Vaccine-induced immune thrombotic thrombocytopenia: what we know and do not know

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The development of vaccines to fight COVID-19 has been a remarkable medical achievement. However, this global immunization effort has been complicated by a rare vaccine-related outcome characterized by thrombocytopenia and thrombosis in association with platelet-activating anti–platelet factor 4 antibodies. In this Spotlight, we will discuss the recently described complication of vaccine-induced immune thrombotic thrombocytopenia (VITT) occurring in response to certain COVID-19 vaccines. Although information about this clinical condition is rapidly evolving, we will summarize our current understanding of VITT.

Introduction

The global effort to curb the spread of the COVID-19 infection has been remarkable for its speed and efficacy. Within 1 year of the arrival of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the world stage, pharmaceutical companies developed and delivered vaccines that have dramatically reduced the burden of COVID-19 disease. In the United Kingdom, 1 dose of a commercially approved vaccine effectively reduced hospitalization and death by >80%;1 in the United States, hospitalization rates from COVID-19 were reduced by 67% and 94% with single and dual vaccination, respectively.2

In late February 2021, initial descriptions of a safety signal emerged with the adenoviral-based (ChAdOx1-S) COVID-19 vaccine distributed by AstraZeneca (AZ).3,4 These reports detailed otherwise healthy individuals developing complications of thrombocytopenia and thrombosis in atypical locations (cerebral and/or splanchnic veins) within weeks of receiving the vaccination. By mid-April 2021, similar complications were described with another adenoviral-based vector (recombinant Ad26.COV2.S) distributed by Johnson & Johnson (J&J).5,6 This syndrome has been variably referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome. For this article, we will use the more specific term VITT, given the temporal relationship of disease with COVID-19 vaccination.

Although descriptions of VITT are recent (<3 months as of this publication), published case reports/case series are relatively few, and research is limited, there is coalescing knowledge about the epidemiology, pathogenesis, diagnosis, and management of this syndrome. In this article, we will review what is currently known and unknown about VITT.

VITT is a vaccine safety signal with adenoviral-based vectors

We know that VITT is a safety signal from adenoviral-based vectors. What made this safety signal discernible was the concurrent presentation of thrombocytopenia and thrombosis, a rare occurrence in the general population and those immunized with nonadenoviral-based SARS-CoV-2 vaccines.

As of 12 May 2021, the estimated incidence of VITT was ~7 to 10 cases per million individuals with the AZ vaccine (~309 cases reported out of 32.9 million doses given in the United Kingdom)7 and ~3.2 cases per million for the J&J vaccine (or 28 cases out of 8.7 million doses administered in the United States)5 (Table 1). The reported rates for the J&J vaccine likely underestimate the true incidence of disease, given the shorter period of J&J vaccine availability (emergency use authorization was granted in the United States on 27 February 2021) and delays in reporting of the syndrome.

The epidemiology of VITT must be considered in the context of similar complications in the general population. The annual incidence of isolated thrombocytopenia, such as immune thrombocytopenia (ITP), or isolated cerebral vein thrombosis (CVT) is higher than that reported for VITT, but when adjusted for the 2-week time frame characteristic of VITT presentations, corresponding rates are lower than that of VITT. ITP in the general population occurs in 16 to 39 cases per million (or 0.61-1.5 cases per million in any 2-week period),8,9 whereas isolated CVT is reported in 13 to 20 cases per million (0.5-0.77 cases per million in any 2-week period).10,11 Although there are no formal studies of thrombocytopenia in association with CVT, other well-known thrombotic thrombocytopenic syndromes, such as thrombotic thrombocytopenic purpura and/or atypical hemolytic uremic syndrome, occur at a frequency of 11.3 cases per million (or 0.43 cases per million in any 2-week period).
Hematologic complications of either isolated ITP or CVT occurring in the wake of COVID-19 vaccination also appear to be lower than reported rates of VITT. Complications of ITP for the 2 messenger RNA (mRNA)-based vaccines have been estimated to occur in 0.8 to 1 case per million, based on reporting to the Vaccine Adverse Event Reporting System (VAERS), whereas isolated CVT after vaccination with BioNTech/Pfizer is 2 cases per million (2 of 489,871). There is also persuasive epidemiologic data on VITT to suggest a class effect among vaccines. The 2 major types of vaccine technologies that have been approved in the United States and Europe include formulations of lipid nanoparticles containing mRNA encoding the SARS-CoV-2 spike protein (BioNTech/Pfizer and Moderna) or replication-defective adenoviral vectors (AZ and J&J) expressing modified DNA for the SARS-CoV-2 spike protein. The AZ vaccine uses a chimpanzee adenoviral vector (ChAdOx1-S) that encodes a modified membrane-bound SARS-CoV-2 spike protein that does not shed, whereas the J&J vaccine uses a recombinant human adenovirus type 26 vector (Ad26.COV2.S) encoding an unmodified spike glycoprotein. To date, of the 200 million doses of mRNA-based vaccines administered in the United States, there have been no documented reports of thrombosis complicated by thrombocytopenia.

