Anti-Factor Xa–Based Monitoring of Unfractionated Heparin: Clinical Outcomes in a Pediatric Cohort

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Objectives To assess clinical outcomes in children treated with unfractionated heparin and monitored using an anti-factor Xa (Anti-FXa)-based nomogram. We also sought to assess the correlation between activated partial thromboplastin time (APTT) and Anti-FXa.

Study design This was a single-center, observational cohort study conducted over a 20-month period that included all pediatric patients (<21 years) who received therapeutic unfractionated heparin and were monitored using an anti–FXa-based nomogram.

Results In total, 95 patients met prespecified inclusion criteria, and 1098 pairs of APTT and Anti-FXa measurements were performed. The median unfractionated heparin dose required to reach therapeutic Anti-FXa goal was significantly greater in infants compared with older children (P <.0001). The median time to achieve therapeutic Anti-FXa was 10 hours (range 2-96 hours) and was significantly shorter in patients who received a bolus compared with those who did not (P = .03). Five (5.3%) major bleeding events were noted. Age, peak Anti-FXa, peak APTT, lowest platelet count, and fibrinogen were not predictive of major and clinically relevant nonmajor bleeds. Moderate correlation between the APTT and Anti-FXa (r = 0.75; 95% CI 0.72-0.77) assays was appreciated.

Conclusions Using an anti–FXa-based nomogram to monitor unfractionated heparin in children is feasible. Although moderate correlation was observed between the APTT and Anti-FXa assays, the APTT frequently overestimated heparin activity. Safety and efficacy of an Anti-FXa nomogram needs further validation. *(J Pediatr 2019;209:212-9)*.

During the last 2 decades, advancement in the treatment and supportive care of critically ill children and the increasing use of central venous catheters has contributed to an increase in the annual rate of venous and arterial thromboembolic events among hospitalized neonates and children.[1,2] Nonetheless, there is a lack of high-quality evidence to guide anticoagulation management in this cohort, and treatment is commonly extrapolated from adult practice.[3]

Although low-molecular-weight heparin and direct oral anticoagulants increasingly are being used to treat and prevent thromboembolism in children, unfractionated heparin remains an important anticoagulant in the inpatient setting, particularly in critically ill patients.[4] Unfractionated heparin exerts its anticoagulant activity primarily via antithrombin-mediated inhibition of thrombin and factors Xa, IXa, and XIa. Given its short half-life and immediate, complete reversibility with protamine sulfate, unfractionated heparin allows close titration of anticoagulation in children perceived to be at high risk of bleeding and those on extracorporeal membrane oxygenation (ECMO) and left ventricular assist devices (LVADs).

Unfractionated heparin drug monitoring is aimed at balancing the anticoagulant effect and the risk of treatment-related bleeding complications. The activated partial thromboplastin time (APTT) is a global test of coagulation that measures the integrity of the intrinsic and common coagulation pathways. Initially described as a screening tool for hemophilia, the APTT has been used widely to monitor unfractionated heparin. Basu et al demonstrated that the risk of recurrent thrombosis in adults receiving unfractionated heparin could be significantly reduced by aiming for a 1.5-2.5 times prolongation of the APTT.[5] Subsequently, it was realized that the measurement of APTT is affected by several preanalytical, analytical, and biological variables, particularly in children.[6] APTT testing is sensitive to inappropriate sample collection, handling, and processing, leading to erroneous results.[7] The measurement of APTT is sensitive to the reagent and coagulometer used for testing, and the implications of the resultant variability in the level of anticoagu-

Anti-FXa	Anti-factor Xa heparin assay
APTT	Activated partial thromboplastin time
CRNMB	Clinically relevant nonmajor bleeding
ECMO	Extracorporeal membrane oxygenation
HIT	Heparin-induced thrombocytopenia
LVAD	Left ventricular assist device

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lation achieved with a fixed APTT goal are significant.[8,9] The lack of standardization of reagents used in APTT testing adds to the interlaboratory variability.[10] In addition, baseline APTT is relatively prolonged in neonates and young infants; hence, absolute APTT therapeutic ranges calculated using adult plasma likely represent subtherapeutic anticoagulation.[6,11,12]

The anti-factor Xa heparin assay (Anti-FXa) is an automated, chromogenic or clotting-based assay that measures the factor Xa neutralizing capacity of heparin and is a more direct measure of the heparin level in the plasma.[13] The measurement of Anti-FXa is also influenced by preanalytical and analytical variables, but it fluctuates less than APTT.[10] More importantly, biological variables like liver disease, increased level of acute-phase reactants, and presence of lupus anticoagulant that affect APTT measurement do not interfere with Anti-FXa testing.[10,14]

