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Full Length Article

Unfractionated heparin dosing requirements in the presence of inflammation during the first six months of life

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ABSTRACT

Background: Critically ill neonates with inflammation secondary to SIRS or sepsis often develop an acquired pro-thrombotic state. Unfractionated heparin (UFH) is commonly prescribed in this population, but these subjects often remain sub-therapeutic or require very high doses of UFH to achieve and sustain therapeutic anti-Xa activity. This is due, in part, to the unique pharmacokinetics/dynamics of this population but may also be influenced by the degree of inflammation.
Objective: To evaluate UFH dosing requirements in neonates and infants < 6 months of age with variable degrees of systemic inflammation. Clinical outcomes of bleeding and clotting will also be examined.
Subjects/methods: A retrospective chart review was performed in infants < 6 months of age treated with intravenous UFH for at least 24 h with intent to reach a goal anti-Xa of 0.3–0.7 U/mL at Children's Hospital Colorado between October 2008 and August 2014. Subjects were divided into two groups, based on their ability to achieve and maintain anti-Xa concentrations between 0.3 and 0.7 U/mL. The relationship between UFH dose (U/kg/h) and inflammatory status (using pediatric age-specific definitions for SIRS, sepsis, severe sepsis, or septic shock) was examined.
Results: Seventy-three subjects were included in the analysis. Twenty-three subjects (mean age = 41.2 days ± standard deviation [SD] 52.3) achieved therapeutic anti-Xa concentrations while fifty subjects (mean age = 43.4 days ± SD 53) did not. The median UFH dose needed in subjects who achieved goal anti-Xa concentrations in the absence of SIRS or sepsis criteria was 24.5 U/kg/h (interquartile range [IQR] = 23.6–25.9) while the median dose of UFH in subjects who achieved goal anti-Xa level in the setting of infection, SIRS, or sepsis of any type was 36.1 U/kg/h (IQR = 34–43.5) ($p < 0.0001$). In subjects who maintained therapeutic anticoagulation, there was a direct relationship between UFH dose and the severity of inflammation as determined by pediatric SIRS/sepsis criteria.
Conclusions: Maintenance of therapeutic UFH levels remains a challenge in infants, especially in those with concomitant inflammatory processes. Infection, SIRS, and sepsis of any type were collectively associated with a 32% increase in unfractionated heparin dose required to achieve and maintain therapeutic anti-Xa serum concentrations.

1. Introduction

1.1. Background

During infancy, the hemostatic system undergoes a marked period of maturation and development. Although plasma concentrations of many coagulation proteins will reach adult values by 6 months of age, significant differences remain until early or late childhood [1–3]. Fortunately, the majority of pro- and anti-coagulant proteins are symmetrically reduced in young infants, thus, the *healthy* neonate is able to maintain hemostatic balance [1]. Systemic illness and inflammation, however, can easily disrupt this delicate balance and predispose infants to either hemorrhagic or thrombotic complications [1,4,5]. It has been postulated that neonates with sepsis may develop an acquired pro-thrombotic state due to consumption of their relatively limited coagulation inhibitors (such as antithrombin, AT) [6].

The use of unfractionated heparin (UFH) has become an important treatment option for young infants and neonates with sepsis and associated disseminated intravascular coagulation. UFH is clinically advantageous, compared to other anticoagulants, due to its short half-life (which allows for rapid dose titration) and ability to be quickly reversed using protamine sulfate. Dosing of UFH in young infants, however, is fraught with slow achievement of therapeutic anticoagulation endpoints. This phenomenon has been described as 'heparin resistance.' The etiology of this resistance is likely multifactorial and includes elevated concentrations of heparin-binding proteins (HBPs), increased heparin clearance and genetic abnormalities [7,8]. Because AT is an important cofactor for heparin activity, low concentration of AT in the neonate, whether congenital or acquired, will result in diminished heparin activity [9]. In clinical practice, infants often require significantly higher doses of UFH to achieve therapeutic plasma concentrations and many times, these concentrations are not achieved until late in the

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treatment course [10,11]. This high dose requirement appears particularly evident in infants with concomitant inflammatory processes, although formal studies validating this observation have not been published.

