2. Segal LN, Clemente JC, Tsay JC, Koralov SB, Keller BC, Wu BG, *et al*. Enrichment of the lung microbiome with oral taxa is associated with lung inflammation of a Th17 phenotype. *Nat Microbiol* 2016;1:16031.
3. Twigg HL III, Knox KS, Zhou J, Crothers KA, Nelson DE, Toh E, *et al*. Effect of advanced HIV infection on the respiratory microbiome. *Am J Respir Crit Care Med* 2016;194:226–235.
4. Morris A, Beck JM, Schloss PD, Campbell TB, Crothers K, Curtis JL, *et al*.; Lung HIV Microbiome Project. Comparison of the respiratory microbiome in healthy nonsmokers and smokers. *Am J Respir Crit Care Med* 2013;187:1067–1075.
5. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: part 2. Correlation between subjects. *BMJ* 1995;310: 633.
6. Lozupone C, Cota-Gomez A, Palmer BE, Linderman DJ, Charlson ES, Sodergren E, *et al*.; Lung HIV Microbiome Project. Widespread colonization of the lung by Tropheryma whipplei in HIV infection. *Am J Respir Crit Care Med* 2013;187:1110–1117.
7. Friedman J, Alm EJ. Inferring correlation networks from genomic survey data. *PLOS Comput Biol* 2012;8:e1002687.
8. Narinesingh SP, Whitby DJ, Davenport PJ. Moraxella catarrhalis: an unrecognized pathogen of the oral cavity? *Cleft Palate Craniofac J* 2011;48:462–464.
9. Yang L, Dunlap DG, Qin S, Fitch A, Li K, Koch CD, *et al*. Alterations in oral microbiota in HIV are related to decreased pulmonary function. *Am J Respir Crit Care Med* 2020;201:445–457.
10. Gilbert JA, Quinn RA, Debelius J, Xu ZZ, Morton J, Garg N, *et al*. Microbiome-wide association studies link dynamic microbial consortia to disease. *Nature* 2016;535:94–103.

Anti-FXa Activity with Intermediate-Dose Thromboprophylaxis in COVID-19

To the Editor:

We read with interest the article by Dutt and colleagues describing measurement of anti–factor Xa (FXa) activity in ward patients with coronavirus disease (COVID-19) as well as those requiring intensive care (1). The authors suggest that patients admitted to an ICU with COVID-19 may warrant a higher starting dose of pharmacological thromboprophylaxis, although the optimal dose in these patients is uncertain pending upcoming randomized controlled trials. Current guidelines from various medical societies suggest routine pharmacological thromboprophylaxis in patients with COVID-19. However, there is a lack of consensus on whether standard-dose or higher intermediate-dose thromboprophylaxis should be used (2–5). We would like to present our experience with measuring anti-FXa activity using a higher, weight-based dose of enoxaparin for thromboprophylaxis. This retrospective observational study was deemed exempt by our institutional review board.

In early April, we noticed a high rate of thrombosis and thromboembolism among critically ill patients with COVID-19, an observation consistent with those in other institutions (6–8). Therefore, we adopted intermediate-dose thromboprophylaxis for critically ill patients with COVID-19 with enoxaparin (0.5 mg/kg twice daily), as described in Table 1, as our new standard of care. The dosages were selected based on several single-center studies suggesting higher rates of attainment of target anti-FXa activity with higher-dose enoxaparin (9, 10). Importantly, the target anti-FXa activity for pharmacologic prophylaxis is not evidence based, and adjusting doses to provide higher attainment of target activity was not demonstrated to improve clinical outcomes.

We monitored anti-FXa activity for the first 40 patients receiving this dosing strategy. Anti-FXa was checked 3–4 hours after the third or fourth dose of the intermediate-dose enoxaparin regimen. The enoxaparin dose was then adjusted as necessary to achieve a target anti-FXa activity of 0.2–0.5 U/ml.

Results are shown in Table 2. Seventy-five percent ($n = 33$) of patients achieved the targeted anti-FXa activity without further dose adjustment. Twenty-five percent ($n = 11$) of patients had their dose adjusted from institutional guideline recommended doses at some point in their hospitalization. Only three patients had dose adjustment because of their anti-FXa activity, with decreased dosage for two patients, one of whom later developed venous thromboembolism. Only two patients had enoxaparin decreased or stopped because of bleeding (hematuria in both cases). Four patients had their dosages increased to a therapeutic regimen because of clinically suspected ($n = 2$) or confirmed ($n = 2$) clotting events. Both patients with confirmed clotting events and one patient with a suspected clotting event were initially on standard-dose thromboprophylaxis before the institutional transition to intermediate-dose thromboprophylaxis.

We achieved a high rate of the targeted anti-FXa activity using this intermediate dosing scheme. Most patients outside the target anti-FXa range were above rather than below goal concentrations. After reviewing this data, our institution decided to continue intermediate-dose thromboprophylaxis but eliminate routine anti-FXa monitoring because it rarely resulted in dose adjustments. Only 2 of the 10 patients with anti-FXa activity of greater than 0.5 U/ml were decreased because of this monitoring, which was likely due to concern over the high rates of thromboembolic complications in this population. In addition, anti-FXa monitoring for thromboprophylaxis is controversial, especially in intensive care (11–13). There is no clear relationship between anti-FXa activity and the safety or efficacy of thromboprophylaxis. Although low anti-FXa activity has been associated with thromboembolism, there is no proven benefit to adjusting the enoxaparin dose to a "target" anti-FXa activity. Furthermore, the target anti-FXa activity of 0.2–0.5 U/ml has not been rigorously validated.

In conclusion, our results may assist others considering intermediate-dose thromboprophylaxis and anti-FXa monitoring in critically ill patients with COVID-19. Our findings suggest that intermediate-dose thromboprophylaxis led to anti-FXa activity according to predefined criteria in most of

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Table 1. Institutional Guidelines

Creatinine Clearance	VTE Prophylaxis Dosing for COVID-19 in Critically Ill			
	<50 kg	50–69 kg	70–79 kg	⩾80 kg
⩾30 ml/min	Enoxaparin 30 mg, s.c., q24h	Enoxaparin 30 mg, s.c., q12h	Enoxaparin 40 mg, s.c., q12h	Enoxaparin 0.5 mg/kg, s.c., q12h, rounded to nearest syringe size
⩽30 ml/min but not hemodialysis	Enoxaparin 30 mg, s.c., q24h		Enoxaparin 40 mg, s.c., q24h	Enoxaparin 0.5 mg/kg, s.c., q24h, rounded to nearest syringe size
Hemodialysis	Do not use enoxaparin; use heparin 5,000 U, s.c., q8–12h	Enoxaparin 30 mg, s.c., q24h		

Definition of abbreviations: COVID-19 = coronavirus disease; FXa = factor Xa; q24h = once every 24 h; VTE = venous thromboembolism. Maximum initial enoxaparin dose = 100 mg, subcutaneously, q12h. Target peak anti-FXa 0.2–0.5 U/ml; draw 3–4 hours after third or fourth dose of regimen. If anti-FXa < 0.2 U/ml, increase dose to next syringe size and keep current frequency. If anti-FXa > 0.5 U/ml, decrease dose to next syringe size or consider package labeled prophylaxis dosing.

the studied patients and may not require routine anti-FXa monitoring. The optimal dose of thromboprophylaxis in critically ill patients with COVID-19 is still unknown pending larger randomized controlled trials. ■

Table 2. Patient Characteristics

	Critically Ill Patients with COVID-19 (*n* = *40*)
Age, yr	64.7 (9.4) [41–90]
Weight, kg	101.1 (31.1) [53.3–186]
Serum creatinine, mg/dl	1.27 (0.64) [0.54–3.37]
Admission D-dimer, μg/ml FEU	3.7 (7.3) [0.43–40.48]
Daily enoxaparin dose, mg, median (IQR) [range]	80 (80–120) [60–160]
Enoxaparin frequency	
Daily	2 (5)
Twice daily	38 (95)
Anti-FXa activity (U/ml)*	0.42 (0.14) [0.19–0.69]
Anti-FXa between 0.2 and 0.5 U/ml*	33 (75)
>0.5 U/ml	10 (23)
<0.2 U/ml	1 (2)
Any dose adjustment†	11 (25)
Dose increased†	7 (16)
Change in weight or renal function	1 (2)
Subtherapeutic anti-FXa	1 (2)
Confirmed/suspected clotting event	4 (9)
New-onset atrial fibrillation	1 (2)
Dose decreased or discontinued†	6 (14)
Change in weight or renal function	3 (7)
Supratherapeutic anti-FXa	2 (5)
Bleeding event	2 (5)

Definition of abbreviations: COVID-19 = coronavirus disease; FEU = fibrinogen equivalent units; FXa = factor Xa; IQR = interquartile range. Continuous variables are presented as mean (SD) [range] unless otherwise noted. Nominal variables are presented as *n* (%).
*Of 44 anti-FXa performed in 40 patients.
†Two patients had doses decreased and increased; one patient had both a dose decrease and a discontinuation of therapy because of elevated anti-FXa and bleeding event, respectively.

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Stephen H. Rappaport, Pharm.D.*
Jenna M. Clark, Pharm.D.
Samantha Delibert, Pharm.D.
Kaylee M. Maynard, Pharm.D.
Paritosh Prasad, M.D.
David C. Kaufman, M.D.
Anthony P. Pietropaoli, M.D., M.P.H.
Caroline M. Quill, M.D., M.S.H.P.
Christine M. Groth, Pharm.D.
University of Rochester Medical Center
Rochester, New York

ORCID ID: 0000-0002-3933-736X (S.H.R.).

*Corresponding author (e-mail: stephen_rappaport@urmc.rochester.edu).

References

1. Dutt T, Simcox D, Downey C, McLenaghan D, King C, Gautam M, *et al*. Thromboprophylaxis in COVID-19: anti-FXa—the missing factor? [letter]. *Am J Respir Crit Care Med* 2020;202: 455–457.
2. Porfidia A, Pola R. Venous thromboembolism and heparin use in COVID-19 patients: juggling between pragmatic choices, suggestions of medical societies and the lack of guidelines. *J Thromb Thrombolysis* 2020;50:68–71.
3. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. Bethesda, MD: National Institutes of Health; 2020 [accessed 2020 Feb 8]. Available from: https://www.covid19treatmentguidelines.nih.gov/.
4. Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, *et al*. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis* 2020;50: 72–81.
5. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, *et al*.; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020;18:1859–1865.

6. Maatman TK, Jalali F, Feizpour C, Douglas A II, McGuire SP, Kinnaman G, *et al*. Routine venous thromboembolism prophylaxis may Be inadequate in the hypercoagulable state of severe coronavirus disease 2019. *Crit Care Med* 2020;48:e783–e790.
7. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, *et al*. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020;18:1743–1746.
8. Becker RC. COVID-19 update: covid-19-associated coagulopathy. *J Thromb Thrombolysis* 2020;50:54–67.
9. Berndtson AE, Costantini TW, Lane J, Box K, Coimbra R. If some is good, more is better: an enoxaparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis. *J Trauma Acute Care Surg* 2016;81:1095–1100.
10. Bickford A, Majercik S, Bledsoe J, Smith K, Johnston R, Dickerson J, *et al*. Weight-based enoxaparin dosing for venous thromboembolism prophylaxis in the obese trauma patient. *Am J Surg* 2013;206: 847–851, discussion 851–852.
11. Hutt Centeno E, Militello M, Gomes MP. Anti-Xa assays: what is their role today in antithrombotic therapy? *Cleve Clin J Med* 2019;86: 417–425.
12. Wei MY, Ward SM. The anti-factor xa range for low molecular weight heparin thromboprophylaxis. *Hematol Rep* 2015;7: 5844.
13. Egan G, Ensom MH. Measuring anti-factor xa activity to monitor low-molecular-weight heparin in obesity: a critical review. *Can J Hosp Pharm* 2015;68:33–47.