The American College of Chest Physicians and the College of American Pathologists recommend that the APTT range used to monitor unfractionated heparin should correspond to a heparin level of 0.3-0.7 units/mL measured by an Anti-FXa assay or 0.2-0.4 units/mL measured by protamine titration.[8,15] With the increased availability of automated Anti-FXa assays in clinical practice, several investigators sought to explore the correlation between the time-trusted APTT and newer Anti-FXa assays.[2,16-18] Pediatric studies have had varying limitations, including retrospective study design, small sample size, and/or heterogeneous patient populations, specifically inclusion of neonates and patients on ECMO and LVADs.[19-24]

A previous study from our institution showed moderate correlation between the APTT and Anti-FXa assays, prompting an institution-wide change to an Anti-FXa based monitoring of unfractionated heparin.[24] The current study is a descriptive analysis to evaluate the clinical outcomes in this pediatric cohort treated with unfractionated heparin and monitored using an Anti-FXa nomogram, specifically looking at its safety and efficacy. In addition, given that we simultaneously obtained APTT values with the Anti-FXa assay, we sought to investigate the correlation between the 2 assays.

Methods

This was a single-center, observational cohort study conducted at the Nationwide Children's Hospital in Columbus, Ohio, a quaternary-care pediatric facility in the Midwest. In September 2015, based on internal quality improvement data and in-line with other major children's hospitals across the nation, there was institution-wide adoption of an anti–FXa-based nomogram to monitor anticoagulation with unfractionated heparin. All pediatric patients receiving therapeutic unfractionated heparin could only receive the drug per this physician-titrated, computerized nomogram. Because this was considered institutional standard of care, individual patient consent was not required; however, the institutional review board at Nationwide Children's Hospital approved the retrospective data collection, analysis and submission for scientific publication.

All pediatric patients, 21 years of age or younger who received unfractionated heparin infusion for treatment or prevention of thromboembolic disease with a target Anti-FXa goal of 0.35-0.7 units/mL were included. Patients for whom unfractionated heparin was being used for anticoagulation of mechanical circuits like LVADs and ECMO, where the duration of unfractionated heparin anticoagulation was <24 hours, where the institutional unfractionated heparin nomogram was not followed, and/or patients on concomitant antiplatelet or warfarin therapy were excluded. Patients undergoing catheter-directed thrombolysis at Nationwide Children's Hospital typically receive fixed-dose unfractionated heparin (10 units/kg/h) periprocedure. We therefore only included post-thrombolysis data for these patients (once they were treated per the anti–FXa-based nomogram).

Anti-FXa Monitoring Protocol for Unfractionated Heparin Infusion

All patients received an initial heparin bolus of 75 units/kg with the exception of neonates <44 weeks of corrected gestational age, patients with stroke, or when the risk of bleeding was perceived to be high. This was followed by initial maintenance unfractionated heparin infusion rate of 28 units/kg/h in patients <1 year of age, 20 units/kg/h in patients between 1 and 17 years of age, and 18 units/kg/h in patients 18-21 years of age. Before starting anticoagulation, complete blood count, APTT, prothrombin time, fibrinogen activity, and d-dimer were obtained on all patients. After unfractionated heparin therapy was commenced, Anti-FXa and APTT were drawn simultaneously from each patient at 4-hour intervals. The unfractionated heparin infusion rate was adjusted to maintain an Anti-FXa between 0.35 and 0.7 units/mL. The Anti-FXa levels were used to titrate the unfractionated heparin infusions based on a standard protocol (Table I). If the APTT was >150 seconds, the patient was monitored closely for bleeding, remaining coagulation measures (platelet count, prothrombin time, fibrinogen) were checked, and sample contamination was ruled out by repeating the

Table I. Nomogram used for the titration of unfractionated heparin infusions

Anti-FXa, units/mL	Unfractionated heparin bolus, units/kg	Time to hold unfractionated heparin infusion, min	Unfractionated heparin infusion rate change	Repeat APTT and Anti-FXa
<0.1	50*	0	Increase 10%	4 h
0.1-0.34	0	0	Increase 10%	4 h
0.35-0.7	0	0	0	24 h†
0.71-0.89	0	0	Decrease 10%	4 h
0.90-1.2	0	30	Decrease 10%	4 h
>1.2	0	60	Decrease 15%	4 h

*No bolus was given in neonates <44 weeks of corrected gestational age, patients with stroke, or when the risk of bleeding was perceived to be too high.
†Once 2 consecutive Anti-FXa levels obtained 4 h apart were therapeutic, Anti-FXa and APTT levels were obtained once every 24 h.