1.2. Importance

The incidence of venous thromboembolism (VTE) in children has increased significantly over the past few decades [12,13], yet the underlying pathophysiology of thromboembolism in children is multifaceted and much about the optimal treatment in specific subpopulations of pediatric subjects is still unknown [14]. Despite these gaps in knowledge, it has been observed that pediatric VTE is associated with an increased risk of in-hospital mortality [15]. Additionally, children who survive the initial thromboembolism are at risk for chronic complications such as recurrent VTE and post-thrombotic syndrome (PTS) [15]. Pediatric patients with VTE are also likely to have a longer length of stay (an increase of 8.1 hospital days) and excess average costs associated with their stay ($27,686) for an admission complicated by VTE [16]. Achieving early and effective anticoagulation is of paramount importance to limit chronic complications and minimize morbidity [17], while still avoiding supratherapeutic levels and the possibility of adverse outcomes due to bleeding complications [1,14].

The present study aims to explore how inflammatory processes influence heparin dosing requirements in neonates and young infants. Ultimately, we hope to better understand the UFH dosing requirements in young infants with concomitant inflammation and develop strategies to achieve rapid and effective anti-coagulation.

2. Materials and methods

2.1. Study subjects

This was a single-center, retrospective, non-interventional electronic medical record review of infants admitted to Children's Hospital Colorado (a 444-bed university-affiliated, freestanding, tertiary care children's hospital and Level I trauma center in the Denver Metro area). Subjects evaluated for inclusion were < 6 months of age (regardless of gestational age at birth); admitted to the neonatal intensive care unit, cardiac intensive care unit, or general medical/surgical inpatient units; and treated with UFH with a goal anti-Xa of 0.3–0.7 U/mL between October 2008 and August 2014. This study protocol was reviewed and approved by the Colorado Multiple Institutional Review Board.

Charts for review were identified using an electronic medical record database and the assistance of a clinical information resource specialist. Infants were eligible for study inclusion if they received UFH for at least 24 h in duration at a minimum starting dose of 15 U/kg/h with therapeutic intent (defined as a documented goal anti-Xa serum concentration of 0.3–0.7 U/mL) and/or evidence of active titrations to reach therapeutic serum concentrations. Subjects were excluded if they had severe thrombocytopenia (defined as platelets less than or equal to 50,000/μL) as this is often considered a clinical contraindication to anticoagulation; required a ventricular assist device, continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO); had evidence of bleeding at initiation of UFH; required solid organ transplantation; or received high dose steroids or concomitant anticoagulant therapy other than UFH.

Subjects meeting inclusion criteria then underwent an extensive chart review to capture inflammatory status, as measured by the presence or absence of infection (either clinical suspicion or proven), SIRS, sepsis, severe sepsis, or septic shock criteria per Goldstein et al. [18]. A rigorous assessment of pediatric SIRS/sepsis criteria was documented throughout UFH therapy with special attention given to criteria during heparin infusion rate adjustments. For subjects who achieved goal anti-Xa serum concentrations at different UFH infusion rates, we reported the mean UFH infusion rate during which the subject met that specific category of SIRS/sepsis. Subjects were then categorized into two groups ("therapeutic" and "non-therapeutic"), based on whether or not they achieved and maintained therapeutic anti-Xa serum concentrations between 0.3 and 0.7 U/mL for two consecutive anti-Xa concentrations, separated by at least 24 h. No changes in the UFH formulation or anti-Xa kit occurred during the study period; testing was done utilizing a Stago – Compact Max as our analyzer and a STA-Liquid Anti-Xa heparin reagent.

