

**Direction**

- 1) A 56-year-old man with severe COVID-19 is under mechanical ventilation because of respiratory failure. Several days later, the patient experiences a sudden deterioration in hemodynamics and dies. What is the most probable cause of his death?
  - a. Massive pulmonary embolism
  - b. Tension pneumothorax
  - c. Myocardial infarction and fulminant ventricular arrhythmias
  - d. All of the above
- 2) A radiologist colleague expresses his/her surprise at the number of pulmonary emboli, which he/she has recently reported in patients with COVID-19, and asks you about the reason for this surge. Which of the following would your answer be?
  - a. Prolonged duration of admission in the majority of patients
  - b. Hypercoagulable state due to hyperinflammation and endothelial damage
  - c. Older age of admitted patients
  - d. Vitamin D deficiency
- 3) A 47-year-old woman with severe symptoms and anticipated need for mechanical ventilation is admitted to the COVID-19 ward. Your first choice is heparin at a prophylactic dose, but her activated partial thromboplastin time (aPTT) is 1.3 times the normal level. Does this finding preclude prophylaxis? What should be done?
  - a. Yes, compression stocking should be provided for this patient.
  - b. Yes, a removable inferior vena cava filter should be inserted.
  - c. No, subcutaneous enoxaparin should be given.
  - d. No, new oral anticoagulants are the best choice.
- 4) In the previous question, what is the most likely cause of prolonged aPTT?
  - a. Unknown history of hemophilia
  - b. Development of antiphospholipid antibodies secondary to COVID-19
  - c. Previous use of aspirin
  - d. Vitamin K deficiency
- 5) A 52-year-old man with a history of ischemic heart disease is admitted to the COVID-19 ward with diarrhea, hypoxemia, and mild respiratory distress. The lab tests reveal prothrombin time (PT) of 10 s, aPTT of 0.9, fibrinogen of 180 mg/dL, D-dimer of 1250  $\mu$ g/L, lactate dehydrogenase (LDH) of 860 U/dL, creatinine of 1.8, blood urea nitrogen of 29, and potassium of 3.4 mEq/L. What do you think has caused these deranged results?
  - a. Hypercoagulopathy of COVID-19 and renal azotemia
  - b. Laboratory errors due to the overload of patients and specimens
  - c. Disseminated intravascular coagulation (DIC) and renal ischemia
  - d. Direct viral invasion to the liver
- 6) In the previous question, what may have caused the shortened aPTT?
  - a. Laboratory error
  - b. Increased levels of coagulation factors, especially FVIII
  - c. Renal failure
  - d. Development of antiphospholipid antibodies secondary to COVID-19
- 7) A previously healthy 63-year-old woman is under mechanical ventilation due to moderate acute respiratory distress syndrome (ARDS) with the following setting for the ventilator: SIMV mode, positive end-expiratory pressure of 18 cmH<sub>2</sub>O, a fraction of inspired oxygen (FiO<sub>2</sub>) of 80%, respiratory rate of 18/min, tidal volume of 420 cc, and peak airway pressure of 30 cmH<sub>2</sub>O. She also receives a prophylactic dose of enoxaparin. The day before, a physician saw bilateral swelling in the patient's lower limbs, and decided to reduce the IV fluids. Today, while moving the patient, you observe sudden sinus tachycardia, hypoxia, and subsequent atrial fibrillation with rapid ventricular response

- with ST-segment depressions in the inferior leads. The endotracheal tube is not displaced. You are the on-call intensive care unit (ICU) physician, and decide to start the infusion of heparin. In echocardiography, you find signs of right ventricular failure with the McConnell sign, septal flattening, and tricuspid annular plane systolic excursion of 15 mm. Blood pressure is 102/64 mm Hg. What will you do next?
- Continue heparin infusion
  - Administer a low dose of alteplase (0.5 mg/kg) in the absence of contraindications
  - Start dobutamine and norepinephrine infusion
  - Give 1 L of normal saline
- 8) In the previous question, what could have been done to prevent such a dramatic turn of events?
- Increasing the dose of prophylactic enoxaparin
  - Adding aspirin to the treatment
  - Prophylactic placement of an inferior vena cava filter
  - Lower limb physical therapy
- 9) In Problem 7, what technique could have been used to check if the patient needed full-dose anticoagulation before the development of pulmonary embolism?
- Serial check of D-dimer
  - Serial thromboelastography (TEG) or rotational thromboelastometry (ROTEM)
  - Serial ultrasound of the lower limb veins
  - Serial check of Factor Xa (FXa) levels
- 10) A 22-year-old woman with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 is visited in the outpatient setting. She has oxygen saturation (SpO<sub>2</sub>) of 92% in the ambient air, and states that she has been taking contraceptive pills (low-dose) for the last two years. What should be recommended to the patient?
- Discontinue the pills and use a non-hormonal method of contraception for the duration of the illness.
  - Oral contraceptive pills do not carry a risk of thrombotic complications.
  - If it is essential to use a pill, it is better to use progestin-based minipills.
  - Both A and C are correct.
- 11) Which statement about the pathophysiology of hypercoagulopathy in COVID-19 is true?
- The inflammatory cascade induced by toll-like receptors is irrelevant to the hypercoagulopathy in COVID-19 at the time.
  - Protein C pathways modulate the inflammatory response and the coagulation cascade toward hypercoagulopathy.
  - Diffuse endotheliitis causes disseminated intravascular coagulation in patients with severe disease.
  - Patients who are already on chronic anticoagulation are at increased risk of hypercoagulopathy.
- 12) A 64-year-old man with a history of the end-stage renal disease, who was on chronic intermittent hemodialysis is under mechanical ventilation due to ARDS caused by COVID-19. The patient is continuously hypotensive, and you decide to put him on continuous renal replacement therapy (CRRT), which requires full-dose anticoagulation. Forty-eight hours later, he needs less FiO<sub>2</sub> and vasopressor support. What do you think has caused this improvement?
- Correction of the electrolyte derangements
  - Removal of the excess fluid
  - Removal of the inflammatory cytokines by CRRT
  - Full anticoagulation has lysed microthromboses in the pulmonary vasculature within 48 hours
- 13) Which medication is shown to reduce D-dimer levels by alleviating the inflammatory response induced by IL-6?
- Statins
  - Tocilizumab
  - Heparins
  - Remdesivir