APTT and Anti-FXa assays on a fresh venipuncture sample. Once 2 consecutive Anti-FXa obtained 4 hours apart were within the therapeutic range, Anti-FXa and APTT were obtained once daily while the patient remained on unfractionated heparin infusion.

Laboratory Assays

The blood samples for coagulation testing were drawn from fresh venipunctures or indwelling catheters via standardized institutional policies.[25] The Anti-FXa and APTT assays were performed using the commercially available STA-R Evolution Analyzer (Diagnostica Stago Inc, Parsippany, New Jersey) using the STA-liquid Anti-FXa reagents and the STA-PTT reagent containing cephalin and a particulate activator (silica) in a buffered medium, respectively. No excess, free antithrombin was added to the Anti-FXa assays.

Bleeding and Thrombotic Complications

Definitions of bleeding complications were based on previously published recommendations from the Perinatal and Paediatric Haemostasis Subcommittee of the International Society on Thrombosis and Hemostasis.[26] Bleeding episodes were categorized as "major" bleeding when bleeding was fatal; bleeding associated with a >2 g/dL drop in the hemoglobin within a 24-hour period; retroperitoneal, pulmonary, or central nervous system bleeding; or bleeding that required surgical hemostasis in an operating room. In addition, "clinically relevant nonmajor bleeding" (CRNMB) was defined as overt bleeding for which a blood product was administered and was not related to the patient's underlying medical problem or bleeding that required medical or surgical intervention outside of the operating room. Lastly, "minor" bleeding was defined as any overt or macroscopic bleeding that did not fulfill the aforementioned criteria.

To investigate the impact of laboratory measures on major and CRNMB events, the Anti-FXa, APTT, fibrinogen, and platelet counts noted at the time of bleeding in these patients were compared with the greatest APTT, Anti-FXa, lowest platelet count, and fibrinogen level for patients with minor/no bleeding (during the course of anticoagulation).

In the cases of arterial or venous thromboembolism, the timing of radiologic follow-up was at the discretion of the treating physician. Thrombus resolution was defined as radiologic evidence of absence or minimal residual clot burden. Thrombus recurrence/progression was defined as any new radiologically proven noncontiguous new thrombus or contiguous progression of previously defined thrombus. In addition, heparin-induced thrombocytopenia (HIT) was considered a treatment complication and defined by a positive ELISA antibody assay followed by a confirmatory functional assay for HIT antibodies.

Statistical Analyses

Standard statistical methods were used to summarize the parameters: mean (±SD) and median (±IQR) for ordinal or continuous scaled parameters. The Spearman correlation coefficient (r) was used to assess correlations. To allow for repeated measurement pairs of APTT and Anti-FXa from the same patient, the previously described method by Bland and Altman was used, allowing for the determination of an overall within-individual relationship between the 2 assays.[27] Analyses were performed using the SAS, version 9.2, software package (SAS institute, Cary, North Carolina).

Results

Over the course of 20 months, 173 patients received therapeutic doses of unfractionated heparin at Nationwide

