Coronavirus disease 2019 (COVID-19): Hypercoagulability

Authors: Adam Cuker, MD, MS, Flora Peyvandi, MD, PhD
Section Editor: Lawrence LK Leung, MD
Deputy Editor: Jennifer S Tirnauer, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Sep 2020. | **This topic last updated:** Oct 12, 2020.

INTRODUCTION

A novel coronavirus was identified in late 2019 that rapidly reached pandemic proportions. The World Health Organization has designated the disease caused by the virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) as coronavirus disease 2019 (COVID-19).

Individuals with COVID-19 may have a number of complex and varied coagulation abnormalities (in the direction of an underlying hypercoagulable state), raising questions about appropriate evaluations and interventions to prevent or treat thrombosis.

This topic reviews evaluation and management of coagulation abnormalities in individuals with COVID-19.

Separate topics discuss the following:

- General management – (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults".)
- Critical care – (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues".)
- Extracorporeal membrane oxygenation (ECMO) – (See "Coronavirus disease 2019 (COVID-19): Extracorporeal membrane oxygenation (ECMO)".)
- Pregnancy – (See "Coronavirus disease 2019 (COVID-19): Pregnancy issues".)
- Anesthesia – (See "Coronavirus disease 2019 (COVID-19): Anesthetic concerns, including airway management and infection control".)

PATHOGENESIS

The pathogenesis of hypercoagulability in COVID-19 is incompletely understood.

Virchow's triad — Hypercoagulability can be thought of in terms of Virchow's triad (see "Overview of the causes of venous thrombosis", section on 'Virchow's triad'). All three of the major contributions to clot formation apply to severe COVID-19 infection:

- **Endothelial injury** – There is evidence of direct invasion of endothelial cells by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, potentially leading to cell injury. Some experts have postulated that endothelial injury, microvascular inflammation, endothelial exocytosis, and/or endotheliitis play a central role in the pathogenesis of acute respiratory distress syndrome and organ failure in patients with severe COVID-19 [1-3]. (See 'VTE' below and 'Microvascular thrombosis' below and "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues", section on 'Clinical features in critically ill patients'.)

  Other observations have suggested a role for neutrophil extracellular traps (NETs), a form of decondensed chromatin extruded by dead or dying neutrophils, in the prothrombotic state in COVID-19 [4,5]. (See "Disseminated intravascular coagulation (DIC) in adults: Evaluation and management", section on 'Role of extracellular cell-free DNA and DNA-binding proteins'.)

  Other sources of endothelial injury include intravascular catheters and mediators of the acute systemic inflammatory response such as cytokines (eg, interleukin [IL]-6) and other acute phase reactants [6]. The contribution of complement-mediated endothelial injury has been suggested [7]. (See "The endothelium: A primer" and "Overview of complications of central venous catheters and their prevention" and "Acute phase reactants".)

- **Stasis** – Immobilization can cause stasis of blood flow in all hospitalized and critically ill patients, regardless of whether they have COVID-19.

- **Hypercoagulable state** – A number of changes in circulating prothrombotic factors have been reported or proposed in patients with severe COVID-19 [8-10]:

  - Elevated factor VIII
  - Elevated fibrinogen
  - Circulating prothrombotic microparticles

- Neutrophil extracellular traps (NETs)
- Hyperviscosity

Hyperviscosity was demonstrated in a series of 15 critically ill patients in the intensive care unit (ICU) [11]. All 15 had elevated plasma viscosity as assessed by capillary viscometry (range, 1.9 to 4.2 centipoise [cP]; normal range, 1.4 to 1.8 cP). Hyperviscosity is thought to promote a hypercoagulable state. It is often associated with monoclonal gammopathies, especially Waldenström macroglobulinemia, but it can also be caused by polyclonal increases in gamma globulins and/or large increases in other proteins such as fibrinogen. (See "Laboratory test reference ranges in adults", section on 'Viscosity, serum'.)

Very elevated levels of D-dimer have been observed that correlate with illness severity; D-dimer is a degradation product of cross-linked fibrin indicating augmented thrombin generation and fibrin dissolution by plasmin [12]. However, high D-dimer levels are common in acutely ill individuals with a number of infectious and inflammatory diseases. Likewise, antiphospholipid antibodies, which can prolong the activated partial thromboplastin time (aPTT), are common in viral infections, but they are often transient and do not always imply an increased risk of thrombosis. (See 'Coagulation abnormalities' below and 'Clinical features' below.)

A potential role for platelet activation in promoting thrombosis has also been discussed, although data are limited [13,14].

Coagulation abnormalities — The predominant coagulation abnormalities in patients with COVID-19 suggest a hypercoagulable state and are consistent with uncontrolled clinical observations of an increased risk of venous thromboembolism. (See 'VTE' below.)

This state has been termed thromboinflammation or COVID-19-associated coagulopathy (CAC) by some experts [15,16]. It appears to be distinct from disseminated intravascular coagulation (DIC), though DIC has been reported in severely affected patients.

Laboratory findings were characterized in a series of 24 selected patients with severe COVID-19 pneumonia (intubated) who were evaluated along with standard coagulation testing and other assays including von Willebrand factor (VWF) and thromboelastography (TEG) [8]:

- Coagulation testing
  - Prothrombin time (PT) and aPTT normal or slightly prolonged
  - Platelet counts normal or increased (mean, 348,000/microL)
  - Fibrinogen increased (mean, 680 mg/dL; range 234 to 1344)
  - D-dimer increased (mean, 4877 ng/mL; range, 1197 to 16,954)
- Other assays
  - Factor VIII activity increased (mean, 297 units/dL)
  - VWF antigen greatly increased (mean, 529; range 210 to 863), consistent with endothelial injury or perturbation
  - Minor changes in natural anticoagulants
    - Small decreases in antithrombin and free protein S
    - Small increase in protein C
- TEG findings
  - Reaction time (R) shortened, consistent with increased early thrombin burst, in 50 percent of patients
  - Clot formation time (K) shortened, consistent with increased fibrin generation, in 83 percent
  - Maximum amplitude (MA) increased, consistent with greater clot strength, in 83 percent
  - Clot lysis at 30 minutes (LY30) reduced, consistent with reduced fibrinolysis, in 100 percent

Testing in this study was performed on arterial blood because the patients had arterial catheters in place, but venous blood can be used. Heparinase was included since most patients were receiving low molecular weight (LMW) heparin.

Other studies have reported similar findings consistent with a hypercoagulable state, including very high D-dimer, VWF antigen and activity, and factor VIII activity [9,17]. One study that performed TEG on 44 ICU patients found a complete lack of clot lysis (LY30 of 0 percent) in 57 percent, referred to as "fibrinolysis shutdown" and associated with a high rate of kidney failure and thromboembolic events [18]. Another study suggested that patients with COVID-19 have higher platelet counts than patients with other coronavirus infections [19]. A series from Ireland that included 50 patients on the regular medical ward reported similar findings to those in ICU patients, including high D-dimer and fibrinogen and normal platelet counts and clotting times [20].

Early case series, including a series of 183 consecutive patients from Wuhan, China, suggested that thrombocytopenia and prolongation of the PT and aPTT were more marked [21-24]. It is not clear why these results differed somewhat from later findings of less severe PT and aPTT prolongation. One possible explanation is that these patients were sicker, perhaps because earlier in the pandemic the disease was not recognized as quickly, resulting in delays in patient presentation and/or treatment. Cases of immune thrombocytopenia (ITP) associated with COVID-19 have been reported [25-28].

Another explanation for an isolated prolonged aPTT is the presence of a lupus anticoagulant (LA) (see "Clinical use of coagulation tests", section on 'Causes of prolonged aPTT'). Two studies have found a high rate of LA in patients with prolonged aPTT (50 of 57 tested individuals [88 percent] and 31 of 34 tested individuals [91 percent]) [17,29]. Another study that retested 10 LA-positive individuals with COVID-19 after weeks found that 9 of the 10 had subsequently become negative [30]. The phenomenon of transient antiphospholipid antibody (aPL)-positivity is common in individuals with acute viral infections and does not constitute antiphospholipid syndrome (see "Diagnosis of antiphospholipid syndrome", section on 'Antiphospholipid antibody testing'). However, LA-positivity may correlate with thrombosis in individuals with COVID-19 [31]. The presence of an LA may lead to an artifactual prolongation of the aPTT but does not reflect an increased bleeding risk; patients with an LA should receive anticoagulation if indicated. (See 'Management' below.)

Some of the markers of deranged coagulation (eg, D-dimer) appear to correlate with illness severity. D-dimer is often increased, sometimes markedly, in individuals with overt DIC and those in the ICU.

Principles of TEG and interpretation of TEG tracings are illustrated in the figure (figure 1) and discussed in more detail separately. (See "Platelet function testing", section on 'Thromboelastography (TEG) and ROTEM' and "Coagulopathy in trauma patients", section on 'Thromboelastography'.)

Distinction from DIC — The hypercoagulable state associated with COVID-19 has been referred to by some as a disseminated intravascular coagulation (DIC)-like state, especially because many affected individuals are acutely ill and meet criteria for probable DIC in a scoring system published by the International Society on Thrombosis and Haemostasis (ISTH) in 2009 [32].

However, the major clinical finding in COVID-19 is thrombosis, whereas the major finding in acute decompensated DIC is bleeding. (See 'Clinical features' below.)

Likewise, COVID-19 has some similar laboratory findings to DIC, including a marked increase in D-dimer and in some cases, mild thrombocytopenia. However, other coagulation parameters in COVID-19 are distinct from DIC. In COVID-19, the typical findings include high fibrinogen and high factor VIII activity, suggesting that major consumption of coagulation factors is not occurring [8]. (See 'Coagulation abnormalities' above.)

In contrast, acute decompensated DIC is associated with low fibrinogen due to consumption of clotting factors. In one of the largest series that reported on thromboembolic events, none of the patients developed overt DIC [33].

Typically, bleeding predominates in acute decompensated DIC and thrombosis predominates in chronic compensated DIC, although there is significant overlap. Thus, the hypercoagulable state in patients with COVID-19 is more similar to compensated DIC than to acute DIC, consistent with the finding that the platelet count and aPTT are typically normal. (See "Disseminated intravascular coagulation (DIC) in adults: Evaluation and management", section on 'Pathogenesis'.)

