A Rapid Guidance Process for the Development of an Anticoagulation Protocol in the COVID-19 Pandemic

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Health care systems have encountered unprecedented challenges during the coronavirus disease-2019 (COVID-19) pandemic, such as standardizing care in the absence of high-quality data. As an emblematic example, preliminary data and early anecdotal experience suggested that a major driver of COVID-19 pathophysiology was hypercoagulability, suggesting the need for aggressive anticoagulation. In this article, we describe the rapid guidance process for the development of an anticoagulation protocol for COVID-19. Preliminary evidence was collected from multidisciplinary experts within our institution to inform the first protocol draft. After implementation, we rapidly acquired data to inform a revision, with subsequent modifications based on higher quality data. The description of this process can inform other health systems when faced with a similar crisis characterized by high patient volumes, poor clinical outcomes, lack of proven effective therapies, and rapid flow of information from multiple sources of variable credibility.

Key words: anticoagulation, COVID-19, coronavirus, protocol, quality

Coronavirus disease-2019 (COVID-19) has emerged as a global pandemic that has placed unprecedented strain on health care systems.¹ The lack of effective therapies placed an additional burden on providers. Hospitals face the daunting problem of clinicians haphazardly trying various treatments based on information from unconventional sources, such as media and press releases. One prime example of this process is the use of therapeutic anticoagulation in patients with severe COVID-19. Early reports from Wuhan, China, suggested that a key pathophysiologic component of severe COVID-19 disease, as defined by Centers for Disease Control and Prevention criteria,² is a procoagulant state.^{3,4} Many clinicians began treating patients with therapeutic anticoagulation based on this preliminary information, leading to a lack of a standardized approach across hospitals. Therefore, the leadership of our health care system utilized a rapid guidance process to develop a clinical protocol to guide management. Lessons learned during the creation and implementation of this protocol are applicable to any health care system faced with a crisis characterized by high volume, poor outcomes, lack of proven effective

therapies, and rapid flow of information from multiple sources of variable credibility (see the Table).

VENOUS THROMBOEMBOLISM PROPHYLAXIS PRIOR TO COVID-19

Prior to the COVID-19 pandemic, venous thromboembolism (VTE) prophylaxis at our institution was protocolized as follows: Patients at low risk of VTE, defined as nonsurgical patients who are ambulatory, younger than 80 years, and have no major VTE risk factors (ie, prior VTE or cancer) were recommended to have early ambulation. All other patients were categorized as high risk and recommended to have pharmacologic anticoagulant prophylaxis unless the bleeding risk was high. Subcutaneous (SC) unfractionated heparin twice daily was the default recommendation for most medical and general surgery patients categorized as high risk for VTE.

Clinical decision support tools included a structured VTE prophylaxis section within the admission order sets for each department. This protocol and clinical decision support tool is still in use for non-COVID-19-infected patients. The order set presents the definitions for risk groups, mandates categorization, and presents default options including sequential compression devices for patients at increased risk of bleeding. In an analysis several years prior to the pandemic, compliance for this order set was 94%.

PRELIMINARY EVIDENCE

In the early days of the COVID-19 outbreak, impressions of increased thrombotic events and coagulopathy were shared by many clinicians from multiple specialties across the hospitals in our system. This increase was confirmed when we retrospectively evaluated the incidence of VTE for medicine patients in our hospital

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Table. Factors Suggesting the Need for a Rapid Guidance Process

Factor	Rationale
Sudden onset of crisis	Lack of time for a standard committee-led process
High volume	Treatment impacts large numbers of patients; requires deploying physicians to wards who are unfamiliar with hospital-based medical processes and subspecialists
Poor outcomes	Urgency in exploring new therapeutic modalities
Lack of an established treatment	Promotes haphazard use of unproven treatments
One or more proposed potential treatments	Need to prioritize therapy
Poor credibility of evidence sources	Requires critical evaluation of available evidence by experts from multiple disciplines
Nonstandard local uptake of treatment approaches	Need to standardize care across health systems

system during the first half of 2020. In the first quarter of 2020 there were 0.7 VTE per 1000 discharges, which increased to 1.1 per 1000 discharges in the second quarter. In response, we convened a multidisciplinary meeting on April 6, 2020 to discuss the preliminary evidence and anecdotal experience. The workgroup was composed of representatives from hematology, pulmonary, critical care, hospital medicine, nephrology, and pathology. The goal of this meeting was to develop a plan for anticoagulation management for COVID-19.

