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Coagulopathy in COVID-19: Cause or Effect?

Announcer:
You're listening to *The Drug Report* on ReachMD, hosted by Linda Bernstein, Pharm.D., Clinical Professor on the Volunteer Faculty of the School of Pharmacy, University of California, San Francisco.

Dr. Bernstein:
Welcome to *The Drug Report* with a special focus on the COVID-19 epidemic.

The *New England Journal of Medicine* recently presented a case report from a hospital intensive care unit in Wuhan China of a COVID-19 patient with clinically significant coagulopathy, antiphospholipid antibodies, and multiple infarcts. He was one of three patients with these findings. All three patients had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as confirmed by RT-PCR assay or serologic testing.

One patient was a 69-year-old man with a history of hypertension, diabetes, and stroke who presented with fever, cough, dyspnea, diarrhea, and headache. He was initially provided supportive treatment but progressed to hypoxemic respiratory failure requiring invasive mechanical ventilation. The patient had lower limb and digit ischemia. Brain imaging showed bilateral cerebral infarcts in multiple vascular territories. It is unclear if these were fresh or old infarcts. He had an elevated prothrombin time, partial thromboplastin time, fibrinogen, and D-dimer. Anticardiolipin IgA antibodies as well as anti–β_2-glycoprotein I IgA and IgG antibodies were present. The two other patients had similar serologic findings.

As background, antiphospholipid antibodies abnormally target phospholipid proteins, and their presence is key to the diagnosis of the antiphospholipid syndrome, an acquired autoimmune disorder that manifests clinically as recurrent venous or arterial thrombosis.

However, these antibodies can also be transiently elevated in critical illness and various infections. It is unknown if the presence of these antibodies are due to other causes of multifocal thrombosis in critically ill patients as may occur in disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic microangiopathy.

In a related article in *Pharmacy Practice News*, it was reported that abnormal clotting, apparently resulting from endothelial damage, has been described in patients with severe COVID-19 disease and that Chinese clinicians recommend initiating prompt anticoagulation therapy in all severe COVID-19 patients.

Bin Cao, MD, with the National Clinical Research Center for Respiratory Diseases in Beijing, described "clots in the small vessels of all organs, not only the lungs but also including the heart, the liver, and the kidney" in a March 19 webinar on the disease cosponsored by the Chinese Cardiovascular Association and the American College of Cardiology.

High D-dimer levels seen in these patients, Dr. Cao said, point to abnormal coagulation throughout the body. “The virus can bind to the endothelial cells and may cause damage to the blood vessel, especially the microcirculation of the small blood vessels.”

In a March 11 paper in *Lancet* involving 191 COVID-19 patients in Wuhan, Dr. Cao and colleagues reported that D-dimer levels over 1 mcg/L at admission predicted an 18-fold increase in the odds of death before discharge. They postulated contributory mechanisms to be systemic pro-inflammatory cytokine responses that are mediators of atherosclerosis directly contributing to plaque rupture through local inflammation, induction of procoagulant factors, and hemodynamic changes, which predispose to ischemia and thrombosis. In addition, angiotensin converting enzyme 2, the receptor for SARS-CoV-2, is expressed on myocytes and vascular endothelial cells, so there is at least theoretical potential possibility of direct cardiac involvement by the virus. Of note, interstitial mononuclear inflammatory infiltrates in

heart tissue has been documented in fatal cases of COVID-19, although viral detection studies were not reported.

William Dager, PharmD, BCPS, a pharmacist specialist at UC Davis Medical Center, said, “There are notable signals suggesting an increased risk for thromboembolism in patients being managed for COVID-19.” As for the causes, “it may be multifactorial, from being sedentary to the impact of management approaches in the more critically ill [patients],” he said.

Katelyn Sylvester, PharmD, BCPS, CACP, the pharmacy manager for anticoagulation services at Brigham and Women’s Hospital in Boston, agreed there are multiple possible underlying mechanisms for abnormal clotting and cardiac damage in COVID-19 and therapeutic anticoagulation versus prophylaxis may need to be considered.

Dr. Sylvester also noted that angiotensin-converting enzyme 2, which is involved in COVID-19 viral entry, is expressed in cardiomyocytes, suggesting that some of the myocarditis that has been seen in COVID-19 could be related to the virus inhabiting those cells and causing cell death.

Any patient who has a significant underlying illness and thus is at risk to be more severely affected by COVID-19 is also at higher risk for clotting and diffuse intravascular coagulopathy in the first place, Dr. Sylvester said. “We need to treat COVID-19 patients like other critically ill patients and use standardized risk assessment scores for prophylactic anticoagulation.”

Ambulatory patients with mild disease likely do not need VTE prophylaxis. Patients in the ICU, and even if on a step-down unit for multiple days, should have pharmacologic prophylaxis if indicated and there is not a contraindication.

Clotting problems and antiplatelet therapy should be included in the daily COVID-19 management process, rather than just focusing on the infection, Dr. Dager said. “Any symptoms consistent with a thromboembolic process such as a [pulmonary embolism] should be addressed and not be presumed to be from the infection.”

For *The Drug Report*, I’m pharmacist Dr. Linda Bernstein.

Announcer:
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