Immune mediated marrow failure in very young children: horse ATG once again out of the magician's hat

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Received: April 14, 2026.
Accepted: April 21, 2026.
Early view: April 30, 2026.

https://doi.org/10.3324/haematol.2026.301004

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Aplastic anemia in children has a complex differential diagnosis. In general, inborn bone marrow failure syndromes involving DNA damage repair, ribosomal protein synthesis, telomere length maintenance and stem cell dysfunction are rare but important diagnoses to consider. Several of these diagnoses can be identified by gene panel screening, but for others functional assays remain important since not all genes are known. Most of the diagnoses of bone marrow failure syndrome have clinical consequences, including adapting conditioning regimens for allogeneic hematopoietic stem cell transplantation (HSCT), as well as implications for follow-up, counseling and screening of families.

Other etiologies involve infectious diseases and autoimmunity. It is generally believed that autoimmunity is rare in very young children. However, in this issue of *Haematologica*, Wittmann Dayagi *et al.*[1] report intriguing data suggesting that this belief may need reconsideration: 30 patients, aged 16-35 months, were treated with - mainly horse antithymocyte globulin (ATG)-based-immunosuppressive treatment (IST) and the response was unexpectedly impressive: not only was the complete response rate 80%, leading to transfusion independency and an overall survival of 100%, the responses were durable with no relapses during prolonged follow-up.

Many issues with a registry-based evaluation as presented here, can (and will) be raised, but to cut a long story short, these excellent results clearly indicate that IST remains a valuable option in young children with aplastic anemia. This is of even greater importance since haplo-identical HSCT, using post-transplantation cyclophosphamide, has revolutionized the access to transplants in many parts of the world.

Let us be clear: if a healthy, matched sibling donor, willing to donate marrow (avoiding chronic graft-*versus*-host disease) is available, no time should be lost to avoid dangerous or even lethal infections or bleeding complications. In large parts of the world well-matched unrelated marrow donors are also considered an excellent option. Even then the differential diagnosis should be evaluated carefully, in order to adapt conditioning regimens if appropriate, e.g., in Fanconi anemia. So, several weeks are needed to come to a plan for appropriate therapy. However, in the absence of a well-matched donor, IST still deserves consideration. HSCT has become safer, but it inherently carries risks, particularly of graft-*versus*-host disease and graft failure. This can potentially affect quality of health and even survival.

IST has a long history of unexpected findings if not surprises: the classical study comparing horse with rabbit ATG[2] is a true hallmark: horse ATG was unexpectedly superior to rabbit ATG. Later, studying the effect of adding eltrombopag to IST in adults, again, it was unexpectedly found that the addition of eltrombopag was beneficial.[3]

Let us now dive deeper into the paper presented in this issue of *Haematologica*. The data stem from North American registries. The diagnostic testing was not complete in all the subjects included. However, it is unexpected for IST to be effective in cases of inherited bone marrow failure. Thus, missed diagnoses of inherited marrow failure would lead to lower response rates. Response evaluation and registration of complications were not done in a systematic, prospective manner. Nevertheless, the unexpectedly high response rates remain remarkable. Some patients were treated decades ago, with now unusual approaches, such as high-dose cyclophosphamide as the immunosuppressive agent.

In clinical practice it would be of great value not only to predict upfront who will respond to IST, but also to know when IST can be concluded to have failed. This would prevent unnecessary loss of time before proceeding to salvage HSCT. The small retrospective series by Wittmann Dayagi *et al*. seems too limited to draw firm conclusions for such a clear timepoint to decide when IST has failed. Having to wait 6 months before deciding whether performing HSCT cannot be avoided is too long for many patients. But after 4-6 months, only half of all patients ultimately responding to IST (defined as transfusion-independent) had done so.

This clearly is challenging. Only the clinical situation (complications, side effects of cyclosporine, donor availability, shared decision-making) can then lead the way.

A major potential risk of IST is a prolonged need of cyclosporine treatment or even dependency on this therapy. This is hardly acceptable in children. The median duration of treatment with this drug in responding patients was 24 months, which seems tolerable, although a registry study is not the ideal setting to evaluate long-term side-effects. The study by Wittmann Dayagi *et al*. again challenges therapy decisions in young children with aplastic anemia. Our therapeutic toolkit is never static: post-transplantation cyclophosphamide continues to change the feasibility of HSCT. Eltrombopag might be of additional value although it is currently not considered beneficial in young children with aplastic anemia.[4] However, based on the data presented by Wittmann Dayagi *et al*. ATG-based IST should not be excluded.

Disclosures

MB is a member of an advisory board for Pfizer. KT has no conflicts of interest to disclose.

Contributions

MB and KT contributed equally to the preparation of this Editorial.

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