2.2. Data collection

Outcome measures and variables were extracted from charts by a single investigator using a standardized data collection form. The following data were collected and reviewed: (i) Demographic information: Name, MRN, gender, age, weight (kg), and estimated gestational age (weeks); (ii) Anti-coagulation information: (a) Indication for anticoagulation; (b) plasma anti-Xa concentrations; (c) diagnosis, thrombosis recurrence, and thrombus resolution on imaging (initial vs. follow-up imaging); and (d) therapy-related information – dose of UFH therapy and complications (major, clinically relevant non-major, and minor bleeding as defined by International Society on Thrombosis and Haemostasis, heparin-induced thrombocytopenia [HIT], and death) [7]; (iii) UFH information: Dose(s), duration of treatment, and number of dose adjustments; (iv) Other anticoagulants including enoxaparin: Dose (s), duration of treatment, indication; (v) Inflammatory states at the time of anticoagulation with UFH: Subjects who meet pediatric age-specific definitions for SIRS, sepsis, severe sepsis, or septic shock criteria per Goldstein et al. [18] or those with confirmed or suspected systemic infection (endocarditis, necrotizing enterocolitis, meningitis, etc.); (vi) Laboratory: white blood cells (WBCs), eosinophil sedimentation rate (ESR), c-reactive protein (CRP), serum creatinine (SCr), alkaline alanine transaminase(ALT),aspartate transaminase (AST), platelets (PLT), hemoglobin (Hgb), hematocrit (Hct), activated partial thromboplastin time (aPTT), AT, and prothrombin time (PT); (vii) Additional information: temperature, urine output, progression of thrombosis after initiation of UFH via ICD coding [intracerebral hemorrhage (ICH), pulmonary embolism (PE), or deep vein thrombosis (DVT)].

2.3. Statistical analysis

A descriptive analysis was performed on each variable in the data set. Results are presented as mean ± standard deviation (SD) and range, or percentage where appropriate. Non-normally distributed data are presented as the median (interquartile range, IQR). A 2-tailed *t*-test, Fishers Exact test, Mann-Whitney *U* test, and one-way ANOVA were used to detect differences between the patient groups. Data were graphed using GraphPad Prism 6© and Microsoft Excel 2010© software.

3. Results

Initial data inquiry identified 152 subjects who met both age and UFH dosing requirements. After exclusion for concomitant anticoagulants (n = 1), CRRT or ECMO (n = 4), UFH therapy for < 24 h (n = 44), anti-Xa levels not reported (n = 2), left ventricular assist device (n = 1), severe thrombocytopenia (n = 3), and failure to meet therapeutic intent criteria (n = 24), a total of 73 subjects remained for evaluation and analysis. Twenty-three subjects (31.5%) achieved therapeutic anti-Xa serum concentrations (group 1) while fifty subjects (68.4%) could not (group 2) - despite doses of UFH up to 50 U/kg/h. Characteristics of the two study groups are shown in Table 1 and do not demonstrate any statistical differences. While not statistically significant, there was a trend towards a lower weight in subjects achieving therapeutic anti-Xa concentrations (p = 0.054).

Information related to UFH dose and indication is described in

Table 1
Characteristics of subjects being treated with unfractionated heparin (UFH) meeting eligibility criteria at the Children's Hospital Colorado. Data are presented as mean ± SD (range) or percentage, as appropriate.

Characteristic	Achieved therapeutic Anti-Xa serum concentrations (n = 23)	Never achieved therapeutic Anti-Xa serum concentrations (n = 50)	p-Value
Age at time of UFH initiation (days)	41.2 ± 52.3 (0–164)	43.4 ± 53 (0–175)	0.87
Male, n (%)	11 (48)	27 (54)	0.80
Weight (kg)	3.2 ± 1.0 (1.1–5.9)	3.8 ± 1.3 (1.9–7.1)	0.054
Estimated gestational age (weeks)	35.8 ± 5.1 (23–42)	36.6 ± 4.1 (23–41.5)	0.48

Table 2. There were significantly more patients with an indication of primary prophylaxis for a cardiac shunt or stent in the group who failed to achieve therapeutic anti-Xa concentrations, p = 0.0017. The highest median UFH infusion rate was 40.0 U/kg/h (IQR = 30–46) for children that achieved therapeutic anticoagulation and 33.0 U/kg/h (IQR = 28–39) in children who did not. Subjects who never reached therapeutic anti-Xa had significantly shorter UFH duration of treatment (71.1 ± 36.9 h vs. 193.1 ± 122.9 h; p < 0.001). The mean anti-Xa activity reported for the twenty-three subjects achieving therapeutic concentrations was 0.50 ± 0.20 U/mL (95% CI 0.45–0.54). The median UFH infusion rate required to achieve therapeutic anti-Xa activity was 34.0 U/kg/h (IQR = 27.3–42.3). The mean AT for subjects that achieved therapeutic anticoagulation was 53% (range 20–89) and 68.7% (range 25–161). AT activity was monitored in fifteen subjects within the therapeutic anti-Xa group. Four subjects who did not have sepsis or meet SIRS criteria had a mean AT of 67.5% (range 45–89). The eleven subjects who had infection, sepsis, or met SIRS criteria had a mean AT of 51% (range 20–76%). Two subjects had AT levels < 40%; however, AT was supplemented in both subjects.

