

# Is it time to re-think a sustainable banking model for the Italian Cord Blood Network?

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Stem cell transplantation from unrelated cord blood (CB) units developed considerably from 2000 for about a decade due to the great interest of the scientific community in using CB transplants in the treatment of patients suffering from haematological diseases. The good results obtained encouraged several countries to establish CB banks and networks of banks to promote the collection of new units and to rapidly expand their inventory, without considering any threshold of total nucleated cells (TNC) in the CB. This trend permitted reaching 744,000 unrelated CB units available for transplantation worldwide<sup>1</sup>.

Recently the introduction of new transplant protocols from related haploidentical donors and the cost of CB transplants have determined a dramatic decrease of CB usage all over the world with a consequent global CB shipping index that fell to 0.45 in 2015<sup>1</sup>. In Italy, we have observed<sup>2</sup> the same negative trend with a dramatic decrease of CB transplants (from 9.5% of total national allotransplants in 2008 to 1.6% in 2015) mainly due to the impressive national increase of haploidentical transplants.

CB public banks have always demonstrated a certain degree of economic vulnerability, even when the usage rate was significantly higher; in fact they can hardly achieve a balance between the resources used for their maintenance and income resulted from CB shipping. Consequently, due to the high running costs, most public cord blood banks need external funding to survive and, specifically, in Italy the Italian Cord Blood Network (ITCBN) must be supported by the public health system.

As a result of the dramatic decrease in CB demand and in the current economic context of limited public health resources, there is increased difficulty in sustaining the activity of CB banks which are struggling to maintain their financial sustainability. Nevertheless, more than 3,000 transplants worldwide are still performed using CB as a source of stem cells, since this type of transplant has many advantages for patients: easy and rapid access, availability of compatible units for patients from ethnic minorities and biological favourable factors, especially for patients with minimal residual disease for whom recent studies<sup>3</sup> confirm CB transplants as the gold standard.

For these reasons we must ensure the survival of public programmes for unrelated CB collection and banking, with the goal of continuing to offer

this life-saving opportunity for patients. However the modified macroeconomic scenario requires substantial changes in terms of organisational models, efficiency and sustainability. It means that the banking policy followed in the last decade is no longer applicable and new strategies must be rapidly found and implemented.

To define the basic elements for decision makers better, many banks in and outside Europe have performed cost analyses<sup>4,5</sup> to acquire a precise evaluation of the economic resources needed to cover CB banking activities and management. The data obtained from these studies represent excellent benchmark elements that, in an analysis of cost-effectiveness and cost-therapeutic value, allow banking strategy to be reconfigured to get new economically sustainable models while preserving the effectiveness for patients.

On the basis of these analyses and by monitoring the characteristics of selected units, many banks adopted some strategies to be able to offer suitable CB with the lowest financial deficit. Several studies<sup>6,7</sup> have confirmed that a higher cell dose of CB correlates with a better outcome of the transplant. Since the majority of CB transplants are currently performed in adult patients, it is clear that units with a higher TNC content (usually  $>120\text{--}150 \times 10^7$ ) are more likely to be selected. Secondly, the choice of CB unit is based on HLA matching, so the level of typing and haplotype frequency also influence the probability of a unit being used.

These pieces of evidence, in addition to the economic pressure, have determined a substantial change in the goal of banking, switching from a quantitative target (storing an established number of units per country) to a qualitative one (storing only the units with a high probability of being used due to characteristics that increase their therapeutic value).

As a result of this trend in a few years we observed a dramatic decrease in the number of new banked unrelated units: from 90,000 new CB units listed worldwide in 2010 to less than the half (40,000) in 2015<sup>1</sup>. The same scenario has been observed in Italy and for this reason since July 2011, the national competent authorities and the Italian banks decided to store only units with a high TNC rate; they established, through a national standard, a pre-freezing threshold of  $150 \times 10^7$

cells, corresponding to  $120 \times 10^7$  at the banking phase (policy not applied to CB from minority ethnic groups).

This strategy has improved the quality of the Italian inventory<sup>8</sup>, since in the last five years the percentage of "higher TNC CB" has increased from 40% to 52%. Unfortunately, because of the choice of Italian transplant centres to switch from CB to haploidentical transplantation, the qualification of the national CB inventory did not result in an increased shipping rate. Therefore, in order to drive costs down and utilisation rates up, is now time to think again how to reorganise the ITCBN to become economically sustainable while complying with the needs of patients. For this purpose, the article by Pupella *et al.* "A cost analysis of public cord blood banks belonging to the Italian Cord Blood Network"<sup>9</sup>, albeit with some declared limits, offers an excellent basis for considerations and evaluations to figure out some urgent interventions.