This ISTH scoring system is based on laboratory findings and is only intended for use in patients with an underlying condition known to be associated with DIC [32]. COVID-19 would qualify based on being a severe infection. Points are given for thrombocytopenia (1 point for platelet count 50,000 to 100,000/microL; 2 points for <50,000/microL), prolonged PT (1 point for 3 to 6 seconds of prolongation; 2 points for more than 6 seconds), low fibrinogen (1 point for <100 mg/dL), and increased D-dimer (2 points for moderate increase; 3 points for "strong" increase). A score of 5 or more points suggests DIC is probable. Despite this, the diagnosis of DIC is made clinically; there is no gold standard and no single test or combination of tests that is pathognomonic. Compared with expert opinion, the ISTH scoring system is reported to have a sensitivity of 91 percent and a specificity of 97 percent [32]. (See 'Coagulation abnormalities' above.)

Regardless of whether the differences from DIC or the similarities are emphasized, many of the basic principles of DIC management apply, including the importance of treating the underlying condition, the importance of basing interventions on the clinical picture rather than on laboratory testing alone, and the need to provide anticoagulation for thrombosis and appropriate hemostatic therapies for bleeding. (See "Disseminated intravascular coagulation (DIC) in adults: Evaluation and management", section on 'Treatment'.)

CLINICAL FEATURES

One of the most striking features of COVID-19 is the wide spectrum of clinical manifestations and outcomes, from asymptomatic to various degrees of organ dysfunction to death. (See "Coronavirus disease 2019 (COVID-19): Clinical features".)

Likewise, the spectrum of thromboembolic manifestations is broad and appears to vary widely among different individuals and different clinical studies.

VTE — Venous thromboembolism (VTE), including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), is very common in acutely ill patients with COVID-19, seen in up to one-third of patients in the intensive care unit (ICU), even when prophylactic anticoagulation is used.

In a large study that involved over 3000 individuals admitted to the hospital, most of whom received prophylactic-dose anticoagulation, risk factors for VTE on multivariate analysis were older age, male sex, Hispanic ethnicity, coronary artery disease, prior myocardial infarction, and higher D-dimer (>500 ng/mL) at hospital presentation [34]. VTE was associated with an increased mortality rate (adjusted hazard ratio [HR], 1.37; 95% CI 1.02-1.86).

Several autopsy studies have emphasized the contributions of hypercoagulability and associated inflammation in patients who die from COVID-19:

- Post-mortem examination of 21 individuals with COVID-19 found prominent PE in four, with microthrombi in alveolar capillaries in 5 of 11 (45 percent) who had available histology [35]. Three had evidence of thrombotic microangiopathy with fibrin thrombi in glomerular capillaries. The average age was 76 years, and most had a high body mass index (BMI; mean, 31 kg/m^2; normal 18.5 to <25). Information on use of anticoagulation prior to death was available for 11, and all 11 were receiving some form of anticoagulation. Underlying cardiovascular disease, hypertension, and diabetes mellitus were common.

- Post-mortem examination of 12 consecutive individuals with COVID-19 (8 male; 10 hospitalized) revealed DVT in 7 of 12 (58 percent) [36]. All cases of DVT had bilateral leg involvement, and none were suspected before death. Of the 12 for whom lung histology was available, 5 (42 percent) had evidence of thrombosis. PE was the cause of death in four. In those who had D-dimer testing, some had extremely high values (two >20,000 ng/mL and one >100,000 ng/mL; normal value <500 ng/mL [<500 mcg/L]). Use of anticoagulation prior to death was only reported in 4 of the 12. The mean BMI was 28.7 kg/m^2; only three patients had a normal BMI, and they had cancer, ulcerative colitis, and/or chronic kidney disease.

- An autopsy study that compared pulmonary pathology from seven individuals who died of COVID-19 found a severe endothelial injury (endotheliitis), widespread thrombosis with microangiopathy and alveolar capillary microthrombi, and increased angiogenesis, all of which were significantly more prominent in the lungs of the patients who died of COVID-19 compared with the lungs of controls who died of influenza or other causes [37]. Endothelial injury is a well-established component of hypercoagulability. (See 'Virchow's triad' above.)

These studies have noted the preponderance of males with a high prevalence of obesity and other chronic medical comorbidities, especially cardiovascular disease, hypertension, and diabetes mellitus. Subsequent studies have demonstrated similar findings [38].

ICU — Case series of intensive care unit (ICU) patients have reported high rates of VTE (range, 20 to 43 percent), mostly pulmonary embolism (PE), and often despite prophylactic-dose anticoagulation:

- A series that included 829 ICU patients with severe COVID-19 reported VTE in 13.6 percent (PE in 6.2 percent and DVT in 9.4 percent), rates that were lower than reported in prior studies [34]. The reason for lower incidence of VTE is not obvious; it might include improved medical care based on incorporation of new evidence, increased use of anticoagulation, or reduced testing due to a high volume of ICU patients.

- A series of 184 sequential patients with severe COVID-19 in the ICU reported PE in 25 (14 percent), DVT in 1, and catheter-associated thrombosis in 2 [33]. The cumulative incidence of VTE (based on different durations of follow-up) was calculated at 27 percent. All were receiving at least standard dose thromboprophylaxis.

- A series of 150 ICU patients reported VTE in 64 (43 percent, mostly PE) and clotting of the extracorporeal circuit in 28 of 29 receiving continuous renal replacement therapy and 2 of 12 undergoing extracorporeal membrane oxygenation (ECMO) [17]. All patients were receiving thromboprophylaxis (mostly low molecular weight [LMW] heparin), 70 percent with prophylactic dose and 30 percent with therapeutic dose.

- Earlier series of ICU patients have reported VTE in 22 to 39 percent of individuals, often despite prophylactic anticoagulation [39-41]. These rates are higher than seen in matched cohorts from comparable populations (individuals in the ICU during the same time interval in the previous year, concurrent patients with influenza rather than COVID-19, and concurrent patients with non-COVID-19 acute respiratory distress syndrome [ARDS]), all of which were below 8 percent [17,39]. Some of the ICU patients have had additional comorbidities including cancer and kidney failure [33].

Rates of DVT are higher in studies that perform routine surveillance with bilateral leg ultrasounds. Two small studies that screened all patients with bilateral leg ultrasounds (34 and 26 patients) observed DVT in 65 to 69 percent, with one showing bilateral clots in 38 percent [42,43]. Some of the DVTs occurred despite the use of anticoagulation prior to admission or institution of prophylactic anticoagulation on admission to the ICU.

VTE risk is in the range where some experts would suggest more aggressive thromboprophylaxis dosing of anticoagulants or even empiric therapeutic-dose anticoagulation for VTE prevention. Some of these studies noted a higher than average body mass index in affected individuals, suggesting that obesity, along with other risk factors, may warrant consideration in decision-making regarding the intensity of anticoagulation. (See 'Possible/uncertain role of therapeutic-level anticoagulation for critically ill patients' below.)

Inpatients (non-ICU) — The rate of VTE in non-ICU inpatients is also increased, but to a lesser extent than ICU patients.

- A retrospective study that included 1240 hospitalized, non-ICU patients documented PE using computed tomography with pulmonary angiography (CTPA) in 103 (8.3 percent) [44]. On multivariable analysis, the risk factors for PE included male sex, high C-reactive protein, and longer delays between symptom onset and hospitalization; however, the magnitude of increased risk was relatively small (odds ratios, approximately 1.03). Anticoagulation was associated with a lower risk of PE.

- A study that included 2505 hospitalized, non-ICU patients reported VTE in 3.6 percent (PE in 2.2 percent and DVT in 2.0 percent) [34]. Patients were only evaluated if symptomatic.

- Earlier studies evaluating symptomatic patients reported slightly higher rates of VTE (approximately 3 to 6 percent) [40,45]. Some developed clots while receiving prophylactic anticoagulation. In one of the studies, half of the VTE events were documented within the first 24 hours after admission, suggesting that thromboprophylaxis might be ineffective because the VTE had already occurred.

- Higher rates of VTE are seen in studies that screen all patients for VTE regardless of symptoms. A study that systematically evaluated 71 non-ICU patients who were hospitalized with COVID-19 for more than 48 hours by performing bilateral lower extremity duplex ultrasounds at the time of discharge found a higher rate of DVT (21 percent) [46]. Only 2 of 15 patients with DVT were symptomatic; five had bilateral involvement. PE occurred in 10 percent, one of which was fatal. Another study involving 84 non-ICU inpatients who were receiving prophylactic-dose anticoagulation used compression ultrasonography of the leg veins to screen, and it documented DVT in 12 percent [47].

Outpatients — We are aware that thrombotic events have been observed in COVID-19 patients who were not admitted to the hospital, but data on the incidence are not available.

Arterial events — There are also reports of arterial thrombosis, including in the central nervous system (CNS). The largest study, which included 3334 individuals (829 ICU and 2505 non-ICU) reported stroke in 1.6 percent and myocardial infarction in 8.9 percent [34]. Risk factors for arterial thrombosis included older age, male sex, Hispanic ethnicity, history of coronary artery disease, and D-dimer >230 ng/mL on presentation. Arterial thrombotic events were associated with increased mortality (adjusted HR 1.99; 95% CI 1.65-2.40).

Other studies have provided additional information on selected types of arterial thrombosis:

- **Stroke** – A single health system identified five cases of acute ischemic stroke associated with COVID-19 over a two-week period, with symptoms suggesting large-vessel occlusion; all patients were under 50 years of age [48]. In other time periods before the pandemic, there were approximately 0.7 large vessel strokes per two-week interval in individuals under age 50.

  In one of the series of ICU patients discussed above, ischemic stroke was observed in 3 of 184 (cumulative incidence, 3.7 percent) [33]. In another one of the series discussed above, cerebral ischemia was seen in 3 of 150 [17]. In the series that included 314 non-ICU inpatients, six (2 percent) had ischemic strokes; an additional three in the ICU had an ischemic stroke [45].