The relationship between the UFH infusion rate and SIRS or sepsis status in the twenty-three infants who achieved therapeutic anticoagulation is illustrated in Fig. 1. Three subjects were therapeutic at two different UFH infusion rates after their SIRS/sepsis criteria changed (thus there are twenty-six data points). Subjects were categorized into two subgroups based on whether they met any criteria for a combined endpoint including any infection, SIRS, or sepsis (Fig. 1, Panel A). A statistically significant difference was detected between the median values for the mean UFH infusion rate required to achieve therapeutic anticoagulation between subjects who did not meet SIRS or sepsis criteria compared with subjects with a combined endpoint of any documented infection, SIRS, or sepsis of any type (24.5 U/kg/h vs. 36.1 U/kg/h; p ≤ 0.0001).

Therapeutic subjects were further classified by the specific pediatric sepsis criteria they met and analyses were performed on UFH infusion rate required to achieve therapeutic anticoagulation (Fig. 1, Panel B). There was no statistically significant difference in the median value for the mean UFH infusion rate required between subjects who did not meet either SIRS or sepsis criteria and those meeting SIRS or sepsis criteria (24.5 U/kg/h vs. 32.9 & 34 U/kg/h respectively; p = ns). A statistically significant difference existed between the median values for the mean UFH infusion rate required in subjects who did not meet SIRS or sepsis criteria and those with documented infection, severe sepsis, or septic shock (24.5 U/kg/h vs. 35.2, 39.8, & 56.3 U/kg/h respectively; p ≤ 0.05, p ≤ 0.05, p ≤ 0.001). A sub-group analysis was done on neonatal subjects (28 days of age or less at the time of UFH initiation) who achieved therapeutic anti-Xa activity. There were no statistically significant differences in the mean UFH infusion rate between neonates and infants > 28 days (37.8 U/kg/h ± 11.5 vs. 33.6 U/kg/h ± 9.5; p = 0.34).

Thrombus resolution rates at 6 months are shown in Fig. 2. Clot resolution was unable to be determined for eight of the twenty-four (33%) patients due to either lack of follow-up imaging (n = 4) or death prior to the endpoint (n = 4). Of the patients who died, two deaths were attributed to cardiac failure, one to airway obstruction, and one to a pulmonary hemorrhage (diagnosed prior to development of the clot and heparin initiation). Bleeding outcomes, defined by the ISTH, are summarized in Fig. 3. There were no statistically significant differences between studied groups in terms of clotting or bleeding. Eight patients in the therapeutic group (34.7%) and eight patients in the non-

Table 2
Anticoagulant information related to unfractionated heparin (UFH) exposure documented in the medical record among young infants and neonates < 6 months of age. Data are presented as mean ± SD (range) or number (percentage), as appropriate. Non-normally distributed data are presented as medians (IQR).

Characteristic	Achieved therapeutic Anti-Xa serum concentrations (n = 23)	Never achieved therapeutic Anti-Xa serum concentrations (n = 50)	p-Value
Starting UFH dose (U/kg/h)	22.9 ± 4.3 (15–30)	19.7 ± 3.1 (15–27)	0.0006
Highest UFH dose reached (U/kg/h)[a]	40.0 (IQR = 30–46)	33.0 (IQR = 28–39)	0.0066[a]
Duration of UFH infusion (hours)	193.1 ± 122.9 (41.5–433)	71.1 ± 36.9 (24–186)	< 0.0001
Therapeutic anti-Xa serum concentration (U/mL)	0.50 ± 0.20 (0.3–1.59)	NA	NA
UFH dose (U/kg/h) to achieve therapeutic anti-Xa[a]	34 (IQR = 27.3–42.3)	NA	NA
Indication, n (%)			
Venous thrombosis	7 (30)	7 (14)	0.12
Arterial thrombosis	8 (35)	9 (18)	0.14
Primary prophylaxis[b]	1 (4)	20 (42)	0.0017
PDA stent clot	0 (0)	1 (2)	1.0
Cerebral Sinovenous Thrombosis (CSVT)	3 (13)	3 (6)	0.37
Clinically suspected thrombus	1 (4)	6 (12)	0.42
Intra-cardiac thrombus	1 (4)	3 (6)	1.0
Intra-caval thrombosis	1 (4)	0 (0)	0.32
Multiple	1 (4)	1 (2)	0.53

