SCIENCE BRIEFS—GUIDANCE FOR OUTPATIENT SETTINGS

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Following Adenovirus Vector COVID-19 Vaccination

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About Us: The Ontario COVID-19 Science Advisory Table is a group of scientific experts and health system leaders who evaluate and report on emerging evidence relevant to the COVID-19 pandemic, to inform Ontario's response. Our mandate is to provide weekly summaries of relevant scientific evidence for the COVID-19 Health Coordination Table of the Province of Ontario, integrating information from existing scientific tables, Ontario's universities and agencies, and the best global evidence. The Science Table summarizes its findings for the Health Coordination Table and the public in Science Briefs.

The Drugs & Biologics Clinical Practice Guidelines Working Group is a group of clinicians and scientists with recognized expertise in drugs, biologics, and clinical care. The Working Group will evaluate existing scientific data, disease epidemiology, drug availability, and implementation issues in order to develop Clinical Practice Guidelines for the treatment of COVID-19 using drugs and biologics. The Working Group reports its findings to the

Interim Guidance for Healthcare Professionals in the Outpatient Setting

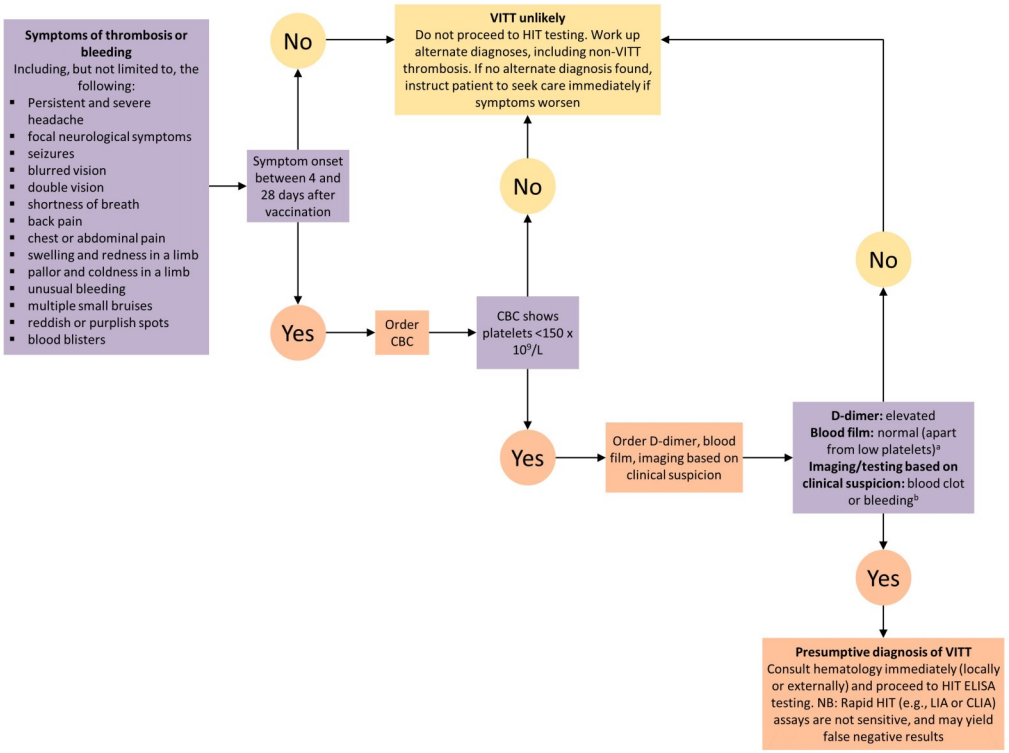

Figure 1. Decision Tree for Diagnosing and Ruling Out VITT

[a]Blood film to rule out platelet clumping as a cause of low platelet count; [b]Not all cases of VITT initially present with a clot or bleeding. Patients with all of the features of presumptive VITT (low platelets, high D-dimer, presenting 4 to 28 days post-vaccination) but NO blood clot or bleeding merit hematology consultation (locally or externally) to consider starting treatment until the results of confirmatory testing are available. VITT, vaccine-induced immune thrombotic thrombocytopenia. CBC, complete blood count. HIT, heparin induced thrombocytopenia. ELISA, enzyme linked immunosorbent assay. LIA, latex immunoturbidometric assay. CLIA, chemiluminescent immunoassay.

What do we know so far?

Adenoviral vector COVID-19 vaccines, including the AstraZeneca/COVISHIELD vaccine and the Janssen/Johnson & Johnson vaccine, are associated with immune thrombosis that is similar to heparin-induced thrombocytopenia (HIT). Women and young people appear to be slightly overrepresented in reported cases, and thrombosis seems to occur 4 to 28 days after vaccination. Affected individuals have antibodies targeted against platelet factor 4 (PF4) that induce massive platelet activation, reducing the platelet count and causing thrombosis.[1–3] This phenomenon

public and the Science Table. Its findings are also summarized in Science Briefs.