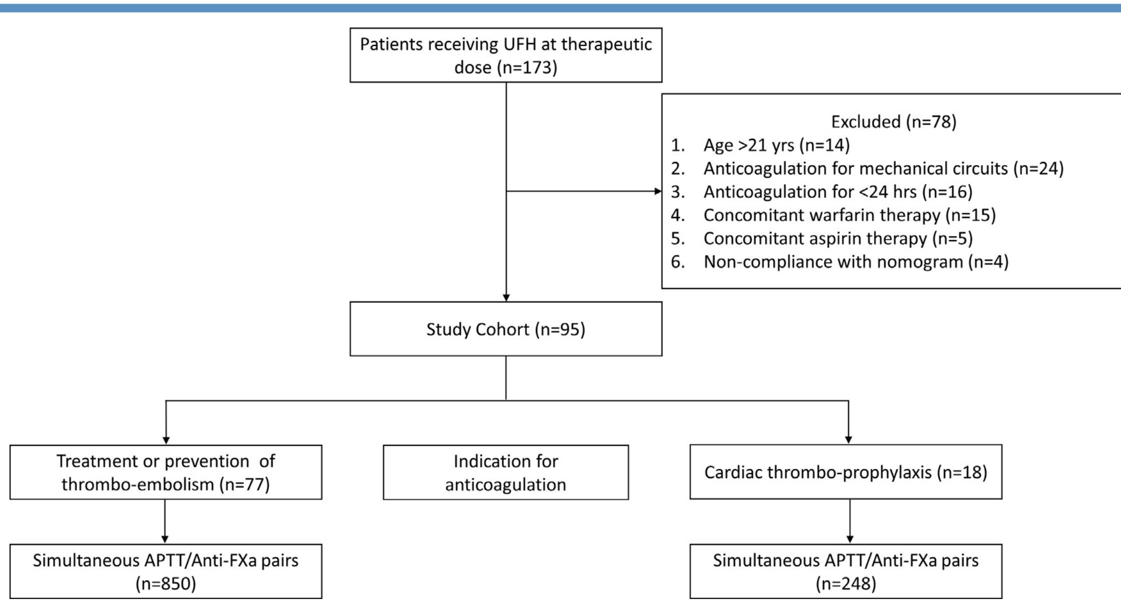

Figure 1. Flow diagram of the screening, enrollment, and final analysis of the study cohort.

Children's Hospital (**Figure 1**). In total, 95 patients were included in the final analysis of this study; there were 1098 pairs of APTT and Anti-FXa measurements performed. The majority of the patients in our study cohort were male (n = 60; 63%). The median age was 8 years (range 0.1-20 years) and one-third of the patients (n = 25; 26%) were infants <1 year of age (range 4 days to 10 months of age). The median weight at the time of anticoagulation initiation was 28.6 kg (range 1.65-131.3 kg). The most common indication for unfractionated heparin use was acute treatment/prophylaxis of thromboembolism (n = 77; 81%) and primary thromboprophylaxis for children with complex congenital cardiac disease (n = 18; 19%). For children with venous thrombosis, indwelling central venous catheter was the single most common risk factor present (**Table II**).

During the study period, the median duration of unfractionated heparin therapy for each patient was 3.5 days (range 1-45 days), and during this time, each patient had a median of 8 pairs of APTT and Anti-FXa assays perfumed (range 1-46). A median unfractionated heparin dose of 22 units/kg/h was required to reach therapeutic Anti-FXa levels, and this was significantly greater in infants <1 year of age as compared with older children (33.9 vs 20 units/kg/h; P <.001).

Each patient had an average of 2.5 (median: 2; range 0.25-8) Anti-FXa measurements performed per day and a mean 1.1 (median: 1; range 0-4.5) infusion rate changes made per day of therapy to maintain plasma heparin levels within the goal range of 0.35-0.7 units/mL. Time to achieve sustained therapeutic Anti-FXa levels was a median of 10 hours (range 2-96 hours), and this duration was significantly shorter in patients who received a heparin bolus at the start of anticoagulation therapy as compared with the patients who did not receive a bolus (5 hours vs 12 hours; P = .03). A bolus dose was not administered in 47 patients. Indications for not administering the bolus included recent surgery (n = 16), ongoing hemorrhage (n = 13), transition from prophylactic to therapeutic dosing (n = 7), coagulopathy (n = 4), stroke (n = 3), prematurity (n = 1), and unknown (n = 3). Overall, 73 patients (77%) achieved sustained therapeutic Anti-FXa levels within 24 hours of starting anticoagulation with unfractionated heparin, and 91 patients (96%) were therapeutic within 48 hours.

Table II. Baseline characteristics of the study cohort

Total patients	95
Male n (%)	60 (63)
Median age, y (range)	8 years (0.1-20 years)
Indication for unfractionated heparin use, n (%)*	
Thromboembolism	77 (81)
Deep vein thrombosis	40 (42)
Pulmonary embolism	11 (11.5)
Thrombosis at rare sites (eg mesenteric, splenic and portal)	10 (10.5)
Arterial thrombosis	9 (9.5)
Intra-cardiac thrombosis	8 (8.4)
Cerebral sino-venous thrombosis	6 (6.3)
Superior vena cava thrombosis	3 (3.1)
Arterial dissection	2 (2.1)
VTE prophylaxis	2 (2.1)
Prophylaxis in CHD	18 (19)
Risk factors for thrombosis n (%)†	
Central venous catheter	31 (32.6)
CHD	29 (30.5)
Obesity	13 (13.7)
Immobility/limited mobility	7 (7.4)
Malignancy	6 (6.3)
Renal disease	5 (5.3)
Estrogen contraceptives	5 (5.3)
Inflammatory bowel disease	2 (2.1)
Trauma	2 (2.1)
Thrombophilia conditions	
FV Leiden Mutation	5 (5.3)
Protein S Deficiency	1 (1)
May-Thurner anomaly	4 (4.2)
Paget-Schroetter syndrome	4 (4.2)
IVC atresia	2 (2.1)
APS	1 (1)
Care setting	
Intensive care	59 (62)
Standard hospital floor	36 (37)

