CLINICAL DECISIONS
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Anticoagulation in Hospitalized Patients with Covid-19

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Man with Covid-19

Jehan F. Chowdhury, D.O.

Mr. Jackson is a 78-year-old man with hypertension and hyperlipidemia who was brought to the emergency department 48 hours ago with a 2-day history of shortness of breath and fever (temperature up to 38.5°C). When he arrived at the emergency department, his temperature was 38.0°C, pulse 95 beats per minute, respiratory rate 22 breaths per minute, and oxygen saturation 98% while he was receiving supplemental oxygen through a nasal cannula at a rate of 2 liters per minute. Examination revealed rales at his lung bases. He was admitted to a medical unit. Laboratory testing on admission revealed a positive result for Covid-19 on a polymerase-chain-reaction assay and an elevated D-dimer level, at 980 ng per milliliter (upper limit of the normal range, 500 ng per milliliter).

Over the past 48 hours, his clinical status has worsened. Oxygen requirements have increased to 15 liters per minute by high-flow nasal cannula, and he has remained persistently febrile, with a temperature as high as 38.5°C. Inflammatory markers (erythrocyte sedimentation rate and C-reactive protein level) have been increasing, and the D-dimer level has increased to 1656 ng per milliliter.

Prophylactic anticoagulation was initiated on admission. Computed tomographic angiography showed no evidence of deep venous thrombosis in the legs or pulmonary embolism. Now that the patient's condition has worsened, you must decide whether the prophylactic doses of anticoagulants should be maintained or whether they should be replaced by an increased dose (i.e., intermediate dose) — and if so, what agent. In addition, you must decide whether anticoagulation, at either prophylactic or intermediate doses, should be continued after Mr. Jackson's discharge from the hospital.

TREATMENT OPTIONS

Which of the following approaches would you take for this patient? Base your choice on the published literature, your own experience, treatment guidelines, and other information sources.

1. **Continue prophylactic anticoagulation during hospitalization and discontinue at hospital discharge.**
2. **Switch to intermediate-dose anticoagulation and continue anticoagulation after hospital discharge.**

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the patient and the points made by the experts, which approach would you choose?

OPTION 1

Continue Prophylactic Anticoagulation during Hospitalization and Discontinue at Hospital Discharge

Lisa K. Moores, M.D.

The available literature to date has documented high rates of venous thromboembolism (VTE), predominantly pulmonary embolism, in hospitalized patients with Covid-19 pneumonia, particularly in critically ill patients admitted to the intensive care unit (ICU). Thrombotic complications have developed in many patients despite the use of prophylactic or, at times, therapeutic doses of anticoagulants, prompting many to advocate the use of higher-than-usual doses of anticoagulants. Some have advocated therapeutic anticoagulation in these patients, at least in those admitted to the ICU.[1] We do, however, have existing, well-

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developed, evidence-based guidelines regarding the approach to thromboprophylaxis in hospitalized medically ill and critically ill patients. To stray from this guidance, we would need to be certain that the rate of VTE is indeed higher among patients with Covid-19 than among similarly ill patients who do not have Covid-19. We would also need to feel confident that increased thromboprophylaxis will be effective and safe.

Like many critically ill patients, patients with Covid-19, such as Mr. Jackson, are clearly at risk for macrothrombosis, since they exhibit all three components of Virchow's triad (stasis of blood flow, hypercoagulability, and endothelial injury). Pathological reports have shown that they also have substantial microthrombosis, or immunothrombosis, related to hypoxemia, endothelial injury, and inflammation. Emerging data regarding the discrepancy between the rate of deep-vein thrombosis and that of pulmonary embolism in patients with Covid-19, and the fact that many of the documented cases of pulmonary embolism occur in the absence of deep-vein thrombosis and are located in the more peripheral pulmonary arteries,[2] have led to the hypothesis that there may be a unique pulmonary embolism phenotype in patients with Covid-19. This phenotype is characterized by thrombi and not emboli — that is, immunothrombosis is probably much more prominent than originally recognized. One report of 66 patients in the ICU, all of whom received standard-dose thromboprophylaxis, noted only a 5% rate of VTE that was not thought to be either catheter-related thrombosis or immunothrombosis.[2] In this context, increased doses of anticoagulants may be ineffective, especially since larger doses are not recommended for other forms of microangiopathy. This may be why some small reports note high rates of VTE even among patients who are receiving full-dose anticoagulation.[3,4] It may therefore follow that upstream therapies, such as antiviral and immunomodulating agents, to reduce the development of immunothrombosis will prove more efficacious than downstream attempts to suppress the coagulation system.

Initial reports revealed limited evidence of bleeding associated with Covid-related coagulopathy, but more data regarding the risk of bleeding are emerging. In a series of 92 patients with Covid-19 who were in the ICU, all of whom received either prophylactic or full-dose anticoagulation, the authors reported a 34% incidence of VTE but also a 21% incidence of major hemorrhagic events, the majority of which (84%) occurred in patients receiving full-dose anticoagulation. Only 50% of those patients had a confirmed thrombosis.[5] In the series, mentioned above, of 66 patients in the ICU who were receiving standard thromboprophylaxis, an 11% rate of major bleeding was noted.[2] These observations suggest that higher doses of anticoagulation confer risk (as would be expected). Such risk should not be undertaken in the absence of evidence of sufficient benefit. Most current guidelines thus recommend standard doses of anticoagulants for thromboprophylaxis in patients hospitalized with Covid-19, while randomized trials are being conducted.[1]

