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Conflict of interest

The authors declare no conflicts.

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Intestinal Ischemic Manifestations of COVID-19



Dear Editors:

We read with interest the article by Norsa et al¹ on intestinal ischemia in patients with coronavirus disease 2019 (COVID-19). They further highlight the coagulopathy known to cause vascular obstructions in patients with severe COVID-19, in whom microthrombi are typically found in the lung circulation; however, also myocardial infarction and ischemic stroke were reported, particularly in the late phase of the disease. The patients reported by Norsa et al had either small or large bowel ischemia, splenic infarct, or pulmonary thromboembolism, which were fatal in 4 of the 7 cases. The mechanisms involved in COVID-19 coagulopathy were analyzed by Grobler et al,² who stressed the importance of early recognition of risk factors for the subsequent development of abnormal clot formation. They concluded that patients need to be treated early in the disease, when high levels of von Willebrand factor and fibrinogen are already present and may interact with activated endothelial cells.² Nicolai et al³ observed that platelets are activated in severe cases of COVID-19, and may be critically involved in neutrophil extracellular trap (NET) formation, a central element of immunothrombosis.³ NETs have high procoagulant potential and could therefore serve as a link to explain altered blood coagulation and microvascular thrombosis in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Indeed, elevated markers of NETosis have been found to correlate with disease severity in COVID-19.³ It remains, however, difficult to understand why only a relatively small proportion of individuals with the coronavirus-defined SARS-CoV-2 will develop a hypercoagulable state.

We were puzzled by similar mechanisms occurring in a different infection known to cause binding of platelets to von Willebrand factor and the vessel wall,⁴ activate endothelial cells⁵ (which will hence release von Willebrand factor), and cause aggregation of platelets to granulocytes,⁶ namely infection by pathogenic strains of *Helicobacter pylori*.^{4–6} This pathogen secretes a protein called

neutrophilic activation factor that attracts neutrophils and causes their oxidative burst. In addition, neutrophilic activation factor is a Toll-like receptor 2 agonist able to induce the expression of interleukin-12 and interleukin-23 by neutrophils and monocytes, cause a remarkable increase in the number of interferon-gamma-producing T cells and decrease of interleukin-4-secreting cells, shifting the cytokine profile of antigen-activated human T cells from Th2 to the Th1 cytotoxic phenotype.⁷ This problem was also reported to be involved in the cytokine storm aggravating COVID-19. Due to antigen mimicry, *H pylori* was also shown to elicit autoantibodies against several human tissues and cells, including platelets; such autoantibodies can disappear after eradication of the infection.⁸ The bacterium is also able to induce autoantibodies against the vessel wall, which can in turn facilitate platelet and granulocyte aggregation and worsen vascular obstruction. Other autoantibodies known to occur in *H pylori* infection are those against phospholipids, leading to an antiphospholipid syndrome that subsides after eradication. As COVID-19 can result in ominous outcomes, every avenue should be pursued in an attempt to reduce its burden. Given their common mechanisms, we believe that pathogenic strains of *H pylori* might contribute to the severity of COVID-19, at least in some cases.

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