APS, antiphospholipid antibody syndrome; *CHD*, congenital heart disease; *IVC*, inferior vena cava; *VTE*, venous thromboembolism.
*Some patients had more than 1 indication for unfractionated heparin use.
†Some patients had more than 1 risk factor for thrombosis.

Correlation Between Anti-FXa and APTT

In our cohort of 95 patients, there was moderate correlation between the Anti-FXa and APTT assays (n = 1098; r = 0.75; 95% CI 0.72-0.77) (**Figure 2**). There were 510 (46.4%) measurements of Anti-FXa that were within the goal range of 0.35-0.7 IU/mL, and only 176 (34.5%) of the corresponding APTT values were within the historically targeted range of 60-85 seconds. For the 510 therapeutic Anti-FXa measurements, the median APTT was 90.5 seconds (range 11 to >250 seconds). Compared with Anti-FXa, the APTT underestimated the heparin activity in 50 of 510 (9.8%) observations and overestimated it in 284 of 510 (55.7%) observations. There was similar correlation between APTT and Anti-FXa assays between infants (n = 25) and children >1 year (n = 70) of age (r = 0.77 vs 0.73; P = .17) as well as patients treated with unfractionated heparin for thrombosis (n = 77) as compared with those treated with unfractionated heparin for cardiac prophylaxis (n = 18) (r = 0.76 vs 0.71; P = .21) (**Figure 2**).

We also analyzed the data comparing Anti-FXa levels with a target APTT ratio of 1.5-2.5 times the baseline. Of those with available baseline APTT, there were 473 measurements of the Anti-FXa that were in the goal range of 0.35-0.7 IU/mL. The APTT ratio was 1.5-2.5 times the baseline in 303 (64%) of them. Compared with the Anti-FXa, the APTT ratio underestimated the heparin activity in 39 of 473 (8.2%) observations, and overestimated it in 131of 473 (27.7%) observations.

Of the 1098 pairs, the source of the specimen could not be determined for 22 specimens. Of the remaining 1076 specimens, 721 were drawn from central venous/arterial lines and 355 through a venipuncture. Median APTT was significantly longer when the specimen was collected from a central venous/arterial line compared with venipuncture (63 vs