Whether to extend thromboprophylaxis beyond discharge in a patient such as Mr. Jackson is also controversial. Here, too, we lack data to know whether patients with Covid-19 are at substantially higher risk for bleeding than other medically ill patients. Current guidelines recommend against routine postdischarge prophylaxis in these patients, given a net harm associated with extended thromboprophylaxis.[6] If we assume that patients with Covid-19 incur the same risk of bleeding as patients without Covid-19 and that the burden associated with symptomatic VTE is similar to that associated with major bleeding, extended thromboprophylaxis would result in a net benefit only if the risk of symptomatic VTE is above 1.8% after hospital discharge.[1] Early data in a small cohort of patients with Covid-19 suggest that the risk of VTE at 30 days is low (0.6%), with a similar rate of major bleeding (0.7%).[7]

We are in a time of unprecedented uncertainty. Clinicians may be faced with the temptation to choose intervention over caution when confronted with ill patients and limited data. We have, however, been trained to practice evidence-based medicine and must be wary of acting too quickly on new observations when the intervention may cause harm. We need more evidence to change our practice.

Disclosure forms provided by the author are available at NEJM.org.

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OPTION 2

Switch to Intermediate-Dose Anticoagulation and Continue Anticoagulation after Hospital Discharge

Jean M. Connors, M.D.

The practice of medicine has been traumatized by the Covid-19 pandemic. With nearly 20 million cases worldwide, Covid-19 presents both logistic challenges, due to the sheer numbers of infected patients during local surges, and medical management challenges, due to a lack of high-quality data to guide clinical care, especially for those who are severely ill. Observational data published since the start of the pandemic have limitations but can provide some direction as we tackle the many issues associated with the care of patients infected with SARS-CoV-2.

Mr. Jackson's clinical condition has deteriorated, with progressive hypoxemia, elevated inflammatory markers, and an increase in D-dimer level to more than 3 times the upper limit of the normal range, a level that is associated with increased mortality,[8] but there is no evidence of VTE on imaging. Although anticoagulation to prevent thrombotic events is now unquestioned in hospitalized patients with Covid-19, the appropriate dose to prevent thrombosis and, potentially, pulmonary microvascular thrombosis is not known. Thromboinflammation associated with Covid-19 results in hypercoagulability, with elevated levels of procoagulant proteins, including fibrinogen, von Willebrand factor, and factor VIII; activation of coagulation; endothelialitis due to viral infection of endothelial cells with loss of protective antithrombotic activity; and pulmonary microvascular thrombosis.[4,9] Data from Wuhan, China, showed that anticoagulation in severe cases of Covid-19 decreased mortality.[10] Reports from Europe and the United States showed that the incidence of VTE was three to four times as high, despite standard prophylactic-dose anticoagulants, among critically ill ICU patients with Covid-19 as among patients who were not in the ICU. Even among patients admitted to the ICU, those with Covid-19 have been found to have a higher incidence of VTE than similarly critically ill patients or ICU patients with a different viral illness.[4,11-13]

Increased anticoagulation is warranted for Mr. Jackson; the sharp increase in oxygen requirement portends ICU admission. Although the use of therapeutic-dose anticoagulation is controversial, "intermediate" intensity anticoagulation, such as enoxaparin at a dose of 0.5 mg per kilogram of body weight twice daily, appears to be necessary in critically ill patients with Covid-19 to prevent thrombosis. About half the experts writing society guidelines for critically ill patients suggest or give consideration for its use (e.g., in the guidelines of the International Society on Thrombosis and Haemostasis, the Royal College of Physicians, and the Anticoagulation Forum) despite the lack of data from randomized, controlled trials. Some centers use weight-based dosing, acknowledging that 40 mg of enoxaparin or the equivalent is inadequate for many patients. A review of past data on VTE prophylaxis in critically ill patients suggests that we may have been undertreating these patients. Heparins rather than direct oral anticoagulants should be used in critically ill patients, owing to pragmatic factors including the shorter half-life, the fact that the dose can be adjusted in patients with acute kidney injury, and the absence of drug–drug interactions. Bleeding rates have generally been low, but the need for prolonged duration of invasive mechanical ventilation confers the usual ICU-associated problems. The risks and benefits of anticoagulation should be assessed as for any critically ill patient.[4,12] Analyses from large health systems' databases suggest that therapeutic-dose anticoagulation is associated with improved outcomes; however, these retrospective analyses have limitations. Mr. Jackson would ideally be enrolled in a randomized clinical trial, such as one registered at ClinicalTrials.gov, to assess the efficacy and safety of escalated doses of anticoagulants in patients with Covid-19.

Although the risk of VTE is increased in critically ill patients with Covid-19, one recent observational study showed that the incidence of VTE events after hospital discharge was low[14]; factors such as shorter length of stay (including earlier patient discharge because of hospital bed shortages), treatment with antiinflammatory and antiviral agents, and use of intermediate-dose anticoagulation in ICU patients may mitigate the postdischarge risk. Previous trials of postdischarge VTE prophylaxis in medically ill patients

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have shown a significant reduction in VTE; however, major bleeding was slightly increased with most tested anticoagulants, with the result that there has been little uptake in practice. Until data from randomized clinical trials showing no net clinical benefit are available, postdischarge VTE prophylaxis should be strongly considered for patients who have been discharged early from the hospital because of bed shortages, patients who are discharged to a rehabilitation facility, or patients with known additional risk factors for VTE, such as obesity, thrombophilia, advanced age, and a history of VTE. Mr. Jackson, by virtue of his age, likely ICU stay, and elevated D-dimer level, is a candidate for standard-dose postdischarge VTE prophylaxis for 14 to 35 days if a randomized clinical trial in which he can enroll is not available.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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