- 14) A 50-year-old woman was admitted to the COVID-19 ward with SpO<sub>2</sub> of 83%. After successful treatment with a combination of remdesivir + dexamethasone + atorvastatin + doxycycline + enoxaparin + famotidine, she is discharged. The temporary continuation of which medication(s) is shown to be beneficial?
- Doxycycline
  - Atorvastatin
  - Anticoagulant (e.g., enoxaparin and rivaroxaban)
  - B and C
- 15) A 64-year-old man with a history of diabetes, hypertension, and Alzheimer's dementia is admitted, and given treatment for moderate-to-severe COVID-19. The patient had a D-dimer of 2140 µg/L on admission. Suddenly he complains of severe and sudden periumbilical abdominal pain. There is no significant finding in the physical examination; accordingly, the on-call intern decides to prescribe a chlorthalidone/clidinium tablet. Two hours later, the daily venous blood gas assessment shows metabolic acidosis; additionally, the pain has intensified and abdominal tenderness is present. The patient is urgently transferred to the operating room with the possible diagnosis of mesenteric ischemia; however, he does not survive the surgery. What is the likely cause of this tragic delay in diagnosis?
- A combination of non-supervision of the inexperienced intern, cognitive barriers, failure to acknowledge the risk factors, and the history of sudden-onset severe abdominal pain must have been the reason.
  - Mesenteric ischemia is almost always fatal. Nothing could have been done for the patient anyway!
  - The medication masked the symptoms for a brief period of time.
  - The elevated D-dimer does not predict the evolution of thrombotic complications.
- 16) A 31-year-old man with opiate use disorder (IV heroin user) is admitted with the diagnosis of aspiration pneumonia and is responding well to the treatment. Later, he develops signs of COVID-19, and PCR confirms the infection. His general condition is not bad, and he is ambulatory. Two days later, he develops sudden pain in the left leg with pallor compared with the other leg. A weak pulse is detected in the posterior tibialis artery. What is the most likely reason for acute limb ischemia in this patient?
- Acute arterial thrombosis due to hypercoagulable state
  - Embolism of vegetation from left heart endocarditis
  - Vasospasm due to vasopressor infusion
  - Aortic dissection
- 17) Which laboratory finding better predicts complications, ICU admission, and death in patients with COVID-19?
- Lymphocyte count < 900 /µL
  - LDH > 300 U/dL
  - D-dimer > 1500 µg/L
  - Respiratory alkalosis
- 18) A 58-year-old man with a history of diabetes is admitted to the COVID-19 ward. The patient was passionately reading a novel (*The Gulag Archipelago*), when he suddenly experienced crushing chest pain. ST-segment elevation was seen in the anterior leads. He was transferred to the cath lab for percutaneous coronary intervention. His interventional cardiologist is worried about the high rates of stent thrombosis in diabetic patients, especially in the presence of COVID-19. He is already on aspirin, atorvastatin, and metoprolol. Adding which medication is most beneficial for the patient?
- Clopidogrel
  - Apixaban
  - Tirofiban
  - Alteplase
- 19) A colleague has come across a randomized clinical trial, which found that the anticoagulation of patients with severe disease at therapeutic dosage conferred better outcomes. He is inspired by the study, and recommends that we follow suit, and administer anticoagulants to patients at therapeutic dosage. You study the article, and find out that this study recruited only 10 patients. What will

you decide about the dosage of enoxaparin given to patients with severe disease for prophylactic purposes in your institution?

- a. You continue the conventional dose of 40 mg daily.
- b. You change to unfractionated heparin 5000 IU q8 hours.
- c. You persuade the hospital to purchase betrixaban, which is shown to be superior to both enoxaparin and heparin.
- d. Believing that the sample size of the study is too small to provide powerful evidence, and that patients frequently suffer venous thromboembolism in spite of the prophylactic dose of enoxaparin, you recommend doubling the dosage of enoxaparin for the time being.

20) A 58-year-old man with localized prostatic cancer was candidated for radical prostatectomy, which was postponed several times due to the COVID-19 pandemic. Finally, the patient is admitted for elective surgery. On the first postoperative day, he has cough, fever, and myalgia. There is excessive hematuria and bleeding from the venous catheter sites. The lab tests show white blood cell count of 13000 / $\mu$ L, hemoglobin of 10.6 g/dL, absolute lymphocyte count of 750 / $\mu$ L, platelets of 340000/ $\mu$ L, D-dimer of 680  $\mu$ g/L, aPTT of 1.7, an international normalized ratio of 1.8, and PT of 22 s. Further workup reveals reduced fibrinogen levels, increased levels of fibrinogen degradation products, and a prolonged bleeding time. What has caused this bleeding disorder, and what should be administered for its reversal?

- a. COVID-19 has caused DIC; fresh frozen plasma (FFP)
- b. Radical prostatectomy has caused the release of urokinase, acting as a fibrinolytic; tranexamic acid
- c. DIC due to thrombotic thrombocytopenic purpura; plasmapheresis and FFP
- d. Undiagnosed dysfibrinogenemia; fibrinogen