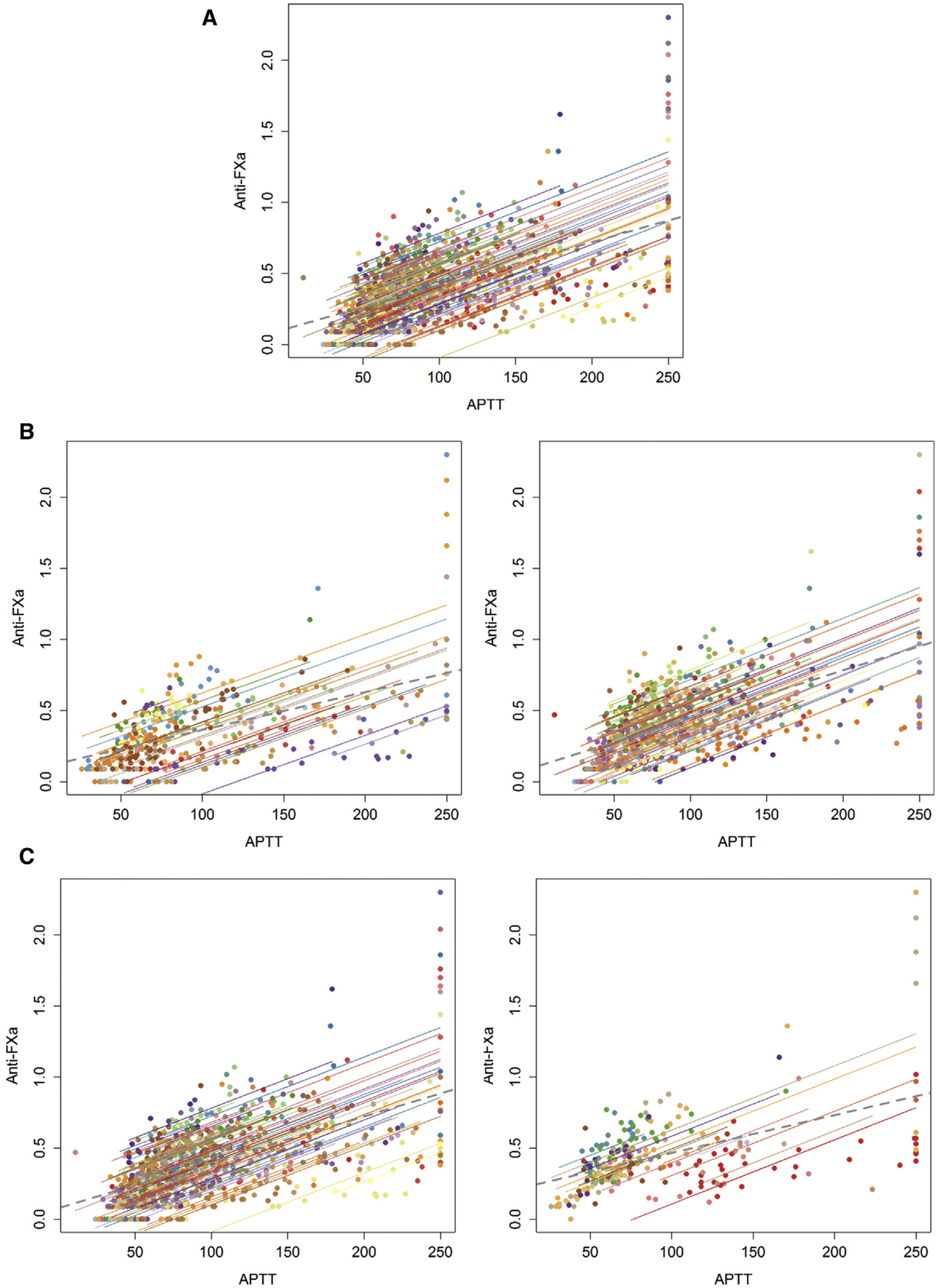

Figure 2. A, Comparison of the Anti-FXa and APTT assays performed simultaneously in 1098 samples (r = 0.74; 95% CI 0.71-0.77). **B,** Comparison of correlation between APTT and Anti-FXa assays between infants <1 year of age (*left side*) (n = 25; r = 0.77; CI 0.72-0.81) and older (*right side*) (n = 70; r = 0.73; CI 0.69-0.76) (*P* .35). **C,** Comparison of correlation between APTT and Anti-FXa assays between patients treated for thrombosis (*left side*) (n = 77; r = 0.76; CI 0.72-0.78) and those treated for cardiac prophylaxis (*right side*) (n = 18; r = 0.71; CI 0.64-0.79) (*P* .21).

Table IV. Comparison of the clinical characteristics of patients who had an episode of major or CRNMB with patients who had minor or no bleeding while being treated with unfractionated heparin

Characteristics	Major/CRNMB (n = 10)	No bleed/minor bleed (n = 85)	*P*
Median age, y (range)	11 (<1-20)	8 (<1-19)	.44
Male sex, n (%)	8 (80)	52 (61)	.32
Unfractionated heparin dose, U/kg/h (range)*	27.2 (20-46)	26.2 (13-56)	.67
Median APTT, s (range)*	121 (79 to >250)	154 (43 to > 250)	.37
Median Anti-FXa, units/mL (range)*	0.51 (0.28-0.9)	0.66 (0-2.2)	.03
Time to therapeutic anticoagulation, h (range)	7 (4-13)	11 (2-96)	.26
Platelet count, 10^3/mL (range)*	197 (30-281)	196 (6-720)	.35
Fibrinogen, mg/dL (range)*	236.5 (155-462)	316 (69-1037)	.38

*Measurements taken at time of bleed for bleeding patients; for nonbleeding patients, greatest encountered APTT and Anti-FXa and lowest reported platelet count and fibrinogen during the course of unfractionated heparin treatment were recorded.

56 seconds; $P = .0002$). In contrast, the median Anti-FXa drawn from central venous/arterial line was lower compared with the venipuncture specimens (0.36 vs 0.40 units/mL; $P = .009$). There was a significantly stronger correlation between the APTT and Anti-FXa assays in the venipuncture specimens (r = 0.86; 95% CI 0.83-0.89), compared with specimens drawn through a potentially contaminated line (r = 0.72; 95% CI 0.68-0.72) ($P < .0001$).