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is similar to HIT, but, unlike HIT, VITT does not require heparin as a trigger. It has been referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT), and Thrombosis Thrombocytopenia syndrome (TTS). In this Science Brief, the term VITT will be used. Published estimates of the incidence of VITT range from 1 case per 26,000 to 1 case per 127,000 doses of AstraZeneca/COVISHIELD administered.[3–6] There have been few reported cases of VITT with the Janssen/Johnson & Johnson vaccine thus far, so it is challenging to calculate a precise frequency, but the incidence of VITT appears to be approximately 1 case per 500,000 vaccine doses administered.[7]

Are certain patients predisposed to VITT?

At this time, it is not clear if certain patients are predisposed to VITT. Early reported cases were predominantly in younger women, however these individuals may have been overrepresented in the vaccinated population in reporting countries. Cases have now been reported in men and in older adults. Since VITT appears immune-mediated and linked to a very specific antigen, an individual with classical risk factors for blood clots, including thrombophilia, a family history of blood clots, a personal history of arterial or venous clots, autoimmune disease, low platelets without a history of clotting, a disorder of platelet function, or who is on birth control or other hormones, or who is pregnant, is probably not at increased risk of VITT. Accordingly, there are no new contraindications to receiving the AstraZeneca/COVISHIELD or Janssen/Johnson & Johnson COVID-19 vaccines. However, Health Canada recommends that individuals who have experienced a previous cerebral sinus vein thrombosis (CVST) with thrombocytopenia or HIT should only receive these vaccines if the potential benefits outweigh the potential risks; they may be at increased risk of VITT.[8,9]

The National Advisory Committee on Immunization (NACI) makes a strong preferential recommendation for mRNA vaccines for all Canadians. NACI has recommended that the AstraZeneca/COVISHIELD or Janssen/Johnson & Johnson vaccines may be offered to Canadians 30 years of age and older, if the benefits outweigh risks of waiting for an mRNA vaccine, the decision to receive the vaccine is informed by risks and consequences of VITT, and the delay to receive an mRNA vaccine is substantial.[10] NACI outlines that risk-benefit decisions should be informed by several factors including the local COVID-19 epidemic conditions, local vaccine supply, an individual's risk of severe illness and death if they develop COVID-19, and their risk of exposure to the SARS-CoV-2 virus.

What should primary care providers and patients look out for post-vaccination?

Patients with VITT may present with CSVT, or with other arterial or venous clots or bleeding. Some symptoms make it more likely that a patient has VITT: persistent and severe headache, seizures, or focal neurological symptoms including blurred or double vision (suggesting CSVT or arterial stroke); shortness of breath, chest, back, or abdominal pain (suggesting pulmonary embolism, acute coronary syndrome, abdominal vein thrombosis, or adrenal hemorrhage); unusual bleeding, bruising, petechiae, or blood blisters (suggesting thrombocytopenia or disseminated intravascular coagulation); or limb swelling, redness, pallor, or coldness (suggesting deep vein thrombosis or acute limb ischemia). VITT seems to occur between 4 to 28 days post-vaccination. Symptoms that begin in this time frame should raise the clinical suspicion of VITT.

What should primary care providers and patients do if concerning symptoms arise?

All patients with unusual, non-severe symptoms following vaccination should have an assessment (virtual or in-person) with their primary care provider, and a diagnosis of VITT should be considered; initial investigations may be done in the primary care setting. Patients with severe symptoms should immediately present to the nearest emergency department.

Clinicians should ask patients about their COVID-19 vaccine history and should draw a complete blood count (CBC). VITT is unlikely if symptom onset falls outside of the 4 to 28 day time frame OR if the platelet count is ≥ 150 x 10^9/L.[1–3,11,12] VITT is more likely if symptom onset falls within the 4 to 28 day time frame AND the platelet count is < 150 x 10^9/L, and such patients should be evaluated at their nearest emergency department for suspected VITT. This will expedite further diagnostic workup, treatment, and urgent hematology consultation (local or external).

Treatment principles for patients with presumptive and confirmed VITT are summarized below.

Treating Patients with Presumptive or Confirmed VITT

1. No heparin
2. Avoid platelet transfusions*
3. First line anticoagulants: direct oral factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban)
4. Consult hematology (in person, virtually, by phone) to discuss treatment, HIT ELISA testing, and functional testing
5. Send HIT ELISA testing before giving IVIG. NB: Rapid HIT assays are not sensitive, and may yield false negative results
6. IVIG 1 g/kg actual body weight daily for at least 2 days

Summary Box. Treating Patients with Presumptive or Confirmed VITT
**Platelet transfusions could theoretically worsen the clotting; if patients present with a life-threatening bleed, platelets should only be transfused under the guidance of a hematologist.*

Is VITT a reportable event?

All suspected adverse events following immunization (AEFI), including thrombosis, thrombocytopenia, and both presumptive and confirmed VITT, should be reported using the provincial AEFI form and sent to the local Public Health Unit. More information on how to report AEFIs can be found on the Public Health Ontario website. Ontario conducts vaccine surveillance safety in collaboration with the Public Health Agency of Canada, and prompt reporting is essential to learn more about this rare but serious thrombotic phenomenon.

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