- **Limb ischemia** – A report described 20 patients with COVID-19 who developed acute limb ischemia at a single institution over a three-month period [49]. This represented a significant increase in limb ischemia over the previous year (16 percent, versus 2 percent in early 2019). Most were male (18 of 20), and the average age was 75 years. Surgical revascularization procedures were performed in 17, of which 12 (71 percent) were successful, a lower-than-expected success rate. Individuals who received postoperative heparin did not require reintervention, although the benefits of postoperative heparin did not reach statistical significance.

  Another report described four patients with acute limb ischemia due to thrombosis, two of whom were young and did not have any comorbidities (a 53-year-old man who developed aorto-iliac thrombosis and a 37-year-old man who developed humeral artery thrombosis) [50]. Both were receiving prophylactic-dose LMW heparin at the time thrombosis developed and both had very high D-dimer (>9000 ng/mL).

Microvascular thrombosis — Autopsy studies in some individuals who have died from COVID-19 have demonstrated microvascular thrombosis in the lungs [7,16,35,37]. (See 'VTE' above.)

Other reports have described perfusion abnormalities in the lung that were explained by thromboembolic disease [51].

The mechanism is unclear and may involve hypercoagulability, direct endothelial injury, complement activation, or other processes.

In the absence of more definitive data regarding mechanisms or therapy, we would not pursue specialized testing for thrombotic microangiopathies (eg, ADAMTS13 activity, complement studies) or specialized therapies (eg, plasma exchange, anti-complement therapy) outside of a research study.

Bleeding — Bleeding is less common than clotting in patients with COVID-19, but it may occur, especially in the setting of anticoagulation.

As examples:

- In a subset of 25 ICU patients who were evaluated for abnormal neurologic findings, one had evidence of intracranial hemorrhage as well as ischemic lesions [17]. Three other patients in this series also had hemorrhagic complications, including two intracerebral bleeds associated

with head trauma and one with hemorrhagic complications of extracorporeal membrane oxygenation (ECMO). Three others in this series had evidence of intracerebral ischemia. (See 'Arterial events' above.)

- In a series of individuals with suspicion for heparin-induced thrombocytopenia (HIT), three of five who were treated with a parenteral direct thrombin inhibitor had a major bleeding event [52].

These observations emphasize the importance of limiting anticoagulation to appropriate indications and, in individuals with suspected stroke, documentation of whether it is ischemic versus hemorrhagic.

EVALUATION

The evaluation of patients with COVID-19 and coagulation abnormalities (suspected or documented) can be challenging due to the limited data on which clinical parameters or coagulation abnormalities should be acted upon and the concerns related to performing diagnostic imaging procedures on acutely ill and potentially contagious patients.

A general approach is as follows, although other decisions may be made by the treating clinicians based on their evaluation of the patient. This approach is consistent with guidance from the International Society on Thrombosis and Haemostasis (ISTH), the American Society of Hematology (ASH), and the American College of Cardiology (ACC) [15,53,54].

Routine testing (all patients)

- **Inpatients** – We assess the following in inpatients with COVID-19:

  - Complete blood count (CBC) including platelet count
  - Coagulation studies (prothrombin time [PT] and activated partial thromboplastin time [aPTT])
  - Fibrinogen
  - D-dimer

  Repeat testing is reasonable on a daily basis or less frequently, depending on the acuity of the patient's illness, the initial result, and the trend in values. Measurement of the D-dimer more than once per day is generally not indicated.

  As noted above, common laboratory findings include (see 'Coagulation abnormalities' above):

  - High D-dimer
  - High fibrinogen
  - Normal or mildly prolonged PT and aPTT
  - Mild thrombocytopenia or thrombocytosis, or normal platelet count

  We do not intervene for these abnormal coagulation studies in the absence of clinical indications. However, these findings may have prognostic value and may impact decision-making about the level of care and/or investigational therapies directed at treating the infection. As an example, increasing D-dimer is associated with poor prognosis, especially if levels are increased several-fold [55]. (See 'Investigational therapies' below.)

  Atypical findings such as a markedly prolonged aPTT (out of proportion to the PT), low fibrinogen, or severe thrombocytopenia suggest that another condition may be present and additional evaluation may be indicated. (See 'Role of additional testing' below.)

  We do not routinely test for thrombotic thrombocytopenic purpura (TTP), other thrombotic microangiopathies, or antiphospholipid antibodies (aPL). There are no therapeutic implications of transiently positive aPL in the absence of clinical findings. Transient aPL positivity is often seen in acute infections. (See "Diagnosis of antiphospholipid syndrome", section on 'Other conditions associated with aPL'.)

  We do not routinely perform imaging for screening purposes, as there is no evidence that indicates this practice improves outcomes, and it may unnecessarily expose health care workers to additional infectious risks. However, imaging is appropriate in individuals with symptoms, as discussed below. (See 'Role of additional testing' below.)

- **Outpatients** – For outpatients, routine coagulation testing is not required. Evaluation of abnormal symptoms or findings on examination is similar to inpatients. (See 'Role of additional testing' below.)

Role of additional testing

Diagnosis of DVT or PE — Evaluation for deep vein thrombosis (DVT) or pulmonary embolism (PE) may be challenging because symptoms of PE overlap with COVID-19, and imaging studies may not be feasible in all cases. The threshold for evaluation or diagnosis of DVT or PE should be low given the high frequency of these events and the presence of additional venous thromboembolism (VTE) risk factors in many individuals. (See 'VTE' above.)

- **DVT** – Individuals with suspected DVT should have compression ultrasonography when feasible according to standard indications. (See "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity".)

- **PE** – We agree with guidance from the American Society of Hematology (ASH) regarding diagnosis of PE, which includes the following [56]:

  - A normal D-dimer (unusual in critically ill individuals with COVID-19) is sufficient to exclude the diagnosis of PE if the pretest probability for PE is low or moderate but is less helpful in those with a high pretest probability. An increase in D-dimer is not specific for VTE and is not sufficient to make the diagnosis. (See "Overview of acute pulmonary embolism in adults", section on 'Clinical presentation, evaluation, and diagnosis'.)

  - In patients with suspected PE due to unexplained hypotension, tachycardia, worsening respiratory status, or other risk factors for thrombosis, computed tomography with pulmonary angiography (CTPA) is the preferred test to confirm or exclude the diagnosis. A ventilation/perfusion (V/Q) scan is an alternative if CTPA cannot be performed or is inconclusive, although V/Q scan may be unhelpful in individuals with significant pulmonary involvement from COVID-19. Consultation with the pulmonary embolism response team (PERT) in decision-making is advised if possible. (See "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism".)

    The role of full-dose anticoagulation if CTPA or V/Q scan is not feasible is discussed below. (See 'Documented or presumed VTE' below.)

Infection control procedures should be followed in patients undergoing imaging studies. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, and prevention", section on 'Infection control in the health care setting'.)

Evaluation of atypical laboratory findings — As noted above, typical laboratory findings of COVID-19 are monitored for their prognostic value. (See 'Routine testing (all patients)' above.)

Laboratory findings that are atypical for COVID-19, such as severe thrombocytopenia (eg, platelet count <50,000/microL), a prolonged aPTT out of proportion to the PT, or a markedly reduced fibrinogen, should be evaluated as done for individuals without COVID-19, as discussed in separate topic reviews:

- Thrombocytopenia – (See "Approach to the adult with unexplained thrombocytopenia".)

- Abnormal coagulation tests – (See "Clinical use of coagulation tests", section on 'Evaluation of abnormal results'.)

Evaluation of bleeding — The evaluation is discussed separately. (See "Approach to the adult with a suspected bleeding disorder" and "Clinical use of coagulation tests", section on 'Patient on anticoagulant'.)

Management of bleeding depends on the underlying cause. (See 'Treatment of bleeding' below.)

MANAGEMENT

Overview of management considerations — Management can be challenging. Hypercoagulability appears to adversely impact prognosis, but there are no high-quality studies to support interventions that go beyond standard indications, and antithrombotic therapies carry risks of increased bleeding [57]. In the absence of high-quality data to guide management, institutions may vary in how aggressively they approach prevention and treatment of thromboembolic complications. Enrollment in clinical trials is encouraged to help determine the best approach [58-60].

Regardless of clinical trial enrollment, adherence to institutional protocols and input from individuals with expertise in hemostasis and thrombosis is advised to balance the risks of thrombosis and bleeding and guide decisions about antithrombotic therapy; bleeding caused by administration of excessive antithrombotic therapy may require prothrombotic treatments that further increase thrombotic risk.

Interim guidance and frequently asked questions have been published by the following organizations:

- International Society on Thrombosis and Haemostasis (ISTH), with guidance on recognition and management [53,61,62]
- Anticoagulation forum [63]
- American Society of Hematology (ASH) [64]
- American College of Cardiology (ACC) [54]

Acknowledging the lack of evidence from randomized trials, we agree with this guidance. Our approach is summarized in the table (table 1) and discussed in the following sections. As noted above, the presence of a prolonged aPTT due to the lupus anticoagulant (LA) phenomenon does not reflect decreased risk of thromboembolic complications (in some individuals, it reflects increased risk) and is not a reason to avoid anticoagulation. (See 'Coagulation abnormalities' above.)

Regardless of the approach used, clinicians should be familiar with potential drug interactions between oral anticoagulants and investigational therapies for COVID-19 [65,66].

Management of coagulation abnormalities in patients with COVID-19 receiving extracorporeal membrane oxygenation (ECMO) is discussed separately. (See "Coronavirus disease 2019 (COVID-19): Extracorporeal membrane oxygenation (ECMO)".)

Individuals with a history of heparin-induced thrombocytopenia (HIT) or active HIT should not receive low molecular weight [LMW] heparin or unfractionated heparin. Alternatives are discussed separately. (See "Management of heparin-induced thrombocytopenia".)