Safety Outcomes

During the course of this study, there were major bleeding events in 5 patients (5.3%), 6 CRNMB events in 5 patients (5.3%), and 15 minor bleeding events in 10 patients (10.5%) (**Table III**; available at www.jpeds.com). There were no significant differences in age, sex, dose of unfractionated heparin, APTT, Anti-FXa, time to therapeutic anticoagulation, platelet count, or fibrinogen levels between patients with major and CRNMB bleeding as compared with patients with minor or no bleeding events (**Table IV**). Protamine reversal was not used for any patient.

Critically high APTT (>250 seconds) was noted on 43 occasions in 21 unique patients and was not associated with an increased risk of major or CRNMB events ($P = .07$). For the 43 recorded APTT values of >250 seconds, the median corresponding Anti-FXa was 0.82 IU/mL (range 0.38 to >2.2 IU/mL). There was no instance of HIT during the course of this study.

Efficacy Outcomes

Seven (7.6%) patients had radiologic progression of their thromboses while on treatment with unfractionated heparin. There were 77 patients for whom unfractionated heparin was initiated for either venous or arterial thrombosis treatment or prevention and, of these, 60 patients had radiologic follow-up available, including 6 of the 7 patients with early radiologic progression of thrombosis. Of these 60 patients, 57 patients (96%) had complete or partial resolution of their thrombosis and 3 (4%) had no resolution of their thrombosis. The median time to achieve a therapeutic Anti-FXa level was 10 hours for patients with complete/partial response and 18 hours for patients with no radiologic resolution of thrombi ($P = .27$).

Discussion

Unfractionated heparin remains the cornerstone of anticoagulant therapy in critically ill children for the treatment and prevention of thromboembolism. The goal of therapeutic drug monitoring for unfractionated heparin is to maximize protection from thrombus progression while minimizing the risk of bleeding.[28,29] Broad availability, automation, and quick turnaround time has popularized APTT to monitor heparin dose within a narrow therapeutic range.[5,8,22,30] However, APTT testing is influenced by preanalytical, analytical, and biological variables that do not reflect in vitro heparin activity.[6-12] Hence, when APTT is used to monitor unfractionated heparin therapy, patients may be exposed to precariously low or high heparin levels, decreasing the therapeutic efficacy of unfractionated heparin, or increasing the risk of bleeding, respectively. Anti-FXa reflects the anticoagulant activity of unfractionated heparin by measuring the ability of heparin–antithrombin complex to inhibit activated factor X. Anti-FXa testing is more expensive and less widely available but demonstrates less susceptibility to interference by biological variables, making it a more direct measure of the anticoagulant effect of unfractionated heparin than APTT.[2,18,19]

In our cohort, each patient had a median of 2 Anti-FXa measurements performed daily and a median of 1 infusion rate change daily to maintain therapeutic unfractionated heparin levels. Previously, several studies have documented that APTT-based protocols lead to more fluctuations in comparison with Anti-FXa,[2,14,19,31] and our study supports that Anti-FXa based monitoring of unfractionated heparin establishes better sustainability of therapeutic levels, promoting durable anticoagulation. Although a pharmacoeconomic analysis of Anti-FXa based monitoring was beyond the scope of the present study, it is likely that increased stability of heparin levels would lead to fewer dose adjustments and laboratory tests, hence reducing the overall institutional costs of such testing.[31]

Failure to achieve therapeutic anticoagulation rapidly in the setting of acute thromboembolism has been associated with an increased risk of thrombus recurrence.[5,32-34] In our cohort, the time to achieve sustained therapeutic anticoagulation based on Anti-FXa levels was a median of 10 hours. Within 24 hours, three-fourths of the patients were within the therapeutic range and within 48 hours, almost all of the patients were within the goal therapeutic range. These results are in keeping with the findings of Trucco et al and support the use of Anti-FXa assay for a relatively rapid achievement of therapeutic anticoagulation.[19] It is unclear whether this translates into improved long-term outcomes in terms of thrombus resolution, because unfractionated heparin was used only for the acute treatment of thrombosis in the hospital setting. The majority of our patients had successful treatment of their thrombi (96%); however, no marked differences were noted in the time to achieve therapeutic Anti-FXa levels between patients with or without response to therapy. In the acute phase, 7.6% of our patients had progression of their thrombi while receiving unfractionated heparin, which is comparable with the 6%-7% rate of recurrent thrombosis when APTT-based monitoring has been employed.[14,22,35]

Our study underscores the importance of using venipuncture specimens, when possible, for measuring coagulation indices for patients receiving anticoagulation. Despite using the standardized institutional protocol of discarding the initial 3-5 mL of blood when collecting specimens from central venous/arterial line—there was obviously evidence of heparin contamination. In addition, our data also suggest that using an APTT ratio of 1.5-2.5 times the baseline, as opposed to a fixed target APTT of 60-85 seconds, is likely beneficial in children, given the age-dependent variability in baseline APTT.

