Memorandum

Date: April 30, 2021
To: BC Physicians, Nurse Practitioners, Pharmacists and other Healthcare Providers
From: BC COVID-19 Therapeutics Committee & Medical Director, Thrombosis Program, VCH
Re: Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)

Situation: Vaccine-induced immune thrombotic thrombocytopenia (VITT), also known as thrombosis with thrombocytopenia syndrome (TTS), is a rare, idiosyncratic life-threatening condition that can arise after COVID-19 vaccination with AstraZeneca (AZ) or Johnson & Johnson/Janssen (JJ) vaccines (not reported with Pfizer or Moderna vaccines). This document with supplemental appendices has been developed through extensive consultation with BC medical experts and physician groups to improve awareness and to help guide screening, diagnosis and management of VITT/TTS.

Background: VITT/TTS is a condition characterized by: 1) symptom onset 4 to 28 days after exposure to AZ or JJ vaccine; 2) platelet count less than 150 x 10^9/L; and 3) thrombosis, especially in uncommon sites such as cerebral venous sinuses and abdominal veins (eg. portal vein), as well as arterial thrombosis. Mortality is estimated to be approximately 20%.

VITT/TTS resembles heparin-induced thrombocytopenia (HIT) in its mechanism, and diagnosis requires the presence of anti-PF4/heparin antibodies. Similar to HIT, early diagnosis is essential because patients can deteriorate rapidly. Currently, the recommended treatment is empiric initiation of intravenous immunoglobulin (IVIG) and a non-heparin anticoagulant. Based on available data, the best estimate of the risk of VITT/TTS after vaccination with AZ or JJ vaccines is 1 in 100,000 doses. In BC, approximately 400,000 doses of the AZ and JJ vaccines are anticipated to be administered, but this number may increase as our vaccination campaign continues.

Assessment and Recommendations: In an effort to best protect British Columbians, BC medical experts have put together 4 documents for dissemination to all physicians and other healthcare providers involved in patient care post-vaccination. These documents (Care Pathway, Primary Care Outpatient Assessment, Key Messages Summary, and a VITT/TTS Poster) aim to educate and support physicians and facilitate rapid diagnosis and treatment of VITT/TTS.

Primary Care Outpatient Assessment
This provides a concise, point-of-care summary on assessing patients for VITT/TTS in the outpatient office. The emphasis is on vaccine history, high index of suspicion for thrombosis, getting a stat CBC when indicated, and sending a patient to the Emergency department if needed.

Clinical Care Pathway of VITT/TTS in British Columbia
This algorithm provides guidance to clinicians on how to screen, triage, diagnose and treat patients in a step-wise approach. Not all steps will be relevant to all clinicians, but an understanding of the expected level of care and the required steps is useful. **As the diagnosis of VITT/TTS requires a HIT ELISA test that is only available at St. Paul's Hospital in Vancouver and at the Royal Jubilee Hospital in Victoria, rapid communication with hematologists and laboratory physicians is critical**.

Key Messages and Caveats for VITT/TTS
These key messages are intended for targeted groups of physicians who will be involved in the care of a patient with suspected or probable VITT/TTS. These statements and recommendations are based on evidence that is rapidly changing, and they should not replace clinician judgement. Case-by-case review with a hematologist or thrombosis specialist is highly recommended.

VITT/TTS Poster
The poster provides an overview of the main questions regarding VITT/TTS: When should VITT/TTS be suspected? What tests should be ordered? What empiric treatment should be started? This information is useful for all healthcare professionals who may be involved in other aspects of the patients' care.

As new data become available regarding the diagnosis and treatment of VITT/TTS, the BC COVID-19 Therapeutics Committee will provide updated recommendations. Please contact Dr. Agnes Lee, Medical Director, VCH Thrombosis program, at alee14@bccancer.bc.ca for questions.