Inpatient VTE prophylaxis

- **Indications** – Venous thromboembolism (VTE) prophylaxis is appropriate in all hospitalized medical, surgical, and obstetric patients with COVID-19 (algorithm 1), unless there is a contraindication to anticoagulation (eg, active bleeding or serious bleeding in the prior 24 to 48 hours) or to the use of heparin (eg, history HIT, in which case an alternative agent such as fondaparinux may be used).
  - **ICU** – All patients with COVID-19 in the intensive care unit (ICU) require thromboprophylaxis. As discussed below, some would empirically use intermediate-dose or therapeutic-dose anticoagulation in severely ill individuals in the absence of documented VTE. (See 'Possible/uncertain role of therapeutic-level anticoagulation for critically ill patients' below.)
  - **Medical (non-ICU)** – All hospitalized medical patients should be treated with prophylactic-dose low molecular weight (LMW) heparin (or unfractionated heparin if LMW heparin is unavailable) for thromboprophylaxis.
  - **Surgical** – Perioperative VTE prophylaxis is especially important for patients with COVID-19 who are hospitalized for a surgical procedure. Details of the timing and choice of agent are discussed separately. (See "Prevention of venous thromboembolism in adult orthopedic surgical patients" and "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)
  - **Obstetric** – We would also use VTE prophylaxis in obstetric patients with COVID-19 who are in the hospital prior to or following delivery. LMW heparin is appropriate if delivery is not expected within 24 hours and after delivery; unfractionated heparin is used if faster discontinuation is needed (eg, if delivery, neuraxial anesthesia, or an invasive procedure is anticipated within approximately 12 to 24 hours or at 36 to 37 weeks of gestation). (See "Coronavirus disease 2019 (COVID-19): Pregnancy issues", section on 'Medical and obstetric care of hospitalized patients' and "Use of anticoagulants during pregnancy and postpartum".)
- **Dosing** – Dosing (subcutaneous) is generally as follows; however, many experts are recommending higher doses for critically ill individuals, especially those in the ICU (see 'Possible/uncertain role of therapeutic-level anticoagulation for critically ill patients' below):
  - Enoxaparin – For patients with creatinine clearance (CrCl) >30 mL/min, 40 mg once daily; for CrCl 15 to 30 mL/min, 30 mg once daily.

    European dosing (by units/kg rather than mg/kg) is as follows [67]:

    - Low intensity of care – 100 units/kg once daily
    - Intermediate intensity of care – 70 units/kg twice daily
    - High intensity of care – 100 units/kg twice daily
  - Dalteparin – 5000 units once daily.
  - Nadroparin – For patients ≤70 kg, 3800 or 4000 anti-factor Xa units once daily; for patients >70 kg, 5700 units once daily. In some cases, doses up to 50 anti-factor Xa units/kg every 12 hours are used.
  - Tinzaparin – 4500 anti-factor Xa units once daily.

  For patients with CrCl <15 mL/min or renal replacement therapy, we use unfractionated heparin, which is much less dependent on elimination by the kidney. The tables have more information about adjustments for kidney impairment (table 2), obesity (table 3), and pregnancy (table 4).
- **Supporting evidence** – LMW heparin is known to reduce the risk of VTE and may have antiinflammatory properties.

  In a retrospective series of 2773 individuals hospitalized with COVID-19, in whom 786 (28 percent) received systemic anticoagulation, anticoagulation was associated with improved in-hospital survival in intubated patients (71 percent, versus 37 percent for those who were not anticoagulated) [68]. Intubated patients represented approximately 14 percent of the cohort; in the cohort as a whole, anticoagulation was not associated with better in-hospital survival (78 versus 77 percent). Bleeding events occurred in 3 percent of the anticoagulated patients and 2 percent of those who were not anticoagulated (not a statistically significant difference).

  In a retrospective study of 449 individuals with severe COVID-19, enoxaparin (40 to 60 mg once daily) appeared to be associated with improved survival when compared with no pharmacologic prophylaxis, especially in those with a high D-dimer [24].

- The survival difference was only seen in a subset of individuals with a high sepsis-induced coagulopathy score (28-day mortality, 40 percent with heparin versus 64 percent without) or a high D-dimer, not in the cohort as a whole.
- The magnitude of benefit was greater in those with higher D-dimer values. The reduced mortality became statistically significant at six times the upper limit of normal (33 versus 52 percent).

One small series (16 patients) used higher prophylactic doses of nadroparin along with clopidogrel and did not report any VTE events; the small size of the study and lack of a control group limits interpretation [9].

As discussed above, a high percentage (25 to 43 percent) of individuals with COVID-19 in the ICU had VTE despite prophylactic-dose anticoagulation, prompting many experts to suggest higher doses. (See 'VTE' above and 'Indications for full-dose anticoagulation' below.)

One study monitored antithrombin (AT) levels and provided AT concentrate for those with decreased levels [9]. However, we generally would not measure AT levels or consider AT concentrate unless an individual was known to have inherited AT deficiency or exhibited heparin resistance in association with a very low AT level. (See "Antithrombin deficiency", section on 'Heparin resistance'.)

Indications for full-dose anticoagulation — Therapeutic-dose (full-dose) anticoagulation (eg, enoxaparin 1 mg/kg every 12 hours) is appropriate in settings discussed in the following sections, including documented or strongly suspected venous thromboembolism (VTE) and clotting of vascular access devices, unless there is a contraindication to anticoagulation (eg, active bleeding or serious bleeding in the prior 24 to 48 hours) or to the use of heparin (eg, history of heparin-induced thrombocytopenia [HIT], in which case an alternative agent such as fondaparinux may be used) (algorithm 1):

Heparin resistance (requirement for very high doses of heparin to achieve a therapeutic aPTT or anti-factor Xa activity) might be a concern in acutely ill patients with COVID-19. A series of 15 individuals in the ICU anticoagulated for VTE noted a very high requirement for unfractionated heparin (8 of 10 required more than 35,000 units per day) or low molecular weight heparin (5 of 5 receiving dalteparin had anti-factor Xa peak below expected [<0.6 international units/mL for twice daily dosing or <1 international units/mL for once daily dosing]) [69]. The reason for heparin resistance was unclear; the authors stated it did not correlate with increased fibrinogen or factor VIII or with decreased antithrombin. Heparin is negatively charged and can interact with a variety of positively charged plasma proteins, some of which behave like acute phase reactants and will compete for heparin binding, accounting for heparin resistance. However, these results have not been confirmed.

For those receiving unfractionated heparin who have either a prolonged aPTT at baseline or heparin resistance, the aPTT may be unreliable, and anti-factor Xa activity should be monitored to guide dosing [63]. Target values for the aPTT and anti-factor Xa activity are listed in the table (table 5).

Documented or presumed VTE — Therapeutic-dose (full-dose) anticoagulation is appropriate for documented VTE, similar to individuals without COVID-19. (See 'Diagnosis of DVT or PE' above.)

Full-dose anticoagulation is also reasonable in some cases of suspected VTE in which standard confirmatory testing is not available or feasible, including the following:

- In patients for whom computed tomography with pulmonary angiography (CTPA) or ventilation/perfusion (V/Q) scan is not feasible, the following may be sufficient to initiate treatment:
  - Confirmation of deep vein thrombosis (DVT) using bilateral compression ultrasonography of the legs.
  - Transthoracic echocardiography or point-of-care ultrasound that demonstrates clot in transit in the main pulmonary artery.
- In patients for whom no confirmatory testing is possible, it may be reasonable to treat empirically with full-dose anticoagulation based on one or more of the following:
  - Sudden deterioration in respiratory status in an intubated patient consistent with pulmonary embolism (PE), especially when chest radiography and/or inflammatory markers are stable or improving and the change cannot be attributed to a cardiac cause.
  - Otherwise unexplained respiratory failure (eg, not due to fluid overload or acute respiratory distress syndrome [ARDS]), especially if the fibrinogen and/or D-dimer is very high.
  - Physical findings consistent with thrombosis (superficial thrombophlebitis or retiform purpura not explained by other conditions).

Clotting of intravascular access devices — Full-dose anticoagulation is appropriate for individuals with recurrent clotting of intravascular access devices (arterial lines, central venous catheters) despite prophylactic-intensity anticoagulation.

Full-dose anticoagulation is also appropriate in those with clotting in extracorporeal circuits (continuous renal replacement therapy, extracorporeal membrane oxygenation [ECMO]). Details are discussed separately. (See "Coronavirus disease 2019 (COVID-19): Extracorporeal membrane oxygenation (ECMO)".)

Possible/uncertain role of therapeutic-level anticoagulation for critically ill patients — The question of treatment-dose anticoagulation for thromboprophylaxis has also been raised in critically ill individuals and those in the ICU who have not had confirmed or suspected acute VTE but are at high risk, as described above. (See 'VTE' above.)

Many centers are recommending intermediate-dose or even therapeutic-intensity anticoagulation in these individuals. (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues", section on 'Venous thromboembolism prevention'.)

Data comparing different levels of anticoagulation (prophylactic, intermediate, or therapeutic dosing) in severely ill or critically ill patients are extremely limited. A small randomized trial (HESACOVID) randomly assigned 20 individuals with severe COVID-19 to receive therapeutic-dose anticoagulation (enoxaparin, 1 mg/kg twice daily) or prophylactic-dose anticoagulation (enoxaparin, 40 mg once daily or unfractionated heparin, 5000 units three times daily); adjustments were made for age, weight, and kidney function as appropriate [70]. Half the patients in the prophylactic group received unfractionated heparin and half enoxaparin. Compared with prophylactic dosing, therapeutic dosing led to fewer days on the ventilator and significant reductions in D-dimer levels. However, confidence in the results is hampered by the open-label design and small size. Larger clinical trials are in progress; enrollment in such trials is encouraged.

As stated by the American Society of Hematology (ASH) and the Global COVID-19 Thrombosis Collaborative Group, empiric full-dose anticoagulation for individuals who do not have VTE remains controversial, since data demonstrating improved outcomes are lacking, and some of the risk factors for VTE are also risk factors for increased risk of bleeding [56,65]. Thus, if VTE is suspected, confirmatory testing should be obtained or other indications for full-dose anticoagulation should be sought if possible, especially in individuals who are not in the ICU. This testing and other findings that support therapeutic-dose anticoagulation are discussed above. (See 'Diagnosis of DVT or PE' above.)