Bleeding complications are a critical concern in children receiving anticoagulation and, in this study, the incidence of major bleeding was approximately 5%, lower than previous studies in children (11%-24%).[2,19,20,36] This difference is not entirely attributable to the exclusion of patients on ECMO or LVADs in the present study. Critically ill children receiving anticoagulation in the intensive care setting and immediately after cardiac surgery formed the majority of our study population (62%). Bleeding complications were independent of the age, sex, unfractionated heparin dose, platelet count, and fibrinogen level (**Table IV**). Previously, APTT in the supratherapeutic range has been associated with major bleeding complications.[18,20,37-39] In our cohort, the APTT was not predictive of bleeding. Given that patients were closely monitored once the APTT was >150 seconds, and other coagulation measures were optimized, it is unclear whether the practice of obtaining APTT assays to complement Anti-FXa monitoring has any added benefit in preventing unexpected bleeding.

In line with previous observations, our study found that there was moderate correlation between the APTT and Anti-FXa assays.[18,19,21,23,24,37,40] In our cohort, when the heparin level was in the therapeutic range as measured by an Anti-FXa assay, the majority of the corresponding APTT measurements were >85 seconds, overestimating the heparin level. If the traditional APTT therapeutic range of 60-85 seconds were to be followed, based on our study, this would place patients at risk of undertreatment, relative to the Anti-FXa target.

The current study has a number of limitations. It was performed at a single center, which limits its applicability to other institutions. Although the APTT and Anti-FXa assays were performed in the same laboratory, on the same analyzer, the authors were not privy to any changes made to the APTT or Anti-FXa reagents that might have occurred during the 20-month study period and their influence on the test results. However, it is unlikely that the reagents changed often enough to cause variability within each patient's test results, given that each patient was monitored for a median of 3.5 days only. Our study was not designed to be a randomized comparison between the APTT and Anti-FXa assays, and full assessment of APTT assay as a measure of anticoagulation is limited by the fact that all unfractionated heparin dose adjustments were made based on the Anti-FXa assay, as described in **Table I**. In addition, for the purpose of this study, an APTT range of 60-85 seconds was considered therapeutic, irrespective of age. The authors recognize the age-based variability of baseline APTT. This limits the generalizability of the current study to other institutions where a 1.5-2.5 times ratio of baseline APTT is considered therapeutic.

Our results provide support to a growing body of literature that suggests the APTT assay does not correlate well with Anti-FXa assay and that the Anti-FXa assay may be considered for optimal monitoring of anticoagulation when using unfractionated heparin treatment. ■

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Table III. Description of the major and CRNMB events noted in patients treated with unfractionated heparin

Patients	Age	Care setting	Indication for treatment	Bleeding event
Major bleeding				
Patient 1	18 y	ICU	CSVT	Hemorrhagic conversion of previously noted cerebral infarcts
Patient 2	7 y	ICU	Mesenteric and left ventricular thrombosis	Hemoperitoneum requiring surgical intervention
Patient 3	5 mo	ICU	Cardiac thromboprophylaxis in CHD	Intracranial hemorrhage
Patient 4	14 mo	ICU	DVT	Bleeding from line-insertion sites associated with >2 g/dL drop in hemoglobin
Patient 5	4 mo	ICU	Cardiac thromboprophylaxis in CHD	Intracranial hemorrhage
CRNMB				
Patient 1	20 y	Ward	DVT	Bleeding from a newly placed colostomy
Patient 2	18 y	Ward	DVT	Bleeding from insertion site of femoral catheter
Patient 3	16 y	Ward	DVT	Bleeding from insertion site of femoral catheter, hematuria
Patient 4	15 y	ICU	Protein S deficiency; thromboprophylaxis	Mediastinal hematoma post video-assisted thoracoscopic procedure
Patient 5	2 y	ICU	Cardiac thromboprophylaxis in CHD; DVT	Hematemesis*
				Bleeding from chest tube*

CHD, congenital heart disease; *CSVT*, cerebral sinovenous thrombosis; *DVT*, deep vein thrombosis; *ICU*, intensive care unit.
*Two distinct bleeding episodes.