[a] Non-normally distributed data are presented as the median (interquartile range, IQR) with p-value calculated via Mann-Whitney.
[b] Primary prophylaxis patients were treated for cardiac stent (n = 1) in the therapeutic group or cardiac shunt (n = 19) & cardiac stent (n = 1) in the non-therapeutic group.

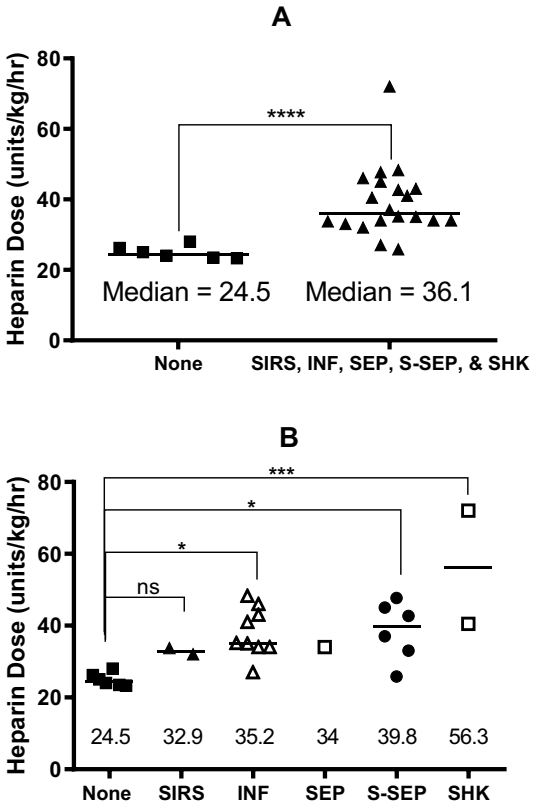

Fig. 1. Relationship between the average unfractionated heparin (UFH) infusion rate (units UFH per kg of patient per hour) and a combination of any infection (INF), SIRS, sepsis (SEP), severe sepsis (S-SEP), or septic shock (SHK) status (Panel A) or broken down by specific pediatric sepsis criteria (Panel B) in twenty-three infants who reached therapeutic anticoagulation. Median infusion rate of UFH for each column is displayed as a line with the specific value indicated below. Some subjects may have been therapeutic at two different UFH infusion rates after their SIRS/sepsis criteria changed.
ns: no statistical difference between studied groups at $p > 0.05$.
*: statistically significant difference between the studied groups at $p \leq 0.05$.
***: statistically significant difference between the studied groups at $p \leq 0.001$.
****: Statistically significant difference between the studied groups at $p \leq 0.0001$.

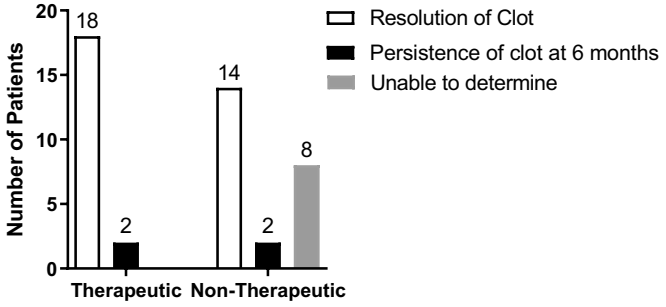

Fig. 2. Thrombus resolution by 6 months for 20 subjects who achieved therapeutic anticoagulation and 24 subjects who did not. Clot resolution was unable to be determined for 8 patients in the non-therapeutic group. The remaining subjects in each group were not being treated for a clot.