Indications for tPA — Tissue plasminogen activator (tPA) is appropriate for usual indications, unless there is a contraindication:

- Limb-threatening DVT – (See "Catheter-directed thrombolytic therapy in deep venous thrombosis of the lower extremity: Patient selection and administration".)
- Massive PE – (See "Approach to thrombolytic (fibrinolytic) therapy in acute pulmonary embolism: Patient selection and administration".)
- Acute stroke – (See "Approach to reperfusion therapy for acute ischemic stroke".)
- Acute myocardial infarction – (See "Acute ST-elevation myocardial infarction: The use of fibrinolytic therapy".)

Consultation with the pulmonary embolism response team (PERT) or stroke team in decision-making is advised if possible.

In contrast, we are not using tPA in individuals with nonspecific findings such as hypoxia or laboratory evidence of hypercoagulability.

Small case series (three to five patients) have described administration of tPA to individuals with ARDS associated with COVID-19 and have reported improvement in some cases [71-73].

Outpatient thromboprophylaxis

Patients discharged from the hospital — Individuals with documented VTE require a minimum of three months of anticoagulation, as discussed separately. (See "Overview of the treatment of lower extremity deep vein thrombosis (DVT)", section on 'Duration of therapy' and "Treatment, prognosis, and follow-up of acute pulmonary embolism in adults".)

Some individuals who have not had a VTE may also warrant extended thromboprophylaxis following discharge from the hospital [65]:

- Based on the low incidence of VTE despite infrequent use of post-discharge prophylactic anticoagulation in available studies such as those mentioned below, we do not use routine post-discharge thromboprophylaxis.
- We consider post-discharge thromboprophylaxis in patients with major prothrombotic risk factors such as a history of VTE or recent major surgery or trauma, as long as they are not at high bleeding risk. Options for post-discharge prophylaxis include those used in clinical trials, such as rivaroxaban 10 mg daily for 31 to 39 days [74].

The risk of post-discharge VTE appears to be similar to that of individuals hospitalized for acute medical illnesses other than COVID-19.

- In one study, which followed 1877 individuals discharged from the hospital following admission for COVID-19 who did not use post-discharge thromboprophylaxis, VTE was diagnosed in only nine (0.48 percent [4.8 per 1000]) [75]. This was similar to the likelihood of VTE in a pre-COVID-19 population (56 events in 18,159 individuals [3.1 per 1000]). In the patients with COVID-19, the median interval between discharge and VTE diagnosis was eight days (range, 3 to 33 days).
- Another study followed a cohort of 163 individuals discharged from the hospital after a COVID-19 admission and found four thrombotic events (cumulative incidence of VTE within 30 days of discharge, 0.6 percent; cumulative incidence of any thrombosis, 2.5 percent); post-discharge thromboprophylaxis was used in only 8 percent of patients [76]. This study also documented two major bleeding events (cumulative risk of major bleeding, 0.7 percent).

This subject is discussed in more detail separately. (See "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults", section on 'Duration of prophylaxis'.)

Patients not admitted to the hospital — Outpatient thromboprophylaxis may also be appropriate for selected individuals with COVID-19 who are not admitted to the hospital, especially those with other thrombotic risk factors such as prior VTE or recent surgery, trauma, or immobilization, noting that this practice is based on clinical judgment. There are no trials that address thromboprophylaxis in outpatients with COVID-19.

If thromboprophylaxis is used in an outpatient, we would use a regimen such as rivaroxaban 10 mg daily for 31 to 39 days [74].

Treatment of bleeding — Bleeding does not appear to be a major manifestation of COVID-19. However, patients may have bleeding for other reasons, including trauma and/or treatment with anticoagulation. (See 'Bleeding' above.)

The approach to bleeding is similar to individuals without COVID-19 and may involve anticoagulant reversal and/or discontinuation, transfusions for thrombocytopenia or hypofibrinogenemia, or specific therapies such as factor replacement.

- Anticoagulant-associated bleeding – (See "Management of warfarin-associated bleeding or supratherapeutic INR" and "Management of bleeding in patients receiving direct oral anticoagulants" and "Reversal of anticoagulation in intracranial hemorrhage".)
- Trauma coagulopathy – (See "Coagulopathy in trauma patients".)
- An underlying bleeding disorder such as immune thrombocytopenia (ITP), hemophilia, or von Willebrand disease (VWD) – (See "Immune thrombocytopenia (ITP) in adults: Initial treatment and prognosis" and "Treatment of bleeding and perioperative management in hemophilia A and B" and "von Willebrand disease (VWD): Treatment of major bleeding and major surgery".)

Antifibrinolytic agents (tranexamic acid, epsilon aminocaproic acid) are generally not used in patients with disseminated intravascular coagulation (DIC), due to the concern that they may tip the balance towards thrombosis. Thus, they should be avoided in patients in whom the COVID-19-associated hypercoagulable state is the predominant finding. (See 'Distinction from DIC' above and "Disseminated intravascular coagulation (DIC) in adults: Evaluation and management", section on 'Prevention/treatment of bleeding'.)

Fibrinogen is often increased in COVID-19, and supplementation with fibrinogen is not required unless there is bleeding that is attributable to hypofibrinogenemia or dysfibrinogenemia (fibrinogen activity level <150 to 200 mg/dL). (See 'Coagulation abnormalities' above and "Disorders of fibrinogen", section on 'Treatment/prevention of bleeding'.)

Role of antiplatelet agents — The role of antiplatelet agents is under study [77,78]. We are not administering antiplatelet therapy outside of standard indications. It is reasonable to continue antiplatelet therapy if the individual is already receiving it for another indication and to use antiplatelet therapy for standard indications.

Investigational therapies — A number of therapies for COVID-19 are under investigation, some of which may impact thrombotic risk. However, effects of these treatments on hemostasis in this patient population have not been well studied. (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults", section on 'COVID-19-specific therapy'.)

Participation in clinical trials is encouraged in order to improve understanding of the most effective and safest means of preventing and treating thrombotic complications of COVID-19. Investigational therapies may be appropriate in life-threatening situations or as part of a clinical trial, and markedly increased D-dimer may be used as one criterion for identifying individuals with a worse prognosis.

Close monitoring for clinical signs of thrombosis or bleeding is advised in all individuals with COVID-19, with input from an individual with expertise in hemostasis and thrombosis in those with severe or unusual presentations.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Coronavirus disease 2019 (COVID-19) – International public health and government guidelines" and "Society guideline links: Coronavirus disease 2019 (COVID-19) – Guidelines for specialty care".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics

patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Coronavirus disease 2019 (COVID-19) overview (The Basics)")
- Society guidelines for patients (see "Society guideline links: Coronavirus disease 2019 (COVID-19) – Resources for patients")

SUMMARY AND RECOMMENDATIONS

- **Hypercoagulable state** – Coronavirus disease 2019 (COVID-19) is associated with a hypercoagulable state associated with acute inflammatory changes and laboratory findings that are distinct from acute disseminated intravascular coagulation (DIC), save for those with very severe disease. Fibrinogen and D-dimer are increased, with typically only modest prolongation of the prothrombin time (PT) and activated partial thromboplastin time (aPTT) and mild thrombocytosis or thrombocytopenia. The presence of a lupus anticoagulant (LA) is common in individuals with a prolonged aPTT. The pathogenesis of these abnormalities is incompletely understood, and there may be many contributing factors related to the acute inflammatory response to the disease. (See 'Pathogenesis' above.)

- **Thrombosis risk** – The risk for venous thromboembolism (VTE) is markedly increased, especially in patients in the intensive care unit (ICU), with case series reporting prevalences of 25 to 43 percent in ICU patients, often despite prophylactic-dose anticoagulation. Pulmonary microvascular thrombosis is also increased. The risk for arterial thrombotic events such as stroke, myocardial infarction, and limb ischemia also appears to be increased. (See 'Clinical features' above.)

- **Laboratory testing** – All patients admitted to the hospital for COVID-19 should have a baseline complete blood count (CBC) with platelet count, PT, aPTT, fibrinogen, and D-dimer. Repeat testing is done according to the patient's clinical status. Outpatients do not require coagulation testing. The main purpose of this testing is to obtain prognostic information that may be used to inform level of care. (See 'Routine testing (all patients)' above.)

- **Imaging** – Imaging studies are appropriate for suspected VTE if feasible. If standard diagnostic studies are not feasible, other options for determining the need for therapeutic-dose anticoagulation are available, as discussed above. Laboratory abnormalities that are not typical of COVID-19 should be further evaluated, as described above. (See 'Role of additional testing' above.)

- **Management** – Management is challenging due to the acuity of the illness and a paucity of high-quality evidence regarding efficacy and safety of different approaches to prevent or treat thromboembolic complications of the disease. Our general approach, which is summarized in the table (table 1) and depicted in the algorithm (algorithm 1), includes:

  - **Thromboprophylaxis** – All inpatients should receive thromboprophylaxis unless contraindicated. Low molecular weight (LMW) heparin is preferred, but unfractionated heparin can be used if LMW heparin is unavailable or if kidney function is severely impaired. Some institutional protocols include more aggressive anticoagulation with intermediate-dose or even therapeutic-dose anticoagulation for thromboprophylaxis. (See 'Inpatient VTE prophylaxis' above and 'Possible/uncertain role of therapeutic-level anticoagulation for critically ill patients' above.)

    Individuals who have not had a VTE are not routinely given thromboprophylaxis after discharge from the hospital. A period of thromboprophylaxis following discharge may be appropriate in selected individuals. (See 'Outpatient thromboprophylaxis' above.)

  - **VTE treatment** – Therapeutic-dose (full-dose) anticoagulation is appropriate to treat deep vein thrombosis (DVT) or pulmonary embolism (PE), unless contraindicated. This is continued for at least three months. (See 'Indications for full-dose anticoagulation' above.)

  - **Bleeding** – Bleeding is less common than thrombosis but can occur. If it occurs, treatment is similar to non-COVID-19 patients and may include transfusions, anticoagulant reversal or discontinuation, or specific products for underlying bleeding disorders. (See 'Treatment of bleeding' above.)

  - **Areas of uncertainty** – Participation in clinical trials is encouraged in order to improve understanding of the most effective and safest means of preventing and treating thrombotic complications of COVID-19. Disease-specific therapies under investigation may impact thrombotic risk, but the effects of these treatments on hemostasis in this patient population have not been well documented. (See 'Investigational therapies' above.)

