Nolan feedback might be necessary to identify this group.
During the past 5 years, Anthony Nolan has had stable positive experience in cord blood provision with the following NetCord-FACT accredited Cord Blood Banks: Melbourne (Australia), Queensland (Australia), FGR (France), Dusseldorf (Germany), Europdonor (Netherlands), Barcelona CBB (Spain), Malaga (Spain), NHSBT (UK), New York CBB (USA), Stemcyte (USA), and several other FACT-accredited CBBs in the NMDP group (USA). We have also had few Anthony Nolan (UK) CBUs successfully provided to the UK and overseas patients. Please note that The Anthony Nolan Cell Therapy Centre holds a license from the Human Tissue Authority, and currently is working towards the NetCord-FACT accreditation (onsite inspection in June 2012). We would be thankful for comments from the users on their experience with different CBBs in order to create a preferential qualified banks list.

If more than 6 units are identified at step b., focus on HLA-DRB1 potential match. Exclude those that have high probability to be HLA-DRB1 mismatch by applying genotype prediction tools. If the patient has a rare HLA-DRB1 allele, CB units with actual allele match should be preferentially selected. Avoid HLA-DRB1 mismatch in both alleles.

Order CB units in each HLA matching level by their TNC content, from highest to lowest.

c. To make a short-list, take the top 6 ordered CBUs. We recommend also to include the CBU with the biggest cell dose on the list (regardless of its HLA matching level) if it is not already included in the top 6.

d. Request Cord Blood Unit Reports on short-listed CBUs and, if necessary, request extended HLA typing to be done. Make sure that the minimum amount of essential data required for ranking is present in the CBU Reports and request missing information if necessary. Based on information received, either confirm or revise the CBU short-list.

Minimum amount of essential data:

- HLA
- TNC
- CD34
- Blood Group
- Eligibility
- Virology: including HBV, HCV, HIV tests
- Sterility
- Presence of physically attached segment to the bag

e. A summary of patient and short listed CBU characteristics can be presented using a modified report model (table 1), which is currently being used by the expert selection committee of the UK CB clinical trial.

5. Ranking (TC search unit). Aim: to select the two best units (either for a double CB transplant or for a single CB transplant including a back up CBU) based on TC criteria/preference out of the 6 (or 7) units short-listed. Transplant Centre physicians make the final decision on the units that need to be reserved and eventually requested for transplantation. TCs may have their own preferences for final ranking. Anthony Nolan recommends considering (and will use for GIAS) the following secondary criteria:

- HLA-C matching at antigen level
- HLA homozygous (blank) CBU is counted as additional “match”
- Double mismatches at the same locus on HLA-Class I
- High resolution matching in HLA Class I loci
- Mother’s HLA typing: NIMA match to prefer and IPA mismatch to be avoided
- CD34 dose
- CFU/Viability
- RBC depletion during cell processing
- Ethnicity

In particular cases where ranking is controversial, an opinion from external experts from Cord Selection Committee can be requested.
6. **Cord Blood Unit request** for reservation or shipment (TC search unit). Aim: to have a formal document on which TC indicates CBUs that need to be fully studied including all mandatory releasing tests to be performed prior to shipment agreement.

7. **Work-up and CBU Release** (AN Harvest Department). Aim: to ensure data provided is correct and meets all requirements for CB units to be shipped to TC stem cell lab before starting of patient conditioning regime. Anthony Nolan recommends ensuring the completion of the following requirements:
   - Certificate of eligibility according to medical background, travel history and behavior questionnaire complying with local regulations
   - Extended IDM testing required by HTA (and EU regulation)
   - Identity verification on CB donor basic HLA on an attached (contiguous) segment (this might also include donor gender and ABO group and maternal haplotype)
   - Potency assessment on reference samples (ideally post-thaw viability or alternatively pre-freezing CFU assays).
**FIGURE 1** Anthony Nolan Cord Blood Unit Search Algorithm

**AN CB Search Algorithm**

TC

SEARCH REQUEST ➔ LISTING ➔ REPORT ➔ SHORT-LIST ➔ WORKUP & RELEASE

AN

SEARCH REQUEST ➔ LISTING ➔ REPORT ➔ SHORT-LIST ➔ WORKUP & RELEASE

**TC**

- SEARCH REQUEST
- LISTING
- REPORT
- SHORT-LIST
- WORKUP & RELEASE

**AN**

- LOCAL
- BMDB
- OTHERS

**Matching:**
- HLA A and B antigen level
- HLA-DRB1 allele level

**6 more reliable units:**
- Qualified CBUs
- 6/6 then 5/6 then 4/6
- HLA-DRB1 prediction
- Higher TNC (>2.5e7 NC/kg)

**Minimal essential data:**
- TNC
- CD34
- Blood Group
- Eligibility
- Virology: including HBV, HCV, HIV tests
- Sterility
- Presence of physically attached segment to the bag

**Release info:**
- Attached segment
- Identity verification
- Extended IDMs
- Certificate of eligibility
- Potency assays (CFU/viability)

**Additional info:**
- Refined HLA: C, High Res, homozygous, NIMA
- Progenitor cell contain: CD34, CFU
- RBC cell depletion
- Ethnicity

**UNIT REQUEST**

**RANKING**

- 6 more reliable units:
  - Qualified CBUs
  - 6/6 then 5/6 then 4/6
  - HLA-DRB1 prediction
  - Higher TNC (>2.5e7 NC/kg)

**Reporting:**

- Local
- BMDB
- Others
FIGURE 2 Summary Search Report Spreadsheet

<table>
<thead>
<tr>
<th>Request Date</th>
<th>Centre Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Search lists</th>
<th>LOCAL BM/DW</th>
<th>EMDIS</th>
<th>OTHERS</th>
<th>anti-HLA Ab</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Sorting Ranking Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB_ID</td>
</tr>
<tr>
<td>-------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RBC depletion</th>
<th>NIMA A</th>
<th>NIMA B</th>
<th>NIMA C</th>
<th>NIMA DRB1</th>
<th>NIMA DQB1</th>
<th>Ethnicity</th>
<th>Identity</th>
<th>Eligibility</th>
<th>Viability</th>
</tr>
</thead>
</table>

| Terminology= FACT n,n n,n A+,- 6, 5 or 4_6 allele1;allele2 allele1;allele2 allele1;allele2 allele1;allele2 10 ,9,8,7,6 or 5_10 1st Y/N Y/N Method/Value |
| AABB Y/N B+,- P= potential 2nd Y/N Y/N Method/Value |
| HTA AB+,- A= actual backup |

| Local O+,- |

<table>
<thead>
<tr>
<th>Steps: Preferences:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform a Local/BMDW/EMDIS/Others Search CN dose &gt;2.5 (higher for small children) High resolution &gt;8/10 and no less than 5/10</td>
</tr>
<tr>
<td>Identify units from qualified banks &gt;=4/6 match and &gt;=2 NIMA dose 1 (higher for small children) NIMA match</td>
</tr>
<tr>
<td>Insert up to 6 units according NC/kg rank per match level CFU/CD34 &gt;10% Ethnicity match</td>
</tr>
<tr>
<td>If don't reach 6, repeat from other accredited banks CB HLA blanks avoid patient HLA Ab specificities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Action:</th>
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<td>Action</td>
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</tbody>
</table>

| Listing | Sorting | Additional info | Summary report | Ranking | Unit request | Workup | Release info | Delivery date |
REFERENCES

BULK STUDIES (PREDOMINANTLY PAEDIATRIC)

• Initial papers on cell dose and engraftment.


• **Specific match.**

STUDIES IN ADULTS


