# Efficacy of Currently Recommended Enoxaparin Dosing Titration for Therapeutic Use in Neonates

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## Introduction

- Inpatient neonates are at risk for venous thromboembolic (VTE) events
- A 2017 review shows an estimated increase from 5.3 hospital-acquired VTE (HA-VTE) events per 10,000 pediatric hospital admissions up to 30-58 events per 10,000 from the early 1990s to 2017[2]
- Literature suggests neonates require larger weight-based doses of enoxaparin compared to older pediatric patients
- The coagulation cascade evolves with age, where the majority of development occurs within the first six months of life[3]
- Enoxaparin binds to antithrombin, enhancing its activity, which then binds to and inactivates Factor Xa (FXa)[1]
- The effect of enoxaparin is measured by the lab measurement of anti-FXa concentrations[1]

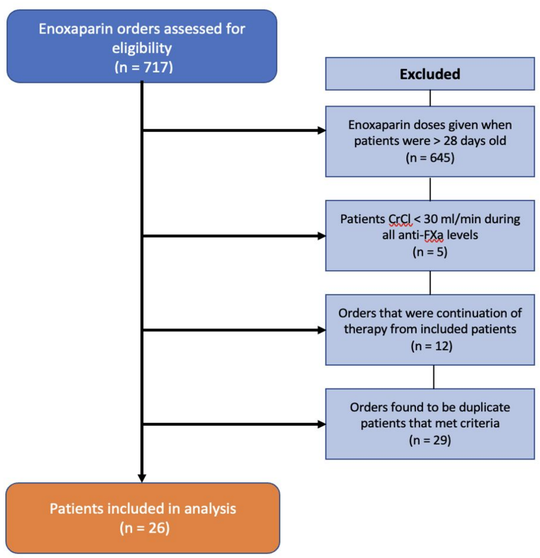
## Specific Aims

- Determine if current published enoxaparin dose titration recommendations are effective in achieving therapeutic anti-FXa concentrations on the first dose titration in neonates

## Methods

- Retrospective chart review from 09/01/2018 to 09/01/2021
- Inclusion criteria:
  - Neonates ( < 28 days)
  - Received at least one treatment dose of enoxaparin
- Exclusion criteria:
  - On mechanical circulatory support (MCS) or renal replacement therapy (RRT) during or within 48 hours of enoxaparin therapy
  - Creatinine clearance (CrCl) < 30 ml/min/m$^2$
- Primary objective: correlation between age (preterm < 37 weeks gestation and term ≥ 37 weeks gestation) and anti-FXa concentrations after the first dose titration when following published enoxaparin titration guidelines in neonates
- Secondary objective: frequency of anti-FXa concentration achievement after first dose titration

### Figure 1: Screening and Enrollment



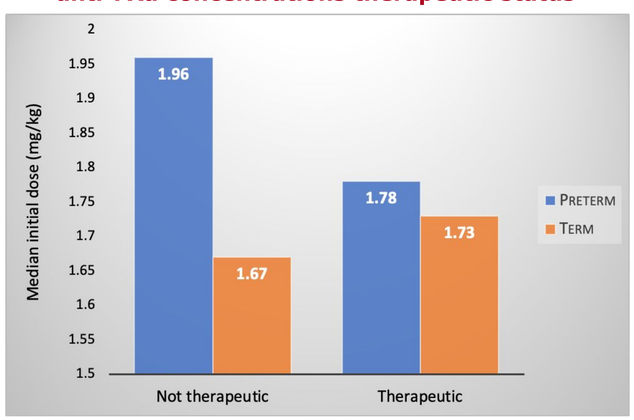

## Results

### Table 1: Baseline Demographics

| Total # of patients N = 26 | Preterm (<37 weeks) N = 6 (23.1%) | Term (≥37 weeks) N = 20 (76.9%) |
|---|---|---|
| Age (days) at first dose, median (IQR) | 15.5 (14-19.3) | 14.5 (9.8-20.8) |
| Sex, N (%) | | |
| Male | 5 (83.3%) | 11 (55%) |
| Race, N (%) | | |
| White | 5 (83.3%) | 7 (35%) |
| Hispanic | 1 (16.7%) | 11 (55%) |
| Other | 0 (0%) | 2 (10%) |
| Weight (kg), median (IQR) | 2.5 (2.3-3.2) | 3.2 (2.9-3.5) |
| SCr* (mg/dL), median (IQR) | 0.3 (0.3-0.4) | 0.3 (0.2-0.4) |
| CrCl^ (mL/min), median (IQR) | 59.6 (53.6-77.8) | 64.3 (52.2-83.8) |
| Urine output*# (mL), median (IQR) | 153.1 (88.5-166.2) | 96.7 (19.9-151.2) |
| PT* (seconds), median (IQR) | 15.1 (14.8-15.3) | 14.3 (14.0-15.6) |
| INR*, median (IQR) | 1.2 (1.1-1.2) | 1.1 (1.1-1.2) |
| Platelet count* (per mcL), median (IQR) | 227 (147.8-334.0) | 231 (190.0-307.0) |

*At baseline
^Calculated via the bedside Schwartz equation
# Calculated over 24 hours