REFERENCES

1. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol 2020; 20:389.
2. Lowenstein CJ, Solomon SD. Severe COVID-19 is a Microvascular Disease. Circulation 2020.
3. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020; 41:3038.
4. Middleton EA, He XY, Denorme F, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. Blood 2020; 136:1169.
5. Hidalgo A. A NET-thrombosis axis in COVID-19. Blood 2020; 136:1118.
6. Begbie M, Notley C, Tinlin S, et al. The Factor VIII acute phase response requires the participation of NFkappaB and C/EBP. Thromb Haemost 2000; 84:216.
7. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res 2020; 220:1.
8. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020; 18:1738.
9. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost 2020; 18:1747.
10. Maier CL, Truong AD, Auld SC, et al. COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? Lancet 2020; 395:1758.
11. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31209-5/fulltext (Accessed on May 27, 2020).
12. Medcalf RL, Keragala CB, Myles PS. Fibrinolysis and COVID-19: A plasmin paradox. J Thromb Haemost 2020.
13. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood 2020; 136:1330.
14. Allegra A, Innao V, Allegra AG, Musolino C. Coagulopathy and thromboembolic events in patients with SARS-CoV-2 infection: pathogenesis and management strategies. Ann Hematol 2020; 99:1953.
15. https://www.hematology.org/covid-19/covid-19-and-coagulopathy (Accessed on April 20, 2020).
16. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost 2020; 18:1559.
17. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020; 46:1089.
18. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis Shutdown Correlation with Thromboembolic Events in Severe COVID-19 Infection. J Am Coll Surg 2020; 231:193.
19. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J Thromb Thrombolysis 2020.
20. Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID19 coagulopathy in Caucasian patients. Br J Haematol 2020; 189:1044.
21. 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.
22. Amgalan A, Othman M. Exploring possible mechanisms for COVID-19 induced thrombocytopenia: Unanswered questions. J Thromb Haemost 2020; 18:1514.
23. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost 2020; 18:1020.
24. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18:1094.

25. Mahévas M, Moulis G, Andres E, et al. Clinical characteristics, management and outcome of COVID-19-associated immune thrombocytopenia: a French multicentre series. Br J Haematol 2020.

26. Lévesque V, Millaire É, Corsilli D, et al. Severe immune thrombocytopenic purpura in critical COVID-19. Int J Hematol 2020.

27. Murt A, Eskazan AE, Yılmaz U, et al. COVID-19 presenting with immune thrombocytopenia: A case report and review of the literature. J Med Virol 2020.

28. Bomhof G, Mutsaers PGNJ, Leebeek FWG, et al. COVID-19-associated immune thrombocytopenia. Br J Haematol 2020; 190:e61.

29. Bowles L, Platton S, Yartey N, et al. Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19. N Engl J Med 2020; 383:288.

30. Devreese KMJ, Linskens EA, Benoit D, Peperstraete H. Antiphospholipid antibodies in patients with COVID-19: A relevant observation? J Thromb Haemost 2020.

31. Reyes Gil M, Barouqa M, Szymanski J, et al. Assessment of Lupus Anticoagulant Positivity in Patients With Coronavirus Disease 2019 (COVID-19). JAMA Netw Open 2020; 3:e2017539.

32. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol 2009; 145:24.

33. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191:145.

34. Bilaloglu S, Aphinyanaphongs Y, Jones S, et al. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA 2020; 324:799.

35. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 2020.

36. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med 2020; 173:268.

37. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med 2020; 383:120.

38. Lax SF, Skok K, Zechner P, et al. Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome : Results From a Prospective, Single-Center, Clinicopathologic Case Series. Ann Intern Med 2020; 173:350.

39. Poissy J, Goutay J, Caplan M, et al. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. Circulation 2020; 142:184.

40. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020; 18:1995.

41. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020; 18:1421.

42. Nahum J, Morichau-Beauchant T, Daviaud F, et al. Venous Thrombosis Among Critically Ill Patients With Coronavirus Disease 2019 (COVID-19). JAMA Netw Open 2020; 3:e2010478.

43. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020; 18:1743.

44. Fauvel C, Weizman O, Trimaille A, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. Eur Heart J 2020; 41:3058.

45. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020; 191:9.

46. Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. J Thromb Thrombolysis 2020; 50:211.

47. Santoliquido A, Porfidia A, Nesci A, et al. Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis. J Thromb Haemost 2020.

48. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med 2020; 382:e60.

49. Bellosta R, Luzzani L, Natalini G, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg 2020.

50. Perini P, Nabulsi B, Massoni CB, et al. Acute limb ischaemia in two young, non-atherosclerotic patients with COVID-19. Lancet 2020; 395:1546.

51. Patel BV, Arachchillage DJ, Ridge CA, et al. Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations. Am J Respir Crit Care Med 2020; 202:690.

52. Patell R, Khan AM, Bogue T, et al. Heparin induced thrombocytopenia antibodies in Covid-19. Am J Hematol 2020.

53. Akima S, McLintock C, Hunt BJ. RE: ISTH interim guidance to recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020; 18:2057.

54. https://www.acc.org/latest-in-cardiology/articles/2020/04/17/14/42/thrombosis-and-coronavirus-disease-2019-covid-19-faqs-for-current-practice.

55. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020; 18:1324.

56. https://www.hematology.org/covid-19/covid-19-and-pulmonary-embolism (Accessed on April 24, 2020).

57. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020; 135:2033.

58. Ciavarella A, Peyvandi F, Martinelli I. Where do we stand with antithrombotic prophylaxis in patients with COVID-19? Thromb Res 2020; 191:29.

59. Maldonado E, Tao D, Mackey K. Antithrombotic Therapies in COVID-19 Disease: a Systematic Review. J Gen Intern Med 2020; 35:2698.

60. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. J Thromb Haemost 2020.

61. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020; 18:1023.

62. Spyropoulos AC, Levy JH, Ageno W, et al. 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.

63. Barnes GD, Burnett A, Allen 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.

64. https://www.hematology.org/covid-19/covid-19-and-coagulopathy.

65. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020; 75:2950.

66. Testa S, Prandoni P, Paoletti O, et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: The Cremona experience. J Thromb Haemost 2020; 18:1320.

67. Peyvandi F, Artoni A, Novembrino C, et al. Hemostatic alterations in COVID-19. Haematologica 2020.

68. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. J Am Coll Cardiol 2020; 76:122.

69. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. J Thromb Thrombolysis 2020; 50:287.

70. Lemos ACB, do Espírito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thromb Res 2020; 196:359.

71. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. J Thromb Haemost 2020; 18:1752.

72. Barrett CD, Oren-Grinberg A, Chao E, et al. Rescue therapy for severe COVID-19-associated acute respiratory distress syndrome with tissue plasminogen activator: A case series. J Trauma Acute Care Surg 2020; 89:453.

73. Christie DB 3rd, Nemec HM, Scott AM, et al. Early outcomes with utilization of tissue plasminogen activator in COVID-19-associated respiratory distress: A series of five cases. J Trauma Acute Care Surg 2020; 89:448.

74. https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation (Accessed on April 21, 2020).

75. Roberts LN, Whyte MB, Georgiou L, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. Blood 2020; 136:1347.

76. Patell R, Bogue T, Koshy A, et al. Postdischarge thrombosis and hemorrhage in patients with COVID-19. Blood 2020; 136:1342.

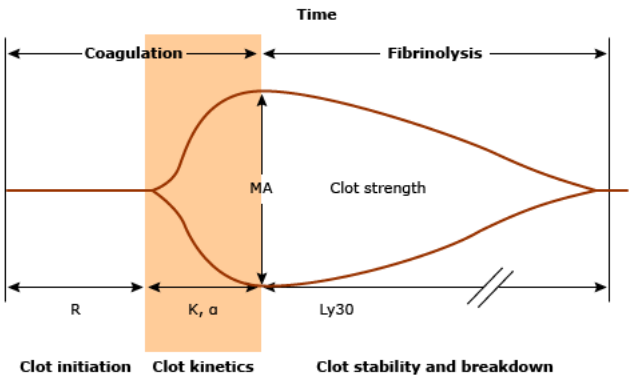
77. DiNicolantonio JJ, Barroso-Aranda J. Harnessing adenosine A2A receptors as a strategy for suppressing the lung inflammation and thrombotic complications of COVID-19: Potential of pentoxifylline and dipyridamole. Med Hypotheses 2020; 143:110051.

78. D'Souza R, Malhamé I, Teshler L, et al. A critical review of the pathophysiology of thrombotic complications and clinical practice recommendations for thromboprophylaxis in pregnant patients with COVID-19. Acta Obstet Gynecol Scand 2020.

Topic 127926 Version 25.0

GRAPHICS

Thromboelastography (TEG) tracing parameters



"R" is the reaction time (the time it takes the coagulation cascade to generate thrombin and fibrin). "K" is the clot firmness. "α" (alpha) is the angle (describes the kinetics of clot formation). MA is the maximum amplitude (describes the maximum clot strength). Ly30 is the percent clot lysis 30 minutes after the MA is reached. Refer to UpToDate topics on platelet function testing and trauma management for details of the use and interpretation of thromboelastography.

TEG® Hemostasis Analyzer Tracing Image reproduced with permission of Haemonetics Corporation. TEG® and Thrombelastograph® are registered trademarks of Haemonetics Corporation in the US, other countries or both.