A first consideration resulting from this analysis is that the production of a new banked CB unit in Italy is - on average - much more expensive (up to 10-fold) than in other European and US banks<sup>4</sup>. This may be due to two main factors: (i) the Italian analysis was performed after the application of the TNC threshold (Bart<sup>4</sup> assumes that the average cost of collection in the USA with an increase in the cut-off to  $150 \times 10^7$  would increase from USD 206 to USD 2,678); and (ii) the Italian scenario is influenced by effects of our national public health system organisation with a typical regional decentralisation.

According to the analysis of Pupella *et al.*<sup>9</sup>, in order to design a unique national strategy to save money while increasing the quality of Italian CB, it could be feasible to act on different phases of banking activities: (i) collection, (ii) characterisation and (iii) storage.

## Collection

The main challenge in the collection phase is currently that of obtaining a higher banking rate of CB. This essentially means increasing the capacity to collect units with a higher TNC. This could have significant economic consequences on the public banks, which now spend resources on units unlikely to be stored.

The quality of CB is primarily determined during collection and the recent consensus of the American College of Obstetricians and Gynecologists<sup>10</sup> to recommend delayed cord clamping for term and preterm infants, could reduce the proportion of units with an acceptable TNC even further, in particular for cords that are clamped more than 120 seconds after delivery (6.2% of units  $>150 \times 10^7$  TNC)<sup>11</sup>. However, even with delayed clamping practices, high quality CB banking is feasible: according to the experience of the national Swedish CB Bank<sup>12</sup> delayed clamping does not have a major effect on collection efficiency if performed

by well-trained obstetricians. Therefore, to improve collection performance, Italian banks need to continue to invest in training obstetricians and mid-wives. This can increase the percentage of collected units that are eligible for CB banking and avoid transport/test costs for units that will be discarded.

There is also a need to optimise donor selection based on maternal and infant characteristics that influence CB quality, in particular on the basis of the ethnic profile of the couple, which could improve the introduction of new or under-represented HLA haplotypes in the inventory.

## Characterisation

The analysis by Pupella *et al.* clearly points out that the test which mainly influences the total CB characterisation costs is HLA typing, which among the analysed banks, varied from a minimum of € 78.59 to a maximum of € 700.5 (an almost 10-fold difference) even though the resolution and the typed HLA *loci* have been the same in our country since 2008 (IBMDR National Standards<sup>13</sup>). This inequality, clearly due to the regional and local organisation of CB HLA typing, must be solved through centralisation of the test in one or a few tissue typing laboratories able to provide the service at competitive costs.

## Storage

In Italy only 6 units with TNC  $<120 \times 10^7$  were selected in the last couple of years<sup>8</sup>; this means that there are more than 15,000 (48%) units in our national inventory with a very low probability of being used. Consequently, the running storage cost could be reduced through a policy of selective discard of cryopreserved units with a low TNC content. Obviously to apply this strategy better, the HLA phenotypes of potentially discardable units must be analysed to avoid to eliminate CB with a unique HLA phenotype or rare alleles.

Recent Italian Bone Marrow Donor Registry (IBMDR) studies (publishing in process) have observed that there are more 6,000 units with not unique HLA phenotypes in our inventory. In contrast, we observed that 82% of new units banked annually introduce a HLA phenotype not yet represented in the ITCBN and 70% of them are not even represented in the adult donor registry. Thus, as already done in France, through the analysis of HLA haplotypes and phenotypes, banks (and their collection facilities) can still introduce rare and new phenotypes into the network, which can be of help in the choice of rationalising or centralising collection or cryopreservation.

Finally, in order to increase the utilisation rate of units with a low TNC content, in recent years, ITCBN banks have developed some projects<sup>14,15</sup> for the

preparation of platelet products, red cell concentrates and eye drops from CB units. These and other novel clinical applications for products obtained from CB can diversify the activities of the banks, making them more sustainable.

Since it is clear that whatever strategy is adopted to make the banks more sustainable will also reduce or centralise some activities, it is essential to involve stakeholders (collection centres, obstetricians, gynaecologists, mothers and the public) to understand the best use of the available resources.

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