therapeutic group (16%) experienced bleeding that was classified as clinically relevant, non-major. All instances of clinically relevant non-major bleeding in both groups were secondary to the patients receiving blood product (and the bleeding was not directly attributable to the patient's underlying medical condition). One subject (4.3%) in the therapeutic group experienced bleeding classified as major due to intracranial nature of the bleed. Eight subjects (16%) in the non-therapeutic group experienced bleeding classified as major due to the nature being pulmonary (n = 3), retroperitoneal (n = 2), or intracranial (n = 3).

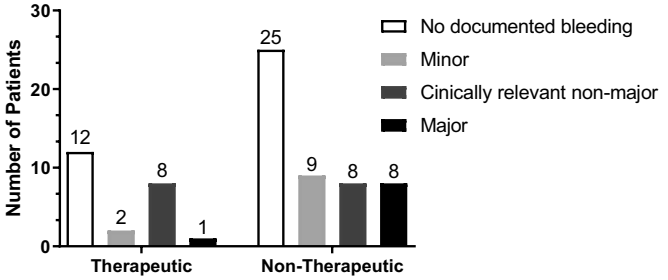

Fig. 3. Bleeding outcomes for both subjects who achieved therapeutic anticoagulation and those who did not as defined by the International Society on Thrombosis and Haemostasis. There were no statistically significant differences between studied groups in terms of bleeding for any of the categories shown.

4. Discussion

The present study provides observational evidence that SIRS, infection, sepsis, and septic shock may influence heparin infusion requirements needed to maintain therapeutic anti-Xa activity in critically ill young infants and neonates. SIRS, infection, and sepsis of any type collectively were associated with a 32% increase in the infusion rate of heparin required to achieve and sustain therapeutic anti-Xa activity in young infants as compared to a similar cohort who did not meet these criteria. Taken together, these data suggest a correlation between the infusion rate of UFH required to achieve therapeutic anticoagulation and the level of inflammation based on the presence of SIRS, infection, sepsis, severe sepsis, or septic shock criteria. These observations also suggest that the dose of UFH required to reach therapeutic anti-Xa activity in these subjects may lie on a continuum that correlates with level of inflammation from infection, sepsis, to severe sepsis, and septic shock.

There have been few clinical outcome studies describing the therapeutic range for UFH in neonates and children. The American College of Chest Physicians (ACCP) recommends that children receiving UFH achieve an aPTT that reflects an anti-Xa range of 0.35–0.7 U/mL [10]. For infants up to 1 year of age, the ACCP recommends a UFH bolus of 75 U/kg followed by a maintenance infusion of 28 U/kg/h. This maintenance infusion rate is 1.4 times higher than that for older children (20 U/kg/h) [10]. Schechter and colleagues studied UFH in 100 infants < 6 months of age and found that only 11% percent achieved therapeutic anti-Xa serum concentrations with the maintenance dose recommendation of 28 U/kg/h from the ACCP (of note, aside from ECMO patients, the patients in this study did not receive an initial heparin bolus) [11]. Schechter and colleagues reported that the median infusion rate of UFH needed to achieve therapeutic anti-Xa for their population was 33 U/kg/h [11]. Findings from Schechter et al. provide some valuable insights; however, 12% of the subjects included in the study were on ECMO which may have led to higher estimates of therapeutic UFH dosing as these subjects often require very high doses of heparin. The differing results suggest that there are other factors influencing the dose-requirement of heparin and/or the anti-Xa concentration in the infant population.