Primary Care Outpatient Assessment

Assess for Risk

- Risk of VITT/TTS is 1 in 100,000
- Only AstraZeneca and Johnson & Johnson (Janssen) vaccines have been associated with VITT/TTS
- **Symptoms occur 4 – 28 days after vaccine** (peak period 6 – 14 days)
- VITT/TTS can occur in all ages and both sexes, but is most commonly reported in younger women
- **Patients with history of blood clots are not more likely to have VITT/TTS

Assess for Clotting

- Have a **high index of suspicion**, ask about all of the following:
  - persistent and severe headache
  - focal neurological symptoms, seizures, blurred or double vision
  - shortness of breath
  - chest pain
  - abdominal pain
  - swelling or redness in a limb
  - pallor or coldness in a limb
  - unusual bleeding or bruising
- If a patient has severe symptoms, send patient to ER directly

Order STAT CBC

- If clotting is suspected, a stat CBC is essential, specifically, platelets < 150 x 10^9/L is required to make a diagnosis
- Send patient to Lifelabs or hospital-based lab with requisition
- **MUST write in requisition "STAT CBC to rule out VITT" to get priority**
- **Include phone number to receive call for abnormal results within 6 hours**
- If D-dimer levels is available at your lab, a normal level excludes VITT/TTS

Further Action

- If patient is unstable and/or **platelet count < 150 x 10^9/L** (cases typically are 20 – 50), send patient to ER for additional urgent testing to allow for timely diagnosis and treatment
- In patients with platelet count >150 x 10^9/L, consider follow up in a few days to ensure resolution of symptoms and/or repeat CBC
- Call Hematologist or RACE Thrombosis for advice if uncertain about thrombosis symptoms or if patient is already known to have a low platelet count (eg. ITP)

VITT/TTS = Vaccine-induced immune thrombotic thrombocytopenia/Thrombosis with thrombocytopenia syndrome
ITP = immune thrombocytopenic purpura

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Clinical Care Pathway of VITT/TTS in British Columbia

ALL patients presenting with thrombosis symptoms 4-28 days after AZ/JJ vaccine exposure should get a STAT CBC at hospital-based labs or Lifelabs

VITT/TTS Suspected
AZ or JJ vaccine 4 – 28 days ago AND
- platelet count <150 x 10^9/L or
- signs or symptoms of thrombosis

Signs of symptoms consistent with **arterial or venous thrombosis** ANYWHERE:
- Severe headache, vision changes or other neurological symptoms
- Unexplained shortness of breath or chest pain
- Unexplained back or abdominal pain
- Swelling or redness in a limb
- Acute pain with pallor in a limb
- Petechiae, easy bruising or bleeding

Send to ED for STAT peripheral smear*, INR, aPTT, D-dimer, fibrinogen and COVID testing
*microangiopathy with red cell fragmentation and hemolysis is rarely described in VITT/TTS

Any one of:
- High D-dimer
- Low fibrinogen
- Abnormal INR/aPTT
- High suspicion of clot

Y → VITT/TTS Possible

- Ask if recent exposure to heparin/LMWH (within 1-4 weeks)
- Call Hematology (if no local Hematology, call 604-875-5000 to page VGH Hematologist)
- **MUST** call Laboratory to do stat HIT assay for query VITT/TTS (draw 2 red and 2 blue top tubes) and complete requisition§
- Order appropriate imaging to look for clots and other labs if indicated

Thrombosis Confirmed or High suspicion of clot

N → Follow up results for HIT ELISA (Immucor assay at St. Paul's (PHC) or Royal Jubilee (VIHA)

Y → VITT/TTS Likely
Start empiric treatment
Do not wait for lab results

HIT ELISA positive

N → VITT/TTS Unlikely

Y → VITT/TTS Likely

N → Manage according to standard practice
Order imaging and labs if needed to rule out thrombosis as dictated by symptoms (eg. CTPA, US, angiogram, ECG, troponin)
ONLY CT/MR venogram can rule out CVST

Thrombosis Confirmed

Y →
- Treat as standard VTE/ATE
- DOAC preferred to avoid HIT
- Check platelet count in 3-5 days

N → VITT/TTS Excluded
Possible post-vaccine ITP – Contact Hematology

- Discuss VITT/TTS treatment with Hematology (and Stroke Neurology if CVST confirmed or suspected)
- Give IVIG 0.5 – 1.0 g/kg daily (max total dose 2.0 g/kg) (**Ensure blood drawn for HIT assay BEFORE giving IVIG**)
- Use non-heparin anticoagulant (eg. apixaban, rivaroxaban, fondaparinux, argatroban)
- Consider fibrinogen or cryoprecipitate if patient bleeding and fibrinogen is less than 1.0 g/L
- Do not give platelet unless life-threatening bleeding or need life-saving surgery
- Lab to confirm samples are sent to McMaster for SRA