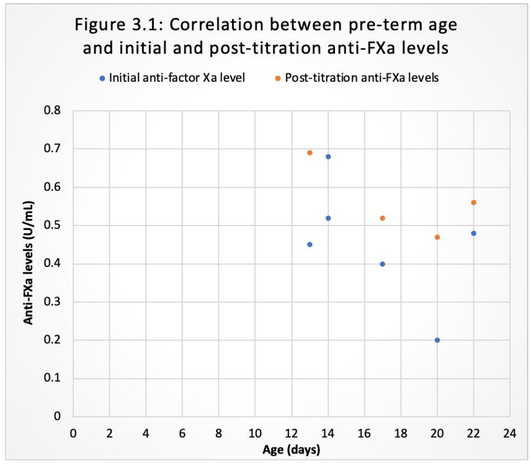
### Figure 2: Median initial enoxaparin doses vs. anti-FXa concentrations therapeutic status



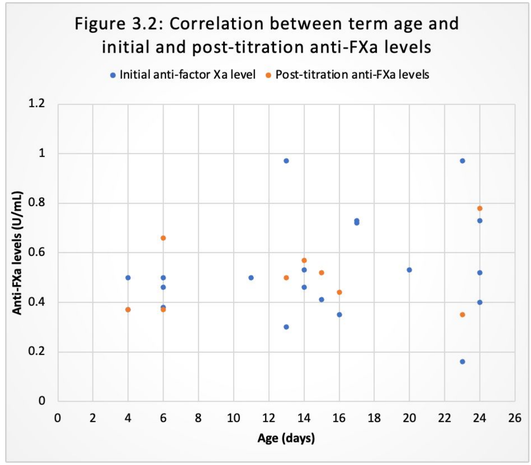

Note: All patients that fell into the not therapeutic category were subtherapeutic. No patients had supratherapeutic levels.

## Results [continued]

### Figure 3: Correlation between age and anti-FXa concentrations before and after titration

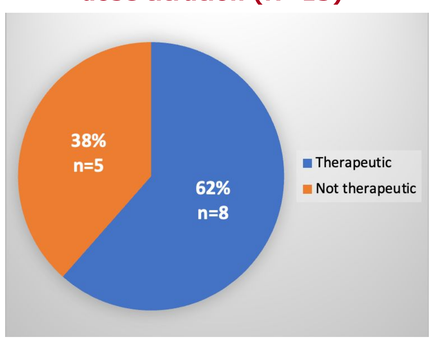



Initial anti-FXa level correlation coefficient (r)= -0.52
Post-titration anti-FXa level correlation coefficient (r)= -0.71



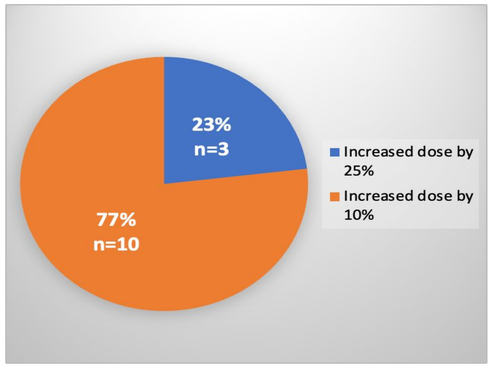

Initial anti-FXa level correlation coefficient (r)= 0.21
Post-titration anti-FXa level correlation coefficient (r)= 0.29

### Figure 4: Frequency of therapeutic anti-FXa concentrations after initial enoxaparin dose titration (N=13)




## Results [continued]

### Figure 5: Frequency of titration recommendation category relative to anti-FXa concentrations (N=13)




## Discussion

- Negative correlation found between preterm and their post-titration anti-FXa concentrations
  - However, may not be truly significant as only two subjects were included
- Higher initial doses required for preterm vs term potentially due to development differences of coagulation cascade between preterm and term neonates
- Majority of patients requiring dose titrations fell into the lower dose titration category, suggesting higher titrations may only be required for select patients with certain conditions
- Limitations included a limited sample size, higher percentage of males, and no grace period for drawn anti-FXa levels

## Conclusion

- Due to the small sample size, it is unclear whether current enoxaparin dosing titration recommendations are adequate to achieve therapeutic anti-FXa concentrations after the first dose titration in neonates
- The discrepancy in therapeutic anti-FXa concentrations achieved between term and preterm neonates may result from differences in the development of the coagulation cascade and resulting clotting factors that enoxaparin inhibits (factor Xa and factor IIa)

## Future Directions

- Further studies should be conducted with larger sample sizes
- Determining which patient characteristics necessitate higher dose titrations may be an area for further research

## References

(1) Greene LA, Law C, Jung M, et al. Lack of anti-factor Xa assay standardization results in significant low molecular weight heparin (enoxaparin) dose variation in neonates and children. J Thromb Haemost. 2014;12(9):1554-1557. doi:10.1111/jth.12641
(2) Witmer CM, Takemoto CM. Pediatric Hospital Acquired Venous Thromboembolism. Front Pediatr. 2017;5:198. Published 2017 Sep 19. doi:10.3389/fped.2017.00198
(3) Jaffray J, Young G. Developmental Hemostasis Pediatric Clinics of North America.