Graphic 100078 Version 1.0

Quick reference for evaluation and management of COVID-19-associated hypercoagulability

Evaluations and monitoring	
Inpatients	▪ Daily PT, aPTT, fibrinogen, D-dimer ▪ Diagnostic imaging studies if feasible for clinically suspected DVT or PE; consult PERT team ▪ Alternative evaluations if standard imaging studies are not feasible
Outpatients	▪ Routine coagulation testing is not required
Management	
Abnormal coagulation studies	▪ Use for prognostic information and level of care ▪ Do not intervene solely based on coagulation abnormalities
VTE prophylaxis	▪ Prophylactic dose anticoagulation for all inpatients ▪ Intermediate or therapeutic dose anticoagulation for selected critically ill individuals (eg, in the ICU) ▪ Possible continued thromboprophylaxis following discharge ▪ Possible thromboprophylaxis in selected outpatients
VTE treatment	▪ Therapeutic (full-dose) anticoagulation for documented or presumptive diagnosis of VTE • Initiate in hospital per standard protocols • Consider extended thromboprophylaxis following discharge ▪ Reserve fibrinolytic agents (eg, tPA) for limb-threatening DVT, massive PE, acute stroke, or acute MI; consult PERT or stroke team
Clotting in vascular catheters or extracorporeal circuits*	▪ Therapeutic (full-dose) anticoagulation ▪ Standard protocols for continuous renal replacement therapy or ECMO
Bleeding	▪ Similar to individuals without COVID-19 • Transfusions for anemia or thrombocytopenia • Anticoagulant reversal and/or discontinuation for anticoagulant-associated bleeding • Specific treatments (eg, factor replacement) for underlying bleeding disorders ▪ Avoid antifibrinolytic agents in individuals with acute decompensated DIC¶

Refer to UpToDate for discussions of COVID-19 management and related topics. Resources are also available from the International Society on Thrombosis and Haemostasis (https://onlinelibrary.wiley.com/doi/10.1111/jth.14853), the American Society of Hematology (https://www.hematology.org/covid-19/covid-19-and-coagulopathy), and the American College of Cardiology (https://www.acc.org/latest-in-cardiology/articles/2020/04/17/14/42/thrombosis-and-coronavirus-disease-2019-covid-19-faqs-for-current-practice).

COVID-19: coronavirus disease 2019; PT: prothrombin time; aPTT: activated partial thromboplastin time; DVT: deep vein thrombosis; PE: pulmonary embolism; PERT: pulmonary embolism response team; VTE: venous thromboembolism; ICU: intensive care unit; tPA: tissue plasminogen activator; MI: myocardial infarction; ECMO: extracorporeal membrane oxygenation; DIC: disseminated intravascular coagulation.
* Includes continuous renal replacement therapy (CRRT; eg, hemodialysis), ECMO, or other extracorporeal circuits.
¶ Acute decompensated DIC is associated with clinical bleeding (and/or thrombosis) and laboratory findings including prolonged PT and aPTT, thrombocytopenia, and hypofibrinogenemia. Antifibrinolytic agents (tranexamic acid and epsilon aminocaproic acid) are avoided because they may tip the balance towards thrombosis. Refer to UpToDate for details.

Graphic 127960 Version 2.0

Anticoagulation in COVID-19 patients

Image

COVID-19 is a hypercoagulable state, and the risk of thromboembolic disease is increased in critically ill (and sometimes well-appearing) individuals. Thromboembolism is typically venous but in some ca
Bleeding is much less common but can occur, including intracerebral bleeding, highlighting the importance of documenting ischemia or thrombosis when feasible.

COVID-19: coronavirus disease 2019; MI: myocardial infarction; PE: pulmonary embolism; DVT: deep vein thrombosis; AF: atrial fibrillation; VTE: venous thromboembolism; tPA: tissue plasminogen activator; PERT: pul
response team; ICU: intensive care unit; LMW: low molecular weight; CrCl: creatinine clearance; RRT: renal replacement therapy; HIT: heparin-induced thrombocytopenia.
* Appropriate testing to document suspected thromboembolism is advised if feasible. Assistance from a specialist (pulmonary, critical care, hematology) may be required. Refer to UpToDate for details of testing.
¶ High-risk features include prior VTE, recent surgery or trauma, immobilization, or obesity.

Graphic 128045 Version 3.0

Suggested dose adjustments of low molecular weight (LMW) heparins in adults with renal insufficiency

	VTE treatment	VTE prophylaxis*
Enoxaparin	**CrCl ≥30 mL/min:** No adjustment **CrCl <30 mL/min:** Reduce to 1 mg/kg once daily	**CrCl ≥30 mL/min:** No adjustment **CrCl <30 mL/min:** Reduce to 30 mg once daily (medical or surgical patients)
Dalteparin	**CrCl ≥30 mL/min:** No adjustment **CrCl <30 mL/min:** Use an anticoagulant with less dependence on renal clearance¶	**CrCl ≥30 mL/min:** No adjustment
Nadroparin (not available in the US)	**CrCl ≥50 mL/min:** No adjustment **CrCl 30 to 50 mL/min:** Reduce dose by 25 to 33% if clinically warranted **CrCl <30 mL/min:** Contraindicated	**CrCl ≥50 mL/min:** No adjustment **CrCl 30 to 50 mL/min:** Reduce dose by 25 to 33% if clinically warranted **CrCl <30 mL/min:** Reduce dose by 25 to 33%
Tinzaparin (not available in the US)	**CrCl ≥30 mL/min:** No adjustment **CrCl <30 mL/min:** Use with caution, although evidence suggests no accumulation with CrCl as low as 20 mL/min	**CrCl ≥30 mL/min:** No adjustment **CrCl <30 mL/min:** Use with caution, although evidence suggests no accumulation with CrCl as low as 20 mL/min

Suggested dose adjustment of LMW heparins for reduced renal function (subcutaneous dosing). Caution should be used in all patients with renal insufficiency, and all patients should be observed for signs of bleeding. Accumulation may occur with repeated doses. An alternative anticoagulant such as unfractionated heparin may be preferred, especially for individuals with CrCL <30 mL/min, renal failure, or receiving dialysis. Examples of alternatives include:[1]

- Unfractionated heparin
- An LMW heparin with lower renal clearance
- A DOAC with low renal clearance (apixaban, renal clearance approximately 25%)

Use of LMW heparin in patients with renal insufficiency has been associated with hyperkalemia. Refer to the UpToDate topics on the use of heparin and LMW heparin in specific clinical conditions, for infants and children, and for acute coronary syndromes and myocardial infarction (for which there are separate tables).

LMW heparin: low molecular weight heparin; VTE: venous thromboembolism; CrCl: creatinine clearance as determined by Cockcroft-Gault equation (a calculator is available in UpToDate); US: United States; DOAC: direct oral anticoagulant.

* Applies to short-term VTE prophylaxis (up to 10 days). For long-term use, periodic anti-factor Xa activity testing may be useful to rule out drug accumulation.

¶ May consider checking anti-factor Xa activity, consistent with some authorities;[2-4] however, ranges have not been established from clinical trials and no dose adjustment nomograms have been clinically validated. Other experts and a 2018 guideline from the American Society of Hematology recommend against checking anti-factor Xa activity and suggest dose adjustments based on information in the product labeling or switching to an alternative anticoagulant such as those listed above. If monitored, levels should be measured 4 to 6 hours after dosing, following at least the third or fourth dose.[Δ]

Δ The following represent peak (4 hours after the dose) expected on-therapy values for therapeutic dosing (for VTE) for anti-factor Xa activity, although these have not been clinically validated:[1,2]

- Enoxaparin twice daily: 0.6 to 1.0 anti-factor Xa units/mL (range, 0.5 to 1.5[5])
- Enoxaparin once daily: >1.0 anti-factor Xa units/mL
- Dalteparin once daily: 1.05 anti-factor Xa units/mL (range, 0.5 to 1.5[6])
- Nadroparin once daily: 1.3 anti-factor Xa units/mL[7]
- Tinzaparin once daily: 0.85 anti-factor Xa units/mL[8]

Data from:

1. *Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Advances 2018; 3257.*
2. *Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e24S.*
3. *Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: Available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 2009; 43:1064.*
4. *Lexicomp Online. Copyright © 1978-2020 Lexicomp, Inc.*
5. *Enoxaparin sodium injection. US FDA approved prescribing information (revised October, 2013). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020164s102lbl.pdf.*
6. *Dalteparin sodium injection. US FDA approved prescribing information (revised May, 2019). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020287s072lbl.pdf.*
7. *Nadroparin calcium injection. Canada product monograph (revised January 2019). Available at: https://pdf.hres.ca/dpd_pm/00049107.PDF.*
8. *Tinzaparin sodium injection. Canada product monograph (May 26, 2017). Available at: https://pdf.hres.ca/dpd_pm/00040736.PDF.*

Graphic 90258 Version 11.0

Suggested doses of low molecular weight heparins in obese patients

	VTE treatment	VTE prophylaxis	Product labeling on use in obese patients
Enoxaparin*	Use standard treatment dosing (ie, 1 mg/kg every 12 hours based on ABW). In patients with a BMI ≥40 kg/m^2, a lower dose (ie, approximately 0.75 mg/kg every 12 hours, based on ABW) was suggested in 2 small case series based on peak anti-factor Xa levels but has not been clinically evaluated.[1,2] Once daily dosing regimens of enoxaparin are **not** recommended.	**BMI 30 to 39 kg/m^2:** Use standard prophylaxis dosing (ie, 30 mg every 12 hours or 40 mg once daily). **BMI ≥40 kg/m^2:** Empirically increase standard prophylaxis dose by 30% (ie, to 40 mg every 12 hours).¶Δ **High VTE-risk bariatric surgery with BMI ≤50 kg/m^2:** 40 mg every 12 hours.[3,4] **High VTE-risk bariatric surgery with BMI >50 kg/m^2:** 60 mg every 12 hours.[4]	Safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/m^2) has not been fully determined, and there is no consensus for dose adjustment. Observe carefully for signs and symptoms of VTE.[5] Marginal increase observed in mean anti-factor Xa activity using ABW and 1.5 mg/kg once daily dosing in healthy obese persons (BMI 30 to 48 kg/m^2) compared with non-obese persons.[5]
Dalteparin	Approved by the US FDA only for extended treatment of cancer-associated VTE. Use standard treatment dosing (ie, 200 units/kg once daily based on ABW for the first month, followed by 150 units/kg once daily for subsequent months).◊ Consider using 100 units/kg every 12 hours based on ABW for patients weighing ≥100 kg.◊[3]	**BMI 30 to 39 kg/m^2:** Use standard prophylaxis dosing (ie, 2500 or 5000 units once daily). **BMI ≥40 kg/m^2:** Empirically increase standard prophylaxis dose by 30% (ie, increase to 3250 or 6500 units once daily).¶Δ[6]	Cancer-associated VTE: Use ABW-based dosing for patients weighing up to 99 kg. Use a maximum dose of 18,000 units per day for patients weighing >99 kg.◊[7]
Tinzaparin (not available in the United States)	Use standard treatment dosing (ie, 175 units/kg once daily based on ABW).	**BMI 30 to 39 kg/m^2:** For orthopedic surgery, use standard prophylaxis dosing (ie, 50 or 75 anti-factor Xa units/kg based on ABW once daily); for general surgery, use standard fixed dosing (ie, 3500 anti-factor Xa units once daily). **BMI ≥40 kg/m^2:** For orthopedic surgery, use standard prophylaxis dosing (ie, 50 or 75 anti-factor Xa units/kg based on ABW once daily); for general surgery, empirically increase fixed dose by 30% (ie, increase to 4500 anti-factor Xa units once daily).¶Δ[6] **Moderate to high VTE-risk bariatric surgery, extended postoperative prophylaxis regimen:** Beginning on postoperative day 1: 75 units/kg once daily based on ABW for 10 days, according to a protocol evaluated at 1 center; patients weighing <110 kg received 4500 units once daily; patients weighing ≥160 kg received 14,000 units once daily.¶[8]	Safety and efficacy in patients weighing >120 kg has not been fully determined. Individualized clinical and laboratory monitoring is recommended (Canada product monograph).[9]

