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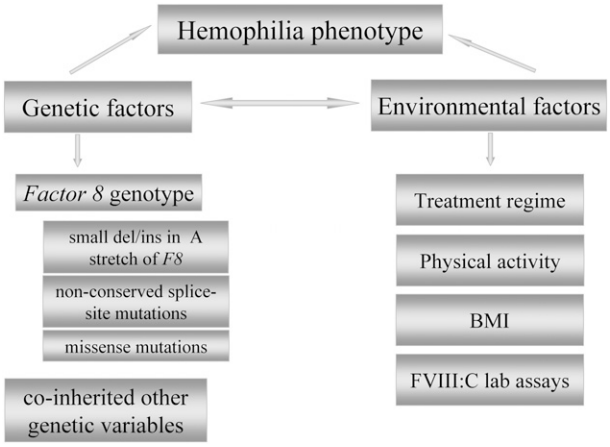

Possible factors affecting the variability of hemophilia phenotype. BMI, body mass index; del/ins, deletions/insertions; FVIII:C, factor VIII activity. Adapted from Pavlova and Oldenburg.[9]

The milder phenotype in these patients may be a result of the presence of residual amounts of endogenous FVIII activity that are undetectable with current routine FVIII activity measurement assays.

The resulting small amount of endogenous FVIII protein not only is associated with a mitigated phenotype of severe hemophilia A but also might protect against inhibitor development. Although the results of Carcao et al show statistical significance, the longest time difference between the groups of patients with null and non-null mutation is only 2.3 months for the age of first joint bleed. This finding raises the question of whether *F8* mutation can affect clinical decisions such as the choice and time of onset of prophylaxis and the application of individualized dose regimens in children with severe hemophilia A. The authors demonstrate that the relatively minor differences in the ages at first bleed and ages at first and second joint bleed, ranging between 1.2 and 2.3 months within the groups with null and non-null mutation, although contributing for the milder clinical phenotype, might not significantly influence the treatment decision, at least at early childhood.

In addition, considerable interpatient phenotypic heterogeneity among patients with the same *F8* mutation suggests that there are other factors than *F8* mutation accounting for mitigating hemophilia phenotype.[8] Although it is believed that the *F8* mutations are the strongest predictor of patient's bleeding tendency, the carefully performed investigations by Carcao et al revise the presence of other factors as genetic alterations and polymorphisms in other hemostatic genes, differences in inflammatory and immune response, and limitations in laboratory diagnostic, as well as environmental factors that alone or together could shape the individual bleeding phenotype in patients with severe hemophilia (see figure). Thus, the authors speculate that differences in the treatment regimens appear to be the largest modifier of hemophilia phenotype rather than *F8* mutation or other genetic variations in coagulation.

Why some individuals with severe hemophilia bleed more than others is still poorly understood. The study of Carcao et al is a prospective one, based on a relatively high number of subjects, and spread a light in finding markers characterizing the clinical phenotype even before the first bleeding occurs. On the basis of the findings of this study, it is reasonable to assume that *F8* mutation, as a genetic marker for the heterogeneity of hemophilia, most likely does not play this role alone but is, rather, a team player together with other factors in this complex process. Thus, identifying factors attenuating the bleeding phenotype in patients with hemophilia could allow us not only to predict the bleeding pattern but also to influence the treatment decisions, such as time of starting the prophylaxis, tailoring it according to bleeding pattern, and they could also suggest potential alternative targets for preventive and therapeutic intervention.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● TRANSPLANTATION

Comment on Boelens et al, page 3981

Better BMT for Hurler syndrome—on the level?

Michael A. Pulsipher[1] [1]UNIVERSITY OF UTAH SCHOOL OF MEDICINE

In this issue of *Blood*, Boelens et al report transplantation outcomes for the largest cohort assembled to date of patients with Hurler syndrome, demonstrating key associations with survival and outlining approaches that result in higher levels of α-L-iduronidase, the enzyme missing in this devastating disorder.[1]

"Time is brain tissue" in this autosomal recessive disease, which is generally recognized only after developmental delay, hepatosplenomegaly, dwarfism, and typical facial changes become apparent in the first 2 years of life. Untreated children become progressively neurologically devastated and generally die of heart failure, although intravenous enzyme replacement therapy can partially mitigate some non-neurologic organ complications (eg, lung, liver, skeletal). The major challenges to these children—neurologic and cardiac deterioration—can be halted, however, with swift and effective allogeneic hematopoietic cell transplantation (HCT).[2]

This article and other recent studies clarify "do's" and "don'ts" in approaching HCT for these patients. First, "do" transplant as early in life and as quickly after diagnosis as possible. Patients younger than the median age at HCT in the Boelens et al study (16.7 months) had a 16% survival advantage. Younger patients with higher intelligence measures and less organ involvement at transplant also have been shown to have better developmental and skeletal outcomes.[3-5] With this in mind, the median delay from diagnosis to transplant of 5.2 months noted in this report should never occur. Referral to HCT should be swift, and patients should receive their procedures within weeks rather than months.