Bozza and colleagues demonstrated that there is a distinct cytokine profile associated with sepsis severity [19]. Specifically they found that the concentrations of IL-1β, IL-6, IL-7, IL-8, IL-10, IL-13, interferon-γ, MCP-1 and tumor necrosis factor-α were significantly higher in septic shock patients than in those with severe sepsis [19]. Shultz and colleagues showed that neonates express inflammatory cytokines such as IL-10, but they lack a mature compensatory anti-inflammatory response

syndrome (CARS) [20]. Thus, anti-inflammatory processes are not compensated in neonates, especially in preterm infants, predisposing them to more harmful effects such as organ damage from inflammatory cytokines [20]. Furthermore, Holub and colleagues reported that elevation of specific biomarkers and HBPs may be dependent on the etiology and source of sepsis [21]. Similar observations have been made in the pediatric population. For example, interleukin- (IL-) 6 was found to be 10 times more concentrated in neonates with gram-negative sepsis than in children with gram-positive sepsis [22]. Cytokines such as interferon-γ, IL-2, and IL-12 have heparin binding properties [23]. Studies suggest IL-12 has a greater binding affinity than antithrombin for heparin [23–25]. More studies are needed to better understand the significance of cytokine inhibitory properties on the anticoagulation effect of heparin. Additionally, cofactors such as AT may change UFH requirement to achieve therapeutic anti-Xa. Not all subjects were evaluated for AT activity; however, 22 assays were assessed on 15 subjects in the therapeutic group. The mean AT for subjects that did not have documented sepsis or meet SIRS criteria was 67.5% (range 45–89%). For subjects with infection or meeting SIRS criteria the AT mean was 51% (range 20–75%). Three of the subjects received AT supplementation. They received a maximum dose of heparin of 32, 58, and 38 units/kg/h.

The bulk of our analysis was focused on the group that achieved a therapeutic anti-Xa as our goal was to highlight the *therapeutic* dose requirement, and this could not be determined in patients who did not meet therapeutic endpoints. There are several possibilities that may explain this result, including a shorter duration of infusion for the non-therapeutic group, which may be secondary to the differences in their indication for receiving UFH (more patients in the non-therapeutic group were being treated for primary prophylaxis). Despite not achieving therapeutic goals with UFH, neonates and infants are a complex and fragile population whose risk of major bleeding is high. In particular premature infants have a high bleeding risk and potential for intraventricular hemorrhage [26]. While this is consistent with literature, it is concerning in light of the high UFH doses required to become therapeutic. It is possible that the higher rate of major and minor bleeding in the non-therapeutic group had to do with interruption in therapy or a reduction in rate in reaction to the bleeding. Conversely, the rate of clinically relevant non-major bleeding was higher in the group that achieved therapeutic endpoints. However, due to the small study size, we would caution against making conclusions based on these observations. Subjects who achieved therapeutic anticoagulation resolved their clots within 6 months based on follow up imaging, and only 4% of infants who achieved therapeutic anticoagulation with UFH suffered major bleeding during treatment vs. 16% of subjects who did not achieve therapeutic coagulation. This is consistent with wide range shown in literature of 1.5–24% [11]. Our data shows that regardless of whether therapeutic UFH was achieved, bleeding outcomes were not significantly different, and most subjects resolved their clots within 6 months. Further studies are needed to identify optimum therapeutic ranges and monitoring parameters for minimizing bleeding risk.

There are limitations to this report. First, the small size of the study must be acknowledged. Nevertheless, it is the only study of its kind reported in pediatrics. Second, it is a single-center study and thus may lack external validity to certain populations (e.g. ECMO, clinically stable subjects undergoing elective surgery, etc.). Larger, prospective pediatric studies are needed to substantiate these findings and to investigate the risks of bleeding as well as recurrent VTE in this setting. Third, although we attempted to ensure anti-Xa measurements were drawn from peripheral lines separate from those where heparin had been infused, this information was not always readily available or verifiable. Fourth, the utility of monitoring anti-Xa activity in this population is controversial. Recent studies suggest that anti-Xa is superior to other tests in *clinically stable children* undergoing diagnostic catheterization in controlled settings; however, these results may not be applicable to critically ill children receiving therapeutic UFH infusions [8,14]. Fifth, the Goldstein paper excluded premature infants. While premature infants were not explicitly studied, the Goldstein criteria for newborns remains the best approximation of SIRS/sepsis criteria we currently have available, thus we evaluated these subjects utilizing the standard criteria for newborns. Finally, it is possible that subjects who did not achieve sustained therapeutic anti-Xa activity would have achieved this activity, but were transitioned to LMWH sooner. Notwithstanding these limitations, the present study provides important preliminary evidence that inflammatory states directly influence heparin infusion requirements in young infants and neonates.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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