

# inside **blood** commentary

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Hanslik et al, page 2091

## aPTT in children receiving UFH: time for a change?

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In this issue of *Blood*, Hanslik et al compare 2 dose protocols for unfractionated heparin in children undergoing cardiac catheterization and demonstrate poor agreement between the 3 assays (anti-Xa, activated partial thromboplastin time [aPTT], and activated clotting times [ACTs]) used to measure heparin's anticoagulant effect.<sup>1</sup>

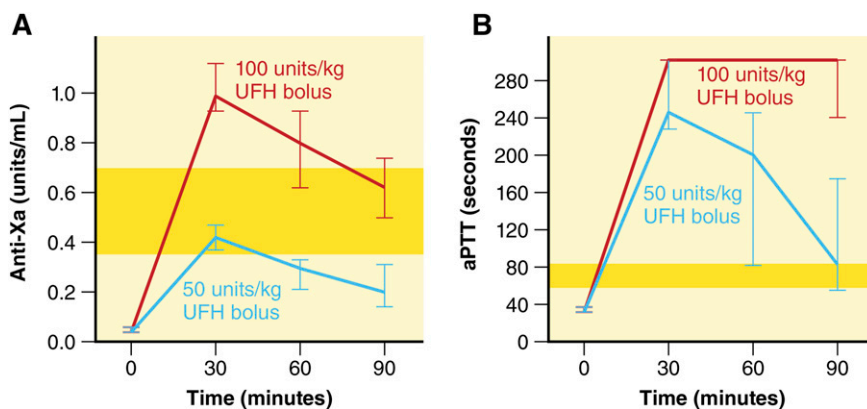
Unfractionated heparin (UFH) remains an important therapeutic modality for anticoagulation in children. Its short half-life and easy reversibility with protamine sulfate make it an attractive option in critically ill children. Although initially described as a screening tool for hemophilia, the aPTT is a global hemostatic assay that reflects the integrity of the intrinsic and common pathways of the in vitro coagulation cascade and is commonly used to monitor UFH.

In a landmark publication in 1972, Basu et al<sup>2</sup> demonstrated that the risk of recurrent thrombosis in adults receiving heparin could be significantly reduced by aiming for a 1.5 to 2.5 times prolongation of the aPTT. A subsequent cohort study by Andrew et al<sup>3</sup> documented a 73% agreement between aPTT and anti-Xa activity in 52 children receiving UFH therapy ( $r^2 = 0.51$ ), and the therapeutic range of 1.5 to 2.5 times baseline was extrapolated for children. Over time, however, it has become apparent that

the aPTT is affected by several preanalytical, analytical, and biological variables, and current guidelines recommend that the therapeutic aPTT range corresponds to an anti-Xa of 0.35 to 0.7 U/mL.<sup>4</sup> Recent studies have documented poor agreement between the 2 assays ( $r^2: 0.08-0.27$ ), with the aPTT frequently overestimating the heparin effect compared with anti-Xa.<sup>5-7</sup>

In the current article, the authors report post hoc analysis on laboratory data collected during a parallel cohort, randomized, double-blinded controlled study comparing 2 dosing protocols of UFH to prevent thromboembolism in children undergoing cardiac catheterization (HEART CAT).<sup>1</sup> The primary clinical outcomes of the study were previously published and did not demonstrate a significant difference in thrombosis or bleeding between high-dose and low-dose UFH.<sup>8</sup> aPTT, anti-Xa, and ACTs were obtained at baseline and 30, 60, and 90 minutes after heparin bolus; in total, 492 blood samples were collected from 149 subjects.

Although all 3 assays discriminated well between high-dose and low-dose UFH, there was poor correlation between the assays. Congruent with previous reports, the aPTT frequently overestimated the UFH effect reported by anti-Xa and was supratherapeutic for all measured time points in both protocols (see figure). In the high-dose arm (100-U/kg bolus followed by continuous infusion), the anti-Xa was supratherapeutic initially, but became therapeutic by 90 minutes. In the low-dose arm (50-U/kg bolus without continuous infusion), the anti-Xa was therapeutic initially but rapidly became subtherapeutic. The authors therefore suggest a 75-U/kg bolus in pediatric subjects undergoing cardiac catheterization procedures. They also conclude that the aPTT was overly sensitive to heparin effect in this cohort and suggest using anti-Xa, with the ACT recommended as a comparably



Time course of anti-Xa and aPTT values (median, 95% confidence interval) comparing high-dose (100-U/kg bolus followed by continuous infusion) vs low-dose (50-U/kg bolus without continuous infusion) UFH dosing protocols. Yellow shaded bars indicate therapeutic ranges. This figure has been adapted from Figure 1 in the article by Hanslik et al that begins on page 2091. Professional illustration by Patrick Lane, ScEYence Studios.

reliable alternative when a bedside test is more appropriate.

