for its action? What are the other erythroid regulators of hepcidin and what are their relative roles compared with ERFE? Will targeting ERFE prove a viable therapeutic strategy to limit iron overload and organ dysfunction in patients with β-thalassemia or other anemias of ineffective erythropoiesis? The answers to these questions will provide new insights into the mechanisms of iron overload and organ dysfunction in patients with iron-loading anemias and may pave the way for new therapies for these disorders.

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THROMBOSIS AND HEMOSTASIS

*Comment on Clark et al., page 452*

# Baby steps in managing CVAD-related thrombosis

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**Clark et al, in this issue of *Blood*, have provided the first robust step in developing an evidence-based strategy for the secondary prevention (ie, prevention of recurrent thrombosis after an index thrombotic event) of venous thromboembolism (VTE) in children with long-term central vascular cannula (CVC).[1] This data has been a long time coming. In 1994, Maureen Andrew and colleagues published the first analysis of the Canadian registry of VTE in children, highlighting the critical role that CVC plays in the etiology of VTE in children.[2]**

Multiple studies confirmed the centrality of CVC in VTE in children. Randomized trials, starting with the PROTEKT trial led by Patti Massicotte, proved incredibly difficult to complete and failed to show any benefit of prophylactic strategies.[3] The inability to identify high-risk children such that the numbers needed to treat were reasonable has remained a stumbling block for prophylaxis trials. While questions of risk stratification still remain unanswered when considering primary prophylaxis, Clark et al have provided important forward steps in developing a secondary prophylaxis strategy.[1]

The team at Children's Hospital of Philadelphia report a retrospective study of patients less than 19 years of age at their center, with an index CVC-VTE between 2003 and 2013. Among 373 patients with an index CVC-VTE, 239 (64.1%) had subsequent CVC placement; 17.4% (65/373) of the patients had recurrent VTE, of which 90.8% (59/65) were CVC-associated. On multivariable survival analysis, each additional CVC (hazard ratio [HR] 12.00; 95% CI 2.78-51.91), congenital heart disease (HR 3.70; 95% CI 1.97-6.95), and total parenteral nutrition dependence (HR 4.02; 95% CI 2.23-7.28) were associated with an increased hazard of recurrence. Full-dose anticoagulation for secondary prophylaxis was associated with decreased odds of recurrent CVC-VTE (odds ratio [OR] 0.35; 95% CI 0.19-0.65), but prophylactic dosing was not (OR 0.61; 95% CI 0.28-1.30). Only 1.3% of CVCs experienced major bleeding with prophylactic or full-dose anticoagulation.[1]

As a single-center retrospective study, there are many limitations, but this is a large cohort study by pediatric VTE standards.[4] The study raises many further questions, for example, about the role of peripherally inserted central catheters vs the role of tunneled catheters and the role of thrombophilia. While less than 20% of children had recurrent VTE, continuing to make the numbers needed to treat balance difficult, there were clearly high-risk groups identified (ie, children with congenital heart disease or dependent on total parenteral nutrition), giving clinicians some guidance as to where to target their efforts. The authors acknowledge that the timing of CVC removal and subsequent timing of insertion of replacement CVC (if required) is a confounding factor that is worthy of considerably more study. But perhaps the most striking result from this study is the success of full-dose anticoagulation in reducing subsequent VTE compared with the negligible effect of prophylactic-dose anticoagulation. Full-dose anticoagulation as secondary prophylaxis with subsequent CVC placement was associated with a 65% reduction in the odds of CVC-VTE recurrence as compared with no anticoagulation. This is consistent

with the 2012 Chest Guidelines recommendation that thromboprophylaxis for children with TPN dependence using vitamin K antagonists targets an INR 2 to 3 (ie, a therapeutic target). However, that recommendation was based on very small numbers of patients without comparison with the outcomes for prophylactic dosing.[5] The size of the cohort presented by Clarke et al, and the clarity of the outcome when compared with prophylactic dosing, despite the study limitations, is very significant. Importantly, the bleeding risk from the full-dose anticoagulation remained acceptably low. Clinicians can feel more confident in using a full-dose secondary prophylaxis strategy for children with previous CVC-VTE.

There remains much work to be done. As mentioned, the timing of CVC removal and replacement likely plays a significant role in the risk of recurrence. Further risk stratification of children is required. Moreover, consideration of broader outcomes than just clot recurrence, including overall mortality and morbidity, relationship of anticoagulation strategy to the incidence of central line-associated bloodstream infections, impact on bone density, and quality of life are important. In partnership with our multidisciplinary teams, further research regarding optimizing central venous access device selection in order to mitigate VTE risk is needed. The role of direct oral anticoagulants will need to be determined, especially in the long-term total parenteral nutrition group, in whom oral feeding is limited or nonexistent. Randomized controlled trials, such as the trial of early anticoagulation initiation in the acute setting,[6] will contribute, but randomized trials in the longer-term specific patient populations will remain difficult to fund, power adequately, and complete. Prospective observational studies such as the Children's Hospital Acquired Thrombosis Consortium[7] and International Pediatric Thrombosis Network[8] are going to be major sources of reliable information going forward.

The first steps are often the hardest, and progress in this field has been stalled for some time. The authors should be congratulated on a carefully performed retrospective analysis that has added another significant piece to an ever-evolving puzzle. When as pediatricians, we watch a baby take those first awkward steps after multiple failures, we know that despite the inevitable further falls, sooner or later, the child will be running. Hopefully, the gathering momentum around reducing the burden of CVC-related VTE in children can continue to move the field forward and improve the antithrombotic care and eventually quality of life of children with complex underlying medical conditions.

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