VITT is pathogenically linked to autoimmune heparin-induced thrombocytopenia

We have preliminary insights into VITT pathogenesis. Published reports indicate that VITT is: (1) an immune complication resembling a variant of autoimmune heparin-induced thrombocytopenia (aHIT), (2) unlikely a byproduct of COVID-19 infection, and (3) independent of anti-SARS-CoV2 protective immunity.

Demonstration of circulating anti–platelet factor 4 (anti–PF4) antibodies in conjunction with thrombocytopenia and thrombosis suggests that VITT is a clinical variant of aHIT. Anti–PF4 antibodies are the hallmark of heparin-induced thrombocytopenia (HIT), a thrombotic disorder caused by the anticoagulant drug heparin. Spontaneous HIT, a rare manifestation of HIT, occurs without prior heparin exposure and, in most cases, is precipitated by recent infection and/or orthopedic surgery. Although disease manifestations in HIT are caused by antibodies directed to ultralarge complexes of PF4 bound to heparin or polyanions, such as glycosaminoglycans, polyphosphates, or DNA, aHIT is associated with anti–PF4 antibodies whose functional effects are largely independent of heparin or polyanions. Pathogenic anti–PF4/heparin antibodies cross-link FcRIIA on platelets, monocytes, and neutrophils to initiate procoagulant cellular responses that generate a profound hypercoagulable state. Thrombotic risk in HIT and/or aHIT is strongly correlated with high levels of circulating anti–PF4 antibodies, as detected by immunoassays and/or functional assays of platelet activation.

It is also clear from recent data that VITT is not an aberrant clinical manifestation of COVID-19 infection. Although COVID-19 is recognized as a hypercoagulable disorder, complications of CVT with or without thrombocytopenia are uncommon in the wake of infection. In a recent study of ~500,000 patients with documented COVID-19, 20 patients developed CVT (0.004%), whereas thrombocytopenia with CVT was noted in only 1 patient. Additionally, most VITT patients do not have active COVID-19 infection as documented by negative SARS-CoV-2 RNA testing at time of disease presentation.

The immune responses to SARS-CoV-2 proteins and PF4, as seen in COVID-19 and VITT patients, respectively, are also non-overlapping. Although high levels of anti–PF4 antibodies are present in nearly all patients with VITT, anti–PF4 antibodies are found at the expected prevalence (~8% to 12%) in hospitalized patients with COVID-19, who are likely exposed to heparin during treatment. There are also no significant differences in the incidence of anti–PF4 antibodies in COVID-19 patients with and without thrombosis to support a pathogenic

### Table 1. Clinical features of VITT associated with AZ and J&J vaccines

| Features | UK cases | US cases |
|----------|----------|----------|
| Total no. of cases | 309 | 28 |
| Total no. of vaccines administered, million | 32.9 | 8.7 |
| Reporting rate, per million | 9.4 | 3.2 |
| No. after first-dose vaccine (%) | 294 (95) | 28 (100) |
| Female (%) | 169 (55) | 22 (78) |
| Age range, y | 18-93 | 18-59 |
| No. of patients <50 y (%) | 129 (42) | 22 (78) |
| No. of patients <70 y (%) | 254 (82) | 28 (100) |
| CVT (%) | 116 (38) | 19 (68) |
| ICH (%) | NR | 10 (36) |
| Death (%) | 56 (18) | 3 (11) |

CVT, cerebral vein thrombosis; ICH, intracerebral hemorrhage; NR, not reported; UK, United Kingdom; US, United States.
role for anti-PF4 antibodies. Finally, serologic studies do not show antigen cross-reactivity between anti-SARS-CoV-2 and anti-PF4 antibodies, signifying that anti-PF4 antibodies are unlikely a byproduct of anti-SARS-CoV-2 immunity.