Clinical trials of antithrombotic therapy in children have been plagued by poor recruitment, early closure, and underpowering. The current study is an example of strategies that can be used to overcome these barriers. Adding a parallel cohort arm to the traditional randomized design allowed for inclusion of subjects who may otherwise have not been eligible for randomization due to scientific, ethical, or logistical reasons.<sup>9</sup> These subjects constitute an important cohort of the disease population, and such a design allows for a more heterogeneous and “real-world” study population. Another challenge with patient recruitment is that thrombosis is a complication of other underlying diseases, and hematologists are often not the primary providers for these complex and often acutely ill patients. It is imperative that clinician scientists in the thrombosis arena include other disciplines such as cardiology, critical care, and surgery to enhance access to potential study patients. In this case, a team composed primarily of cardiology investigators have added substantially to our knowledge of anticoagulants in children by studying heparinized patients undergoing cardiac catheterization.

The results of this study, however, need to be interpreted with caution. UFH was used in relatively stable children undergoing diagnostic catheterization in controlled settings. As most patients received a single dose of UFH, the results may not be applicable to critically ill children receiving therapeutic UFH infusions. With regard to superiority of anti-Xa over aPTT, the decision remains unclear. A recent retrospective study did not show a difference in bleeding outcomes or time to therapeutic range after transitioning from an aPTT-based nomogram to an anti-Xa-based one.<sup>10</sup> The anti-Xa is more specific to heparin activity and is less affected by preanalytic variables. However, it is more expensive and does not take into account heparin’s anti-IIa activity, which may contribute to its therapeutic effect. Standardized collection of clinical outcome and safety data, particularly data on clot resolution, recurrence, bleeding, and rates of postthrombotic syndrome from prospective trials, are needed to help decide if the aPTT is truly obsolete in patients receiving heparin.

*Conflict-of-interest disclosure: The authors declare no competing financial interests.* ■

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## ● ● ● IMMUNOBIOLOGY

Comment on van Keimpema et al, page 2098

# FOXP1 inhibits plasma cell differentiation

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After antigen contact, B cells rapidly differentiate and cycle through several phenotypical intermediaries before entering 1 of 2 longer-lived stages, the memory B cell or the plasma cell. In this issue of *Blood*, van Keimpema et al identify a role for the forkhead transcription factor FOXP1 in inhibiting the very last differentiation stage: plasma cell differentiation.<sup>1</sup> They show that FOXP1 directly represses several key regulators of plasma cell differentiation. Although FOXP1 is strongly expressed in naïve B cells, it is lost as B cells enter germinal center differentiation.<sup>2</sup> However, it is re-expressed in memory B cells where it correlates with immunoglobulin class switch recombination status, with immunoglobulin (Ig)G-switched memory B cells expressing lower levels of FOXP1. Interestingly, this correlates with a trait of IgG-switched memory B cells to being more likely to enter plasma cell differentiation<sup>3</sup> (see figure).

**T**he forkhead box or FOX proteins are a family of transcriptional regulators, typically displaying the forkhead motive, a 100-amino-acid protein motive involved in DNA binding. The original fork head protein was described in *Drosophila melanogaster* and is involved in regulating terminal differentiation.<sup>4</sup> Immunologists are aware of the family mainly through FOXP3, the master regulator for regulatory T cells.<sup>5</sup> Less has been published on FOXP1, which has been largely studied in connection with embryonic and brain development. Similar to other transcription factors, FOXP1 can act as

a transcriptional inducer or repressor.<sup>2</sup> Transcriptional regulation plays an important role in the development of lymphoma. Increased activities of genes that inhibit terminal plasma cell differentiation, eg, *Paired Box 5 (Pax5)*, *B cell lymphoma 6 (Bcl6)*, *Spi-B*, or loss of function of *Positive Regulatory Domain 1 (Prdm1)*, the gene coding for BCL10-interacting MAGUK protein 1 (BLIMP1), are often associated with B-cell non-Hodgkin lymphomas. Similarly, translocation of *FoxP1* has been shown to be associated with poor prognosis in diffuse large B-cell lymphoma<sup>6</sup> and other lymphomas.