Workgroup members shared several important clinical observations. Pulmonary physicians described that the pathophysiology of patients with severe COVID-19 when intubated was consistent with pulmonary vascular disease/thromboemboli, and highlighted evidence for increased dead space ventilation. One physician had empirically given one patient thrombolysis and noted transient improvement in respiratory distress and hemodynamics.⁵ Pathologists described their preliminary autopsy findings of extensive pulmonary thromboses and microthrombi in the pulmonary vasculature.⁶ Nephrology reported a significant number of thrombosed vascular access lines.

These observations from physicians within our institution and the relatively low rigor of the evidence that was available suggested that anticoagulation may be an important aspect of COVID-19 treatment. During this period of the pandemic, information was rapidly developing as was the number of COVID-19 cases and deaths in our health system. A health-system-wide protocol was developed to create a uniform approach, which would provide anticoagulation for patients whose outcomes could be improved and avoid fully anticoagulating patients who were unlikely to benefit.

INITIAL PROTOCOL DEVELOPMENT

After the initial meeting, a smaller group of physicians from hematology, intensive care, hospital medicine, cardiology, and pharmacy met on April 8, 2020, and devoted their efforts toward the rapid development of an anticoagulation protocol for hospitalized patients with COVID-19. To inform the drafting of this protocol, we obtained data on anticoagulation in COVID-19 from many untraditional sources including society online forums, preprint servers, and social media. In addition, we reached out to neighboring institutions in New York City who shared their experience and protocols. We noted that the landscape of anticoagulation strategies ranged from conservative, providing primarily prophylaxis-dose anticoagulation, to aggressive, which had a lower threshold for providing treatment-dose anticoagulation. Our workgroup felt it necessary to be aggressive given our anecdotal experience and the preliminary published evidence from Wuhan, China, suggesting high rates of thrombotic events.^{3,4}

Risk stratification was an important feature of our early discussions, in particular to decide whether therapeutic dose anticoagulation would be administered. To support the decision-making process, we attempted to identify features that have been associated with intensive care unit (ICU) admission and mortality in COVID-19 reports. Markers of disease severity, such as oxygen requirement, elevated C-reactive protein, and elevated D-dimer, were thought to be early predictors of poor outcomes.⁷⁻⁹ However, our review did not identify any strong evidence for any single marker or risk score to determine whether the patient would decompensate or benefit from anticoagulation. Given the lack of rigorous evidence, the workgroup determined that specific parameters would not replace clinician judgment; rather, the protocol would provide a list of factors for consideration when formulating the clinical decision.

Patients with nonsevere disease were recommended to receive prophylactic anticoagulation with low-molecular-weight heparin (LMWH), typically SC enoxaparin 40 mg daily. However, we also allowed for the use of apixaban 2.5 to 5 mg twice daily, as this is less reliant on renal function. For patients with severe disease as defined by the treating physician, the consensus was that they warranted therapeutic anticoagulation. Patients hospitalized outside of the ICU were recommended to receive therapeutic anticoagulation. Of note, this VTE prophylaxis strategy is significantly more intensive than other high-risk settings, such as postsurgical and routine ICU care. The workgroup developed specific management strategies for patients with severe chronic kidney disease, including patients requiring renal replacement therapy. The use of intraventricular hemorrhage (IVH) was minimized on the medical wards to reduce the risks of transmitting infection to staff, given the need for dosing changes and partial thromboplastin time (PTT) monitoring. The use of IVH in our ICUs was facilitated by a system, which provided access to the IV pumps outside the patient rooms.

Of note, interim guidance from the International Society of Thrombosis and Haemostasis (ISTH) from March 25, 2020, recommended prophylactic anticoagulation with LMWH for hospitalized COVID-19 patients but did not comment on the use of therapeutic anticoagulation.¹⁰ In contrast, our protocol was significantly more aggressive in recommending therapeutic dose anticoagulation in hospitalized patients without evidence of a VTE.

