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Vaccine-induced immune thrombotic thrombocytopenia: why, what, who, and how?
This is a letter to the editor in response to AJEM29876
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We thank the authors for their letter regarding our narrative review published in The American Journal of Emergency Medicine, “Thrombosis with Thrombocytopenia Syndrome Associated with COVID-19 Vaccines”. The authors raise several important considerations of vaccine-induced immune thrombotic thrombocytopenia (VITT), a condition primarily associated with exposure to the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and AD26.COV2.S (Johnson & Johnson) vaccine that results in thrombocytopenia and thrombotic events.

The authors of the letter discuss why VITT occurs in the absence of heparin, the populations and locations affected, the association with the Oxford-AstraZeneca and Johnson & Johnson vaccines, and underlying pathophysiology. VITT is an autoimmune condition arising from antibodies that directly activate platelets which triggers
This causes a consumptive coagulopathy leading to thrombocytopenia, elevated D-dimer levels, and hypofibrinogenemia. Initial reports found high levels of IgG antibodies against platelet factor 4 (PF4) in patients with VITT.\textsuperscript{4-7} Thus, this pathophysiology resembles heparin-induced thrombocytopenia (HIT), but in classic HIT, antibodies recognize the complex formed between PF4 (positively charged) and heparin (negatively charged).\textsuperscript{8} The complete pathophysiology of VITT is not completely understood, specifically how adenovirus vector vaccines function as a trigger of the condition, but components of these vector vaccines may interact with PF4 and result in VITT.\textsuperscript{2,9,10} These components may include the viral capsid, edetic acid or other human proteins, spike proteins, and others.\textsuperscript{9,10} The clinical characteristics of VITT and HIT overlap significantly. In VITT, thrombosis may include deep vein thrombosis and pulmonary embolism, as well as atypical sites (e.g., splanchnic vein thrombosis, cerebral vein thrombosis, etc.) and arterial thrombosis.\textsuperscript{1-3}

VITT occurs almost exclusively in those receiving the Oxford-AstraZeneca or Johnson & Johnson vaccine.\textsuperscript{11,12} The majority of cases occur in patients less than age 60 years; however, while the first cases occurred in predominantly female patients, more current literature suggests both males and females are affected.\textsuperscript{2,12} Comorbidities may play a role in development of VITT, including history of autoimmune disease, cancer, arterial disease, and venous thrombosis.\textsuperscript{12}

Ultimately, the benefit of vaccination far outweighs the risk of VITT.\textsuperscript{1-3} Clinicians should consider VITT in patients with severe headache, visual changes, abdominal pain, nausea
and vomiting, back pain, dyspnea, leg pain/swelling, or skin/mucosal findings suggestive of consumptive coagulopathy (petechiae, bleeding, easy bruising). Complete blood count demonstrating thrombocytopenia, markedly elevated D-dimer, and evidence of thrombosis should prompt therapy with non-heparin anticoagulation. A positive PF4-heparin enzyme-linked immunosorbent assay (ELISA) confirms the diagnosis. Hematology consultation can be helpful.

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