Legend

ATE	Arterial thromboembolism
AZ	AstraZeneca
CTPA	CT pulmonary angiogram
CVST	Cerebral venous sinus thrombosis
DOAC	Direct oral anticoagulant (apixaban, rivaroxaban)
ED	Emergency Department
HIT	Heparin-induced thrombocytopenia
ITP	Immune thrombocytopenic purpura
IVIG	Intravenous immunoglobulin
JJ	Johnson & Johnson
SRA	Serotonin release assay (platelet activation assay)
TTS	Thrombosis and thrombocytopenia syndrome
VITT	Vaccine-induced immune thrombotic thrombocytopenia
VGH	Vancouver General Hospital
VTE	Venous thromboembolism

§McMaster lab requisition: https://fhs.mcmaster.ca/plateletimmunology/vipit.html

Version date: 30April2021

Key Messages and Caveats for VITT/TTS

Emergency Medicine
Primary Care

- Peak period of onset of thrombosis symptoms associated with VITT/TTS is 6 – 14 days after vaccine
- Check if heparin/LMWH exposure within 1 – 4 weeks (if positive, this could be heparin-induced thrombocytopenia [HIT])
- Most cases of VITT present with platelets <50 x 10^9/L and D-dimer is typically > 4x ULN
- MUST draw blood work for HIT testing and tell lab to arrange for VITT/TTS testing PRIOR to giving IVIG
- MUST order CT/MRI venogram to rule out cerebral venous sinus thrombosis (CVST) if bad headache or neurological symptoms
- Do not give platelet transfusion unless discussed with Hematology
- Call Hematology if vaccine-associated ITP or evidence of red cell fragments (schistocytes) on smear

Hematology
Internal Med
Neurology

- Treat as VITT/TTS unless ruled out with ELISA/SRA (IVIG + use non-heparin anticoagulant +/- steroids)
- If platelets <150 x 10^9/L and D-dimer highly elevated, BUT no thrombosis, consider IVIG only or prophylactic anticoagulation while awaiting HIT ELISA results
- If only thrombosis and platelets >150 x 10^9/L, start anticoagulant treatment (DOAC preferred) and monitor CBC to exclude early stage of VITT/TTS
- Platelet transfusion only if life-threatening bleeding or life-saving surgery indicated, and only AFTER IVIG has been given
- Consider fibrinogen replacement if less than 1.0 g/L and active bleeding
- Plasma exchange has been used in refractory cases (failure of IVIG and anticoagulant) with variable outcomes

Laboratory
Transfusion Medicine

- Review peripheral smear to rule out other causes of thrombosis + thrombocytopenia
- Sensitivity of HIT ELISA is considered sufficiently high to exclude VITT/TTS (optical density [OD] >2.0 in most cases)
- Non HIT ELISA assays have insufficient sensitivity and unknown specificity
- Serotonin release assay (SRA) at McMaster requires 2 red (or gold) top and 2 blue top tubes and completed lab requisition (https://fhs.mcmaster.ca/plateletimmunology/vipit.html)
- Store plasma and serum for all suspected cases (vaccine timing +/- platelets <150 x 10^9/L +/- thrombosis)
- Other thrombophilia testing not required nor recommended

Reference ASH FAQ on VITT/TTS: https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia

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Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)/ Thrombosis and Thrombocytopenia Syndrome (TTS) Poster

Most important interventions to reduce morbidity and mortality are early diagnosis and empiric IVIG treatment

When to suspect VITT/TTS?

- AZ or JJ vaccine 4 – 28 days prior to onset of thrombosis symptoms
- Severe headache, visual changes or other neurological symptoms
- Signs or symptoms of other types of clotting (eg. chest pain, leg swelling, abdominal pain)
- Unusual bruising, bleeding or petechiae

What tests to order?

- STAT CBC to check platelet count ($<150 \times 10^9$/L)
- Coagulation tests to check for clotting: D-dimer, INR, aPTT, fibrinogen
- HIT ELISA to confirm presence of anti-PF4 antibodies
- CT/MRI venogram and other imaging if other sites of clots suspected

What empiric treatment to start?

- DO NOT GIVE PLATELETS
- IVIG 0.5 – 1.0 g/kg daily (maximum 2 g/kg total dose)
- Non-heparin anticoagulant (eg. direct oral anticoagulant, argatroban)
- Contact Hematology or Thrombosis Specialist

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