Another "do" on the list may break a long-held allogeneic HCT commandment—"transplant with the best HLA match possible, fully matched sibling donor first choice, with fully matched unrelated donor second." Boelens et al show that event-free survival (EFS) with fully-matched siblings and 6/6 HLA-matched cords is equivalent (81% at 5 years). It can be agreed that the strongest likelihood of survival would occur with these 2 stem cell sources; however, I explain more about the risks of using a sibling later in this comment. If either of these 2 stem cell sources is not available, survival numbers fall (5-year EFS 68% for 5/6 cords, 66% for 10/10 unrelated marrow, 57% for 4/6 cords, and 41% for mismatched unrelated marrow), although survival has improved in recent years (EFS 75% for HCT after 2004). Thus, when is it worth the risk to use mismatched cords over a matched unrelated donor, and should a sibling donor always be used?

The biggest weakness noted in using noncord donors has been the high rate of partial chimerism (30%-50%). Much of this is related to earlier failed attempts at T-cell depletion and reduced-intensity conditioning approaches[6]; until better approaches to T-cell depletion and reduced-intensity conditioning for these patients eliminate this issue, these methods of HCT are high on the list of "don'ts." Boelens et al further describe mixed chimerism in sibling and unrelated donor procedures in a little more than 25% of the transplants performed (see table). This outcome is assuredly better when targeted intravenous busulfan approaches are used (something the authors point to as leading to improved engraftment). However, worry remains: if the patient survives HCT and is a mixed chimera, or even a full donor chimera from a sibling donor who is a carrier, will there be sufficient levels of enzyme to deliver what the patient needs to avoid neurologic deterioration? Sibling carrier status has been linked to lower enzyme levels,[7] and patients who do not achieve at least "normal" enzyme levels have been shown to have worse neurologic outcome in some small series.[5] More work by this international collaborative group looking specifically at enzyme levels achieved with various stem cell sources and their effect on neurologic outcomes is promised in the article and will help clarify the importance of this measure.

The next "do" suggested by this paper is that unrelated cord blood seems to be the stem cell source of choice for most patients. If our goal is to move to HCT quickly and recipients of 5/6 cords and 10/10 unrelated donors have similar survival, the cord wins because it is readily accessible with less worry about partial chimerism using established regimens. Boelens et al show that only 7% of cord blood recipients had mixed chimerism, and 95% had normal enzyme levels (see table). This is in sharp contrast to sibling and unrelated donors, where 33% had mixed chimerism and 37% had low enzyme levels. Low enzyme expression in sibling donor recipients also occurs because many sibling donors are heterozygotes (carrier status of sibling donors was not available to the authors so correlations with enzyme level are not reported). Even when donors are not carriers (unrelated donors or cord blood), there are polymorphisms leading to marked differences in expression of enzymes associated with many inborn errors of metabolism.[8] This fact has led some centers to choose cord blood units based on both HLA match and enzyme expression levels.

So, is a final "do" shown by Boelens et al that we should not use a matched sibling donor for patients with Hurler syndrome? Although survival for unrelated donors has improved over the past decade, this has occurred in related donor procedures as well. A choice to not use a sibling carrier may be best for long-term neurologic outcomes, but it comes with an increased risk of transplant-related mortality that a family must understand when transplant options are reviewed. More data correlating long-term enzyme expression with stem cell source and recipient outcomes is needed to bolster confidence in the existing data. How about the use of a noncarrier sibling or fully matched unrelated donor? These are certainly acceptable stem cell sources, but approaches designed to achieve full-donor chimerism must be used to ensure normal enzyme levels are achieved. Should cord blood units and sibling or unrelated donors be screened for

Relationship among stem cell source, chimerism, and post-HCT enzyme levels

	Matched sibling, n (%)	Matched unrelated, n (%)	T-cell–depleted unrelated, n (%)	Unrelated cord blood, n (%)
Chimerism				
Full (>95%)	21 (70%)	26 (74%)	9 (50%)	69 (93%)
Mixed (50%-95%)	6 (20%)	6 (17%)	4 (22%)	5 (7%)
Mixed (10%-50%)	3 (10%)	3 (9%)	5 (28%)	0
Missing	0	0	1	5
Enzyme level				
Normal	16 (62%)	23 (66%)	5 (56%)	64 (98%)
Low	10 (38%)	12 (34%)	4 (44%)	1 (2%)
Missing	2	0	9	14

Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. Adapted from Boelens et al that begins on page 3981.

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enzyme expression or polymorphisms related to risk of lower expression? These are important study questions as research moves forward. Further study will help as we consider breaking the most sacred commandment of HCT: "sibling donors are always better than unrelated donors"—in the case of Hurler syndrome, this may not always be true.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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