REASSESSING AND REVISING

The initial protocol was released to the entire health system on April 10, 2020. A critical element of the rollout was rapid safety assessment, which was particularly prudent given that the protocol was based on largely anecdotal evidence. While we felt the benefits of therapeutic anticoagulation outweighed the risks of clinically significant bleeding, this was an assumption that had not been rigorously evaluated. Quantitative evaluation, including assessment of bleeding rates, was initiated, but results would not be timely enough to provide any early signal on protocol performance. To provide rapid feedback, the gastroenterology department provided qualitative estimation of clinically significant gastrointestinal bleeding since protocol implementation and neuroradiology provided daily reports on intracranial hemorrhage. A workgroup member investigated each intracranial hemorrhage to determine whether the bleeding event was due to the anticoagulation protocol. The assessment included a determination of the anticoagulant received, if any, the temporal relationship between anticoagulation administration and the bleeding event, and whether there were other indications for anticoagulants.

Our anecdotal evidence suggested a slight increase in clinically significant bleeding and identified several intracranial hemorrhages deemed to be related to the anticoagulation protocol. Although bleeding is expected given the increased exposure to therapeutic anticoagulation and whether this number of bleeding events was greater than would be expected had the protocol not been established, the workgroup felt it was important to reassess the protocol.

Our committee met again on April 21, 2020, 11 days after initial protocol launch, to reassess the protocol. Quantitative data were not yet available on outcomes such as mortality. Input across specialties pointed toward anecdotal improvements in the outcomes of COVID-19 ICU patients. Based on our experience, a review of guidelines from other centers and societies, and the emerging literature in the short interval since the protocol was implemented,^{4,11,12} there was consensus that the anticoagulation protocol should be revised.

The revised protocol was released on April 28, 2020, and had several key enhancements relative to the initial version. First, in recognition that standard prophylaxis dosing may be inadequate, the revised protocol recommended “aggressive prophylaxis” (enoxaparin 30 mg SC every 12 hours) for patients without severe COVID.⁹ This dose has been used for patients un-

dergoing total knee or hip arthroplasty.¹³ Second, the protocol changed the recommended intensity of anticoagulation for patients with severe COVID manifestations on the medicine wards from treatment dose to intermediate-dose anticoagulation (enoxaparin 1 mg/kg SC every 24 hours). This dose of enoxaparin, while not common, has been evaluated as a prophylactic strategy in pancreatic cancer where there is a high thrombotic risk balanced against bleeding concerns.¹⁴ In addition, this dosing schedule required only one visit by nursing during the day, which minimized infection exposure. Lastly, the revised protocol recommended therapeutic anticoagulation for COVID-19 patients with a confirmed VTE or patients who had a very high clinical suspicion for VTE but were unable to undergo testing due to the infectious risk.

Contemporaneous society guidelines from this period were published. The ISTH released guidance from the Scientific and Standardization Committee on May 27, 2020, which recommended prophylactic dose anticoagulation with LMWH in hospitalized COVID-19 patients. The guideline further stated that intermediate-dose LMWH may be considered.¹⁵ Similarly, the Anticoagulation Forum released interim guidance on May 21, 2020, which also suggested prophylactic dose LMWH in hospitalized patients and intermediate-dose VTE prophylaxis in ICU patients with enoxaparin 40 mg SC twice daily, enoxaparin 0.5 mg/kg SC twice daily, heparin 7500 U SC 3 times daily, or a low-intensity heparin infusion.¹⁶ Although the American Society of Hematology did not publish guidelines during this period, the society's journal, *Blood*, did publish a perspective piece on June 4, 2020. This expert guidance similarly recommended standard-dose VTE prophylaxis for all hospitalized patients and escalated-dose VTE prophylaxis in ICU patients.¹⁷ These society recommendations were generally aligned with our revised institutional protocol in terms of the use of intermediate-dose anticoagulation. They also advocated against the use of biomarker-driven (ie, D-dimer) anticoagulation decision-making.¹⁵⁻¹⁷

We now plan to analyze our data, and assess any additional evidence to inform the next revision, in particular as we prepare for the potential for additional waves of COVID-19 cases. Each cycle in this process has needed to be dynamic, vigilant, and flexible to accommodate shifting evidence in the face of a devastating illness.

CONCLUSIONS

In response to emerging data and trends during the COVID-19 pandemic, hospitals and health systems have had to adapt at an unprecedented speed. The development of clinical protocols has traditionally been based on an abundance of high-quality evidence. This was clearly not possible during this pandemic, as the number of severely ill patients began to mount, necessitating the creation of policies and protocols based instead on imperfect evidence and expert consensus. As demonstrated in our experience, a rapid guidance

process featuring an interdisciplinary committee, which dynamically adapts to new evidence from unconventional sources, is essential to create therapeutic guidance during a pandemic such as COVID-19.

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