All doses shown are for patients with normal renal function and are for subcutaneous administration. For dose adjustment due to renal impairment, refer to individual Lexicomp monograph.
Anti-factor Xa testing: Clinically stable patients weighing up to 144 kg (enoxaparin) or 190 kg (dalteparin¶) or 165 kg (tinzaparin) with BMI <40 kg/m^2 may receive low molecular weight heparin for VTE treatment adjusted according to ABW without anti-factor Xa testing[10]. Generally, anti-factor Xa monitoring is not recommended, but it can be considered for patients with BMI ≥40 kg/m^2 who are unstable, experience unexpected thromboembolic or bleeding complications, or require prolonged VTE treatment.

VTE: venous thromboembolism; ABW: actual (total) body weight; BMI: body mass index; US FDA: US Food and Drug Administration.
* Conversion: 1 mg enoxaparin approximately equal to 100 international units enoxaparin.
¶ Rounding of dose may be necessary depending on product detail. Refer to Lexicomp monograph included with UpToDate.
Δ An empiric dose increase of approximately 30% for fixed prophylactic doses of low molecular weight heparin for VTE prophylaxis for patients who are morbidly obese is based on clinical experience and analysis of pharmacodynamic and clinical outcomes data.[6]
◊ According to the United States approved dalteparin prescribing information, a fixed dose of 18,000 units per day is recommended for patients weighing >99 kg who are being treated for cancer-associated VTE. However, guidelines suggest that dalteparin dose should be based on actual body weight.[6] Capped dalteparin dose of 18,000 units per day is not recommended.

References:
1. *Deal EN, Hollands JM, Riney JN, et al. Evaluation of therapeutic anticoagulation with enoxaparin and associated anti-Xa monitoring in patients with morbid obesity: A case series. J Thromb Thrombolysis 2011; 32:188.*
2. *Lalama JT, Feeney ME, Vandiver JW, et al. Assessing an enoxaparin dosing protocol in morbidly obese patients. J Thromb Thrombolysis 2015; 39:516.*
3. *Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. Obes Surg 2002; 12:19.*
4. *Borkgren-Okonek MJ, Hart RW, Pantano JE, et al. Enoxaparin thromboprophylaxis in gastric bypass patients: Extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis 2008; 4:625.*
5. *Enoxaparin sodium US prescribing information (revised October 2017) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020164s110lbl.pdf (Accessed on November 13, 2018).*
6. *Nutescu EA, Spinler SA, Wittkowsky A, et al. Low-molecular-weight heparins in renal impairment and obesity: Available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 2009; 43:1064.*
7. *Dalteparin sodium injection US prescribing information (revised May 2017) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020287s069lbl.pdf (Accessed on November 13, 2018).*
8. *Tseng EK, Kolesar E, Handa P, et al. Weight-adjusted tinzaparin for the prevention of venous thromboembolism after bariatric surgery. J Thromb Haemost 2018; 16:2008.*
9. *Tinzaparin sodium injection Canada product monograph (revised May 2017) available at https://pdf.hres.ca/dpd_pm/00040736.PDF (Accessed on November 13, 2018).*
10. *Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest 2012; 141:e24S.*

Graphic 65464 Version 16.0

Use of heparins during pregnancy

Heparin	Dose level	Dose
LMW heparin	Prophylactic*	Enoxaparin 40 mg SC once daily
		Dalteparin 5000 units SC once daily
	Intermediate¶	Enoxaparin 40 mg SC once daily, increase as pregnancy progresses to 1 mg/kg once daily
		Dalteparin 5000 units SC once daily, increase as pregnancy progresses to 100 units/kg once daily
	Therapeutic	Enoxaparin 1 mg/kg SC every 12 hours
		Dalteparin 100 units/kg SC every 12 hours
Unfractionated heparin	Prophylactic	5000 units SC every 12 hours
	Intermediate¶	First trimester: 5000 to 7500 units SC every 12 hours
		Second trimester: 7500 to 10,000 units SC every 12 hours
		Third trimester: 10,000 units SC every 12 hours
	Therapeutic	Can be given as a continuous IV infusion or a SC dose every 12 hours. Titrated to keep the aPTT in the therapeutic range.

Doses apply to pregnant women receiving heparin for venous thromboembolism prophylaxis. Therapeutic dose level refers to doses used both for prophylaxis in individuals at especially high risk and for treatment of venous thromboembolism. This dosing table should **not** be used in women with prosthetic heart valves. Refer to the UpToDate topic on anticoagulant use in pregnancy for details of administration and monitoring. Refer to UpToDate topics on specific pregnant patient populations for other dosing recommendations (eg, prosthetic heart valve, atrial fibrillation, treatment of deep vein thrombosis or pulmonary embolism).

LMW: low molecular weight; SC: subcutaneously; IV: intravenous; aPTT: activated partial thromboplastin time; ACCP: American College of Clinical Pharmacy; ACOG: American College of Obstetricians and Gynecologists.

* Prophylactic dosing may require modifications for extremes of body weight; refer to the UpToDate table on LMW heparin dosing in obesity for details.

¶ Our "intermediate" dose level differs from that used in society guidelines (eg, ACCP, ACOG). Some clinicians prefer to use a different "intermediate" dose level such as enoxaparin 40 mg SC every 12 hours; however, this entails a significant increase in the number of injections over the course of the pregnancy.

Graphic 91838 Version 8.0

Nomogram for adjusting unfractionated heparin in adults using anti-factor Xa activity *or the aPTT**

Bolus: 80 units/kg (using total body weight) **Maximum** = 10,000 units		
Initial infusion rate: 18 units/kg/hr (using total body weight) **Maximum** = 2000 units/hr		
If using anti-factor Xa activity* (IU/mL)	**Response**	**If using aPTT* (seconds)¶**
0.00 to 0.09	▪ Bolus 25 units/kg ▪ Increase infusion by 3 units/kg/hr ▪ Repeat assay in 6 hours	<40
0.10 to 0.19	▪ Increase infusion by 2 units/kg/hr ▪ Repeat assay in 6 hours	40 to 49
0.20 to 0.29	▪ Increase infusion by 1 unit/kg/hr ▪ Repeat assay in 6 hours	50 to 69
0.30 to 0.7	▪ NO CHANGE (within therapeutic range) ▪ Repeat assay in 6 hours ▪ Once therapeutic for two assays, may change to once daily assays	70 to 110¶
0.71 to 0.79	▪ Decrease infusion by 1 unit/kg/hr ▪ Repeat assay in 6 hours	111 to 120
0.80 to 0.89	▪ STOP INFUSION for 1 hour, then decrease by 2 units/kg/hr ▪ Repeat assay 6 hours after restarting the infusion	121 to 130
0.90 to 0.99	▪ STOP INFUSION for 1 hour, then decrease by 3 units/kg/hr ▪ Repeat assay 6 hours after restarting the infusion	131 to 140
1.00 to 1.09	▪ STOP INFUSION for 2 hours, then decrease by 4 units/kg/hr ▪ Repeat assay 6 hours after restarting the infusion	141 to 150
≥1.10	▪ STOP INFUSION for 2 hours, then decrease by 5 units/kg/hr and notify clinician ▪ Repeat assay 6 hours after restarting the infusion	>150

This is one example of a weight-based heparin dosing nomogram using either anti-factor Xa activity **or** activated partial thromboplastin time (aPTT) for therapeutic heparin dosing (eg, for acute venous thromboembolism). All doses are based on actual body weight in kilograms. The initial and subsequent bolus doses, infusion rate changes, as well as dosing intensity based on the indication for unfractionated heparin (eg, venous thromboembolism, stroke, acute coronary syndrome) should be established separately for each institution. Refer to UpToDate for additional details.

aPTT: activated partial thromboplastin time; IU: international units.

* Only one measurement (the anti-factor Xa activity level **or** the aPTT) should be used; they are rarely concordant.

¶ The therapeutic ranges for the aPTT (corresponding to an anti-factor Xa activity of 0.3 to 0.7 IU/mL) are dependent on local reagents and instrumentation and must be established by each individual institution.

Courtesy of Allison E. Burnett, PharmD, PhC, CACP.

Graphic 122945 Version 2.0

Contributor Disclosures

Adam Cuker, MD, MS Grant/Research/Clinical Trial Support: Alexion [PNH]; Bayer; Novo Nordisk; Pfizer; Sanofi; Spark[Hemophilia]; Takeda. Consultant/Advisory Boards: Synergy [PNH, Fabry disease]. **Flora Peyvandi, MD, PhD** Consultant/Advisory Boards: Sanofi; Roche. Speaker's Bureau: Sanofi; Grifols. **Lawrence LK Leung, MD** Nothing to disclose **Jennifer S Tirnauer, MD** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy