6. Maatman TK, Jalali F, Feizpour C, Douglas A II, McGuire SP, Kinnaman G, et al. Routine venous thromboembolism prophylaxis for patients with severe coronavirus disease 2019. Crit Care Med 2020;48:e783–e790.

7. Litijos 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, Miliello 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;7:844.

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.

Copyright © 2020 by the American Thoracic Society

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.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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

*This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rcrm.202007-2913LE on September 15, 2020
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. 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. [Published erratum appears in Can J Hosp Pharm 68:247].
3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-847.
4. Lucatelli P, De Rubeis G, Citone M, Lucarelli NM, Pasqualini V, Sturiale M, et al. Heparin-related major bleeding in covid-19-positive patient: perspective from the outbreak. Cardiovasc Intervent Radiol 2020;43: 1216-1217.
5. Deshpande C. Thromboembolic findings in COVID-19 autopsies: pulmonary thrombosis or embolism? Ann Intern Med 2020;173: 394-395.

Copyright © 2020 by the American Thoracic Society

COVID-19–related Respiratory Failure and Lymphopenia Do Not Seem Associated with Pneumocystosis

To the Editor:

We read with great interest the letter “A Case of COVID-19 and Pneumocystis jirovecii Coinfection” by Menon and colleagues (1) that reports a cooccurrence of coronavirus disease (COVID-19) and pneumocystosis in an 83-year-old non–HIV-infected female. The authors hypothesize that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection led to a state of functional immune suppression related to lymphocytopenia (absolute lymphocyte count 1,090 cells/μl), predisposing the patient to Pneumocystis jirovecii infection. In this case, mycological arguments for pneumocystosis were a positive qualitative real-time PCR assay on a tracheal aspirate and a serum (1,3)-β-D-glucan at 305 pg/ml. Also, subtle cystic images were observed on her computed tomographic scan and the patient was receiving inhaled and low-dose oral corticosteroid therapy for a history of asthma and ulcerative colitis.

A follow-up serum obtained 1 week after initiating treatment showed an important decrease in the amount of β-glucan. This is surprising, as it is usually known to diminish very slowly or even increase (median decline of 17 pg/ml; range, −334 to 205) (2, 3). The patient was treated and promptly exubated (on Day 7 of hospitalization); it would therefore be interesting to know on which day the anti-Pneumocystis treatment was initiated because clinical improvement is usually expected after 4–8 days (4).

PCR is of great interest for the diagnosis of pneumocystosis in non–HIV-infected patients. However, as stated by the authors, its great sensitivity can lead to the detection of low fungal loads and has made the distinction between colonization and infection a regular problem.

We have recently seen hundreds of patients with COVID-19 in our institution (La Pitié-Salpêtrière hospital, a 1,850-bed tertiary care center in Paris, France), many of whom were managed in ICUs. In line with previous data indicating that severe forms of COVID-19 are associated with lymphopenia (5), many of our patients had an absolute lymphocyte count below 1,000/μl. Taking into account that this condition represents a documented risk factor for pneumocystosis (6) and the lack of knowledge concerning the susceptibility of these patients to fungal complications, we performed P. jirovecii PCR assays (targeting the mitochondrial large subunit ribosomal RNA) on all respiratory samples obtained from patients under mechanical ventilation or venovenous extracorporeal membrane oxygenation (ECMO) support.

A total of 423 PCR assays were performed on respiratory samples obtained from 145 patients with severe, proven SARS-CoV-2 infections (mean, 2.9 samples per patient; range, 1–11) between March 12 and April 27 (Table 1). Among them, 22 patients had preexisting recognized risk factors for pneumocystosis, 6 other patients were HIV infected but with relatively abundant CD4+ cells, and 22 other patients received corticosteroids as treatment for their COVID-19. Most of them (79%; 113/143) had lymphocytopenia (<1,000 cells/μl). Almost all P. jirovecii PCR assay results were strictly negative (99.3%; 420/423).

We found three positive results in 2 among the 145 patients (1.4%). The first patient was a 78-year-old woman with diabetes and hypertension admitted to the ICU (March 12, Day 1) for COVID-19–related respiratory failure. She had lymphocytopenia (nadir: 410/μl), was not tested for β-D-glucan, and had a low fungal load in BAL sampled at Day 3 (740 copies/ml; 2.9 log). Her respiratory state improved. She later developed bacterial and thrombotic complications that lead to her death on Day 43 from hemorrhagic shock with no evidence of respiratory failure.

The second patient was a pregnant woman with obesity (body mass index, 40.4 kg/m2), type 2 diabetes, and chronic hypertension. She was admitted to the ICU (March 20, Day 1) in a severe respiratory state (PaO2/FIO2 < 100 mm Hg; SAPS II score = 65) that required venovenous ECMO support. She presented concomitant transient lymphocytopenia (770–1,420/μl). A low P. jirovecii load was detected in two BAL samples.

Hassan Burhan, M.B. Ch.B.
Liverpool University Hospitals National Health Service Foundation Trust
Liverpool, United Kingdom

*Corresponding author (e-mail: tina.dutt@liverpoolft.nhs.uk).

Copyright © 2020 by the American Thoracic Society

CORRESPONDENCE

1734 American Journal of Respiratory and Critical Care Medicine Volume 202 Number 12 | December 15 2020