VITT is a clinically distinct syndrome

We recognize that VITT is a clinically distinctive syndrome with (1) a propensity for cerebral and/or splanchnic vein thromboses, (2) laboratory features showing consumptive coagulopathy in association with anti-PF4 seropositivity, and (3) poor outcomes.

To date, the largest numbers of cases with VITT seen in association with the AZ (n = 242) and J&J (n = 15) vaccines have been reported by the Medicines and Healthcare Products Regulatory Agency in the United Kingdom and the Centers for Disease Control and Prevention (CDC) in the United States, respectively (Table 1). Although initial reports indicated disease predisposition in younger female patients, a larger data set from the United Kingdom suggests a more modest age and sex imbalance. Disease incidence appears to be lower among individuals over the age of 70 years (18% with AZ and none with J&J) with a slight female predominance (1.4:1, female to male for AZ; see Table 1). Published case series do not show any consistent association with medical comorbidities, including use of oral contraceptive pills, hormonal therapy, cardiovascular disease, or thrombophilia. The majority of subjects present after 1 dose of vaccine, often within weeks of immunization. Presenting symptoms are reflective of underlying thrombosis and include headaches, nausea, vomiting, and/or abdominal pain. CVT is the most common site of thrombosis and occurs in 38% to 80% of reported cases, followed by involvement of the splanchnic bed (portal, spleen, and/or mesenteric veins). These atypical sites of thrombosis in VITT stand in distinction to those in HIT and aHIT, where thromboses occur in more typical locations, such as deep venous thrombosis, pulmonary embolism, and/or arterial thromboses.

The laboratory features of VITT indicate a consumptive coagulopathy (thrombocytopenia, low fibrinogen, and elevated D-dimer), which is only seen in the most severe cases of HIT. When performed, tests for acquired thrombophilias such as antiphospholipid antibodies, paroxysmal nocturnal hemoglobinuria, ADAMTS13 deficiency, and myeloproliferative neoplasms are usually normal. Circulating anti-PF4/heparin antibodies are detectable in most patients using enzyme-linked immunosorbent assays (ELISAs) but not latex immunoturbidometric assays, the latter of which is a technique that relies on competitive inhibition with latex particles coated with a monoclonal HIT-like monoclonal antibody. Although most reports demonstrate a strong correlation of anti-PF4 seropositivity with functional assays of platelet activation, a recent case series of J&J vaccine subjects indicated low rates of positivity in functional assays (only 1 of 9 VITT subjects had platelet-activating antibodies). Clinicians should be aware that functional studies may yield false-negative results in VITT, as standard platelet-activation assays for detection of HIT antibodies, such as the serotonin release assay, rely on low (0.1-1 U/mL) and high (10-
100 U/mL) doses of heparin to demonstrate heparin-dependent activity. VITT antibodies show PF4-dependent activity and may lose reactivity in the presence of heparin.27 Ideally, functional assays for VITT antibodies should be performed in the presence or absence of added PF4.

VITT is a morbid complication associated with high fatality rates. Where reported, cerebral hemorrhage complicates thrombosis in 26% to 80% of published case series3,4,14,15 and is the leading cause of death. Case fatality in patients with VITT is ~20% (Table 1), likely due to delayed recognition of clinical symptoms and signs by affected individuals and/or providers. It is too early to understand the long-term outcomes in those recovering from CVT and/or splanchnic vein thromboses.

**VITT should be managed as a HIT-like syndrome**

We have sufficient evidence in the form of shared clinical and laboratory features between VITT and aHIT to approach the management of VITT as a HIT-like syndrome. In the published case series, treatment with unfractionated heparin or low-molecular-weight heparin and/or platelet transfusions may have contributed to disease progression,3,14 whereas treatment with nonheparin anticoagulants and IV immunoglobulin (IVIG) was often associated with recovery. Based on these reports and established protocols for treatment of HIT, we recommend the following approach to the management of VITT patients (Figure 1). For recently vaccinated patients (within 4-30 days) presenting with new symptoms (headaches, visual changes, nausea, vomiting, abdominal pain, shortness of breath, chest pain, etc), we advise initial testing with a complete blood count, D-dimer, and fibrinogen, as abnormalities would identify patients with severe manifestations of the syndrome. If all of these laboratory tests are normal, then VITT is less likely; however, patients should be followed, and laboratory testing repeated should symptoms persist. If there is only isolated thrombocytopenia, with normal D-dimer and fibrinogen, and no thrombosis, a diagnosis of vaccine-induced ITP12,35 should be considered, particularly if the patient had received 1 of the mRNA-based vaccines. If there is evidence of consumptive coagulopathy as indicated by decreased platelets, elevated D-dimer, and/or low fibrinogen, we advise obtaining imaging studies and an anti-PF4 ELISA for documentation of VITT.