Reply to Rappaport *et al.*

From the Authors:

We read with interest the communication from Rappaport and colleagues describing their experience measuring anti–factor Xa (FXa) activity in critically unwell patients with coronavirus disease (COVID-19) infection, receiving intermediate-dose thromboprophylaxis with enoxaparin (0.5 mg/kg twice daily) as standard care. The authors conclude that their results suggest anti-FXa monitoring is not required for critically unwell patients receiving an escalated regime of thromboprophylaxis.

The authors measured anti-FXa activity in 40 critically unwell patients within 48 hours of admission and reported the need for dose adjustment thereafter to obtain a target anti-FXa activity of 0.2–0.5 U/ml. Seventy-five percent of patients achieved the target anti-FXa range with no further dose adjustment.

This contrasts with our own report (1), in which only 5% of intensive treatment unit patients (majority intubated) managed using a standard thromboprophylaxis regime (40 mg enoxaparin once daily) achieved target anti-FXa activity (0.2–0.4 U/ml). The authors did not define "critically unwell patients" as those requiring mechanical ventilation; however, these reports together provide support for more intensive thromboprophylaxis regimes for patients with severe COVID-19 infection admitted to the intensive treatment unit.

As highlighted in our research correspondence, we agree that uncertainty remains about the value of anti-FXa monitoring in patients receiving thromboprophylaxis with low molecular heparin (2). Nevertheless, in the absence of clinical trial data confirming an optimal anticoagulation strategy for a condition with a recognized spectrum of thrombosis and clinically relevant bleeding (3, 4), we suggest that the use of anti-FXa activity to inform dosing should not be completely dismissed.

Patients with COVID-19 demonstrate dynamic flux in their clinical progress accompanied by underlying changes in their inflammatory and coagulopathic state (5). Such fluctuations may influence heparin resistance and low–molecular weight heparin clearance. It is unclear whether Rappaport and colleagues measured anti-FXa serially during hospitalization to determine consistent activity within the target range and whether such fluctuations reflected changes in disease severity or outcomes. One of four patients, not an insignificant proportion, required dose adjustment and six of 11 patients experienced a bleeding or confirmed/suspected thrombotic event. The corresponding anti-FXa measured ahead or at the time of these events is not provided. Bleeding complications in patients with COVID-19 are reported in the literature and, in addition to thrombotic outcomes, represent important endpoints for ongoing randomized controlled clinical trials.

Since the start of the COVID-19 pandemic, despite an evolution in anticoagulation regimes for the prevention of thrombotic complications based mainly on retrospective data, we believe the relationship between patient-specific factors for thrombosis and hemorrhage and anti-FXa concentrations remain an important consideration. Until we understand further the discordance of the anti-FXa in COVID-19, its relevance, and the targets one should aim for to achieve safe and effective hemostasis, we would urge caution against disregarding anti-FXa activity as a potential tool in a patient group with a high risk of thrombosis and bleeding while receiving anticoagulation. ■

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Tina Dutt, M.B. Ch.B., M.R.C.P., F.R.C.Path., Ph.D.*
David Simcox, M.B. Ch.B.
Liverpool University Hospitals National Health Service Foundation Trust
Liverpool, United Kingdom

Colin Downey, I.B.M.S.
Liverpool Clinical Laboratories
Liverpool, United Kingdom

Daniella McLenaghan, M.B. Ch.B.
Charlotte King, M.B. Ch.B.
Manish Gautam, M.B. B.S.
Liverpool University Hospitals National Health Service Foundation Trust
Liverpool, United Kingdom

Steven Lane, Ph.D., M.Sc., B.Sc.
University of Liverpool
Liverpool, United Kingdom

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