If imaging studies reveal thrombosis, we recommend hospitalization, initiation of treatment with nonheparin anticoagulants and avoidance of platelet transfusions. A significant proportion of these patients also have intracerebral hemorrhage, however, which can complicate initial management. Although current neurosurgical guidelines recommend anticoagulation in those with intracranial hemorrhage,36,37 anticoagulation decisions in this setting should be individualized and occur in collaboration with neurological or neurosurgical specialists. Adjunctive therapies for management of severe VITT thromboses include treatments used for refractory HIT, such as IVIG,38,39 plasma exchange,40,41 and mechanical thrombectomy.42,43 For bleeding complications, we suggest IVIG and/or prednisone to improve platelet counts and cryoprecipitate and/or fresh frozen plasma for correction of coagulopathy. Case reports also indicate that patients may present with thrombocytopenia, coagulopathy, and anti-PF4 antibody positivity, but without thrombosis,44 in which case, patients should be managed similarly as patients with thrombosis using nonheparin anticoagulants until platelet counts and coagulopathy resolve. Once patients recover, we recommend continuing oral anticoagulation for a minimum of 3 months.

For additional guidance on diagnosis and management, the reader is referred to recent guidelines based on expert opinions from the American Society of Hematology,45 the International Society on Thrombosis and Haemostasis,46 and the British Society for Haematology.47

**Many unknowns remain about VITT**

We concede that the knowledge base informing this review is currently limited; emerging data may shift our current understanding and there remain many more unknowns than knowns. We still do not have clarity on the incidence of disease and impact of age, sex, and race, as surveillance systems are passive, and many cases are likely unreported. Whether the class effects and differences seen in VITT incidence associated with AZ and J&J vaccines are related to the DNA cargo, contaminants, or the adenovirus vector itself is also unknown at this time. A number of questions remain about PF4’s causative role in the immune response and identification of biomarkers and/or genetic susceptibility that could portend thrombotic risk. Finally, there remain uncertainties regarding management and long-term outcomes: how long should patients be treated with anticoagulation, are future adenoviral-based vaccines or therapies contraindicated, and should VITT patients avoid heparin in their future?

Despite these unknowns, our knowledge of this disease has progressed at a remarkable pace. With increased disease awareness and recognition of this syndrome by providers and the public alike, future cases should help refine our clinical understanding and improve clinical outcomes.

**Authorship**

Contribution: G.M.A. and T.L.O. wrote and reviewed the manuscript.

Conflict-of-interest disclosure: G.M.A. serves as a consultant for AstraZeneca and Novartis. T.L.O. declares no competing financial interests.

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**Footnote**

Submitted 17 May 2021; accepted 27 May 2021; prepublished online on Blood First Edition 1 June 2021. DOI 10.1182/blood.2021012152.
REFERENCES

1. Bernal JL, Andrews N, Gower C, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England.

2. Tenforde MW, Olson SM, Self WH, et al; HAIVEN Investigators. Effectiveness of Pfizer-BioNTech and Moderna vaccines Against COVID-19 among hospitalized adults aged ≥65 years - United States, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(18):674-679.

3. Grenacher A, Thiele T, Warkentin TE, Weisser K, Kyriel PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCoV-19 vaccination [published online ahead of print 9 April 2021]. N Engl J Med. doi:10.1056/NEJMoa2104840.

4. Schultz NH, Sørvoll IH, Michelsen AE, et al. mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS) [published online ahead of print 30 April 2021]. Vaccine. doi:10.1016/j.vaccine.2021.04.054.

10. Otite FO, Patel S, Sharma R, et al. Trends in heparin-induced thrombocytopenia antibodies after ChAdOx1 nCoV-19 vaccination [published online ahead of print 16 April 2021]. N Engl J Med. doi:10.1056/NEJMoa2105385.

16. Grenacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. J Thromb Haemost. 2017;15(11):2099-2114.

17. Brandt S, Krauel K, Jaax M, et al. Polyphosphates form antigenic complexes with platelet factor 4 (PF4) and enhance PF4-binding to bacteria. Thromb Haemost. 2015;114(6):1189-1198.

18. Cines DB, Yarovoi SV, Zaitsev SV, et al. Polyphosphate/platelet factor 4 complexes can mediate heparin-independent platelet activation in heparin-induced thrombocytopenia. Blood Adv. 2016;1(11):62-74.

19. Grenacher A, Alban S, Dummel V, Franz G, Mueller-Eckhardt C. Characterization of the structural requirements for a carbohydrate based anticoaguant with a reduced risk of inducing the immunological type of heparin-associated thrombocytopenia. Thromb Haemost. 1995;74(3):886-892.

20. Krauel K, Weber C, Brandt S, et al. Platelet factor 4 binding to lipid A of Gram-negative bacteria exposes PF4/heparin-like epitopes. Blood. 2012;120(16):3345-3352.

21. Jaax ME, Krauel K, Marshall T, et al. Complex formation with nucleic acids and aptamers alters the antigenic properties of platelet factor 4. Blood. 2013;122(2):272-281.

22. Arepally GM, Padmanabhan A. Heparin-induced thrombocytopenia: a focus on thrombosis. Arterioscler Thromb Vasc Biol. 2021;41(1):141-152.

23. Baroletti S, Hurwitz S, Conti NA, Fanikos J, Piazza G, Goldhaber SZ. Thrombosis in suspected heparin-induced thrombocytopenia occurs more often with high antibody levels. Am J Med. 2012;125(1):44-49.

24. Warkentin TE, Sheppard JL, Moore JC, Sigoun CS, Kelton JG. Quantitative interpretation of optical density measurements using PF4-dependent enzyme-immunoassays. J Thromb Haemost. 2008;6(8):1304-1312.

25. Zwicker JI, Uhl L, Huang WY, Shaz BH, Bauer KA. Thrombocytopenia and ELISA optical density values in hospitalized patients with heparin-induced thrombocytopenia. J Thromb Haemost. 2004;12(2):2133-2137.
thrombocytopenia: a review. Expert Rev Hematol. 2019;12(8):685-698.

40. Jaben EA, Torloni AS, Pruthi RK, Winters JL. Use of plasma exchange in patients with heparin-induced thrombocytopenia: a report of two cases and a review of the literature. J Clin Apher. 2011;26(4):219-224.

41. Warkentin TE, Sheppard JA, Chu FV, Kapoor A, Crowther MA, Gangji A. Plasma exchange to remove HIT antibodies: dissociation between enzyme-immunoassay and platelet activation test reactivities. Blood. 2015;125(1):195-198.

42. Cingoz F, Tavlasoglu M, Ali Sahin M, Kurkluoglu M. Inferior vena cava thrombectomy in a patient with heparin-induced thrombocytopenia via inflow occlusion technique on beating heart. Interact Cardiovasc Thorac Surg. 2012;15(4):774-776.

43. Sachithanandan A. Pulmonary embolectomy in heparin-induced thrombocytopenia and thrombosis? Safety of heparin use. Interact Cardiovasc Thorac Surg. 2010;11(5):681.

44. Thaler J, Ay C, Gleixner KV, et al. Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia ( VIPIT) [published online ahead of print 20 April 2021]. J Thromb Haemost. doi:10.1111/jth.15346.

45. American Society of Hematology. Thrombosis with Thrombocytopenia Syndrome (also termed Vaccine-induced Thrombotic Thrombocytopenia). [https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia. Accessed 25 May 2021.]

46. Nazy I, Sachs LJ, Arnold DM, et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: communication from the ISTH SSC Subcommittee on Platelet Immunology. J Thromb Haemost. 2021;19(6):1585-1588.

47. Pavord S, Lester W, Makris M, Scully M, Hunt B. Guidance from the Expert Haematology Panel (EHP) on Covid-19 Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT). British Society for Haematology (https://b-s-h.org.uk/media/19590/guidance-version-17-on-mngmt-of-vitt-20210420.pdf), 20 April 2021, 1-5. Accessed 19 May 2021.